Acta Biomed 2018; Vol. 89, Supplement 8: 44-52 DOI: 10.23750/abm.v89i8-S.7917

Review

A non-invasive method for the diagnosis of upper GI diseases

Alberto Barchi[1], *Chiara Miraglia*[1], *Alessandra Violi*[1], *Ginevra Cambiè*[1], *Antonio Nouvenne*[1], *Mario Capasso*[1], *Gioacchino Leandro*[2], *Tiziana Meschi*[1], *Gian Luigi de' Angelis*[1], *Francesco Di Mario*[1]

[1] Department of Medicine and Surgery, University of Parma, Parma, Italy; [2] National Institute of Gastroenterology "S. De Bellis" Research Hospital, Castellana Grotte, Italy

Summary. Upper-GI diseases are one of the most relevant issue in primary care. Nowadays they are still responsible for about 100 million ambulatory care visits only in the US. The diagnosis of almost every upper-GI condition is still deputed to invasive tests such as upper gastrointestinal endoscopy, gastroesophageal manometry or radiography. The possibility of analysing serum markers like Pepsinogens I and II, produced by gastric mucosa, in order to assess the functional characteristics of the upper GI tract has spread itself since the 80's especially in the diagnosis of peptic ulcer. The discovery of *Helicobacter pylori* by Marshall and Warren in 1983 and the scientific consecration of its role in the pathogenesis of gastric cancer and peptic ulcer (crystallized in Peleo Correa's Cascade, 1992), led to an increase importance of non-invasive tests, raising the attention towards the assessment of both immunoglobulins anti-H.p. and Gastrin hormone produced by antral G cells, as an implementation of the panel of gastric markers. This narrative review aims to analyze the huge landscape of non-invasive tests for diagnosis of GI diseases, studying the literature of the recent years. (www.actabiomedica.it)

Key words: stomach, gastritis, diagnosis, Gastrin-17, pepsinogens, *Helicobacter pylori*, GERD

Introduction

It's widely known that upper-GI diseases are one the most important issue in primary care. The prevalence of upper-GI symptoms in primary care is still relevant: only in the U.S., up to now digestive diseases account for more than 100 million ambulatory care visits annually but comparatively less is known about the true burden of gastrointestinal (GI) symptoms. The most commonly reported symptoms are heartburn/reflux (30.9%), abdominal pain (24.8%), bloating (20.6%), diarrhoea (20.2%), and constipation (19.7%). Less common symptoms are nausea/vomiting (9.5%), dysphagia (5.8%), and bowel incontinence (4.8%) (1). Moreover, there is also an economical issue: in 2015, annual health care expenditures for gastrointestinal diseases in the U.S. totalled $135.9 million, being oesophageal disorders ($18.1 millions) one of the most expensive. Yearly, there were more than 54.4 million ambulatory visits with a primary diagnosis for a GI disease, 3.0 million hospital admissions, and 540,500 all-cause 30-day readmissions (2). In 2004, GERD was by far the most frequently first-listed digestive system condition at ambulatory care visits in the U.S., constituting 17.5% of all digestive system diagnoses, while there were about 700,000 ambulatory care visits with peptic ulcer as the first-listed diagnosis and an equal number in which it was a secondary diagnosis (3). Concerning upper-GI cancers, The Surveillance, Epidemiology, and End Results **(SEER)** program provides considerable information on cancer burden, as shown in figure 1. Between 2011 and 2015, approxi-

