Clinical measurement of gastrointestinal motility and function: who, when and which test?

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Abstract

Symptoms related to abnormal gastrointestinal motility and function are common. Oropharyngeal and esophageal dysphagia, heartburn, bloating, abdominal pain and alterations in bowel habit are amongst the most frequent reasons for seeking medical attention from internists or general practitioners, and are also common reasons for referral to gastroenterologists and colorectal surgeons. However, the non-specific nature of gastrointestinal symptoms, the absence of definitive diagnosis on routine investigations (such as endoscopy, radiology, or blood tests), and the lack of specific treatments make disease management challenging. Advances in technology have driven progress in the understanding of many of these conditions. This Review serves as an overview for a series of Consensus Statements on the clinical measurements of gastrointestinal motility, function and sensitivity. A structured, evidence-based approach to the initial assessment and empirical treatment of patients presenting with gastrointestinal symptoms will be discussed, followed by an outline of the contribution of modern physiological measurement on the management of patients in whom the cause of symptoms has not been identified with other tests. Discussions will include indications for and utility of high-resolution manometry, ambulatory pH-impedance monitoring, gastric emptying studies, breath tests and investigations of anorectal structure and function in day-to-day practice and clinical management.

Competing interests

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Biography

Mark Fox is Professor of Gastroenterology at St. Claraspital, Basel, Switzerland. His work is focused on the development and application of investigations to describe the structure, function and sensitivity of the digestive tract. He holds positions at the Universities of Zürich, Nottingham and Zhejiang and is chair of the International Working Group for Gastrointestinal Motility and Function.

Peter J. Kahrilas is the Gilbert H. Marquardt Professor in Medicine at the Feinberg School of Medicine at Northwestern University in Chicago where he has been faculty since 1986. His research is on oesophageal and oropharyngeal physiology and pathophysiology, on which he has published ~340 original papers.

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Key points

- Symptoms have poor specificity for gastrointestinal diseases and there is a marked overlap between 'organic disease' (including major motility disorders) and functional gastrointestinal disease, underlining the need for testing to guide treatment
- New technology has driven progress, improved our understanding of gastrointestinal physiology, and has revolutionized the clinical measurement of gastrointestinal motility and function from oropharynx to anorectum
- Adherence to validated methodology is essential for the assessment of GI motility and function, in order to provide meaningful results
- Diagnoses based on valid, objective metrics (e.g. Chicago Classification for oesophageal motility disorders, gastric emptying retention time and colonic transit times) are replacing subjective assessment of physiological studies
- High-resolution manometry has improved the inter-observer agreement and accuracy of diagnoses in patients with disorders of oesophageal and anorectal motility and function
- The importance of abnormal visceral sensitivity has been demonstrated in patients with functional gastrointestinal diseases.

Glossary

Dysphagia - difficulty or discomfort in swallowing, as a symptom of disease
Achalasia - a condition in which the lower oesophageal sphincter muscle fails to relax, preventing food from passing from the esophagus into the stomach
High-resolution manometry - a diagnostic system that measures intraluminal pressure activity from the throat to the stomach using a series of closely spaced pressure sensors.
Visceral sensitivity - term used to describe the intensity of sensation (for example, fullness or pain) induced by stimulation applied to the abdominal organs (viscera). Hypo-sensitivity indicates that stimulation induces less intense sensation than normal. Hyper-sensitivity, indicates that stimulation induces more intense sensation than normal.
Intraluminal impedance - a catheter-based method to detect presence of food, fluid or gas within the lumen of the esophagus. Measuring impedance at multiple sites (multichannel) allows for determination of the direction of movement of esophageal contents. Combined with pH-measurement this technique is considered the gold-standard for detection of acid *and* non-acid reflux events.
Oesophagogastric junction - a complex valve composed of an intrinsic, smooth muscle element (lower esophageal sphincter, gastric cardia) and an, extrinsic striated muscle element (diaphragm).
Contraction reserve – term used to describe the increase in esophageal contractility seen in response to physiological challenge (for example, multiple rapid swallows, reflux)
Aerophagia - a condition, thought to be a learned habit, in which excessive air swallowing leads to gastric distension and abdominal bloating
Supragastric belching - a condition, thought to be a learned habit, in which air is repetitively sucked into the oesophagus and then immediately expelled (belched)
Gastrointestinal Scintigraphy – a test in which a radiolabeled substance (for example, eggbeater meal) is ingested to provide a non-invasive and quantitative measure of gastric emptying and / or oro-caecal transit.
Gastric accommodation – a term used to describe the relaxation of the stomach (reduction in gastric tone and increase in compliance) that follows ingestion of a meal.
Defecography - a test in which a series of images are taken as a patient goes through the process of having a bowel movement to assess for the presence of any structural or functional pathology.
Biofeedback therapy - a specialist form of physiotherapy used to treat constipation and faecal incontinence in which sensors record muscle activity (for example, abdominal wall, anal sphincter) and give feedback to the patient to improve technique.
Rectocele - a herniation (bulge) of the front (anterior) wall of the rectum into the back (posterior) wall of the vagina. It occurs when the fibrous tissue between the rectum and the vagina (rectovaginal septum) becomes thin and weak over time.
Intussuception - a process in which a segment of intestine, in this case rectum, telescopes (invaginates) into the lower rectum or anal canal, causing structural outlet obstruction and difficulty with defecation.

