Prior Authorization Review Panel  
MCO Policy Submission

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<th>Plan: Aetna Better Health</th>
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**Type of Submission – Check all that apply:**

- [ ] New Policy
- [X] Revised Policy*
- [ ] Annual Review – No Revisions
- [ ] Statewide PDL

*All revisions to the policy must be highlighted using track changes throughout the document.

Please provide any clarifying information for the policy below:

**CPB 0396 Gastrointestinal Function: Selected Tests**

This CPB has been revised to state that gastric emptying breath tests (GEBT) are considered experimental and investigational for gastroparesis and for all other indications because of insufficient evidence of its effectiveness.

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<th>Name of Authorized Individual (Please type or print):</th>
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<td>Dr. Bernard Lewin, M.D.</td>
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Aetna considers the use of colonic motility studies (colonic manometry) medically necessary to guide decision-making for surgery in children with refractory colonic motility / defecatory disorders.

Aetna considers radionuclide gastric emptying study medically necessary for the evaluation of gastrointestinal motility disorders, and gastroparesis.

Aetna considers magnetic resonance enterography medically necessary to evaluate and monitor Crohn's disease and other small bowel disorders.

Aetna considers electrogastrography experimental and investigational because its clinical utility has not been established.

Aetna considers high resolution esophageal pressure topography (HREPT) experimental and investigational because its clinical utility has not been established.

Aetna considers a wireless capsule for measuring gastric emptying parameters (SmartPill GI Monitoring System) experimental and investigational for the evaluation of gastric disorders (e.g., gastroparesis), intestinal motility disorders (e.g., chronic constipation), and all other indications

*Please see amendment for Pennsylvania Medicaid at the end of this CPB.*
because of inadequate published evidence of its diagnostic performance and clinical utility over conventional means of measuring gastric emptying.

Aetna considers the gastric emptying breath test (GEBT) experimental and investigational for gastroparesis and for all other indications because of insufficient evidence of its effectiveness.

Aetna considers 3D high-resolution manometry for quantification of esophago-gastric junction contractility experimental and investigational because its clinical utility has not been established.

See also: CPB 0616 - Gastrointestinal Manometry (../600_699/0616.html) and CPB 0691 - Exhaled Breath Tests (../600_699/0691.html).

Background
There are several tests that have been trialed for the evaluation and diagnosis of transit and motility disorders of the gastrointestinal (GI) tract. The gold standard and most commonly performed test to evaluate gastric emptying is gastric scintigraphy, a radionuclide gastric emptying study used for the evaluation of gastrointestinal motility disorders, and gastroparesis. Colonic motility studies (colonic manometry) can help guide decision-making for surgery in children with refractory colonic motility / defecatory disorders. Magnetic resonance enterography is used to evaluate and monitor Crohn's disease and other small bowel disorders. However, there are alternative methods, such as electrogastrography, wireless motility capsule (WMC), high resolution esophageal pressure topography (HREPT), and 3D high-resolution manometry, that have been also been considered for use in the evaluation and diagnosis of GI function.

Colonic motility studies are used to assess the flow of intraluminal contents, the motions of the colonic wall that induce flow, and the control systems that integrate and regulate these processes. The approaches employed have consisted of manometric techniques to record colonic contractions, barostatic methods to measure colonic tone, and recordings of myoelectric signals from the colon that initiate and control muscular contractions. However, the study of colonic motility in a clinical setting proves to be difficult. Accurate positioning of the probes via colonoscopy requires pre-procedure cleansing of the colon, which raises the possibility of altered physiology. Recording of intra-luminal pressure, by means of manometric catheters inserted per rectum, requires prior bowel cleansing, which may modify colonic motility. In contrast to other segments of the gastro-intestinal tract, contents move through the colon in hours or days, instead of seconds to minutes; thus, prolonged observations are needed. Moreover, in contrast
to the upper gastro-intestinal tract, in which reliable manometric recordings can be obtained, the larger diameter of the colon hinders the accurate detection of manometric events. Furthermore, interpretation of intra-luminal pressure measurements is complicated, because many contractions of the colonic wall do not occlude the lumen and therefore are detectable by manometry only if they cause significant pressure changes. And finally, all of these techniques, which continue to be used extensively in a research context, have not yet been standardized for routine clinical use.

Ghoshal et al (2007) stated that constipation is a common problem, which may be due to slow transit or fecal evacuation disorders. Though the screening test of colonic transit study using radio-opaque markers given at 0, 24 and 48 hours followed by abdominal X-ray at 72 hours is a good protocol in the West, it is not suitable for Indians who have a rapid gut transit. Nine patients with adult Hirschsprung disease, 11 with chronic intestinal pseudo-obstruction diagnosed using standard investigations and 11 healthy subjects were evaluated by colonic transit study using radio-opaque markers (SGmark), 20 each at O, 12 and 24 hours followed by an abdominal X-ray at 36 and 60 hours. The cut-off was determined by using receiver operating characteristic (ROC) curves, and sensitivity, specificity, positive and negative predictive values and diagnostic accuracy were determined. The total number of markers retained in the abdomen and those in the right segment at 36 hours in patients with Hirschsprung disease and chronic intestinal pseudo-obstruction was higher than that in healthy subjects though the number in the left and rectosigmoid segments were comparable. The abdominal X-ray at 60 hours, total number of markers and number in all segments were higher in patients with Hirschsprung disease and chronic intestinal pseudo-obstruction than in healthy subjects. The best cut-off by ROC curves at 36 and 60 hours was 30 and 14 markers, respectively. The sensitivity, specificity, positive and negative predictive values, diagnostic accuracy and area under the ROC curve at 36 hours were 90 %, 82 %, 90 %, 82 %, 87 % and 0.9, respectively; the corresponding values at 60 hours were 95 %, 100 %, 100 %, 92 %, 97 % and 0.99, respectively. The authors concluded that using the proposed protocol, the colonic transit study is able to distinguish patients with specific motility disorders causing constipation such as Hirschsprung disease and chronic intestinal pseudo-obstruction from healthy subjects with reasonable sensitivity and specificity, and shows that an abdominal X-ray at 60 hours is better than one at 36 hours. This was a small study reporting a moderate sensitivity and specificity of the colonic transit study; its findings need to be validated.

In a review on radionuclide gastro-esophageal motor studies, Mariani et al (2004) noted that radionuclide transit/emptying scintigraphy provides a means of characterizing exquisite functional abnormalities with a set of low-cost procedures that are easy to perform and widely available, entail a low radiation burden, closely reflect the physiology of the tract under evaluation, are well-tolerated and require minimum cooperation by patients, and provide
quantitative data for better inter-subject comparison and for monitoring response to therapy. Despite the relatively low-degree of standardization both in the scintigraphic technique per se and in image processing, these methods have shown excellent diagnostic performance in several function or motility disorders of the upper digestive tract. Dynamic scintigraphy with a radioactive liquid or semi-solid bolus provides important information on both the oropharyngeal and the esophageal phases of swallowing, thus representing a useful complement or even a valid alternative to conventional invasive tests (e.g., stationary esophageal manometry) for evaluating abnormalities of oropharyngo-esophageal transit. Clinical applications of esophageal transit scintigraphy include disorders such as nutcracker esophagus, esophageal spasm, non-cardiac chest pain of presumed esophageal origin, achalasia, esophageal involvement of scleroderma, and gastro-esophageal reflux and monitoring of response to therapy. Scintigraphy with a radiolabeled test meal represents the gold standard for evaluating gastric emptying, whereas more recent radionuclide methods include dynamic antral scintigraphy and gastric SPECT for assessing gastric accommodation. Clinical applications of gastric-emptying scintigraphy include, among others, evaluation of patients with dyspepsia and evaluation of gastric function in various systemic diseases affecting gastric emptying.

Maurer and Parkman (2006) stated that nuclear medicine offers a variety of studies for evaluating motility throughout the gastrointestinal tract. Gastric emptying remains the "gold standard" for studying gastric motor function, but its application in most centers remains limited to measuring only total gastric emptying in spite of data that show assessment of both fundal and antral function is of clinical value for evaluating patients with dyspepsia. Smith and Ferris (2003) noted that the diagnosis of diabetic gastroparesis may be confirmed by demonstrating gastric emptying delay during a 4-hr scintigraphic study. This is in agreement with the report by Stassen (2005) who noted that the diagnosis of diabetic gastroparesis may be confirmed by scintigraphy assessment of gastric emptying, preferably using a solid meal. Feigenbaum (2006) stated that the gold standard for the diagnosis of gastroparesis is a gastric emptying study. Furthermore, the AGA's medical position statement on diagnosis and treatment of gastroparesis (Parkman et al, 2004) stated that gastric emptying scintigraphy of a radiolabeled solid meal is the best accepted method to test for delayed gastric emptying.

Ziessman and associates (2009) examined if a study of clear liquid gastric emptying has added value for the diagnosis of gastroparesis over a study of solid emptying alone. A total of 101 patients underwent both solid and liquid gastric-emptying studies, acquired sequentially on the same day. A 30-min (1-min frames) liquid study (300 ml of water with 7.4 MBq [0.2 mCi] of (111)In-diethylenetriaminepentaacetic acid) was followed by a standardized 4-hr solid-meal study (a (99m)Tc-sulfur colloid-labeled egg-substitute sandwich meal). Emptying was quantified as a best-fit exponential emptying rate (T1/2) for liquids and percentage emptying at 4 hrs for solid emptying. A total of 30 healthy volunteers underwent a study of clear liquid emptying to establish
normal values. The results of the liquid and solid studies were compared. (111)In liquid
downscatter into the subsequent (99m)Tc solid meal results was analyzed. The upper range of
normal for clear liquid emptying (T1/2) for healthy volunteers was 22 mins (mean +/- 3 SDs) and
19 mins (mean +/- 2 SDs). Of 101 patients, delayed emptying was found in 36 % of liquid and
16 % of solid studies. Of all patients with normal solid emptying, 32 % had delayed liquid
emptying. (111)In downscatter into the (99m)Tc window was not generally significant. The
authors concluded that for the detection of gastroparesis, a 30-min study of clear liquid gastric-
emptying has considerable added diagnostic value over a study of solid emptying alone.

Hyett et al (2009) evaluate the prognostic value of gastric emptying studies on the morbidity
associated with diabetic gastroparesis. This was a parallel cohort study of 3 groups. Group A (n
= 94) contained diabetics (type 1 and type 2) with classic symptoms of gastroparesis (including
early satiety, post-prandial fullness, bloating, abdominal swelling, nausea, vomiting, and retching)
and delay in radionucleotide gastric emptying study. Group B (n = 94) contained diabetic
subjects with classic symptoms of gastroparesis but negative scintigraphy. Group C (n = 94)
contained diabetic subjects without symptoms of gastroparesis. Data were gathered on the
number of days hospitalized and hospitalizations, office visits, emergency department (ED) visits,
death rate, glycosylated hemoglobin levels (HbA1c), medications and past medical history.
Group A had significantly more hospital days per 1,000 patient days (25.5) than both Group B
(5.1; p < 0.01) and Group C (2.3; p < 0.01). Group A also had significantly more hospitalizations,
office visits and ED visits than both Group B and Group C. Deaths and mean HbA1c level did
not differ between the groups. Group A patients were more likely to have cardiovascular disease
(19.2 % versus 6.4 % A versus C; p < 0.05), hypertension (63 % versus 43 % A versus C; p =
0.005) and retinopathy (33 % versus 11.7 % A versus C; p < 0.001). The authors concluded
that a delayed radionucleotide gastric emptying study predicts negative health outcomes in
diabetics with symptoms of gastroparesis. They identified a correlation between diabetic
gastroparesis and cardiovascular disease, hypertension and retinopathy which may indicate an
underlying vascular etiology.