All Races

Site	Incidence[a] (2011-2015) Total	Males	Females	US Mortality[b] (2011-2015) Total	Males	Females	Survival[c] (%) (2008-2014) Total	Males	Females
All Sites	439.2	483.0	409.9	163.5	196.8	139.6	66.9	66.4	67.5
Oral Cavity & Pharynx:	11.3	17.1	6.3	2.5	3.9	1.3	64.8	64.0	66.9
Lip	0.7	1.1	0.3	0.0	0.0	0.0	88.4	88.2	89.3
Tongue	3.4	5.2	1.8	0.6	0.9	0.4	65.8	66.1	64.8
Salivary gland	1.3	1.7	1.0	0.3	0.4	0.1	71.6	64.0	82.1
Floor of mouth	0.5	0.7	0.3	0.0	0.0	0.0	52.9	51.9	55.2
Gum & other oral cavity	1.5	1.8	1.3	0.4	0.5	0.3	59.2	55.2	64.3
Nasopharynx	0.6	0.9	0.4	0.2	0.3	0.1	61.6	59.4	66.8
Tonsil	2.0	3.4	0.7	0.2	0.4	0.1	73.9	74.5	70.9
Oropharynx	0.4	0.7	0.2	0.3	0.4	0.1	45.8	47.1	40.8
Hypopharynx	0.6	1.0	0.2	0.1	0.2	0.0	32.9	32.9	32.5
Other oral cavity & pharynx	0.3	0.4	0.1	0.4	0.7	0.2	45.1	47.7	35.5
Digestive System:	81.1	98.8	66.3	41.3	53.0	31.7	43.5	41.2	46.3
Esophagus	4.2	7.2	1.7	4.0	7.2	1.5	19.2	18.9	20.0
Stomach	7.2	9.8	5.2	3.2	4.3	2.3	31.0	28.4	35.1
Small intestine	2.3	2.6	2.0	0.4	0.5	0.3	67.6	66.8	68.4
Colon & Rectum:	39.4	45.2	34.5	14.5	17.3	12.2	64.5	64.1	64.9
Colon	27.7	30.7	25.3	-	-	-	63.6	63.6	63.6
Rectum	11.7	14.6	9.2	-	-	-	66.6	65.2	68.6
Anus, anal canal & anorectum	1.8	1.5	2.1	0.3	0.2	0.3	67.4	60.8	71.4
Liver & intrahepatic bile duct	8.8	13.6	4.7	6.4	9.4	3.8	17.7	17.5	18.4
Gallbladder	1.2	0.9	1.4	0.6	0.5	0.7	18.2	18.4	18.1
Other biliary	1.9	2.3	1.5	0.4	0.5	0.4	17.5	18.8	16.1
Pancreas	12.6	14.4	11.2	10.9	12.6	9.5	8.5	8.8	8.3
Retroperitoneum	0.4	0.4	0.4	0.1	0.1	0.1	54.2	52.9	55.4
Peritoneum, omentum & mesentery	0.5	0.1	0.9	0.3	0.1	0.4	32.0	38.2	31.5
Other digestive system	0.7	0.8	0.6	0.3	0.4	0.3	8.6	7.1	10.2

Figure 1. Age-adjusted SEER Incidence and U.S. Death Rates and 5-Year Relative Survival (Percent) By Primary Cancer Site, Sex Time Period

mately 243,000 people were diagnosed with digestive system cancers, which represented 18% of all cancers and were second only to genital system cancers for the most commonly affected organ system. The most common cancer of the upper-GI tract was Gastric Cancer with a reported incidence of 7.2/100,000 followed by Oesophageal cancers (4.2/100,000). Concerning survival, despite the low incidence of these upper-GI neoplasms, compared with colorectal cancers, they were associated with lower 5-year survival rate (2008-2014), 31/100,000 for gastric neoplasms and 19.2/100,000 for oesophageal ones, against 64.5/100,000 for colorectal cancers (3, 4).

Upper gastrointestinal endoscopy

The increasing reliance by physicians on endoscopy and the appreciation by the general public that upper endoscopy (EGD) is useful for diagnosis, surveillance, treatment, or exclusion of important gastroduodenal diseases, led to an increasing demand for open-access endoscopy. Every year in the U.S. more than 6 million of EGD are performed against a total number of 17,800,000 endoscopies (2), as shown in figure 2. This allows physicians to directly schedule elective, common endoscopic procedures for their patients without prior consultation. Unfortunately, this has also resulted in a considerable increase in overall costs and waiting lists for EGD. Moreover, a substantial rate of inappropriateness of EGD indications has been reported, which has also been associated with a marked decrease of its diagnostic efficacy. An Italian prospective, multicentre study has evaluated the appropriateness rate of 6270 upper endoscopies and the indication for EGD was considered appropriate, according to ASGE criteria, in 77.1% of the cases, whereas it was judged inappropriate in the remaining 22.9% of the examinations. In detail, the inappropriateness rate widely ranged, from 2.8% to 59.1%, among the different centres taking into examination. This study assessed that the probability of endoscopic

Procedure	Number
Colonoscopy	10,964,034
Upper endoscopy	6,069,647
Flexible sigmoidoscopy	313,045
Upper endoscopic ultrasound	178,417
Endoscopic retrograde cholangiopancreatography	169,510
Lower endoscopic ultrasound	17,727
Total	**17,712,380**

Source: MarketScan Commercial Claims and Encounters and Medicare

Figure 2. Estimated Annual Number of Endoscopic Procedures in the United States, 2013

detection of a clinically relevant finding was distinctly higher when the procedure was performed for an appropriate, as opposed to an inappropriate indication (5). Therefore, it is clear how appropriateness is the key word for EGD in clinical practice, especially in relation to costs, quality of assistance and nonetheless in the relevance of findings.

