Comparative Effectiveness Research Review Disposition of Comments Report

Research Review Title: *Wireless Motility Capsule Versus Other Diagnostic Technologies for Evaluating Gastroparesis and Constipation: A Comparative Effectiveness Review*

Draft review available for public comment from August 9, 2012 to September 6, 2012.

Research Review Citation: Stein E, Berger Z, Hutfless S, Shah L, Wilson LM, Haberl E, Bass EB, Clarke JO. Wireless Motility Capsule Versus Other Diagnostic Technologies for Evaluating Gastroparesis and Constipation: A Comparative Effectiveness Review. Comparative Effectiveness Review No. 110. (Prepared by Johns Hopkins Evidence-based Practice Center under Contract No. 290 2007 10061-I.) AHRQ Publication No. 13-EHC060-EF. Rockville, MD: Agency for Healthcare Research and Quality; May 2013. www.effectivehealthcare.ahrq.gov/reports/final.cfm

Comments to Research Review

The Effective Health Care (EHC) Program encourages the public to participate in the development of its research projects. Each comparative effectiveness research review is posted to the EHC Program Web site in draft form for public comment for a 4-week period. Comments can be submitted via the EHC Program Web site, mail or email. At the conclusion of the public comment period, authors use the commentators' submissions and comments to revise the draft comparative effectiveness research review.

Comments on draft reviews and the authors' responses to the comments are posted for public viewing on the EHC Program Web site approximately 3 months after the final research review is published. Comments are not edited for spelling, grammar, or other content errors. Each comment is listed with the name and affiliation of the commentator, if this information is provided. Commentators are not required to provide their names or affiliations in order to submit suggestions or comments.

The tables below include the responses by the authors of the review to each comment that was submitted for this draft review. The responses to comments in this disposition report are those of the authors, who are responsible for its contents, and do not necessarily represent the views of the Agency for Healthcare Research and Quality.

Source: http://effectivehealthcare.ahrq.gov/search-for-guides-reviews-and-reports/?pageaction=displayproduct&productID=1498
Published Online: May 20, 2013

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer-1	General	I believe that the target audience is clearly defined. The questions asked are clearly stated and answered as well as the data allow.	Thank you for your feedback!
Peer Reviewer-1	General	I suggest that the authors decide whether to use generic, proprietary or both descriptions for therapeutic interventions i.e. bisacodyl vs. Dulcolax or bisacodyl (Dulcolax). The problem with proprietary names is many for the same generic compound.	Throughout the report, we tried to use the generic terms for all medications. We asked a copy editor to make sure that this was changed consistently throughout the report.
Peer Reviewer-1	Intro	No specific comments	Thank you for reviewing our report!
Peer Reviewer-1	Methods	The authors clearly state the conditions of their data acquisition and analysis of the published literature	Thank you for reviewing our report!
Peer Reviewer-1	Results	The results from studies which are all different are analyzed and presented fairly. The authors are to be commended.	Thank you for reviewing our report!
Peer Reviewer-1	Discussion/ conclusion	These are presented objectively with the limitation of the available studies. Clearly, what is needed are prospective comparative studies employing WMC, scintigraphy and Sitzmarks simultaneously performed in normal subjects, gastroparetics and constipated patients. The authors make this point.	Thank you for reviewing our report!
Peer Reviewer-1	Clarity and usability	The authors have performed a superb, meticulous review of the literature available on the use of wireless motility capsule (WMC) to evaluate and influence treatment of patients with gastroparesis and/or constipation associated with colonic inertia.	Thank you for reviewing our report!
TEP 1	General	I think this section was appropriate in defining the population to be assessed.	Thank you for reviewing our report!
TEP 1	Intro	The introduction to the frequency of Gastroparesis in Diabetics I believe underestimates the population of Diabetics with Gastroparesis symptoms which I regard as at least 3 million based on the literature. The point here is Gastroparesis is not a rare diseaese.If celiac sprue is now thought to be 1% of the US population then Gastroparesis is more than that.	We added and updated the Executive Summary and main report: Newer estimates of prevalence report a higher rate 24.2/100,000 inhabitants, some estimates that more than 1.5 to 3 million Americans may be affected with gastroparesis.
TEP 1	Methods	Yes they were well explained.	Thank you
TEP 1	Results	Given the fact that there are still limited studies to none outside tertiary Motility Centers these limitations were expressed.	Thank you

Commentator & Affiliation	Section	Comment	Response
TEP 1	Results	Also the effect of the results of wireless capsule results on clinical decision making and outcome have not been explored or only minimally.	We found low strength of evidence that wireless motility capsule changed treatment decisions as compared with scintigraphy for KQ1. Three studies evaluated that issue and reported a change in management in 50-69% of patients. Likewise there were two studies that addressed this issue for KQ3 and did suggest that WMC changed management versus radiopaque markers. There was no data for KQ2 or KQ4. We agree that these studies were small and the overall strength of evidence for this outcome was either low or insufficient for all our key questions.
TEP 1	Discussion/ conclusion	Implications could be better. One clear advantage for the wireless motility capsule is the fact that it will be available and utilized in GI practises all over this country and for that matter the world. Unlike Scintigraphy it is standardized and the same method will be performed everywhere. Hence the data can be fully exchanged-- not always not believed and repeated with different methods, also every office practise with nursing support can do this unlike Tertiary centers required for Antral -duodenal motility which is performed in very few places and colonic scintigraphy done in 2 or 3 places.	We added to page 49 of the main report, "In our review of the literature, scintigraphy was performed using a wide variety of methods, as was radiopaque marker testing. In contrast there is a single method by which the wireless motility capsule is reported to be performed. In addition, wireless motility capsule can be performed in any office with a nurse, while antroduodenal manometry or colonic scintigraphy can only be performed with experts at an academic center with specialized equipment and large investments of time. In this way, capsule may prove to be more reproducible and more standardized than some of the other testing modalities. Currently, there is also only one type of software in use, which may make testing more comparable between centers as well. No studies directly assessed using capsule internationally or in a community-based environment to measure this effect to date."

Commentator & Affiliation	Section	Comment	Response
TEP 1	Discussion/ conclusion	There is also not enough emphasis that by obtaining a total gut profile the management will change and certainly the patient's trust in the care and treatment being recommended will be better. 20 to 30%of Gastroparetics have slow colonic and around 10 to 20% of constipated patients have slow gastric emptying. This information can impact on treatment plans and help explain more symptoms than a scintigraphy test or Sitz marker alone.	We already state in the Discussion (Key Findings for KQ2), "The incremental benefit for wireless motility capsule in diagnostic evaluation of suspected gastroparesis is consistent with the nature of the disorder and the tests, since the wireless motility capsule offers pressure data and motility data which are not discernible by scintigraphy alone, as well as lower gastrointestinal motility data which can be implicated as a cause of symptoms in patients with combinations of motility disorders. Measurable benefit may be gleaned from the additional reported information in combination with scintigraphy especially with regard to identification of a more diffuse motility disorder." Additionally, we added in the Potential Niche of the Wireless Motility Capsule section of the Discussion, "Since patients may have more than one of these disorders causing their symptoms, identifying the co-existent disorder becomes an important component of the work up for some of these patients. Is a test with the ability to detect more than one disorder like wireless motility capsule better than existing modalities that focus in only one region?"
TEP 1	Clarity and usability	I would expand the conclusions and hence potential policy implications with the messages of " availability, accessability, standardization, no radiation, easily repeated Re follow up of treatment effects"	We agree and added to the Conclusion of the Discussion: It is reported to be accessible, standardized, emit no radiation, reproducible and able to be made available in locations remote from academic centers, in stark contrast to the limited availability and utility of other testing modalities in current practice.
TEP 1	Clarity and usability	Also the yet to be fully realized benefits of analysing the Motility parameters and data which is being analized currently and will be analysed in more detail and depth with ongoing studies. There should continue to be the caviet that impact on clinical outcome is still work in progress.	This was addressed in the future research needs document, as we do not have the data to analyze or report at this time. We cannot report on motility parameter value that has not yet been determined to be clinically useful in this document, although it is likely a very true comment.
TEP 2	General	Good; Overall, a well done document. Below are my comments for additions/modifications	Thank you so much.
TEP 2	General	The document should mention that the Wireless Motility Capsule assess transit through the entire GI tract, obtaining gastric emptying, small bowel transit, and colonic transit.	On ES-7 (paragraph on wireless motility capsule) and in main body in the Introduction chapter, second sentence under Wireless Motility Capsule, we added, "It can detect specific transit times in the stomach, small bowel, and colon and thus both upper and lower GI disorders simultaneously with a single device."

Commentator & Affiliation	Section	Comment	Response
TEP 2	General	There is some data that suggests that wireless motility capsule affects patient management.	There is data that reflects the role of wireless motility capsule in patient management, however it is not often presented in a comparative fashion as specified in our inclusion criteria. Mostly determined to be insufficient for and needing future study by this report and the corresponding research needs article.
TEP 2	General	For the gastric section, suggest inserting: Some patients with gastroparesis may have evidence of a diffuse GI motility disorder, as indicated by delayed small intestinal and/or colonic transit, in addition to the delayed gastric emptying. The prolongation of colonic transit in gastroparetic patients indicates that dysmotility beyond the stomach in GP is present, and it could be contributing to symptom presentation. The wireless motility capsule can assess gastric emptying, small bowel transit, and colonic transit in a single test. Without WMC whole gut transit would be assessed by whole gut transit scintigraphy which is available at only select centers or the use of two tests: gastric emptying scintigraphy and radioopaque markers. Thus, WMC can help eliminate the need for other tests. WMC findings can influence management by changing treatments. Sarosiek I, Selover KH, Katz LA, Semler JR, Wilding GE, Lackner JM, Sitrin MD, Kuo B, Chey WD, Hasler WL, Koch KL, Parkman HP, Sarosiek J, McCallum RW. The assessment of regional gut transit times in healthy controls and patients with gastroparesis using wireless motility technology. Aliment Pharmacol Ther. 2010 Jan 15;31(2):313-22.; Kuo B, Maneerattanaporn M, Lee AA, Baker JR, Wiener SM, Chey WD, Wilding GE, Hasler WL. Generalized transit delay on wireless motility capsule testing in patients with clinical suspicion of gastroparesis, small intestinal dysmotility, or slow transit constipation. Dig Dis Sci. 2011 Oct;56(10):2928-38.	We agree that we can emphasize/explain whole gut benefit of wireless motility capsule in more clarity to demonstrate potential benefit. We added these points throughout the Introduction chapter of the report. We added to the Evaluation of Possible Gastroparesis section, "Some patients with diagnosed gastroparesis may also have evidence of a diffuse GI motility disorder, as indicated by delayed small intestinal and/or colonic transit, in addition to the delayed gastric emptying. Management of these patients is different, as the prolongation of colonic transit in gastroparetic patients indicates that dysmotility beyond the stomach in GP is present, and it could be contributing to symptom presentation." Under the Wireless Motility Capsule subheading, we added, "the wireless motility capsule can assess gastric emptying, small bowel transit, and colonic transit in a single test. The only other single test that assesses whole gut transit would be whole gut transit scintigraphy which is available at only select centers, alternatively, multiple tests such as: gastric emptying scintigraphy and radiopaque markers can be combined to attempt to assess the transit in multiple locations of the gut."

Commentator & Affiliation	Section	Comment	Response
TEP 2	General	For the colonic section, suggest inserting: Some patients with delayed colonic transit may have evidence of a diffuse GI motility disorder, as indicated by delayed gastric emptying and/or small intestinal transit, in addition to the delayed colonic transit. This can be detected with the wireless motility capsule in a single test. Delayed gastric emptying in a patient with delayed colonic transit indicates that dysmotility above the colon is present, and it could be contributing to symptom presentation. WMC findings can influence management by changing treatments. The WMC can help eliminate the need for other tests: the WMC measures both gastric emptying and colonic transit. Without WMC, these assessments would be done with two tests - gastric emptying scintigraphy and radioopaque markers. The presence of delayed gastric emptying in patients with colonic inertia reduces the efficacy of total colectomy in these patients. These findings suggest potential benefits of the WMC method in constipation. Kuo B, Maneerattanaporn M, Lee AA, Baker JR, Wiener SM, Chey WD, Wilding GE, Hasler WL. Generalized transit delay on wireless motility capsule testing in patients with clinical suspicion of gastroparesis, small intestinal dysmotility, or slow transit constipation. Dig Dis Sci. 2011 Oct;56(10):2928-38.; Rao SS, Mysore K, Attaluri A, Valestin J. Diagnostic utility of wireless motility capsule in gastrointestinal dysmotility. J Clin Gastroenterol. 2011 Sep;45(8):684-90.	We agree that we can strengthen our emphasis on this benefit. We added to the Wireless Motility Capsule subheading in the Introduction, “For patients with both colonic and gastric emptying delay, a wireless motility capsule can detect both disorders. Without the capsule, physicians would need two tests to make these assessments--gastric emptying scintigraphy and radiopaque markers.” We added to the Use of Colon Transit Testing to Guide Treatment section, “Some patients with delayed colonic transit may have evidence of a more diffuse GI disorder, such as gastric or small bowel transit delay. It is important to detect the accompanying disorder, since patients with colonic inertia and gastric emptying delay have poorer outcomes from total colectomy.”
TEP 2	Abstract	Suggest adding to abstract: The wireless motility capsule, by assessing transit through each of the stomach, small intestine, and colon, has the capability to eliminate tests, when an assessment of whole gut transit is desired.	We found a low strength of evidence at best for this capability, I would prefer to describe this in the discussion completely rather than call it out in the abstract as suggested. I believe it is a valid point that still may need more proof in order to fully embrace.

