

Project Name: ECG-based Signal Analysis Technologies

Project ID: CRDD1008

Disposition of Comments

Table 2: Public Review Comments

¹ Names are alphabetized by last name.

² Affiliation is labeled “NA” for those who did not disclose affiliation.

³ If listed, page number, line number, or section refers to the draft report.

⁴ If listed, page number, line number, or section refers to the final report.

Reviewer Name¹	Reviewer Affiliation²	Section³	Reviewer Comments	Author Response⁴
Lance Austein, MD, FACP	Primary care physician, Brooklyn, NY	General comment	<p>I have reviewed this Draft Report. I am a primary care physician in a diverse urban private practice. I have had much practical experience with Premier Heart’s technology. The advantages for a primary care practice are significant. It can be done promptly, there is no need for a referral, preauthorization or other “barrier to care.”</p> <p>It is standardized. A conventional electrocardiogram has limited sensitivity for detecting CAD, and is “interpreter dependent.” The 3DMP test is standardized and interpreted with mathematical formulas by an online-computer. The scoring system and pathological suggestions are standardized and easier to interpret affording the practitioner a “risk assessment and stratification,” that has practical “bedside” utility.</p> <p>My practice has been utilizing Premier Heart’s 3CMP technology since Spring, 2007. I have found it especially useful for chest pain and for patients with multiple coronary risk factors to guide my work-up and interventions, sometimes avoiding cardiology consultations and the accompanying costly diagnostic evaluation. I look forward to more peer-reviewed literature on the utility and cost-effectiveness of this technology.</p>	Thank you for the comment about your experience.

V. Desiderio	Patient	General comment	<p>I owe my life to MCG. As a middle aged Caucasian male I was tested by the usual procedures: EKG, Stress Test, Echo and CT, only to be told I was fine and everything was ok. WRONG!!</p> <p>When tested by MCG I learned that I had severe CAD. I've been able to reverse the degree level of CAD from an MCG severity score of 9 (Dangerous) to a manageable 4.</p>	Thank you for the comment about your experience.
Mary Drake	NA	General comment	<p>My observation and comments related to the importance of improvement in detection of CAD is based on personal experience. The following excerpt from this report grabbed my attention.</p> <p>“An enhanced ECG-based test might demonstrate greater positive or negative predictive values, thereby limiting the harms associated with delays in treatment, or by providing the diagnostic information necessary to avoid invasive diagnostic or therapeutic interventions [pgs 1, 10].”</p> <p>Had there been more accurate test methods I would not have been subjected to an unnecessary heart cath six years ago. The heart cath was clear and no blockages found. It was only after such an intrusive test, that I was diagnosed with muscle spasms due to anxiety!!! Diagnostic intervention was totally backwards and was a waste of medical dollars.</p> <p>Yes, if I had had a cardiac event, it would have been a good thing that they pursued every diagnostic measure possible, but I was not a victim to CAD and the procedure placed me under undue risk. Although I understand the liability the medical facility carried and the need for informed patient consent this procedure could have been avoided with enhanced diagnostic equipment. I am a widow with 2 minor children at home and had to sign documents acknowledging I could die on the table during this procedure. If I had died unnecessarily, as a result of this procedure, who would have taken care of my children? How many other people in the U.S. are subjected to this invasive form of testing unnecessarily?</p> <p>Being subjected to this unnecessary heart cath procedure also presented a vasospasm due to the intern moving too aggressively within the heart chamber. To this day (on occasion) I can sense a vasospasm, where I had never had that condition before (prior to the heart cath). There is a vital need to improve non-invasive testing for CAD.</p>	Thank you for the comment about your experience.

Michael Imhoff, MD PhD	Ruhr-University Bochum, Germany	General comment	<p>I am pleased to provide my opinion to the draft TA (TA) “ECG-based Signal Analysis Technologies” Prepared by the Duke Evidence-Based Practice Center under contract to the Agency for Healthcare Research and Quality (AHRQ). My comments relate to the referenced evaluation of Premier Heart MCG (or 3DMP).</p> <p>As I was involved in the detailed statistical analysis of three of the four trials of MCG included in the TA, namely Grube 2007, Grube 2008, Hosokawa 2008, I would like to comment on some apparent misperceptions by the authors of the draft TA.</p>	Thank you for the comments. Specific comments by this reviewer are addressed below.
Michael Imhoff, MD PhD	Ruhr-University Bochum, Germany	General comment	<p>Of all methods reviewed in the draft TA only MCG was directly compared against the diagnostic “gold standard” for the detection of coronary stenosis (CS), namely coronary angiography (CA). To the best of my knowledge these studies (and the previous study with MCG by Weiss 2002) were the only published studies to directly compare a resting ECG method against CA for the detection of CS in sufficiently large patient populations.</p> <p>In these three studies the observed actually incidence of hemodynamically relevant CS was 32%, 40.7% and 48% respectively. This is considered intermediate risk (ACC/AHA 2002), and not “high risk” as falsely stated by the authors of the draft TA.</p>	<p>These three studies (Grube 2007, Gruge 2008, Hosokawa 2008) enrolled patients scheduled for coronary angiography. Clinical symptoms and/or indications for angiography were not reported.</p> <p>Therefore, we were uncertain about the clinical risk profile of these patients for CAD. The text has been revised to describe the sample studied more clearly (pg 30). The rates of CAD described by the reviewer are accurately reported in the evidence tables. In addition, a 4th study (Weiss 2002), using a similar approach, found a 57% prevalence of CAD.</p>

Michael Imhoff, MD PhD	Ruhr-University Bochum, Germany	Pg 50, lines 1-3	<p>The sample sizes of these three individual studies each and the size of the metaanalysis (Strobeck 2009) are sufficient to have confidence that sensitivity and specificity of MCD for the detection of CS is applicable to other patients with CS.</p> <p>It should be noted that in the studies by Grube et al. the presence of risk factors for CS did not alter the diagnostic performance of MCG. Therefore, there is no reason to assume that MCG does not perform with similar sensitivity and specificity in populations with low or very low risk of CS.</p> <p>Using Bayes' correction for positive (PPV) and negative predictive values (NPV) it can be shown that MCG may be highly suitable for ruling out CS in low and very low risk subject. Based on the study results an NPV of nearly 99% can be expected for these subjects, i.e., a negative MCG (score < 4.0) will rule out hemodynamically relevant CS with 99% certainty.</p> <p>From a biostatistical perspective the conclusion by the authors of the draft TA that "Test performance characteristics for this device appear to be generally good, but the findings from the published studies do not apply to the target population for this report" [p.50; II. 1-3] is not justified by the study results. Quite on the contrary, the study results for MCG indicate that MCG may very suitable to rule out CS in the patient populations in question.</p>	<p>We agree that the sample sizes are sufficient to produce relatively precise estimates of sensitivity and specificity as shown by our summary estimates and 95% confidence interval. However, we disagree that these results can be applied with confidence to populations at low to intermediate risk. For diagnostic test accuracy studies, the best documented design factors that affect risk of bias or variation include: demographic features, disease prevalence and severity, and distorted selection of participants (Whiting P et al. Ann Intern Med 2004;140:189-202).</p>
Michael Imhoff, MD PhD	Ruhr-University Bochum, Germany	Pg 51, lines 8-9	<p>The authors of the draft TA also state "Only the PRIME ECG has been directly compared to the standard 12-lead ECG" [p.51, II. 8-9]. This statement seems unjustified, as MCG was also compared to 12-lead ECG in the study by Weiss 2002 (see table 5 of the original article).</p> <p>Of course, I am available for further discussion of this matter. Thank you very much for the opportunity to comment on the draft TA.</p>	<p>Thank you for the comment. We have included data on the ECG from the Weiss et al. study (pg 32 and elsewhere).</p>