Non-invasive approach

A renewed interest for a non-invasive approach to gastric diseases has been observed in the last 20 years. This is probably related to low specificity and sensibility of alarm symptoms, as well as to the above-mentioned limits of upper endoscopy. EGD is in fact bothersome and expensive; nonetheless sampling errors and pathologist intra-observer discrepancies can limit the findings of gastric biopsies. Furthermore, a negative EGD with no relevant histological alterations rule out organic lesions and premalignant conditions, but does not help the management of functional diseases, such as dyspepsia or the non-erosive reflux disease (NERD). Gastropanel® (Biohit Oyj, Helsinki, Finland) is a panel of the following biomarkers: *Pepsinogens I (PGI)* (n.v.: 30-160 μg/l), *Pepsinogens II (PGII)* (n.v.: 3-15 μg/l), *Gastrin-17 (G-17)* (n.v.: 1-7 pmol/l) and *Helicobacter pylori IgA and IgG antibodies* (n.v.: <30 EIU). It permits the indirect evaluation of both the secretory and morphological status of the gastric mucosa. PGI is produced only in the corpus-fundus of the stomach, while PGII it can be found also in the antrum, cardia and in the Brunner glands. Gastrin-17 is an endocrine hormone, produced by the antral G cells, which controls by negative feedback the acid production of the stomach. Lastly, the possibility to evaluate the presence of Anti-H.p. antibodies is crucial due to the widely known impact of H.p. infection on the functionality of gastric mucosa. Since the 80's, before the H.p. era, in the scientific world began to spread the idea of using serum pepsinogens as a "non-invasive gastric biopsy". Today, thanks to improvements in the knowledge of gastric physiology and physiopathology, the effectiveness of the evaluation of the above-mentioned serum gastric markers in a wide range of upper gastrointestinal diseases and conditions is proved.

Dyspepsia

The dosage of these markers finds his main indication in the so-called dyspeptic patients. Dyspepsia is a functional GI disorder consisting in a wide range of symptoms. The international Consensus Report "Rome III" tried to simplify the dyspeptic picture, focusing on two groups of symptoms: 1. The meal-induced symptoms such as *post-prandial fullness and early satiation*; 2. *Epigastric pain and epigastric burning*, excluding other symptoms such as nausea and vomiting (6). The main challenge in these patients has always been whether to perform an EGD or an abdominal US, since the principal worry of the physician has been to misunderstand an organic problem. In the Maastricht III Consensus Report was suggested an algorithm that contemplate to perform an EGD with biopsy sampling in dyspeptic patient older than 45 years, unless alarm features were

present (7a). Through years the possibility of avoiding EGD, with an improvement in the patient's management and a considerable economical saving, has spread leading up to the most recent Maastricht V Consensus Report (7b) in which the statement "An endoscopy-based strategy should be considered in patients with dyspeptic symptoms, particularly in low prevalence *H. pylori* populations." was rejected with a "very low" level of evidence and weak recommendation. Moreover, in the same Consensus it was assessed with a high level of evidence, that Pepsinogen serology is the most useful non-invasive test to explore the gastric mucosa status, making room for the implementation of GastroPanel® in management algorithm of dyspepsia (7, 8).

H. Pylori related gastritis

Several studies have been showing the role of PGI, PGII and PGI/PGII ratio in the determination of acute gastritis associated with *Helicobacter pylori* infection (11, 12). In a Chinese study on 395 subjects, it was assessed a statistically significant link between levels of PGI, PGII and the PGI/PGII ratio with age in healthy subjects and in H.p. infected ones. In particular, higher levels of PGI and above all PGII were found in subjects from the 65-year-old age group against the 35-44-year-old age group. It was nonetheless determined a positive correlation between H.p. IgG levels and PGI, PGII and G-17, while a negative correlation was found with PGI/PGII ratio (9). This inverse correlation between PGI/PGII ratio and acute gastritis seems to suggest the possibility of a slighter more rapid increase in PGII levels than PGI in presence of acute inflammation of gastric mucosa, such as the one caused by *Helicobacter pylori* infection. An Italian study (10) showed a clear increase in PGII levels in H.p.+ patients with active or chronic gastritis compared with lower levels in H.p.- patients. In addition, a slight lower increase in PGI levels resulting in a significant decrease of PGI/PGII ratio, was reported. To strengthen this correlation, has to be mentioned from the literature an American study on a model of acute H.p. infection, consisting of 18 H.p. negative volunteers who were orally inoculated with H.p. which showed PGII levels rising more rapidly than PGI levels, and within two weeks, 94% of inoculated patients showed PGII levels above normal cut-off value against only 72% of them showing elevated PGI values (13). Furthermore, it was assessed an important relation between PGII values and H.p. eradication, showing a relevant decrease of PGII values from 17.5 μg/ L to 8.2 μg /L in eradicated subjects compared with a statistically not significant decrease ($p<0.03$) of the same value in not eradicated subjects (9). These results suggest not only a role of PGII as a biomarker for inflammation but also in the assessment of H.p. eradication.