Commentator & Affiliation	Section	Comment	Response
TEP 2	General	The strength of evidence for WMC to assess gastric emptying compared to scintigraphy is moderate and not low as stated in the abstract. The correlation between WMC GET and gastric emptying scintigraphy GES-4 h was 0.73 when the tests are performed concurrently (Kuo). In another study, the capsule residence time in the stomach correlated very strongly with percent gastric retention of the Tc-99 radiolabel at 120 minutes (r=0.95) and at 240 minutes (r=0.73) (Maqbool). References: Kuo B, McCallum RW, Koch K, Sitrin M, Wo W, Chey W, Hasler W, Lackner J, Katz L, Semler J, Hutson A, Parkman HP. Comparison of Gastric Emptying of a Non-digestible Capsule to a Radiolabeled Meal in Healthy and Gastroparetic Subjects. Aliment Pharmacol Ther 2008;27(2):186-96.; Maqbool S, Parkman HP, Friedenberg F. Wireless Capsule Motility: Comparison of the SmartPill GI Monitoring System with Scintigraphy for Measuring Whole Gut Transit. Digestive Diseases and Sciences 2009; 54 (10):2167-74. doi:10.1007/s10620-009-0899-9.	The Kuo study is included and is in our opinion the main paper that evaluates this issue. One of the limitations of our review was that we excluded studies that did not have a comparison for wireless motility capsule or did not look at patients with either gastroparesis or constipation, and hence the Maqbool study was excluded from our analysis based on these initial parameters (as all patients were normal without disease). Because of the low number of included studies and our pre-defined criteria for assessment of strength of evidence detailed in the method section, the strength of evidence for this KQ was low.
TEP 2	Abstract	From the abstract results, I suggest removing the last line "No studies directly assessed use of WMC in combination with other tests to detect colon transit delay." This is confusing, as the prior lines mention the studies comparing WMC to radiopaque markers.	We agree. This point can be seen in the Executive Summary and main document with better clarity; one sentence is not enough.
TEP 2	Executive Summary	"It has been recommended by the American Neurogastroentrology and Motility Society (ANMS) and designated a technology to be watched by the American College of Gastroenterology (ACG)." Suggest adding that The American Gastroenterological Association (AGA) also mentioned that this was a technology with great promise. Ref: Wang TC, Fleischer DE, Kaufman PN, Malagelada JR, McDonald WJ, McQuaid KR, Montrose M, Pasricha PJ, Powell DW, Rose S, Rowe WA, Todisco A; AGA Institute Future Trends Committee. The best of times and the worst of times: sustaining the future of academic gastroenterology in the United States--Report of a Consensus Conference Conducted by the AGA Institute Future Trends Committee. Gastroenterology. 2008 Feb;134(2):597-616.	Under the Wireless Motility Capsule section of the Introduction in both the Executive Summary and the main report, we added, "The American Neurogastroenterology and Motility Society (ANMS) recommend its use and the American College of Gastroenterology considers it a technology that has great promise and should be watched."

Commentator & Affiliation	Section	Comment	Response
TEP 2	Executive Summary	"Other disadvantages are that radiographic imaging must be used to confirm elimination of the capsule when it fails to pass spontaneously and that the device can fail at a rate up to 3 percent in some studies." If there is not confirmed passage of the capsule, radiographic image was used in the clinical research studies. When the test is performed clinically, a radiographic image is performed if the passage is not confirmed and the patient is having symptoms.	Thank you. We have changed the Wireless Motility Capsule section of the Introduction to reflect this clinically important difference. We now state, "Disadvantages of the capsule include failure to capture data (requiring repeat testing) and delay or total failure to pass. When the capsule fails to pass and patients have symptoms, then a patient may need x-rays to detect retention. In rare cases, endoscopic or surgical removal may be necessary. The capsule is not viable for patients with a possible stricture, altered anatomy, or severe pyloric stenosis."
TEP 2	Abstract	Suggest adding to abstract: The wireless motility capsule, by assessing transit through each of the stomach, small intestine, and colon, has the capability to eliminate tests, when an assessment of whole gut transit is desired.	We feel that although this is likely a true statement, the evidence is not sufficient for such a strong statement from our review and that we didn't assess whole gut transit/small bowel transit as a part of our review since it was outside of our original scope. I believe previous edits in response to your suggestions have also clarified the role of the wireless motility capsule in whole gut transit detection to address this issue.
Peer Reviewer-2	General	Superior quality of the report	Thank you for reviewing our report!
Peer Reviewer-2	General	It is clinically relevant, but very redundant. The exclusion of some of the references seems too stringent, example Cassily et al	We have organized this report consistent with AHRQ guidance for systematic reviews. In revising the report we have edited this report with an eye towards improving readability and reducing redundancy. Consistent with other comparative effectiveness reviews developed under the Effective Health Care program, we required a comparison group for inclusion. This resulted in the exclusion of articles, such as the Cassily et al paper referenced by the peer reviewer.
Peer Reviewer-2	Introduction	Complete and well done. Did not mention linclotide or Amitiza. Also bisacdyl may be more of a prokinetic.	We have modified this under the Basic Management subsection for Constipation in the Introduction chapter.
Peer Reviewer-2	Methods	I think the exclusion were too stringent. It is difficult to understand the exclusion of a manuscript that compares antroduodenal manometry with WMC but then state no studies measured and compared both parameters.	Our inclusion and exclusion criteria were designed to find the best studies that addressed our Key Questions and were developed with input from our Technical Expert Panel. Two studies that compared wireless motility capsule with antroduodenal manometry, Cassilly Neurogastroenterol Motil 2008 and Brun Neurogastroenterol Motil 2012, were excluded because they were not conducted in a population with gastroparesis.

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer-2	Results: Table A	Should be antroduodenal not anorectal manometry in Table A, first part.	In Table A, the term "anorectal manometry" is correct. The paper states, "anorectal outlet function testing was not avoided by WMC performance (0%)."
Peer Reviewer-2	Discussion/ conclusion	extensive	The final report was reviewed by a medical writer to help with readability.
Peer Reviewer-2	Clarity and usability	This paper is long and much of this is redundancy	We have organized this report consistent with AHRQ guidance for systematic reviews. In revising the report we have edited this report with an eye towards improving readability and reducing redundancy.
TEP 3	General	Quality of the report: Good. The report is clinically meaningful and I believe the important questions are answered. My main concern is that 6/11 studies were meeting abstracts and the robustness of the data from these non-peer reviewed abstracts may be in question. It would be helpful to know how the analysis might change with exclusion of these abstracts. I would recommend showing the combined data and then separately for papers and abstract for key results.	Thank you very much for this excellent suggestion. We added a qualitative sensitivity analysis, which involved for each section of the results: • Statement of the number of peer-reviewed papers and the number of abstracts included • A summary of the results based on the peer-reviewed manuscripts • A statement about whether or not the conclusions would change based on the data from the abstracts • Noting when results from abstracts in the tables and text • Including the number of studies and the number of abstracts in the strength of evidence tables. We state in the Data Analysis and Synthesis section of the Methods that we conducted a sensitivity analysis.
TEP 3	Introduction	No major concerns	Thank you for reviewing our report!
TEP 3	Executive Summary	"prokinetic medications like erythromycin" – would cite metoclopramide here instead of erythromycin as the latter is considered to be second line therapy	In the Use of Gastric Emptying Testing to Guide Treatment sections in the Introduction chapter of the main report and Executive Summary, we now state, "… prokinetic use, like metoclopramide or erythromycin…"
TEP 3	Executive Summary	constipation treatments should also include polyethylene glycol (miralax - osmotic) and lubiprostone (prokinetic)	We added polyethylene glycol (Miralax®) to the list in the Etiology and Clinical Course section of the Introduction in the Executive Summary and the main report.
TEP 3	Methods	Agree with inclusion and exclusion criteria used. Statistics appear appropriate.	Thank you for reviewing our report!
TEP 3	Methods; Figure A	Figure A – why were 7 articles found by hand searching and not pubmed/ovid? Please elaborate	Most of the articles found by hand searching were meeting abstracts, which are not consistently indexed in PubMed and EMBASE.

Commentator & Affiliation	Section	Comment	Response
TEP 3	Methods	As stated above, there are a small number of studies included (N=11) but the usage of meeting abstracts needs to be justified since they are not peer reviewed, or would show data separately to determine influence on results	Thank you very much for this excellent suggestion. We added a qualitative sensitivity analysis, which involved for each section of the results: • Statement of the number of peer-reviewed papers and the number of abstracts included • A summary of the results based on the peer-reviewed manuscripts • A statement about whether or not the conclusions would change based on the data from the abstracts • Noting when results from abstracts in the tables and text • Including the number of studies and the number of abstracts in the strength of evidence tables. We state in the Data Analysis and Synthesis section of the Methods that we conducted a sensitivity analysis.
TEP 3	Results	Again as mentioned would show data separately for abstracts versus papers	Thank you very much for this excellent suggestion. We added a qualitative sensitivity analysis, which involved for each section of the results: • Statement of the number of peer-reviewed papers and the number of abstracts included • A summary of the results based on the peer-reviewed manuscripts • A statement about whether or not the conclusions would change based on the data from the abstracts • Noting when results from abstracts in the tables and text • Including the number of studies and the number of abstracts in the strength of evidence tables. We state in the Data Analysis and Synthesis section of the Methods that we conducted a sensitivity analysis.
TEP 3	Results	Might consider analysis of "clean data" alone where patients were clearly off of prokinetics and narcotics during the motility studies or show the data when these parameters are excluded. It is unclear whether the study populations truly have the disease in question.	Most of the manuscripts reported that patients were off of prokinetics and narcotics, but most abstracts did not report on this. We are not able to conduct this analysis because it was largely redundant with the abstract sensitivity analysis.
TEP 3	Discussion/ conclusion	The implications, limitations and future research sections appear to be clear	Thank you for reviewing our report!

Commentator & Affiliation	Section	Comment	Response
TEP 3	Executive Summary	it is unlikely that wireless capsule motility would be used only in cases where the diagnosis remains in question since the standard tests already have excellent sensitivity and specificity. It should be stated that a more clear indication would be in patients suspected of having more than one regional motility disorder.	We did not find that the expert consensus agreed with this suggested use. The consensus guidelines reflect use of this as a first test to eliminate use of other tests in all patients since the rate of detection of coexistent disease is so great in gastroparetics and those with slow-transit constipation. The guidelines currently say that it is a replacement test.
TEP 3	Executive Summary	you state that in 3 studies wireless capsule altered management for patients with gastroparesis. More detail should be added about how management was altered. In addition, studies with traditional scintigraphy and outcomes are not cited. Would they not be expected to show similar changes in outcomes?	Reviewing the literature on the original research and clinical basis of scintigraphy was beyond the scope of this review. We did review the articles which compared scintigraphy to wireless motility capsule. We included the few details that were mentioned in the articles which documented change in management.
TEP 3	Clarity and usability	The report appears to be well structured and organized. Given the low level of evidence, it does not appear that this report in its current state can inform policy makers about the true diagnostic accuracy of WMC compared to the gold standards of scintigraphy and colonic marker studies. Certainly in patients with abnormal results, the data can be useful to drive management, but more information is required to determine if subsequent testing should occur in the setting of a normal WMC test and if patients with abnormal WMC require confirmatory testing.	The report concluded that WMC is at least comparable to other modalities for diagnosis of slow-transit constipation or gastroparesis, which is likely sufficient for it to be covered for suspected cases. We identified this area as an evidence gap and it was included as part of the future research needs report to also highlight this issue. In areas where the evidence is lacking or inconclusive, physicians must exercise clinical judgment. Thank you.
Peer Reviewer3	General	Quality of the report: Fair	Thank you for reviewing our report!
Peer Reviewer-3	General	This report is a good attempt to summarize the available literature to answer the 4 questions that the authors set out to answer, 2 for gastroparesis and 2 for slow transit constipation. The questions are appropriate and explicitly stated. It suffers from 1 major defect which is beyond the authors control and 2 that are. The one that is beyond the authors control is the number of studies to draw on and the quality of the few studies that exist. It is my opinion that there simply is not enough information to even attempt to answer the questions poised. The authors do state that the evidence is from the 11 studies (6 prospective) is low but I would go a step further and say that an attempt to write an AHRQ-quality paper is futile with the number and quality of papers available.	We knew before starting the project that the wireless motility capsule was a relatively new diagnostic test and that there would not be a large number of studies evaluating it. Synthesizing available information is of benefit in this case. Knowing what the evidence does and does not say about the benefits and harms helps decisionmakers make better informed decisions.

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer-3	General	The size of the wireless pill is large. Therefore the pill will not pass from the stomach to the small intestine until phase 3 of the MMC. At this point it is likely measuring T90 not T50. There should be a paragraph addressing the meaning of measuring emptying of a large object versus the <3mm chime that usually leaves the stomach. On the other hand the ability to look at small intestinal contractions is an advantage.	We added to the Wireless Motility Capsule section of the Introduction, "The pill itself is a large object, which remains large as it passes out of the stomach and into the small intestine. This differs slightly from the regular digestion process, in that the body usually moves food to the small intestine when the stomach has reduced the particles to a size no larger than 3 mm. Physicians can determine the capsule has exited from the stomach when gastric baseline pH rises rapidly (by 3 or more pH units) to a pH greater than 4."
Peer Reviewer-3	General	A limitation of colon transit measurement that should be commented on is the lack of ability to know where the capsule is and to address movement. Scintigraphy, markers and tube colonic motility studies can to various degrees to this and at least localize to right or left side which may give clinically useful information. The time needed to carry out the entire test should also be commented on as it is several days.	We added to the Wireless Motility Capsule section of the Introduction, "One disadvantage is that there is only a single point of detection during the wireless motility capsule study (data gathering can only occur where the capsule in located) and there is no way to find out the specific location of the capsule, beyond knowing if it has exited an area (stomach, small intestine, or colon)."
Peer Reviewer-3	Introduction and abstract	I will include [my comment on] the structured abstract here. While the conclusions are reasonable the statement that WMC is similar to current modalities is not, in my view. It is equivalent but not similar as it measures other parameters than current modalities. The introduction is well written. Gastric scintigraphy reference should be the consensus statement reference on how it should be carried out rather than reference 5. There likely should be a reference of the poor correlation between symptoms and gastric emptying in the ES-2 line 38 onwards.	We revised the abstract to say, "comparable in accuracy." The second comment regarding the poor correlation between symptoms and gastric emptying is valid but requires a long discussion likely for another venue. This is a known fact but not specifically relevant to detection or lack of detection of gastric emptying delay. We tried to incorporate this thought into our method of analysis of comparison between gastric scintigraphy and wireless motility capsule.
Peer Reviewer-3	Methods	The search criteria are stated and appropriate. The inclusion and exclusion criteria are also appropriate. Limited stats were possible given the low numbers.	Thank you for reviewing our report!
Peer Reviewer-3	Results	The tables are appropriate as is the layout.	Thank you for reviewing our report!
Peer Reviewer-3	Discussion/ conclusion	The future research section should emphasis the need for larger multicenter studies with investigators not associated with the current capsule development. Also the development of a smaller capsule and localizing software would be significant advantages	We added this statement to the Future Research Needs section of the Discussion, "In study design, multi-center trials may be needed to enroll patients in sufficient quantity to be meaningful. Preferably, these trials would be led by investigators independent from the corporation that makes wireless motility capsule."
Peer Reviewer-3	Clarity/usability	The report is well written, easy to read and follow. It is of limited clinical use due to the number and quality of the data analyzed.	We felt that it was important to note the current state of the literature, as the stakeholders involved wanted to understand the available evidence.

