

## ***Ingestible pH and Pressure Capsule***

**Effective:** February 1, 2019

**Next Review:** October 2019

**Last Review:** January 2019

### **IMPORTANT REMINDER**

Medical Policies are developed to provide guidance for members and providers regarding coverage in accordance with contract terms. Benefit determinations are based in all cases on the applicable contract language. To the extent there may be any conflict between the Medical Policy and contract language, the contract language takes precedence.

PLEASE NOTE: Contracts exclude from coverage, among other things, services or procedures that are considered investigational or cosmetic. Providers may bill members for services or procedures that are considered investigational or cosmetic. Providers are encouraged to inform members before rendering such services that the members are likely to be financially responsible for the cost of these services.

### **DESCRIPTION**

These capsules are used to measure the time it takes for a meal to empty from the stomach and/or small bowel or whole gut. It is proposed for evaluating delayed gastric emptying or conditions related to slow bowel transit time.

### **MEDICAL POLICY CRITERIA**

Measurement of gastrointestinal transit times including gastric emptying and colonic transit times using an ingestible pH and pressure capsule is considered **investigational** for all indications, including but not limited to suspected gastroparesis, constipation, or other gastrointestinal motility disorders.

*NOTE: A summary of the supporting rationale for the policy criteria is at the end of the policy.*

### **CROSS REFERENCES**

None

### **BACKGROUND**

The ingestible pH and pressure capsule, which may also be referred to as a wireless motility capsule, measures pH, pressure, and temperature changes to signify passage of the capsule through portions of the gastrointestinal tract. For example, an increase of two or more pH units usually indicates gastric emptying, and a subsequent decrease of one or more pH units usually indicates passage to the ileocecal junction. This differs from esophageal pH monitoring for gastroesophageal reflux disease which measures pH levels in various ways such as through catheters, impedance or a temporarily implanted device such as the Bravo. The ingestible pH and pressure capsule also differs from the wireless capsule endoscopy (i.e., PillCam™) which is a capsule swallowed by the patient that transmits video images wirelessly.

Gastroparesis is a chronic disorder characterized by delayed gastric emptying in the absence of mechanical obstruction. Symptoms of gastroparesis are often nonspecific and may mimic other gastrointestinal disorders. It can be caused by many conditions; most commonly it is idiopathic, diabetic or postsurgical. The test considered the reference standard for gastroparesis is called gastric emptying scintigraphy. The patient ingests a radionuclide-labeled standard meal, and then images are performed at 0, 1, 2, and 4 hours postprandially to measure how much of the meal has passed beyond the stomach. A typical threshold to indicate abnormal gastric emptying is more than 10% of the meal remaining at 4 hours after ingestion.

Many patients with gastroparesis or symptoms of gastroparesis also have coexisting lower gut involvement. Testing for small and large bowel motility disorders includes manometry, colonic transit study, whole gut or colonic transit scintigraphy, radio-opaque markers, and orocecal breath tests. These tests are often used in combination to assess symptoms of gastrointestinal dysmotility and for diagnostic evaluation.

## **REGULATORY STATUS**

In 2006 an ingestible capsule (SmartPill™ Motility Testing System [Medtronic], previously SmartPill® GI Monitoring System [Given Imaging]) was cleared for marketing by the U.S. Food and Drug Administration (FDA) via a 510(k) application with the indication for use in adult patients to evaluate delayed gastric emptying (K092342). Gastric emptying is signaled when the pH monitor in the capsule indicates a change in pH from the acidic environment of the stomach to the alkaline environment of the small intestine. While SmartPill does not measure 50% emptying time, it can be correlated with scintigraphically measured 50% emptying time. The capsule also measures pressure and temperature throughout its transit through the entire gastrointestinal (GI) tract, allowing calculations of total GI transit time.

In 2009 the FDA expanded the use of the SmartPill to determine colonic transit time for the evaluation of chronic constipation and to differentiate between slow versus normal transit constipation in adults. When colonic transit time cannot be determined, small and large bowel transit times combined can be used instead.

The SmartPill is not for use in pediatric patients.

Note: This policy does not address wireless capsule endoscopy (PillCam™), patency capsule (PillCam™ Patency Capsule, previously referred to as Agile Patency system), or esophageal pH monitoring.