Gastro-oesophageal reflux disease and Barrett's oesophagus

As previously mentioned, GERD is the most diagnosed digestive condition in primary care. A recent review showed that GERD has a prevalence ranging from 9.8% to 18% in Europe, 18.1%-27.8% in Northern America, with the lowest incidence found in East Asia (2.5%-7.8%) (14). The first line treatment for GERD patients with typical symptoms such as heartburn and/or regurgitation is the PPI prescription, but in those patients, who suffer from NERD or that refer atypical GERD symptoms such as asthma, it can be difficult to prescribe PPI treatment or perform further examination (e.g. pH-metry or impedance-pH). Several studies have shown that fasting G-17 levels could be a surrogate marker of high basal acid output which predisposes to gastric acid reflux (17, 18). A recent Italian study confirmed that in a population of GERD/NERD patients, the ones with Los Angeles A esophagitis and B esophagitis as well as NERD patients showed a basal G17 value, which was significantly lower ($p=0.0001$) than that seen in the control group, by taking a cut-off <1.9 ng/dL (19). As we know from the physiopathology under the umbrella of NERD patients, there are numerous patterns of reflux, such as proper acid reflux, non-acid reflux or functional heartburn (FH). G-17 could be used in order to single out these patterns, that have been standardized by means of Impedance-Ph. An Italian study based on a pool of 35 patients suffering from heartburn, subdivided in 3 groups for 3 different patterns of reflux by Impedance-Ph, demonstrated that G-17 levels well

correlated with the three different categories of patients included in the NERD umbrella, suggesting its use as a surrogate marker of NERD, non-acid reflux disease or FH, without the need of performing invasive tests (20). A major concern in GERD is Barrett's Oesophagus (BO), a precancerous metaplastic lesion, strongly related with a higher risk of oesophageal cancer. A Finnish case-control study, for the first time, observed that low G-17 value could be a risk factor for BO (15), even if other studies seemed to exclude that serum gastric markers could correlate with the severity of GERD (16). Another Italian study (21) demonstrated a significant reduction in fasting G-17 levels in patients with both Erosive Esophagitis an BO in comparison to patients with a normal oesophagus, suggesting a predictive role of G-17 in the early prevention of oesophageal cancer.

Chronic Atrophic Gastritis

PGI levels decrease in corpus atrophic gastritis. Several studies have demonstrated that the decrease is proportional to the severity of atrophy. Furthermore, because of the acid-gastrin negative feedback, the presence of corpus atrophy is confirmed by high levels of Gastrin 17 (22, 23). An Italian study involving 287 patients with a histologically evaluated gastric mucosa, subdivided these patients into 5 groups: Normal (N), Non atrophic chronic gastritis (NCAG), Antrum atrophic gastritis (AAG), Multifocal atrophic gastritis (MAG) and Corpus atrophic gastritis (CAG). The aim of that study was to compare serological values of PGI and G-17 with histological evaluation. The study demonstrated a statistically significant ($p<0.001$) decrease of PGI levels in the CAG group versus N and NCAG group. On the opposite, the study showed a significant ($p<0.001$) increase of G-17 values in CAG patients compared to N and NCAG ones, in according with physiopathology (24). Even though production of G-17, as it's acknowledged, mainly by antral G cells, could suggest a role of this serum marker in the diagnosis of antral atrophy, several studies through years have not been capable of discriminating whether there is a statistically significant correlation between these tools. Some studies agree that G-17 could be used as a quite sensible marker for antral atrophy, due to its decrease caused by antral G cells loss (22, 26); on the other hand, studies still argue G-17 role in antral atrophy screening due to very low sensibility and specificity levels (25, 27). Nevertheless, the literature widely agrees that when atrophy involves both antrum and corpus, serum gastric markers (PGI, PGII, and G-17) fall down (22-24). In the last 15 years, many studies performed worldwide have analyzed the accuracy of PGI or a combination of PGI with other biomarkers such as GastroPanel® in order to detect atrophic gastritis. However, the results in the literature are often difficult to compare because of several differences:

1. Studies performed in different countries with different H. pylori and gastric lesions epidemiology
2. Types of cohort (asymptomatic or dyspeptic)
3. Different techniques to evaluate biomarkers (ELISA or RIA)
4. Different outcomes (CAG or Antrum predominant atrophic gastritis or APAG)

Despite all the above-mentioned differences, as shown in figure 3, low PGI or PGI/PGII ratio appear to have both moderate sensitivity and good specificity (23, 24, 29-31). A recent systematic review with metanalysis has evaluated 20 studies for a total of 4241 subjects, in order to assess the performance of serum panel test (GastroPanel®) for the diagnosis of atrophic gastritis regardless of the site in the stomach. The summary sensitivity was 74.7% (95% confidence interval (CI), 62.0-84.3) and the specificity was 95.6% (95%CI, 92.6-97.4). With a prevalence of atrophic gastritis of 27% (median prevalence across the studies), the negative predictive value was 91% (28).

Gastric Cancer

According to Lauren's classification (32, 34), both intestinal and diffuse types of gastric cancer are linked to gastric inflammation and several studies culminating in Peleo Correa's cascade (33), have confirmed the role of H.p. infection in the pathogenesis of cancer as a precancerous condition. GastroPanel® could be, for instance, a useful examination to select subjects with premalignant conditions (p.e. atrophy; H.p. infection),

Serological Test	Outcome	Population (n)	Sensitivity (CI 95%)	Specificity (CI 95%)	Authors
PGI/PGII Ratio	APAG	Asymptomatic (147)	55% (38-71)	68% (59-76)	Ricci et al.
G-17	APAG	Asymptomatic (147)	48% (32-65)	73% (64-80)	Ricci et al.
GastroPanel (postprandial G-17	ACG	Dyspeptic (404)	83% (74-92)	95% (92-97)	Vaananen et al.
GastroPanel (fasting G-17)	ACG	Dyspeptic (287)	64% (59-70)	93% (89-96)	Germanà et al.
GastroPanel (fasting G-17)	ACG	Dyspeptic (94)	57% (not reported)	95% (not reported)	Nardone et al.
GastroPanel (fasting G-17)	ACG	Asymptomatic (180)	0%	100%	Graham et al.

Figure 3. Sensitivity and Specificity values for serological tests form different works

potentially at risk of gastric cancer. An important Japanese prospective cohort study evaluated the incidence of gastric cancer, performing an EGD annually to 6983 participants of a health program. Gastric cancer development was significantly associated with low PGI levels, with Hazard Ratio's of 8 or 6 according to negative or positive IgG-H.p. antibodies, respectively (35). An important metanalysis (37), with the goal of assessing the availability of serum gastric markers in the follow-up of high-risk patients for gastric cancer (p.e. patients with precancerous lesions such as gastric dysplasia or atrophic gastritis), found that, as for the diagnosis of dysplasia, studies considering pepsinogen I <50 mg/L and pepsinogen I/II ratio <3 obtained sensitivity 65% and specificity ranging from 74%-85%, both with Negative Predictive Value >95%. Authors assumed that, from these data, further studies of this test in the management of high-risk patients seem to be worthwhile. Throughout the years, several studies confirmed the linkage between low serum PGI and higher risk of cancer especially together with the presence of H.p. infection (36, 38, 40, 41). In a Japanese cohort prospective study, serum Pepsinogens levels were assessed in a pool of 101,892 asymptomatic patients. Those with a positive PG test and those with a negative PG test took EGD every 2 and 5 years, respectively. Early-stage gastric cancers and intestinal-type intramucosal cancers accounted for 80% and 39% of all the detected cancers, respectively. Therefore, the authors were able to conclude that Serum PG measurement for mass screening of gastric cancer achieve high recruitment for EGD in intended individuals, a favourable detection rate of gastric cancer and an extremely high proportion of early-stage gastric cancer in all the detected cancers (39). A positive family history (having a first-degree relative with gastric cancer) is a risk factor for gastric cancer (42). The magnitude of the relative risk differs by country and study, ranging from 2 to 10 (43). Positive family history could be a risk factor as a result of shared environment, for example, passing of H. pylori from parents to children, or because of shared genetic factors (44). Considering

