

Mistakes in clinical investigation of gastrointestinal motility and function and how to avoid them

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Symptoms related to abnormal gastrointestinal motility and function can occur from the moment food is swallowed to the time stool is passed into the toilet. A recent UEG survey indicated that dysphagia, heartburn, bloating, abdominal pain and changes to bowel habit are each reported by 5–15% of the general population.¹ These symptoms are frequent reasons for seeking medical attention from general physicians and for referral to specialist gastroenterologists. Most patients with these symptoms do not have neoplasia, infection or inflammation on initial investigation, but rather so-called functional gastrointestinal symptoms.^{2,3}

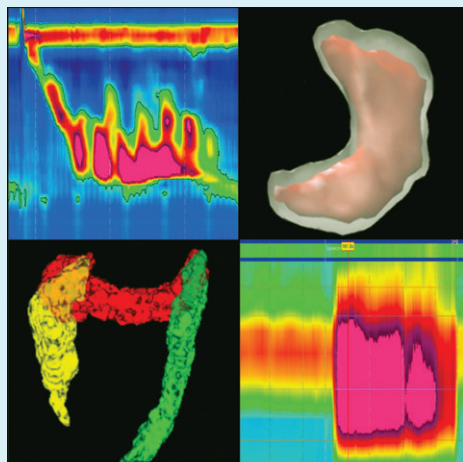


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For patients with mild symptoms, negative tests provide reassurance and simple, symptomatic management might be all that is required (e.g. acid suppression, stool regulation). However, for those with severe symptoms that persist on therapy, ruling out life-threatening disease is not sufficient, and referral to the neurogastroenterology and motility (NGM) laboratory for physiological measurements is often indicated.

Clinical investigations aim to explain the cause of symptoms and establish a diagnosis that can guide rational treatment. Until recently, it could be argued that manometry, scintigraphy, breath tests and related tests rarely provided this information. As a result, only patients with suspected major motility disorders (e.g. achalasia, severe reflux disease or faecal incontinence) were routinely referred to the NGM laboratory for tests. Technological advances, such as high-resolution manometry (HRM), now provide objective measurements not only of motility, but also of function in terms of the movement (and digestion) of ingested material within the gastrointestinal tract. Furthermore, the ability to associate events (such as bolus retention, reflux or gas production) with symptoms provides an indication of visceral sensitivity and can identify what is causing patient complaints.

Here, I discuss frequent mistakes in clinical investigation of gastrointestinal motility and function based on a series of consensus documents published by members of the International Working Group for Disorders of Gastrointestinal Motility and Function.

Mistake 1 Failing to perform endoscopy and/or imaging in the presence of alarm features

The initial assessment of patients with gastrointestinal symptoms must identify 'alarm features' that could indicate the presence of neoplasia, ulceration or inflammation in the digestive tract and require urgent endoscopy and/or imaging (see list in figure 1). In practice, identification is based on clinical history and the results of laboratory investigations, including a full blood count, clinical chemistry for renal and liver function, calcium, thyroid

function and coeliac serology. Serological tests or a urea breath test should be considered if *Helicobacter pylori* infection is suspected. Additionally, stool calprotectin levels are used to screen for inflammatory bowel disease (IBD) and are also raised in many cases of advanced neoplasia.

Prospective trials and meta-analyses indicate that the presence of alarm symptoms is associated with a 5–10% risk of serious disease, compared with a 1–2% risk in patients without alarm symptoms.^{3,4} Early endoscopy is indicated to exclude 'organic' pathology in this

group and also in patients who have raised stool calprotectin levels. Endoscopy should also be performed in patients who have an existing functional gastrointestinal disease (FGID) diagnosis if alarm features develop, in patients who have severe symptoms that fail to respond to therapy and if there is a persistent change in symptoms during follow up. If endoscopy is performed, biopsy samples should be acquired to test for infection (e.g. *H. pylori*) or inflammation (e.g. coeliac disease, microscopic colitis). This is appropriate even if appearances are normal.

