State of the art GastroPanel and Acetium innovations for the unmet need
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Innovations for the development of safe, ethical and cost-effective treatment of dyspepsia and Helicobacter pylori infection.

Gastrointestinal disorders are a growing global medical, ethical and economic problem. They are among the most common types of complaints made to primary care physicians worldwide and are associated with a substantial healthcare and economic burden. Despite being one of the world’s largest therapeutic areas and presenting huge burdens on healthcare systems and economies globally, many of the diseases of the gastrointestinal tract are still poorly understood, and treatment (diagnosis & therapy) options are far from optimal, leaving many patients dissatisfied with their current treatment and others left without effective and safe treatment (43).

Without a diagnosis, many resort to risky self-treatments for dyspepsia and heartburn. The aging of the population increases the occurrence of serious illnesses, such as gastric, oesophageal and colorectal cancer, and conditions associated with vitamin B12 and trace element deficiencies. This places a rapidly growing burden on health and well-being and affects working capacity and ability to prolong working careers. Outdated guidelines and tests, such as the 13C urea breath test (UBT) and stool antigen test, that may even lead to treatment errors should be replaced with modern, reliable tests and guidelines for dyspepsia and H. pylori infection in primary health care (Figure, Table, Appendix).

The state of the art, safe and cost-effective GastroPanel examination does not involve any of the serious medical problems presented as follows. The 13C urea breath test (UBT), stool antigen test and antibody tests do not detect atrophic gastritis which is caused by H. pylori infection or an autoimmune disease. The diagnosis of in most cases asymptomatic atrophic gastritis is important because of the associated risks, including gastric and oesophageal cancer and malabsorption of vitamin B12, iron, magnesium, calcium and some drugs. Calcium deficiency causes osteoporosis, and vitamin B12 deficiency can cause Alzheimer’s disease, dementia, depression and polyneuropathy, as well as high homocysteine content in the body, which in turn is thought to be an independent risk factor for atherosclerosis, heart attacks and strokes.

The absorption of dipyridamole, some iron products and antifungals (fluconazole, itraconazole), thyroxine and atazanavir is considerably impaired in an anacidic stomach. Atrophic gastritis in the gastric corpus and PPI therapy cause anacid-ity (aclorhydria) of the stomach. The risk of pneumonias and, in senior citizens, even the risk of fatal infections (such as giardiasis, malaria, Clostridium difficile and E. coli EHEC) has been shown to increase significantly in an anacidic stomach. H. pylori gastritis may also develop into antral atrophic gastritis, which increases the risk of peptic ulcer disease and gastric cancer. If both antrum and corpus mucosa are atrophic, this condition is the highest risk for gastric cancer known to date.

Furthermore, none of the aforementioned three H. pylori tests provides any information on excessive gastric acid secretion, which in patients with gastro-oesophageal reflux disease may cause complications of this disease. Such complications are often asymptomatic and include ulcerative oesophagitis and Barrett’s oesophagus, which may lead to oesophageal cancer if left untreated. In addition, the 13C urea breath test and stool antigen test may give up to 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 currently receiving antibiotics or PPIs.

Pasechnikov et al have made the following pertinent conclusions (25): “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 test 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.” (Figure and Table).

The ageing population results in an increase in serious conditions such as atrophic gastritis caused by *Helicobacter pylori* infection or autoimmune disease, gastro-oesophageal reflux disease, gastric-, oesophageal- and colon cancers and peptic ulcer diseases as well as the deficiency of vitamin B12, iron and calcium. Vitamin B12 deficiency may lead to dementia, depression, polyneuropathy and high homocysteine, that is thought to be an independent risk factor for atherosclerosis, heart attacks and strokes. Calcium deficiency is a growing risk factor for osteoporosis. This puts an increasingly heavy burden on public health care, people's well-being and the ability to manage longer at work and in working life. Moreover, many treatment practices are inadequate and outdated, such as the 13C urea breath- and stool antigen tests used in the “test and treat strategy” for the treatment of dyspepsia and *H. pylori* infection (Table ).

Approximately one third of the Finnish population has dyspeptic complaints. Dyspeptic symptoms include constant or intermittent upper abdominal pain, bloating, heartburn, belching and nausea. However, of all visits to general practitioners the proportion of dyspepsia patients is possibly as low as less than 5 percent, as people are dissatisfied with the current treatment of dyspepsia which is not widely available. Dyspeptic complaints lead to repeated examinations and the use of over-the-counter (OTC) products, such as proton pump inhibitors (PPIs) and even yoghurts for abdominal discomfort. Dyspeptic complaints, which reduce the quality of life and working ability, may have either a functional or an organic cause. Irritable bowel syndrome (benign intestinal symptoms) may be associated with functional dyspepsia, and, as much as 50 percent of dyspepsia symptoms may originate from the colon, especially in the elderly population.

