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Review Article

Diagnosis of the Patients with Upper Abdominal Symptoms (Dyspepsia) Using Non-Invasive Serological Tests

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Abstract

Dyspepsia belongs among the most frequent clinical symptoms complained by the patients within the primary health care. On the basis of the non-specific symptoms alone, functional dyspepsia cannot be distinguished from a number of clinically important diseases of extra-gastric origin: celiac disease (CD), lactose intolerance (LI), inflammatory bowel disease (IBD), irritable bowel syndrome (IBS), and colorectal neoplasia (CRC) suggested by fecal occult blood (FOB). Far too often in the current clinical practice, the patients are offered invasive endoscopy as the first-line diagnostic test.

This diversity of clinical conditions behind the symptoms that are non-specific enough to preclude the correct diagnosis on clinical grounds alone, emphasizes the need for a coherent diagnostic algorithm. Such a diagnostic algorithm is proposed in the present communication, based on a rational and targeted use of a series of well characterized non-invasive (blood) tests targeting the specific gastrointestinal disorders.

Replacing gastroscopy by a serum biomarker panel (GastroPanel® test) as the first-line diagnostic tests, it is possible to stratify the patients into three categories at different risk for gastric cancer (GC), in addition to reaching the specific diagnosis of gastric functional disorders. Low Risk: Because of the very high negative predictive value (NPV) of GastroPanel® test, the patients with normal biomarker profile can be examined for disorders outside the stomach. The intermediate risk category includes the subjects testing Helicobacter pylori (HP)-positive with no indication of atrophic gastritis (AG). For those patients, the algorithm consists of HP-eradication and its control using optional diagnostic tests. If the symptoms continue after HP-eradication, a feasible option is to make gastroscopy that enables i) direct visualization of HP or ii) testing the biopsy with HP Quick tests.

The patients at high risk for subsequent GC include all those with GastroPanel® test implicating AG. In this high-risk category, one cannot avoid performing gastroscopy to confirm the AG diagnosis, its severity and topography in the stomach, i.e. antrum, corpus or both. Additional information can be obtained by complementing the targeted biopsies with the laboratory tests for CD, LI and vitamin-B12 deficiency, not infrequently associated with AG, particularly of the autoimmune origin.

Taken together, replacing gastroscopy by GastroPanel® as the first-line diagnostic test in patients with dyspeptic complaints allows a rational diagnostic algorithm whereby carefully selected non-invasive tests are applied to screen for specific clinical conditions all sharing in common the non-specific clinical symptoms. Substantial savings in health care costs can be achieved while avoiding up to 80% of unnecessary gastroscopies by screening the dyspeptic patients at first by GastroPanel® test.

Keywords: *Dyspepsia; Symptoms; Non-Specific; Diagnostic Algorithm; Non-Invasive Testing; GastroPanel®; Atrophic Gastritis; Gastric Cancer; Risk Stratification; Cost Savings*

Introduction

Dyspeptic symptoms are among the most common abdominal complaints [1], experienced by 25-40% of the people during their lifetime [1,2]. Within the primary health care, most of these patients are primarily treated (e.g. with proton pump inhibitors, PPI) without confirmation of the proper diagnosis at first [3-5]. Majority of these complaints are due to functional dyspepsia or gastro-esophageal reflux disease (GERD), while a small minority are classified organic in origin [4,6]. Of the latter, the two most important clinical conditions are Helicobacter pylori (HP) infection and atrophic gastritis (AG), two conditions that are closely interrelated [7,8].

HP is the causal agent for clinically important diseases in gastric and duodenal mucosa [7,9-11], and, in 1994, IARC classified HP-infection as group I human carcinogen [12]. This bacterial infection initially affects only the antral mucosa causing superficial gastritis. If not eradicated, HP-infection progresses to chronic corpus-predominant gastritis or pangastritis, with mucosal atrophy as the end result [13,14].

