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SOCIETY PUBLICATIONS
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June 22, 2011

Richard A. Justman, MD
Chairman, Medical Technology Assessment Committee
United Healthcare
5901 Lincoln Drive
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Dear Dr. Justman,

The American Gastroenterological Association is the trusted voice of the GI community. Founded in 1897, the AGA has grown to include 17,000 members from around the globe who are involved in all aspects of the science, practice and advancement of gastroenterology. The AGA Institute (AGA) administers the practice, research and educational programs of the organization.

The AGA was recently contacted by United Healthcare (UHC) to review the draft medical policy on the topic of **Gastrointestinal Motility Disorders, Diagnosis and Treatment** (policy # 2011T0415G). This draft policy addresses several technologies and therapies for gastrointestinal motility disorders, which we address in our comments.

Electrogastrography

We agree with the conclusion that although electrogastrography (EGG) is a promising technology, EGG has not yet been standardized for routine clinical use in investigating the mechanisms of gastric motility and sensation in patients with gastric motility disorders or motion sickness.

Gastric Electrical Stimulation Therapy

We agree with the conclusion that gastric electrical stimulation therapy using the Enterra™ Therapy System is proven for the treatment of chronic, intractable, or drug-refractory nausea and vomiting secondary to gastroparesis of diabetic or idiopathic etiology when provided according to U.S. Food and Drug Administration (FDA) labeled indications. We applaud United Healthcare for taking the lead in recognizing that technologies which are granted a humanitarian device exemption (HDE) by the U.S. Food and Drug Administration such as the Enterra™ Therapy System, are not experimental or investigational in patients whose gastroparesis has proven to be refractory to other treatments.

Colonic Manometry

As noted in the draft policy, the AGA medical position statement on constipation (2000) states that colonic manometry is not generally available and is not appropriate for most patients, except in the research setting.[1] The AGA is currently reviewing and updating this medical position statement, which is over 11 years old, and will be issuing revised guidance on this issue within the year.

Colonic manometry assesses colonic muscle function, peristalsis and tone, which are important in the evaluation of complex and clinically poorly responsive colonic dysfunction, pseudo-obstruction, and severe symptomatic constipation and diarrhea in pediatric and adult populations. In the evaluation of these patients, standard radiologic and endoscopic diagnostic tests are often normal, and anorectal manometry and defecography provide no information regarding colonic dysfunction. The assessment of colonic motor function and tone can identify the underlying mechanism responsible for the patient's symptoms, and guide therapeutic management. In view of such, we believe that colonic manometry can be a beneficial tool in the diagnostic assessment of selected adult and pediatric patients as described above.

Wireless Motility Capsule

We agree with your conclusion that in the evaluation of patients with gastroparesis, once macroscopic abnormalities are eliminated through endoscopic examination, delayed gastric emptying should be documented through a reproducible diagnostic test. There are limitations with gastric emptying scintigraphy, including lack of standardization of meal composition, timing of image acquisition, and lack of appropriate normal values with some meals. Patients with gastroparesis may suffer from motility abnormalities in the midgut or hindgut, for which patients may be evaluated by observing the passage of orally administered radiopaque markers (ROM) on abdominal x-ray. However, a ROM study provides only a qualitative assessment of colon transit at discreet intervals, requires a minimum of two or more visits, may not distinguish dynamic motility disorders in the small and large intestine, and is associated with radiation exposure.

Patients with gastroparesis can have normal or altered motility of the small and/or large intestine, and patients with severe constipation can have normal or altered motility of the foregut and/or midgut. Treatment for these various situations differs significantly, depending on whether the motility abnormality is localized or generalized. For example, a patient with upper abdominal symptoms, abnormal gastric emptying and small bowel motility dysfunction but normal colonic motility would be treated differently than a patient with abnormal gastric emptying and abnormal midgut and hindgut motility. Similarly, a patient with constipation and no structural / luminal abnormality of the colon who has normal colonic transit and normal anorectal manometry would be treated differently (e.g. bulking agents) than a patient with constipation and abnormal colonic transit. In the latter

situation, it is essential to simultaneously assess gastric emptying and small bowel motility, for proceeding with colectomy in a patient with colonic stasis could have a disastrous outcome in a patient with gastroparesis and diffuse motility disorder.