Commentator & Affiliation	Section	Comment	Response
TEP 4	General	This was an exhaustive and comprehensive review of the WMC technology including the randomized comparative studies in gastroparesis with scintigraphy, the comparative studies with radiopaque markers in constipation and the validation study as well as other studies including the two retrospective diagnostic outcome studies.	Thank you for reviewing our report!
TEP 4	General	The review brings up several major gaps in current knowledge of this technology and highlights both the strengths and weaknesses as far as current evidence is concerned regarding the technology.	Thank you for reviewing our report!
TEP 4	General	The review does not acknowledge that motility disorders are complex to evaluate, and each condition such as gastroparesis or constipation is not a single cause disease but is caused by multiple pathophysiological mechanisms and as such no single test can provide all the answers and serve as a gold standard.	Under Use of Colonic Transit Testing to Guide Treatment, we added, "Colon transit disorders can be complex to sort out. A single test may not reflect the full complexity of a patient's motility disturbances. For example, anorectal dysfunction can impact colonic transit, but must be assessed by anorectal manometry separate from other transit testing."
TEP 4	General	Because there is no gold standard comparison with scintigraphy alone for evaluating gastroparesis is an incomplete exercise. Whether one should compare with breath tests may have to be considered. Ideally a long term follow up study should be performed to look at clinical outcome in a prospective manner.	Since breath tests are not approved for use and also not used clinically in the US for this indication, we believed that they were outside of the scope of our current analysis. Our decision to exclude breath testing was confirmed with the Key Informants. We followed AHRQ guidance for summarizing test performance in the absence of a gold standard. Please see chapter 9 of the Methods Guide for Medical Test Reviews, which is available at http://effectivehealthcare.ahrq.gov/ehc/products/246/558/Methods-Guide-for-Medical-Test-Reviews_Full-Guide_20120530.pdf. We were unable to perform some of the recommendations due to the lack of data.
TEP 4	General	Having used this technology in clinical practice I do not believe that some of the limitations outlined based on lack of evidence are clinically relevant, but agree from a scientific purpose this is accurate.	The limitations are designed to reflect the technical nature of our review of the literature, and we agree that they may not be relevant to day to day practice. They are necessary to assess in this type of review.

Commentator & Affiliation	Section	Comment	Response
TEP 4	General	I believe the comments can be softened as this is an emerging technology and to the best of my knowledge over a 25 year career, I have not seen any motility technology that has been so rigorously tested and has been shown to be useful in day to day evaluation of gastroparesis or constipation.	Previous edits have strengthened our support as a whole for wireless motility capsule as well as better assessment of accuracy sensitivity/specificity. The conclusion now reads: "It is reported to be accessible, standardized, emit no radiation, reproducible and able to be made available in locations remote from academic centers, in stark contrast to the limited availability and utility of other testing modalities in current practice." We need to discuss limitations and so they are listed appropriately.
TEP 4	General	The most important point the review misses is that this tool is the only tool available for evaluation of a diffuse gastrointestinal motilioty disorder in a non-invasive manner, using a standardized technology and without radiation and minimum inconvenience to the patient. This aspect should be emphasized.	We agree that we can emphasize/explain whole gut benefit of wireless motility capsule in more clarity to demonstrate potential benefit. We added these points throughout the Introduction chapter of the report. We added to the Evaluation of Possible Gastroparesis section, "Some patients with diagnosed gastroparesis may also have evidence of a diffuse GI motility disorder, as indicated by delayed small intestinal and/or colonic transit, in addition to the delayed gastric emptying. Management of these patients is different, as the prolongation of colonic transit in gastroparetic patients indicates that dysmotility beyond the stomach in GP is present, and it could be contributing to symptom presentation." Under the Wireless Motility Capsule subheading, we added, "the wireless motility capsule can assess gastric emptying, small bowel transit, and colonic transit in a single test. The only other single test that assesses whole gut transit would be whole gut transit scintigraphy which is available at only select centers, alternatively, multiple tests such as: gastric emptying scintigraphy and radiopaque markers can be combined to attempt to assess the transit in multiple locations of the gut."
TEP 5	General	Quality: good; The report is clinically meaningful. The target population and audience are well defined. The key questions are appropriate and explicitly stated.	Thank you for reviewing our report!
TEP 5	Introduction	The introduction is well written.	Thank you for reviewing our report!

Commentator & Affiliation	Section	Comment	Response
TEP 5	Introduction	An additional fact that deserves mention is that it is difficult clinically to distinguish gastroparesis with symptoms driven by delayed emptying from functional dyspepsia where delayed gastric emptying is part of the clinical syndrome. There are ample references that describe the prevalence of delay in gastric emptying in settings wherein criteria for functional dyspepsia are fulfilled. This overlap is also highlighted in the study published in Clin Gastroenterology and Hepatology by Pasricha et al (2011 Jul;9(7):567-76.e1-4). This point is relevant as it adds to the low yield when using an objective test like the gastric emptying study assessing symptomatic patients.	We agree that the overlap between the two disorders can be significant and this is an excellent point. We did not include this point in our discussion as the patients in the studies we reviewed were felt to have gastroparesis by either scintigraphy or symptoms combined with clinical course. Functional dyspepsia was not specifically detailed in these patients and while we agree entirely with the comment, we felt we could not adequately comment on this feature given the limitations of the papers reviewed. This was added as a limitation of the identified literature.
TEP 5	Executive Summary	The full value (or lack thereof) of prokinetics is not well described (page 12 or ES-2, lines 41-48). Erythromycin is associated with profound tachyphylaxis limiting its benefit. Metoclopromide also exhibits tachyphylaxis. Cisapride had benefit in prokinetic activity, but drug interactions limited its value. and so on...	We agree and have edited the section on Use of Gastric Emptying Testing to Guide Treatment to reflect this. Both metoclopramide and erythromycin are associated with profound tachyphylaxis limiting any intended benefit.
TEP 5	Executive Summary	ES-5, Outcomes of constipation evaluation. An important point in the evaluation of chronic constipation is to identify and distinguish outlet constipation from slow colonic transit, as this will change direction of management.	We have changed the Introduction to reflect this. We have added, "Colon transit disorders can be complex to sort out. A single test may not reflect the full complexity of a patient's motility disturbances. For example, anorectal dysfunction can impact colonic transit, but must be assessed by anorectal manometry separate from other transit testing. When anorectal or outlet dysfunction is identified via anorectal manometry or balloon expulsion testing, biofeedback therapy can be used for treatment."
TEP 5	Methods	The studies are well selected, with appropriately stated strategies and inclusion/exclusion criteria.	Thank you for reviewing our report!
TEP 5	Methods	The report could improve if the authors pooled data from prospective studies with controls (especially the two on gastroparesis) and generated new values that would be more representatitve than just the reported ranges.	We would love to have been able to conduct a meta-analysis of these studies. We consulted with several statisticians and methodologists to determine what methods would be most appropriate. However, we are unable to pool the results because we do not have a sufficient number of studies that made similar comparisons using similar outcome measures. We added more detail of what we considered in the Data Analysis and Synthesis section of the Methods chapter.
TEP 5	Results	The results section is well presented	Thank you for reviewing our report!

Commentator & Affiliation	Section	Comment	Response
TEP 5	Discussion/ conclusion	The biggest weakness of studies comparing WMC to scintigraphy is that sensitivity is compared using clinical symptoms of gastroparesis. As described in my comments under b) above, this has significant problems. I think direct comparisons of gastric empyting time with WMC to 4 hour and maybe 2 hour scintigraphy findings have more value. WMC only assesses solid phase empyting of undigestible solids, and therefore indirectly assesses the intactness of the MMC which is responsible for this phase of emptying. Therefore, the intent of the comparison should be to determine how well WMC detected gastric emptying times can be extrapolated into the emptying curves generated with scintigraphy. In such comparisons, only studies that included both normals and subjects with gastroparesis will be of value. In addition to sensitivity and diagnostic accuracy calculated from pooled numbers, concordance (positive, and negative) and discordance rates will be worthwhile.	We would love to have been able to conduct a meta-analysis of these studies. We consulted with several statisticians and methodologists to determine what methods would be most appropriate. However, we are unable to pool the results because we do not have a sufficient number of studies that made similar comparisons using similar outcome measures. We added more detail of what we considered in the Data Analysis and Synthesis section of the Methods chapter. We analyzed wireless motility capsule versus clinical gastroparesis where available and also versus scintigraphy emptying time where available. We did not have the required information to make the suggested comparison, although we agree that such information would have been useful in better defining correlation of the two devices.
TEP 5	Clarity and usability	I think the answer to Key question 1 is rather generous. I'm not sure what 'clinical gastroparesis' is (for reasons described above), and only direct comparisons of emptying time make sense. In the Kuo 2008 study, gastroparetics had only 4-13% of their meal retained at 4 hours, which would suggest that their emptying delay was only modest and probably mostly in the early phase of emptying - the authors may want to discuss the implication of these baseline characteristics of subjects. The second study (Reddymasu 2010) has not been published as a full manuscript. Therefore, the data is shaky at best, and not particularly conclusive.	Most of the studies defined clinical gastroparesis as symptoms consistent with gastroparesis and an abnormal gastric emptying study by local criteria before enrollment in the study. We agreed with you that this often presented a heterogeneous group and made direct comparison challenging. However, we felt that the conclusions were valid based on the evidence presented and the strength of evidence criteria detailed in the method section.
TEP 5	Clarity and usability	A major drawback of WMC in assessing constipation is that it can totally miss outlet constipation - this requires the study to be used with at least one other objective test, either Sitz markers (which defeats the purpose) or anorectal manometry, which has it's own issues.	We have changed the Introduction to reflect this. We have added, "Colon transit disorders can be complex to sort out. A single test may not reflect the full complexity of a patient's motility disturbances. For example, anorectal dysfunction can impact colonic transit, but must be assessed by anorectal manometry separate from other transit testing. When anorectal or outlet dysfunction is identified via anorectal manometry or balloon expulsion testing, biofeedback therapy can be used for treatment."

Commentator & Affiliation	Section	Comment	Response
TEP 5	Clarity and usability	A potential advantage of WMC is that it assesses total gut transit time and small bowel transit time in addition to colonic transit. However, the value of small bowel transit time in clinical gastroenterology is unclear.	We agree entirely and made the point of whole gut transit being assessed in the discussion section. We did not focus on small bowel wireless motility characteristics in our study as there was minimal data available.
TEP 5	Clarity and usability	Cost comparisons are also worthwhile mentioning in more detail. WMC is not covered by major carriers and involves paperwork and negotiation with hospitals and insurance carriers. It is more expensive.	In this particular type of review for AHRQ, cost-effectiveness analysis is not permitted. Unfortunately it is beyond the scope of this current review to assess barriers to access.
TEP 5	Clarity and usability	It seems evident that this is technology that needs to find a better niche than the one it is marketed for. Comparative and outcome studies need to be better designed, perhaps using all comers with foregut dyspeptic symptoms compared to normal volunteers, both groups undergoing clinical questionnaire and objective testing with scintigraphy and WMC.	We have reflected this in the future research needs document in our review of future research needs.
TEP 5	Clarity and usability	I feel the conclusions (ES-22) are generous for gastroparesis. Sensitivity needs to be pooled and better defined. The two studies that reported sensitivity and had non-gastroparetic controls	We would love to have been able to conduct a meta-analysis of these studies. We consulted with several statisticians and methodologists to determine what methods would be most appropriate. However, we are unable to pool the results because we do not have a sufficient number of studies that made similar comparisons using similar outcome measures. We added more detail of what we considered in the Data Analysis and Synthesis section of the Methods chapter.
Public Comment: Braden Kuo	Executive Summary	Standard meal does not include juice as reviewers suggest demonstrating lack of standardization.	In the Gastric Scintigraphy section of the Introduction, we have changed to water as suggested.
Public Comment: Braden Kuo	Executive Summary	reviewers state X-rays required if capsule fails to pass- this is inaccurate. There is a clinical protocol which is line with Given endoscopic capsule recommendations. If the capsule is found to pass the ceacum, then radiological confirmation is not required but optional if clinically indicated.	We added a caveat to needing an x-ray. We have changed the Wireless Motility Capsule section of the Introduction to reflect this clinically important difference. We now state, “Disadvantages of the capsule include failure to capture data (requiring repeat testing) and delay or total failure to pass. When the capsule fails to pass and patients have symptoms, then a patient may need x-rays to detect retention. In rare cases, endoscopic or surgical removal may be necessary. The capsule is not viable for patients with a possible stricture, altered anatomy, or severe pyloric stenosis.”