<p>Mitchell W. Krucoff MD, FACC</p>	<p>Duke University Medical Center/Duke Clinical Research Institute</p>	<p>General comment</p>	<p>In addition to the strengths/weaknesses of coronary angiography as a gold standard for comparison, it should be pointed out that low risk patients who are referred for coronary angiography constitute a heavily selected, and almost certainly biased, subset of low risk patients in clinical practice for whom novel ECG technologies apply.</p> <p>Thus, another option not mentioned in this report is the use of combined assessments in prospectively assigned subgroups, eg. Low risk who go to cath and low risk who do not go to cath. The latter group might fall into either an imaging co-gold standard, and/or even a clinical diagnostic time period (eg did/did not have coronary diagnosis over 12 month follow up).</p> <p>The current paper's approach to the diagnostic comparator (gold standard) is very traditional, at a time when AHRQ, CMS and other federal agencies, as well as health care in general, are in need of more efficient, practical and clinically relevant directions for new technology assessments.</p>	<p>We revised the text to describe the potential utility of a reference standard that uses imaging plus followup (pg 22).</p>
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<p>Daniele Marangoni MS</p>	<p>Advanced Consultants & Engineering, Verona, Italy</p>	<p>General comment</p>	<p>I have a MS in BioMedical Engineering. I have been a co-author of several peer review published papers on Risk assessment of Cardiac events (see my web page). I have been a technology expert in several Clinical trials. I work as a Consultant and Editor of the Biotechnology Web Page: www.alternans.org.</p> <p>What I found incorrect in the Draft TA "ECG-based Signal Analysis Technologies" document to lump the MCG with SAECG: there is no link and the averaging technique is only used as a input filter to improve Signal/Noise ratio to perform later a optimized frequency domain analysis. The key theory concept of this MCG method is the Cross Correlation between 2 biological signals (lead II and V5) in the frequency domain. The Cross Correlation and Phase Shift (together with other 4 mathematical transformations) provides the information about the abnormal response of the Heart system (Myocardium and intracardiac flow) between 2 signals used as input/output in the Systems Theory.</p> <p>With analogy to Acoustic system, the stereo output of a broken bell sound or earthquake (frequency domain recordings in 2 sites) provides the location and size of the bell defect or earthquake.</p> <p>Therefore there is no link between the MCG system and other ECG systems. The MCG is a very innovative system and the Meta-Analysis of the published papers provides the clinical results. Please ask the authors of this TA to correct this remark.</p> <p>Presently, I am conducting as Technology Expert a Clinical Evaluation Project using MCG technology comparing to Coronary Angiography, before and after angioplasty. My evaluation of MCG methodology has been very positive.</p> <p>If you have questions or comments, please contact me.</p>	<p>Thank you for the comment. The text has been revised throughout to clarify that the 3DMP/MCG uses mathematical signal analysis that is distinct from signal averaging technology.</p>
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<p>Charles K. Miceli, MD, FACC, FACP, FCCP</p>	<p>Private practice, NY</p>	<p>General comment</p>	<p>I have been in practice for over thirty years in the field of Cardiology and Internal Medicine. For the past two years I have had the opportunity to use the MCG technology in the diagnosis and treatment of coronary artery disease. I have found it to be invaluable. I am sure you will be inundated with responses such as mine that will tell you that the MCG technology should not be lumped with Signal Analysis Technology. Please find a number of cases that I have compiled from my private practice to show you how I use it and how it will benefit all in the diagnosis and treatment of CAD.</p> <p>[Here Dr. Miceli provides nine case reports of his patients. See Appendix A for the full comments.]</p> <p>Conclusion: In my practice, the MCG test is invaluable. How do I use it? -score of 0---Reassurance. -score of 1 or 2---Exercise, life style modification, asa and Statin. Retest in 1 year. -score of 3---Most likely like scores of 1 and 2. Treat the same but add stress test. If abnormal stres, treat as 4-7. -score of 4-7---Treat as 1-3, but add stress testing. If positive send for cath. If negative (50% will have negative stress test), consider adding beta blocker or other agents as in the Courage Trial and retest in 3 months. Follow carefully. Cath if symptoms occur. -scores greater than 7---Verify the accuracy with repeat testing , treat as 4-7 and consider cath or at least cta of coronary arteries. -MCG provides a role for the detection of coronary artery disease, the continued followup and evaluation of coronary artery disease, as well as in the pre-operative evaluation. Coronary artery spasm can be detected, as well.</p>	<p>Thank you for the comment about your experience.</p>
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Kotaro Obunai, MD	Makiminato Central Hospital	General comment	<p>I am pleased to submit a brief comment on the draft technology assessment report regarding, "ECG-based Signal Analysis Technologies" prepared by the Duke Evidence-Based Practice Center under contract to the Agency for Healthcare Research and Quality (AHRQ). My comment relates to the above-referenced evaluation of the MCG (or 3DMP) technology of Premier Heart, Inc. and is based on my knowledge of the published data and personal clinical experiences with the MCG technology.</p> <p>After reading the TA reports I became concerned that there might be a misconception that the MCG technology is a form of signal averaging ECG or body surface mapping ECG technology. MCG technology uses an entirely new integrative approach, building a mathematical model of the entire cardiac system and ignoring conventional time-based ECG technology, which signal averaging ECG and body surface mapping ECG does employ. MCG technology has been developed to evaluate which symptomatic patients need (or do not need) further tests, such as stress imaging or coronary angiography. This explains why the MCG technology has been evaluated in such a manner described in the published data.</p>	Thank you for the comment. The text has been revised throughout to clarify that the 3DMP/MCG uses mathematical signal analysis that is distinct from signal averaging technology.
Kotaro Obunai, MD	Makiminato Central Hospital	General comment	<p>As stated in the draft report, stress test with imaging has been accepted as a non-invasive way to diagnose myocardial ischemia. However, it is well known that stress test with imaging is time and labor consuming, expensive, and not completely non-invasive. Also stress test is operator dependent and the test quality varies from one institution to another depends on the skills and experiences of the physicians and personnel performing the test. In the real world practice, the accuracy of the stress test with imaging could be poorer than we believe from the published data, which was demonstrated at well qualified institutions. As a board certified interventional cardiologist, trained both in the US and Japan, I have seen so many patients globally who had undergone unnecessary coronary angiogram just because of abnormal stress imaging. Many physicians have been looking for a true non-invasive, operator-independent testing which they can utilize in their office to detect/rule-out ischemia in their patients. Based on my experience with MCG technology in my practice, MCG is accurate, safe, and can be reliably performed by trained personnel within 10 minutes.</p> <p>I would hope that authors will re-examine the uniqueness of MCG technology, re-evaluate the appropriateness of the study design and study results, and re-consider their conclusions in their report.</p>	Stress testing is minimally invasive, requiring only peripheral intravenous access to administer pharmacological agent or radioisotope for imaging.