The exact mechanism by which HP-infection causes gastric cancer (GC) remains to be elucidated, but there is little doubt that HP-associated AG is the single most important risk factor for distal (non-cardia) GC [8,14-18]. It is estimated that 50% of all GC cases develop through the "Correa cascade" [16,19-21], leading from HP-associated gastritis to mucosal atrophy, intestinal metaplasia (IM), dysplasia (intraepithelial neoplasia; IN), and invasive adenocarcinoma. There are some implications that early eradication of HP-infection can slow down or even revert this cascade [7,13]. Because this process takes several decades, there should be good prospects for early detection of gastric cancer precursor lesions [22], but the problem is the lack of a suitable test for GC screening [23]. Furthermore, most of the patients report only a short period of symptoms before the diagnosis of GC, and up to 40% report no dyspeptic symptoms at all [24,25].

In addition to the conditions of gastric origin, also other well defined clinical diseases cause non-specific (multiple type) clinical symptoms sharing many features in common with dyspepsia. Such conditions include e.g. celiac disease (CD) [26-28], lactose intolerance (LI) [29-32], inflammatory bowel disease (IBD) [33-36], irritable bowel syndrome (IBS) [33-36] and (particularly among elderly people) neoplastic lesions of the colon [37]. The clinical symptoms in all these conditions are non-specific enough to preclude the correct diagnosis on clinical basis alone [26-37].

Conventional clinical diagnosis of dyspepsia and related symptoms

Several diagnostic tests are available for dyspeptic symptoms, including endoscopy, radiography and testing for HP-infection [25]. In patients with the symptoms suspected to be of stomach origin, endoscopy with targeted biopsies remains the gold standard diagnostic tool, disclosing HP-infection, AG, IN as well as their topography [8,14]. However, this invasive method is uncomfortable, distressing and quite costly, which precludes its use as the diagnostic tool in population-based screening. This emphasizes the need for rapid, accurate and inexpensive non-invasive tests for screening and monitoring of the patients with dyspeptic symptoms [23-25]. As to the diagnosis of CD, its confirmation requires a complex set of approaches [26-28]. Confirmation of LI necessitates duodenal biopsies and their analysis by laboratory tests [29-32]. As to IBD and IBS, colonoscopy is the gold standard diagnostic test [33-36]. The same applies to colorectal neoplasia, usually suggested first by the detection of fecal occult blood (FOB) [37].

Proposed diagnostic algorithm based on non-invasive tests

In the public health sector, cost savings are the global issue, dictated by the restricted public health investments in most countries. Another "mega-trend" is a tendency to replace invasive diagnostic tests by non-invasive tests as far as possible. A clear advantage of many of these non-invasive diagnostic tools is their versatility and adaptability for immediate testing at the outpatient department or at doctor's office, i.e. point-of-care (POC) testing.

During the past years, a huge number of POC tests have been developed for a wide variety of diagnostic purposes, mostly utilizing the principle of lateral flow, invented by the founder of Biohit Oyj (Helsinki, Finland) [38]. Starting from the late 1980's the company has

developed a series of innovative diagnostic tests, including those based on ELISA technology and those utilizing the lateral flow principle [39]. The whole diagnostic portfolio of the company shares one feature in common: all Biohit tests are targeted to diagnosing the diseases affecting the gastrointestinal tract. The current repertoire of Biohit diagnostic tests include the following patent-protected tests. ELISA-based tests: 1) GastroPanel®; 2) Active Vitamin-B12®; 3) Biohit Calprotectin®, and 4) Biohit Total 25OH D-vitamin®. The Quick Test family includes: 1) Lactose Intolerance Quick Test®; 2) Helicobacter Pylori UFT300 Quick Test®; 3) Helicobacter Pylori Quick Test®; 4) ColonView Quick Test®; 5) Celiac Disease Quick Test® [39].

The use of these tests for specific diagnosis of the respective diseases has been described in several recent reports also in this journal [37,40-50]. However, there is no systematic review concerning the algorithm how these different diagnostic tests could be optimally used in the non-invasive diagnosis of patients who complain non-specific abdominal symptoms clearly falling within the ambiguous category of dyspepsia. In the present communication, we propose a rational and targeted use of our non-invasive tests in the diagnostic algorithm for sorting out the different disease categories among the patients who search medical attention due to non-specific dyspeptic symptoms [1-4].