Symptoms related to abnormal gastrointestinal function can occur from the moment food is swallowed to the time faeces are expelled from the body (**figure 1**). Dysphagia **[G]** , heartburn, bloating, abdominal pain and changes to bowel habit are very common in the general population (1). A survey published in 2014 reported that the prevalence of GERD, dyspepsia and IBS vary between 5-15% in European countries.(1) These symptoms are amongst the most frequent reasons for seeking medical attention from general physicians and are also common grounds for referral to specialist gastroenterologists.(1) These functional gastrointestinal diseases (FGIDs) impact on activities of daily living, reduce work-related productivity and incur high direct and indirect health care costs.(2) Indeed, although life expectancy is normal in FGID patients,(3) the burden of disease in terms of quality of life can be compared to those with cardiac failure or advanced malignancy.(4)

The success of modern, scientific medicine is based on identifying and treating the patho-physiological basis of so-called organic disease (for example neoplasia, inflammation, achalasia and other major motility disorders). However, this approach has not been realized in the field of FGIDs. The Rome IV criteria published in 2016 classify these conditions based on the presence of specific, digestive symptoms for at least 3 months of the 6 months prior to diagnosis, in the absence of other diseases on appropriate investigation.(5) This process can include endoscopy (with biopsies), medical imaging and laboratory tests to rule out cancer and conditions such as peptic ulceration, celiac disease and colitis. For patients with mild symptoms, negative tests provide reassurance and simple, symptomatic management might be all that is required (for example, acid suppression, stool regulation). However, for those with severe symptoms that persist on therapy, ruling out life-threatening disease is not sufficient, and referral for specialist investigations of gastrointestinal motility and function is often indicated.

The aim of physiological investigations is to explain the cause of digestive symptoms and establish a diagnosis that can guide rational and effective treatment. Until the introduction of high-resolution manometry (HRM) about ten years ago, and even today for certain other investigations, it could be argued that investigations of gastrointestinal motility and function rarely provided this information. As a result, only patients with clinical suspicion of major motility disorders such as achalasia **[G]**, severe reflux disease or fecal incontinence under consideration for surgery were referred for tests. Even in this group, many diagnoses were subjective and based on the clinical presentation rather than the results of physiological measurement.(6) Technological advances have improved the reliability and clinical utility of these investigations. The neurogastroenterology and motility laboratory now provides measurements not only of motility but also of function in terms of the movement (and digestion) of ingested material within the gastrointestinal tract. This approach is important because symptoms do not usually occur unless abnormal motility disrupts function. The

measurement of visceral sensitivity **[G]** in clinical practice remains a challenge; however, the ability to associate gastrointestinal events (such as contractions, bolus retention, reflux, accelerated or delayed colonic transit) with symptoms provides some indication of how the patient responds to a stimulus. This association is important because both hypersensitivity and hyposensitivity are frequent causes of symptoms and disease in patients referred for investigation.(7)

[H1] Method

This paper provides an introduction to a series of reviews initiated by the International Working Group for Disorders of Gastrointestinal Motility & Function and published by *Nature Reviews in Gastroenterology and Hepatology.* These reviews summarize the state-of-the-art in clinical measurement of the pharyngeal swallow, esophageal motility (8), gastro-esophageal reflux disease (9), gastric and intestinal function (10) and anorectal continence and defecation (11). The lead authors of each review were invited to contribute to the current manuscript. Consensus was achieved through careful evaluation and discussion of available literature, and expert agreement when recommendations lacked supporting evidence. All authors consented to the final version of the manuscript.

The first part of this paper provides a structured, evidence-based approach to the initial management of patients with symptoms related to Disorders of Gastrointestinal Motility & Function. The second part outlines the contribution of the neurogastroenterology and motility laboratory to the diagnosis and treatment of patients in whom no cause of symptoms or disease has been identified on endoscopy, radiology and other appropriate investigations. In the latter section, unless otherwise stated, contents were based on the published consensus documents.

[H1] Initial management

The primary aim of the initial assessment of patients with gastrointestinal symptoms is to identify 'alarm features' such as dysphagia, anemia or weight loss that could indicate the presence of neoplasia, ulceration or inflammation in the digestive tract (**Box 1**). If present, then it is obligatory to perform endoscopy and/or imaging depending on the presenting complaint. Prospective trials and meta-analysis indicates that the presence of alarm features is associated with 5-10% risk of life-threatening disease, compared to 1-2% risk in patients without these markers.(12, 13) Conversely, if no symptoms or signs of life-threatening conditions are present, then invasive investigation is not necessarily required.(14, 15) Rather, the Rome Criteria recommend that the diagnosis of FGIDs is based on clinical presentation and negative results on appropriate tests (**Box 2**).(5) Although no item in the clinical history is diagnostic, there are many features that help to differentiate patients with