**History of the GastroPanel innovation**

The GastroPanel and GastroSoft innovations are based on the long Finnish research and co-work tradition into chronic gastritis and associated gastric diseases (36-41), and on the Nobel price awarded discovery of *Helicobacter pylori* and the role of this novel bacterium in gastritis and peptic ulcer diseases (43-44), as well as on the microplate analysis innovations. These innovations 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. They resulted, among other things, in rapid and massive development of reliable and safe non-radioactive microplate immunoassays, on which the GastroPanel biomarker ELISA-tests are based (45).

The GastroPanel blood tests along with the GastroSoft report interpretation have been developed to determine the function and status of gastric mucosa (Figure and Table). The GastroPanel examination improves the diagnosis of dyspepsia, *H. pylori* infection and in most cases asymptomatic atrophic gastritis and their associated risks, and promotes correctly targeted, evidence-based and effective disease prevention and treatment in primary care. With the help of the GastroPanel examinations it is possible to diagnose reliably whether the gastric mucosa in a patient with dyspepsia-type complaints is “healthy” or “affected”. The examination also determines whether the patient is at risk of complications associated with gastro-oesophageal reflux disease (GORD) due to high acid output (secretion). The GastroSoft report on GastroPanel results helps the doctor to refer the correct patients for a life saving gastroscopy and avoids gastroscopy procedures being performed on patients with a healthy gastric mucosa.
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sa (the loss of appropriate glands and
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time, which promotes safe, ethical and
cost-effective disease treatment and
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ey early, potentially life-saving diagnosis.

Depending on the patient's age, 2 to
12 percent of the adult population has
atrophic gastritis of the gastric mucosa
(the loss of appropriate glands and
function of the antrum and/or the cor-

most cases, asymptomatic atrophic gas-
tritis could be detected only by means
of invasive gastroscopy and histologi-
cal examination of the collected biop-
sies. Now, this can be done in a simple
and even more reliable way with the
GastroPanel examination from a blood
sample. Moreover, atrophic gastritis is
associated with risks such as gastric or
oesophageal cancer, peptic ulcer disease
and vitamin B12, iron and calcium defi-
ciencies, which increase the importance
of the early diagnosis of atrophic gas-
tritis caused by H. pylori infection or
autoimmune diseases.

GastroPanel examination contains
determinations of pepsinogen I, pep-
sinogen II and amidated gastrin-17
levels and H. pylori antibodies from a
blood sample (plasma) and GastroSoft
report (Figure 2). The GastroPanel
tests are reimbursed by KELA - the
Social Insurance Institution in Fin-
land.

The acute need to develop
a treatment practice
for dyspepsia and H. pylori infection

The various treatment practices of dys-
pepsia and H. pylori infection that are
only based on H. pylori tests (the 13C
urea breath test and stool antigen test)
and trial treatments with proton pump
inhibitors (PPIs) do not enable doctors
to provide the best possible, available,
state-of-the-art, safe diagnosis, treat-
ment and prevention of diseases, and
thus are neither medically recommend-
ed nor cost-effective, as they can delay
the correct diagnosis and treatment, or
even result in serious malpractice (31,
35–37, Table).

The 13C urea breath test and stool
antigen test or solely H. pylori anti-
body tests for dyspepsia and H. pylori
infection are unable to detect atrophic
gastritis caused by H. pylori infection or
autoimmune diseases. In addition, the
13C urea breath test and stool antigen
test may give even 50% false negative
results if the patient has atrophic gas-
tritis, MALT lymphoma or bleeding
peptic ulcer disease, or if the patient is
receiving antibiotics or PPI medica-
tion. Consequently, the 13C urea
breath test and stool antigen test may
give false negative results in the very
cases where it is of particular impor-
tance to detect the H. pylori infection
and where the patient should be treat-
ed, e.g. because of the risk of gastric
cancer. H. pylori tests alone do not
detect atrophic gastritis of the corpus
and/or antrum mucosa (Table).

