Executive Summary of Multifunction Cardiogram (MCG)

Introducing Multifunction Cardiogram (MCG)

Multifunction Cardiogram (MCG) is a completely new approach to the diagnosis of myocardial ischemia caused by coronary heart disease. MCG Technology utilizes systems analysis principles (reference 15) and is, to our knowledge, the first example of a commercially available information technology solution in the discipline of "Clinical Computational Electrophysiology." MCG is a problem solving technology that mathematically "decomposes a system (cardiovascular) into its component pieces for the purpose of the studying how well those component parts work and interact to accomplish their purpose"[1] MCG solves an intractable problem - the lack of accurate detection of myocardial ischemia caused by coronary artery disease. Following decades of research and development, through the diligent work of two generations of dedicated scientists, clinicians, and engineers, MCG technology has successfully demonstrated its capability in the detection of myocardial ischemia caused by obstructive coronary disease (CAD) in multiple independently conducted clinical validation trials (References 3 to 10) with high sensitivity (89-100%), specificity (83-94%), and accuracy (90 to 100%). For easy access, MCG digital signal analysis uses reporting servers available around the world 24/7/365 through the internet to deliver highly accurate, rapid, automatic, and objective cardiovascular functional assessments. MCG's capabilities for the detection of early, intermediate, and late stage myocardial ischemia go far beyond conventional diagnostic stratagem. MCG provides a uniquely positioned high-quality diagnostic tool to clinicians for making critical diagnostic and clinical management decisions in the a timely, affordable, and dependable manner at patient's bedside in real time. Currently, MCG testing is reported by physicians with Current Procedural Terminology (CPT) Code 0206T[2].

Background

ECG stress testing, nuclear scintigraphy, stress echocardiography, and other various types of cardiac stress imaging testing are considered the standard non-invasive techniques for evaluating cardiac ischemia. While these are recognized as sensitive tests for the detection of CAD in two or more large epicardial vessels, it also has been widely acknowledged that they have relatively poor specificity as shown by evidence of a high number of false positive results. There is growing consensus that this lack of specificity results in a significant number of unnecessary coronary angiographies, thereby subjecting many patients to the potential risks involved with invasive procedures and radiation exposure without expected commensurate clinical benefit. For example, in 2010, Patel and colleagues (1) published an analysis of the American College of Cardiology National Cardiovascular Data Registry, which included 397,954 patients without known CAD who were undergoing elective angiography. Coronary artery disease was absent (i.e., less than

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[1] *Systems Analysis and Design for the Global Enterprise by Lonnie D. Bentley p.160 7th edition*

[2] *Current descriptor of 0206T: AMA CPT 2013 Descriptor for MCG Technology 0206T Released January 1, 2012 Implemented July 1, 2012. Computerized database analysis of multiple cycles of digitized cardiac electrical data from two or more ECG leads, including transmission to a remote center, application of multiple nonlinear mathematical transformations, with coronary artery obstruction severity assessment*

20% stenosis in all vessels) in 39.2% of patients. The authors created four separate models for the prediction of true positive results in angiography based upon: 1) Framingham score alone; 2) Framingham score plus other clinical factors (i.e. body mass, and other co-morbidities); 3) Framingham score, clinical factors, and the presence of symptoms; 4) results of non-invasive testing (i.e. stress testing).The analysis produced the following results:

> "Finally, although a positive non-invasive test was associated with the presence of obstructive coronary artery disease, the addition of information obtained from non-invasive tests had a limited effect on the model's predictive ability over and above the effect achieved from the addition of clinical risk factors and symptoms."

This study clearly identifies the limitations of the use of non-invasive testing for the selection patients most likely to benefit from coronary angiography. The authors conclude with the following statement:

> "Our data support ongoing efforts to improve overall strategies for patient selection, including, but not limited to improving the quality of non-invasive testing in order to determine the optimal decision-making algorithm for the evaluation of suspected obstructive coronary artery disease."

Another large scale investigation of ~600,000 patients from 220 US Hospitals (2) and data from the PREMIER database of 2700 acute-case hospitals in the US[3], also confirmed these results. The results are summarized below:

Studies	Population	Source	Result
Patel, et al; NEJM	398,978	ACC database	38% yield
Medscape	~600,000	JAMA; 2014	40% yield