organic disease and FGID (**table 1**). One pointer is that patients with a defined etiology tend to have discrete symptoms that remain stable over time, whereas those with functional etiology often complain of multiple and changeable symptoms (for example, dyspepsia, IBS and fibromyalgia).(16, 17) Another factor is that patients seeking medical attention for functional gastrointestinal symptoms have a ~50% rate of psychiatric disease such as anxiety, depression or somatization, compared with ~20% with 'organic' conditions (such as peptic ulceration, colitis) and ~10% of the general population.(18, 19) Furthermore, the presence of psychosocial stressors (such as unemplyment, bereavement) is associated with more frequent complaints of symptoms, more time off work and failure to respond to specific management.(20) Many experts ask patients to complete standardized questionnaires to ensure that clinically relevant psychopathology in patients wtih FGID is recognized early in the diagnostic process.

After initial assessment, if abnormal gastrointestinal motility and function is considered the probable cause of symptoms, then this diagnosis should be communicated to the patient. Patients with symptoms and signs suggestive of aspiration or a major motility disorder, especially in association with impaired food intake and nutritional health, require early referral to the neurogastroenterology and motility laboratory. For the remainder, a trial of empirical treatment is recommended before further investigation is considered. A general approach to the initial assessment and management of patients is presented (**figure 2**).

For esophageal and dyspeptic symptoms a short course of twice daily PPI therapy is recommended.(14, 15) Meta-analyses show that acid suppression usually improves symptoms related to gastro-oesophageal reflux and can be effective also in functional dyspepsia. (21-23) At the same time a test and treat approach for *Helicobacter pylori* infection is appropriate although the effect on symptoms is modest (number needed to treat >10 in placebo-controlled trials).(23)

For intestinal and colorectal symptoms first-line treatment includes antispasmodic agents (such as hyoscyamine), increased dietary fiber or artificial fiber supplements (for example, psyllium preparations) and other medications that regulate bowel frequency and consistency (such as polyethylene glycol (PEG) for constipation and loperamide for diarrhea).(24) A trial of antiemetic or prokinetic medications (for examples, ondansetron, domperidone, stimulant laxatives) can also be considered. If initial therapy does not improve symptoms, then low-dose antidepressant therapy (such as amitriptyline, mirtazapine or citalopram) has been shown to be effective in a range of functional gastrointestinal symptoms, in particular nausea and abdominal pain.(25-27) The benefit of these medications is thought to be related primarily to reduction in visceral hypersensitivity; however, some antidepressants have effects also on motility. For example, mirtazepine accelerates gastrointestinal transit in animal studies,(28) and has been shown to have symptomatic benefits in

functional dyspepsia and refractory gastroparesis in small clinical trials.(29, 30) Similarly, amitryptiline slows colonic transit and inhibits rectal contractility in patients with fecal incontinence.(31) Non-pharmacological therapy is also of proven value and is preferred by many patients. This includes: the involvement of dieticians to manage food intolerance(32) and to facilitate nutrition in patients with symptomatic gastroparesis through education on the use of small particle diets (33); physiotherapists to treat symptoms related to muscle tension in the abdominal wall, diaphragm and pelvic floor (for example, bloating, rumination, constipation due to evacuation disorders caused by pelvic floor dyssynergia);(34, 35) and therapists to support patients with psychiatric co-morbidity (27).

Many patients in primary care respond well to this simple, empirical management; however, an important minority report persistent symptoms during treatment or adverse effects of therapy. In these individuals, referral for investigations of gastrointestinal motility and function to assess the causes of symptoms is appropriate (**Table 2**). Others might insist on investigation prior to embarking on potentially costly and / or time consuming management (for example, dietary therapy). Increasing evidence reviewed for the International Working Group for Disorders of Gastrointestinal Motility and Funciton indicates that the results of these tests can identify clinically relevant pathology and guide rational management (8-11).

[H1] Disorders of Swallowing

For oropharyngeal dysphagia and related symptoms (for example, cough related to swallowing), the first investigation is a video fluoroscopic swallowing exam, which can visualize the structure and function of the oropharynx and document laryngeal penetration or overt aspiration (36). An alternative approach favoured by ear nose and throat specialists that can assess laryngopharyngeal motor and sensory function is Fiberoptic Endoscopic Evaluation of Swallowing (FEES) (37). However, if imaging and endoscopy do not deliver a definitive diagnosis, then HRM, ideally combined with impedance, could identify the cause of symptoms and determine the risk of aspiration.(38-40) In the future, brain imaging and other neurophysiological tools might enable characterization of the sensorimotor integration processes involved in deglutition.(41) It is hoped that an analysis of these complex data will identify the mechanism of oropharyngeal dysphagia and direct effective management.

Important progress has been made in the clinical investigation of esophageal dysphagia. Advances in catheter technology now provide a near continuous, high-resolution representation of pressure activity from the mouth to the stomach (6). Moreover, the combination of manometry with intra-

luminal impedance **[G]** enables simultaneous assessment of motility and bolus movement through the esophagus.(6, 42) A key insight from these studies is that dysphagia and other symptoms are rarely caused by abnormal motility unless it is accompanied by impaired function.