Abdominal ultrasound to exclude gallbladder stones and other abdominal pathology is part of the routine evaluation in many European countries; however, CT should not be performed routinely, especially in young females, to avoid unnecessary exposure to radiation. In patients with negative test results who have ongoing symptoms, it is not appropriate to repeat endoscopic or other investigations without a clear indication because the costs are significant and the

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- Dysphagia
- Recurrent vomiting
- Weight loss
- An abdominal mass or lymphadenopathy
- Evidence of gastrointestinal blood loss
- Iron deficiency anaemia
- Recent onset of abdominal symptoms or a change in bowel habit in patients over 45 years old

Figure 1 | Alarm features in patients with gastrointestinal symptoms.

reassurance provided is minimal, as is the impact they have on treatment.⁵

Mistake 2 Over-investigating patients with functional gastrointestinal symptoms

Symptoms of heartburn, abdominal pain, bloating and changes in bowel habit are not alarm symptoms and it is a mistake to perform endoscopy and/or imaging in all comers, especially younger patients. To avoid over-investigation, an effort should be made to differentiate patients with organic and functional disease. One pointer is that patients who have a defined, organic aetiology tend to have discrete symptoms that remain stable over time, whereas those who have a functional aetiology often complain of multiple gastrointestinal and other symptoms that change over time (e.g. dyspepsia, irritable bowel syndrome [IBS], chronic headache, fibromyalgia).⁶

Another factor is that patients seeking medical attention for functional gastrointestinal symptoms have an ~50% rate of psychiatric disease, such as anxiety, depression or somatization, compared with ~20% for patients with organic conditions (e.g. peptic ulceration, colitis) and ~10% for the general population.⁷ Furthermore, the presence of psychiatric disease or psychosocial stressors (e.g. unemployment, bereavement) is associated with more frequent complaints of symptoms, negative perceptions of the condition (e.g. fear of cancer), more time off work and failure to respond to standard treatment.⁸ Awareness of these factors can clarify the causes of disease and guide the clinician towards a more holistic and effective management strategy.

After initial assessment, if an FGID is considered the likely cause of symptoms, then this should be communicated to the patient and empirical, symptomatic treatment offered. For oesophageal and dyspeptic symptoms a trial of twice daily PPI therapy is recommended. Acid suppression usually improves symptoms

related to gastro-oesophageal reflux and can also be effective for functional dyspepsia. For intestinal and colorectal symptoms first-line treatment includes antispasmodic agents (e.g. hyoscyamine), increased dietary fibre or artificial fibre supplements (e.g. psyllium preparations) and other medications that regulate bowel frequency and consistency (e.g. polyethylene glycol [PEG] or stimulant laxatives [sodium picosulphate] for constipation and loperamide for diarrhoea).

Nonpharmacological therapy is also of proven value and is preferred by many patients. Dieticians may be involved to manage food intolerance and to facilitate adequate nutrition

in patients who have symptomatic gastroparesis and food intolerance. Physiotherapists can treat symptoms related to muscle tension in the abdominal wall, diaphragm and pelvic floor (e.g. bloating, reflux, rumination, pelvic floor dyssynergia). Therapists may also be involved to support patients who have a psychiatric comorbidity.

Mistake 3 Not referring patients with persistent symptoms to the NGM laboratory

Patients with symptoms suggestive of a major motility disorder, especially in association with

Symptom/indication	First investigation	Second investigation
• Pharyngeal dysphagia*, chronic cough, aspiration, globus sensation	• Video fluoroscopic swallowing exam (VFSE), or ear, nose and throat (ENT) examination by fiberoptic endoscopic evaluation of the swallow (FEES)	• High-resolution manometry (HRM) ± impedance, ± pH-impedance-monitoring (if reflux disease suspected)
• Oesophageal dysphagia*	• HRM ± impedance, ± provocative testing (e.g. rapid drink challenge, multiple rapid swallows, solid test meal)	• Timed barium swallow, ideally with fluid and solid material
• Typical and atypical reflux symptoms, including chest pain [‡]	• HRM ± impedance, ± provocative testing (e.g. rapid drink challenge, multiple rapid swallows, solid test meal) • + pH or pH-impedance-monitoring	• Prolonged catheter-free pH-monitoring
• Dyspepsia (postprandial fullness, bloating, nausea, abdominal pain, weight loss* (25% with functional disease)	• 'Nutrient drink test', gastric emptying study (scintigraphy, ¹³ C breath test); strict adherence to standard methodology is essential	• HRM ± impedance + pH-impedance-monitoring (to exclude GORD) • Antroduodenal manometry (to exclude major motility disorders)
• Abdominal bloating, chronic diarrhoea with suspected small intestinal bacterial overgrowth (SIBO), food intolerance or bile acid diarrhoea/malabsorption	• Lactose H ₂ -breath test if intolerance to milk products suspected • Dietary advice, with low FODMAP or exclusion diet	• Glucose or lactulose H ₂ -breath test ± oro-caecal transit time (validity questioned, see text) • Endoscopy with aspiration of duodenal secretion • ⁷⁵ SeHCAT, C4 or faecal bile acid to diagnose bile acid diarrhoea • Intestinal and colonic transit time (scintigraphy, wireless motility capsule)
• Chronic constipation or evacuation disorder	• Anorectal HRM with balloon expulsion ± defecography (barium or MRI)	• Whole-gut or colon transit time ('Sitzmarks'® test, scintigraphy, wireless motility capsule)
• Faecal incontinence	• Anorectal HRM, endoanal ultrasonography	• Rectal barostat