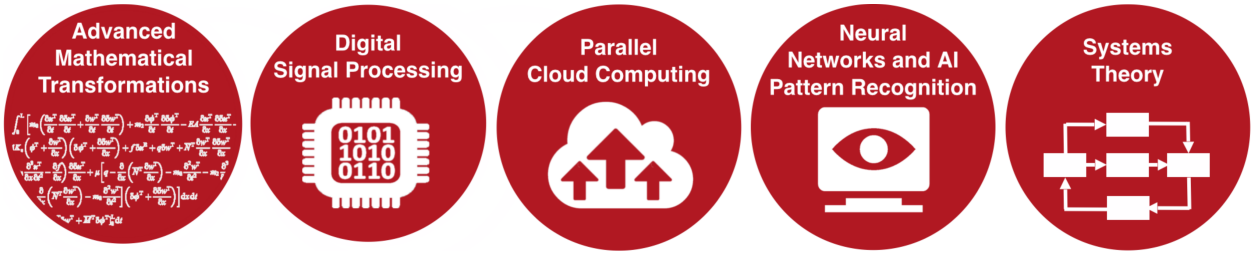
The Traditional ECG is Obsolete

The world, even now, still clings to a technology that has not improved in its 120 year long lifespan. ECGs (electrocardiograms) continue to be used essentially unchanged from their initial design and implementation by Willem Einthoven in 1889. By fundamental design omissions, ECGs do not measure the complex electro-mechanical properties of the heart, which are generated from the interaction between the heart and the body's intracardiac blood supply/flow. ECGs also ignore complex inter-lead communications, and are essentially only useful for detecting various arrhythmias and perhaps ~30% acute myocardial severe ischemia cases.

MCG is the 21st-Century successor to the traditional ECG.

Multifunction Cardiogram (MCG) uses systems theory mathematical models based on the La Grange-Eüler theory, by combining the results of using 6 mathematical transformations derived from the fusion of both coordinates via a Laplace Transformation. MCG applies systems engineering theories, taking into account the heart's interactions with both internal and external factors as part of a greater whole. It uses multiple mathematical functions to analyze the interactions of the human body's complex organ system's bioelectrical signaling-feedback-network. Each of these mathematical transformations of a pair of bioelectric signal vectors illuminates a *different facet* of the workings of the cardiovascular system.

MCG heralds a new era of diagnosis that explores the "intranet" of an individual's cardiovascular system to obtain vast swathes information previously left untouchable and unknowable by traditional methods. MCG Technology leverages a combination of the best technology disciplines currently available to science and enterprise.



MCG Technology platform offers unprecedented speed, accessibility, and comprehensive analysis of cardiac functions

Through parallel cloud computing, MCG delivers its results in less than 15 minutes – *before the physician even has to leave the patient's bedside.* It provides an objective, statistically generated measure of cardiovascular disease burden, allowing the physician to conclusively determine if the patient can be sent home or requires immediate care. MCG provides characterization for at least 26 pathological and physiopathological conditions, compared to the ECG which can only provide reliable identification on 1 physiopathological condition and partial identification on 8 others (e.g. heart attack underway, heart attack in the past, STEMI, etc., please see a comparison chart in Appendix 1).

Multifunction Cardiogram (MCG) Technology is a New Approach to the Diagnosis of Myocardial Ischemia

MCG is a non-invasive test that provides an objective and quantitative detection of myocardial ischemia caused by coronary artery disease (CAD), helping to address the industry's unmet needs especially due to limitations of widely used stress tests and stress imaging modalities. MCG does not require stress, the use of any drug, or exposures to radiation on the patient. Rather, it uses six mathematical transformations to analyze cardiac electrical signals. These

transformations enable detection and analysis of functional changes to an individual's electromyocardial physiologic functions[3] that result from alterations in coronary artery blood flow. Instead of merely retrieving a sum of information about the electrical activity of cardiomyocytes at a single point at a time during a single cardiac cycle, as a traditional ECG does, MCG is specifically engineered to isolate the components of the digitized resting ECG signal data over an 82-second period from ECG Lead V5 and II, a pair of left ventricular leads, thereby obtaining complete information about the dynamic interaction of the myocardium and intracardiac blood flow over multiple cardiac cycles. MCG digitizes the individual's electrical signals via its patented digital bioelectrical signal processing, (DBSP) deconstructs them via the aforementioned mathematical transformations into multiple functional components (called indices or mathematical structural elements), and then reconstructs them by mathematically integrating the indices into a cohesive pattern that allows for rapid computerized pattern recognition. By comparing the individual's MCG DBSP out put pattern to other patterns contained in a large empirical clinical/MCG database (described below), it is possible to model, quantify, and understand the ongoing stress-strain interaction between the myocardium and intracardiac blood flow, which results in the ability to identify chronic or acute ischemic alterations, among other pathologies of the heart, quantitatively and objectively. MCG Technology's clinical application using a combined DBSP, Empirical Clinical/MCG Data-mining and Supervised Machine Learning approach is unprecedented.