The AGA believes that integrated measurement of gastric emptying, gastrointestinal tract transit time, pH, and pressure using the wireless motility capsule (WMC) system should be considered for patients with suspected gastroparesis and gastrointestinal (GI) tract motility disorders. A single comprehensive test which can reproducibly assess gastric emptying along with evaluation of motility in the midgut and hindgut, without exposure to radiation, is beneficial in patients who remain symptomatic and refractory to empirical treatment.

Our conclusions are based on the following:

- Patients with dysmotility disorders of the gut often present with abdominal pain, bloating, dyspepsia, nausea and vomiting. These symptoms, whether alone or in combination, cannot identify whether the dysmotility is localized to the stomach, or the area of the gut that has dysmotility.
- Approximately 20% of patients thought to have isolated gastroparesis are found to have concurrent motility disorders of the lower gut.
- Over 18% of patients thought to be suffering solely from prolonged colon transit are found to have gastroparesis as their dominant motility disorder.
- The assumption that gastric scintigraphy has 100% sensitivity / 100% specificity for detecting gastroparesis is flawed.
- The assumption that ROM, a non-standard test, is a reference test with 100% sensitivity / 100% specificity for the evaluation of colonic dysmotility, is flawed and erroneous.
- As treatments and therapeutic approaches for gastroparesis and prolonged colon transit time differ greatly, accurate diagnosis is imperative to provide appropriate treatment and successful clinical outcomes in these challenging patients.
- Other diagnostic options are limited. Often times, multiple endoscopic, radiologic, scintigraphic and motility tests are performed in an attempt to isolate the area of dysmotility. The availability of reproducible small intestinal scintigraphy is limited to a handful of academic centers in the U.S., and small intestinal motility studies remain a research tool.
- In comparison, the WMC system can reproducibly distinguish slow (abnormal) transit from normal transit while providing regional transit times for the foregut, midgut and hindgut, which is important when evaluating GI motility disorders and guiding appropriate therapeutic options. Pressure contraction data from the antrum and duodenum can be used to calculate motility indices, which can replace the need for separate gastric emptying scintigraphy and ROM studies.

The WMC system is indicated for use in evaluating adult patients with suspected delayed gastric emptying, such as idiopathic and diabetic gastroparesis, functional non-ulcer dyspepsia, chronic constipation and whole-gut and/or regional motility disorders.[2] [3] The AGA has reviewed the UHC analysis of the clinical literature, and we *respectfully disagree* with the draft conclusion that the evidence is insufficient to support that the WMC system is proven for the diagnosis of GI motility disorders.

Rao (2010) addressed the diagnostic utility of WMC versus conventional tests (scintigraphy & ROM) in suspected GI dysmotility patients, and the impact of overlapping motility disorders on patient management. WMC provided new diagnostic information in 53% of suspected lower GI patients and 47% of the suspected upper GI patients. Additionally, WMC detected generalized motility disorder in 51% of patients. The new diagnostic information reflects the well established overlap in regional dysmotility in a subset of symptomatic patients. This study documented WMC findings influencing patient management in 30% of lower GI patients and 88% of upper GI patients as a direct result of the new diagnostic information. [4]

The AGA *respectfully disagrees* with the statement that these findings need to be confirmed as these findings have already been confirmed by Sarosiek (2010) in 34 gastroparetics and Camilleri (2010) in 158 patients with chronic constipation. Both investigators noted that 18 % of their respective study populations were delayed in the GI region remote to their primary symptoms. Sarosiek identified delay in the colon for the gastroparetics and Camilleri identified delay in the stomach for the patients with chronic constipation.[5] [6] Similar findings have been reported in earlier studies by Sadik (2003) and Bonapace (2000). More importantly, the additional transit delays are new findings that cannot be detected by conventional ROM or gastric scintigraphy tests, significantly informing patient management.[7] [8]

The draft bases its conclusions on Kuo (2008), relying on the assumption that scintigraphy had 100% sensitivity / 100% specificity for detecting gastroparesis and WMC has 87% sensitivity / 92% specificity, implying that WMC is not as accurate.