Table 1 | Clinical investigation of gastrointestinal motility and function. *Alarm symptom; endoscopy or imaging should be performed prior to physiological investigation. [‡]Caution, ischaemic heart disease must be excluded prior to physiological investigation.

aspiration, impaired food intake or nutritional health, require early referral for specialist tests. For the remainder, some will respond to symptomatic management, as detailed above; however, others will not improve despite appropriate management and/or have adverse effects of therapy. For individuals who have persistent symptoms, referral to the NGM laboratory is appropriate (Table 1). Referring patients for investigation to confirm diagnosis before embarking on time-consuming and/or costly management (e.g. dietary therapy or bio-feedback training) is also legitimate. Increasing evidence reviewed by the International Working Group for Disorders of Gastrointestinal Motility and Function indicates that the results of specialist tests can identify clinically relevant pathology and guide rational management.⁹⁻¹²

Mistake 4 Using outdated technology to assess oesophageal motility and function

Technological advances have markedly improved the accuracy and clinical utility of oesophageal manometry. High-resolution catheters with closely spaced sensors provide a near continuous representation of pressure activity from the mouth to the stomach.¹³ HRM metrics have been validated against independent measurements of oesophageal function and are used by the Chicago Classification system to diagnose motility disorders.¹⁴

The classification of motility disorders is hierarchical, which focuses attention on clinically relevant findings. Most important, abnormal oesophagogastric junction (OGJ) function is considered first because failure of the OGJ to relax and/or open in achalasia and outflow obstruction has a greater effect on bolus transport than abnormal peristalsis, such as spasm or aperistalsis. In addition, the Chicago Classification makes a clear distinction between major motility disorders and minor abnormalities. Major motility disorders are never observed in healthy individuals and are always associated with clinical disease, whereas minor abnormalities are 'outside the normal range' but can be observed in patients without symptoms and, occasionally, in healthy individuals. In the former group there is a clear rationale for treatment directed at correcting the pathology.¹⁴ In the latter group, the association of minor motility disorders with patient symptoms is less certain and other factors could also be involved (e.g. acid reflux, visceral hypersensitivity).

Prospective studies have established that HRM improves interobserver agreement and increases diagnostic accuracy when compared with 'conventional' manometry with line

tracings from ≥ 8 sensors (CLT).¹⁵ Direct comparison of the techniques showed that the odds of an incorrect oesophageal motility diagnosis were 3.3 times higher with CLT than with HRM assessment, and the odds of incorrect identification of a major motility disorder requiring specific management were 3.4 times higher with CLT than with HRM.¹⁵ Furthermore, a randomised controlled trial reported a significantly increased diagnostic yield for major motility disorders with HRM compared with CLT, in particular for achalasia (26% versus 12%).¹⁶

The combination of manometry with intraluminal impedance enables simultaneous assessment of motility and bolus movement through the oesophagus. This is important because dysphagia and other symptoms are rarely caused by abnormal motility unless it is accompanied by impaired function, such as bolus retention or reflux. This approach has been applied to assess oesophageal function during the 'rapid drink challenge' and when eating a solid test meal.¹⁷⁻¹⁹ In serial diagnostic studies this approach increased the diagnostic yield of HRM for major oesophageal motility disorders. Patient reports of symptoms during a solid test meal also established motility disorders as the cause of oesophageal symptoms¹⁸ and selected patients who profited from specific clinical management (e.g. outlet obstruction in patients with dysphagia after fundoplication²⁰). Extending HRM observations after the meal can also be of interest in patients who have therapy-resistant reflux and other post-prandial symptoms. These observations can differentiate typical reflux events from behavioural disorders such as rumination syndrome.²¹