Commentator & Affiliation	Section	Comment	Response
Public Comment: Braden Kuo	Executive Summary	Reviewers state patients must be able to stop PPI- Michalek paper shows PPI stoppage not necessary and that gastric passage of the capsule can still be read on PPIs with a less prominent change in gastric to duodenal pH. Cessation of acid suppression is more ideal but not absolutely necessary.	In the Wireless Motility Capsule section of the Introduction of the Executive Summary and main report, we have changed the statement to read, "Patients ideally should be able to tolerate stopping proton pump inhibitors and histamine 2 blockers before testing."
Public Comment: Braden Kuo	Executive Summary	ROM referred to as reference standard. Camilleri paper describes ROM as a non- ref standard. Because ROM is not a reference standard, assessment of device agreement was examined between ROM and WMC. Reviwers suggest ROM distribution represents information on region of colon delay. This is unsupported in more recent literature. No mention that ROM fails to even measure colonic transit and that it lacks indication of severity.	We added to the Radiopaque Markers section of the Introduction, "Another disadvantage is that radiopaque markers truly assess oro-cecal transit and are not necessarily specific to the colon, since they must be swallowed and passed out the anus to complete the test. Any motility delaying transit in stomach, small bowel or in anorectal outlet obstruction would also show up as a positive radiopaque marker test with retained markers, but there is no simple way to differentiate between disorders." We agree that radiopaque markers are an imperfect reference standard. We modified the report to refer to radiopaque markers as a non-reference standard and reported positive percent agreement and negative percent agreement instead of sensitivity and specificity. These distinctions are described in the methods. We followed the guidance from the AHRQ Methods Guide for Medical Test Reviews and the FDA Statistical Guidance on Reporting Results from Studies Evaluating Diagnostic Tests.
Public Comment: Braden Kuo	Executive Summary	WMC disadvantage is in 5% ceacal entry missing:. While this may occur, it is important to point out that ROM has similar limitations and cannot specifically denote only colonic transit but rather oral colonic transit and cannot distinguish segmental delays 100% of the time compared to 5% with EMC. To address the 5% missing segmental colonic transit timer, Camilleri reports combined small large bowel transit useful surrogate for CTT.	We added to the Wireless Motility Capsule section of the Introduction, "Camilleri has reported a use of the combined small bowel and colon transit time to allow for interpretation of these cases."

Commentator & Affiliation	Section	Comment	Response
Public Comment: Braden Kuo	Executive Summary	WMC cannot distinguish from outlet obstruction. Nor can ROM distinguish outlet obstruction	We agree and have changed the report to reflect this. Under Use of Colonic Transit Testing to Guide Treatment, we added, "Colon transit disorders can be complex to sort out. A single test may not reflect the full complexity of a patient's motility disturbances. For example, anorectal dysfunction can impact colonic transit, but must be assessed by anorectal manometry separate from other transit testing." We also added, "When anorectal or outlet dysfunction is identified by anorectal manometry, biofeedback therapy can be used for treatment."
Public Comment: Braden Kuo	Executive Summary	Exec summary is silent on the advantages of a full GI profile compared to single region conventional tests which can provide additional information with less amounts of diagnostic testing. But it does not suggest WMC diagnostic utility head to head is inferior to conventional tests.	This was also addressed in previous comment and mentioned, but as stated earlier, there has been no trial to date proving this benefit is helpful. It is important to establish a link between the use of a test and the outcomes patients and clinicians care about. Prospective data needs to confirm the benefit in a consistent way before we can comment on diagnostic utility or head-to-head comparison for inferiority or non-inferiority.
Public Comment: Braden Kuo	Executive Summary; discussion	Previous clinical practice guidelines fail to address key question to whether it is adjunct or can replace conventional tests. The most recent guidelines from American and European Motility Society in 2011 recommend the WMC for the assessment of gastric emptying, small bowel transit time, colonic transit time and whole gut transit. There is no mention or implication of the WMC as an adjunct test from this position statement. The recommendation for measurement of GI transit implies that it is on equal footing to the other techniques mentioned in the review.	We have edited the Discussion of the Executive Summary and main report to state, "Should it be used as a stand-alone test? What should be done when wireless motility capsule is normal but clinical suspicion remains? Or is it better used as an adjunct test after conventional testing has been completed in cases where the diagnosis remains in question? Recommendations from the ANMS practice guidelines suggest that wireless motility capsule can be used in the diagnostic work up of patients with suspected gastroparesis and slow-transit constipation as well as those with more generalized motility disorders, but these are consensus guidelines. There was no specific information about when or how wireless motility capsule should be applied. Thus, these are questions that have not been clearly addressed in previous clinical practice guidelines. "

Commentator & Affiliation	Section	Comment	Response
Public Comment: Braden Kuo	Executive Summary	It remains unclear where WMC should be used in the diagnostic algorithm and whether it is equivalent or superior to conventional tests.	We have edited the Discussion of the Executive Summary and main report to state, "Should it be used as a stand-alone test? What should be done when wireless motility capsule is normal but clinical suspicion remains? Or is it better used as an adjunct test after conventional testing has been completed in cases where the diagnosis remains in question? Recommendations from the ANMS practice guidelines suggest that wireless motility capsule can be used in the diagnostic work up of patients with suspected gastroparesis and slow-transit constipation as well as those with more generalized motility disorders, but these are consensus guidelines. There was no specific information about when or how wireless motility capsule should be applied. Thus, these are questions that have not been clearly addressed in previous clinical practice guidelines. "
Public Comment: Braden Kuo	Executive Summary	Reviewers recognize increased sensitivity with WMC especially if pressure included but report its unclear if this has clinical implications. If an abnormality was detected in either or both pressure or transit, the results had impact upon management in many cases in the Kuo/Hasler paper. All the impact of a full GI profile with new abnormalities detected in regions away from focus of symptoms also impacted management.	While we understand your intent, we felt as a team that prospectively enrolled patients would be more informative about clinical implications of wireless motility capsule than retrospective data collection. There is the potential for bias in a retrospective review of charts which may not have been present in a prospective analysis. Results of the Kuo/Hasler paper indicate a change in management. However because of the study design this raises questions about causality, whether or not the wireless motility capsule testing led to changes in clinical management or whether other factors did as well.
Public Comment: Braden Kuo	Executive Summary	Reviwers cite lack of pre specification and randomness in enrollment as key limitation of many studies. There was prespecification for acceptance criteria for normal and patients with gastroparesis in Kuo paper for constipated subjects in Camilleri paper.	By definition a retrospective study precludes random assignment, unless the patients were prospectively assigned. Prespecification was judged based on uniformity of testing, which by your article was not done consistently in all patients. But we agree that you did prespecify many of the desired criteria. We agree that the Camilleri study was prospective.

Commentator & Affiliation	Section	Comment	Response
Public Comment: Braden Kuo	Executive Summary	GES and WMC evaluate different physiologic parameters and therefore some direct comparisons are difficult. As discussed in Kuo APT paper, GES measures emptying of a meal and WMC represents emptying of an indigestible object after the emptying of a meal. In most cases, delayed meal emptying translates into delayed indigestible object emptying which is why there is a good correlation between the two tests. As a result, WMC indirectly measures what GES measures but also measures another factor which can contribute to gastroparesis which GES cannot measure which accounts for its higher sensitivity in detecting abnormalities in patients with symptoms of gastroparesis.	We added this statement to the Key Findings section of the Discussion, "When comparing wireless motility capsule with gastric scintigraphy, one should keep in mind that wireless motility capsule measures emptying of an indigestible object after the emptying of a meal, while gastric scintigraphy measures emptying of a meal. In a sense, then, wireless motility capsule indirectly measures what gastric scintigraphy measures. Good correlation between the two tests indicates that delayed meal emptying generally translates into delayed indigestible object emptying. "

Commentator & Affiliation	Section	Comment	Response
Public Comment: Braden Kuo	General	The overall concordance reported for WMC to conventional GI segmental transit tests (76% and 81% for radio-opaque markers and gastric emptying scintigraphy respectively, Rao J of clinical gastro) combined with the overall diagnostic gain reported by both Kuo and Rao suggest advantages to deployment of WMC early in place of the conventional motility transit tests in diagnostic workup. A motility profile of the full GI tract is especially advantageous in refractory patients with negative endoscopy and diffuse motility disorder symptoms. Even when symptom presentation is limited predominantly to the upper or lower abdominal region; given the occurrence of abnormal motility remote from symptom loci assessment of the full GI profile seems reasonable. Rao noted generalized delay in 51% of his subjects. Kuo noted (DDS) generalized delay or abnormal transit in two or more regions in 35% of clinical patients while isolated regional delays were observed in 32 % of patients. He noted that symptom profiles were similar between patients with normal transit, isolated delay, and generalized delay. Kuo noted somewhat lower overall concordance to conventional tests of 62% in his study. This was offset by new abnormal findings in 53% of patients including other GI segment delay in many of those in whom discordance as observed. WMC testing resulted in changes in management in 84% of patients. The additional abnormal motility findings of a full GI tract motility profile counterbalance the level of discordance observed especially when discordance is partially attributed to day to day variability in physiologic function suggested by the author, a result of conventional test and WMC test being conducted weeks to months apart. (Kuo APT)	Some of these comments have already been addressed based on concerns of previous reviewers. We strengthened wording about overall diagnostic utility of wireless motility capsule in generalized detection of delay. We know that other motility disorders would be treated if they are found in sites distant from the suspected primary motility disorder, and reflected that as important to clinical decision making in the background. I am not certain that it is a statistically valid assumption that the new findings of distant site abnormalities offset a lower concordance. There may have been some element of bias in the retrospective review which contributed. It is hard to tell from the reported data in the article. We agree that this ability to detect disease in more than one location is important and have highlighted this feature in the discussion and in the background. Unfortunately, there are insufficient results to determine non-inferiority or superiority based on the current literature and the limited number of published studies.

Commentator & Affiliation	Section	Comment	Response
Public Comment: Braden Kuo	General	The authors note patients recruited for the studies presented primarily at major tertiary motility centers but there is one community GI practice which contributed patients as well. They also acknowledge their population is likely to be more severe than those presenting at a community GI practice. The tertiary center setting may account in part for the prevalence of diffuse delay observed. However since routine workup of patients with symptoms of motility disorders almost always includes some testing to rule out alarm condition and demonstration of non- responsiveness to therapy prior to any consideration of motility testing some stratification between less and more severe patients already occurs at the community GI practice. Further, given the community GI practice continues to encounter difficulty obtaining either gastric emptying scintigraphy or radio opaque marker tests consistent with professional society recommended protocols, ensuing doubts over adequacy of test results may prompt further radiologic testing as surrogates for motility testing or to exclude alarm conditions. In an analyses of one major national insurance carrier's data base (Abstract DDW 2012) over 3 million endoscopic or radiologic tests were repeat tests within one year of the original test in patients with primarily motility disorder symptoms compared to 180,000 conventional motility tests performed. The additional sensitivity resulting from the complete GI profile and the availability of a standardized test protocol also favors an option for replacement of these conventional tests with WMC test. The community GI physician is likely to detect more abnormal motility sooner in the clinical service line and have more complete information to inform clinical management decreasing testing at tertiary academic centers and additional referrals.	We acknowledge this limitation of our group analysis of tertiary care centers. It is unclear if the community based -center to which you refer had any special connection to the academic center (shared staff etc.), and we agree that we might better reflect this. Overall, the generalization is still correct that most of the advanced motility testing reported in the literature comes from tertiary care centers. We strengthened the language explaining the portability and potential reproducibility of wireless motility capsule to reflect this important potential for usefulness in the community based on previous comments by other reviewers. We added to page 49 of the main report, "In our review of the literature, scintigraphy was performed using a wide variety of methods, as was radiopaque marker testing. In contrast there is a single method by which the wireless motility capsule is reported to be performed. In addition, wireless motility capsule can be performed in any office with a nurse, while antroduodenal manometry or colonic scintigraphy can only be performed with experts at an academic center with specialized equipment and large investments of time. In this way, capsule may prove to be more reproducible and more standardized than some of the other testing modalities. Currently, there is also only one type of software in use, which may make testing more comparable between centers as well. No studies directly assessed using capsule internationally or in a community-based environment to measure this effect to date."

Commentator & Affiliation	Section	Comment	Response
Public Comment: Braden Kuo	General	References for comments 143, 144: Kuo B, Maneerattanaporn M, Lee AA, Baker JR, Wiener SM, Chey WD, Wilding GE, Hasler WL. Generalized transit delay on wireless motility capsule testing in patients with clinical suspicion of gastroparesis, small intestinal dysmotility, or slow transit constipation. Dig Dis Sci. 2011 Oct;56(10):2928-38. Rao SS, Mysore K, Attaluri A, Valestin J. Diagnostic utility of wireless motility capsule in gastrointestinal dysmotility. J Clin Gastroenterol. 2011 Sep;45(8):684-90. Semler JR, Swallow EW, Kuo B. Prevalence of Repeat Testing for GI Symptoms Potentially Indicative of Functional and Motility Disorders. Gastroenterology. 142 Suppliment 1 S399 (2012)	Thank you for providing these references.
Public Comment: Braden Kuo	General; limitations	Large prospective randomized studies addressing the impact of motility testing on patient outcomes is lacking for both conventional tests and the wireless motility capsule test. The draft mentions the lack of literature describing impact of wireless motility capsule testing on outcomes but should extend this limitation to their discussion on conventional motility testing literature including scintigraphy and ROM. The strength of the literature is similar for those techniques as well. Both Rao and Kuo report that WMC testing impacted patient management in more than 55 to 67% of their cases. Abnormal findings obtained with conventional tests can also be expected to impact patient management and these are reported (need citation for GES) to occur in 20-45% of these studies. The full GI motility profile accounts for a higher percent abnormal findings and higher percent impact on management. Similar enhancements in abnormal findings may be realized with conventional tests if more than one is prescribed for a patient.	Assessing the previously determined gastric emptying study and other baseline test profiles and limitations is beyond the scope of this review. However, we added to the discussion, "Note that there are few prospective randomized studies of gastric scintigraphy or radiopaque markers and multiple methods of practice of these tests." We also added to the conclusions, "Although we found limited evidence on the impact of wireless motility capsule testing on patient outcomes, we should acknowledge that it is also true that little evidence exists on the impact of conventional motility testing."