## **EVIDENCE SUMMARY**

Evaluation of a diagnostic technology typically focuses on the following three parameters. Analytic validity is evaluated by comparing test measurements with a gold standard. Clinical validity (i.e., sensitivity, specificity, and positive and negative predictive value) is evaluated by the ability of a test to accurately predict the clinical outcome in appropriate populations of patients. The sensitivity of a test is the ability to detect a disease when the condition is present (true positive). The specificity is the ability to detect the absence of a disease or outcome when the disease is not present (true negative). Clinical utility is a key aspect in evaluating clinical test performance. Clinical utility is based on demonstration that the diagnostic information can be used to improve patient outcomes. Additionally, when considering invasive monitoring, any improvements in patient outcomes must be outweighed by device-related risks associated with testing.

## **ANALYTIC VALIDITY OF WIRELESS PRESSURE AND PH CAPSULE**

### **Gastric Emptying**

Although gastric emptying scintigraphy is considered the reference standard for evaluating gastric emptying, several issues complicate its use as a reference test. Until recently, there has been a lack of standardization of the test.<sup>[1]</sup> Differences in the test meal used, patient positioning, frequency, duration, and interpretation of imaging all limit the clinical utility of the test. Significant day-to-day variability in the rate of gastric emptying has been noted.<sup>[2]</sup>

There is limited knowledge regarding the capability of the gastric emptying test to discriminate between healthy individuals and those with known gastroparesis due to lack of standardization of the test and small patient samples in published studies. One study, which proposed a threshold of normality at 10% meal retention at 4 hours, included only 123 healthy subjects.<sup>[3]</sup> The cutoff point was set to include 95% of normal persons. However, it appears to be unknown if this same threshold adequately identifies persons who would otherwise be classified as having gastroparesis and who are candidates or responders to treatment.

### **Systematic Reviews and Technology Assessments**

A 2013 systematic review of 12 studies on the ingestible capsule was published by the Agency for Healthcare Research and Quality (AHRQ).<sup>[4]</sup> While studies that included only healthy participants were excluded from the AHRQ review, studies were included in the review that used comparison groups consisting of healthy, asymptomatic (i.e., without symptoms of gastroparesis or constipation) participants as controls, thus limiting interpretation of the comparisons regarding the diagnostic accuracy of the wireless motility capsule (WMC). Overall, the strength of evidence in the available studies on the ingestible capsule was found to be low. Diagnostic accuracy with the ingestible capsule was considered comparable to gastric scintigraphy in 7 studies with diagnostic agreement ranging from 58% to 86% for test agreement when results were positive and 64% to 81% when test results were negative. There was moderate correlation between the ingestible capsule and gastric emptying scintigraphy on transit data and device agreement in 5 studies with correlation coefficients ranging from 0.69 to 0.71. Authors concluded WMC may be a viable diagnostic option; however, numerous limitations of the data, including insufficient numbers of study participants, variable administration of the motility test, and different demographic characteristics between the control and treatment groups, limit the strength of these findings.

In 2012 BCBSA conducted a technology assessment which concluded that the evidence is insufficient to determine whether the wireless motility capsule improves net health outcomes or

is as beneficial as any established alternative for diagnosis and evaluation for patients with gastroparesis.<sup>[1]</sup>

## **Non-randomized Studies**

A 2013 study by Green assessed SmartPill and gastric emptying scintigraphy in 22 pediatric patients with severe upper gastrointestinal symptoms.<sup>[5]</sup> Of 20 evaluable patients who had both tests, 9 patients had delayed gastric emptying identified by scintigraphy. SmartPill was 100% sensitive and 50% specific for delayed gastric emptying. Patients also underwent antroduodenal manometry for detection of motor abnormalities. SmartPill identified motor abnormalities in 17 patients, compared with 10 detected by antroduodenal manometry. However, there does not appear to be a reference standard for motor abnormalities. Thus it cannot be determined whether SmartPill is more sensitive or whether it has a higher false-positive rate for detection of motor abnormalities.

Cassilly evaluated the SmartPill and simultaneous gastric emptying scintigraphy in 15 healthy subjects.<sup>[6]</sup> The capsule was ingested immediately after ingesting the radiolabeled test meal. In this study, the mean time for 50% gastric emptying by scintigraphy was 95 minutes, 90% gastric emptying by scintigraphy was 194 minutes, and gastric residence time by SmartPill was 261 minutes. The correlation of SmartPill to 50% gastric emptying time was 0.606 and to 90% gastric emptying time was 0.565. The average amount of meal remaining in the stomach at the time the SmartPill exited the stomach was 5.4%. This study only shows modest correlation of the SmartPill and gastric emptying scintigraphy. The study is too small to establish reference values for the SmartPill.