Mistake 5 Diagnosing reflux disease based on symptoms alone

The sensitivity and specificity of a diagnosis based on reflux symptoms, especially in patients who have persistent symptoms on PPI therapy, is inconsistent with the results of objective measurements of oesophageal reflux. In a large clinical study from 2010, heartburn and acid regurgitation were present in only 49% of patients with pathological levels of acid exposure during pH-studies;²² conversely, 23% of patients with 'typical reflux symptoms' had normal levels of acid exposure.²² Physiological studies are also performed in patients with atypical symptoms that can be triggered by gastro-oesophageal or supra-oesophageal reflux, such as epigastric pain, chronic cough or pharyngeal symptoms (e.g. hoarseness, sore throat, globus sensation); however, in

this patient group only a minority of tests are positive.²³ Overall, the weak association between patient symptoms and the presence of pathological reflux highlights the importance of objective measurements to differentiate patients who have GORD-related symptoms from those who have functional disease (e.g. hypersensitivity) or symptoms unrelated to reflux.

Guidelines recommend that the diagnosis of GORD be based either on ambulatory pH-studies or, ideally, combined pH with multiple intraluminal impedance studies.²⁴ The sensitivity of the investigation is optimal if PPI medications are stopped at least 5 days before the study. The advantage of the combined system is that impedance can detect all reflux events, irrespective of acidic content.

In patients who fail to respond to PPI therapy, weakly acidic reflux that extends into the proximal oesophagus or pharynx is an important cause of symptoms (e.g. regurgitation and cough).^{23, 25} Additionally, impedance measurements can detect the movement of air through the oesophagus and document behavioural conditions, such as aerophagia and supragastric belching, that can be the cause of symptoms in patients who otherwise have negative results.²⁶

Limitations of these ambulatory studies include catheter intolerance in ~10% of patients and a similar proportion in whom catheter-related nasopharyngeal discomfort disturbs normal eating, work or sleep, leading to false-negative results.^{27, 28} In such situations wireless pH-monitoring provides an alternative method that is well tolerated by most patients.²⁷ A further advantage of this technology is that this catheter-free approach enables prolonged (up to 96h) monitoring, which improves the ability to demonstrate an association between acid reflux and symptoms. As a result, wireless pH-monitoring studies are reported to identify a significant link between reflux and symptoms in up to 1 in 3 patients who previously had negative catheter-based test results!²⁸

The classification of ambulatory reflux studies is based on the presence or absence of pathological acid exposure and/or an increased number of reflux events (acid and otherwise) detected by impedance measurements and a close temporal association between reflux events and patient symptoms.²⁴ To compensate for high day-to-day variability in these metrics, the Lyon Consensus from 2018 recommends that a conclusive diagnosis of GORD can be made not only in patients who have severe acid exposure ($>6\%$ pH $<4/24$ h), but also in patients who have borderline acid exposure (4–6% pH $<4/24$ h) if supported by other data (e.g. positive symptom association, or an

unstable OGJ [hiatus hernia] on manometry).²⁴

This classification system is clinically relevant in that patients who have objective evidence of GORD on physiological measurement have a markedly better response to medical or surgical therapy (typically 70–90%) than patients who have typical symptoms and normal acid exposure ('reflux hypersensitivity') and the association of reflux events with symptoms is weak or absent (typically 30% response).²⁹ In the latter group with functional heartburn, treatment with antidepressants that aims to reduce visceral sensitivity is recommended. A systematic review of this approach in patients with functional oesophageal syndromes reported improvement in 23–61% of patients compared with those receiving ongoing PPI therapy alone.³⁰

Mistake 6 Using nonstandard methodology in gastric emptying studies

There is a marked overlap between symptoms reported by patients who have primary motility disorders and those who have FGIDs in whom altered motility is only one among several mechanisms responsible for symptoms.³¹ It is also known that there is important day-to-day variation in measurements of gastrointestinal motility and function. On this basis, adherence to a validated methodology, for which there are published 'normal' values obtained from a large and representative population is essential. In addition, only results that are clearly pathological and consistent with clinical history should be interpreted as diagnostic of disease. This is well illustrated by studies of gastric emptying by scintigraphy, ¹³C breath tests or the wireless motility capsule. These investigations provide diagnostic information in cases of excessively rapid (dumping) or delayed (gastroparesis) gastric emptying.³¹