The diagnostic algorithm for dyspeptic complaints

The proposed algorithm for the rational application of the diagnostic tests in the management protocol of dyspeptic patients is illustrated in figure 1. Although not extremely complex, this diagram is explained for simplicity in the following. The leading principle of this proposal is based on the fact that invasive gastroscopy [8,14,23-25] is replaced by Biohit GastroPanel® test as the first-line diagnostic tool [40-49]. The rational for this has been explained in a number of recent reviews [40,43,44,46], and will be shortly discussed later.

GastroPanel® test is a biomarker panel of four stomach-specific biomarkers (PGI, PGII, G-17, HPAb), as detailed elsewhere [51-53]. The results are interpreted by a special software (GastroSoft®) that distinguishes eight distinct marker profiles [42,43,46,51-53]. These refined diagnostic categories can be stratified to three groups with different risk and different management indications: 1) normal marker profile; 2) HP-infection (with no atrophy), and 3) Atrophic gastritis (AG) in the antrum, corpus, or pangastritis: AGA, AGC, AGpan, respectively. In the proposed algorithm, the subsequent diagnostic conduct should be clearly different in these three risk groups (Figure 1).

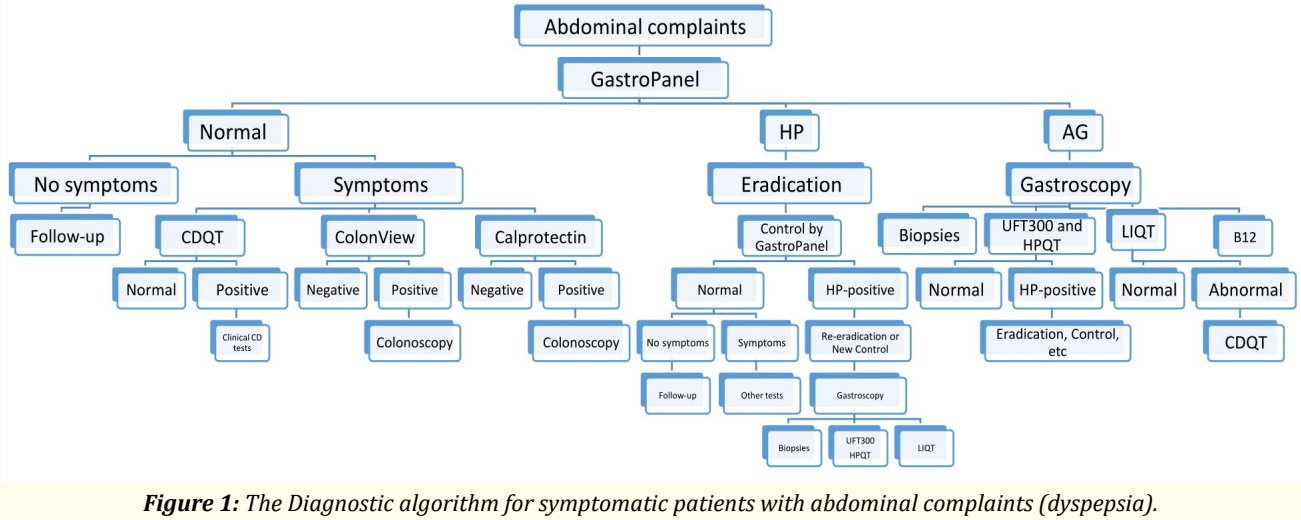

Figure 1: *The Diagnostic algorithm for symptomatic patients with abdominal complaints (dyspepsia).*

HP: Helicobacter pylori; AG: Atrophic Gastritis; CDQT: Celiac Disease Quick Test®; Calprotectin: Biohit Calprotectin®; UFT300: Helicobacter Pylori UFT300 Quick Test®; HPQT: Helicobacter Pylori Quick Test®; LIQT: Lactose Intolerance Quick Test®; B12: Active Vitamin-B12®

Normal biomarker profile

Starting from the group where GastroPanel® test results in a normal marker profile, the continuation should depend on the symptoms. In the most favorable scenario, with a normal marker profile and the patient no longer reporting clinical symptoms, the likelihood is very low for a significant gastric pathology even in a long term, as shown by the longitudinal cohort studies [47]. Thus, these subjects can be safely returned to a regular path, with no need to additional examinations.