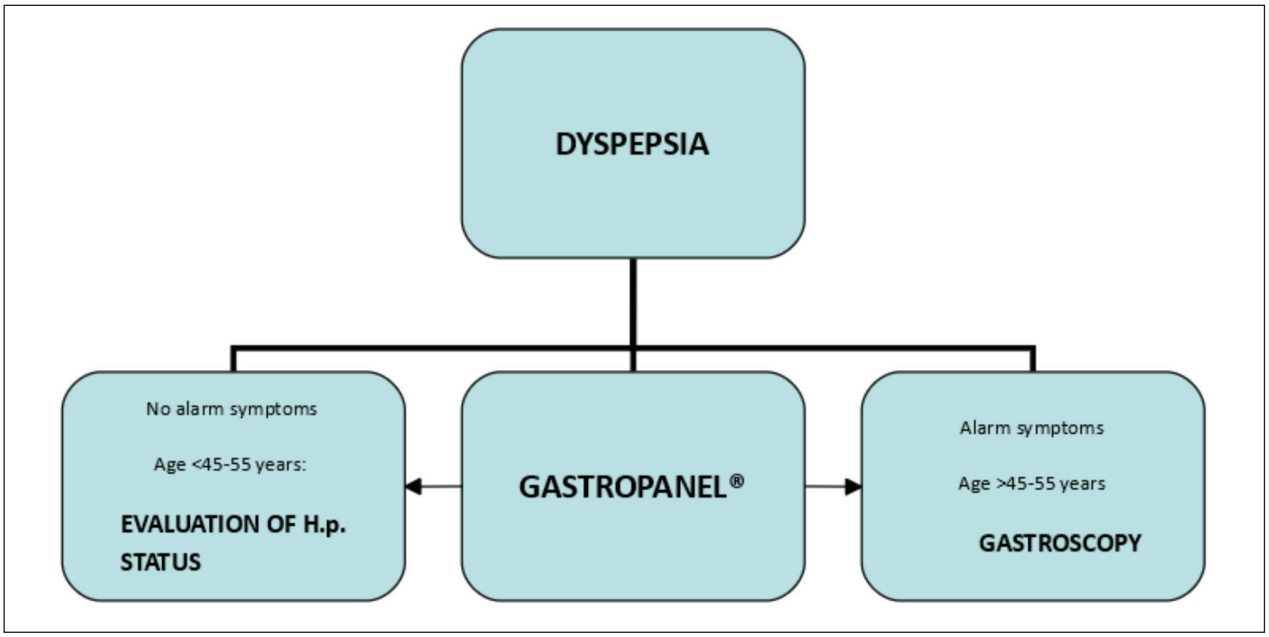

Figure 4. Management algorithm for dyspepsia

these assumptions, an Italian case control study evaluating dyspeptic patients with or without first degree relatives affected by gastric cancer, found interestingly that patients with a positive family history had lower PGI levels and a higher rate of pre-malignant histological alterations than ones with a negative family history (45).

Conclusions

In the last 15 years, plenty of studies on serum gastric markers as a non-invasive approach to the diagnosis of upper-GI diseases have showed that a more profound knowledge of the functionality and morph structural characteristics of the stomach are important in order to discriminate patients that actually need a more invasive diagnostic approach from those who don't. In fact, the implementation of non-invasive test like GastroPanel® in the diagnostic algorithm of upper-GI diseases could save, for example lots of EGD with a relevant improvement in costs and patient's quality of life. From the literature, GastroPanel®, thanks to the high specificity and negative predictive value, seems to be useful in a wide range of upper-GI conditions such as the diagnosis of NCAG, the follow-up of CAG, the evaluation of antrum atrophy, which is a risk stage for gastric cancer and peptic ulcer, in the stratification of patients with GERD and in the management of gastric cancer, with a special focus on familiarity as one of the main risk factors. Above all, the introduction of serum gastric markers evaluation seems to be central in the management algorithm of dyspeptic patients, as shown in figure 4.