Franz Ritucci, MD	American Academy of Urgent Care Medicine	General comment	<p>I have read the Draft TA and I am very concerned because it appears that there is not a clear understanding of what MCG technology is really all about. It appears that the authors tried to "fit" this technology into an existing paragram, which truly does not exist for this new technology. I am forced to call your attention to this very basic concept.</p> <p>This ultimately effects the manner in which clinical trials are designed and how one would apply this technology in every day clinical practice. I believe the authors need to look at the the studies that were performed with MCG the comparison to coronary angiography, the pre-test risk of the study population, the meta-analysis of the trials and the consistency of the data in multiple important sub groups of patients, the authors should re-evaluate the fundamental assumptions fo the TA report and re-exam the answers.</p> <p>I believe that the study in it's existing format does not properly position MCG technology.</p>	<p>Thank you for the comment. The text has been revised throughout to clarify that the 3DMP/MCG uses mathematical signal analysis that is distinct from signal averaging technology.</p> <p>The Premier Heart website claims "The results from MCG have been <u>validated in double-blind clinical studies</u> where our system has demonstrated accuracy comparable to coronary angiography (90% overall sensitivity, 85% specificity)" and "...provides a quick, accurate, non-invasive and stress-free method for detection and diagnosis of myocardial ischemia." Our stakeholders were specifically interested in evidence on how these technologies perform in patients with chest pain at low to intermediate risk for CAD.</p>
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Joseph T. Shen, MD	Premier Heart, LLC	General comment	<p>I am pleased to submit comments on the draft technology assessment “ECG-based Signal Analysis Technologies” Prepared by the Duke Evidence-based Practice Center under contract to the Agency for Healthcare Research and Quality (AHRQ). Our comments relate to the evaluation of the 3DMP (or MCG or mfEMT) by Premier Heart (hereinafter referred to as MCG).</p> <p>Dr. John Strobeck has informed me¹ that he has been invited to perform a peer review of the technology assessment (TA), and has shared his reviews of the TA with the coauthors² of the four published peer-reviewed articles describing the results of double blind, prospective, clinical trials validating the ability of MCG to accurately identify patients with relevant coronary stenosis. As the principle architect of the MCG technology I agree with his masterful explanations of the underlying technology, the detailed analysis of the results of the clinical trials, and his overall views on the TA.</p> <p>In the spirit of providing accurate, genuine and truthful information to the interested public and supporting AHRQ, I am submitting clinical and technical MCG Technology white papers, to contribute to further understanding of MCG technology in preparation of the final TA.</p> <p>¹I am also the patent holder for the MCG technology and a shareholder of Premier Heart ²Aside from myself none of the coauthors of the papers serves as paid consultants to Premier Heart, shareholders of Premier Heart or have any financial relationship with Premier Heart. They have generously contributed their time and expertise in the interest of public health & advancing diagnostic technology.</p> <p>Dr. Shen included the following papers: Shen JT. The Multiphase Functional Cardiogram: A Clinical Overview. Premier Heart, LLC, 2010 Shen JT, Fedel E, Graziano M. The Multiphase Functional Cardiogram: Diagnostic Technology Overview. Premier Heart, LLC, 2010</p>	Thank you for the additional materials. We have used the material provided to revise the text and ensure that our description of the technology is accurate.
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<p>John E. Strobeck, MD, PhD</p>	<p>Heart-Lung Associates of America, PC</p>	<p>General comment</p>	<p>Note: Dr. Strobeck also includes some comments and perspectives from Dr. Shen.</p> <p>After reading the draft TA I became concerned that there was no clear understanding of exactly what MCG technology is, how the MCG device actually works, and therefore, how and why the published clinical trials were designed the way they were, and how the device should be positioned as an effective tool in clinical practice. It is my hope that by calling attention to the uniqueness of the MCG technology, highlighting the differences between it and traditional ECG-based technologies, further explaining the clinical trial design, the reasons for the comparison to coronary angiography, the pre-test risk of the study population, the meta-analysis of the trials, and the consistency of the data in multiple important subgroups of patients, the authors will re-evaluate the basic assumptions of the TA report, reexamine the answers to some of their key questions with respect to MCG, and re-consider many of their conclusions regarding the MCG, and reflect those changes in the final TA.</p> <p>[Dr. Strobeck included an 18-page Review Report including 4 tables and a figure, plus 28 citations. We have included his major concerns from his introductory paragraph, as well as the complete text of his “Conclusion and Summary.” See Appendix B for the full document.]</p> <p>The final TA should include MCG and contain a more detailed discussion of, the technology. To this end, I have three major concerns about the draft TA that will be discussed in my peer review: 1) the author’s description of the MCG technology is inaccurate, 2) the assessment of the population selected for the clinical trials data is inaccurate, and 3) the conclusions with respect to the demonstrated clinical usefulness of MCG and its current status as a diagnostic tool are inaccurate.</p> <p><i>(Comment continued on next page)</i></p>	<p>Concern #1. Thank you for the comment. The text has been revised throughout to clarify that the 3DMP/MCG uses mathematical signal analysis that is distinct from signal averaging technology.</p> <p>Concern #2. The three studies mentioned by the reviewer enrolled patients scheduled for angiography. Clinical symptoms and indications for angiography were not reported. Therefore, we were uncertain about the clinical risk for CAD. The text has been revised to describe the sample studied more clearly (pg 30). The rates of CAD described by the reviewer are accurately reported in the evidence tables. In addition, a 4th study (Weiss 2002), using a similar approach, found a 57% prevalence of CAD.</p> <p>Concern #3. We have included and described all published literature identified by our search or by peer reviewers. We have not found any reports that provide data on the effects on further diagnostic testing, treatment, or clinical outcomes.</p>
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John E. Strobeck, MD, PhD	Heart-Lung Associates of America, PC	General comment	<p><i>(Continuation of previous comment)</i></p> <p>MCG is a computer-based, computational electrophysiology systems analysis tool that physicians can use to make accurate and timely diagnosis of relevant CAD at the point of care. It is not comparable to SAECG or other direct ECG-based waveform analysis techniques, and has many distinct differences and advantages over those older technologies.</p> <p>The MCG clinical trials conducted thus far have clearly included patients with “intermediate pre-test risk” of CAD, not “high pre-test risk” patients as the draft TA concluded. I agree with the authors desire to have all new non-invasive, ECG-based technologies designed to detect coronary disease, compared to coronary angiography. To my knowledge, MCG is the only technology where such a comparison has been done. Furthermore, in my opinion, it is not appropriate to compare a technology like MCG to an “add-on” ECG-based technology, the intended use of which is entirely different from the intended use of MCG.</p> <p>I believe that the accuracy of MCG for the diagnosis of relevant coronary disease has been definitively validated through well-designed prospective double-blind clinical trials comparing MCG to coronary angiography, and that it has performed very well over a 2 1/2 year time frame as a clinically useful early diagnostic tool for physicians at the point of care treating symptomatic patients with known or suspected coronary disease. It has definitely reduced the number and complexity of “add-on” stress or stress-imaging tests I have ordered since beginning to use the device.</p>	See responses immediately above.
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John E. Strobeck, MD, PhD	Heart-Lung Associates of America, PC	General comment	<p>I believe that the stated goals of the draft TA assume an existing US coronary diagnostic paradigm into which the MCG technology does not fit. The core assumption of the TA is that new ECG-based technologies will be better than the traditional ECG at “evaluating” symptomatic patients who are at low or intermediate risk of coronary events (according to the ACC/AHA 2002 Guideline Update for Exercise Testing [8]) or coronary artery disease. Thus, the diagnostic paradigm assumed in the TA document is that newer ECG technologies are “add-on” technologies that will merely improve the treating physician’s ability to select patients for stress-ECG testing or stress-imaging with either echocardiography or scintigraphy. The MCG is not designed to fit this paradigm because it is designed to be a highly <u>accurate predictor of who does not need stress testing or coronary angiography</u>.</p>	<p>Our mandate was to evaluate these devices for the detection of CAD in patients with chest pain with a low to intermediate prior probability of CAD (see key questions). We agree that another application of these devices might be to evaluate patients with a higher prior probability of CAD, such as those with symptoms of acute coronary syndrome. Our report does not assume the diagnostic paradigm of MCG as an “add-on” test; rather, we discuss alternative paradigms (e.g., add-on, substitution) that might be applied to evaluating a new diagnostic test.</p>
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John E. Strobeck, MD, PhD	Heart-Lung Associates of America, PC	General comment	With reference to the selection methodology, it is clearly stated in all four trial publications that the study populations represented convenience samples of patients scheduled for coronary angiography. Since patients with acute coronary syndrome or acute coronary ischemia schedule for emergency cardiac catheterization were not included in the study populations. The final sample did represent a “consecutive” sample of patients scheduled for elective coronary angiography.	These studies enrolled patients scheduled for coronary angiography. Clinical symptoms and/or indications for angiography were not reported. Therefore, we were uncertain about the clinical risk profile of these patients for CAD. The text has been revised to describe the sample studied more clearly, including the description of a “convenience sample” (pg 23). We have not described the samples as consecutive samples, since the primary reports did not describe them in this way.
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John E. Strobeck, MD, PhD	Heart-Lung Associates of America, PC	General comment	<p>MCG is a technology that has been prospectively shown to accurately predict the presence of relevant coronary stenosis in patients at intermediate risk of CAD in well-designed clinical trials. [2, 7, 24-26] While I appreciate that the draft TA described the MCG trials as well-designed, I disagree with the conclusion that MCG is merely a “promising” diagnostic tool. I believe that the foregoing discussion of MCG technology, and of the design, and statistical evaluation of the MCG clinical trials in this peer review demonstrates that the accuracy and validity of MCG in detecting relevant coronary stenosis is well validated and supported by the trial results. It is my hope that the final TA will incorporate these concepts and conclude that MCG is a validated, clinically useful early diagnostic test for patients at low to intermediate risk for coronary disease.</p> <p><u>References:</u></p> <p>2. Weiss MB, Narasimhadevara SM, Feng GQ, Shen JT. Computer-enhanced frequency domain and 12-lead electrocardiography accurately detect abnormalities consistent with obstructive and nonobstructive coronary artery disease. Heart Dis. 2002;4:2-12.</p> <p>7. Strobeck JE, Shen JT, Singh B, et al. Comparison of a two-lead, computerized, resting ECG signal analysis device, the MultiFunction-CardioGram or MCG (a.k.a. 3DMP), to quantitative coronary angiography for the detection of relevant coronary artery stenosis (>70%) - a meta-analysis of all published trials performed and analyzed in the US. Int J Med Sci 2009;6(4):143-55.</p> <p>24. Hosokawa J, Shen JT, Imhoff M. Computerized two-lead resting ECG analysis for the detection of relevant coronary artery stenosis in comparison with angiographic findings. Congestive Heart Failure 2008 14: 25 1 -260.</p> <p>25. Grube E, Bootsvelde A, Buellfeld, L Yuecel S, Computerized two-lead resting ECG analysis for the detection of coronary artery stenosis after coronary revascularization Int. J. Med. Sci. 2008, 5(2): 50-61.</p> <p>26. Grube E, Bootsvelde A, Yuecel S, et al. Computerized two -lead resting ECG analysis for the detection of coronary artery stenosis. Int. J. Med Sci. 2007; 7: 249-263.</p>	<p>Thank you for the comment. We have carefully updated the report to respond to peer review comments, but the revisions did not warrant a change to the final conclusions. MCG has been evaluated carefully in samples selected for coronary angiography, and we report that it has performed well in this setting. However, our mandate was to focus on patients with chest pain at low to intermediate pre-test probability for CAD as described in our key questions and analytic framework. The differences in our report's target population vs. the samples in which MCG has been evaluated, along with the absence of data for effects on diagnostic/treatment decisionmaking and clinical outcomes, lead us to stand by the conclusion that MCG is a promising diagnostic tool in patients at high risk or with known CAD.</p>
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Tom Williams	None stated	General comment	I found too many inaccuracies in the assessment for 3DMP/MCG. MCG is "not" signal averaged based. This technology is not an add on to current ecg technology. ECG's are a snapshot in time, if you will. MCG appears to examine the differences from cycle to cycle and compares them to a database of normal and abnormal cases similar to the native databases found in bone-densitometry units. I do not see this approach in current modalities, per se. I feel that the AHRQ may have made some false assumptions and a more indepth understanding of this diagnostic tool is necessary and warranted before an adequate assessment can be made.	Thank you for the comment. The text has been revised throughout to clarify that the 3DMP/MCG uses mathematical signal analysis that is distinct from signal averaging technology.
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Appendix A