For symptomatic patients, however, the conduct should be different. With a normal GastroPanel® marker profile, it is highly unlikely that a significant gastric pathology will be find on gastroscopy either [42,43,46-48,51-53]. Because of this, the next diagnostic step should not be gastroscopy, but instead, the origin of the symptoms should be searched for from other sources. With the Biohit tests [39], the logical next step is to institute i) CDQT (Celiac Disease Quick test®) to exclude CD [26-28,50], ii) ColonView® Quick Test to exclude FOB [37], and iii) Biohit Calprotectin® to exclude and/or to make the differential diagnosis between IBD and IBS [33-36]. The latter two tests are made from a fecal sample and thus can be performed from the same samples. While delivering the fecal samples to the laboratory, the patient can be tested with CDQT on that occasion. With these three tests, it should be straightforward to find CD [50] and to make the distinction between IBD and IBS [33-36], whereas the confirmation of a positive ColonView test necessitates the use of colonoscopy. Colonoscopy is indicated also to control the IBD/IBS and the severity of the former (i.e. colitis ulcerosa or Crohn's disease). As to the confirmation of CD suggested by the CDQT, clinical diagnostic measures should be applied, as discussed in detail elsewhere [26-28,50]. Self-explanatory, colonoscopy is not indicated if ColonView and Calprotectin results are negative, and similarly, a negative CDQT excludes CD with high degree of accuracy [50].

Helicobacter pylori infection with no mucosal atrophy

As discussed in a series of reviews [44,52,53], GastroPanel® is the most comprehensive test for diagnosis of HP-infection, devoid of the caveats (false positive- and false negative results) inherent to the commonly used HP tests (i.e. 13C-UBT and stool antigen test). In this diagnostic algorithm (Figure 1), GastroPanel® detection of HP-infection (with no AG) should prompt the eradication therapy, as instructed by the international consensus reports [7,54]. In the state-of-art practice, the success of this eradication therapy should always be controlled. For this control, there are several options also among the Biohit tests: GastroPanel®, HP Quick Test® and the HP UFT300 Quick Test® [39]. The latter two necessitate the use of gastroscopic biopsy, however, and as such do not represent purely non-invasive tests like GastroPanel®.

The downside of GastroPanel® test in the control of HP eradication is inherent to the method itself (serological HPAb test). HP antibodies decay relatively slowly, and even after a successful eradication, the HPAb seroconversion usually takes place only after several months. This makes GastroPanel® not an ideal test for immediate control of HP eradication [44,52,53]. The HP Quick Tests are devoid of this restriction. However, a seroconversion observed in GastroPanel® test can be considered as a sign of successful HP-eradication. Because of a major individual variation in the times of seroconversion, this can happen sometimes three months after eradication. If accompanied by disappearance of the symptoms as well, this can be considered as an indication of successful eradication. If, however, the symptoms continue even if the post-treatment GastroPanel® test is negative, this should be an indication for searching the origin of the symptoms from outside the stomach [4,52,53] (Figure 1).

In the case that the post-treatment GastroPanel® test is positive for HP, one has different options. In considering those, the timing of the sample is important. If the time interval to completion of the eradication is long enough, e.g. 6 months, one can consider that a positive GastroPanel® test suggests a true HP-infection and a failed HP-eradication. In that case, the logical next step is to repeat the eradication using another treatment combination. If this is done, also the control of the eradication should be arranged, using any of the available methods. Another option is to refer such patients to gastroscopy, in particular if they have symptoms. This enables direct visualization of HP in the biopsies, and testing of the biopsy using either of the HP quick tests (Figure 1). Once biopsies are being taken, one can also be analysed using LIQT to exclude the presence of LI.