However, the reliable detection of H.
pylori infection, atrophic gastritis and
high acid output is particularly impor-
tant as these conditions may progress
into gastric and oesophageal cancer.
For this reason, every dyspeptic and
asymptomatic patient with atrophic
gastritis, high acid output and untreated
H. pylori infection with symptoms
should be referred for a gastroscopy
without delay and for any necessary
treatment.

H. pylori infection and the precan-
cerous lesions progressing from atro-
phic gastritis (intestinal metaplasia,
dysplasia) due to H. pylori infection
or an autoimmune disease have been
observed to progress into gastric can-
cer. In cases where only an H. pylori
infection diagnosis is made, even a
successful H. pylori eradication treat-
ment with antimicrobial medication
and PPI medication cannot cure pre-
cancerous lesions or early stage cancer
due to H. pylori infection and atrophic
gastritis. Early diagnosis and surgical
treatment is necessary to improve the
prognosis and to prevent unnecessary
deaths due to gastric cancers.

A normal GastroPanel result in a
dyspepsia patient indicates that the
gastric mucosa is healthy and functions
normally, meaning that the patient
does not have H. pylori infection (gas-
tritis) or atrophic gastritis. Confirmation
that the stomach does not show
signs of gastritis is very important
since it shows that the person with
the dyspeptic complaints could have
a non-gastric condition (e.g. biliary or
pancreatic conditions, lactose intoler-
ance, celiac disease) or a colorectal
condition. High acid output increases
a risk of the CORD complications,
erosive oesophagitis and Barrett's
oesophagus.

However, it must be recalled, that
GastroPanel is not a gastric or oesopha-
geal cancer test. It only reveals atrophic
gastritis of the corpus mucosa that is
caused by H. pylori infection or an
autoimmune disease. GastroPanel also
reveals atrophic gastritis of the antrum
mucosa caused by H. pylori infection,
which may strongly increase a risk of
gastric cancer and peptic ulcer disease.
Gastric cancer is thought to develop as
a result of several consecutive changes
as presented by Correa's cascade of
gastric carcinogenesis (35). Moreover,
GastroPanel reveals high acid output
of the stomach (33).

Some gastric cancers, due to H.
pylori infection, develop without histo-
logically observable atrophic gastritis.
Therefore, the early reliable diagnosis
of H. pylori infection made by the Gas-
troPanel examination might even be
life saving (Table). A small proportion
of gastric cancers are hereditary.

GastroPanel examination

GastroPanel is recommended as a
primary examination at any age, if
the patient has dyspepsia including
symptoms of GORD. GastroPanel is

(4 H. pylori infection or atrophic gas-
tritis) and normal stomach acidity. Up
to 40 percent savings can be achieved
with this procedure in endoscopy costs
alone. Easily available and state of the
art, safe and cost-effective, the Gas-
troPanel blood tests encourage people
with dyspepsia to consult a doctor in

The correct diagnosis and treatment, or
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Figure. The levels of the GastroPanel-biomarkers, pepsinogen I (PG I) and pepsinogen II (PG II), basal gastrin-17 (G-17b) 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 millimetres of the adult gastric mucosal surface area (about 80 000 square millimetres). 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 conducts the GastroPanel blood tests. However, the diagnosis of atrophic gastritis obtained with GastroPanel is positively aligned 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.

also the examination of choice, if the purpose is to screen for atrophic gastritis with associated risks in a "health check" of asymptomatic patients over 45 years of age. In addition to the reliable diagnosis of _H. pylori_ infection and atrophic gastritis of the corpus and/or antrum mucosa, GastroPanel also provides information on high acid output (secretion) in the corpus of the stomach, which may increase the risks of complication in GORD patients. These include erosive oesophagitis and Barrett's oesophagus, both of which can progress into oesophageal cancer if left untreated.

High levels of gastrin-17 help to confirm the presence of atrophic gastritis of the corpus (diagnosed on the basis of pepsinogen I levels and/or the ratio of pepsinogen I and pepsinogen II) which can result in gastric and oesophageal cancer. Low levels of pepsinogen I and/or of pepsinogen I/pepsinogen II-ratio together with low levels of gastrin-17 indicate that the gastric mucosa is atrophied throughout. This is the most severe and significant risk factor for gastric cancer.

The levels of gastrin-17 in the blood reflect the structure and function of the lowermost part of the stomach (antrum). The GastroPanel gastrin-17 test measures the levels of gastrin-17 (amidated peptide hormone) with a specific receptor only in the parietal cells of the corpus of the stomach. Gastrin-17 is secreted exclusively by the G-cells of the antrum and it stimulates the gastric hydrochloric acid secretion of the parietal cells of the corpus. High hydrochloric acid secretion from the corpus, in turn, reduces gastrin-17 secretion from the antrum.