References

1. Almario, Christopher V., et al. Burden of Gastrointestinal Symptoms in the United States: Results of a Nationally Representative Survey of Over 71,000 Americans. The American journal of gastroenterology (2018): 1.
2. Peery, Anne F., et al. Burden and Cost of Gastrointestinal, Liver, and Pancreatic Diseases in the United States: Update 2018. Gastroenterology (2018).
3. Everhart, James E., and Constance E. Ruhl. Burden of digestive diseases in the United States part I: overall and upper gastrointestinal diseases. Gastroenterology 136.2 (2009): 376-386.
4. National Cancer Institute SEER cancer statistics review 1975-200
5. Hassan, Cesare, et al. Appropriateness of upper-GI endoscopy: an Italian survey on behalf of the Italian Society of Di-

gestive Endoscopy. Gastrointestinal endoscopy 65.6 (2007): 767-774.
6. Tack, Jan, and Nicholas J. Talley. Functional dyspepsia—symptoms, definitions and validity of the Rome III criteria. Nature reviews Gastroenterology & hepatology 10.3 (2013): 134.
7a. Malfertheiner, Peter, et al. Current concepts in the management of Helicobacter pylori infection: the Maastricht III Consensus Report. *Gut* 56.6 (2007): 772-781.
7b. Malfertheiner, P., et al. Management of Helicobacter pylori infection—the Maastricht V/Florence consensus report. Gut66.1 (2017): 6-30.
8. Tack, Jan, et al. Functional gastroduodenal disorders. Gastroenterology 130.5 (2006): 1466-1479.
9. Shan, Jin-Hua, et al. Changes with aging in gastric biomarkers levels and in biochemical factors associated with Helicobacter pylori infection in asymptomatic Chinese population. World journal of gastroenterology 23.32 (2017): 5945.
10. Di Mario, Francesco, et al. Usefulness of serum pepsinogens in Helicobacter pylori chronic gastritis: relationship with inflammation, activity, and density of the bacterium. Digestive diseases and sciences 51.10 (2006): 1791-1795.
11. Wagner S, Haruma K, Gladziwa U, Soudah B, Gebel M, Bleck J, Schmidt H, Manns M (1994) Helicobacter pylori infection and serum pepsinogen A, pepsinogen A, and gastrin in gastritis and peptic ulcer: significance of inflammation and effect of bacterial eradication. Am J Gastroenterol 89:211-218
12. Plebani M, Basso D, Cassaro M, Brigato L, Scrigner M, Toma A, Di Mario F, Rugge M (1996) Helicobacter pylori serology in patients with chronic gastritis. Am J Gastroenterol 91:954-958
13. Nugalieva, Zhannat Z., Antone R. Opekun, and David Y. Graham. Problem of distinguishing false-positive tests from acute or transient Helicobacter pylori infections. Helicobacter11.2 (2006): 69-74.
14. El-Serag, Hashem B., et al. Update on the epidemiology of gastro-oesophageal reflux disease: a systematic review. Gut63.6 (2014): 871-880.
15. Sipponen, Pentti, et al. Low circulating levels of gastrin-17 in patients with Barrett›s esophagus. World Journal of Gastroenterology: WJG 11.38 (2005): 5988.
16. Monkemuller, K., et al. Serum gastrin and pepsinogens do not correlate with the different grades of severity of gastro-oesophageal reflux disease: a matched case-control study. Alimentary pharmacology & therapeutics 28.4 (2008): 491-496.
17. Landi, S., et al. P. 01.13: Gastrin-17 as a Non-Invasive Marker for Gerd: A Prospective Study on Sample of 777 Consecutive Patients. Digestive and Liver Disease 49 (2017): e137.
18. De Bortoli, N., et al. P. 06.20 Gerd diagnosis in 340 patients with atypical or extra-esophageal symptoms by using a non-invasive surrogate test. Digestive and Liver Disease 50.2 (2018): e187.
19. Goni, Elisabetta, et al. Mo1135 Gastrin 17 As Non-Invasive Marker of Reflux Disease. Gastroenterology 148.4 (2015): S-616.
20. Savarino, Edoardo V., et al. Gastrin 17 in Singling Out Patients with Different Patterns of Refluxate: A Pilot Study Using Impedance-pH as Reference Standard. Gastroenterology 152.5 (2017): S653.
21. Morana, E., et al. PA. 6 Gastrin-17 (G-17): a serological bio-marker for diagnosis of gastro-esophageal reflux disease (GERD). Digestive and Liver Disease 40 (2008): S77-S78.
22. Sipponen, P., et al. Atrophic gastritis serum levels of amidated gastrin-17 and pepsinogen i in atrophic gastritis: an observational case-control study. Scandinavian journal of gastroenterology 37.7 (2002): 785-791.
23. Väänänen, H., 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 multicentre study. European journal of gastroenterology & hepatology 15.8 (2003): 885-891.
24. Germaná, B., et al. 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 37.7 (2005): 501-508.
25. Leja, M., et al. Value of gastrin-17 in detecting antral atrophy. Advances in medical sciences 56.2 (2011): 145-150.
26. Agréus, Lars, et al. Rationale in diagnosis and screening of atrophic gastritis with stomach-specific plasma biomarkers. Scandinavian journal of gastroenterology 47.2 (2012): 136-147.
27. Leja, Marcis, et al. The validity of a biomarker method for indirect detection of gastric mucosal atrophy versus standard histopathology. Digestive diseases and sciences 54.11 (2009): 2377-2384.
28. Zagari, R. M., et al. Systematic review with meta-analysis: diagnostic performance of the combination of pepsinogen, gastrin-17 and anti-Helicobacter pylori antibodies serum assays for the diagnosis of atrophic gastritis. Alimentary pharmacology & therapeutics 46.7 (2017): 657-667.
29. Ricci, Chiara, et al. Serological markers for gastric atrophy in asymptomatic patients infected with Helicobacter pylori. The American journal of gastroenterology 99.10 (2004): 1910.
30. Nardone, G., et al. Diagnostic accuracy of the serum profile of gastric mucosa in relation to histological and morphometric diagnosis of atrophy. Alimentary pharmacology & therapeutics22.11-12 (2005): 1139-1146.
31. Graham, David Y., et al. Noninvasive versus histologic detection of gastric atrophy in a Hispanic population in North America. Clinical Gastroenterology and Hepatology 4.3 (2006): 306-314.
32. Lauren, Pekka. The two histological main types of gastric carcinoma: diffuse and so-called intestinal-type carcinoma: an attempt at a histo-clinical classification. Acta Pathologica Microbiologica Scandinavica 64.1 (1965): 31-49.
33. Correa, Pelayo. Human gastric carcinogenesis: a multistep and multifactorial process—first American Cancer Society award lecture on cancer epidemiology and prevention. Cancer research 52.24 (1992): 6735-6740.