Tipnis et al (2012) compared oro-anal transit time (OTT) measured by radio-opaque markers
with colon motility (CM) findings in children with chronic constipation and evaluated clinical
outcomes in children with chronic constipation evaluated by OTT and CM studies. A total of 24
children with chronic constipation (12 girls; median age of 12 years [3 to 18 years]; median
symptoms of 87 months [6 to 186 months]) who underwent OTT and CM studies were reviewed.
The OTT was determined using commercially available Sitzmarks. Patients were studied for a
median of 23 months (4 to 60 months) and outcomes reviewed. All 5 children with normal OTT
had normal CM; however, only 47 % (9/19) of children with slow OTT had an abnormal CM. The
abnormal CM findings were total colonic pseudo-obstruction in 3 and left colonic pseudo-
obstruction in 6 children. Of the 9 children with abnormal CM, 5 were managed surgically, 1 with
medicine escalation, and 3 were lost to follow-up; all 6 children with known follow-up have more bowel movements and less soiling. Of the 15 children with normal CM, 10 were managed with medication escalation, 3 with behavioral intervention, and 2 surgically. Of these 15 children, 8 improved, 1 did not change, 2 worsened, and 4 were lost to follow-up. The authors concluded that OTT studies may be helpful to predict which children should be referred for CM studies. Normal OTT studies may predict normal colon manometry; however, abnormal OTT studies may not predict abnormalities in colonic manometry in children with chronic constipation. Therefore, patients with slow transit marker studies should be assessed by colon manometry to evaluate colon neuromuscular integrity. This study did not evaluate the impact of colon manometry for patient management or disease outcomes.

Conklin (2013) stated that for several decades esophageal manometry has been the test of choice to evaluate disorders of esophageal motor function. The recent introduction of high-resolution manometry for the study of esophageal motor function simplified performance of esophageal manometry, and revealed previously unidentified patterns of normal and abnormal esophageal motor function. Presentation of pressure data as color contour plots or esophageal pressure topography led to the development of new tools for analyzing and classifying esophageal motor patterns. The current standard and still developing approach to do this is the Chicago classification. The author concluded that while this methodical approach is improving the diagnosis of esophageal motor disorders, it currently does not address all motor abnormalities.

Vela (2014) stated that treatment options for achalasia include oral pharmacologic therapy, endoscopic injection of botulinum toxin, pneumatic dilation, and myotomy (conventionally by laparoscopy, but more recently by an endoscopic approach). Oral pharmacologic agents have fallen out of use because of insufficient efficacy and frequent side effects. Endoscopic injection of botulinum toxin is safe and has good short-term effectiveness, but as the effect invariably wears off after a few months, this treatment is reserved for patients who are not candidates for more definitive treatments. Pneumatic dilation and surgical myotomy are currently considered the most effective treatments, with similar effectiveness in randomized controlled trials (RCTs) with follow-up of up to 2 years. The risk/benefit ratio and choice of therapy depend on patient characteristics (e.g., age, co-morbidities, disease stage, prior treatments), patient's preference, and locally available expertise. Treatment of patients who fail or relapse after initial therapy is challenging and the success rate of pneumatic dilation or myotomy in this group is lower compared with previously untreated patients. The recently developed per-oral endoscopic approach to myotomy has achieved excellent results in early uncontrolled studies, but high-quality RCTs are needed to ensure widespread adoption is reasonable. The authors also noted that retrospective data suggested that achalasia subtypes as defined by HREPT may guide treatment choice, but confirmation in prospective outcome studies is awaited.
Rao et al (2011) noted that scintigraphy is recommended for detection of altered small intestinal transit in subjects with suspected diffuse GI motility disorder but is available in a limited number of centers.

The Society of Nuclear Medicine and Molecular Imaging (SNMMI) and the European Association of Nuclear Medicine (EANM)’s practice guideline for small-bowel and colon transit (Maurer et al, 2013) noted that “A position paper from the American Neurogastroenterology and Gastrointestinal Motility Society and the European Society of Neurogastroenterology and Motility states that scintigraphy is recommended for “detection of altered small-intestine transit in subjects with suspected diffuse gastrointestinal motility disorder” and that colon transit scintigraphy “offers reproducible and accurate performance,” as it measures whole-gut and regional colon transit in patients with suspected colonic motility disorders or more diffuse disorders involving the stomach or small intestine”.

Kuribayashi et al (2015) note that recently reported normal values for esophageal motility obtained by high-resolution manometry (HRM) using a system with a Unisensor catheter were significantly different from those obtained by the ManoScan, which could result in a wrong diagnosis. To clarify whether these differences were due to system or subject differences, these investigators compared the manometric parameter values between ManoScan and a new system with a Unisensor catheter (Starlet) in the same subjects. A total of 103 volunteers without any symptoms related to esophageal motility disorders were recruited. Esophageal HRM was performed using both the ManoScan and the Starlet in all subjects. Data from the ManoScan were analyzed using ManoView, and data from the Starlet were analyzed by a program with e-sleeve function. Integrated relaxation pressure, distal contractile integral, contractile front velocity (CFV), intra-bolus pressure, and distal latency were calculated by both analyzing programs, and the values of these parameters were compared between the 2 systems by a signed rank test. Data from a total of 97 participants were analyzed. The values of all parameters, except CFV, measured by the Starlet were significantly higher than those obtained by the ManoScan (p < 0.01). The authors concluded that both systems can measure esophageal motility appropriately; nevertheless, they confirmed that the 2 systems showed different values of the parameters defined by the Chicago criteria; these differences should be recognized to evaluate esophageal motility precisely.

Herregods et al (2015) stated that esophageal HRM has rapidly gained much popularity worldwide. The Chicago Classification for esophageal motility disorders is based on a set of normative values for key metrics that was obtained using one of the commercially available HRM systems. Thus, it is of great importance to evaluate whether these normative values can be used for other HRM systems as well. In this review, these investigators described the presently available HRM systems, the currently known normative thresholds and the factors that influence
them, and evaluated the use of these thresholds. Numerous factors including the type of HRM system, demographic factors, catheter diameter, body position during testing, consistency of bolus swallows, and esophageal length have an influence on the normative data. It would thus be ideal to have different sets of normal values for each of these factors, yet at the moment the amount of normative data is limited. The authors suggested broadening the normal range for parameters, as this would allow abnormal values to be of more significance. In addition, they suggested conducting studies to examine the physiological relevance of abnormal values and stress that for each system different normative thresholds may apply.

The American College of Gastroenterology’s clinical guideline on “Management of gastroparesis” (Camilleri et al, 2013) noted that “Alternative approaches for assessment of gastric emptying include wireless capsule motility testing and 13C breath testing using octanoate or spirulina incorporated into a solid meal; they require further validation before they can be considered as alternates to scintigraphy for the diagnosis of gastroparesis”. (Conditional recommendation, moderate level of evidence).

An UpToDate review on “Approach to the adult with nausea and vomiting” (Longstreth, 2014) states that “Gastroparesis -- Nausea may be a feature of gastroparesis but there is a poor correlation among symptoms, gastric dysrhythmias, and gastric emptying rate. Gastric motor dysfunction can be identified by special tests (such as gastric scintigraphy) in a large proportion of these patients. A noninvasive method of recording gastric myoelectrical activity or slow waves from cutaneous leads placed over the stomach (electrogastrography) reveals abnormalities in some patients. There is no evidence that correction of these abnormalities improves symptoms; thus, the role of this procedure in management is uncertain”.

**Electrogastrography**

Cutaneous electrogastrography (EGG) is a non-invasive test that detects gastric arrhythmias by recording the frequency and regularity of gastric myoelectrical activity. It has been used to investigate the mechanisms of gastric motility and sensation in patients with gastric motility disorders or motion sickness. By means of surface electrodes, EGG records gastric myoelectrical activity from the surface of the body. The cutaneous signals are low in amplitude, and thus must be markedly amplified. The resultant signals are heavily contaminated with noise, and visual analysis alone of EGG signals is inadequate. Consequently, EGG recordings require special methodology for acquisition, processing and analysis.

There appears to be a close relationship between gastric myoelectrical activity and gastric motility. Although it has been reported that EGG satisfactorily reflects frequency of internal gastric myoelectrical activity, there is not acceptable correlation with gastric contractions or
gastric emptying. Many attempts have been made to relate EGG “abnormalities” with clinical syndromes and diseases. Although abnormalities of the electrogastrogram have been described in a variety of disorders, their specificity and their prevalence in patients with functional gastrointestinal disorders have not been determined. Electrogastrography cannot determine the etiology of detected abnormalities because there are no specific EGG patterns to differentiate one epigastric condition from another. The clinical role of EGG remains to be established, and its proponents need to demonstrate that EGG results can affect therapeutic decisions.

An American Gastroenterological Association guideline on nausea and vomiting (AGA, 2001) concluded that “the place of such tests of motor function as gastric emptying studies, electrogastrography, and manometry have not been defined, and the yield of such diagnostic studies has not been adequately compared with a therapeutic trial of an antiemetic and/or prokinetic agents.” An American Gastroenterological Association guideline on constipation (AGA, 2000) stated that colonic manometry “is not generally available and is not appropriate for most patients, except in research settings.” The consensus opinion of the American Motility Society Clinical GI Motility Testing Task Force on the performance and clinical utility of EGG (Parkman et al, 2003) stated that no therapies have convincingly demonstrated in controlled studies that correcting abnormalities detected by EGG improves upper gastrointestinal symptoms. Proposed clinical indications for performance of EGG in patients with unexplained nausea, vomiting and dyspeptic symptoms must be validated by prospective controlled investigations.

In an editorial on EGG, Verhagen (2005) stated that because of its low sensitivity and specificity, EGG can not be used as a diagnostic clinical tool. In certain diseases, EGG may be useful in defining a subgroup of patients. However, at present there is no evidence to support a role for EGG in the diagnostic work-up of patients or in directing therapy.

Abid and Lindberg (2007) examined if there is a correlation between electrical activity measured by EGG and contractile activity of the stomach as measured by antro-duodenal manometry (ADM). These researchers also studied if the underlying motility disorder could be predicted from EGG parameters. They compared 21 parameters measured from EGG with 8 parameters measured from ADM. The ability of EGG to identify the underlying diagnosis was tested by comparing EGG parameters for each diagnosis group against other patients. The study comprised recordings from 148 patients (125 females). Their median age was 45 years (range of 17 to 76). These investigators found few and weak correlations between EGG and ADM. Specifically the correlation between parameters reflecting the response to meal was poor ($r = -0.07, p = 0.39$). The discriminatory power of EGG for underlying motility disorder was also low. Patients with slow transit constipation (STC) showed a lower post-prandial power in normogastric (3.7 +/- 0.5 versus 4.0 +/- 0.5) and tachygastriac (3.5 +/- 0.4 versus 3.7 +/- 0.4)
regions, a lower percentage of time with normogastria [87.2 % (56.5 to 100) versus 95.7 % (0 to 100)], and a higher percentage of time with tachygastria [9.3 % (0 to 33) versus 3.5 (0 to 100)] and bradygastria [1.8 % (0 to 20) versus 0 % (0 to 17.1)]. Patients with irritable bowel syndrome had a higher percentage of time with normogastria [96.5 % (62.5 to 100) versus 93.3 % (0 to 100)] and a less unstable dominant frequency as measured by the instability coefficient [15 (3 to 77) versus 24 (2 to 72)]. The authors concluded that EGG and ADM seem to measure different aspects of gastric motor activity but can not show a spatial correlation. The diagnostic value of EGG is poor, but EGG may have some value for the identification of patients with STC.

It should also be noted that the AGA's medical position statement on diagnosis and treatment of gastroparesis (Parkman et al, 2004) does not mention the use of electrogastrography.