Commentator & Affiliation	Section	Comment	Response
Public Comment: Braden Kuo	General; sens/spec comparison of GES to WMC	Patients with persistent symptoms of gastroparesis including nausea, vomiting, early satiety, epigastric pain or discomfort for more than 6 months and a documented delayed gastric emptying test within the past two years conducted according to local standards were tested simultaneously with the wireless motility capsule and gastric emptying scintigraphy. Forty six percent (22/48 patients) of this sample population which met current criteria for clinical gastroparesis (symptoms plus documented delayed emptying) showed delay by scintigraphy while 65% (31/48) showed delayed with the wireless motility capsule test. There was 86% (19/22) agreement between positive scintigraphy results and positive WMC results. In the largest head to head study where WMC and gastric emptying scintigraphy were done simultaneously, there was overall reasonable agreement on delayed emptying. An additional 19 percent of patients with clinical gastroparesis were also delayed by WMC but normal by scintigraphy and three patients (6%) were normal by WMC but delayed by scintigraphy. Sarosiek further reported the presence colonic delay in this population in 18% of the gastroparetic population with WMC. Gastroparetics with fewer than 3 bowel movements per week were excluded from the study. Overall there were 31% more abnormal findings detected ((19% +18%)-6%) with WMC than with gastric emptying scintigraphy.	We agree with this reviewer regarding this information and referred to Kuo study in our report. We use this as a key reference for Key Question #2 where we summarize that "adding wireless motility capsule testing to conventional motility testing improves diagnostic accuracy in patients with suspected gastroparesis". Because the study by Sarosiek does not specifically mention whether the 18% of patients determined to have abnormal colonic transit were separate from the 46% of patients with abnormal scintigraphy and the 65% of patients with abnormal WMC gastric transit, we did not feel that we could add the 18% directly to the values already computed in Kuo's study (as that may be counting some patients twice) and did not feel that we had sufficient information to make that conclusion.

Commentator & Affiliation	Section	Comment	Response
Public Comment: Braden Kuo	General; lack of indication of outlet obstruction with WMC	No relationship has been observed between pressure or transit data provided by the wireless motility capsule and the condition of outlet obstruction. The draft review suggests the ispersal pattern of radio opaque markers may indicate the location of impaired function in the colon. We note at least two reports showing the dispersal pattern of radio opaque markers in the colon fails to adequately distinguish outlet obstruction. References: Cowlam S, Khan U, et al. ; Validity of Segmental Transit Studies in Routine Clinical Practice, to Characterize Defacatory Disorder in Patients with Functional Constipation. Colorectal Disease 10, 818 (2008) Eltringham MT, Khan U, et al., Functional Defecation Disorder as a Clinical Subgroup of Chronic Constipation: Analysis of Symptoms and Physiological Parameters. Scandinavian Journal of Gasrtoenerology, ; 43 262 (2008)	We agree and have tried to make this clearer. We have edited the Discussion to state, "In the assessment of constipation, one cannot separate patients with slow-transit constipation from defecatory dysfunction based on only colonic transit time so further motility testing like balloon expulsion or anorectal manometry and clinical judgment is needed to evaluate defecation."
Public Comment: SmartPill Corp	Executive Summary	Safety profile and addressing comment that there is a requirement for radiologic exam when wireless motility capsule body exit is unconfirmed .	This has been fixed.
Public Comment: SmartPill Corp	Executive Summary	a. Response: Saad reports in his technical review of the wireless motility capsule[10] the company guidelines that state no specific follow up is necessary if, based on capsule pH data, the capsule is retained in the colon. Prokinetic therapy or endoscopy is indicated if the capsule is retained in the stomach. Saad reported 13 of twenty reports of prolonged retention occurred in the colon, five in the stomach and two in the small bowel out of shipments of 6000 capsules. The rate of retention requiring intervention is 0.1% (6/6000) compared to 1.4% overall for capsule endoscopy[11].	We have changed the Wireless Motility Capsule section of the Introduction to reflect this clinically important difference. We now state, “Disadvantages of the capsule include failure to capture data (requiring repeat testing) and delay or total failure to pass. When the capsule fails to pass and patients have symptoms, then a patient may need x-rays to detect retention. In rare cases, endoscopic or surgical removal may be necessary. The capsule is not viable for patients with a possible stricture, altered anatomy, or severe pyloric stenosis.”

Commentator & Affiliation	Section	Comment	Response
Public Comment: SmartPill Corp	Executive Summary	b. The Smartpill Corporation's internal guidelines for its customer service department state that if evidence of cecal passage is present from wireless motility capsule data that the capsule will likely eventually pass and radiologic examination for capsule exit is not required in absence of symptoms. This guideline was developed by the company from a review of their clinical study data and from potentially reportable events referred to customer service and approved by its product advisory board.	Thank you. We have reflected this fact in the current draft based on previous reviewers' comments. We have changed the Wireless Motility Capsule section of the Introduction to reflect this clinically important difference. We now state, "Disadvantages of the capsule include failure to capture data (requiring repeat testing) and delay or total failure to pass. When the capsule fails to pass and patients have symptoms, then a patient may need x-rays to detect retention. In rare cases, endoscopic or surgical removal may be necessary. The capsule is not viable for patients with a possible stricture, altered anatomy, or severe pyloric stenosis."
Public Comment: SmartPill Corp	Executive Summary	The term reference standard is misapplied in reference to radio opaque markers (ROM) in the diagnosis of chronic constipation.	We agree that radiopaque markers are an imperfect reference standard. We modified the report to refer to radiopaque markers as a non-reference standard and reported positive percent agreement and negative percent agreement instead of sensitivity and specificity. These distinctions are described in the methods. We followed the guidance from the AHRQ Methods Guide for Medical Test Reviews and the FDA Statistical Guidance on Reporting Results from Studies Evaluating Diagnostic Tests.
Public Comment: SmartPill Corp	Executive Summary	Response: Chronic constipation is a symptom based disorder not readily defined by a unifying pathophysiological abnormality. In discussions prior to conduct of our multicenter prospective clinical study validating wireless motility capsule to ROM the FDA concurred ROM is a non-reference standard because it cannot define constipation in anywhere near 100 percent of the population presenting with symptoms.	We agree that radiopaque markers are an imperfect reference standard. We modified the report to refer to radiopaque markers as a non-reference standard and reported positive percent agreement and negative percent agreement instead of sensitivity and specificity. These distinctions are described in the methods. We followed the guidance from the AHRQ Methods Guide for Medical Test Reviews and the FDA Statistical Guidance on Reporting Results from Studies Evaluating Diagnostic Tests.

Commentator & Affiliation	Section	Comment	Response
Public Comment: SmartPill Corp	Executive Summary	Based on discussions with the FDA the following comments were included in the introduction to the clinical study protocol[2]. - Similar to other symptom-based disorders, chronic constipation is not defined by a unifying pathophysiological abnormality. In fact, a number of physiological abnormalities have been implicated in the development of chronic constipation. The two main physiological abnormalities include delayed colonic transit (slow transit constipation or STC) and the inability to coordinate the series of events necessary to allow the normal evacuation of stool from the rectum (dyssynergic defecation or DD). Studies from secondary and tertiary care centers (see Table 2) have found that 15-47% of constipated patients have evidence of STC while 25-59% have DD. STC and DD can coexist in the same patient. An additional 24-71% of patients have normal results on physiological testing (5) and are diagnosed as normal transit constipation (NTC) (5,6,7,8). Prevalence data become critically important when designing or interpreting data from studies evaluating novel tests for patients with chronic constipation. For example, if the expected prevalence of STC is 40-50% in patients with complaints of constipation, a test which flawlessly identifies STC would be expected to have a “sensitivity” of 40-50% in this group of patients, In other words, the true sensitivity of the test can only be determined after taking into consideration the prevalence of the specific physiological abnormality that the test is intended to identify.	Based on previous reviewers comments, we have strengthened the language separating defecatory dysfunction from slow-transit constipation and clarified its wording in the diagnostic work up. We did try to describe the difficulties in assessing different populations in our review of study limitations and in our results section. We have edited the Discussion to state, "In the assessment of constipation, one cannot separate patients with slow-transit constipation from defecatory dysfunction based on only colonic transit time so further motility testing like balloon expulsion or anorectal manometry and clinical judgment is needed to evaluate defecation." Thank you.
Public Comment: SmartPill Corp	Executive Summary	As summarized in Table 2, the prevalence of slow and normal transit constipation varies considerably from study to study. Variability most likely results from differences in severity of the condition in the population studied, differences in the ROM criteria used to define normality (test method standardization is lacking), and inherent variability in colonic transit (9).	Yes, thank you, we described this in our limitations and in our results. It is important to understand these population differences.

Commentator & Affiliation	Section	Comment	Response
Public Comment: SmartPill Corp	They have a Table entitled: Prevalence rates (%) of constipation type in symptomatic patient populations	ROM's clinical utility is limited to distinguishing between slow transit and normal transit constipation. Therefore the sensitivity of ROM is also limited by the prevalence of slow transit in the population studied. Given the prevalence of slow transit reported in the prior ROM studies listed in table 2 a sensitivity of less than 50% for both ROM and SP will not be surprising. Based on feedback from our clinical experts device equivalence will be supported if agreement exceeds 65%.	It was hard to compare between the different studies which exact sensitivity and specificity would universally apply due to differences in population. Instead we focused on agreement between the tests, where a 10% difference or less would be considered adequate. This would allow for each population to be individually addressed provided the tests were comparable to each other in ability to detect. We agree and tried to graphically represent the data, display it in tables and describe it to such effect.
Public Comment: SmartPill Corp	Executive Summary	As you note WMC fails to detect cecal entry 5% of the time and therefore colonic transit time is missing in up to 5% of tests.	This was also addressed in previous comment and mentioned by previous reviewers. We added to the Wireless Motility Capsule section of the Introduction, "Camilleri has reported a use of the combined small bowel and colon transit time to allow for interpretation of these cases."
Public Comment: SmartPill Corp	Executive Summary	Response: We suggest a fair assessment of this issue should include the comment that WMC offers a strong surrogate for colonic transit when it is not available, combined small large bowel transit. Camilleri et al[1] reported positive device agreement between wireless motility capsule and combined small large bowel transit and ROM of 80% and negative agreement of 91%. These values are identical to the values he reports for the agreement between wireless motility capsule colonic transit times and ROM.	We did reference this fact in this updated draft. Thank you.
Public Comment: SmartPill Corp	Executive Summary	Table A. The draft report states adding WMC to GES improves sensitivity and reports GES sensitivity ranges from 42%-51% while GET=61%-66%.	We agree.
Public Comment: SmartPill Corp	Executive Summary	Response: The report should reflect that the population tested was enriched for a positive test for gastric emptying scintigraphy. Gastroparetic subject eligibility required both 6 months of gastroparetic symptoms and a previous documented delayed gastric emptying test within the past two years. Therefore WMC showed higher sensitivity than gastric emptying scintigraphy in a population specifically enriched for delayed gastric emptying measured by scintigraphy.	Thank you. We added text to reflect this point.
Public Comment: SmartPill Corp	Executive Summary	Table B- reports concordance between ROM and WMC was 80%.	We agree.

Commentator & Affiliation	Section	Comment	Response
Public Comment: SmartPill Corp	Executive Summary	Response: The overall concordance reported by Camillari[1] between wireless motility capsule and ROM is 87%. He reported that positive agreement between ROM and wireless motility capsule colonic transit was 80% and the negative agreement was 91%. It is more accurate to report overall concordance or both positive and negative concordance.	In Table B, we are summarizing the results from multiple studies, not just the Camilleri study. In Table 13, we report individual study results. The data in this table is correct.
Public Comment: SmartPill Corp	Executive Summary	Little data is available to support determination of the optimal timing of wireless motility capsule testing in the diagnostic and therapeutic approach to patients with symptoms of possible gastroparesis or slow transit constipation.	We tried to address this fact with more clarification over the current guidelines and the specific uncertainty of the diagnostic work up in general for motility disorders. We reflected the fact that wireless motility capsule is an alternative test to conventional tests as per ANMS guidelines.
Public Comment: SmartPill Corp	Executive Summary	Response: The wireless motility capsule is a validated alternative to the conventional transit tests: gastric emptying scintigraphy and radio opaque markers.[1,7] The scarcity of data addressing optimum timing for use of wireless motility capsule in the diagnostic workup of patients applies equally to these conventional transit tests and should be mentioned. Further any evidence supporting the timing of introduction of conventional motility tests in the diagnostic and therapeutic approaches applies equally to the wireless motility capsule given the comparability of the methods through correlation and device agreement has been demonstrated.	We tried to address this fact with more clarification over the current guidelines and the specific uncertainty of the diagnostic work up in general for motility disorders. We reflected the fact that wireless motility capsule is an alternative test to conventional tests as per ANMS guidelines.
Public Comment: SmartPill Corp	Introduction	Currently, wireless motility capsule testing is being used in a complementary fashion as an addition to reference standard tests like scintigraphy. Whether it can replace or should supersede other testing methods is controversial.	In the Introduction, we have added, "Currently, wireless motility capsule testing is recommended as an alternative test instead of scintigraphy, however in cases that are still suspected but indeterminate, whether it can replace or should supersede other testing methods is controversial."

Commentator & Affiliation	Section	Comment	Response
Public Comment: SmartPill Corp	Introduction	Response: The position paper[3] by the joint American and European neurogastroenterology and motility societies reports the wireless motility capsule is an alternative to both gastric emptying scintigraphy and radio opaque markers rather than a compliment. The report on the prevalence of generalized transit delay in functional GI disorders by Kuo[8] reports the primary reason for presence of both gastric emptying scintigraphy evaluation and a wireless motility capsule evaluation in patients enrolled was lack of availability of the wireless motility capsule test when the gastric emptying scintigraphy test was ordered. This report further comments it is likely future reports will likely produce further data demonstrating the absence of need to perform both tests in an individual.	We have edited the Discussion of the Executive Summary and main report to state, "Should it be used as a stand-alone test? What should be done when wireless motility capsule is normal but clinical suspicion remains? Or is it better used as an adjunct test after conventional testing has been completed in cases where the diagnosis remains in question? Recommendations from the ANMS practice guidelines suggest that wireless motility capsule can be used in the diagnostic work up of patients with suspected gastroparesis and slow-transit constipation as well as those with more generalized motility disorders, but these are consensus guidelines. There was no specific information about when or how wireless motility capsule should be applied. Thus, these are questions that have not been clearly addressed in previous clinical practice guidelines. "
Public Comment: SmartPill Corp	Introduction	We are not aware of any published clinical demonstrating the complimentary nature of the tests. All published evidence points to them as alternative measures for assessment of gastric emptying.	We have changed the introduction to reflect this, "Currently, wireless motility capsule testing is recommended as an alternative test instead of scintigraphy." We sought to define the evidence for wireless motility capsule as a complementary or replacement test because these are the dilemmas faced by physicians and patients in practice. Thus, we sought to demonstrate which was in evidence and determine if more evidence is needed.