The AGA *respectfully disagrees* and believes this study demonstrates the improved diagnostic accuracy of WMC when compared to the more widely available, but substandard, scintigraphy test. We believe your analysis incorrectly identifies device agreement as sensitivity and specificity. The study reported WMC sensitivity as 0.65 and specificity of 0.87, while 4-hour scintigraphy had sensitivity of 0.44 and specificity of 0.93. The more widely used 2-hour scintigraphy had a sensitivity of 0.34 and a specificity of 0.93.

The inclusion criteria for the prospective study required both symptoms and documentation of a prior delayed scintigraphy test. The reclassification of patients based on the

scintigraphic results conducted simultaneously with WMC was additionally presented to provide a measure of the positive device agreement between the two devices in healthy and gastroparetic populations (92% & 87%, respectively). The diagnostic accuracies of detecting gastroparesis in the population by WMC and 4-hour scintigraphy as measured by area under the curve (AUC) were not statistically different. In addition, the AUC equivalency between WMC and scintigraphy, a proven statistical measure of clinical utility, demonstrates that WMC is as beneficial as the established alternative (scintigraphy) for diagnosing gastroparesis. In view of such, the conclusion that "the available studies do not provide sufficient evidence to determine whether the diagnostic accuracy of the SmartPill equals or exceeds the diagnostic accuracy of conventional techniques for assessment of gastrointestinal motility," is incorrect.

Kuo also found that scintigraphy was only 30-40% sensitive in detecting delayed gastric emptying in symptomatic gastroparetic patients with previously abnormal scintigraphic testing. The WMC was 20% more sensitive - not less - than scintigraphy when done simultaneously during the trial in the intended use symptomatic population. The assumption that scintigraphy was 100% sensitive and specific is a flawed assumption because patients already had a previously abnormal scintigraphic test to enter the trial. As a result, scintigraphy demonstrates only fair reliability at making the diagnosis of delayed gastric emptying in patients with gastroparesis and WMC has a higher sensitivity. The increased sensitivity of the WMC may reflect detection of additional gastric fasting, physiological abnormal gastroparetic function that is unavailable to detection using scintigraphy. [9]

In Rao (2009), the draft states that the shortcomings of this study include failure to report sensitivity/specificity of WMC for detecting delayed motility using ROM as the reference standard. Additionally, in the normal group, WMC indicated that colonic and whole-gut transit times were slower in women than in men, which may suggest that the larger proportion of women in the constipated group may have influenced the apparent accuracy of WMC for detection of constipation.

The AGA *respectfully disagrees* with both of these critiques. The FDA classifies devices such as ROM with low sensitivity and specificity as "non-reference standards." It further recommends that comparisons be based on device agreement, not sensitivity/specificity for such devices. The AHRQ's *Methods Guides for Medical Tests Review* specifically addresses how to perform meta-analysis of test performance evidence when there is an imperfect reference standard. The AHRQ recommends assessing concordance of different tests instead of test accuracy when there is an imperfect reference standard. In this case, the analysis should focus on device agreement instead of sensitivity and specificity and whether one test can be used in place of the other. [10] In view of such, the assumption that ROM is a reference standard has led to an incorrect assumption.

The prevalence of females in the sample patient population reflects the prevalence observed in clinical practice. Any bias to sensitivity introduced by prevalence of women in the disease group would similarly be reflected in the ROM results. Thus, WMC and ROM would both be expected to be effected similarly by any gender bias. [11]

In Camilleri (2010), UHC assumes that ROM has 100% sensitivity and 100% specificity and that WMC reported colonic transit time measurements with 80% sensitivity (95%CI 67%-98%) and 91% specificity (CI 83% to 96%) and WMC small and large bowel transit time measures with 79% sensitivity (CI 67% to 89%) and 91% specificity (CI 83% to 96%). The draft does not reach a conclusion; rather it postulates that because the confidence intervals did not overlap 100% either WMC is not as accurate as ROM or ROM is not an absolutely accurate test.