Atrophic gastritis

When GastroPanel® biomarker profile indicates atrophic gastritis (AG) either in the antrum (AGA). in the corpus (AGC) or in both (AGpan) [40-49], the conduct should be straightforward. Gastroscopy with directed biopsies is mandatory to establish the severity of AG as well as its topography (AGA, AGC, AGpan) and possible accompanying IM or IN in the gastric mucosa. The authors are practically unanimous in that the gastroscopy and directed biopsies are the gold standard diagnosis for AG, because of the associated high risk for subsequent GC [7-21]. When the updated Sydney System (USS) for classification of gastritis is used, the sites of the biopsies are standardized [55,56]. The same is true with the OLGA and OLGIM classifications introduced by Rugge., *et al* [57,58].

Together with the biopsies used for morphological classification of AG [55-58], one additional biopsy can be easily taken to be analyzed for HP using the HP Quick Tests [39]. If confirmed by any of these means (biopsy or quick tests), HP infection must be treated and the treatment should be controlled using any of the available diagnostic techniques [7,51-54]. In the same procedure, one additional biopsy from the small intestine can be taken and analyzed using LIQT. A normal LIQT excludes also the possibility of CD, whereas an abnormal LIQT should be accompanied by CDQT, because the frequent co-existence of CD and LI [26,28,50].

Yet another line of diagnosis that should not be ignored in patients with biopsy-confirmed AGC is the measurement of vitamin-B12 [40,59-64]. In patients with severe AG, irrespective whether caused by HP-infection or autoimmune disease (AAG), absorption of vitamin-B12 is almost invariably impaired leading to pernicious anemia (PA) with a variety of clinically important sequels. Many of those, neurological complications in particular, can develop relatively rapidly and become irreversible if not diagnosed on time and adequately substituted [40,59-64].

Characteristics of the Non-Invasive GastroPanel® test

To replace the invasive gastroscopy as the first-line diagnostic test, an alternative diagnostic algorithm was proposed, based on the rational and targeted use of several non-invasive diagnostic tests developed by Biohit Oyj (Helsinki, Finland). The properties of all these tests are described on the company website [39], and also reported in several recent studies [32,37,40,41-48,51-53]. Of all these tests, the GastroPanel® represents a completely unique innovation of Biohit Oyj, with no equivalent competitor on the market. Because of this, the GastroPanel® test is shortly introduced in this context. For a more detailed account, the reader is being referred to a series of recent communications on the subject [41-48,51-53].

Test principles

GastroPanel® test has been on the market for several years by now, and during that time, it has been validated in clinical studies in Finland and elsewhere [47,65-67]. Due to the inherent characteristics of the natural history of AG/AAG, the PGI values (and PGI/PGII ratio) remain within normal range as long as AG of the corpus (AGC) is graded only mild. However, mild AG/AAG is a poorly reproducible diagnostic category even among experienced pathologists, and because of this, mild AG of the corpus should never be used as the study endpoint in calculating the performance indicators of the PGI, PGI/PGII, as repeatedly emphasized [47,48,65-67]. The correct way of calculating the predictive indicators of PGI and PGI/PGII ratio for AGC is to use the combined moderate/severe AG as the study endpoint [41,49].

To provide an unbiased estimate of the accumulated evidence, two recent meta-analysis have been performed with a systematic review of all studies published on GastroPanel® test since its introduction in the early 2000's [41,49]. Both meta-analyses gave practically similar results, despite some methodological differences. In both analyses, the pooled sensitivity of GastroPanel® in detection of AG exceeded 70% and the pooled specificity was close to 95% [41,49]. Both meta-analyses concluded that GastroPanel® test appears to be a reliable tool for the diagnosis of AG, and applicable for both screening of the subjects or populations at high-risk of GC [41,49].

Interpretation of the results

GastroPanel® is optimized for use in context with the USS classification of gastritis [55,56]. Both the USS and the GastroSoft® software use five diagnostic categories to classify the biopsies and the GastroPanel® results, respectively. These include: 1) normal mucosa, 2) superficial (HP) gastritis, 3) AGA, 4) AGC, and 5) AG in both antrum and corpus (AGpan) [55,56]. In addition to these five categories related to stomach morphology, three other marker profiles are produced by GastroSoft®, being specific for functional disturbances with normal morphology [43,44,46,51-53].