Commentator & Affiliation	Section	Comment	Response
Public Comment: SmartPill Corp	Introduction	We further note unreported data from the Kuo[7] study that demonstrates the strong positive agreement between wireless motility capsule and gastric emptying scintigraphy. Eighty six percent of subjects delayed by gastric emptying scintigraphy were delayed by the wireless motility capsule. The diagnostic tests measure different physiologic mechanisms, emptying of a low fat meal compared to emptying of a non-digestible solid but the emptying of the non-digestible wireless motility capsule depends first on the emptying of the meal as Cassilly[9] showed. Thus if the meal is delayed the capsule will be delayed. The average percent meal retained in healthy subjects when the wireless motility capsule emptied was 2.5% ±2.6% in the Kuo study. Consequently the capsule will not empty until most of the meal empties or well below the 10% of meal remaining cutoff used as a threshold for delay for the gastric emptying scintigraphy test. This explains the strong positive agreement between the two diagnostic tests. Given the additional GI segmental transit motility profile provided by the wireless motility capsule and strong positive agreement between the two tests it is reasonable to view the capsule as a more complete full GI profile alternative to gastric emptying scintigraphy rather than a compliment to it.	The prospective trials proving these statements are currently lacking in general community practice or in academic practice. Thus, we have a hard time making the same conclusions or suggestions based on the current evidence. We agree that it is likely superior to current testing modalities for a multitude of reasons, however, those are currently facts not in evidence based on the stringent criteria we applied to the studies we analyzed.
Public Comment: SmartPill Corp	Introduction	Controversy regarding the role of capsule testing in the diagnostic evaluation of constipation was addressed at the 2011 ANMS conference. Some experts thought that it would likely be a complementary test rather than an independent test for patients with this disease.	We have changed the Introduction to reflect this, "Experts debated the timing of wireless motility capsule in the evaluation of patients with suspected motility disorders, especially concerning the FDA approval pending for some of the newer prokinetic/secretagogue medications." [One of the authors was physically present at the meeting during the actual discussion, however we agree there was no formal document published with this information to reference.]

Commentator & Affiliation	Section	Comment	Response
Public Comment: SmartPill Corp	Introduction	a. Response: This comment lacks a specific reference and we unaware of any evidence that it compliments ROM rather than it is a valid alternative to ROM for the measure of colonic transit. In light of the evidence presented from the multicenter prospective clinical study[2] showing the wireless motility capsule is a valid measure for slow transit constipation[1] and the joint US and European Society position paper on the evaluation of gastrointestinal transit in clinical practice reporting the comparable clinical utility of wireless motility capsule to ROM for the evaluation of colonic transit we feel the language should be modified to reflect it is a validated alternative to ROM.	We agree that validity testing was performed, and we agree that there was evidence of concordance between the tests, however since radiopaque markers is a non-reference standard and there is little guidance on the exact diagnostic work up of either test, we still feel that is any area led by consensus and not by evidence per se. Thus, controversial from the point of view of an evidence-based review. We modified the statement. We edited the Introduction to reflect this: "Experts debated the timing of wireless motility capsule in the evaluation of patients with suspected motility disorders, especially concerning the FDA approval pending for some of the newer prokinetic/secretagogue medications."
Public Comment: SmartPill Corp	Introduction	b. The wireless motility capsule does not offer diagnostic information informing the presence of a functional outlet obstruction disorder. However we also note recent references in the literature demonstrate contrary to earlier opinion the distribution of ROM in the colon does not inform the presence or absence of outlet obstruction[3,4]. Finally note Rao[6] reported the location of the capsule on day 2 or day 5 x-ray was associated strongly with the colonic region where the majority of ROM were retained.	We have changed the Introduction to reflect this. We have added, "Colon transit disorders can be complex to sort out. A single test may not reflect the full complexity of a patient's motility disturbances. For example, anorectal dysfunction can impact colonic transit, but must be assessed by anorectal manometry separate from other transit testing. When anorectal or outlet dysfunction is identified via anorectal manometry or balloon expulsion testing, biofeedback therapy can be used for treatment."
Public Comment: SmartPill Corp	Introduction	c. We suggest the language be modified to reflect the comparable not complimentary diagnostic role of wireless motility capsule to ROM supported in the professional society joint position paper[3] and references to the literature on the relative lack of relationship between ROM and positive physiologic measures of outlet obstruction.	The position paper was a consensus document and we were seeking to prove or disprove the facts stated therein via the existing evidence. We agree that wireless motility capsule may actually be a replacement test, but we would like to prove or demonstrate proof that it is in no way complementary at this time. In fact, wireless motility capsule may have an additional role as a complementary test when clinical suspicion is high and when other tests are indeterminate (i.e., if someone didn't have access to wireless motility capsule in their practice they might do the other tests available to them), as in some of the patients Kuo described. But we have made changes throughout to reflect that the overall evidence is referencing its role as a replacement and not complementary test.

Commentator & Affiliation	Section	Comment	Response
Public Comment: SmartPill Corp	Colonic scintigraphy	Regarding: We did not include any studies that addressed this comparison.: Response: Please note your draft review reference #51 reports the correlation between whole gut scintigraphy and wireless motility capsule as r=0.6 in 10 healthy patients.	The reviewed population of interest was suspected or actual patients with gastroparesis or constipation. Unfortunately, this is very good evidence of the comparability in healthy subjects, but we sought to define the wireless motility capsule correlation in these other populations.
Peer Reviewer-4	General	I have read the documents for the wireless motility capsule and congratulate the authors for their meticulously detail to this issue. First, let me say that I agree with the conclusions of the review and particularly about the low strength of evidence that the wireless motility capsule will improve outcomes of care for either gastroparesis or constipation. I will divide my review into gastroparesis and then constipation sections with a few comments about each before I make specific suggestions.	Thank you for reviewing our report!
Peer Reviewer-4	General	Gastroparesis is a real disorder and the diagnosis is quite evident when symptoms are severe and classic. Patients exhibit weight loss associated with retentive vomiting and other symptoms of delayed gastric emptying. In such patients, which represent the most severe tip of the iceberg, diagnosis is often confirmed by the finding of a gastric bezoar on endoscopy, the failure to empty barium from the stomach during an upper GI series and both in the absence of a mechanical or pharmacologic cause for these symptoms. For less classical presentations, the diagnosis depends upon the findings of admittedly imperfect tests which are often done poorly in clinical practice and which often lead to misinterpretation. It is unproven as to whether the 4 hour gastric emptying study will improve upon the admittedly flawed traditional methods but it would bring some uniformity to the field. In my opinion, the diagnosis of gastroparesis is often inappropriately applied to patients who have the symptoms quoted in your introduction but which are by no means specific for delayed gastric emptying. Because tests provide objective data, they often provide an convenient if incorrect assessment of the primary disorder. Indeed, there is a body of evidence to suggest that gastric emptying times do not correlate well with symptoms, that symptoms often improve in the absence of any improvement in gastric emptying and that improvement in	We have emphasized the complexity in the diagnostic workup. We agree that this is a test that assists with clinical decisionmaking, and doesn't replace clinical expertise. The purpose of this systematic review is to assess the benefits and harms reported in the available evidence about the wireless motility capsule in comparison to other modalities used in clinical practice. Presenting the benefits and harms will allow providers and patients to make better informed decisions about care. We tried to reflect your cautions in the document, and your concerns were echoed by other reviewers, thank you. On page 8 of the Introduction, we have added, "Colon transit disorders can be complex to sort out. A single test may not reflect the full complexity of a patient's motility disturbances." And, on page 3, we have added, "Motility disorders are difficult entities to diagnose. Multiple contributing factors make pathophysiology more complex, thus physicians can have difficulty gathering a unifying diagnosis from a single test."

Commentator & Affiliation	Section	Comment	Response
		gastric emptying (by what few prokinetic drugs that are available) is not always associated with improvement of symptoms. Most of the available drugs have anti-emetic effects on the central nervous system rather on gastric motility and indeed, in my experience and that of others, many patients with a diagnosis of "gastroparesis" actually gain weight during their illness. Thus, I think that the large group of patients who are diagnosed to have "gastroparesis" represent a very heterogenous group of individuals, only a small percentage of which have true gastroparesis, and that gastric emptying studies often inappropriately focus the attention of physicians on the stomach whereas the gastric emptying patterns may often (at best) be a surrogate marker for what may be going on centrally. Therefore, I view with some skepticism any test which seeks to neatly characterize a patient's diagnosis on the basis of emptying measures. With that said, I'd like to make specific comments in the order in which they appear in the gastroparesis section:	
Peer Reviewer-4	Results KQ 1/2	Antroduodenal manometry is now used very infrequently and is more of an investigative tool than a clinically important test. This is because it has not been shown that the manometric patterns have clinical importance in terms of the management of the patient. Distinctions between myopathies and neuropathies are of interest but are relatively unimportant in management of these patients. I would include in the methods of testing: barium UGI series- if the barium does not empty from the stomach in the absence of a mechanical obstruction, gastroparesis is the diagnosis and no further testing is necessary. Gastric scintigraphy is used when patients do not have an abnormal barium study which is the least sensitive of the available tests.	We added text clarifying the infrequent use of antroduodenal manometry. We elected to exclude barium imaging in our key questions after discussion with our key informants. Barium imaging is used to evaluate a mechanical obstruction, but does not evaluate gastric emptying.
Peer Reviewer-4	Results KQ 1/2	A small point, but it is the egg whites or albumin that are radio labelled and this is why Egg Beaters are used rather than eggs. I would prefer the term opiates to narcotics, again a small point but one more consistent with their pharmacologic classification.	We replaced narcotics with opiates and changed the reference to the radio labeling.
Peer Reviewer-4	Results KQ 1/2	I think expulsion time rather than expellation time is more commonly used and the patient swallows the pill rather than takes the pill.	We made this replacement.

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer-4	Results KQ 1/2	A low residue diet is easier to empty from the stomach (not to digest) and is the major reason why dietary fiber is excluded. It is physicians rather than patients who decide about using prokinetics or any other drug.	We made these changes. Thank you.
Peer Reviewer-4	Results KQ 3/4, general	Unlike gastroparesis, constipation is a symptom based diagnosis and on page 15, paragraph 1, I would emphasize that constipation is defined as fewer than three bowel movements per week and the term “symptoms of constipation” seems to be a redundancy.	We have provided the following definitions in the Executive Summary, "The definition of constipation has been established with slight variation by multiple professional societies, but usually constipation is defined as fewer than two bowel movements per week or a decrease in a person’s normal frequency of stools that is accompanied by straining, difficulty passing stool, or passage of hard solid stools." and in the Introduction, "Patients who have fewer than two bowel movements per week must be assessed by their medical history and a physical examination to exclude malignant or organic causes of constipation."

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer-4	Results KQ 3/4, general	I believe that patients of all ages with warning signs accompanying constipation should be investigated. The issue of patients over the age of 50 is really one of screening rather than diagnostic colonoscopy. This is not always made clear in reviews of this subject. All patients over the age of 50, whether they are constipated or not, should have screening colonoscopy and this is independent of the topic in question.	Page 3 of the Executive Summary now reflects this sentiment, "Clinicians should ask about warning signs such as new onset of symptoms, obstructive symptoms, rectal bleeding, unintentional weight loss, or family history of early colon cancer. A rectal examination can help to delineate rectal function and tone and exclude a low rectal cancer. Investigation with colonoscopy is indicated if fecal occult blood, iron deficiency anemia, or any other warning signs are detected. Patients with symptoms of constipation and warning signs should be investigated with colonoscopy, as should all patients over 50 years of age who have never received a screening colonoscopy; however, the yield of colonoscopy in patients with constipation with warning signs is low. Once organic causes of constipation are excluded, a diagnosis of functional constipation can be made." We have provided the following definitions in the Executive Summary, "The definition of constipation has been established with slight variation by multiple professional societies, but usually constipation is defined as fewer than two bowel movements per week or a decrease in a person's normal frequency of stools that is accompanied by straining, difficulty passing stool, or passage of hard solid stools." and in the Introduction, "Patients who have fewer than two bowel movements per week must be assessed by their medical history and a physical examination to exclude malignant or organic causes of constipation."
Peer Reviewer-4	Results KQ 3/4, general	In the last paragraph under Definition and Prevalence, according to the Hinton study, greater than 20% of markers retained at Day 5 is diagnostic of slow transit. Thus, in clinical practice, 24 markers are given as a single capsule on Day 0 and a single abdominal x-ray is obtained on Day 5. The presence of five or more markers is indicative of slow transit. It is not clear to me whether the statistics cited refer to prevalence or incidence of slow transit constipation; prevalence may be a better term.	We added to the Definition and Prevalence section of Constipation, "Other studies list a prevalence of 0.17 percent."