With the introduction of HRM technology it was necessary to develop a new classification system to diagnose esophageal motility disorders. The Chicago-Classification, now in its third iteration,(43) is based on objective measurements acquired during a series of ten 'single water swallows'. The metrics used in this analysis have been validated in physiological studies of esophageal function.(43) The system is hierarchical, with oesophagogastric junction **[G]** (EGJ) dysfunction considered first because failure of the EGJ 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 (44). In addition, the Chicago classification makes a clear distinction between major motility disorders which are never observed in healthy individuals and are always associated with clinical disease, from minor abnormalities which are "outside the normal range" but can be observed in patients without dysphagia and, occasionally, in healthy individuals. In the former group with conditions such as achalasia or spasm there is a clear rationale for treatment directed at correcting the pathology.(43) In the latter group, the association of minor motility disorders with patient symptoms is less certain and other factors could also be involved (for example, acid reflux, visceral hypersensitivity) (45, 46). Compared with conventional manometry with $\leq$8 sensors, the assessment of esophageal motility using HRM has been shown to have a higher inter-observer agreement and to increase diagnostic yield and accuracy for motility disorders.(47-49) The findings also influence clinical management. Based on HRM measurements three subtypes of achalasia are defined based on the absence or presence of pan-esophageal pressurization (type I and II, respectively) and spasm (type III).(50) This classification is used to guide treatment decisions and predicts the outcome of endoscopic and surgical management.(50, 51) The effect of this technology on the diagnosis and management of achalasia is detailed in a Consensus Statement published in 2017 (8).

One key weakness of standard HRM studies is that, in the absence of major dysmotility, the results do not explain the cause of symptoms because few patients experience dysphagia on swallowing small volumes of water (52). Studies have applied HRM, ideally with impedance, to assess esophageal function during normal drinking and eating (52-54). This approach can reveal major esophageal motility disorders not detected by standard tests (**figure 3**) (54). For example, a study published in 2015 has shown that including a test meal increases the diagnostic yield of HRM for clinically relevant outlet obstrution in patients with dysphagia after fundoplication. The majority of those with outlet obstruction responded to balloon dilatation of the fundoplication wrap.(55) Additionally, the combination of HRM with a test meal can clarify the severity of minor motility

disorders and, by associating esophageal dysfunction to symptoms, provide some insight into the role of visceral sensitivity in patients with functional dysphagia.(52, 56) Extending HRM observations after the meal can also be of interest in patients with therapy resistant reflux and other post-prandial symptoms. These observations can differentiate typical reflux events from behavioral disorders such as rumination syndrome and supra-gastric belching.(34)

[H1] GERD

GERD is common worldwide, with at least 1 in 10 of the general population experiencing heartburn or acid regurgitation 2-3-times per week.(1) In the absence of alarm symptoms, the initial clinical diagnosis of GERD is based on the symptomatic presentation and response to empiric antisecretory therapy.(57) Further investigations are indicated in patients with persistent symptoms on treatment with high-dose acid suppression (PPIs twice daily), those with alarm symptoms and those under consideration for anti-reflux surgery (58, 59).

Endoscopy is performed to detect mucosal disease in the esophagus and exclude other pathology such as peptic ulcer or cancer. Erosive reflux disease (ERD) or Barrett esophagus are present in ~30% of patients referred for investigation off PPI treatment, but less than one in ten in patients on acid suppressants (60). Non-erosive (or endoscopy negative) reflux disease (NERD) is diagnosed in patients with symptoms, but without mucosal erosions or metaplasia on endoscopic examination.(57, 61)

The sensitivity and specificity of a symptomatic diagnosis, including empiric response to PPI therapy, is not always consistent with the results of objective measurements of esophageal reflux (62). 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 48-hr wireless (Bravo) pH-studies;(63) whereas, conversely, 23% patients with “typical reflux symptoms” had normal levels of acid exposure.(63) 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 (for example, hoarseness, sore throat, globus sensation); however, in this patient group only ~25% of tests are positive.(64) Overall, the weak association between patient symptoms and the presence of pathological reflux highlights the importance of objective measurements to differentiate patients with GERD-related symptoms from those with functional disease (for example, reflux hypersensitivity) or symptoms unrelated to reflux.

Esophageal motility testing with HRM can identify a hypotensive EGJ and/or morphological abnormalities at the EGJ (hiatus hernia), both of which contribute to the pathophysiology of reflux

(65-67). However, transient lower oesophageal sphincter relaxation (TLESR), the most common mechanism of reflux, is not evaluated on routine motility testing despite validation of HRM criteria for the identification of these events (68). Esophageal clearance of refluxate is optimal with normal esophageal peristalsis; whereas, ineffective esophageal motility (fragmented peristalsis, weak peristalsis) or absent contractility can contribute to prolonged residence times of esophageal refluxate and lead to increased esophageal acid exposure (69, 70). Provocative (or "adjunctive") testing during HRM can be used to identify patients with ineffective motility who can augment peristalsis when challenged with repetitive swallowing (multiple rapid swallows, rapid drink challenge) or a solid test meal.(54, 71-75) Demonstation of an effective 'contraction reserve' **[G]** is particularly important if antireflux surgery is being considered (72, 73). Characterization of EGJ integrity and esophageal body motor function with contraction reserve constitute essential elements of motility evaluation in GERD.