Krusiec-Swidergol and Jonderko (2008) checked on reproducibility of parameters of a multi-channel electrogastrogram in adults after intake of typical, applied in EGG, test meals. Recordings of multi-channel electrogastrograms were accomplished in 4 blocks comprising 18 subjects (9 healthy volunteers and 9 patients with functional gastro-intestinal disorders) each. Every subject had 2 examinations taken 1 to 2 days apart, and a 3rd one was accomplished at least 2 weeks before or after the 2 other sessions. The registration involved a 30-min fasted and a 2-hr post-prandial period after one of the meal stimuli tested within a given block: 400 ml water, 400 g yoghurt (378 kcal), a scrambled eggs sandwich (370 kcal), a pancake (355 kcal). From among the parameters reflecting the propagation of the gastric slow waves, the average percentage of slow wave coupling (APSWC) exhibited a good (coefficient of variation for paired examinations CV(p) less than or equal to 10 %) to moderate (10 less than CV(p) less than or equal to 30 %) reproducibility. On the other hand, the reproducibility of the maximum dominant frequency difference and the spatial dominant power difference was found to be unsatisfactory. The reproducibility of the multi-channel EGG parameters did not differ between healthy volunteers and patients with functional gastrointestinal disorders. Gender or the kind of a test meal did not affect the reproducibility of the EGG parameters either. The medium-term reproducibility was not any worse than the short-term one. From among the parameters of a multi-channel EGG intended to quantify the propagation of slow waves, only the APSWC offers a reproducibility potentially good enough for clinical applications.

Calder and colleagues (2017) stated that routine screening and accurate diagnosis of chronic GI motility disorders represents a significant problem in current clinical practice. Electrogastrography (EGG) provides a non-invasive option for assessing gastric slow waves, as a means of diagnosing gastric dysrhythmias, but its uptake in motility practice has been limited partly due to an incomplete sensitivity and specificity. These investigators presented the development of a human whole-organ gastric model to enable virtual (insilico) testing of gastric electrophysiological dispersion in order to improve the diagnostic accuracy of EGG. The model
was developed to simulate normal gastric slow wave conduction as well as 3 types of
dysrhythmias identified in recent high resolution gastric mapping studies: (i) conduction block,
(ii) re-entry, and (iii) ectopic pace-making. The stomach simulations were then applied in a
torso model to identify predicted EGG signatures of normal and dysrhythmic slow wave profiles.
The resulting EGG data were compared using percentage differences and correlation
coefficients. Virtual EGG channels that demonstrated a percentage difference over 100 % and a
correlation coefficient less than 0.2 (threshold relaxed to 0.5 for the ectopic pace-maker case)
were further investigated for their specific distinguishing features. In particular, anatomical
locations from the epigastric region and specific channel configurations were identified that could
be used to clinically diagnose the 3 classes of human gastric dysrhythmia. The authors
concluded that these locations and channels predicted by simulations present a promising
methodology for improving the clinical reliability and applications of EGG.

An UpToDate review on “Overview of gastrointestinal motility testing” (Lembo, 2017) states that
“Specialized motility tests such as antroduodenal manometry and electrogastrography are not
widely performed and their role in clinical practice has not been well established”.

Poscente and Mintchev (2017) attempted to enhance the clinical utility of EGG, which has been
recorded since 1922, but is clinically un-utilized. An innovative method to salvage the promise of
EGG was proposed by introducing a preliminary procedure, while maintaining the electrodes,
standardized equipment, and signal processing utilized in the well-established EGG testing of
today. The proposed enhanced EGG (EEGG) protocol involves swallowing an ingestible capsule
containing miniature electronic oscillator embedded in an expandable, self-disintegrable,
biocompatible pseudobezoar residing in the stomach for the duration of the test. Experiments
were performed on 8 mongrel dogs (23.8 ± 3.3 kg); 4 were administered an active EEGG
capsule, while the rest were given a de-activated (battery removed) capsule. Pharmacologically
facilitated gastric motility revealed a significant (p < 0.01) Pearson correlation between gastric
motility indices obtained by force transducers implanted directly on the stomach, and the motility
indices obtained by EGG. A particular emphasis was made on preserving standard EGG-
related hardware and software in order to facilitate the introduction of the proposed EGG in
environments that already utilize standard EGG testing. The expanded intra-gastric
pseudobezoar containing the miniature electronic oscillator was retained during the tests, and
could be disintegrated on demand. The authors concluded that EGG is a new modality to
record reliably and non-invasively gastric motility utilizing the same recording setup used in
present-day plain EGG. Its clinical utilization promises to revive a non-invasive gastric testing
that is fading in oblivion.
The authors stated that as with any innovative idea, a lot more needs to be done before this radically new approach in the non-invasive ambulatory assessment of gastric motility becomes a reliable clinical tool for diagnosing gastric dyspepsia and/or gastroparesis. First and foremost, the clinical community should clearly defend and loudly support the need for such a single, non-invasive and inexpensive test. Second, controlled clinical trials on humans should take place in order to explicitly show the real diagnostic value of such testing, including its sensitivity and specificity. Third, the existing EGG insurance codes should be re-visited so that the routine EGG is replaced by EEGG and it enters the clinical mainstream, rather than remain forever “a research tool” of little consequence, administered free of charge only now and again and here and there by curious investigators.

Ortigoza and associates (2018) obtained objective measures indicative of GI maturity using 3 non-invasive technologies -- EGG, abdominal near-infrared spectroscopy (NIRS), and bowel sound/acoustics (AC) monitoring. These 3 approaches were used simultaneously to obtain physiologic measures of the GI system of 18 preterm and 5 term neonates who were tolerating enteral feedings. Measures of EGG slow wave voltage (EGG dominant power) and AC signal amplitude (AC dominant power) were obtained after spectral density analysis. Mean abdominal regional saturations (A-rSO2) were obtained directly from NIRS. The relationship of these 3 measures with post-menstrual age (PMA) was assessed. The results of the 3 methods differed depending on whether the measurements were pre-prandial or post-prandial. Post-prandial EGG dominant power increases with PMA (r=0.67, p=0.003), both pre- and post-prandial abdominal NIRS mean regional saturation increase with PMA (r=0.73, p<0.001 and r=0.55, p=0.025). The authors concluded that EGG, abdominal NIRS, and AC, when used simultaneously, can provide objective and synergistic measures that correlate with PMA. They stated that these findings may be helpful in the assessment of feeding readiness because they reveal quantitative measures suggestive of the developmental process of the gut. These preliminary findings need to be validated by well-designed studies.

Lim and colleagues (2018) stated that minimal change esophagitis (MCE) is a reflux disease without mucosal breaks, known to be partially associated with abnormal gastric motor function; EGG is used to assess gastric motor function in a non-invasive fashion. These investigators determined the relationship between MCE and gastric myo-electrical activity (GME) recorded on EGG in children. They retrospectively assessed the records of 157 children without underlying disease who underwent both EGG and upper GI endoscopy between January 2010 and June 2015. The children were stratified according to the appearance of the esophagus (normal versus MCE). Between-group differences in EGG parameters and their correlation with each MCE finding were statistically analyzed. Only the power ratio, 1 of the EGG parameters analyzed, differed significantly between the 2 groups (MCE, 1.68 ± 3.37 versus normal, 0.76 ± 1.06; p <
0.05), whereas the other parameters, such as dominant frequency, dominant power, and the ratio of abnormal rhythm, showed no differences. Among children with MCE, significant correlations were noted between erythema and power ratio (p < 0.05), friability and post-prandial dominant frequency (p < 0.05), and edema and/or accentuation of mucosal folds and pre-prandial frequency (p < 0.05). Helicobacter pylori (H. pylori) infection correlated with post-prandial arrhythmia (MCE, 33.59 ± 15.52 versus normal, 28.10 ± 17.23; p < 0.05); EGG parameters did not differ between children with normal esophagus and those with biopsy-proven chronic esophagitis. The authors concluded that in children with MCE, gastric dysmotility may affect the development of MCE, manifesting as EGG abnormalities; H. pylori infection may also affect GME. Moreover, they stated that larger prospective investigations are needed to confirm these findings.

The authors stated that this study had several drawbacks. First, the group of children with MCE was significantly larger than the group of children with normal esophagus, and the age distribution of the 2 groups was also significantly different. This drawback was associated with the retrospective, single-center design of this study. Second, these investigators only measured the correlation of each EGG parameter with each endoscopic finding, and did not consider any objective measures of disease severity. Third, the exact relevance of each EGG parameter remained unclear. Moreover, these researchers did not assess the correlation between EGG parameters and endoscopic findings in children with normal esophagus. Fourth, although 24-hour esophageal pH monitoring represents a good evaluation for the diagnosis of GERD of non-erosive type (NERD), they could not perform 24-hour esophageal pH monitoring in this study because of the reluctance of the pediatric patients and their parents. Finally, there was no follow-up evaluation of children with MCE after treatment. The authors stated that further in-depth studies with prospective design and larger sample size, and covering several age groups, are necessary. Specifically, a study on whether the severity of symptoms, recurrence, medication, or other medical conditions and evaluations are reflected in EGG parameters would be helpful.

An UpToDate review on “Gastroparesis: Etiology, clinical manifestations, and diagnosis” (Camilleri, 2018) states that electrogastrograms have been used in patients with gastroparesis but are predominantly as research tools. Its role in clinical practice has not been defined.

Colonic Motility Studies

Dinning and colleagues (2016) noted that the past few years have seen an increase in the number of research and clinical groups around the world using high-resolution manometry (HRM) to record contractile activity in the anorectum and colon. Yet despite the uptake and growing number of publications, the clinical utility and potential advantages over traditional...
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manometry remain undetermined. Nearly all of the publications in the field of anorectal and colonic HRM have been published within the last 3 years. These studies have included some data on normal ranges in healthy adults, and abnormalities in patient groups with constipation or fecal incontinence, anal fissure, perineal descent, rectal cancer, and Hirschsprung's disease. Most of the studies have been conducted on adults, with only 3 published studies in pediatric populations. Very few studies had attempted to show advantages of HRM over traditional manometry. The authors concluded that high-resolution anorectal and colonic manometry provided a more comprehensive characterization of motility patterns and coordinated activity; this may help to improve the understanding of the normal physiology and pathophysiology in these regions. To-date, however, no published study has conclusively demonstrated a clinical, diagnostic, or interventional advantage over conventional manometry.

An UpToDate review on “Etiology and evaluation of chronic constipation in adults” (Wald, 2017) states that “Colonic manometry evaluates intraluminal pressure activity of the colon and rectum and provides detailed information about the qualitative aspects such as pattern of motor activity and quantitative aspects of colonic motility. It can be combined with a barostat apparatus to assess colonic tone, compliance, and sensation. Patients can be identified to have normal, myopathic, or neuropathic colon as well as sensory dysfunction. As yet, there is no evidence that such information has added value to the management of chronic constipation in clinical practice and this test is available for clinical use in only selected centers”.

Jaung and colleagues (2017) stated that abnormal colonic pressure profiles and high intraluminal pressures are postulated to contribute to the formation of sigmoid colon diverticulosis and the pathophysiology of diverticular disease. These investigators reviewed the evidence for abnormal colonic pressure profiles in diverticulosis. All published studies investigating colonic pressure in patients with diverticulosis were searched in 3 databases (Medline, Embase, Scopus). No language restrictions were applied. Any manometry studies in which patients with diverticulosis were compared with controls were included. The Newcastle-Ottawa Quality Assessment Scale (NOS) for case-control studies was used as a measure of risk of bias. A cut-off of five or more points on the NOS (fair quality in terms of risk of bias) was chosen for inclusion in the meta-analysis. A total of 10 studies (published 1962 to 2005) met the inclusion criteria. The studies followed a wide variety of protocols and all used low-resolution manometry (sensor spacing range 7.5 to 15 cm); 6 studies compared intra-sigmoid pressure, with 5 of 6 showing higher pressure in diverticulosis versus controls, but only 2 reached statistical significance. A meta-analysis was not performed as only 2 studies were above the cut-off and these did not have comparable outcomes. The authors concluded that this systematic review of manometry data showed that the evidence for abnormal pressure in the sigmoid colon in patients with diverticulosis is weak. Existing studies utilized inconsistent methodology, showed
heterogeneous results and were of limited quality. They stated that higher quality studies using modern manometric techniques and standardized reporting methods are needed to clarify the role of colonic pressure in diverticulosis.