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer-4	Results KQ 3/4	Dulcolax is the trade name of bisacodyl and the latter should be used. This is also true for Colace, which is a trade name for ducosate. Again, under radio-opaque markers, the description should be shortened to a single x-ray at Day 5, which is taken with overpenetrated films (110 keV) in order to reduce x-ray exposure. We no longer focus on the areas of colon that have the greatest delays, since studies have shown that this does not predict pathophysiology or treatment. The only exception to this statement is the patient who accumulates markers in the rectum and are not passed; this would strongly suggest a defecation disorder.	We have revised this report and have used generic names for medications throughout. To address the second comment about radiopaque markers, we edited the Introduction of the Executive Summary and main report to state, “In its simplest form, such testing is performed by having the patient ingest the radiopaque markers on day 0 and then taking x-ray at Day 5, which is taken with overpenetrated films (110 keV) in order to reduce x-ray exposure. We no longer focus on the areas of colon that have the greatest delays, since studies have shown that this does not predict pathophysiology or treatment. The only exception to this statement is the patient who accumulates markers in the rectum and does not pass them; this would strongly suggest a defecation disorder. Marker retention allows identification of patients with slow transit.”
Peer Reviewer-4	Results KQ 3/4	The re-evaluation of colon transit with the use of laxatives seems to be a European recommendation and is infrequently performed in the United States. What is meaningful is the patient’s clinical response to laxatives and it would be only rarely that I would repeat colon transit while on laxatives and then only because the clinical response was not entirely clear. Also specifically, slow transit constipation is an indication for colectomy in the absence of a defecation dysfunction and in the absence of more generalized intestinal pseudo-obstruction. The potential advantage of the capsule would be to detect delayed gastric and/or small intestinal transit in such patients, something which is only done with scintigraphy in specialized centers. However, there are no data that confirms that such information from the capsule has importance in determining suitability for surgery.	We have made changes and addendums as requested. The Use of Colonic Testing to Guide Treatment in the Introduction chapter now states, “If testing confirms the presence of slow-transit constipation (colonic inertia) without use of laxatives, then the next step in evaluation at some centers is transit testing with use of laxatives. Only after demonstrating colonic inertia should surgery be considered as a potential therapy.” We have also added, “Some patients with delayed colonic transit may have evidence of a more diffuse gastrointestinal disorder, such as gastric or small bowel transit delay. Detection of the accompanying disorder is important, since patients with colonic inertia and gastric emptying delay have poorer outcomes from total colectomy.”
Peer Reviewer-4	Results KQ 3/4	Unlike gastric motility, there is little evidence to support the statement that obtaining pressure patterns in the colon (either with multiple stationary transducers or with a single capsule transducer which is moving at variable speeds through the colon) has any significant important role to play in the clinical management of adult patients with slow transit constipation.	Under the section of Colonic Manometry of the Introduction chapter, we have added, "It is uncertain how this information should be used to guide management of adults with slow transit constipation."

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer-4	Results KQ 3/4	I assume that the sensitivity and specificity of these tests refer to slow transit constipation. However, this is an incomplete assessment as patients can have clinical constipation with normal transit and certainly with defecatory disorders. Therefore, the sensitivities and specificities quoted for the capsule and markers are of uncertain clinical importance to me. A better comparison is the true/false positives and negatives of the capsule vs markers or scintigraphy which is essentially equivalent to markers.	We have made multiple changes throughout the report in reference to radiopaque markers. We focus on positive and negative percent agreement and concordance as suggested between wireless motility capsule and radiopaque markers.
Peer Reviewer-4	Clarity/ usability	I am in complete agreement with your key findings and conclusions. The wireless capsule is a nifty bit of technology and a future advantage might be to use a single technique with known standards to unify the workup for patients with both gastroparesis and constipation. I have no problem with the validation studies, but as this review mentions, whether the capsule has added value in the management of these somewhat difficult patients is far from proven.	Thank you for your help and review.
TEP 6	General	Overall quality: good	Thank you for reviewing our report!
TEP 6	General	Overall, I feel this review offers a realistic and balanced review of this emerging technology. The report is meaningful, the target population and audience are well explained, and key questions are appropriate and clearly stated.	Thank you for reviewing our report!
TEP 6	General	However as with other reviews in this field, I believe an equally critical view of the reference technologies (e.g. gastric scintigraphy for gastroparesis, radioopaque markers [ROM] for constipation) is lacking. For readers unfamiliar with this area, one is left with the impression that WMC parameters have been inadequately tested vs. “established” standards of upper and lower gut motility testing. In fact as described below, gastric scintigraphy is performed using multiple methods that would not qualify as equivalent technologies using the criteria employed for this review. For example in a paper by Guo et al. in DDS in 2001, there was nearly a one third discordance in emptying values depending on whether gastric retention was measured at 2,3, or 4 hours. Others have shown that adding 3 and 4 hour retention values to 2 hour testing “increases” the sensitivity of gastric emptying scintigraphy	We have added to the Introduction the following to reflect this, "Furthermore, most of the available tests have some inconsistency in performance that make their interpretation difficult in some cases." On the first page of the Introduction, we added, "Many of the traditional testing modalities inconsistency in performance that make their interpretation difficult and complex for providers." We agree, and many of the other reviewers echoed the sentiments suggested here. In response, throughout the paper we tried to emphasize the underlying complexity and in the methods and results tried to focus on the lack of standardization represented in the studies reviewed. Wireless motility capsule usually had fairly good reporting for the precise reasons you mentioned, and in fact it was the opposite of the other tests which often were done

Commentator & Affiliation	Section	Comment	Response
		for diagnosis of gastroparesis. Given that many community centers use nonstandardized meals, measure nonstandardized parameters such as half times of emptying, and often perform testing before and after prokinetic stimulation with drugs such as metoclopramide, the diagnosis of gastroparesis in one city bears only marginal relation to its diagnosis in adjacent cities. One strength of the WMC method not mentioned in this review is that the values obtained in one center are reliably transferred to those of other centers as the method and interpretations are rigorously standardized. I am in agreement with the authors of this review that comparisons of sensitivity and specificity values between methods is of limited value when the utility of such a method in clinical management has not been defined. This is equally true for gastric scintigraphy and WMC measures of gastric emptying. These same concerns can be raised for ROM determinations of slow colon transit. There are numerous different ROM methods reported in the literature that have not been compared to one another. The most commonly employed method—obtaining a single radiograph at 5 days after ingesting a marker capsule provides a binary result while the more quantitative Metcalf method generates a transit value. It is inconceivable that such measures would not be discordant. Furthermore in this review, I see no acknowledgment that all ROM techniques measure whole gut rather than colon transit. It is not possible given the infrequent radiographs to know when the markers leave the stomach and small bowel. This explains most of the apparently longer "colon" transit times observed with ROM vs. WMC methods. Furthermore as with gastric scintigraphy standard reference technologies, ROM reference standards have not been rigorously validated to impact management of patients with refractory constipation. In this way, they are no better or worse than WMC test results.	locally prior to the referral or if done in the academic center were not always done consistently beyond the validation studies. We have also discussed different statistical references to non-reference standard modalities such as radiopaque in the Methods chapter. Thank you for helping.

Commentator & Affiliation	Section	Comment	Response
TEP 6	General	One of the strengths of the WMC method which is only briefly discussed is its capability to evaluate transit in several regions in a single test. It is not uncommon (in tertiary practice at least) for clinicians to desire quantification of gastric emptying, colonic transit, and sometimes small bowel transit in patients with generalized symptomatology.	On ES-7 (paragraph on wireless motility capsule) and in main body in the Introduction chapter, second sentence under Wireless Motility Capsule, we added, "It can detect specific transit times in the stomach, small bowel, and colon and thus both upper and lower GI disorders simultaneously with a single device."
TEP 6	Introduction	On page 1 under evaluation of possible gastroparesis, no mention is made of gastric emptying breath testing. Although not yet approved in the US, it is in wide use in Europe.	Consistent with other reviews developed under the Effective Health Care program, we have restricted the technologies to those available in the US, to improve the relevance and applicability to clinical practice in the US. We do include off-label use of drugs and technologies available in the US. Since gastric emptying breath testing is not available in the US we did not include this in the review. We also did not look at small bowel transit as part of our current review as we thought it was beyond the scope of our comparative effectiveness, since there are limited comparisons. Thus, this was not a focus of our review.
TEP 6	Introduction	On page 12, the determinations of myopathic vs. neuropathic patterns (particularly in relation to pressure values) are relevant only to the small intestine. Many gastric neuropathies give a flat line pattern similar to myopathic disease.	Under Antroduodenal Manometry section of the Introduction, we have added, "These are patterns of small bowel disease. Many gastric neuropathies show a flat line pattern similar to myopathic disease."
TEP 6	Introduction	On page 12, I am unaware of any patients to date who have undergone surgical removal of the WMC. Given the different patient populations tested with WMC vs. endoscopy capsules, it is likely the risk of capsule retention in the small bowel is less for WMC.	Thank you. Although no one required surgery in the literature that we reviewed, some people have already required endoscopic retrieval. This is however a possibility and this outcome should be followed and then if no cases occur after a certain time period in post-marketing surveillance it may be taken off the list of possibilities. The wireless motility capsule is an indigestible large-sized object ingested by highly selected patients with nausea/vomiting. While the risk of capsule retention is low, it is still an important outcome to report.
TEP 6	Introduction	On page 14, the list of potential therapies of constipation is incomplete and does not include the laxative most often recommended by gastroenterologists (PEG 3350). Also missing are lubiprostone and now linaclotide.	We added PEG 3350 to the Basic Management section of Constipation in the Introduction chapter and the Executive Summary.

Commentator & Affiliation	Section	Comment	Response
TEP 6	Introduction	On page 14 under the section on ROM, the Metcalf method should be mentioned here. As stated above, it produces quantitative values for oroanal transit that may be superior to the binary values provided by simpler SitzMarker techniques. As a consequence, this method is preferred in a number of academic centers in the US.	Under the Radiopaque Markers section of the Introduction, we state, "Some centers also use other testing methods, such as the Metcalf method."
TEP 6	Introduction	On page 15, the inability of WMC to distinguish defecatory dysfunction from slow colon transit is no different than ROM techniques. If one suspects this condition, balloon expulsion testing and/or anorectal manometry are needed whether WMC or ROM are performed to test for colon transit defects.	Thank you. We agree and have tried to make this clearer. We have edited the Discussion to state, "In the assessment of constipation, one cannot separate patients with slow-transit constipation from defecatory dysfunction based on only colonic transit time so further motility testing like balloon expulsion or anorectal manometry and clinical judgment is needed to evaluate defecation."
TEP 6	Introduction	On page 37, despite what some clinicians believe, electrogastrography is really a test of altered myoelectric function and has not convincingly been shown to test for gastroparesis. In my opinion, this sentence could be removed.	We referenced the tests since some centers have reported its use.
TEP 6	Introduction	On page 39, the mention of use of 25% retention as a more stringent cutoff for diagnosing gastroparesis was an off the cuff remark by a single investigator that is unsubstantiated by any data in the field. All papers in this area use cutoffs of 20% retention to distinguish mild from moderate delay and 35% to distinguish moderate from severe, thus a 25% value has no basis in investigation.	Under the Controversy section for Gastroparesis in the Introduction, we now state, "Experts debated the need for stricter criteria for diagnosing gastroparesis and whether greater retention of gastric content was likely to relate to greater severity of disease, which recent literature has questioned."
TEP 6	Introduction	Also on page 39, I am not sure that the statement “greater retention of gastric content is related to greater severity of disease” is valid. Many studies including the largest in the field (Pasricha et al., CGH 2011) show essentially no relation of symptom severity to gastric retention. This paper includes a sizable number of patients with normal emptying, many of whom have disabling symptoms.	Under the Controversy section for Gastroparesis in the Introduction, we now state, "Experts debated the need for stricter criteria for diagnosing gastroparesis and whether greater retention of gastric content was likely to relate to greater severity of disease, which recent literature has questioned. (Pasricha et al., CGH 2011) Nevertheless, this may still have implications for how physicians use capsule testing to treat patients with abnormal gastric emptying. Previous consensus recommendations from 2008 established baseline standards for scintigraphy and suggested that grading the severity of gastric emptying delay was relevant to clinical research, but did not establish how that grading would affect decisions about patients."

Commentator & Affiliation	Section	Comment	Response
TEP 6	Introduction	Also on page 39, I would like to see data to support the contention that WMC testing is being used in complementary fashion as an addition to reference standards. This certainly is not necessary if one believes the methods are substantially equivalent. When covered by insurance, most clinicians at my center do not perform ROM measures for slow transit constipation as WMC tests provide determinations of gastric and small bowel transit in addition to colon measures. Since many of our WMC tests are being used to determine appropriateness of colectomy for refractory slow transit and since such surgeries are relatively contraindicated if there is concurrent generalized dysmotility, WMC provides all needed testing and obviates the additional requirement for gastric scintigraphy in these individuals. At most lectures I have attended on such testing, WMC methods are primarily advocated as replacements rather than adjuncts to scintigraphy and ROM tests.	Thank you for this input, your sentiments were also shared by several of the other peer reviewers. The questions we have to answer are the current use and the future use. I.e., Should wireless motility capsule be used when other methods are inconclusive, do they add anything? Unfortunately, this was not as clear as we would have liked in the draft systematic review. We have made changes throughout the document to reflect this change, but we still think it is a valid research question until reproducibility, outcomes and therapeutic response data are more firmly established.
TEP 6	Methods	I believe the Methods are well designed and this section is well written. I have very few concerns about this aspect of the manuscript.	Thank you for reviewing our report!
TEP 6	Methods	On page 18, the concordance rate chosen for this analysis (80%) seems reasonable, however is this determination based on comparable studies and/or is this an accepted concordance rate for these types of studies? As stated above, this standard is not met by the reference methods used for these comparisons. Concordance rates between different scintigraphic measures of gastric emptying falls short of 80%; I am less familiar with the ROM literature, but is suspect that single radiograph ROM determinations of whole gut transit probably do not show >80% concordance with those from Metcalf methods.	We elected to look at concordance as it was listed in the Methods Guide for Medical Test Reviews as an option when there was no gold standard. The cut-off of 80% is a bit arbitrary, but we chose it based off of the 10% difference in sensitivity the studies were powered to detect. Less emphasis was placed on concordance in the final report.
TEP 6	Results	The detail level in the Results section is appropriate. The data are presented in a readable manner and, for the most part, are complete. Tables are comprehensive and exhaustive. The studies included were appropriate.	Thank you for reviewing our report!
TEP 6	Results	In Table A on page 21, antroduodenal manometry is misspelled. In the KQ1 comparison of WMC vs. scintigraphy, the mention of anorectal manometry is not pertinent to a discussion of gastroparesis testing.	Thank you. We made these corrections.