Guidelines recommend that the diagnosis of GERD be based either on ambulatory pH-studies or, ideally, combined pH with multiple intraluminal impedance studies (58, 59). The sensitivity of the investigation is optimal if PPI medications are stopped at least 7-days prior to the study. The advantage of the combined system is that impedance can detect all reflux events, irrespective of acidic content, and also indicates the proximal extent of reflux events. In patients that fail to respond to PPI therapy, weakly acidic reflux that extends into the proximal esophagus or pharynx is an important cause of both "typical" symptoms (especially regurgitation) and "atypical" symptoms (especially cough).(64, 76) Additionally, impedance measurements can detect the movement of air through the esophagus and document behavioral conditions such as aerophagia **[G]** and supragastric belching **[G]** that can be the cause of symptoms in patients with otherwise negative results in ambulatory reflux studies.(77) 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 (78, 79). In such situations wireless pH-monitoring (Bravo, Medtronic, USA) provides an alternative method that is well tolerated by most patients.(78) A further advantage of the Bravo system 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.(80) Wireless pH-monitoring studies are reported to identify GERD in at least 1 in 3 patients with previously negative catheter-based tests.(79)

As detailed in an accompanying Consensus Statement by the GERD working group (9)**,** 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.(81)

To compensate for high day-to-day variability in these metrics, the Lyon Consensus from 2018 recommends that GERD can be diagnosed not only in patients with severe acid exposure (>6% pH <4 / 24h), but also in patients with borderline acid exposure (4-6% pH<4/24h) if supported by other data (for example, unstable esophago-gastric junction (hiatus hernia), ineffective esophageal motility).(81) Reflux hypersensitivity is diagnosed in patients with normal acid exposure and/or number of reflux events, but a positive reflux-symptom association. The diagnosis of 'functional heartburn **[G]** ' is applied in the remainder of patients with reflux symptoms, but without objective evidence of esophageal disease. This classification system is clinically relevant in that it has been shown that patients with objective evidence of GERD on physiological measurement have markedly better response to medical or surgical therapy (typically 70-90%) than patients with typical symptoms in whom acid exposure is normal and the association of reflux events with symptoms is weak or absent (typically 30% individuals).(82-85) In the latter group treatment with antidepressants with the aim of reducing visceral sensitivity is recommended. A systematic review of this approach in patients with functional esophageal syndromes reported improvement in 23% to 61% of patients compared to ongoing PPI therapy alone.(86)

[H1] Disorders of gastric emptying and digestion

Abnormal gastrointestinal motility and sensitivity have been documented in a range of conditions such as gastroparesis, functional dyspepsia and IBS (87). An accompanying Consensus Statement explores a range of technologies used to assess gastric and intestinal function (10)**.** Measurement of delayed or accelerated gastric emptying and small intestinal transit times by scintigraphy **[G]** , ^{13}C breath tests or the wireless motility capsule (SmartPill, Medtronic, USA) provide diagnostic information in cases of excessively rapid (dumping) or delayed gastric emptying (gastroparesis).(88, 89) To obtain reliable results it is essential that validated methodology is applied. For example, solid test meals might be more sensitive to gastroparesis, whereas, liquid test meals might better detect acceleration of early gastric emptying associated with gastric dumping. The low-fat, 'eggbeater' meal **[G]** is the best-established test meal used with gastric scintigraphy.(90, 91) Using this method, delayed gastric emptying is documented in ~40% of patients with functional dyspepsia and up to 75% of patients with chronic unexplained nausea and vomiting.(92-94) An association between dyspeptic symptoms and gastric emptying is observed in some, but not all, studies.(94-100) Severely delayed emptying (gastroparesis or gastric failure) is associated with post-prandial vomiting, weight loss, poor health status and poor outcome of therapy.(94, 101, 102) However, the results do not necessarily predict clinical response to metoclopramide, or other prokinetic and antiemetic medications.(103, 104) More sophisticated investigations assess gastric accommodation **[G]**, contractility and sensitivity (for

example, gastric barostat, single-photon emission computed tomography (SPECT), MRI). These measurements correlate more closely than gastric emptying with patient symptoms (for example, postprandial fullness is associated with impaired accommodation and viscera hypersensitivity); however, these tests are not widely available and are reviewed elsewhere.(88, 105, 106) Early experience with methods that use scintigraphy to document gastric filling (accommodation), contractility *and* emptying with concurrent assessment of patient symptoms show promise in early trials.(107, 108)