Arbizu and co-workers (2017) evaluated the change in colon manometry (CM) parameters and interpretation comparing results when the study was performed the same day after the motility catheter was placed under anesthesia or the following day. CM catheter was placed with colonoscopy under anesthesia and recorded on day 1 and repeated on day 2. Study parameters including motility index during fasting, post-prandial and post-Bisacodyl challenge phase; gastro-colonic response; number, presence and propagation of high amplitude propagating contractions (HAPCs); and, study interpretation were compared between both the days. Motility index (fasting, post-Bisacodyl phase, p < 0.05), HAPC number (10.1 versus 6.6, p = 0.01) and the proportion of patients having HAPCs (92 % versus 70 %, p = 0.002) was significantly higher on day 2 versus day 1. HAPC propagation improved on day 2 versus day 1 (fully propagated, 49 % versus 37 %; partially propagated, 43 % versus 33 %; absent 8 % versus 30 %). Study interpretation changed from day 1 to day 2. On day 1, 37 % had a normal study and 63 % had an abnormal study. On day 2, all patients with a normal study on day 1 remained normal, and patients with an abnormal study on day 1, 53 % remained abnormal and 47 % had a normal study. The authors concluded that CM parameters were affected the day the catheter was placed with colonoscopy under anesthesia. The number, presence, and propagation of HAPCs were significantly higher/improved on day 2 compared to day 1. Overall, CM interpretation changed from abnormal to normal from day 1 to day 2 in 47 % of the patients.

Tanaka and associates (2018) noted that the prevalence and severity of irritable bowel syndrome (IBS) declines with age, but the cause of this is unknown. In a prospective study, these researchers tested 2 hypotheses: First, autonomic nervous system (ANS) responses to eating and bowel distention, measured by heart rate variability (HRV), differs by age in IBS patients. Second, HRV is correlated with colonic motility and IBS symptoms. A total of 156 Rome III positive IBS patients and 31 healthy controls underwent colonic manometry with bag distention in the descending colon, followed by ingestion of an 810-kcal meal. HRV, evaluated by low frequency (%LF; 0.04 to 0.15 Hz) component, high frequency (%HF; 0.15 to 0.40 Hz) component, and the LF/HF ratio, was measured during colonic distention and after the meal. Motility index and subjective symptom scores were simultaneously quantified. Both colonic distention and eating decreased %HF and increased the LF/HF ratio, and both indices of ANS correlated with age. In IBS patients, %HF negatively correlated with the post-prandial motility index after adjusting for age. The %HF and LF/HF ratios also correlated with psychological symptoms but not bowel symptoms in IBS patients. The authors concluded that these findings suggested that, decreased vagal activity is associated with increase in age and greater post-prandial colonic motility in patients with IBS, which may contribute to post-prandial symptoms.
The authors stated that this study had several limitations. First, blood glucose and lipid levels were not monitored when assessing the response to eating. These changes in metabolism may affect colonic motility, vascular regulation, or emotional state. Total meal calories may also affect colonic motility, but variations in calories consumed were unlikely to contribute to error variance in this study because subjects consumed a standard high-fat meal. Second, the number of male subjects was too small to test for sex differences. A previous study reported sex differences in ANS in IBS patients. However, the findings of this study suggested that age may have a greater impact on HRV than does sex. Third, as the post-hoc analyses, these investigators set 37 years to divide the young and old age groups based on the ratio of LF/HF changes by age, which might be biased. However, misleading conclusions appeared to be unlikely since the post-prandial motor activity significantly correlated with the post-prandial %HF even in all IBS patients. A study previously proposed that QT and RR variability may be different among young (20 to 35 years), middle-aged (40 to 55 years), and elderly (above 60 years) subjects. They stated that further validation studies are needed to confirm the cut-off point by age on autonomic nervous function in patients with IBS.


Rao and associates (2004) stated that the colonic neuromuscular dysfunction in patients with constipation and the role of colonic manometry is incompletely understood. These researchers studied prolonged colonic motility and evaluated its clinical significance; 24-hour ambulatory colonic manometry was performed in 21 patients with slow-transit constipation and 20 healthy controls by placing a 6-sensor solid-state probe up to the hepatic flexure. Quantitative and qualitative manometric analysis was performed in 8-hour epochs; subjects were followed-up for 1 year. Constipated patients showed fewer pressure waves and lower area under the curve (AUC) \( p < 0.05 \) than controls during daytime, but not at night. Colonic motility induced by waking or meal was decreased \( p < 0.05 \) in patients. High-amplitude propagating contractions (HAPCs) occurred in 43 % of patients compared to 100 % of controls and with lower incidence \( 1.7 \) versus \( 10.1, p < 0.001 \) and propagation velocity \( p < 0.04 \). Manometric features suggestive of colonic neuropathy were observed in 10, myopathy in 5, and normal profiles in 4 patients; 7 patients with colonic neuropathy underwent colectomy with improvement. The remaining patients were managed conservatively with 50 % improvement at 1 year. The authors concluded that patients with slow-transit constipation exhibited either normal or decreased pressure activity with manometric features suggestive of colonic neuropathy or myopathy as evidenced by absent HAPC or attenuated colonic responses to meals and waking. These researchers stated that in refractory patients, colonic manometry may be useful in characterizing the underlying pathophysiology and in guiding therapy.
Brown and colleagues (2005) noted that patients with rectal prolapse have abnormal hind-gut motility. These investigators examined the effect of rectal prolapse surgery on colonic motility. A total of 12 patients undergoing sutured rectopexy were studied before and 6 months after surgery by colonic manometry, colonic transit study and clinical assessment of bowel function. The results were compared with those from 7 control subjects. Before surgery, colonic pressure was greater in patients than controls (p < 0.050); controls responded to a meal stimulus by increasing colonic pressure; this increase was absent in patients. After rectopexy, colonic pressure reduced towards control values and patients' colonic pressure response to a meal returned; HAPCs were observed in all controls, but in only 3 patients before and 2 patients after surgery; 3 patients had prolonged colonic transit before and 8 after rectopexy. The authors concluded that patients with rectal prolapse have abnormal colonic motility associated with reduced HAPC activity. Rectopexy reduced colonic pressure; but failed to restore HAPCs, reduce constipation or improve colonic transit.

van den Berg and co-workers (2006) defined the predictive value of colonic manometry and contrast enema before cecostomy placement in children with defecation disorders. Medical records, contrast enema, and colonic manometry studies were reviewed for 32 children with defecation disorders who underwent cecostomy placement between 1999 and 2004. Diagnoses included idiopathic constipation (n = 13), Hirschsprung's disease (n = 2), cerebral palsy (n = 1), imperforate anus (n = 6), spinal abnormality (n = 6), and anal with spinal abnormality (n = 4). Contrast enemas were evaluated for the presence of anatomic abnormalities and the degree of colonic dilatation. Colonic manometry was considered normal when HAPCs occurred from proximal to distal colon. Clinical success was defined as normal defecation frequency with no or occasional fecal incontinence (FI). Colonic manometry was carried out on 32 and contrast enema on 24 patients before cecostomy. At follow-up, 25 patients (78 %) fulfilled the success criteria. Absence of HAPCs throughout the colon was related to unsuccessful outcome (p = 0.03). Colonic response with normal HAPCs after bisacodyl administration was predictive of success (p = 0.03). Presence of colonic dilatation was not associated with colonic dysmotility. The authors concluded that colonic manometry was helpful in predicting the outcome after cecostomy. Patients with generalized colonic dysmotility were less likely to benefit from use of antegrade enemas via cecostomy. Normal colonic response to bisacodyl predicted favorable outcome.

Mugie and colleagues (2013) noted that in adults, colonic manometry and colonic scintigraphy are both valuable studies in discriminating normal and abnormal colonic motility. These researchers compared the diagnostic yield and tolerability of colonic manometry and colonic scintigraphy in children with severe constipation. A total of 26 children (mean age of 11.4 years, 77 % boys) who had received colonic manometry and colonic scintigraphy as part of a colonic motility evaluation were included. Manometry was performed as per department protocol. After
swallowing a methacrylate-coated capsule containing indium-111, images were taken at 4, 24,
and 48 hours, and geometric centers were calculated. Results of both tests were categorized in
3 groups: normal, abnormal function in the distal part of the colon, and colonic inertia. Cohen κ
was used for the level of agreement. Patients and parents completed a questionnaire regarding
their experience. Colonic scintigraphy showed normal transit time in 20 %, delay in the distal
colon in 48 %, and colonic inertia in 32 % of patients. Colonic manometry was normal in 40 %,
abnormal in the distal colon in 40 %, and colonic inertia was diagnosed in 20 %; the κ score was
0.34. All 5 patients with colonic inertia during manometry had a similar result by scintigraphy; 88
% of patients preferred scintigraphy over manometry and 28 % of parents preferred colonic
manometry over scintigraphy. The authors concluded that colonic manometry and colonic
scintigraphy had a fair agreement regarding the categorization of constipation; scintigraphy was
well-tolerated in pediatric patients and may be a useful tool in the evaluation of children with
severe constipation.

Liem and associates (2014) stated that colonic manometry is used in evaluating children with
defecation disorders unresponsive to conventional treatment. The most commonly reported
protocol in pediatrics consists of a study that lasts approximately 4 hours. Given the wide
physiological variations in colonic motility throughout the day, longer observation may detect
clinically relevant information. These researchers compared prolonged colonic manometry
studies in children referred for colonic manometry with the more traditional short water-perfused
technology. Colonic manometry studies of 19 children (8 boys, mean age of 9.4 ± 0.9, range of
3.9 to 16.3) with severe defecation disorders were analyzed. First, a "standard test" was
performed with at least 1-hour fasting, 1-hour post-prandial, and 1-hour post-bisacodyl
provocation recording. Afterwards, recordings continued until the next day. In 2 of the 19
children, prolonged recording provided extra information. In 1 patient with functional non-
retentive FI who demonstrated no abnormalities in the short recording, 2 long clusters of HAPCs
were noted in the prolonged study, possibly contributing to the FI. In another patient evaluated
after failing use of antegrade enemas through a cecostomy, short recordings showed colonic
activity only in the most proximal part of the colon, whereas the prolonged study showed normal
motility over a larger portion of the colon. The authors concluded that prolonged colonic
measurement provided more information regarding colonic motor function and allowed detection
of motor events missed by the standard shorter manometry study.

El-Chammas and colleagues (2014) noted that colon manometry is usually performed using the
8-pressure sensor water-perfused manometry system. High-resolution manometry (HRM), using
closely spaced solid-state pressure recording sensors, provided more detailed information of gut
luminal pressure changes, and, by displaying the HRM data as a pressure topography plot
(PTP), helps with data interpretation. These investigators compared the colon and rectal luminal
pressure data obtained using 8 pressure sensors and displayed as conventional line plot (CLP)
with data obtained using a custom-made solid state manometry catheter with 36 pressure recording sensors and displayed as PTP. They evaluated colon manometry patterns during fasting, response to meal, and bisacodyl stimulation in 10 patients with constipation and stool expulsion disorders. Data from 8 pressure sensors were displayed as CLP and data from 36 pressure sensors as PTP; 2 gastroenterologists independently interpreted these studies. They calculated variability in interpreting colon, rectal, and anal manometry data. Inter-mode, inter-observer, and intra-observer reliability were good-to-excellent for recognizing colon contraction patterns when data were displayed as PTP compared with when displayed as CLP, whereas the reliability for recognizing anal contractions were poor-to-excellent. The authors concluded that colonic and anal manometry patterns were easily recognized when HRM data were expressed as PTP. Obtaining information of colonic luminal pressure changes with rectum and anal pressure changes using HRM could aid in better understanding the pathophysiology of pediatric constipation and stool expulsion disorders.