The interpretation of GastroPanel® test with GastroSoft® has been described in detail in a series of recent reports [41-45,47-49,51-53]. These reviews include detailed descriptions of the eight diagnostic marker profiles that are possible to obtain with GastroPanel® test. It is not feasible to re-iterate this discussion in the present communication, but suffice it to list these profiles: 1) normal profile; 2) high acid output; 3) low acid output due to proton pump inhibitor (PPI) medication; 4) superficial (non-atrophic), HP-associated gastritis, with 3 options (4.1. active HP-infection; 4.2. successful HP eradication; 4.3. failed HP eradication); 5) atrophic gastritis of the corpus (AGC); 6) atrophic gastritis of the antrum (AGA); 7) atrophic gastritis of the antrum and corpus (AGpan); and 8) panel profile in context of PPI medication. For details, the reader is being referred to the recent communications [41-45,47-49,51-53].

Long-term predictive value confirmed in longitudinal cohort studies

In addition to the great value of GastroPanel® in the diagnosis of dyspeptic symptoms as well as in screening of asymptomatic subjects for the risk conditions of GC, this test has been recently studied also in longitudinal settings to assess the value of its biomarkers as long-term predictors of GC [47,68].

The first of these studies assessed the predictive value of GastroPanel® biomarkers in a case-control setting nested within a cohort of Caucasian population in Western Siberia [47]. Both the cases and controls for this study were derived from a population-based cohort of 45-69-year-old subjects (n = 9.360) in the HAPIEE (Health, Alcohol and Psychosocial Factors In Eastern Europe) study, enrolled in Novosibirsk (Siberia) during 2003 - 2005. Cases represent all GCs reported to the Cancer Registry until 2012, being matched (1:2) with healthy controls (COs). Altogether, 156 (52 GCs and 104 COs) serum samples collected at study entry were available for GastroPanel® analysis. Conditional logistic regression models (uni- and multivariate) were used to analyse this matched case-control setting. The biomarker levels below cut-off at baseline predicted the development of GC as follows (OR; 95%CI): PGI (2.9; 95%CI: 1.3 - 6.4), PGII (9.0; 95%CI: 1.8 - 44.3), PGI/PGII (3.3; 95%CI: 1.5 - 7.3); G-17 (1.8; 95%CI: 0.7 - 4.8), and HP-Ab (0.4; 95%CI: 0.1 - 1.3). In a multivariate model adjusted for age, sex, and all four biomarkers, PGI/PGII ratio was the most powerful independent predictor of GC (OR = 2.9; 95% CI: 1.01 - 8.0). Indeed, this was the first time in a Caucasian population, where PGI, PGII and PGI/PGII ratio were shown to be reliable longitudinal predictors of incident GC [47].

The second longitudinal study was completed in Northern China [68]. The authors analyzed the role of GastroPanel® biomarkers in identifying high-risk individuals and predicting the risk of developing (GC). Among 12,112 participants with prospective follow-up from an ongoing population-based screening program using both serology and gastroscopy, the authors conducted a multi-phase study involving a cross-sectional analysis, a follow-up analysis, and an integrative risk prediction modeling analysis [68]. In the follow-up analysis, low PGI levels and PGI/II ratios were associated with higher risk of developing GC, and both low (< 0.5 pmol/l) and high (> 4.7 pmol/l) G-17 levels were associated with higher risk of developing GC. In their risk prediction modeling, the five biomarkers combined yielded a C statistic of 0.803 (95%CI = 0.789 - 0.816) and improved prediction beyond traditional risk factors (P < 0.001) for identifying precancerous lesions at enrollment. Similarly, higher serological biopsy scores based on the five biomarkers at enrollment were associated with higher risk of developing GC during follow-up (p for trend < 0.001). Accordingly, GastroPanel® test could be used to identify the high-risk individuals for further diagnostic gastroscopy, and to stratify the individuals' risk of GC, thus guiding a targeted screening and tailored prevention [68].