Antroduodenojejunal (ADJ) manometry is used to exclude major gastric and intestinal motility disorders in patients with severe, therapy-resistant constipation (a contraindication for colectomy) and also in patients with suspected intestinal obstruction but with no definitive diagnosis on radiology (109). ADJ manometry may also differentiate between myopathic and neuropathic pathology (88). Similarly, colonic manometry provides insight into the causes of lower gastrointestinal symptoms and disease (110). Unfortunately, these studies are difficult and time consuming (ideally 24h) to perform and analyze. For this reason, most clinicians apply non-invasive tests to assess intestinal and colonic transit time using scintigraphy, wireless motility capsule or radio-opaque markers (whole-gut transit time only). Objective evidence of slow transit indicates the need for more intensive laxative or prokinetic therapy. Conversely, if these investigations show normal intestinal and colonic transit, then the diagnosis is most likely to be a FGID such as IBS.(111) However, there is a marked and unclear overlap between patients with intestinal dysmotility and patients with FGIDs in whom altered gastrointestinal motility is only one among several pathological mechanisms responsible for symptoms (87, 88). One potential advantage of the wireless motility capsule is that it collects information about multiple parameters including gastric, small bowel and colonic transit (that is, function), intra-luminal pressure (that is, motility) and pH-measurements (a surrogate for bacterial fermentation in the large bowel) (112, 113). This investigation can be performed in office-based practice; however, as yet, it is uncertain whether the information acquired can replace scintigraphy, manometry or influence management.

One type of investigation *not* covered in the consensus document is the Hydrogen Breath test. These tests document malabsorption of lactose, fructose and other carbohydrates that are present in the diet and can be a cause of bloating, diarrhea and other symptoms, based on the principle that hydrogen is not produced by human metabolism, but is a product of bacterial fermentation in the gastrointestinal tract (114, 115). In healthy individuals, hydrogen is produced when nutrients are not fully absorbed in the small bowel but are fermented in the colon. Rapid diffusion into the blood stream and then the lung allows gas produced in the colon to be detected in the breath within 3 min of the substrate coming into contact with bacteria.(116) If the increase in breath hydrogen is associated with

the onset of typical abdominal symptoms, then the presence of food (for example, lactose) intolerance is confirmed. The risk of intolerance increases with the dose and the amount of gas produced by the bacteria but also with patient factors.(117, 118) For example, many patients with lactase deficiency and IBS experience bloating, pain and diarrhea after ingestion of 20g lactose (500ml milk); whereas, healthy individuals with lactase deficiency tolerate this amount of lactose without difficulty.(117)

Hydrogen breath tests using glucose or lactulose as the substrate are also used to detect small intestinal bacterial overgrowth (SIBO); however, studies have highlighted limitations of these investigations (119, 120). False-negative tests are common due to the presence of bacteria that do not produce hydrogen and the addition of methane measurements improves sensitivity only slightly (115). False positives are common due to high variability in gastrointestinal function and, in the case of lactulose, effects of the substrate on intestinal transit time.(121) As a result, the clinical relevance of these findings is debated. Some of these limitations can be addressed by combining the lactulose hydrogen-breath test with an independent assessment of orocaecal transit time by scintigraphy. This approach can differentiate between an early increase in breath hydrogen due to SIBO and rapid orocaecal transit time both of which are thought to be causes of symptoms in patients with IBS.(121)

[H1] Disorders of Anorectal Function

The rectum and anal sphincter act together with the pelvic floor musculature to maintain fecal continence and control defecation (122). Problems with anorectal function are common in the general community, especially in women that have had children, individuals with previous anorectal surgery and in the elderly (123, 124); however, many patients find it embarrassing to describe these problems (125). In particular stool incontinence might not be revealed unless specific questions are asked. Standard questionnaires and the Bristol Stool Score can be very helpful for this purpose (125, 126).

As detailed in the accompanying Consensus Statement by the anorectal working group (11), physiological investigations are indicated in patients with fecal incontinence, chronic constipation and difficulties in passing stool (so-called evacuation disorders) that do not respond to empirical treatment with medications that regulate stool consistency and pelvic floor training. It is important to appreciate that these disorders frequently co-exist, which will affect management.(127) Clinical investigations of anorectal function include endoanal ultrasonography, manometry, measurements of rectal function and balloon expulsion. Additionally, defecography **[G]** can image the structure and function of the pelvic floor at rest and during simulated defecation.(128)

Although less well established than esophageal HRM, anorectal HRM has been shown to document the function of the internal and external anal sphincter in more detail than conventional manometry

and with a high-degree of inter-observer agreement.(129, 130) In patients with continence problems this assessment is combined with endoanal ultrasonography to image the structure of the anal sphincter (**figure 4**). Measurements of rectal function can also be obtained during the same investigation, which is important because 20-40% of patients with fecal incontinence have normal anal sphincter function but either a small, non-compliant rectum or abnormal rectal sensitivity, both rectal hyposensitivity and rectal hypersensitivity impairs the ability to maintain fecal continence (122, 131, 132). Together, these findings provide important insight into the causes of passive, urge and combined incontinence and fecal seepage. The results of these tests can direct specific management. For example, specialist biofeedback therapy **[G]** is often effective for individuals with an intact sphincter that are unable to maintain squeeze pressure and also those with urgency related to visceral hypersensitivity.(133, 134) By contrast, this form of training is less useful if symptoms are related to pathology that cannot be improved by training (for example, weak internal sphincter, grossly impaired rectal sensation (134)). Surgical repair of the anal sphincter is usually reserved for patients with a weak squeeze pressure related to a large tear in the external sphincter. In others, application of sacral nerve stimulation is often effective (135), with follow up of prospectively registered patients reporting ongoing improvement in faecal continence in 71% with full continence achieved in 50% at a median of 7 years after implantation (136).