Commentator & Affiliation	Section	Comment	Response
TEP 6	Results	In Table B on pages 22-23, there should be some clarification of why the SOE for WMC testing for colon transit vs. ROM is low. The test concordance does meet your standard of 80%, thus other factors must weigh down your assessment. Needs for X-ray testing to exclude capsule retention are quite rare in clinical practice. They were much higher in the trials which had per protocol X-ray requirements.	Strength of evidence was low for other factors (risk of bias, precision, etc.) We reassessed this in light of our updated literature search. We believe the issue of x-ray is somewhat based on the population. These were highly selected study patients. If conducted in real life, the timing of capsule needs to not coincide with MRI testing for other purposes, and x-ray may be needed to confirm passage in this real life scenario. We made changes to the evidence report to reflect that the x-ray requirement in clinical use (as opposed to research use) is only for symptoms and suspected retention.
TEP 6	Results	On page 57, it would be instructive to better explain which criteria lead the investigators to reach a conclusion of SOE. As mentioned above, the concordance rate for WMC for gastric emptying is <80% but this is not seen for WMC measures of colon transit, thus other factors must be operant.	Only four of the studies referred to were manuscripts in refereed journals, while the remainder were abstracts or post-hoc analyses. In addition, two of the trials involved high risk of bias. Thus, bias was a major issue impacting the SOE.
TEP 6	Results	On page 64 under the section on Harms, the Kuo paper had a defined protocol for obtaining radiography to exclude capsule retention. Thus, the 46% requirement has no relation to clinical practice.	We feel that it is important to report this figure, but we explained why so many required radiography.
TEP 6	Results	On page 65, I am curious what criteria are used to discriminate between medium and high risk of bias. Reference 32 is listed as a High risk of bias for assessing resource utilization. However, this same article as well as very similar references 33 and 37 are listed as Medium risk of bias for determining treatment decisions. It seems to me that extracting data pertaining to treatment decisions and decisions to obtain additional testing would be of similar reliability and likely similar risk of bias.	We agree and revised the ratings of the risk of bias in this study to be consistent. Please see Appendix D of the full report for details of individual study quality assessment for studies.
TEP 6	Results	On page 71, as stated above the absolute transit values for WMC and ROM are not comparable because the ROM values always include gastric emptying and small bowel transit times in their overall calculation. Thus, it would be expected that ROM would be at least 6-7 hours longer than WMC even if the particles were identically handled by the GI tract.	We have added a sentence to the Transit Times results section for KQ3 stating, "Transit times do differ between testing modalities as radiopaque marker testing includes gastric and small bowel transit time, whereas wireless motility capsule does not."
TEP 6	Discussion/ conclusion	The implications of these analyses are well stated and I agree with the conclusions and much of the discussion that follows.	Thank you for reviewing our report!

Commentator & Affiliation	Section	Comment	Response
TEP 6	Discussion/ conclusion	On page 79, it would be appropriate to include a discussion of utility of WMC methods in characterizing generalized transit defects. The only other testing with this capability is whole gut scintigraphy—a method currently available only at 3 centers in the US.	We did reflect this sentiment throughout.
TEP 6	Clarity/ usability	The report is well structured and organized. The points are well presented. However, I have some concern with this manuscript in that the reference standards (gastric scintigraphy, ROM) are not held up to any true standard in terms of concordance, reproducibility, or clinical relevance. An unsophisticated reader of this manuscript would come away with the impression that the WMC technology is promising but needs substantially more investigation prior to being considered a comparable measure of slow gastric or colon transit. In fact, the standard scintigraphy and ROM measures have essentially been grandfathered in after decades of use without ever having been mandated to demonstrate the same consistency and reliability of newer technologies such as the WMC (and future tests such as gastric emptying breath tests).	We did reflect this sentiment throughout.
TEP 7	General	Quality of the report: good	Thank you for reviewing our report!
TEP 7	General	This is an overall well done systematic review/health technology assessment that follows standard and accepted methods for this type of research. It is an important review. I will provide my comments separated by some general comments and major/minor comments, the latter will generally be appearing in the order of the page numbering in this document.	Thank you for reviewing our report!
TEP 7	General	I am wondering whether or not pooling of the diagnostic test accuracy data wouldn't have been possible. I feel that some of the explanations provided, e.g. that the populations are heterogeneous is an insufficient reason.	We would love to have been able to conduct a meta-analysis of these studies. We consulted with several statisticians and methodologists to determine what methods would be most appropriate. However, we are unable to pool the results because we do not have a sufficient number of studies that made similar comparisons using similar outcome measures. We added more detail of what we considered in the Data Analysis and Synthesis section of the Methods chapter.

Commentator & Affiliation	Section	Comment	Response
TEP 7	General	I believe that some of the tables, currently appearing in the main text, would also be helpful for the Executive Summary. I realize that this is an issue of presentation and primarily related to formatting, but I believe that readers would be helped by seeing some of the very useful tables up front.	We agree, but we are limited by space requirements of the executive summary as standardized by AHRQ.
TEP 7	Search results	I question if it was necessary to research Medline and Embase from inception given that I believe the mortality capsule was not available when Medline and Embase were designed or for the time that they actually go and include literature. In regards to the Results shown in the abstract I believe that there should be some discussion at a different point in the manuscript about the choice of the reference standard because some of these values of diagnostic test accuracy may be a function of the reference standard that was chosen and a comparison against several possible reference standards might be helpful.	This is a valid point. When we were developing the search strategy, we were debating whether or not to include the precursors to the wireless motility capsule. Thus, our search is a little broader than what it needs to be.
TEP 7	Executive Summary	I think it would be helpful to have the conceptual framework that the reviewers were following in the Executive Summary because it will make this review much more understandable.	We have added the analytic framework to the Executive Summary (Figure A).
TEP 7	Executive Summary	It would be helpful to say how the American Neurogastroenterology Motility Society did, in fact, recommend the use of the capsule rather than just providing that it has been recommended. Was it a strong recommendation? On what basis?	It was a consensus document and the method wasn't specified, except expert review of the evidence.
TEP 7	Executive Summary	In regards to the selection of outcomes, a general strategy, in my view, should be that the patient important outcomes or patient-centered outcomes should really be the primary outcomes. It seems to be counter intuitive to list them as other outcomes when we are really interested in seeing if there is an important difference in how patients feel about their disease or the consequences of their disease.	A patient-centered approach is a principle of the Effective Health Care Program. Patient-centered outcomes are clearly identified in the analytic framework. Furthermore, we sought out patient-centered outcomes in the existing literature, and the absence/presence of any findings is presented in the evidence report. We have revised the wording of this paragraph to indicate that patient-centered outcomes are important as well.

Commentator & Affiliation	Section	Comment	Response
TEP 7	Executive Summary	The authors state that they searched Medline and Embase from 1966 and 1974; I do not believe that this is consistent with inception for these databases as the times of recording have been changed. The authors may just want to check that. In regards to study selection, as mentioned above and all the other methods, I believe that these methods are completely appropriate and described in the necessary detail.	We did not search EMBASE Classic, which covers the dates 1947-1973. Therefore, 1974 is the correct date for EMBASE. PubMed's indexing of articles prior to 1966 is limited.
TEP 7	Executive Summary	In regards to the quality assessment and applicability on page ES7 it would be helpful to describe in detail how QUADAS 2 was modified, in particular as applicability has become an item of QUADAS 2, rightly or not. However, it would be important to describe that.	We now list the quality items in the Executive Summary, under the Quality Assessment section. Applicability is assessed separately in our review.
TEP 7	Executive Summary	It might be important to (re)consider the use of the terms “clinically meaningful difference”, given that this clinically meaningful difference cannot be derived from just looking at sensitivity and specificity without modeling and careful consideration of the downstream consequences. I would suggest choosing a difference term. Furthermore, the term clinically meaningful is probably obsolete regardless and should be related to patient important or population important outcomes. This is a suggestion for the authors to consider the wording.	We now use the term "potentially important difference" instead of "clinically meaningful difference" throughout the report.
TEP 7	Executive Summary	I would suggest saying in the first paragraph “…in another three studies…” in the sentence that starts with – “After contacting...”	We agree this suggestion is clearer. In the results section describing study quality we changed this to "In another three studies where blinding was not reported, after contacting the authors, we were able to confirm that the results were interpreted independently." There was no change to similar text in Results.
TEP 7	Table A	In table A it would be helpful for the reader (to enhance understanding and for transparency) to give the key reasons for downgrading the strength of evidence. This could be done by saying, low due to…. and then list for instance imprecision and I think this would apply to the Tables that follow with the key questions on the pages until ES13.	While we think this is an excellent idea, we feel that it would be redundant in the table to repeat "low strength of evidence due to moderate risk of bias and imprecise results." We provide details about the evidence grading in the Discussion section of the Executive Summary.

Commentator & Affiliation	Section	Comment	Response
TEP 7	Executive Summary	In the last paragraph it would be helpful to speak about complications such as situations where the capsule is not excreted.	Other reviewers had emphasized that retention is not very common and investigation is only required for those with symptoms, which does not occur as often in this population than others receiving capsule tests. They had suggested we deemphasize this. We agree, based on the fact that we found no cases of capsule retention reported with any significant consequence.
TEP 7	Executive Summary	Please clarity the difference between medium and moderate risk of bias. I believe this is just terminology that needs to be corrected (as there is no difference). Along these lines in the paragraph starting with, overall, I am puzzled why this decision has been made to not use meta-analysis. A meta-analysis could tell the authors if the difference in the population is of any relevance. What if, for instance, the performance is similar in the difference patient populations? I also believe it should be described what is meant by heterogeneity of data. If it relates to the sentence that starts on line 40, then I would suggest that this is said clearly. Furthermore, and this relates to the following pages, the last paragraph on ES17, it would be important to say whether or not the heterogeneity was truly explored and if, for instance, different diagnostic criteria or thresholds or cutoffs account for any differences. Along these lines it would be very helpful to show forest plots despite the fact that no pooling was preformed because it will provide the reader with a graphical image on how the information was used to either pool or not pool.	Thanks for your comment. “Moderate” risk of bias should be listed as “medium” risk of bias. We have made these corrections in the report. We intended to meta-analyze the evidence when possible. In revising the report and in response to your comment, we consulted with several statisticians and methodologists to determine what methods would be most appropriate. However, we are unable to pool the results because we do not have a sufficient number of studies that made similar comparisons using similar outcome measures. We added more detail of what we considered in the Data Analysis and Synthesis section of the Methods chapter. We did add figures plotting the sensitivity and specificity of the studies.

Commentator & Affiliation	Section	Comment	Response
TEP 7	Executive Summary	It would be helpful to say whether or not the studies in group C were case control studies and if they really should have been included. In regards to paragraphs preceded by B and C, isn't the question really whether or not there was diagnostic uncertainty and should that not be clarified?	The reviewer refers to subpoints in the "Limitations" section of the Executive Summary. In this subpoint we had noted that many studies included non-diseased study participants in diagnostic accuracy studies, and also that clinical diagnosis was used as the reference standard. The goal of our review was to compare the wireless motility capsule to existing tests for gastroparesis and chronic constipation. Ideally, the reference standard in this design of study is the existing test and the study population includes only patients with disease. However, many studies chose to include non-diseased patients in the study population and comparison of the wireless motility capsule to the reference standard. We included these results because they addressed our goal and key questions, though have noted these issues as limitations. In terms of diagnostic uncertainty of the reference standard: we have added as a limitation of our review, "Scintigraphy and radiopaque markers are acknowledged by experts in the field to have imperfect diagnostic accuracy. There are several options to account for the imperfection of the reference standard. We chose to incorporate 2 of these in our review 1) We presented the results as if the reference standard had no measurement error and acknowledge this imperfection. 2) We present concordance of the test results when available. We did not attempt to adjust the results to correct for the measurement error. This adjustment would have required assumptions that we did not have sufficient data to justify. Another option is to examine patient outcomes according to the wireless motility capsule. We had included patient outcomes (need for medications, additional tests) as outcomes in our review. Unfortunately, there was insufficient reporting on these outcomes to make them the focus of the review."

Commentator & Affiliation	Section	Comment	Response
TEP 7	Executive Summary	It would be important to say, if the criteria that were used to assess the strength of evidence should elucidate if industry funding actually induced bias, which could be reflected in publication bias and the risk of bias etc. Funding by industry alone probably is not a bias but rather a surrogate for other methodological criteria that should be elucidated by going through a structured process of evaluating the strength of evidence.	We chose not use information on industry funding in our strength of evidence grading. We have however included industry funding in our assessment of individual study quality. This is described in the methods section, and details of our assessment of individual study quality can be found in Appendix D.
TEP 7	Executive Summary	Given that you had no response from industry and in case that you did make strong efforts, then publication bias is indeed highly likely given what we know about publication bias.	We acknowledge this as a limitation, and have mentioned this in our discussion section. One of our limitations is "(h) We attempted to assess publication bias by contacting the manufacturer of the wireless motility capsule and requested any unpublished data, but received no response."
TEP 7	Executive Summary	It might be helpful to provide some other clear findings, which include the need for a well designed reference study, standard as well as high quality designs that may even be randomized.	As a follow-on to this systematic review, we are conducting a future research needs project. For further details about this EHC product http://www.effectivehealthcare.ahrq.gov/search-for-guides-reviews-and-reports/?pageaction=displayproduct&productid=521. We have addressed these concerns in the future research needs document. In addition we have added text in the Future Research Needs section of the discussion with specific details about study design and considerations.
TEP 7	Results	The mentioning of correlation coefficients is of limited value in my view. If the authors believe that these correlation coefficients have a high value they should explain why and describe that in the Methods.	We agree that correlation coefficients are of limited value. However, some studies only correlation coefficients to describe the results between the two tests.
TEP 7	Results	The sentence starting with, theoretically, could possibly be taken out. It is probably the wrong place to make this assumption, given that this is an EPC report focusing on the available evidence.	We deleted the sentence, “Theoretically, wireless motility capsules should not require x-ray in standard use, however delay or failure of passage is possible and may require x-ray to detect retention.”

Commentator & Affiliation	Section	Comment	Response
TEP 7	Clarity/ usability	In summary, I enjoyed reading this report. My main suggestions relate to issues of dealing with heterogeneity and formatting of the report as well as providing plots of the various data. Thank you for involving me in this review.	We have appreciated your thoughtful feedback on this evidence report. We have provided figures summarizing the diagnostic accuracy of the wireless motility capsule in comparison with gastric scintigraphy (Figure 5) or radiopaque markers (Figure 6). We have also provided more detail in the Methods chapter about the types of analyses we wanted to conduct and why we were unable to conduct them.