Rodriguez and associates (2017) stated that over the last few years, the study of the colon and anorectal function has experienced great technical advances that have facilitated the performance of the tests and have allowed a more detailed characterization of reflexes and motor patterns. As a result, researchers have achieved a much better understanding of the pathophysiology of children with defecation problems. Anorectal and colonic manometry are now commonly used in all major pediatric referral centers as diagnostic tools and to guide the management of children with intractable constipation and fecal incontinence, especially when a surgical intervention is being considered. The authors highlighted some of the recent advances in pediatric colon and anorectal motility testing including indications and preparation for the studies, and how to perform and interpret the tests. This update has been endorsed by the North American Society for Pediatric Gastroenterology, Hepatology and Nutrition (NASPGHAN).

Surjanhata and co-workers (2018) noted that chronic constipation may be categorized as normal transit (NTC), slow transit (STC), or outlet obstruction. Colonic wake response is a relative increase in colonic motility upon awakening. Colonic manometry studies have demonstrated attenuated wake response in STC. These researchers evaluated wake response among healthy (H), NTC, and STC patients using wireless motility capsule (WMC). A retrospective study of WMC data from a multi-center clinical trial and a tertiary gastroenterology clinic was performed; WMC motility parameters of contraction frequency (Ct) and area under the contraction curve were analyzed in 20-min windows 1-hour before and after awakening. T-tests compared parameters between H, NTC, and STC. Linear regression analysis was performed to determine if outlet obstruction confounded data. A receiver operating characteristic curve (ROC) demonstrated optimal Ct cut-offs to define blunted wake response. A total of 62 H, 53 NTC and 75 STC subjects were analyzed. At 20, 40, and 60 mins after awakening, STC subjects had significantly lower mean Ct when compared to H (p < 0.001) and NTC(p < 0.01). Linear
regression demonstrated that outlet obstruction was not associated with a decreased wake response ($\beta = 3.94$, $\text{CI}: -3.12$ to $1.00$, $p = 0.27$). Defined at the Ct threshold of 64 at 20-min post-wake, blunted wake response sensitivity was 84 % and specificity was 32 % for chronic constipation. The authors concluded that findings of an impaired wake response in subjects with STC and not NTC added further evidence to neuronal dysfunction as an etiology of STC, and identified a possible temporal target for pharmacologic intervention.

Furthermore, an UpToDate review on “Overview of gastrointestinal motility testing” (Lembo, 2019) states that “Indications for small bowel and colon motility testing include chronic constipation, chronic diarrhea, dyspepsia, chronic idiopathic intestinal pseudoobstruction, scleroderma, and malabsorption. Radio-opaque marker study can only assess colonic motility, whereas scintigraphy and wireless motility capsule can be used to assess gastric, small bowel, and colon transit times”.

**Gastric Emptying Breath Testing**

The Gastric Emptying Breath Test (GEBT) is a non-radioactive, non-invasive, orally administered test, intended for use in the measurement of emptying of solids and aid in the diagnosis of delayed gastric emptying (gastroparesis) in symptomatic adults. The GEBT incorporates a stable isotope carbon-13, denoted as $^{13}$C, in the GEBT test meal.

GEBT was developed to purportedly aid in the diagnosis of delayed gastric emptying, known as gastroparesis. This condition is characterized by slow or nonmovement of food from the stomach to the small intestine due to improper contractions of stomach muscles. Gastroparesis may result from conditions such as Parkinson’s disease, diabetes or following intestinal surgery. Gastric scintigraphy is considered the gold standard for diagnosing gastroparesis.

The GEBT is conducted over a four hour period after an overnight fast and reportedly measures how fast the stomach empties solids by measuring carbon dioxide in an individual’s breath. Before the test begins, baseline breath tests are conducted and the individual eats a specially made protein test meal enriched with carbon-13. This substance is then measured via breath testing at multiple time points after the meal to determine the rate of gastric emptying.

In March 2016, Carin Diagnostics, formerly known as Advanced Breath Diagnostics, announced the release of the U.S. FDA approved $^{13}$C-Spirulina Gastric Emptying Breath Test (GEBT) intended for measurement of the rate of solid-phase gastric emptying and aid in the diagnosis of gastroparesis in symptomatic adults. The Cairn GEBT helps to identify gastroparesis by measuring the rate of excretion of a special form of carbon dioxide in the patient’s breath. Patients consume a precisely-formulated egg mixture containing pharmaceutical-grade Spirulina

Proprietary
platensis, a nutritional blue green algae, that has been enriched with carbon-13. Consuming the 13C-enriched test meal gives rise to 13CO2. The test system utilizes a gas isotope ratio mass spectrometer for the measurement of the ratio of 13CO2 to 12CO2 in breath samples (BioSpace, 2016).

Camilleri (2018) states that alternatives to scintigraphy include 13C breath testing using spirulina incorporated into a solid meal; however, while the test has the “advantage of avoiding radiation that is associated with scintigraphy, further studies are needed before they can be routinely recommended for evaluation of delayed gastric emptying”.

The spirulina 13C breath test was approved by the US Food and Drug Administration to diagnose gastroparesis in April 2015. Approval was based in part on a prospective, single-site, cohort study (PRO-DC-004) of 115 adult patients who underwent simultaneous scintigraphy and spirulina 13C breath test to validate the GEBT for use in diagnosis and monitoring of delayed gastric emptying. The analysis of effectiveness was based on the comparison of GEBT and scintigraphy at six different time points. Results from this validation study showed that the GEBT demonstrated specificity, as compared to scintigraphy, ranging from 89%-98% (between 45 and 240 minutes). At 80 percent specificity, the 13C-spirulina breath test samples at 150 and 180 minutes had a combined sensitivity of 89 percent for delayed gastric emptying (FDA, 2015; Camilleri, 2018; Szarka et al, 2008). However, additional studies are needed to validate these results before 13C breath tests can be used routinely (Camilleri, 2018).

Sangnes et al. (2019) aimed to compare gastric emptying of radiopaque markers (ROM) with GEBT in the evaluation of patients with diabetes and symptoms compatible with gastroparesis. The authors evaluated 45 patients with type 1- or type 2 diabetes who had symptoms of gastroparesis. The main strength of the study was that all patients were on intravenous glucose-insulin infusion during testing, thereby minimizing the glucose level’s effect on gastric emptying, as well as avoiding iatrogenic hypoglycemia. The authors found that 40% of patients had delayed gastric emptying of ROM, while 55% had delayed gastric emptying of GEBT. Correlation between ROM and GEBT was not significant. Compared to GEBT, sensitivity for a positive ROM test was 0.52, while specificity was 0.74. In women, they found a higher specificity of 0.92, sensitivity 0.47. Difference in HbA1c between patients with positive and negative results was of borderline significance for both tests. GEBT (p=0.008) correlated with HbA1c. Patients with any late complications of diabetes had higher gastric retention of ROM (p=0.028), while patients with polyneuropathy (p=0.014) and diabetic wounds (p=0.004) had slower emptying with GEBT. None of the methods identified significant associations between gastric emptying and symptom scores, age or diabetes duration. The authors concluded that as a measure of gastric emptying, the
ROM test has benefits of being affordable and available. Compared to GEBT, the method has low diagnostic reliability; however, before continued use, the authors recommend additional studies validating the test in diabetes patients.

Wireless Motility Capsule (SmartPill)

An approach for evaluating gastric motility function in patients with functional dyspepsia and other upper functional gastrointestinal disorders is the use of an ambulatory diagnostic test pill, the SmartPill (SmartPill Corporation; Buffalo, NY). Wireless gastrointestinal (GI) motility monitoring is a diagnostic procedure performed to evaluate suspected gastroparesis (delayed gastric emptying) or colonic transit time for chronic constipation. During wireless GI motility monitoring, the individual swallows a small capsule (approximately the size of a multivitamin) that contains sensors to measure peristaltic pressure, pH and temperature. As the capsule moves through the GI tract, radiofrequency signals are transmitted to a wireless data receiver, which is usually worn on the individual’s belt. After excretion, the receiver is returned to the physician, who downloads the data and analyzes the results. An example of a wireless GI motility monitoring system includes, but may not be limited to, the SmartPill GI monitoring system 2.0.

On July 20, 2006, the United States Food and Drug Administration cleared the SmartPill GI Monitoring System through the 510(k) process for use as an aid in evaluating patients with suspected motility disorders such as gastroparesis. This wireless, ingestible, medical device assesses pH and pressure in the gastrointestinal lumen. When the capsule reaches the duodenum, the change in pH (from acidic to alkaline) indicates this transition, allowing an assessment of gastric emptying. The single-use, disposable, wireless capsule is slightly larger than a multi-vitamin (26 mm by 13 mm). As it passes through the gastrointestinal tract, miniaturized sensor technology measures pressure, temperature, and pH, as well as real and elapsed time. Acquired data are continuously transmitted over very low power radiofrequencies to a small receiver that can be worn on the patient’s belt. Although the capsule normally has a transit time ranging from 24 to 48 hours, it is capable of transmitting data continuously for more than 72 hours in patients with reduced motility. Once the device has passed, the data set is downloaded from the receiver to a laptop computer, and special software provides tools for data analysis and a graphical user interface that indicates when gastric emptying, small bowel/large bowel transit, and total gastrointestinal tract transit time of the capsule has occurred. It should be noted that the SmartPill is intended to supplement, not replace, current gastrointestinal motility procedures such as endoscopy, duodenal manometry, and gastric emptying scintigraphy.

Kuo and associates (2006) reported their experience with the use of the SmartPill in 86 healthy subjects and 60 patients with documented gastroparesis by scintigraphy. The wireless capsule had a moderate sensitivity and specificity for half-time gastric emptying measurement (71 % and
74%, respectively). These findings, originally reported in an abstract, were subsequently published in a full-length article. Kuo et al (2008) compared gastric emptying time (GET) and gastric emptying scintigraphy (GES) by assessing their correlation, and compared GET and GES for discriminating healthy subjects (n = 87) from gastroparetics (n = 61). Fasted subjects were ingested capsule and [(99m)Tc]-SC radiolabeled meal. Images were obtained every 30 minutes for 6 hours. Gastric emptying time and percentage of meal remaining at 2/4 hours were determined for each subject. The sensitivity/specificity and receiver operating characteristic analysis of each measure were determined for each subject. Correlation between GET and GES-4 hour was 0.73 and GES-2 hour was 0.63. The diagnostic accuracy from the receiver operating characteristic curve between gastroparetics and healthy subjects was GET = 0.83, GES-4 hour = 0.82 and GES-2 hour = 0.79. The area-under-the-curve analysis of overall accuracy indicated that there were no statistically significant differences between the SmartPill and scintigraphy for detection of gastroparesis. The 300-min cut-off time for GET gives sensitivity of 0.65 and specificity of 0.87 for diagnosis of gastroparesis. The corresponding sensitivity/specificity for 2- and 4-hour standard GES measures were 0.34/0.93 and 0.44/0.93, respectively. Although the SmartPill was able to distinguish normal state from disease, a case-control study is insufficient for evaluating test characteristics. Prospective, randomized, controlled trials are needed to ascertain the clinical value of the SmartPill. Furthermore, since the SmartPill itself does not empty like a meal from the stomach, the technology is likely to only provide an estimate of upper gastro-intestinal transit.