34. Fox, James G., and Timothy C. Wang. Inflammation, atrophy, and gastric cancer. The Journal of clinical investigation 117.1 (2007): 60-69.
35. Watabe, H., et al. Predicting the development of gastric cancer from combining Helicobacter pylori antibodies and serum pepsinogen status: a prospective endoscopic cohort study. Gut54.6 (2005): 764-768.
36. Miki, Kazumasa. Gastric cancer screening using the serum pepsinogen test method. Gastric cancer 9.4 (2006): 245-253.
37. Dinis-Ribeiro, M., et al. Meta-analysis on the validity of pepsinogen test for gastric carcinoma, dysplasia or chronic atrophic gastritis screening. Journal of Medical Screening 11.3 (2004): 141-147.
38. Karimi, Parisa, et al. Gastric cancer: descriptive epidemiology, risk factors, screening, and prevention. Cancer Epidemiology and Prevention Biomarkers 23.5 (2014): 700-713.
39. Miki, Kazumasa, et al. Long-term results of gastric cancer screening using the serum pepsinogen test method among an asymptomatic middle-aged Japanese population. Digestive Endoscopy 21.2 (2009): 78-81.
40. Abnet, C. C., et al. Plasma pepsinogens, antibodies against Helicobacter pylori, and risk of gastric cancer in the Shanghai Women's Health Study Cohort. British journal of cancer 104.9 (2011): 1511.
41. Ren, Jian-Song, et al. Serum pepsinogens and risk of gastric and esophageal cancers in the General Population Nutrition Intervention Trial cohort. Gut (2009).
42. Bernini M, Barbi S, Roviello F, Scarpa A, Moore P, Pedrazzani C, et al. Family history of gastric cancer: a correlation between epidemiologic findings and clinical data. Gastric Cancer 2006;9:9-13.
43. La Vecchia C, Negri E, Gentile A, Franceschi S. Family history and the risk of stomach and colorectal cancer. Cancer 2006;70:50-5
44. Yaghoobi M, Bijarchi R, Narod S. Family history and the risk of gastric cancer. Br J Cancer 2009;102:237-42.
45. Di Mario, F., et al. 'Serological biopsy in first-degree relatives of patients with gastric cancer affected by Helicobacter pylori infection. Scandinavian journal of gastroenterology 38.12 (2003): 1223-1227.

Correspondence:
Barchi Alberto
Department of Medicine and Surgery,
University of Parma, Parma, Italy;
Tel. +393348630784
E-mail: alberto.barchi@studenti.unipr.it