High fasting levels of gastrin-17 (over 10 pmol/l) in a GastroPanel examination usually indicate an achlorhydric stomach (from PPI medication or atrophic gastritis of the corpus mucosa). If an _H. pylori_ infection is not detected after fasting, low levels of gastrin-17 only indicate high acid secretion of the corpus mucosa.

If the patient has an _H. pylori_ infection, low fasting levels of gastrin-17 may indicate atrophic gastritis of the antral mucosa caused either by an infection or by high acid secretion of the corpus of the stomach, if the corpus is healthy (no atrophic gastritis). The cause of low levels of gastrin-17 can be determined by protein stimulation, which can be performed as early as the GastroPanel examination by also measuring fasting levels of gastrin-17 and protein-stimulated levels of gastrin-17 twenty minutes after protein solution intake. In atrophic gastritis of the antrum, low levels of gastrin-17 are not increased by protein stimulation (over 5 pmol/l), and the more severe the atrophic gastritis is, the less the low levels are increased by protein stimulation. If protein stimulation increases the low levels (over 5 pmol/l), the patient has no corpus atrophy and a very acidic stomach.

### Affected gastric mucosa

The GastroPanel examination provides a great deal of reliable information on whether the patient's gastric mucosa shows _H. pylori_ infection and atrophic gastritis (10, 11). If the mucosa is affected, the examinations will also provide information on whether the patient just has non-atrophic _H. pylori_ gastritis or an atrophic gastritis of the corpus (achlorhydric stomach), the antrum, or both. It will also provide information on the severity of the atrophic gastritis, evaluated in the GastroSoft report.

The 13C urea breath and stool antigen tests for _H. pylori_ infection diagnosis cannot detect atrophic gastritis as they only detect whether the patient has an ongoing _H. pylori_ infection or not, nothing else (13-16). Therefore, neither test, nor the serological antibody tests, can be used to decide whether the gastric mucosa is atrophied or not, as can be done with the GastroPanel examination, or by means of a biopsy examination in connection with gastroscopy. GastroPanel is an examination that comprehensively reports on the health of the stomach and the structure and function of the mucosa. Consequently, GastroPanel gives much more important information and is thus safer than simple _H. pylori_ tests (Table, Figure).

The diagnostic reliability of GastroPanel is high (10, 11, 17, 18). In a study conducted in northern Sweden on a population of 1,000 people, the sensitivity and accuracy of GastroPanel was 89% (86%-91%) and 90% (86%-93%) compared with gastroscopy-biopsy examination. GastroPanel focused on detecting whether the gastric mucosa was healthy or not (11). In a similar study in Japan, the sensitivity and accuracy were 95% and 93% respectively (17). GastroPanel reliably detects atrophic gastritis (10, 24). In such patients, further evaluation (e.g. by gastroscopy and histological biopsy examination) is necessary due to the risks associated with the condition and these patients should be referred for consultation with a specialist irrespective of the patient's age (12).

### Healthy gastric mucosa — very low risk of gastric conditions regardless of patient age

From the clinical praxis perspective, a dyspepsia patient with a “healthy” gastric mucosa (meaning that there is no _H. pylori_ infection and no atrophic gastritis) means a very low risk or likelihood of gastric disease conditions. Therefore, abdominal complaints in such patients are likely not to be caused by a gastric condition, but by something else.

Since the likelihood of gastric conditions is practically non-existent in such dyspepsia patients, gastroscopy as a routine examination is often a waste of resources. This also applies to elderly patients with dyspeptic complaints, which often are due to colorectal conditions (12).

According to various guidelines issued several years ago, gastroscopy should always be performed in dyspepsia patients over the age of 45-55.
Table. Summary of the data provided by the GastroPanel examination and the $^{13}$C-urea breath test or stool antigen test of the “test and treat” strategy. 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 $^{13}$C-urea breath test or stool antigen test with the GastroPanel examination.