Together with the published meta-analyses [41,49], these two studies [47,68] implicate that due to its high specificity for both AGA and AGC as well as its extremely high longitudinal predictive value, GastroPanel® is truly a test for stomach health and disease. In other words, testing GastroPanel-negative at any time point during one's life-time precludes (with > 95% probability) a significant gastric pathology for several years ahead. At the meantime, however, a GastroPanel® marker profile implicating AGC is a powerful independent predictor of an incident GC in a long-term longitudinal setting [47,68].

Conclusions

Dyspepsia belongs among the most frequent clinical symptoms complained by the patients within the primary health care. Far too often, the patients are offered an invasive endoscopy as the first-line diagnostic test [8,14,25]. Gastroscopy as an invasive technique is felt uncomfortable and distressing by most patients. It is also quite costly precluding its adoption for population-based screening. On the basis of symptoms alone, functional dyspepsia cannot be distinguished from a number of clinically important diseases that necessitate specific diagnostics tests, including 1) CD that requires a complex set of clinical approaches [26-28], 2) LI necessitating duodenal biopsies analyzed by laboratory tests [29-32], 3) IBD and IBS for which colonoscopy is the gold standard diagnostic test [33-36], and finally 4) colorectal neoplasia usually suggested first by the detection of FOB [37].

This diversity of clinical conditions behind the symptoms that are non-specific enough to preclude the correct diagnosis on clinical grounds alone, emphasizes the need for a cogent diagnostic algorithm [23-25]. Such a diagnostic algorithm is proposed in the present communication, based on a rational and targeted use of a series of well characterized non-invasive (blood) tests targeting the specific gastrointestinal disorders (Figure 1).

Using a serum biomarker panel (GastroPanel® test) as the first-line diagnostic tests, it is possible to stratify the patients into three categories at different risk for GC, in addition to reaching the specific diagnosis of gastric functional disorders [41-45,47-49,51-53]. Because of the very high negative predictive value (NPV) of the GastroPanel® test [47,68], it is possible to subject the patients with normal biomarker profile to diagnostic procedures searching the origin of the symptoms outside the stomach. Such conditions include CD, FOB, and IBD/IBS, readily diagnosed by CDQT, ColonView Quick Test and Calprotectin, respectively. Only for test-positive patients, other clinical tests (for CD) and colonoscopy are indicated.

The intermediate risk category between the normal biomarker profile and AG includes the subjects testing HP-positive but with no indication of AG in GastroPanel® (Figure 1). For those patients, gastroscopy is not generally indicated, but the algorithm consists of HP-eradication and its control by optional tests [7,54]. The limitation of GastroPanel® in the control of HP-eradication is based on the fact that HPAb seroconversion is a slow process, and one should wait at least for 6 months before making the re-testing. If the symptoms continue after HP-eradication, a feasible option is to make gastroscopy that enables i) direct visualization of HP or ii) testing the biopsy with HP Quick tests.

The patients at high risk for subsequent GC include all those with GastroPanel® test implicating AG [40-49,51-53,68]. In this high-risk category, one cannot avoid performing gastroscopy to confirm the AG diagnosis, its severity and topography [55-58]. Additional information can be obtained by complementing the targeted biopsies with the laboratory tests e.g. for HP infection (HP Quick Tests), LI, CD and vitamin-B12 assay (Figure 1). This allows confirmation/exclusion of celiac disease, lactose intolerance, and vitamin-B12 deficiency, not infrequently associated with AG, particularly of the autoimmune type [26-36].

Taken together, replacing gastroscopy by GastroPanel® as the first-line diagnostic test in patients with dyspeptic complaints allows a rational diagnostic algorithm whereby carefully selected non-invasive tests are applied to screen for specific clinical conditions that share in common the non-specific clinical symptoms. Using this approach, one can preserve invasive endoscopies (gastroscopy, colonoscopy) only for those patients testing positive with the respective laboratory tests. This leads to substantial savings in health care costs as com-

pared with the usual practice of using endoscopy as the first-line diagnostic tool [69]. It has been estimated that up to 80% of unnecessary gastroscopies could be avoided by screening the dyspeptic patients by GastroPanel® test [40-44,46,48,51-53].

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