Kuo evaluated 87 healthy subjects and 61 subjects with symptoms and prior positive test results for gastroparesis using both the SmartPill and gastric emptying scintigraphy.<sup>[7]</sup> In this study, subjects ingested the capsule just before ingesting the standard meal. This resulted in 5 subjects who passed the SmartPill in less than 30 minutes, who were then subsequently considered to have invalid tests. Sixteen other subjects had equipment malfunctions, and 2 others dropped out. Among the remaining 125 subjects, the correlation of SmartPill emptying time and scintigraphy at 2 hours was 0.63, and between SmartPill emptying time and scintigraphy at 4 hours was 0.73. In terms of the capability to discriminate between gastroparetic patients and healthy subjects, the area under the curve (AUC) was 0.83 for SmartPill, 0.82 for scintigraphy at 4 hours, and 0.79 for scintigraphy at 2 hours (all  $p > 0.05$  for statistical significance), indicating similar capability for discriminating between the two patient groups. At a cutoff point of 300 minutes for the SmartPill, which was established by calculating the ideal cutoff point from the data, the sensitivity was 65% and specificity was 87%. The sensitivity and specificity for scintigraphy using an established cutoff point from the literature of 10% at 4 hours was 44% and 93%.

Maqbool assessed SmartPill and gastric emptying scintigraphy in 10 healthy asymptomatic subjects.<sup>[8]</sup> Emptying time assessed by SmartPill was correlated with the percent meal retained at 2 and 4 hours. The correlation between SmartPill and 2-hour scintigraphy was 0.95. The correlation between SmartPill and 4-hour scintigraphy was 0.70

These data have several shortcomings regarding the use of the SmartPill in diagnosing gastroparesis, and as a result, the diagnostic accuracy is not well defined. These shortcomings include:

All of the studies included healthy asymptomatic subjects either entirely or as part of a control group. Healthy subjects do not represent the clinically relevant group under consideration for a diagnosis of delayed gastric emptying. The relevant population of subjects should have symptoms or are being considered for the diagnosis of gastroparesis.

Because of the change in the protocol for use of the SmartPill from ingesting the capsule before the standard meal to after the standard meal to avoid fast exit of the SmartPill from the stomach, the results of Kuo may no longer represent the performance of the device as it is now intended to be used. The cutoff point for sensitivity and specificity was not prespecified; using visual inspection to identify a cutoff point overestimates the diagnostic characteristics of the test.

Although there was moderate correlation between SmartPill gastric emptying time and scintigraphy, the current reference test, scintigraphy is an imperfect gold standard with limited reliability. This creates difficulties in defining the sensitivity and specificity of SmartPill.

Although overall, the AUCs between the SmartPill and scintigraphy were similar, the modest correlation between the two tests means that there are often discordant results. What such discordant results mean in terms of diagnosis and treatment are uncertain.

## **COLON TRANSIT TIME**

### **Systematic Reviews and Technology Assessments**

A 2013 systematic review of 12 studies on the ingestible capsule was published by the Agency for Healthcare Research and Quality (AHRQ).<sup>[4]</sup> While studies that included only healthy participants were excluded from the AHRQ review, studies were included in the review that used comparison groups consisting of healthy, asymptomatic (i.e., without symptoms of gastroparesis or constipation) participants as controls, thus limiting interpretation of the comparisons regarding the diagnostic accuracy of the wireless motility capsule (WMC). Overall, the strength of evidence in the available studies on the ingestible capsule was found to be low. Three studies that evaluated transit time reported similar sensitivity and specificity for the ingestible capsule and scintigraphy. Authors concluded WMC may be a viable diagnostic option; however, numerous limitations of the data, including insufficient numbers of study participants, variable administration of the motility test, and different demographic characteristics between the control and treatment groups, limit the strength of these findings.

In 2012 BCBSA conducted a technology assessment which concluded that the evidence is insufficient to determine whether the wireless motility capsule improves net health outcomes or is as beneficial as any established alternative for diagnosis and evaluation of colon transit time.<sup>[9]</sup>

### **Randomized Controlled Trial**

In 2010, Camilleri compared the wireless motility capsule to radio-opaque markers in 158 patients with chronic functional constipation.<sup>[10]</sup> In this multicenter validation study, the authors reported positive percent agreement between the wireless motility capsule and radio-opaque markers was approximately 80% for colon transit time and small and large bowel transit time. No serious adverse events occurred in the study.

### **Non-randomized Studies**

In the study by Maqbool (2009), healthy asymptomatic individuals underwent simultaneous whole-gut scintigraphy and SmartPill assessment of whole gut transit times.<sup>[8]</sup> The two techniques correlated with each other reasonably well. Tartera (2017) had similar findings in a cohort of 73 healthy adults that evaluated gastric emptying, small bowel, colon, and whole gut transit using the SmartPill.<sup>[11]</sup>

In another study by Rao, normal subjects and subjects with constipation had whole gut transit times assessed with radio-opaque markers and the SmartPill.<sup>[12]</sup> The diagnostic accuracy of the two techniques in differentiating the two groups of patients was similar.