The full comments from Dr. Miceli follow.

#1. MB.

-60-year-old male with family history of coronary artery disease, hyperlipidemia and hypertension - Asymptomatic -Negative stress echocardiograms -MCG score of 2 -On his own went for cardiac catheterization with 20% LAD obstruction seen

This case emphasizes that the low score was indicative of only mild disease and this patient could have avoided cardiac catheterization.

#2. TP

-History of hypertension and hyperlipidemia -Elevated calcium score in 2007 -MCG score of 3.5 and asymptomatic -Stress echocardiogram: Difficult to perform. Exercise for 11 minutes and 30 seconds. Suggestion of septal hypokinesis in all views.

-Patient elected to go for cardiac catheterization

Catheterization: Showed normal coronary arteries with a mild diminished left ventricular function and mild diffuse left ventricular hypokinesis consistent with a mild cardiomyopathy.

This case emphasizes again the low score would indicate no significant obstruction. However patients with cardiomyopathy can have an elevated score. His true score was probably lower.

#3. CM

-80-year-old female with shortness of breath with exertion -Risk factor of hypertension and diabetes -MCG score of 8 -Cardiac catheterization: Significant critical right coronary artery lesion.

-Patient underwent stenting

-A few weeks postoperatively she presented with atypical chest pain -Repeat MCG score was now zero

-2 days later she complained of chest pain that sounded like GERD -Repeat MCG score still zero -Cardiac catheterization repeated and stent open

This case exemplifies how a severe score predicted significant disease and how after stenting, the MCG score could now predict whether or not the patient had a patent stent. Her chest pain was related to GERD not coronary artery disease.

#4. SR

-Patient weighed over 350 pounds

-Patient had prior coronary artery stenting many years ago -The patient developed shortness of breath, questionable secondary to weight -MCG score of 7.5 -Cardiac catheterization: Stent restenosis. Patient underwent angioplasty and stenting -Patient no longer short of breath

-8 months later patient developed shortness of breath just tying his shoes -Patient insisted the stented closed -Repeat MCG score of 2 -Repeat cardiac catheterization showed stents patent

This case shows how a high score predicted disease. Stenting caused a marked drop in his score. It predicted that the cardiac catheterization would be normal.

#5. HG

-Patient wheelchair-bound, heavyset with a history of right coronary artery occlusion -Patient admitted to the hospital with congestive heart failure -Troponin level was positive -ST segment elevations in the anterior precordium -Cardiac catheterization: Total right coronary artery obstruction but LAD was normal - The patient had repeated episodes of congestive heart failure -Repeat cardiac catheterization without

change -Patient presented to me for evaluation -I suspect the coronary artery spasm -I did 5 MCG tests showing "consistently inconsistent numbers"
 -This was consistent with coronary artery spasm -Patient was placed on Procardia and she's been asymptomatic since

This case shows how MCG can predict coronary artery spasm. Since this case I have had many others in which there is "consistently inconsistent numbers". This is where a score can vary between zero and an elevated number in multiple tests without consistency.

#6. JC

-60-year-old male with prior inferior wall myocardial infarction -MCG score 5.5, May 20, 2008 -MCG score 5.0 March 20, 2009 -CTA 2008-LAD greater than 65% obstruction, right coronary artery obstructed - Patient refused cardiac catheterization -Patient asymptomatic

This case exemplifies how MCG scores are very consistent even a year later. In my experience I found a patient can have a score of 2.0 and a year later be the same and another patient can have a score of 4.5 and be the same a year later. It also reflects a score of 5 being consistent with coronary artery disease.

#7. NV

-67-year-old male with multiple cardiac stents -Always asymptomatic -Stress echocardiogram periodically very abnormal -Each time he goes for an angiogram, it shows a significant lesion needing a stent -MCG score 4.0 on May 2008 -CTA showed patent stents -Patient developed a kidney stone and needed a ureteral stent -During his hospital stay he developed new right bundle branch block and atrial fibrillation - EKG showed new inferior- posterior wall myocardial infarction -After hospitalization MCG score repeated and was 7 -Tracings pre MI and Post MI difference was night and day -Graph of power in Watts versus frequency in Hertz, showed very little power produced from his heart after the myocardial infarction.

This case exemplifies the elevated score being consistent with a recent infarction and ischemia. It also shows how the recent myocardial infarction affected the power spectrum giving credence to the mathematical formulations produced by the MCG technology.

#8. BK

-63-year-old female with prior coronary artery disease -Cardiac catheterization 2007: 50-60% stenosis of the circumflex -LAD had a 50% lesion -Patient had stent to a large right posterior descending branch - Asymptomatic on medical treatment -MCG score 1.5, repeated last year at 3 and now 4.5 -Her stress test was normal until MCG 4.5 -Recent stress echo showed new septal hypokinesis with exertion -Repeat cardiac catheterization showed severe disease in the circumflex and LAD -Patient underwent cardiac stenting to these lesions

This exemplifies how MCG scores can be used in a serial fashion to monitor an individual who was coronary artery disease and predict when a stress test would become positive. Her initial low MCG score was probably secondary to collateral circulation.

#9. AC

-66-year-old female who needed an abdominal aneurysm resection -MCG score of 2.5 and 3 -History of emphysema -Stress echo: Poor exercise capacity of only 3 minutes with shortness of breath -Did shortness of breath represent emphysema or an anginal equivalent?
 -Stress echo showed possibility of inferior and septal hypokinesis but heart rate very low and inadequate exercise -Cardiac catheterization preoperatively negative

This case shows how MCG scores can be used preoperatively for medical clearance. A low score would indicate the patient did not need further workup. A higher score would indicate the need for cardiological consultation and workup prior to surgery. This particular individual needed cardiac catheterization because

of high risk surgery but in less high risk surgeries, a low MCG score would indicate low risk for cardiac disease and the patient could be cleared medically.

Conclusion

In my practice, the MCG test is invaluable.

How do I use it?

-score of 0---Reassurance.

-score of 1 or 2---Exercise, life style modification, ASA and Statin. Retest in 1 year.

-score of 3---Most likely like scores of 1 and 2. Treat the same but add stress test.
If abnormal stress, treat as 4-7.

-score of 4-7---Treat as 1-3, but add stress testing. If positive send for cath. If negative (50% will have negative stress test), consider adding beta blocker or other agents as in the Courage Trial and retest in 3 months. Follow carefully. Cath if symptoms occur.

-scores greater than 7---Verify the accuracy with repeat testing, treat as 4-7 and consider cath or at least cta of coronary arteries.

-MCG provides a role for the detection of coronary artery disease, the continued followup and evaluation of coronary artery disease, as well as in the pre-operative evaluation. Coronary artery spasm can be detected, as well.

Appendix B

The full comments from Dr. Strobeck follow.