Cassilly et al (2008) examined if the SmartPill wireless pH and pressure capsule given with a meal empties from the stomach with return of the fasting phase III migrating motor complex (MMC) or during the fed pattern with the solid meal. A total of 15 normal subjects underwent antro-duodenal manometry and ingestion of a radio-labeled meal and the SmartPill. In 5 subjects, emptying of the SmartPill was studied in the fasting period by ingesting the SmartPill with radio-labeled water. The SmartPill emptied from the stomach within 6 hours in 14 of 15 subjects. SmartPill pressure recordings showed high amplitude phasic contractions prior to emptying. SmartPill gastric residence time (261 +/- 22 mins) correlated strongly with time to the first phase III MMC (239 +/- 23 mins; r = 0.813; p < 0.01) and correlated moderately with solid-phase gastric emptying (r = 0.606 with T-50 % and r = 0.565 with T-90 %). Nine of 14 subjects emptied the capsule with a phase III MMC. In 5 subjects, the SmartPill emptied with isolated distal antral contractions. In 5 subjects ingesting only water, SmartPill gastric residence time (92 +/- 44 mins) correlated with the time to the first phase III MMC (87 +/- 30 mins; r = 0.979; p < 0.01). The SmartPill given with a meal primarily empties from the stomach with the return of phase III MMCs occurring after emptying the solid-phase meal. However, in some subjects, the SmartPill emptied with isolated antral contractions, an unappreciated mechanism for emptying of a non-digestible solid.
A study that compared the SmartPill with radiopaque markers for detection of delayed colonic transit in chronically constipated versus normal adults found that sensitivity of detection was higher for the SmartPill but did not report whether this increase was statistically significant. Rao et al (2009) assessed regional and colonic transit time with the SmartPill in constipated and healthy subjects and compared this with a radiopaque market. Seventy-eight constipated (Rome II) and 87 healthy subjects ingested a 260-kcal meal, a radiopaque marker capsule, and the SmartPill. Subjects wore a data receiver and kept daily stool diaries for 5 days. SmartPill recordings assessed colonic transit time, whole-gut transit time, small-bowel transit time, and gastric emptying time. Abdominal radiographs on days 2 and 5 assessed radiopaque marker transit. Sensitivity, specificity and receiver operating characteristics (ROCs) of each technique and utility were compared. Gastric emptying time, colonic transit time, and whole-gut transit time were slower (p < 0.01) in constipated subjects than controls. Colonic transit time was slower in women than men (p = 0.02). Day 2 and day 5 radiopaque marker transits were slower (p < 0.001) in constipated subjects. Correlation of the SmartPill colonic transit time with radiopaque markers expelled on day 2/day 5 was r = 0.74/r = 0.69 in constipation, and r = 0.70/r = 0.40 in controls, respectively. The diagnostic accuracy of the SmartPill colonic transit time to predict constipation from ROC was 0.73, with a specificity of 0.95. The authors reported that these were comparable with those of day 5 ROM (ROC, 0.71; specificity, 0.95).

Maqbool et al (2009) compared the SmartPill with whole gut transit scintigraphy to determine whether the SmartPill system could serve as a test for measurement of whole gut motility and transit. A total of 10 healthy, asymptomatic subjects underwent simultaneous whole gut scintigraphy and SmartPill assessment of whole gut transit. All subjects completed the study per protocol and experienced natural passage of the pill. Capsule residence time in the stomach correlated with percent gastric retention of the Tc-99 radiolabel at 120 mins (r = 0.95) and at 240 mins (r = 0.73). Small bowel contraction-min(-1) measured by the SmartPill correlated with small bowel transit % (r = 0.69; p = 0.05) and with isotopic colonic geometric center at 24 hrs following ingestion (r = 0.70, p = 0.024). Capsule transit time correlated with scintigraphic assessment of whole gut transit. The authors concluded that SmartPill capsule assessment of gastric emptying and whole gut transit compares favorably with that of scintigraphy. Wireless capsule motility shows promise as a useful diagnostic test to evaluate patients for gastro-intestinal transit disorders and to study the effect of prokinetic agents on gastro-intestinal transit.

A study comparing the SmartPill to radio-opaque markers in persons with constipation found the SmartPill to be somewhat less accurate, if radioopaque markers are considered the gold standard for assessing colonic transit. Camilleri et al (2010) proposed to validate the SmartPill wireless motility capsule, that measures pH, pressure and temperature, to radio-opaque marker measurement of colon transit in patients with symptomatic constipation evaluated at multiple centers. Of 208 patients recruited, 158 eligible patients underwent
simultaneous measurement of colonic transit time (CTT) using radio-opaque markers (Metcalf method, cut-off for delay greater than 67 hours), and wireless motility capsules (WMC) (cut-off for delay greater than 59 hours). The study was designed to demonstrate substantial equivalence, defined as diagnostic agreement greater than 65% for patients who had normal or delayed radioopaque marker transit. Fifty-nine of 157 patients had delayed radio-opaque marker colonic transit. Transit results by the 2 methods differed: radio-opaque marker median 55.0 hours [IQR 31.0 to 85.0] and Smartpill (43.5 hours [21.7 to 70.3], p < 0.001). The positive percent agreement between Smartpill and radio-opaque markers for delayed transit was approximately 80%; positive agreement in 47 by SmartPill/59 by radio-opaque marker or 0.796 (95% confidence interval [CI]: 0.67 to 0.98); agreement versus null hypothesis (65%) p = 0.01. The negative percent agreement (normal transit) was approximately 91%: 89 by Smartpill/98 by radioopaque marker or 0.908 (95% CI: 0.83 to 0.96); agreement versus null hypothesis (65%), p = 0.00001. Overall device agreement was 87%. The authors stated that there were significant correlations (p < 0.001) between radio-opaque markers and Smartpill transit (CTT [r = 0.707] and between radio-opaque markers and combined small and large bowel transit [r = 0.704]). There were no significant adverse events. The authors stated that there are potential pitfalls with using all capsules to measure gut transit including technical failures, inability to swallow the capsule, the potential for non-passage of or intestinal obstruction by the capsule in stenosing gut disorders, and greater cost relative to the radio-opaque marker transit method. Application of the Smartpill is contraindicated in patients with known esophageal or intestinal strictures, and children under 18 years of age, in whom validation studies have not yet been completed.

Tack and Janssen (2010) reviewed recent progress in gastro-duodenal motility and sensitivity in health and in disease. The authors stated that although gastric and small intestinal motility remain an important focus of research, including the application of the SmartPill wireless motility monitoring capsule, duodenal sensitivity and low-grade duodenal inflammation are new areas of interest in the pathogenesis of functional dyspepsia. A number of genetic polymorphisms associated with functional dyspepsia are being investigated, but large-scale studies are still lacking.

Timm and colleagues (2011) noted that the SmartPill has not been validated with dietary interventions. Thus, these researchers conducted a controlled cross-over trial to examine if the device could detect a significant difference in transit time after 10 healthy subjects (5 men and 5 women) consumed 9 g of wheat bran (WB) or an equal volume, low-fiber control for 3 days. A paired-t test was used to determine differences in transit times. Colonic transit time decreased by 10·8 (S.D. 6·6) hours (p = 0·006) on the WB treatment. Whole-gut transit time also decreased by 8·9 (S.D. 5·4) hours (p = 0·02) after the consumption of WB. Gastric emptying time (GET) and small-bowel transit time did not differ between treatments. Despite encouraging
results, the present study had several limitations including short duration, lack of randomization and unusable data due to delayed gastric emptying of the capsule. With minimal participant burden, the SmartPill technology appears to be a potentially useful tool for assessing transit time after a dietary intervention. This technology could be considered for digestive studies with novel fibers and other ingredients that are promoted for gut health.

Willis and associates (2011) explored the feasibility and sensitivity of a new technology for measuring GET in appetite research, and compared appetite after subjects consumed macronutrient- and fiber-matched liquid and solid meals. A total of 14 women (body mass index [BMI] of 21.2 +/- 0.3) participated in this randomized, cross-over study. On 2 separate days, fasted subjects consumed liquid (fruit juices and skim milk) and solid (oatmeal, blueberries, and apples) breakfasts. Both meals had 10 g of fiber and 410 kcal. Gastric emptying time was assessed with the SmartPill GI Motility System, appetite was assessed with visual analog scales, and food intake was measured at lunch. Despite the same amount of fiber, GET was about 1 hour longer after the oatmeal than after the liquids. Subjects were less hungry after the oatmeal than after the liquids. Satisfaction and fullness were marginally improved with the oatmeal compared to the liquids. There was a negative association between GET and hunger. Lunch-time food and beverage intake did not differ between treatments. The authors concluded that the SmartPill appears feasible and sensitive in appetite research, but has limitations.

The BlueCross BlueShield Association Technology Evaluation Center (BCBSA, 2012) concluded that the wireless motility capsule does not meet the TEC criteria. The TEC assessment concluded that the limited body of evidence on the diagnostic characteristics of SmartPill does reveal correlations between SmartPill and other tests that indicate some capability to distinguish diseased from nondiseased persons. The assessment stated, however, because of the types of subjects included in the studies, particularly healthy patients, and the lack of a reference standard for the disease of interest (slow-transit constipation) in some studies, the diagnostic characteristics of SmartPill are uncertain. The assessment noted that there are no studies that ascertain whether use of the SmartPill in addition to or instead of alternative methods of diagnosis improves patient outcomes.

The Federal Agency for Healthcare Research and Quality (AHRQ, 2011) has commissioned a comparative effectiveness review of the wireless motility capsule compared to other diagnostic technologies for evaluating gastroparesis and constipation. The AHRQ has stated that the current gold standard diagnostic methods for motility disorders include scintigraphy and the use of radiopaque markers. In discussing the considerations for conducting the review, the AHRQ explained: "The SmartPill procedure has been described as having advantages to current standard testing methods including less radiation exposure, a more standardized diagnostic approach, convenience, and a more detailed diagnostic profile; however, the technology may
have limited patient selection, contraindications, and may not always avoid radiation exposure"
Regarding the current available evidence, the AHRQ stated that "[t]he SmartPill has not been
studied extensively in the context of other testing methods, and most available studies have
been sponsored by the manufacturer."

The AHRQ (2012) review will address several controversies surrounding the use of the SmartPill
wireless motility capsule for gastroparesis. One controversy identified by AHRQ is whether
grading the severity of gastric emptying delay affects decisions about patients. They plan to
address this question by evaluating data on how treatment decisions differ between scintigraphy
and the wireless motility capsule. Another controversy that they plan to address is the lack of
information regarding whether or not scintigraphy or wireless motility capsule testing could offer
any guidance in assessing response to treatment or whether they would remain purely
diagnostic tools. The AHRQ review plans to address this issue by looking for data on treatment
response in terms of patient-reported outcomes. The AHRQ stated that it is unclear which
populations would benefit most from the wireless motility capsule or which order of testing is best
to diagnose patients. The AHRQ noted that the wireless motility capsule testing is currently being
used in a complementary fashion as an addition to reference standard tests like scintigraphy.
The AHRQ stated that it is controversial whether the wireless motility capsule can replace or
should supersede other testing methods.

The AHRQ review (2012) will also examine the evidence for the wireless motility capsule in
constipation. Among the advantages of capsule testing identified by AHRQ is that it provides a
more complete picture of colonic transit (like whole bowel scintigraphy might if it were more
widely available); whereas, radiopaque marker testing, the current reference standard, only
offers static imaging. The AHRQ stated however, that it is uncertain at this point whether all the
extra data will be useful to change outcomes in any way. The AHRQ stated that more studies
must be done as the wireless motility capsule gets adopted into wider use. The AHRQ review will
address the controversy regarding the role of wireless motility capsule testing in the diagnostic
evaluation of constipation; the AHRQ commented that some experts think that the wireless
motility capsule would likely be a complementary test rather than an independent test for patients
with this disease.

Kuo et al (2011) (i) defined prevalence of generalized dysmotility using WMC, (ii) related to
symptoms in suspected regional delay, (iii) compared results of WMC testing to
conventional transit studies to quantify new diagnoses, and (iv) assessed the impact of
results of WMC testing on clinical decisions. Wireless motility capsules transits were analyzed
in 83 patients with suspected gastroparesis, intestinal dysmotility, or slow transit constipation.
Isolated regional delays were observed in 32 % (9 % stomach, 5 % small bowel, 18 % colon).
Transits were normal in 32% and showed generalized delays in 35%. Symptom profiles were similar with normal transit, isolated delayed gastric, small intestinal, and colonic transit, and generalized delay (p = NS). Compared to conventional tests, WMC showed discordance in 38% and provided new diagnoses in 53%. Wireless motility capsules testing influenced management in 67% (new medications 60%; modified nutritional regimens 14%; surgical referrals 6%) and eliminated needs for testing not already done including gastric scintigraphy (17%), small bowel barium transit (54%), and radio-opaque colon marker tests (68%). The authors concluded that WMC testing defines localized and generalized transit delays with suspected gastroparesis, intestinal dysmotility, or slow transit constipation. Symptoms do not predict the results of WMC testing. Wireless motility capsules findings provide new diagnoses in greater than 50%, may be discordant with conventional tests, and can influence management by changing treatments and eliminating needs for other tests. They stated that these findings suggested potential benefits of this method in suspected dysmotility syndromes and mandate prospective investigation to further define its clinical role.