<table>
<thead>
<tr>
<th>The diagnosis for</th>
<th>The GastroSoft report states:</th>
<th>$^{13}$C-urea breath test or Stool antigen test report:</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Functional vs. organic dyspepsia.</strong></td>
<td>YES</td>
<td>NO</td>
</tr>
<tr>
<td>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.</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>H. pylori infection</strong> (gastritis)</td>
<td>YES</td>
<td>NOT RELIABLE (1)</td>
</tr>
<tr>
<td><strong>Atrophic gastritis</strong> (damaged and severely dysfunctional gastric mucosa of the corpus or antrum or both)</td>
<td>YES</td>
<td>NO</td>
</tr>
<tr>
<td>The risks (due to atrophic gastritis) of</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Gastric cancer</strong> (in antrum and / or corpus)</td>
<td>YES (2)</td>
<td>NO</td>
</tr>
<tr>
<td><strong>Vitamin B12 deficiency</strong> (corpus)</td>
<td>YES</td>
<td>NO</td>
</tr>
<tr>
<td><strong>Calcium, zinc and iron deficiency</strong> (corpus)</td>
<td>YES (7)</td>
<td>NO</td>
</tr>
<tr>
<td><strong>Peptic ulcer disease</strong> (antrum)</td>
<td>YES (3)</td>
<td>NO</td>
</tr>
<tr>
<td>The risks of GORD complications</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Oesophagitis and Barrett’s oesophagus</strong></td>
<td>YES (4)</td>
<td>NO</td>
</tr>
<tr>
<td>If necessary, a recommendation for</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Gastroscopy and biopsy examination</strong></td>
<td>YES</td>
<td>NO</td>
</tr>
<tr>
<td><strong>Treatment of H. pylori infection</strong></td>
<td>YES (8)</td>
<td>NOT RELIABLE (1)</td>
</tr>
<tr>
<td>Determination of vitamin B12 and homocysteine</td>
<td>YES</td>
<td>NO</td>
</tr>
<tr>
<td>Determination of calcium and iron</td>
<td>YES</td>
<td>NO</td>
</tr>
<tr>
<td>Follow-up examination to monitor</td>
<td></td>
<td></td>
</tr>
<tr>
<td>the incidence of atrophic gastritis</td>
<td>YES (5)</td>
<td>NO</td>
</tr>
<tr>
<td>the healing of the H. pylori infection</td>
<td>YES</td>
<td>NOT RELIABLE (1)</td>
</tr>
<tr>
<td>the possible healing of atrophic gastritis</td>
<td>YES</td>
<td>NO</td>
</tr>
</tbody>
</table>

1. The $^{13}$C-urea breath test and stool antigen test may give up to 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 the 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 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 gastro-oesophageal reflux disease (GORD).
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), H. pylori infection has to be treated (6). If the patient has atrophic gastritis this should also be treated. 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 of osteoporosis and hip fracture. Hypochlorhydric states such as atrophic gastritis and partial gastrectomy have long been known to cause iron deficiency anaemia.
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.
copies with their associated histological diagnoses, performing gastritis caused by an associated with cancer. However, cancer incidence is primarily increased with age. How prevalence and incidence of gastric cancers. Oesophageal or gastric cancers are advertised for stomach complaints. Yogurts are aggressively and heavily advertised for stomach complaints.

The most feared causes of dyspepsia are oesophageal or gastric cancers. According to statistics, the average prevalence and incidence of gastric cancer increases steeply with age. However, cancer incidence is primarily associated with Helicobacter pylori gastritis and atrophic gastritis caused by an H. pylori infection or an autoimmune disease, the prevalence of which in the population increases with age. However, age is not an independent risk factor for gastric cancer (6). The likelihood of gastric cancer and other significant gastric conditions is equally low in 70-year-old Finns with a “healthy” stomach (gastric mucosa) and in 30-year-olds with a “healthy” stomach (20).

The most important uses for the GastroPanel examination are in primary care. The examinations give the physician an opportunity to improve an early, safe and cost-effective treatment chain that is based on objective evidence. Physicians in primary care have not had such an opportunity before the introduction of the GastroPanel examination. If GastroPanel reveals atrophic gastritis, high acid output or untreated H. pylori infection with symptoms, the dyspeptic and asymptomatic patients should be referred for a potentially lifesaving gastroscopy without delay and for any necessary treatment.

Cost savings in endoscopy

With respect to the specificity of dyspepsia diagnoses, performing gastroscopy with their associated histological biopsy examinations in all patients would naturally be the best option, which is also the orthodox medical approach. However, lack of resources and the incurred costs have limited this strategy. Now, however, medical support and cost savings can be combined as follows.

Computational savings can be achieved when invasive, expensive and sometimes even risky gastroscopic examinations are reduced with easy and safe GastroPanel examination and the resources saved can then be used for other procedures, e.g. other endoscopies (21).