Peer Review Report – John E. Strobeck, MD, PhD Introduction

I believe that the stated goals of the draft TA assume an existing US coronary diagnostic paradigm into which the MCG technology does not fit. The core assumption of the TA is that new ECG-based technologies will be better than the traditional ECG at “evaluating” symptomatic patients who are at low or intermediate risk of coronary events (according to the ACC/AHA 2002 Guideline Update for Exercise Testing [8]) or coronary artery disease. Thus, the diagnostic paradigm assumed in the TA document is that newer ECG technologies are “add-on” technologies that will merely improve the treating physician’s ability to select patients for stress-ECG testing or stress-imaging with either echocardiography or scintigraphy. The MCG is not designed to fit this paradigm because it is designed to be a highly accurate predictor of who does not need stress testing or coronary angiography. That is why MCG was compared directly to coronary angiography in several prospective double blind clinical trials in which it predicted with over 87% accuracy whether patients have actual coronary stenosis requiring intervention or not. MCG does more than “evaluate” patients who are at low or intermediate risk of having coronary artery disease, as a first step in the traditional diagnostic algorithm -it can render other diagnostic tests unnecessary and may allow selected patients to proceed directly to angiography. In other words, the MCG clinical trials asked a different question than that being asked in the draft TA, namely, whether MCG could accurately predict which patients, from a group whose physicians believed needed coronary angiography, actually did need coronary angiography because they had relevant coronary stenosis. As a result of this consideration, it appears that the draft TA’s underlying assumptions, and objectives, are not completely in synch with how MCG works and with the MCG clinical trial design and results. I am pleased that the authors evaluated the MCG technology and found the published trials to have been well-designed and conducted. The final TA should include MCG and contain a more detailed discussion of, the technology. To this end, I have three major concerns about the draft TA that will be discussed in my peer review: 1) the author’s description of the MCG technology is inaccurate, 2) the assessment of the population selected for the clinical trials data is inaccurate, and 3) the conclusions with respect to the demonstrated clinical usefulness of MCG and its current status as a diagnostic tool are inaccurate.

Through highlighting and commenting on these issues, it is my hope that the information provided in my peer review will be helpful to the authors, and that they will seriously consider my comments, research analysis, and my real-life community clinical experience using MCG when they prepare the final version of the TA document. I have come to the conclusion, after a full review of the underlying biomathematics and basic science of the MCG technology, the prospective MCG clinical trial design and data analysis, and the first-hand clinical experience I and many other physicians in the US and world-wide have had with the device in our clinical practices, that the MCG is a well-validated diagnostic tool, and, that if used early in a symptomatic patient's evaluation, is able to very accurately predict which patients who are considered "at low or intermediate risk" of coronary artery disease by ACC/AHA 2002 criteria [8], actually do not have relevant coronary stenosis at the time of examination (i.e. stenosis >70% in one or more major epicardial coronary vessels or >50% left main stenosis which would require percutaneous or surgical coronary intervention) and, therefore, do not need further advanced stress testing, stress-imaging, angiography, or hospital admission for the detection of significant coronary disease.

Classification of the MCG, How it Works, and How it Differs from the SAECG

With regard to the description of the technology, there are fundamental differences between the MCG technology and conventional ECG measurements and analysis techniques. First and foremost MCG is simply not a signal averaging electrocardiogram (SAECG). In order to properly evaluate the MCG, it is critical that the authors fully appreciate the mathematical and "systems-analysis" approach relying on a digitized "reference clinico-pathologic database" against which the MCG analyzes the recorded electrocardiographic signals forming the basis of the test.

MCG is a computer-based, systems-analysis tool, using a computational mathematic model based on LaGrange-Euler coordinates to measure the stress-strain relationships between the myocardium and intracardiac blood flow. MCG converts data obtained from two resting left ventricular leads (V5 and Lead II) into multiple mathematical functions useful in the detection of the presence or absence of obstructive coronary disease and local and/or global myocardial ischemia due to relevant coronary stenosis (defined as > 70% stenosis of the large epicardial coronary arteries and > 50% stenosis of the left main coronary artery).

The draft TA incorrectly defines MCG as being a type of Signal Averaging ECG (SAECG). On page 15 of the assessment, the TA contains the following definition of SAECG:

SAECG is a noninvasive technique for computing the average of numerous ECG complexes, which, in turn, increases the signal-to-noise ratio, allowing for the detection of small, microvolt signals. This technique is most often used in the detection of low amplitude signals at the terminal portion of the QRS complex (also known as ventricular late potentials). These late potentials may reflect inflammation, edema, fibrosis, or infarct, but not ischemia

Then under the title “SAECG-Based Device”, on page 27, implying ECG-based Signal Analysis device, the draft TA describes the general operations of MCG as the following:

The 3DMP device (also referred to as 3DMP/MCG/mfEMT) utilizes ECG data from two of the 12 standard leads (leads II and V5), to perform frequency and time domain analyses. Recordings for over 82 seconds are amplified, digitized, encrypted, and sent securely over the internet to Premier Heart Datacenter where signal analysis and six mathematical transformations are performed. The data are matched to a large empirical database to determine a "Final Diagnosis" and "Severity Score" and securely reported these data back over the internet within several minutes to the requesting provider.

It appears to me that the authors did not realize that the MCG is not a Signal Average ECG technology, and that it does not detect low amplitude late potentials from the terminal portions of the QRS complexes to reflect inflammation, edema, fibrosis, or infarct [Page 15]. In fact, MCG technology completely ignores the familiar time-based ECG waveforms such as the traditional P, QRS (including the late potentials), ST, and T waves that are typically read from an analog ECG plot in favor of an entirely new diagnostic paradigm-shift toward direct detection and quantitative measurement of myocardial ischemia due to CAD. The 166 indices extracted by submitting the ECG signals to multiple mathematical transformation functions represents new information that conventional ECG methods have never been able to show or analyze in the past.

For further clarification, the MCG technology harvests multiple cycles of resting ECG analog signals from leads II and V5, then digitizes, encrypts and securely transmits the resting ECG data along with the patient's demographic information to Premier Heart's data center for processing. After receipt of the data by the server, the system performs a Fast-Fourier-Transformation of the signals from each lead, preparing them for further mathematical transformations, including determination of the auto-power spectrum, the transfer function, the phase-angle shift, the impulse response, the coherence function, and the cross-correlation function of each lead. The details of the six functions have been discussed elsewhere. [1, 2, 26]. These six transformation functions, along with the amplitude histogram of leads II and V5 comprise the backbone of the systems-analysis "engine," which evaluates the dynamic interactions between heart muscle chambers and the intracardiac blood flow. Abnormal expressions of these functions can assist physicians in the detection of coronary ischemia from very early to very late stages. The functions are used to extract the non-linear functional relationships between the two leads, which are distilled to a set of indices, and then matched against existing patterns in a large empirical database to determine the presence or absence of local and/or global ischemia, and produce an overall disease severity score, 0-20, completely unlike the conventional ECG technologies cited in the draft Technology Report (See Fig. 1 below for an overview of the MCG process).

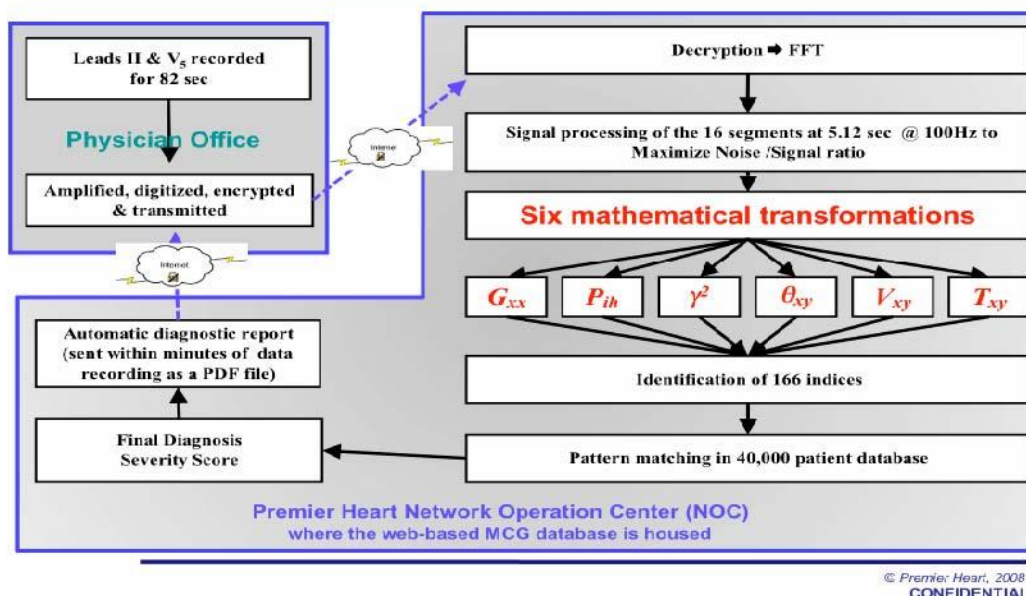


Fig. 1 – MCG Operational Flowchart

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Table I. below is a useful comparison between the conventional ECG Analysis – a reductionistic approach, and MCG Analysis – a systems-analysis approach. Among the significant differences to be noted are:

- A conventional ECG adopts the Einthoven Model – a plot of voltage over time which only considers the unidirectional electrical output of the heart – where MCG's approach is based on a LaGrange–Eüler mathematical model which reflects the multidimensional interaction between the myocardium (the solid) and intracardiac blood flow (the liquid) in a dynamic system (the beating heart).
- Where conventional ECGs (including SAECG) focus on portions of single cardiac cycles on individual leads, MCG instead uses an integrative “view over time”, operating on two leads simultaneously and evaluating multiple cardiac cycles. This allows MCG analysis to extract non-linear, multifunctional relationships which reveal latent information unavailable to conventional ECG techniques.
- Conventional ECG typically requires a subjective “over-read” by an experienced clinician to avoid misdiagnosis, which introduces both subjectivity and delay. In contrast, MCG's extensive, clinically validated, empirical, reference clinicopathological, patient database allows it to provide an entirely objective and quantitative diagnostic assessment quickly – often within minutes.