## **CLINICAL UTILITY OF WIRELESS PRESSURE AND PH CAPSULE**

In a 2015 retrospective review of patients who underwent evaluation with SmartPill for suspected multiregional gastrointestinal dysmotility, Arora reported abnormal test results in 109 of 161 (67.7%) of subjects.<sup>[13]</sup> Of these patients, multiregional dysmotility was diagnosed in 54 (49.5%). Although this study demonstrated a high yield of diagnosis among patients with a particular suspected condition, it did not demonstrate improved patient outcomes compared to standard tests.

The 2013 systematic review by AHRQ found there was limited evidence available on the clinical impact of testing with the ingestible capsule.<sup>[4]</sup> Therefore, the evidence was insufficient to draw conclusions regarding the impact of ingestible capsule testing results on treatment and management decisions.

In 83 patients evaluated for gastroparesis, small intestinal dysmotility and constipation, Kuo found wireless motility capsule testing resulted in a new diagnosis in 44 patients (53%).<sup>[14]</sup> Clinical management changes were recommended in 65 patients. These included changes in medication regimens in 39 patients (60%) and in nutrition programs in 9 patients (13.8%). Four patients (6.2%) were referred to surgery for colectomy. Abnormal gastric emptying or small intestinal transit times did not influence patient management at all ( $p=NS$ ). Abnormal colon transit times did not influence nutritional program changes ( $p=0.72$ ) but did influence medication changes ( $p=0.02$ ) and resulted in a trend toward increased surgical referrals ( $p=0.12$ ). The authors believe wireless motility capsule testing eliminated the need for nuclear gastric emptying testing in 9 of 52 patients (17.3%), barium radiography testing in 7 of 13 patients (53.8%), and radio-opaque marker testing in 41 of 60 patients (68.3%). The authors noted a need for prospective studies to further understand wireless motility capsule testing and its role in patient management.

In 86 patients with persistent symptoms of gastrointestinal dysmotility, despite normal endoscopic and radiologic test results, Rao found evaluations with wireless motility capsule testing resulted in new diagnostic information in 26 of 50 patients (53%) with lower gastrointestinal symptoms (LGI) and 17 of 36 patients (47%) with upper gastrointestinal symptoms (UGI).<sup>[15]</sup> Clinical management was influenced by wireless motility capsule testing in 30% of patients with LGI symptoms and in 50% of patients with UGI symptoms. The authors indicated the retrospective nature of this study limited interpretation of results.

## **ADVERSE EVENTS**

In terms of adverse events reported in the study by Kuo, 5 subjects of 67 who did not retrieve the capsule required a second additional plain x-ray beyond 5 days to demonstrate that the capsule had been passed.<sup>[14]</sup> Another patient had ingested a laxative that caused the capsule

to be entrapped in a viscous mass. An unsuccessful endoscopy and treatment with intravenous erythromycin was required to pass the capsule from the stomach.

The U.S. Food and Drug Administration (FDA) has received adverse event reports, which can be found on the Manufacturer and User Facility Device Experience website.<sup>[16]</sup> For example, in one report the capsule was trapped in the patient's ileum and required hospitalization with NG tube, IV fluids, and bedrest.<sup>[17]</sup> In another example, the patient vomited and choked on the capsule three days after ingestion, requiring performance of self-administered abdominal thrusts to dislodge the capsule.<sup>[18]</sup> Other reported adverse events included entrapment of the capsule in the esophagus, stomach, and small intestine, some requiring endoscopic removal.

## PRACTICE GUIDELINE SUMMARY

There are no evidence-based clinical practice guidelines from U.S. professional associations that address the use of ingestible pH and pressure capsules for any indication. Four consensus-based position statements have been published, all of which note the lack of sufficient evidence on the impact of the technology on patient management and health outcomes.<sup>[19-22]</sup>

## SUMMARY

The research regarding ingestible pH and pressure capsules (i.e., SmartPill™) for the evaluation of gastric emptying time and colon transit time is limited. For example, studies have included populations that are not representative of patients who may be offered this treatment option. These studies have not furnished information showing health outcomes are improved as a result of evaluation with ingestible pH and pressure capsules. Therefore, ingestible pH and pressure capsules are considered investigational.

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## CODES

Codes	Number	Description
CPT	91112	Gastrointestinal transit and pressure measurement, stomach through colon, wireless capsule, with interpretation and report
HCPCS	None	

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