The prevalence of healthy gastric mucosa in Finnish patients with dyspepsia has varied between 50 percent and 70 percent in recent surveys (1, 10, 11, 22). If the estimated prevalence of persons with a healthy stomach is 60 percent, the estimated costs of gastroscopy and biopsy examination are €400, and the costs of GastroPanel examination are €90. In endoscopic examinations, it is possible to achieve 40 percent cost savings. These cost savings will be obtained if a GastroPanel examination is performed first on all patients, and no gastroscopic examination performed when the GastroPanel results are normal (i.e. a gastric mucosa without H. pylori infection and atrophic gastritis).

With this procedure, the cost savings could be approximately €150,000 per year per 1,000 dyspepsia patients. Taking into account the whole population, these savings would be very sizeable (the prevalence of dyspepsia in Finland is one third of the population of 5.3 million). This procedure would not put patients’ health at risk. The chances that some significant gastric condition due to H. pylori infection and atrophic gastritis (such as peptic gastric ulcer, duodenal ulcer or gastric cancer) would be left undetected and untreated would be minimal.

The cost savings described above naturally depend on the unit costs of the examinations and especially on how well the guideline of “no gastroscopy on persons with a healthy stomach” is followed. Cost savings increase with a general rise in “healthy” stomachs within the population. Cost savings are approximately 50% if the proportion of persons with a healthy stomach is 70 percent.

Savings concerning early diagnosis and prevention

Safe, ethical and cost-effective diagnosis, treatment and prevention of conditions associated with dyspepsia-type complaints can be developed and reduce the costs for healthcare, improve quality of life and help people manage longer in working life.

1. Dyspepsia patients with H. pylori infection and atrophic gastritis caused by an H. pylori infection or an autoimmune disease should always be diagnosed or excluded using a GastroPanel examination and considered before prescribing PPI medication for dyspepsia and GORD or providing antimicrobial and PPI eradication therapy for an H. pylori infection.

The simple and unreliable H. pylori tests offered for the diagnosis of dyspepsia and H. pylori infection cannot detect, in most cases, asymptomatic atrophic gastritis, which is also why the risks associated with this condition will remain unexplored. Moreover, the 13C urea breath tests and stool antigen tests may give up to 50% false negative results for H. pylori infection if the patient has atrophic gastritis, MALT lymphoma or a bleeding peptic ulcer disease or if the patient is currently receiving antibiotics or PPI medication. In addition, the H. pylori tests do not reveal high acid output. The GastroPanel examination does not have these serious medical and ethical problems (Table and Appendix 1).

2. PPI medication or PPI medication and antimicrobial H. pylori eradication therapy do not cure early gastric cancer caused by H. pylori infection nor conditions associated with atro-
Appendix. - The GastroPanel and Acetium innovations are together a unique combination that can help to prevent gastric and oesophageal cancers. GastroPanel detects atrophic gastritis and the related gastric and oesophageal cancer risks while the conditions are still treatable. Atrophic gastritis of the corpus, which is usually irreversible, leads to permanent achlorhydria. In an achlorhydric stomach, microbes from the mouth can survive and produce acetaldehyde from sugars and alcohol present in food (1). In the new cancer classification issued by WHO in October 2009, acetaldehyde present in alcoholic beverages and formed from ethanol endogenously is in Group 1, together with carcinogens such as asbestos, tobacco and benzene (2).

Globally, acetaldehyde exposure mediated by gastrointestinal tract microbes or tobacco smoke is associated with approximately four million new cases of cancer each year, nearly 40 per cent of all cancers. These include upper aerodigestive tract, colon and pulmonary cancers (3). Biohit has developed products and a method to reduce physical and nutritional exposure to acetaldehyde (4-7).

The same ethical and legislative principle concerns all Group I carcinogens, regardless of the source of the carcinogen. Physical and nutritional exposure to them should be reduced by all means possible. The Acetium capsule, protected by patents, is the only means of inactivating carcinogenic acetaldehyde in the stomach, thus helping to prevent gastric and oesophageal cancers. Acetium capsules are available over the counter without prescription. They are recommended at meals and when consuming alcohol for those with

1. achlorhydria caused by atrophic gastritis (diagnosed by GastroPanel)
2. an untreated Helicobacter pylori infection (diagnosed by GastroPanel)
3. a long term use of antacids (PPIs, H2-receptor antagonists)
4. a resected stomach.