- MCG's diagnostic accuracy is unaffected by common resting ECG abnormalities such as arrhythmias, pacemaker rhythms, baseline ST-T abnormalities, or bundle branch blocks which can negatively impact conventional ECG technology accuracy. Where conventional ECG has ~50% sensitivity for diagnosis of CAD [Page 14] MCG has an overall sensitivity of 92.9% [Page 46, table 8] when compared directly to the reference standard – coronary angiography [2, 7, 2426].

Traditional ECG vs. MCG



	<i>[I] Conventional ECG Reduction Approach</i>	<i>[II] MCG, a Multifunction Cardiogram Systems Analysis Approach</i>
A	Simplifies the ECG data by mapping it to a single dipole, plotted on a the <u>Einthoven ECG 2-D scale Model</u> (time vs. voltage).	Processes the ECG data to produce a <u>LaGrange-Euler multifunctional model</u> which accurately represents the solid/liquid interaction of a beating heart.
B	Segmental, single-cycle approach, focusing on a single lead at a time, and evaluating sections of the waveform (e.g. ST Segment, T-Wave, late QRS waveform potential such as SAECG...)	Operates on two leads simultaneously (II & V5), and across multiple cardiac cycles to extract non-linear functional relationships between the two LV leads.
C	Requires an on-site experienced clinician to interpret (or over-read) tracings to avoid misdiagnosis.	Compares transmitted ECG data to a large, clinically validated, digital, multi-patient database to produce a real-time diagnosis of cardiac ischemia/coronary artery disease <u>from two decades of research</u> .
D	Accuracy <u>impaired</u> by common resting ECG abnormalities (e.g. arrhythmias, bundle branch blocks).	Accuracy <u>unaffected</u> by common resting ECG abnormalities.
E	Provides a <u>subjective and qualitative</u> assessment.	Provides an <u>objective, quantitative</u> measure of disease severity.

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Table I – Comparison of Conventional ECG and MCG

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In summary, MCG is a non-traditional systems-analysis tool that builds a mathematic model to detect myocardial ischemia due to underlying obstructive coronary artery disease. It is not a Signal Average ECG (SAECG) or any other modified ECG waveform analysis technology, but rather an entirely new methodology based on a multifunction mathematical model of the electro-mechanical function of the heart and an analysis of the integrity of that system over multiple cardiac cycles, not a portion of one cycle.

Clinical Trial Design, Comparison to Angiography, and Pre-test Risk of Trial Population

Table II contains the aggregate data from the four published prospective double-blind clinical trials referenced in the draft assessment [2, 7, 24-26]. The goal of these trials was to validate MCG's accuracy in detecting hemodynamically relevant coronary artery disease, defined as 50% or greater stenosis of the Left Main and 70% or greater stenosis of the epicardial coronary arteries, as determined by comparison to the coronary diagnostic "Gold Standard" – coronary angiography.

Meta Analysis Data Table [Ref. #1]



	Sample Size	True Positive	True Negative	False Positive	False Negative	Sensitivity	Specificity	Positive Predictive Value	Negative Predictive Value	% Correct	% With Critical Stenosis via coronary angiogram
Combined	1076	426	515	94	41	91.2%	84.6%	81.9%	92.6%	87.5%	43.4%
USA	136	72	45	17	2	97.3%	72.6%	80.9%	95.7%	86.0%	54.4%
Asia	189	73	97	15	4	94.8%	86.6%	78.4%	97.1%	89.9%	40.7%
Germany	751	281	373	62	35	88.9%	85.7%	81.9%	91.4%	87.1%	42.1%
Female	390	121	221	38	10	92.4%	85.3%	76.1%	95.7%	87.7%	33.6%
Male	686	305	294	56	31	90.8%	84.0%	84.5%	90.5%	87.3%	49.0%
< 65 years	623	216	332	47	28	88.5%	87.6%	82.1%	92.2%	88.0%	39.2%
≥ 65 years	453	210	183	47	13	94.2%	79.6%	81.7%	93.4%	86.8%	49.2%
Female, < 65 years	184	43	121	12	8	84.3%	91.0%	78.2%	93.8%	89.1%	27.7%
Female, ≥ 65 years	206	78	100	26	2	97.5%	79.4%	75.0%	98.0%	86.4%	38.8%
Male, < 65 years	439	173	211	35	20	89.6%	85.8%	83.2%	91.3%	87.5%	44.0%
Male, ≥ 65 years	247	132	83	21	11	92.3%	79.8%	86.3%	88.3%	87.0%	57.9%
No Revasc.	827	351	367	74	35	91.0%	83.2%	82.6%	91.3%	87.5%	46.7%
PCI	188	47	120	15	6	88.7%	88.9%	75.8%	95.2%	88.8%	28.2%
CABG	61	28	28	5	0	100.0%	84.8%	84.8%	100.0%	91.8%	45.9%
Revasc. Of Any Type	249	75	148	20	6	92.6%	88.1%	78.9%	96.1%	89.6%	32.5%

Summary Of Overall MCG Data For The Detection of Relevant Coronary Stenosis. Revasc. = coronary revascularization in medical history; PCI = Percutaneous coronary intervention in medical history; % Correct = % of patients correctly identified as having relevant coronary stenosis or not by MCG compared to coronary angiogram.

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Table II – MCG Meta-Analysis Trial Results [7]

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Clinical trials directly comparing a resting ECG-based diagnostic method with coronary angiography are rare – in fact I am unaware of any such trials. MCG accuracy was compared directly to coronary angiography for the following reasons:

1. MCG's fundamental purpose is the detection of coronary ischemia due to obstructive coronary disease. Coronary Angiography has been the definitive and most accurate tool used to diagnose relevant, "interventionable" coronary artery disease. The authors of the draft TA also agree with this conclusion regarding coronary angiography as the preferred standard for diagnosing coronary disease [Page 6, Table].

2. Resting ECG analysis, including the 12-lead ECG, typically has significantly less sensitivity in detecting ischemia. Clinical studies have reported a wide range of sensitivity from 20% to 70%, and the accuracy is subject to the reader's knowledge of a patients' history of or lack thereof, previous myocardial infarction [9,10].

3. Stress-ECG testing also has limited sensitivity and specificity, particularly in the detection of single-vessel CAD, as well as detection in women, and patients with underlying arrhythmia, baseline ST-T abnormalities, and conduction disturbances. In addition, exercise ECG has a reported specificity of 80%, under ideal clinical trial conditions, however, in routine clinical use its sensitivity is typically not better than 50-60%, and shows significant gender bias [11,13-15].

4. Stress-imaging techniques such as stress-nuclear or stress-Echo testing have a wide range of reported sensitivities and specificities in detecting severe myocardial ischemia, are frequently limited by attenuation defects, heart rates achieved during testing, spatial resolution of the perfusion or wall motion images, ECG gating problems, conduction disturbances such as bundle branch block, and the extent of disease (often obstructive disease needs to be present in two or more epicardial coronary arteries before there is accurate detection).

Therefore, it was elected not to compare MCG to the above less accurate modalities and instead compare MCG directly to the coronary angiogram [2, 7, 24-26]. When the comparison was made, as evidenced by the data in the meta-analysis Table II, there was considerable accuracy and a high negative predictive value (NPV) shown for MCG in the whole study population as well as important sub-groups such as women vs men, age <65 vs age >65, male age < 65 vs male age >65, female age <65 vs female age >65, patients with no previous revascularization vs patients with previous revascularization of any type, patients with previous PCI vs patients with no previous revascularization, and patients with CABG vs patients with no previous revascularization.