The low-fat, 'eggbeater' meal is the best-established test meal used with scintigraphy.³² Using validated methods, delayed gastric emptying is documented in approximately 40% of patients who have functional dyspepsia and up to 75% of patients who have chronic unexplained nausea and vomiting.^{33, 34} The presence of severely delayed emptying (>3 times the upper limit of normal ['gastric failure']) is associated with postprandial vomiting, weight loss, poor health status and poor response to therapy.^{34, 35} The clinical relevance of less severe delays in gastric emptying is uncertain. These results do not associate with symptom severity or the response to prokinetic and antiemetic medications;³⁶ however, they may predict poor

response to amitriptyline (antidepressant) therapy.³⁷

To obtain meaningful results, the most appropriate test meal should be applied. For example, solid test meals might be more sensitive to gastroparesis, whereas, liquid might better detect acceleration of early gastric emptying associated with gastric dumping.³¹ It may also be possible to extract more, and more clinically relevant, information from existing tests. For example, increasing the size (volume) of the test meal may facilitate measurement of gastric filling (accommodation) and sensitivity, both of which are relevant in the assessment of patients with functional dyspepsia.³⁸

Mistake 7 Over-interpreting hydrogen breath test results

Hydrogen breath tests document the malabsorption of lactose, fructose and other carbohydrates, which are present in the diet and can be a cause of bloating, diarrhoea and other symptoms. The test is based on the principle that hydrogen is not produced by human metabolism, but is a product of bacterial fermentation in the gastrointestinal tract.³⁹

In healthy individuals, hydrogen is produced when nutrients are not (or not fully) absorbed in the small bowel and come into contact with microbiota in the large bowel. If hydrogen is detected in the breath, then the diagnosis of carbohydrate malabsorption can be made. If the increase in breath hydrogen is associated with the onset (or increase) of typical abdominal symptoms, then the presence of food intolerance is demonstrated. However, the interpretation of these results is complex because the risk of malabsorption increases with the dose of substrate, rapid oro-caecal transit and the amount of gas produced by the microbiota.^{40, 41}

Patient factors also have a key role. For example, many IBS patients with lactase deficiency experience bloating, pain and diarrhoea after ingestion of 20g lactose; whereas, most healthy individuals with lactase deficiency tolerate this amount of lactose without difficulty.⁴⁰ Conversely, almost all those with lactase deficiency will experience symptoms after ingestion of 40–50g lactose (equivalent of 1,000ml milk), which is the dose most often applied in clinical studies.⁴⁰ The interpretation of other hydrogen breath tests (e.g. fructose) is even more complex because the absorption of the substrate is not genetically determined and, therefore, much more variable. Thus, the clinical relevance of a positive breath test must consider both technical and clinical factors.

Hydrogen breath tests using glucose or lactulose as the substrate are also used to detect small intestinal bacterial overgrowth (SIBO); however, studies have highlighted the limitations of these investigations.^{42, 43} False-negative tests are frequent due to the presence of bacteria that do not produce hydrogen and the addition of methane measurements improves sensitivity only slightly.³⁹ False positives are frequent due to high variability in gastrointestinal transit time and, in the case of lactulose, the effects of the substrate on intestinal transit.⁴⁴ Many of these limitations can be addressed by combining the hydrogen breath test with an independent assessment of oro-caecal transit time by scintigraphy. This approach can differentiate an early increase in breath hydrogen due to SIBO from a rapid oro-caecal transit time, both of which may be relevant in IBS patients.⁴⁴

Mistake 8 Failing to assess both anal sphincter and rectal function in patients who have faecal incontinence

The rectum and anal sphincter act together with the pelvic floor musculature to maintain faecal continence.⁴⁵ Physiological investigations of the rectum and anal sphincter are indicated in patients who have faecal incontinence that does not respond to empirical treatment with medications and basic pelvic floor training. No one investigation provides all the information required to understand the pathological basis of disease.

High-resolution anorectal manometry (HR-ARM) documents the functional anatomy of the internal and external anal sphincters in more detail than conventional manometry and with a high degree of interobserver agreement.^{46, 47} In patients with continence problems HR-ARM is combined with endoanal ultrasonography to image the structure of the anal sphincter. Measurements of rectal function should also be obtained during the same investigation. This is important because 20–40% of patients with faecal incontinence have normal anal sphincter function but either a small and/or noncompliant rectum and/or abnormal rectal sensitivity (both rectal hyposensitivity and rectal hypersensitivity impair the ability to maintain faecal continence).^{48, 49}