The AGA *respectfully disagrees* as it appears the reviewers have confused device agreement measurements with sensitivity and specificity. The purpose of the Camilleri study was to demonstrate substantial equivalence, defined as diagnostic device agreement >65%. Sensitivity and specificity were not used primarily because ROM is not a gold standard and as such, cannot be viewed as a reference standard. In fact, what was reported for colonic transit was positive % agreement ~ 80% (95% CI = 67%-98%) and 91% negative device agreement (95% CI = 83% to 96%). Colonic transit and small bowel transit reported 79% positive device agreement and 91% negative device agreement.[5]

This data shows excellent device agreement and, more importantly, equal or better sensitivity. Further, the WMC is a quantitative measure that provides assessment of severity of underlying dysmotility. In the AGA's opinion, the ROM test in clinical practice is, at best, qualitative with reports routinely reporting "few" or "many" ROM remaining but rarely an official count. Finally, ROM routinely requires a minimum of 2 flat panel KUB x-rays, and often more, which increases costs and radiation exposure.

Camilleri (2010) is the prospective validation study that provides sufficient evidence demonstrating that WMC is an accurate test when compared to ROM for determining colonic transit time. The AGA views WMC as being a validated colonic transit test and as such should be a covered procedure by UHC.[5]

The critique of Sarosiek (2010) was that the study did not compare WMC with another technique for assessment of gastrointestinal motility.

This study demonstrated that WMC can be used to identify a subset of patients who have dysmotility of overlapping regions. The patients in this study were derived from the Kuo (2010) study and were confirmed gastroparetics both by multiple scintigraphy tests as well

as WMC. Because scintigraphy cannot assess colonic transit, it is not a study design flaw to review the colonic transit times derived from WMC test results. Rather, this study speaks to the shortcomings of the existing standard scintigraphy test as it was unable to identify the 18% of confirmed gastroparetics who also suffered from delayed transit beyond the stomach. Thus, this study supports the AGA's position that WMC is a single diagnostic test that can replace single region transit tests such as scintigraphy and ROM.[6]

The review of Kloetzer (2010) states that the study did not compare WMC with another technique for assessment of gastrointestinal motility.

The AGA *respectfully disagrees.* Kloetzer included an analysis of patients who had been previously diagnosed as gastroparetic. Because scintigraphy is only capable of providing an estimate of gastric transit without any additional pressure information, it was not feasible to retrospectively compare pressure profiles between WMC and scintigraphy. The study effectively demonstrated the use of the additional data derived from WMC over scintigraphy to differentiate between healthy and gastroparetic patients based upon phasic pressure profiles on the stomach and small intestine. Statistically significant diminished pressure profiles were seen in the severely delayed gastroparetic group versus the gastroparetic group as a whole, demonstrating the diagnostic utility of using WMC pressure as a means to identify severity of delay in the stomach. [12]

In a study by Cassilly (2008), WMC pressure profiles were assessed simultaneously with those recorded by antroduodenal manometry (ADM) to determine the physiological mechanism of stomach emptying of a non-digestible solid. This study showed that the WMC empties from the stomach in the fasted state associated with either high amplitude antral contractions or phase III Migrating Motor Complexes. The authors reported similar pressure profiles recorded by ADM and WMC when the capsule resides in the antroduodenal region, demonstrating the relevance of the WMC recorded pressure profiles with respect to ADM measured frequency of contractions. As ADM cannot measure gastric emptying a direct comparison of the diagnostic accuracy of WMC to ADM for gastric emptying is not feasible, rather ADM provides an indication of the condition of gastric motor function in a patient. Kloetzer reports cutoffs values for WMC gastroduodenal motor function that inform the clinician of the condition of the gastroduodenal motor function; no cutoffs are published for ADM motor function. The difference in design (free floating capsule versus stationary catheter) of the pressure recording devices requires development of independent cutoffs for normal and abnormal pressure patterns. [13]

In its analysis of Timm (2011), the draft concluded that the study limitations included short duration, lack of randomization and unusable data due to delayed gastric emptying of the capsule.