In patients with chronic constipation or an evacuation disorder, the balloon expulsion test documents the ability of a patient to defecate a small, water-filled balloon from the rectum. If this 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.(137) Qualitative assessment of anorectal function by HRM can detect abnormal anorectal pressure activity and function in patients with dyssynergic defecation (for example, paradoxical contraction of the anal sphincter or inadequate push effort) with a high level of agreement with the results of MR-defecography.(138) However, as yet, valid quantitative measurements of anorectal pressure activity during defecation have not been established.(139) Defecography is particularly useful in detecting structural conditions that impair the passage of stool.(138) The results of manometry and imaging has 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 to 20% treated with laxatives alone.(140) Whereas in those with excessive pelvic floor descent, large retaining rectocele **[G]** with obstructive intussusception **[G]** or prolapse, surgery is often required to restore functional anatomy. In cases in which no pathology is identified, a colonic transit test using Sitzmarks or scintigraphy or the wireless motility capsule can be very helpful to confirm slow-transit constipation.(87) 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.(111) In such cases treatments should be targeted towards improving visceral hypersensititivty or addressing psychosocial stressors, including a past history of abuse.

Conclusions

Symptoms related to abnormal gastrointestinal motility and function are very common; however, the non-specific presentation, the absence of definitive diagnosis on endoscopy and other tests, the co-existence of psychosocial issues, and the lack of specific treatments make the management of FGIDs challenging. The initial assessment must rule out life-threatening disease and select patients either for further investigation or a trial of empirical, symptomatic management. In the past, the role of physiological investigations was limited; however, advances in technology and methods can now provide more meaningful assessment of gastrointestinal motility and function. Accurate and objective measurements enable definitive diagnoses that can have a direct effect on treatment decisions in clinical practice. However, even when no specific treatment can be offered, based on the results of these tests, a clear explanation of the causes of symptoms can be therapeutic in itself. Well-informed patients are more satisfied, cope with their condition better and seek medical attention less frequently than those that have not been fully informed.(141)

Looking ahead (Box 3), new insights from basic and clinical science are needed to better understand the pathological basis of disorders of gastrointestinal motility and function. At the same time, there is a need for novel investigations and methods that identify not only abnormal motility but also abnormal sensitivity. Advances on all of these fronts are required to define patients with specific phenotypes of neurogastroenterology and motility diseases that respond to specific treatments.

Box 1| Alarm features

- Dysphagia, bolus obstruction or odynophagia (pain on swallowing)
- Recurrent vomiting
- Evidence of blood loss from gastrointestinal tract or iron deficiency anemia
- Involuntary weight loss (>5% baseline)
- Abdominal mass or pathological lymph nodes
- New presentation of digestive symptoms or change in bowel habit in patients aged >45 years

Box 2 | Initial investigations in functional gastrointestinal disease

- Full blood count, renal, liver and thyroid function tests, calcium levels, test coeliac serology including anti-transglutaminase antibody
- Serology or a urea breath test for *Helicobacter pylori* infection (acid suppression medications should be stopped for ≥1 week prior to test)
- Stool tests including fecal calprotectin levels to screen for colonic pathology (colitis, large polyps) and fecal occult blood can also be considered; imaging is preferred to fecal elastase to detect pancreatic pathology
- Gastrointestinal endoscopy in presence of alarm features or in patients with persistent symptoms despite initial medical management; Even in the absence of macroscopic disease, appropriate biopsies are taken to exclude eosinophilic esophagitis (dysphagia), *H. pylori* infection (dyspepsia), celiac disease or sprue (dyspepsia, diarrhea), microscopic colitis (diarrhea)
- Abdominal ultrasonography to exclude gall bladder and other abdominal pathology is routine in many European countries; however, diagnostic yield is low unless clinical suspicion of specific disorders is present(142, 143)
- CT should not be routine, especially in young women, to avoid unnecessary exposure to radiation

Box 3 | Open research questions

- The clinical utility of numerical data over pattern recognition in certain tests (e.g. antral motility index in gastroparesis, balloon expulsion and rectoanal pressure gradient in evacuation disorders) requires further study

- Clinical investigations to explain the causes of symptoms in patients with functional gastrointestinal disease might require assessment of gastrointestinal structure, motility and sensation, which generally requires more than one modality of measurement
- Current tests of gastrointestinal sensation require validation; new technology and methodology are under development to facilitate evaluation of visceral sensitivity in routine practice
- Outcome studies are required to assess indications, based on motility measurements, for new therapies (e.g. pyloric botulinum toxin injection, sacral nerve stimulation)
- Although the usefulness of some gastrointestinal function tests on diagnosis and decisions on management have been established, further studies on cost-benefit of physiological measurement in clinical practice are warranted

Table 1 |: Clinical features of organic versus functional disease

Patients with 'organic disease' with diagnosis based on unique pathology on histology or clinical measurement (e.g. neoplasia, inflammation, major motility disorders, severe GERD) and functional gastrointestinal diseases with diagnosis based on characteristic symptoms supported by the absence of unique pathology on investigations (e.g. dyspepsia, IBS).