It is also important to note that MCG had already been retrospectively validated during the painstaking development of the large, multi-patient, clinical-pathologic database used by the technology in the above referenced clinical trials that prospectively evaluated each patient's MCG data. The purpose of the blinded, MCG clinical trials referenced in the TA was to prospectively validate the accuracy of MCG technology in detecting relevant coronary stenosis. The authors of the TA themselves expressed a desire to see such a comparison to coronary angiography with regard to the other technologies discussed as that type of trial design provides a valuable degree of insight into the true accuracy and usefulness of any coronary diagnostic technology under study.

In summary, the decision to evaluate MCG by direct comparison to coronary angiography was reached based upon the revolutionary nature of the MCG technology, limitations of the other existing diagnostic modalities available, and the desire to validate MCG against the best available reference standard, coronary angiography.

With regard to the selection and enrollment of patients in the prospective clinical trials, Page 37 of the draft TA includes the following statement: “(MCG) Study quality was good with two exceptions” The first exception was... “it was unclear if subjects were selected at random or consecutively”. With reference to the selection methodology, it is clearly stated in all four trial publications that the study populations represented convenience samples of patients scheduled for coronary angiography. Since patients with acute coronary syndrome or acute coronary ischemia scheduled for emergency cardiac catheterization were not included in the study populations. The final sample did represent a “consecutive” sample of patients scheduled for elective coronary angiography.

The second exception was that “The (trial) selection criteria likely selected for a sample population with greater disease severity than would be seen in the population of interest”. [Page 37] I believe this is an incorrect conclusion. Table III shows the risk age and gender-adjusted criteria to which the draft TA referred.

Table III. Pre-Test Probability of CAD by Age, Gender, and Symptoms

Age	Typical/Definite	Atypical/Probable	Nonanginal (yrs)	Gender	Angina Pectoris	Angina Pectoris	Chest Pain	Asymptomatic
30–39	Men	Intermediate	Intermediate	Low	Very low			
	Women	Intermediate	Very low	Very low	Very low			
40–49	Men	High	Intermediate	Intermediate	Low			
	Women	Intermediate	Low	Very low	Very low			
50–59	Men	High	Intermediate	Intermediate	Low			
	Women	Intermediate	Intermediate	Low	Very low			
60–69	Men	High	Intermediate	Intermediate	Low			
	Women	High	Intermediate	Intermediate	Low			

High: Greater than 90% pre-test probability; **Intermediate:** Between 10% and 90% pretest probability; **Low:** Between 5% and 10% pre-test probability; **Very Low:** Less than 5% pre-test probability. Note no data exists on Pre-Test Probability of CAD in patients below age 30 or above age 69. Reproduced with permission from ACC/AHA 2002 Guideline Update for Exercise Testing (8).

Based on the published meta-analysis of the MCG clinical trials, the patients who participated in the published trials had an overall pre-test probability of coronary disease ranging from 32% to 54% in the different study center populations, and from 28% to 58% in study subpopulations, using the criteria in the 2002 ACC/AHA Guideline Update for Exercise Testing. This range is clearly an intermediate risk range, not a high-risk range as suggested in the draft TA.

We understand that the 2002 ACC/AHA criteria above refer to the determination of risk of individuals, not groups of patients, however the bottom-line from the practicing physician's perspective is whether patients actually have critical coronary stenosis at the time of exam and whether they will be managed medically or by surgical or percutaneous intervention. While it is possible the MCG trials enrolled some patients who might be classified at high risk according to the ACC/AHA guidelines, the results of actual angiography on all enrolled patients showed that, as a group, the pre-test risk of relevant coronary stenosis was intermediate with a low "a priori" risk (defined by a knowledge of the actual population rates).

Bayes' theorem allows calculation of the positive (PPV) and negative predictive values (NPV) for any "a priori" risk (prevalence of the disease in the population in question) based on the sensitivity and specificity determined in clinical studies in populations that may have different disease prevalence [27]. Table IV shows the calculated PPV and NPV for different a priori risks based on the sensitivity and specificity determined from the meta-analysis across all four blinded, prospective

MCG trials [2, 7, 24-267].

Patient

Population

Disease Incidence Sensitivity Specificity PPV NPV

MCG Overall

Study Population

43.4% 91.2% 84.6% 81.9% 92.6%

Very Low Risk 5.0% 91.2% 84.6% 23.7% 99.5%

Low Risk 10.0% 91.2% 84.6% 39.6% 98.9%

20.0% 91.2% 84.6% 59.6% 97.5%

30.0% 91.2% 84.6% 71.7% 95.7%

40.0% 91.2% 84.6% 79.8% 93.5%

50.0% 91.2% 84.6% 85.5% 90.6%

60.0% 91.2% 84.6% 89.9% 86.5%

70.0% 91.2% 84.6% 93.2% 80.5%

Intermediate Risk

80.0% 91.2% 84.6% 95.9% 70.7%

High Risk 90.0% 91.2% 84.6% 98.2% 51.7%

Table IV – Calculated Positive & Negative Predictive Values based on MCG meta-analysis[27]

These calculations show that MCG has a very high ability to rule out hemodynamically relevant stenosis in subjects with very low to intermediate risk (NPV > 90% for risk < 50%; NPV > 97% for risk < 20%). Therefore, MCG is, from a statistical perspective, especially suited to prevent unnecessary coronary angiography in patients with low to intermediate “a priori” risk of CAD. One practical consequence of this is that when MCG is employed early in the patient’s evaluation, a significant number of patients will not need to undergo any form of “add-on” stress-imaging testing, angiography, or even hospital admission if their MCG severity scores are low (i.e. < 4.0). Because MCG testing can be performed at the point of care, the management of these patients can be dramatically improved and the overall cost of care reduced. No ECG-based Signal Analysis technology has been able to make this type of determination with the accuracy of the MCG. In the typical community setting, most patients experiencing symptoms of chest pain will be seen first by their internist or family physician. If MCG testing is performed by them and confirms a very low likelihood of relevant coronary stenosis treatment can continue without the need for cardiology consultation and/or additional “add-on” stress testing or stress imaging. The MCG score could also easily be incorporated as a pre-certification screen for any subsequent “add-on” testing by Medicare or Commercial carriers.

The Draft TA's Conclusions Regarding the MCG Technology

MCG is a technology that has been prospectively shown to accurately predict the presence of relevant coronary stenosis in patients at intermediate risk of CAD in well-designed clinical trials. [2, 7, 24-26] While I appreciate that the draft TA described the MCG trials as well-designed, I disagree with the conclusion that MCG is merely a “promising” diagnostic tool. I believe that the foregoing discussion of MCG technology, and of the design, and statistical evaluation of the MCG clinical trials in this peer review demonstrates that the accuracy and validity of MCG in detecting relevant coronary stenosis is well validated and supported by the trial results. It is my hope that the final TA will incorporate these concepts and conclude that MCG is a validated, clinically useful early diagnostic test for patients at low to intermediate risk for coronary disease.

Experience Using MCG in My Clinical Cardiology Practice for the Past 2.5 Years

I have been in the practice of clinical cardiology in northern New Jersey for the past 25 years. I currently perform coronary angiography and own and use nuclear and ultrasound diagnostic equipment in my office. The Nuclear Cardiology Board personally certifies me and my nuclear laboratory is certified by the Inter-societal Commission on Nuclear Laboratories. I care for a generally elderly population that is composed of Medicare beneficiaries (65%) and non-Medicare beneficiaries (35%) many of whom have known or suspected coronary disease. The introduction of MCG into my office 2 1 years ago has created a profound change in the way I manage my patients with symptoms suspicious of underlying coronary disease. I also have concluded that in the case of the MCG clinical trials that the trial design comes very close to the way I feel it is appropriate to use the MCG in clinical practice. Thus, I believe the trial design and published trial results are very applicable to the real life situations I encounter in the community practice of cardiology, which increases my comfort level using the device. I have found through testing a large number of symptomatic patients, that patients with no evidence of ischemia determined by MCG and an overall MCG severity score of <4 can safely be managed medically with attention to coronary risk factor reduction and adoption of a healthy lifestyle. These patients, in my practice, are not referred for

stress testing or stress-imaging, or angiography unless a significant change (worsening) occurs in MCG results when performed as necessary in follow up (e.g., if symptoms worsen significantly). In my view, this clinical use and application of the MCG technology is readily supported by all four of the MCG clinical trials. In the overall MCG trial population, approximately 40% of the patients who were scheduled for and underwent coronary angiography had overall MCG severity scores less than 4.0 and thus, could safely have been managed medically, and avoid all additional testing including angiography.