The results of Timm supported the WMC's ability to assess the impact of therapies in the colon. This was a pilot study designed to assess changes in colonic transit from introduction of fiber in to a diet of healthy subjects. The results demonstrated significantly reduced colonic transit measured by WMC, suggesting its effectiveness to assess the effects of therapeutic intervention on colonic transit. The subjects were healthy volunteers with normal transit time (<73hrs whole gut transit) under non-test conditions, and it was anticipated that the addition of fiber would shorten this duration. The WMC was expected to exit the body within the three-day time period, thus completing the trial. The slightly higher prevalence of unusable gastric emptying data is attributable to the modified meal provided with the WMC containing a significantly higher caloric content which is expected to delay emptying relative to the standard meal. [14]

The assessment of Michalek (2011) concluded that the study did not confirm the utility of the findings in improving patient outcomes. AGA *respectfully disagrees* with the conclusion that Michalek did not confirm improvement in health outcomes. This study demonstrated that PPI's did not interfere with the ability to detect gastroparesis with WMC in patients who underwent the test while remaining on PPI therapy. Furthermore, this study demonstrated that PPI's did not have an impact on gastric emptying transit time. Health outcomes are improved, as a patient does not undergo the physical burden of discontinuing a necessary therapeutic treatment in order to undergo WMC testing. The literature regarding discontinuation of PPI's during a gastric emptying scintigraphy test is equivocal and as such, a patient may be required to remain on PPI's.[15]

The ECRI Analysis provided a broad summary of the body of evidence and the study designs. Their analysis raised the following concerns:

1. The studies reported in the literature do not appear to be reported in the diagnostic cohort groups the device is intended for and therefore device accuracy cannot be assessed. Studies were done only in healthy people of populations where the condition was previously identified.
2. No accepted reference standard has been applied in the reported studies.
3. Data analyses were conducted in unmasked data sets leading to potential for overestimation of accuracy.
4. All reported studies are technical or feasibility studies and therefore do not provide acceptable information on diagnostic accuracy or safety.

Studies have been conducted that specifically address the concerns raised in the ECRI review. Camilleri (2010) compared the performance of WMC to detect slow transit constipation in subjects with chronic constipation to ROM, used for assessing slow transit constipation. The study was neither a technical study nor a feasibility study, but rather a validation study specifically designed to assess the accuracy of WMC cutoff for normal versus delayed colonic transit defined in Rao (2009). The validation study was conducted in

the intended use patient cohort and investigators were blinded to all subject's colonic transit profiles. The prevalence of slow transit found by both methods was consistent with the prevalence of slow transit reported in the literature in chronic constipation (36-38%). The use of an independent study cohort to validate WMC cutoff avoided sample bias that can produce inflated sensitivity results. The study demonstrated excellent device agreement and equivalent sensitivity between the two methods. In Kuo (2008) the wireless motility capsule was compared to the reference standard for gastric transit or gastric emptying scintigraphy. Unblinded cutoffs were based on healthy population reference values and therefore not subject to interpretation bias.[4 5 9]

The WMC device has been shown to be safe, with no serious adverse events reported through three multicenter clinical studies involving more than 450 healthy subjects and patients with functional GI disorders, the intended use population. A search of MedWatch, the FDA safety reporting website notes three reportable events involving WMC occurring in 2008 and 2009. All three events involved prolonged retention in the GI tract and all resolved satisfactorily.

The analysis by Hayes, Inc. mistakenly introduces the assumption that scintigraphy and ROM are 100% sensitive and specific and because WMC does not demonstrate 100% sensitivity and specificity, it is not as accurate. Hayes states that additional studies are needed to determine whether WMC improves clinical decision making in the diagnosis and treatment of motility disorders.