Clinical features	**Organic disease - cause evident, secondary to defined aetiology**	**Functional disease - cause not evident, probable primary aetiology**
Age	Older (> 45 years)	Younger (< 45 years)
Gender	Equal in men and women	More common in women than men (in caucasian population)
Timing of consent	Defined onset	Poorly defined onset
Symptoms	Specific symptoms - pain rarely prominent	Multiple, diffuse symptoms - pain often prominent
Comorbidities	No other issues	Other functional syndromes common
Psychiatric comorbidities or psychological stress	Equivalent to or slightly elevated compared to the general population	Much more common than the general population
Intolerances	No history of intolerance to medications or diet	Self-reported intolerance to medications and diet
Therapeutic response	Response to specific therapy	Poor response to therapy
Diagnosis and outcome	Doctor and patient usually satisfied with diagnosis and outcome	Doctor and patients often unsatisfied or frustrated with diagnosis and outcome due to non-specific symptoms and lack of specific and effective treatments

Table 2: Clinical investigation of gastrointestinal motility and function

Symptom	**First Investigation**	**Second Investigation**
Pharyngeal Dysphagia *, chronic cough, aspiration, globus sensation	Video Fluoroscopic Swallowing Exam (VFSE), or ENT examination by Fiberoptic Endoscopic Evaluation of the Swallow (FEES)	High-Resolution Manometry (HRM) ± Impedance, ± pH-Impedance-Monitoring (if reflux disease suspected)
Esophageal 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, incl. 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, abdomonal pain, weight loss * (25% with functional disease)	„Nutrient Drink Test“, Gastric emptying study (Scintigraphy, ^{13}C- Breath Test) *strict adherence to standard methodology essential.*	HRM ± Impedance + pH-Impedance-Monitoring (to exclude GERD) Antroduodenojejunal Manometry (to exclude major motility disorders)
Abdominal bloating, chronic diarrhea with suspected small intestinal bacterial overgrowth (SIBO), food intolerance or bile acid diarrhea / 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 fecal bile acid to diagnose bile acid diarrhea 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, wirelesss motility capsule)
Fecal Incontinence	Anorectal HRM, Endoanal ultrasonography	Rectal Barostat

*Alarm Symptom. Endoscopy or imaging should be performed prior to physiological investigation.

‡Caution, Ischemic Heart Disease must be excluded prior to physiological investigation. ENT, ear, nose and throat.

Figure 1: Gastrointestinal Symptoms of functional gastrointestinal disease. Note that overlap between different areas of the GI tract and symptoms can exist.

Figure 2: Management algorithm for patients with functional gastrointestinal symptoms.

Figure 3: Example of Esophageal High-Resolution Manometry with Impedance

Esophageal motility is assessed by manometry with pressure represented by colors (see scale on right (mmHg)). Esophageal function is assessed by impedance measurements that detect the passage of fluid or food from the pharynx to the stomach (purple superimposed on manometry image). The water swallows show normal motility and function as assessed by the Chicago Classification system. Esophageal spasm occurs with the test meal and impedance shows retention of solids in the proximal esophagus. This bolus retention is cleared during rapid drink challenge with no evidence of EGJ outlet obstruction (or achalasia).

Figure 4: Example high-resolution anorectal manometry and endoanal ultrasonography in health and faecal incontinence. High-Resolution Anorectal Manometry (upper panel) and Endoanal Ultrasonography scans (lower panel) are shown. The structure and function of the healthy anal sphincter is shown in a volunteer (left). The muscle layers of the internal and external anal sphincter are clearly demonstrated on ultrasonography. Baseline pressure is maintained by tonic contraction of the internal sphincter. There is a rapid increase in pressure during voluntary squeeze contraction of the external sphincter. Note that the external sphincter extends below the internal sphincter, and this facilitates return of any stool in the anal canal to the rectum. The structure and function of the anal sphincter is disrupted in a patient with fecal incontinence following an obstetric injury (right). There is an acute tear in the external sphincter indicated by white lines at 12 and 2'o-clock positions. This is associated with failure to increase pressure during voluntary „squeeze" seen in the corresponding manometry image. Continence function was restored following surgical sphincter repair.

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Author contributions

All authors researched data for the article, made substantial contributions to discussion of content and reviewed or edited the manuscript before submission. M.F. wrote the article.

Competing interests statement

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