The patient with an MCG score 2 4.0 does not have as clear a path to follow. There are currently no prospective clinical trials showing that these patients can be managed in any specific manner or by any specific treatment algorithm. While it is my understanding that further trials and a comprehensive patient registry are being planned and need to be done to clarify how best to manage a patient with an MCG severity score 2 4.0, in my clinical experience, and based on data from the Courage Trial [28], patients with scores 2 4.0 and : 7.5, have been managed safely through adherence to evidence-based optimum medical management of suspected coronary disease with the use of further advanced stress-imaging or coronary angiography only when there is symptomatic failure of optimum medical management. The decision to perform additional stress-imaging tests in this situation, however, must remain with the treating physician, based on the clinical circumstances and his judgment in each case. A patient with an MCG result showing significant local or global ischemia and a severity score > 7.5, should, in my view, be strongly considered for coronary angiography, independent of the result of any other stress-imaging tests or lack of progression of symptoms. This clinical pathway will also require further controlled clinical trial data to fully support its adoption in routine clinical practice.

It is my understanding that a number of avenues of further research are being pursued at this time by Premier Heart, Inc. to help address the clinical management questions that arise when the MCG severity score is ≥ 4.0 , including measurement of the MCG score before and after a pharmacologic stress is applied. Information such as this could further enhance our understanding of ischemic syndromes in general as well as the device's function and limitations.

Conclusion and Summary of Peer Review Findings

MCG is a computer-based, computational electrophysiology systems analysis tool that physicians can use to make accurate and timely diagnosis of relevant CAD at the point of care. It is not comparable to SAECG or other direct ECG-based waveform analysis techniques, and has many distinct differences and advantages over those older technologies.

The MCG clinical trials conducted thus far have clearly included patients with "intermediate pre-test risk" of CAD, not "high pre-test risk" patients as the draft TA concluded. I agree with the authors' desire to have all new non-invasive, ECG-based technologies designed to detect coronary disease, compared to coronary angiography. To my knowledge, MCG is the only technology where such a comparison has been done. Furthermore, in my opinion, it is not appropriate to compare a technology like MCG to an "add-on" ECG-based technology, the intended use of which is entirely different from the intended use of MCG.

I believe that the accuracy of MCG for the diagnosis of relevant coronary disease has been definitively validated through well-designed prospective double-blind clinical trials comparing MCG to coronary angiography, and that it has performed very well over a 21 year time frame as a clinically useful early diagnostic tool for physicians at the point of care treating symptomatic patients with known or suspected coronary disease. It has definitely reduced the number and complexity of "add-on" stress or stress-imaging tests I have ordered since beginning to use the device.

I would appreciate the opportunity to meet with or have a conference call with the authors of the draft TA to discuss the fine points of discussions contained in this peer review, and to explain them in more detail, if necessary.

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References

1. Feng G. ECG and EEG Multiphase Information Analysis (A collection of unpublished notes, thesis, papers and published articles from mid seventies to the late eighties translated into English from Chinese), First Edition. USA: American Medical Publishers; 1992.
2. Weiss MB, Narasimhadevara SM, Feng GQ, Shen JT. Computer-enhanced frequency domain and 12-lead electrocardiography accurately detect abnormalities consistent with obstructive and nonobstructive coronary artery disease. *Heart Dis.* 2002;4:2-12.
3. Batchelor, G.K. (1973), *An introduction to fluid dynamics*, Cambridge University Press, ISBN 0-521-098 17-3
4. Lamb, H. (1994) [1932], *Hydrodynamics* (6th ed.), Cambridge University Press, ISBN 9780521458689
5. Ammar KAMDa, Kors JAPb, Yawn BPMdMc, et al. Defining unrecognized myocardial infarction: A call for standardized electrocardiographic diagnostic criteria. *American Heart Journal* 2004;148(2):277-284.
6. Salerno SM, Alguire PC, Waxman HS, et al. Competency in interpretation of 12-lead electrocardiograms: a summary and appraisal of published evidence. *Ann Intern Med* 2003;138(9):751-60.
7. Strobeck JE, Shen JT, Singh B, et al. Comparison of a two-lead, computerized, resting ECG signal analysis device, the MultiFunction-CardioGram or MCG (a.k.a. 3DMP), to quantitative coronary angiography for the detection of relevant coronary artery stenosis (>70%) -a meta-analysis of all published trials performed and analyzed in the US. *Int J Med Sci* 2009;6(4):143-55.
8. Raymond J. G, Gary J. B, J. Timothy B, et al. ACC/AHA 2002 Guideline Update for Exercise Testing A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on Exercise Testing)
9. Ammar KA, Kors JA, Yawn BP, Rodeheffer RJ. Defining unrecognized myocardial infarction: a call for standardized electrocardiographic diagnostic criteria. *Am Heart J.* 2004; 148:277-284.
10. Mant J, McManus RJ, Oakes RA, et al. Systematic review and modeling of the investigation of acute and chronic chest pain presenting in primary care. *Health Technol Assess.* 2004;8:1-158.
11. Tak T, Gutierrez R. Comparing stress testing methods. Available techniques and their use in CAD evaluation. *Postgrad Med.* 2004; 115:61-70.
12. Gibbons RJ, Balady GJ, Beasley JW, et al. ACC/AHA Guidelines for Exercise Testing.

A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on Exercise Testing). *J Am Coll Cardiol.* 1997; 30:260-311.

13. Anthony D. Diagnosis and screening of coronary artery disease. *Prim Care.* 2005; 32:931-946.
14. Cox JL, Teskey RJ, Lalonde LD, Iles SE. Noninvasive testing in women presenting with chest pain: evidence for diagnostic uncertainty. *Can J Cardiol.* 1995; 11:885-890.
15. Curzen N, Patel D, Clarke D, et al. Women with chest pain: is exercise testing worthwhile? *Heart.* 1996; 76: 156-160.
16. Mowatt G, Vale L, Brazzelli M, Hernandez R, Murray A, Scott N, Fraser C, McKenzie L, Gemmell H, Hillis G, Metcalfe M. Systematic review of the effectiveness and cost-effectiveness and economic evaluation, of myocardial perfusion scintigraphy for the diagnosis and management of angina and myocardial infarction. *Health Technol Assess.* 2004; 8:1-207.
17. Elhendy A, Bax JJ, Poldermans D. Dobutamine stress myocardial perfusion imaging in coronary artery disease. *J Nucl Med.* 2002; 43:1634-1646.
18. Morise AP, Diamond GA, Detrano R, Bobbio M. Incremental value of exercise electrocardiography and thallium-201 testing in men and women for the presence and extent of coronary artery disease. *Am Heart J.* 1995; 130:267-276.
19. Geleijnse ML, Krenning BJ, Soliman OI, et al. Dobutamine stress echocardiography for the detection of coronary artery disease in women. *Am J Cardiol.* 2007;99:714-717.
20. Marwick TH, Shaw L, Case C, Vasey C, Thomas JD. Clinical and economic impact of exercise electrocardiography and exercise echocardiography in clinical practice. *Eur Heart J.* 2003; 24:1153-1163.
21. Smart SC, Bhatia A, Hellman R, et al. Dobutamine-atropine stress echocardiography and dipyridamole sestamibi scintigraphy for the detection of coronary artery disease: limitations and concordance. *J Am Coll Cardiol.* 2000; 36:1265-1273.
22. Cox JL, Teskey RJ, Lalonde LD, Iles SE. Noninvasive testing in women presenting with chest pain: evidence for diagnostic uncertainty. *Can J Cardiol.* 1995; 11:885-890.
23. Curzen N, Patel D, Clarke D, et al. Women with chest pain: is exercise testing worthwhile? *Heart.* 1996; 76: 156-160.
24. Hosokawa J, Shen JT, Imhoff M. Computerized two-lead resting ECG analysis for the detection of relevant coronary artery stenosis in comparison with angiographic findings. *Congestive Heart Failure* 2008 14: 25 1 -260
25. Grube E, Bootsvelde A, Buellfeld, L Yucel S, Computerized two-lead resting ECG analysis for the detection of coronary artery stenosis after coronary revascularization *Int. J. Med. Sci.* 2008, 5(2): 50-61
26. Grube E, Bootsvelde A, Yucel S, et al. Computerized two -lead resting ECG analysis for the detection of coronary artery stenosis. *Int. J. Med Sci.* 2007; 7: 249-263.

27. Altman DG, Bland JM. Diagnostic tests: predictive values. *BMJ* 1994;309:102
28. Boden WE, O'Rourke RA, Teo KK, and the COURAGE Trial Research Group. Optimal medical therapy with or without PCI for stable coronary disease. *N Engl J Med.* 2007 Apr 12; 356(15):1503-16.