It will take years to obtain conclusive information on Acetium’s efficiency in the prevention of gastric and oesophageal cancer. We will need population studies targeted at high-risk groups and aiming for systematic reduction of acetaldehyde exposure. Unfortunately, randomised intervention studies on Acetium are not possible for ethical reasons, due to the Group 1 carcinogenicity classification of acetaldehyde (www.acetium.com/test reveals acetaldehyde exposure).

Literature

Osteoporosis-related fractures per year in Finland. Besides the human tragedy, hip fractures alone (approximately 7,000/year) cause moderately estimated healthcare costs of over €100 million a year (The Finnish Medical Journal 22/2008, vol. 63, pp. 2033–40). This number may increase as the population ages.

3. The Pharmaca Fennica entry (2009, III, p. 1829) for a PPI product includes the following warning: “If the patient has alarming symptoms (e.g. significant, unexplained weight loss, repeated vomiting, dysphagia, haematemesis or melaena) and a suspected or diagnosed gastric ulcer, the possibility of malignancy should first be excluded since PPI therapy may alleviate the symptoms and delay the diagnosis.” Unfortunately, this warning is very often too late.

4. The National Cancer Institute (Bethesda, MD) published an article together with the Cancer Institute & Hospital, Chinese Academy of Medical Sciences (Beijing) in 2008 confirming earlier results that year that atrophic gastritis of the corpus (achlorhydric stomach and associated carcinogenic acetaldehyde produced by microbes of the mouth) may increase the risk of oesophageal cancer (24). The study showed that the GastroPanel tests, pepsinogen I and II, can detect atrophic gastritis of the corpus even more reliably than biopsy examinations performed in connection with gastroscopy.

5. In the treatment of osteoporosis, the following should be taken into account to improve cost-effectiveness: a possible achlorhydric stomach, the result of PPI medication and atrophic gastritis of the corpus, which is, in most cases, asymptomatic and which can be detected with a GastroPanel examination. Calcium deficiency due to an achlorhydric stomach is a cause of osteoporosis and therefore increases the risk of hip fractures (26). There are 35,000 to 40,000 osteoporosis-related fractures per year in Finland. Besides the human tragedy, hip fractures alone (approximately 7,000/year) cause moderately estimated healthcare costs of over €100 million a year (The Finnish Medical Journal 22/2008, vol. 63, pp. 2033–40). This number may increase as the population ages.

6. When the goal is to obtain cost savings in healthcare, it should be taken into account that patients with autoimmune conditions, such as ulcerative colitis, thyreoiditis, diabetes, MS, SLE and rheumatoid arthritis, may have concurrent asymptomatic atrophic gastritis of the corpus with its associated risks, such as gastric and oesophageal cancer and vitamin B12 deficiency, caused by an autoimmune disease. Vitamin B12 deficiency is increasing as the population ages and is developing into a public health problem (34). Vitamin B12 deficiency may cause dementia, depression, polyneuropathy and a high concentration of homocysteine in the body. This is thought to be an independent risk factor for atherosclerosis, heart attacks and strokes. The GastroPanel examination could undoubtedly promote safe treatment and reduce the days spent in institutional and hospital care, as well as reduce other treatment and sickness-leave costs and alleviate human suffering. Tests to examine the causes of these conditions could take place in outpatient or hospital care or in institutions for the elderly or the mentally disabled.

7. Based on the Finnish Setti studies, conducted over ten years ago and on the follow-up of the study subjects, it has been estimated that GastroPanel screening of people of 45 years through early detection of H. pylori infection and asymptomatic atrophic gastritis and referral for gastroscopy and biopsy examination would improve the prognosis of 250 to 300 patients with precancerous lesions or early gastric cancer (8, 9).

8. The GastroPanel examination also provides information on the risk of peptic ulcer disease caused by an H. pylori infection. Peptic ulcer diseases and the use of anti-inflammatory analgesics cause complications (e.g. bleeding) that cause 200 to 300 deaths each year in Finland (30).

9. Based on the above, the risk of oesophageal cancer would seem to be increased by: 1) the acidic stomach content that flows back into the oesophagus, which is why the stomach is “treated” to become achlorhydric with PPI medication (there were close to 10% of the population (464,000) on PPI medication in Finland who received sickness insurance reimbursements by the Social Insurance Institution in 2007, Lääkeinfo, The Finnish Medical Journal 4/2009, vol. 64, p. 296–299); or 2) carcinogenic acetaldehyde produced by microbes in an achlorhydric stomach due to corpus atrophy. About 500 million people worldwide have an achlorhydric stomach due to corpus atrophy.