Brun et al (2012) evaluated the ability of WMC to detect phase III MMC and correlated it with the simultaneous measurements by ADM. A total of 18 patients underwent simultaneous ADM and WMC. Migrating motor complexes were identified first on ADM and then correlated with WMC events occurring simultaneously. Frequency of contractions per min, area under the pressure curve (AUC), and motility index (MI) and criteria for amplitude thresholds of contractions representing MCCs on WMC tracings were defined. In 18 patients, a total of 29 MMCs were recorded by ADM. Wireless motility capsule detected 86% of MMC events measured by ADM. Hundred percent (10/10) of MMCs in stomach were detected by WMC, whereas 79% (15/19) of MMCs were detected in small bowel (SB). The sensitivity and specificity of WMC high amplitude contractions to represent phase III MMC were 90% and 71.8% in the stomach; 73.7% and 84.7% in SB, respectively, and negative predictive value was 99.9% in both regions. The authors concluded that WMC was able to detect the phase III MMCs as the high amplitude contractions with good fidelity. Wireless motility capsule does not detect the propagation of MMC. Using the pressure thresholds, WMC can detect high amplitude contraction representing phase III MMC with favorable sensitivity/specificity profile and 99.9% negative predictive value. They stated that this observation may have clinical significance, as the absence of high amplitude contractions recorded by WMC during fasting state suggested absence of MMCs; further studies are needed to determine the potential use of these results in clinical practice for diagnosis and profiling of gastro-intestinal motility disorders.

Tran et al (2012) noted that the WMC is an ambulatory non-invasive and non-radioactive diagnostic sensor that continuously samples intra-luminal pH, temperature, and pressure as it moves through the gastro-intestinal (GI) tract. These researchers summarized the data obtained in clinical trials with the WMC and discussed its role in clinical practice. The United States Food
and Drug Administration has approved the SmartPill GI monitoring system for the evaluation of gastric emptying time in patients with suspected gastroparesis, the evaluation of colonic transit time in patients with suspected chronic constipation, and for the characterization of pressure profiles from the antrum and duodenum. Clinical studies have shown that WMC-measured GI transit times can distinguish patients with motility abnormalities similarly to conventional testing. However, the WMC offers the advantage of providing a full GI-tract profile, enabling the detection of multi-regional GI transit abnormalities in patients with suspected upper or lower GI dysmotility. The WMC also characterizes pressure profiles of the GI tract and impaired pressure profile limits are reported for the antrum and duodenum. In comparison with manometry, interpretations of pressure measurements obtained by the WMC are limited by an inability to detect a peristaltic pressure wave front, and further investigation is needed to develop clinical applications. The authors concluded that WMC is a novel technology offering a non-invasive, non-radioactive, standardized method to evaluate intra-luminal pH, temperature, and pressure, allowing for the measurement of gastric, small bowel, colon, and whole GI transit times. As a single ambulatory test, it allows for an assessment of isolated and diffuse motility transit abnormalities. Interpretation of frequency of contractions (Ct) measurements obtained by the WMC is limited compared with manometry testing, but continues to evolve. Clinical studies with the WMC indicated that it should be considered for the evaluation of regional and whole gut transit time in patients with suspected upper or lower dysmotility, particularly if there are concerns about multi-regional dysmotility. The drawbacks of this study were "[w]hile the WMC provides a full GI tract-transit profile in a standardized protocol, the pressure profiles are limited by nonstationary, single point pressure measurements throughout the GI tract. As a new method of measuring GI Ct, new standards need to be developed and validated before the relevance of this information is clear. The WMC, with only one pressure sensor, is unable to detect a pressure wave front, which limits its utility in comparison to traditional manometric testing. However, with the invasive nature and limited availability of manometry, the WMC may have significant potential as further investigation continues to evolve the clinical utility of WMC pressure data. The WMC can not distinguish the absolute time of emptying of a meal or distinguish between liquid and solid emptying; rather it measures the total meal emptying. Furthermore, the WMC measures gastric emptying indirectly through the use of a physiologic meal. Scintigraphy testing leads to a more physiologic assessment of transit time. As a nondigestible capsule that needs to be ingested, the WMC should not be administered to those patients with suspected strictures, fistulas, or GI obstructive symptoms. In addition, it should be used with caution for anyone with a history of gastric bezoars, dysphagia, or disorders of swallowing, recent GI surgery, Crohn’s disease, or diverticulitis."

Rauch et al (2012) used a novel WMC to compare gastric emptying and SB transit times in critically ill trauma patients and healthy volunteers. These investigators evaluated gastric emptying, SB transit time, and total intestinal transit time in 8 critically ill trauma patients. These
Gastrointestinal Function: Selected Tests

Data were compared with those obtained in 87 healthy volunteers from a separate trial. Data were obtained with a motility capsule that wirelessly transmitted pH, pressure, and temperature to a recorder attached to each subject's abdomen. The gastric emptying time was significantly longer in critically ill patients (median of 13.9; interquartile range [IQR]: 6.6 to 48.3 hours) than in healthy volunteers (median of 3.0; IQR: 2.5 to 3.9 hours), p < 0.001. The SB transit time in critically ill patients was significantly longer than in healthy volunteers (median of 6.7 hours; IQR: 4.4 to 8.5 hours versus median of 3.8 hours; IQR: 3.1 to 4.7 hours), p = 0.01. Furthermore, the capsules passed after 10 (IQR: 8.5 to 13) days in the critical care group and 1.2 (IQR: 0.9 to 1.9) days in healthy volunteers (p < 0.001). The authors concluded that both gastric emptying and SB transit were delayed in critically ill trauma patients. The drawbacks of this study were the small number of critically ill patients, and exclusion of patients with increased intra-abdominal pressure, open abdominal injury, and exploratory laparotomies. Also, these researchers measured gastric emptying and SB transit time only once during the ICU stay because it is not possible to start a new capsule examination until the previous one has passed from the body. Although delayed gastric emptying is most common in the first 3 days after ICU admission, the authors can not exclude disturbance of intestinal motility later in the critical care course. Furthermore, both enteral feeding as well as anti-acid therapies can alter intra-luminal pH, complicating identification of the capsule's transition from the stomach to small intestine. The authors stated that "[d]espite the use of H2 blockers, all patients had a distinct pH pattern to identify the passage of the capsule. Nguyen et al has shown in a retrospective study that morphine/midazolam and propofol can alter gastric emptying. It seems that patients under propofol-based sedation have a lower incidence of delayed gastric emptying. Although sedation and analgesia requirements were similar among the critically ill group, we can not exclude that the pharmacologic effect of propofol/midazolam and fentanyl/morphine could have contributed to the prolonged gastric emptying time and small bowel transit time".

Weinstein et al (2013) stated that gastro-esophageal reflux disease (GERD) and gastric acid hyper-secretion respond well to suppression of gastric acid secretion. However, clinical management and research in diseases of acid secretion have been hindered by the lack of a non-invasive, accurate and reproducible tool to measure gastric acid output (GAO). Thus, symptoms or, in refractory cases, invasive testing may guide acid suppression therapy. These researchers presented and validated a novel, non-invasive method of GAO analysis in healthy subjects using a wireless pH sensor, SmartPill (SP) (SmartPill Corporation, Buffalo, NY). A total of 20 healthy subjects underwent conventional GAO studies with a nasogastric tube. Variables impacting liquid meal-stimulated GAO analysis were assessed by modelling and in-vitro verification. Buffering capacity of Ensure Plus was empirically determined. SmartPill GAO was calculated using the rate of acidification of the Ensure Plus meal. Gastric emptying scintigraphy and GAO studies with radiolabelled Ensure Plus and SP assessed emptying time, acidification rate and mixing; 12 subjects had a second SP GAO study to assess reproducibility. Meal-
stimulated SP GAO analysis was dependent on acid secretion rate and meal-buffering capacity, but not on gastric emptying time. On repeated studies, SP GAO strongly correlated with conventional basal acid output (BAO) \((r = 0.51, p = 0.02)\), maximal acid output (MAO) \((r = 0.72, p = 0.0004)\) and peak acid output (PAO) \((r = 0.60, p = 0.006)\). The SP sampled the stomach well during meal acidification. The authors concluded that SP GAO analysis is a non-invasive, accurate and reproducible method for the quantitative measurement of GAO in healthy subjects. They stated that SP GAO analysis could facilitate research and clinical management of GERD and other disorders of gastric acid secretion. These findings from a feasibility study using health subjects need to be validated by well-designed studies using patients with gastric disorders.

An UpToDate review on “Etiology and diagnosis of delayed gastric emptying” (Camilleri, 2013) states that “A potential alternative to manometry is a capsule (“SmartPill”), which is swallowed, and can simultaneously measure phasic pressure amplitudes and pH as it traverses different segments of the gastrointestinal tract. The characteristic change in pH between stomach and small intestine provides an indication of the gastric emptying time for a non-digestible solid > 1 cm long. The SmartPill given with a meal empties primarily during the phase III MMCs occurring after emptying the solid-phase meal. However, in some patients, the SmartPill empties with isolated antral contractions, an unappreciated mechanism for emptying of a non-digestible solid”.

Hasler et al (2014) stated that testing to define delayed gastric emptying is needed to diagnose gastroparesis; rapid emptying is found in other patients. Commonly performed methods of gastric emptying testing include scintigraphy and breath testing. The SmartPill WMC system is FDA-approved for evaluating suspected delayed emptying in gastroparesis and functional dyspepsia. The device measures transit in the stomach, small intestine, and colon by detecting characteristic pH transitions; and quantifies pressure waves in each gut region. Wireless motility capsules gastric emptying times correlate with scintigraphic measures. Incremental benefits of WMC testing in patients with suspected gastroparesis include delineation of pressure abnormalities and small intestinal and colonic transit delays. The authors concluded that acceptance of trial data confirming usefulness of WMC testing in suspected gastric motor disorders has been hampered by small sample sizes and design limitations. They stated that ongoing multi-center studies will validate the utility of WMC methods in patients with suspected gastroparesis and other upper GI motor disorders.

Rozov-Ung et al (2014) evaluated the ability of a wireless motility capsule to detect drug effects on GET and gastric contractility. A total of 15 healthy adults were administered in random order saline, erythromycin IV 150 mg, or morphine IV 0.05 mg/kg body weight. Subjects ate a standard meal after each infusion, and subsequently ingested the motility capsule. Data were recorded for 8 hours, and the results were analyzed using the manufacturer's software. Gastric emptying time was significantly faster after erythromycin than either saline or morphine.
Morphine tended to delay emptying of the capsule compared to saline. There was a trend toward a greater frequency of gastric contractions with erythromycin and a reduced frequency of gastric contractions with morphine that did not reach statistical significance. The authors concluded that a wireless motility capsule successfully detected acceleration of gastric emptying induced by erythromycin, and retardation of gastric motility caused by morphine. They stated that these results indicated that a wireless motility capsule is a promising technique to assess pharmacologic effects on gastric transit and contractility and aid in development of drugs for gastric motor disorders.

Yung and colleagues (2016) noted that there are scarce data looking at SmartPill assessment of patients with known/suspected small-bowel Crohn's Disease (CD). In a pilot study, these researchers examined the feasibility and safety of SmartPill to assess gut motility in this group. Over 1 year, patients with known/suspected CD, referred for small-bowel capsule endoscopy (SBCE), were invited to participate and 12 were recruited (5 males and 7 females, mean age of 44.2 ± 16.6 years). They underwent hydrogen breath test to exclude small-bowel bacterial overgrowth, patency capsule (Agile), and provided stool samples for fecal calprotectin (FC).