The AGA *respectfully disagrees* with Hayes, for the assumptions that the standard reference test (gastric emptying scintigraphy) and the non-standard reference test (ROM) are 100% sensitive and 100% specific are not scientifically supported. As stated previously, the draft analysis incorrectly identifies device agreement as sensitivity and specificity. The gastroparetic inclusion criteria for the prospective study in Kuo (2008) require both symptoms and documentation of a prior delayed scintigraphy test. The reclassification of patients based on the scintigraphic results conducted simultaneously with WMC was additionally presented to provide a measure of the positive device agreement between the two devices in healthy and gastroparetic populations (92%/87% respectively). [9]

Furthermore, Hayes noted that "an 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" (Kuo 2008). In fact, this AUC equivalency argues strongly in favor of coverage, for it establishes that WMC is as beneficial as the established alternative in diagnosing or treating a disease state. When coupled with WMC's validated accuracy for measuring colonic transit, WMC is more beneficial than gastric emptying scintigraphy for evaluating patients with overlapping motility disorders, especially as they cannot be identified solely on the basis of symptoms and/or gastric scintigraphy.

As noted previously, there is a significant improvement in sensitivity demonstrated by WMC over scintigraphy. Kuo (2008) reported WMC sensitivity as 0.65 and specificity of 0.87 while 4-hour scintigraphy had sensitivity of 0.44 and specificity of 0.93. The more widely used 2-hour scintigraphy had a sensitivity of 0.34 and a specificity of 0.93. The Hayes analysis is inaccurate in its conclusion, for this study demonstrates that 4-hour scintigraphy when compared to same day scintigraphy is less sensitive than WMC.

With respect to WMC compared to ROM, Hayes introduces an unsupportable assumption of 100% sensitivity & specificity of ROM. As previously stated, ROM is not considered to be a gold standard but rather a non-standard reference test and, as such, cannot be assumed to be 100% sensitive or 100% specific.

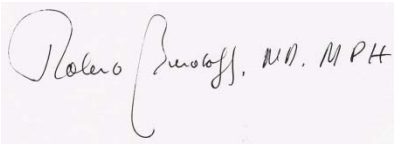
With respect to the conclusion that additional studies are needed to determine whether WMC improves clinical decision making in the diagnosis and treatment of GI disorders, we respectfully refer the reviewers to the compendium of studies documenting significant overlap in dysmotility (Sarosiek 2010; Camilleri 2010; Rao 2009) as well as Rao (2010) that definitively demonstrate significant new diagnostic findings and associated changes in patient management and treatment in both upper and lower GI dysmotility patients.[4 5 6 11] We are at a loss to understand what further information would be gained by additional studies that would only serve to confirm what is already known, while increasing the clinical and financial burden on patients who otherwise would not have access to a comprehensive and reproducible test with inter-rater reliability, the only test which can identify the presence or absence of coexisting motility abnormalities across the foregut, midgut and hindgut.

The AGA is committed to providing payors with the most current and relevant clinical evidence on all technologies utilized by physicians and medical staff in gastroenterological practice. In this era of accountable care where the goal is to provide the right test for the right patient in a cost-efficient manner, we recommend that you reconsider your draft coverage determination for the wireless motility capsule and include this technology as being proven for patients who are undergoing evaluation for suspected gastroparesis and GI tract motility disorders. The results of this comprehensive study can help physicians diagnose the condition appropriately and recommend targeted treatment for the individualized patient.

If you have any questions or concerns, please contact Adam R. Borden, MHA, Manager of New Technologies and Reimbursement at the AGA at 301-941-2629 or aborden@gastro.org. Thank you for engaging the AGA in the review of this draft policy and for your consideration of these important issues.

Sincerely,

Lawrence R. Kosinski, MD, MBA, AGAF
Chair, AGA Institute Practice Management and Economics Committee



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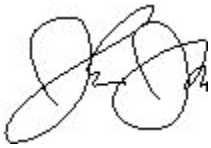

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