Together, the results of these investigations provide insight into the causes of passive, urge and combined incontinence and faecal seepage. The results of these tests can direct specific management. For example, specialist biofeedback therapy is often effective for individuals who have an intact sphincter but are unable to maintain squeeze pressure and

also those with urgency related to visceral hypersensitivity.^{50, 51} By contrast, this form of training is less useful if symptoms are related to pathology that cannot be improved by training (e.g. a weak internal sphincter, grossly impaired rectal sensation⁵¹). Surgical repair of the anal sphincter is usually reserved for patients who have a weak squeeze pressure related to a large tear in the external sphincter. In others, the application of sacral nerve stimulation is often effective;⁵² a follow up of prospectively registered patients reported ongoing improvement in faecal continence in 71%, with full continence achieved in 50% at a median of 7 years after implantation.⁵³

Mistake 9 Not confirming manometry results with an independent test of evacuation in patients with constipation and evacuation disorders

The assessment of patients who have chronic constipation or an evacuation disorder is a challenge. The clinical history and physical examination, including digital rectal examination, do not provide a definitive diagnosis.⁵⁴ Moreover, all current investigations of anorectal function have limitations. In particular, it can be difficult and embarrassing for patients to simulate defecation. Repeating measurements with detailed instruction and verbal feedback increases the chance that a meaningful assessment of patient behaviour is obtained and reduces the false-positive rate for dyssynergic defecation.⁵⁵

Measurement of anorectal function by HR-ARM can detect abnormal anorectal pressure activity and function in patients who have dyssynergic defecation (e.g. absent push effort, paradoxical contraction of the anal sphincter) with a high level of agreement with the results of MR-defecography.⁵⁶ However, simple quantitative measurements of anorectal pressure activity during defecation have yet to be established.⁵⁷ On this basis, it is important to confirm the results of manometry with a qualitative test of defecation. The balloon expulsion test documents the ability of a patient to defecate a small, water-filled balloon from the rectum. If expulsion is not achieved within a set time limit, then this is a marker of impaired evacuation that might be secondary to structural or functional abnormalities of the pelvic floor or anal sphincter.⁵⁸ Alternatively or additionally, defecography can document the efficacy with which contrast agent is evacuated from the rectum and detect structural conditions (e.g. intussusception, enterocele) that impair the passage of stool during simulated defecation.⁵⁹

The results of these tests have a direct effect on clinical management. If outlet obstruction is related to dyssynergic defecation then biofeedback therapy is effective in up to 80% of patients, compared with 20% of patients effectively treated with laxatives alone.⁶⁰ By contrast, for those who have excessive pelvic floor descent, a large retaining rectocele with obstructive intussusception or prolapse, surgery is often required to restore functional anatomy. In cases in which no pathology is identified, a colonic transit test using radiopaque markers, scintigraphy or a wireless motility capsule can help to confirm slow-transit constipation. If transit is slow, then more intensive laxative or prokinetic therapy is required. Conversely, if this test shows normal transit, then the likely diagnosis is IBS or a related FGID with altered awareness of gastrointestinal function.⁶¹

Mistake 10 Failing to communicate the results to the patient

An effective and trusting doctor-patient relationship is the basis for successful management in clinical medicine in general, and for disorders of gastrointestinal motility and function in particular. If such a relationship is in place, then presenting the patient with a clear diagnosis, an explanation of what causes symptoms and simple advice about how to self manage the condition is always well received and may be all that is required. For example, in patients with 'noncardiac chest pain', well-informed patients are more satisfied, cope with symptoms better and seek medical attention less frequently.⁶² These findings were independent of the final diagnosis and disease severity.⁶² Good communication is an essential part of any treatment plan!

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- International Working Group for Disorders of Gastrointestinal Motility and Function [<https://www.idigest.ch>].

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- Constipation [<https://www.ueg.eu/education/online-courses/constipation/>].
- Dyspepsia [<https://www.ueg.eu/education/online-courses/dyspepsia/>].
- Irritable bowel syndrome [<https://www.ueg.eu/education/online-courses/irritable-bowel-syndrome/>].

Mistakes in...

- Mistakes in gastro-oesophageal reflux disease diagnosis and how to avoid them [<https://www.ueg.eu/education/latest-news/article/article/mistakes-in-gastro-oesophageal-reflux-disease-diagnosis-and-how-to-avoid-them/>].
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- ‘Rome IV: New diagnostic criteria for functional GI disorders’ session at UEG Week 2016 [<https://www.ueg.eu/education/session-files/?session=1594&conference=144>].
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