Patients ingested PillCam SB2 and SmartPill 4 hours apart. Using unpublished data, 33 healthy controls also were identified for the study; p < 0.05 was considered statistically significant. Of the 12 patients enrolled, 10 underwent complete SmartPill examination (1 stomach retention, 1 drop-out). PillCam was complete in 10 (1 drop-out, 1 stomach retention). Mean fecal calprotectin was 340 ± 307.71 mcg/g. The study group had longer transit times and lower gut motility index than did the controls. The difference in motility appeared to be statistically significant (p < 0.05). Longer transit times for SmartPill (not statistically significant) may have been due to different specifications between the capsules. Limitations included transient SmartPill signal loss (5/10 studies). The authors concluded that this was the first pilot study to attempt combining SBCE and SmartPill to evaluate small-bowel CD. Data on motility in CD are scarce. Multi-modal information can provide a clearer clinical picture. Despite concerns about capsule retention in CD patients, SmartPill appeared safe for use if a patency capsule is employed beforehand. Moreover, they stated that statistical significance should be interpreted with caution given the small sample size. Other limitations of this pilot study included potential selection bias, as patients with significant SB inflammation were excluded due to fear of capsule retention, and the SmartPill signal loss (resulting in incomplete data sets in 5/10 completed WMC examinations).

Vilz and associates (2016) stated that post-operative ileus (POI) is a frequent complication after abdominal surgery (AS). Until today, neither a prophylaxis nor an evidence-based therapy exists. This originates from the absence of objective parameters evaluating the severity and duration of POI resulting in clinical trials of modest quality. The SmartPill, a capsule which frequently measures pH value, temperature and intra-luminal pressure after swallowing, offers an
Diaz Tartera and colleagues (2017) noted that there is interest in ultimately combining endoscopy and motility assessments. Gastric emptying (GET), small bowel transit time (SBTT), colon transit time (CTT) and whole gut transit time (WGTT) are conveniently obtained by SmartPill WMC that records luminal pH, temperature and pressure. Reproducibility within same subjects and accuracy of software derived times (MotiliGI) were investigated for diagnostic application; GET and SBTT were separately measured using video capsule endoscopy (VCE). These researchers evaluated the same subject reproducibility of WMC, accuracy of software derived transit times and relate to Pillcam SB (small bowel) VCE motility data. A total of 73 healthy adults ingested a 260 kcal mixed meal followed by WMC tests. Food intake was permitted after 6 hours. Regional transit data was obtained for GET, SBTT and CTT, the sum yielding WGTT; 19 subjects repeated WMC tests 2 or 4 weeks later; a separate 70 underwent VCE while fasted. Visually derived data from WMC yielded GET 3.46 ± 0.27, SBTT 5.15 ± 0.21, CTT 20.76 ± 1.19 and WGTT 29.53 ± 1.28 hours (mean ± SEM). Pearson's correlation coefficients (r) against software derived results were: GET 0.78 (p < 0.0001), SBTT 0.28 (p < 0.05), CTT 0.96 (p < 0.0001), WGTT 0.99 (p < 0.0001). VCE yielded lower GET (0.71 ± 0.08 hours) and SBTT (4.15 ± 0.13 hours). The authors concluded that GET, SBTT, CTT and WGTT obtained by WMC were commensurate with literature values, including by other methods. Visually and software derived transit times had strongest correlations for CTT and WGTT; WMC
yielded longer GET and SBTT than VCE, perhaps due to meal related effects on motility. This study was carried out using healthy volunteers; it did not provide any data on patients with GI motility disorders.

3D High-Resolution Manometry for Quantification of Esophago-Gastric Junction Contractility

Lin and colleagues (2017) stated that the esophago-gastric junction (EGJ) is a complex sphincter composed of both the crural diaphragm (CD) and lower esophageal sphincter (LES). Three dimensional high-resolution manometry (3D-HRM) provides a dynamic 360 degrees representation of EGJ pressure in which the CD has a distinct pressure signature. These researchers developed 3D-HRM metrics to quantify the vigor of CD contractility, best eliminate the CD contribution and thereby isolate the LES component of EGJ contractility, and compare these metrics with conventional HRM metric of EGJ contractility. A total of 20 healthy subjects underwent 3D-HRM studies; 2 novel 3D-HRM EGJ metrics, 3D-DHA , and 3D-LES pressure (3D-LESP) were devised and calculated to best approximate the CD and LES components of the composite EGJ pressure topography. These values were then compared to conventional HRM metrics of EGJ contractility, the EGJ contractile integral (EGJ-CI), inspiratory EGJ pressure and expiratory EGJ pressure. Mean 3D-DHA correlated most strongly with EGJ-CI (r = 0.82, p < 0.001), while the 3D-LESP correlated most strongly with inspiratory EGJ pressure (r = 0.91 p < 0.001) and expiratory EGJ pressure (r = 0.85, p < 0.001). The authors devised novel 3D-HRM metrics to quantify the CD (3D-DHA ) and LES (3D-LESP) elements of EGJ contractility. Both measures correlated strongly with conventional HRM metrics of EGJ contractility. The 3D-DHA , in particular, correlated strongly with the EGJ-CI suggesting that both are largely determined by CD contractility. These researchers hoped that future studies will show these new metrics useful in quantifying elements of the anti-reflux barrier in mechanistically defined subsets of GERD patients.

CPT Codes / HCPCS Codes / ICD-10 Codes

Information in the [brackets] below has been added for clarification purposes. Codes requiring a 7th character are represented by "+".

<table>
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<tr>
<th>Code</th>
<th>Code Description</th>
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<tr>
<td></td>
<td>Electrogastrography or colonic motility studies (colonic manometry):</td>
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<td>CPT codes covered for indications listed in the CPB:</td>
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<td>Code</td>
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<tr>
<td>91117</td>
<td>Colon motility (manometric) study, minimum 6 hours continuous recording (including provocation tests, eg, meal, intracolonic balloon distention, pharmacologic agents, if performed), with interpretation and report</td>
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CPT codes not covered for indications listed in the CPB:

- 91132  | Electrogastrography, diagnostic, transcutaneous                                                                                                               |
- 91133  | Electrogastrography, diagnostic, transcutaneous; with provocative testing                                                                                  |

ICD-10 codes covered if selection criteria are met:

- K59.00 - K59.09 Constipation                                                                                                                                  |
- R15.0  | Incomplete defecation                                                                                                                                            |

Wireless capsule for measuring gastric emptying parameters (SmartPill GI Monitoring System):

CPT codes not covered for indications listed in the CPB:

- 91112  | Gastrointestinal transit and pressure measurement, stomach through colon, wireless capsule, with interpretation and report |

ICD-10 codes not covered for indications listed in the CPB [not all-inclusive]:

- K20.0 - K31.9 Diseases of esophagus, stomach and duodenum                                                                                     |
- K55.011 - K64.9 Diseases of intestines                                                                                                          |
- Q43.1 - Q43.2 Hirschsprung's disease and other congenital functional disorders of the colon                                                        |
- R10.0 - R19.8 Symptoms involving digestive system and abdomen                                                                                 |

Radionuclide gastric emptying study:

CPT codes covered if selection criteria are met:

- 78264  | Gastric emptying imaging study (eg, solid, liquid, or both)                                                                                                |
- 78265  | Gastric emptying imaging study (eg, solid, liquid, or both); with small bowel transit                                                                        |
- 78266  | Gastric emptying imaging study (eg, solid, liquid, or both); with small bowel and colon transit, multiple days                                                  |

ICD-10 codes covered if selection criteria are met:

- K20.0 - K31.9 Diseases of esophagus, stomach and duodenum                                                                                     |
- K31.84  | Gastroparesis                                                                                                                                             |
- K55.011 - K64.9 Diseases of intestines                                                                                                        |
- Q43.1 - Q43.2 Hirschsprung's disease and other congenital functional disorders of the colon                                                      |
- R10.0 - R19.8 Symptoms involving digestive system and abdomen                                                                               |

Magnetic resonance enterography:

CPT codes covered if selection criteria are met:
<table>
<thead>
<tr>
<th>Code</th>
<th>Code Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>72197</td>
<td>Magnetic resonance (eg, proton) imaging, pelvis; without contrast material(s),</td>
</tr>
<tr>
<td></td>
<td>followed by contrast material(s) and further sequences</td>
</tr>
<tr>
<td>74183</td>
<td>Magnetic resonance (eg, proton) imaging, abdomen; without contrast material(s)</td>
</tr>
<tr>
<td></td>
<td>followed by contrast material(s) and further sequences</td>
</tr>
</tbody>
</table>

ICD-10 codes covered if selection criteria are met [not all-inclusive]:

- C17.0 - C17.9 Malignant neoplasm of small intestine
- K50.00 - K50.919 Crohn's disease [regional enteritis]
- K57.00 - K57.13 Diverticular disease of small intestine

**Gastric emptying breath tests (GEBT):**

CPT codes not covered for indications listed in the CPB:

- 0106U Gastric emptying, serial collection of 7 timed breath specimens, non-radioisotope carbon-13 (13C) spirulina substrate, analysis of each specimen by gas isotope ratio mass spectrometry, reported as rate of 13CO2 excretion

ICD-10 codes not covered for indications listed in the CPB [not all-inclusive]:

- K31.84 Gastroparesis

**3D high-resolution manometry** - no specific code:

ICD-10 codes covered if selection criteria are met [not all-inclusive]:

- K21.0 Gastro-esophageal reflux disease with esophagitis
- K21.9 Gastro-esophageal reflux disease without esophagitis

The above policy is based on the following references:

**Electrogastrography**


34. Longstreh GF. Approach to the adult with nausea and vomiting. UpToDate [online serial]. Waltham, MA: UpToDate; reviewed February 2014.

35. Camilleri M. Gastroparesis: Etiology, clinical manifestations, and diagnosis. UpToDate [online serial]. Waltham, MA: UpToDate; reviewed February 2014.

36. Lembo AJ. Motility testing: When does it help? UpToDate [online serial]. Waltham, MA: UpToDate; reviewed February 2015.

38. Lembo AJ. Overview of gastrointestinal motility testing. UpToDate [online serial]. Waltham, MA: UpToDate; reviewed January 2017.


42. Camilleri M. Gastroparesis: Etiology, clinical manifestations, and diagnosis. UpToDate [online serial]. Waltham, MA: UpToDate; reviewed September 2018.

Colonic Motility Studies


22. Camilleri M. Etiology and diagnosis of delayed gastric emptying. UpToDate [online serial]. Waltham, MA: UpToDate; reviewed February 2013.


36. Lembo AJ. Overview of gastrointestinal motility testing. UpToDate [online serial]. Waltham, MA: UpToDate; reviewed June 2019.

Wireless Capsule for Measuring Gastric Emptying (SmartPill GI Monitoring System)


2. SmartPill Corporation. SmartPill wins 510(k) release from FDA. The SmartPill GI Monitoring System will be available to GI professionals this fall. News Release. Buffalo,


23. BlueCross BlueShield Association (BCBSA), Technology Evaluation Center (TEC). Wireless motility capsule in the diagnosis and evaluation of gastroparesis or slow-transit constipation. TEC Assessment Program. Chicago, IL: BCBSA; October 2012;27(4).

Radionuclide Gastric Emptying Study


High Resolution Esophageal Pressure Topography (HREPT)

3D High-Resolution Manometry


Gastric Emptying Breath Testing (GEBT)

2. Camilleri M. Gastroparesis: Etiology, clinical manifestations, and diagnosis. UpToDate [online serial]. Waltham, MA: UpToDate; reviewed September 2018.
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AETNA BETTER HEALTH® OF PENNSYLVANIA

Amendment to
Aetna Clinical Policy Bulletin Number: 0396
Gastrointestinal Function: Selected Tests

There are no amendments for Medicaid.