In an achlorhydric stomach caused by atrophic gastritis of the corpus due to H. pylori infection, autoimmune disease or PPI medication, oral microbes can multiply and produce carcinogenic acetaldehyde from the sugars and alcohol that are a part of a normal diet. Acetium capsules taken with meals are available to inactivate
10. The GastroPanel examination warns of the complication risks of GORD associated with an acidic stomach. Erosive oesophagitis and Barrett's oesophagus are asymptomatic in as many as one third of reflux patients and which can progress into oesophageal cancer if left untreated. Some researchers recommend gastroscopy for differential diagnosis of non-erosive reflux disease (NERD) and erosive reflux disease (ERD) and an effective PPI medication for ERD only (Gut 2006; 55 suppl VA 267). In the gastroenterology symposium held in Helsinki in 2008, neither Finnish nor foreign researchers could give a clear answer as to when and how often a patient with GORD should be referred for a gastroscopy in the absence of alarming symptoms clearly demanding immediate gastroscopy.

It is clear that endoscopies are performed too rarely and possibly also too late, since the 13C urea breath tests and stool antigen tests for instance fail to provide information on the potential complication risks of GORD in dyspepsia patients, asymptomatic patients wanting a health check, or patients with atrophic gastritis. If the GastroPanel examination shows that the content of the stomach is highly acidic, even an asymptomatic GORD patient may have a complication risk of GORD. In these cases especially an endoscopy and the required treatment are recommended.

Conclusions

Depending on the patient's age, 2 to 12 percent of the adult population has atrophic gastritis of the gastric mucosa caused by H. pylori infection or an autoimmune disease that in most cases is asymptomatic or associated with dyspepsia-like symptoms.

Before the GastroPanel innovation, atrophic gastritis could be detected only with an invasive gastroscopy and histological examination of the biopsies collected in connection with the procedure. The diagnosis of atrophic gastritis, its location (corpus or antrum or both) and its severity can now be detected in a simpler, more reliable way with GastroPanel examination, which outperforms plain H. pylori tests and is performed on a blood sample and includes the GastroSoft report (10, 11, 17, 23–25).

When people with dyspepsia who have not had appropriate examinations and treatment find out about how the GastroPanel examination can be performed safely and easily on a blood sample (many are afraid of invasive gastroscopy), many with dyspeptic-type complaints may not stay home anymore and wait for their condition to worsen, and many others might give up risky self medication (with over-the-counter products, using PPIs and certain yoghurts for abdominal discomfort and heartburn) and seek examination and treatment in time.

If a patient with dyspepsia or wanting a health check does not have any alarming symptoms requiring immediate gastroscopy, it is recommended that the state of the art GastroPanel is used as a primary examination to secure the early selection of right patients for referral for endoscopy and to promote the development of safe, ethical and cost-effective diagnosis and prevention of diseases (Table, Figure and Appendix).

If the GastroPanel examination reveals atrophic gastritis, high acid output or an untreated H. pylori infection with symptoms, the dyspeptic and asymptomatic patients should be referred for a potentially lifesaving gastroscopy without delay and for any necessary treatment.

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The Chairman and Founder of Biohit Oyj, Professor Osmo Suovaniemi, M.D., Ph.D., was also the Founder of Labsystems Oyj (est. 1971, the first OTC company listed on the stock exchange in Finland in 1984) and the joint venture Eflab Oy (est. 1978 by the family Suovaniemi and the American company Flow General Inc.). These companies have "revolutionised laboratory routines worldwide in the 1970s and 1980s" through Suovaniemi’s innovations in the adjustable single- and multi-channel Finnpipettes and vertical measurement principle (Suovaniemi equation, A = km, where A is absorbance, k is a constant and m is a mass to be measured) for non-radioactive and safe microplate immunoassays, analysers and analysing systems (TEKES, The National Technology Agency of Finland 2001: These innovations are “Paving the Way for Evidence Based Medicine”). Since its establishment Biohit has also applied Suovaniemi's aggressive innovation and patenting strategy. In January 2000, twenty new companies listed on the Helsinki stock exchange altogether possessed 11 patents, whereas Biohit alone possessed 16 patents in Finland (www.biohit.com/About Us/History: Aggressive Innovation and Patenting Strategy and www.google.com/search Suovaniemi equation). Diagnostic products, such as the GastroPanel examination, are components for company’s analysing systems and more generally for the vertical measurement principle based microplate analysers and analysing systems world-wide (hundreds of thousands on the market place).
Literature