MCG engineering process requires that both the step-by-step analysis and the information in the database are thoroughly verified and clinically validated internally. Firstly, the indices and patterns obtained from the mathematical transformations are derived from the empirical clinical data to have identifiable and reproducible clinical meaning. Secondly, all patient data added to the database, which is used for data-mining and machine learning algorithm development, has also been very carefully vetted and documented by clinical experts in accordance with the FDA Good Manufacturing Practice Guidelines and ISO 13485 Standards. The index cluster and pattern for each patient's data are correlated with the findings of coronary angiography and any other accepted gold standard diagnostic tools, such as myocardial perfusion imaging or MPI, Functional Fractional Reserve or FFR, in addition to the final diagnosis. Before a patient's clinical data as well as MCG data are accepted into the development database, at least two double-blinded independent clinical experts must agree on the patient's clinical diagnosis, while not knowing of the patient's MCG results. If there is a disagreement, a third expert is brought in to break the impasse. Any patient with unreliable data (e.g., inability to determine the record source, incomplete data entry, the patient's diagnosis and out come results were unverifiable, or has an an uninterpretable MCG data due to poor quality tracings) is not included in the database. As the database's population grew, additional requisite multi-step, internal verification, and validation are performed dictated by the requisite engineering procedures. After these internal verification/validation procedures are complete and the system's final iteration meet the original design intentions, external system wide peer review trials are then carried out (i.e. the published clinical trials discussed below). The trials were designed to ask and answer specific questions relating to how accurately MCG predicts the existence of significant coronary artery disease in

[3]. These are referred to as transformations of auto or cross power functions.

patients scheduled to undergo coronary angiography (References 3 to 8). In this regard, beyond just CAG, the most recent trials compared MCG to Functional Fractional or FFR + CAG (Amano et al. 2015 Reference 9), Reserve Classical Syntax Score or SS, and Functional Syntax Scores or FSS + CAG (Shinoda et al. 2015, reference 10) are the latest in our evidence gathering efforts.

It is important to note that MCG is not a Signal Averaged ECG (SAECG), nor is it any type of modified ECG waveform analysis technology. Rather, it is an entirely new methodology based on a multifunction mathematical model of the electro-mechanical function of the heart using relational electrical data over multiple cardiac cycles instead of electrical data from a portion of one cardiac cycle (e.g. information contained in the standard "P, QRS, S-T" and T-wave segments from each individual lead). The conceptual difference between an ECG and MCG is as follows: the ECG treats the heart as a single dipole that emits electrical currents into a three dimensional space as vectors. Physicians must be trained in how to read and interpret each of the single cycle ECG waveforms, which are broken into segments that are measured (e.g. the degree of S-T segment elevation or depression) one lead and one cardiac cycle at a time, and then integrate the data from each lead into a single interpretation that, in terms of detecting ischemia, is a rather insensitive snapshot of the heart. MCG, on the other hand, treats the heart as a whole organ by transforming the synchronous (and simultaneously collected) multi-cycle electrical data into a mathematical model that can be easily deconstructed into components and then reassembled to obtain a detailed understanding of the real-time *in vivo,* dynamic interactions between intracardiac blood flow and the myocardium. The result is that the indices discovered from this mathematical analysis extract (or generate) additional, heretofore unknown, information from the two cardiac leads, allowing identification of ischemia in a way that is impossible with traditional ECG technology. Unlike with a conventional ECG, the detection of ischemia using MCG is completely automated, and no physician expert reading or interpretation is required. Therefore, no "disagreement" between interpreters is possible for each test.

MCG has been cleared by the FDA as an aid to diagnosis by means of analysis of ECG waveforms in the frequency domain (power spectral estimate). The attached Exhibit 2 includes the FDA clearance and the instructions for use.

Appendix 2 is a comparison of MCG and ECG.

Performance of an MCG Test: A Four Step Process

MCG is performed in the following four steps.

Step 1:

Multiple cycles of complete resting ECG analog signals from leads II and V5 are recorded by a portable device from a patient at the point of care. The recorded signals are then digitized, encrypted and securely transmitted along with the patient's demographic information to a central data center for processing.

Step 2:

The computers at the central data center perform a Fast-Fourier-Transformation of the signals from each lead, preparing them for a series of additional mathematical transformations. Research over the last three decades has demonstrated that these mathematical functions are able to extract physiological information embedded in between the two left ventricular leads, II and V5.

Step 3:

MCG mathematically transforms the complex non-linear information obtained in Step 2. The mathematical transformations employed include multiple non-linear mathematical functions such as auto and cross power spectra, cross-correlation, coherence, impulse-response and phase shift. These functions produce 166 indices. The index patterns from an individual patient are compared to similar patterns obtained from people with or without heart disease whose MCG data has been entered into a large empirical database. This database consists of over 40,000 individuals, of whom 27,000 had various degrees of CAD, and whose CAD status and severity are included in the database and have been confirmed by coronary angiography. Importantly, the database also contains MCG results from normal people as well as many patients who have one or more non-ischemic cardiac diseases. Therefore, the database is used to distinguish MCG patterns in patients with cardiac ischemia from MCG patterns in patients with non-ischemic cardiac disease and those with both cardiac ischemia and non-ischemic cardiac disease(s). Approximately 13,000 of the patients in the database have had normal coronary angiograms or have been determined to have no evidence of CAD after independent evaluations by two cardiologists. The database has been carefully accumulated over many years, and MCG patterns of each entrant have been validated and correlated with the presence (or absence) and severity of CAD, from as little as 30% single vessel disease to 100% occluded coronaries with or without collateral formations. The database has been designed to be robust and to minimize bias by including, among other things, 49% of its data from women and an age range of 14-100 in the CAD and non-CAD groups, as well as people with many forms of heart disease (e.g., arrhythmias, hypertrophy, cardiomyopathy), in addition to CAD. The database also contains other clinical and diagnostic data from all 40,000+ patients, including information about other non-cardiac disease entities.

Step 4:

Based on the comparison to the reference database, an overall MCG disease severity score (ranging from 0 to 22) is reported.

(See Appendix 3 for an overview of the MCG test process).

Clinical Application

MCG data has been used to predict the findings of coronary angiography in several carefully designed and well-conducted prospective double-blind validation clinical trials (Weiss 2002, Grube

2007, Grube 2008, and Hosokawa 2008, which are included as references 3, 4, 5 and 6, respectively). These trials were conducted in seven countries and three continents (North America, Asia and Europe). In these studies, MCG tests were performed on patients who were scheduled for elective coronary angiography by cardiologists who, on the basis of clinical impression and standard non-invasive testing, believed that the patients were at an intermediate to high risk of having relevant coronary artery stenosis (CAS). Relevant CAS was defined as a 70% or greater stenosis of one or more major epicardial arteries or a 50% or greater occlusion of the left main coronary artery. The patients in these trials represent "real-world" cases, much like the patients studied by Patel. In this regard, it is not surprising that the percentage of patients (~40%) who were found to have relevant CAS in each of these trials was similar to the percentage who had relevant CAS in the Patel study. This means that even though the treating cardiologists believed that some patients in these four trials were at high risk for significant CAD, the patients studied in these trials were, in reality, at intermediate risk of having significant heart disease rather than at high risk. Therefore, these trial results are directly applicable to most patients seen with suspected CAD. These four trials of MCG were designed to compare the accuracy of MCG versus the accuracy of the standard of care (i.e. clinical impression coupled with standard noninvasive testing) in predicting the existence of relevant CAS. This direct comparison to predict the findings of coronary angiography – the gold standard test - has never, to our knowledge, been published in the medical literature from 1949 to the present. Among all the peer review published trials (References 3, 4, 5, 6, 7, 8, 9, and 10), in the first four clinical trial (References 3, 4, 5, 6, and 7), Dr. Joseph Shen, Premier Heart's Founder and MCG Technology Developer, contributed to the technology description sections of the manuscripts. All of these trials were also independently monitored by a former NIH fellow Dr. Alan Berson (Appendix 5) to ensure the double-blinded trial design integrity and data quality of the trials. The data analysis was performed by an independent bio-statistician, Dr. Michael Imhoff, MD, PhD of Germany, a man with unimpeachable reputation, personal, and professional integrity, and quality standards.

The studies were all similarly designed as follows:

- All patients (n=1076) underwent MCG prior to coronary angiography for any indication.
  - Angiographers and staff at each study site were blinded to all MCG results and findings.
- Coronary angiography was recorded digitally and underwent central review by two independent cardiologists who were blinded to the MCG test results.
- An MCG score of 4.0 or higher was considered indicative of a hemodynamically relevant coronary artery stenosis of >70% in at least one large-sized vessel.
- All of the trials, whether single or multi-center from three continents in seven countries, produced statistically reproducible results.

Each of the trials had similar findings. Strobeck et al. (2009, reference 7) combined the results of these studies into a meta-analysis that reported the following:

- MCG correctly classified 941 of the 1076 patients with or without relevant stenosis (See Table 1.)

- § Sensitivity/specificity: 91.2%/84.6% (in agreement with above mentioned peer review published trials).
- § Positive/negative predictive value: 81.9%/92.6% (in agreement with above mentioned peer review published trials).
- § The results were similar across all studies and were not affected by sex, ethnicity, geographic location or Framingham risk score.

Table 1.

A Meta-analysis of all peer review published third-party validation trials I							
	n	*a-priori*	*Correct*	*Sensitivi*	*Specifici*	*PPV*	*NPV*
Total	*1076*	*0.434*	*0.875*	*0.912*	*0.846*	*0.819*	*0.926*
Female	*390*	*0.336*	*0.877*	*0.924*	*0.863*	*0.761*	*0.957*
Male	*686*	*0.490*	*0.873*	*0.908*	*0.840*	*0.845*	*0.905*
< 66	*623*	*0.392*	*0.880*	*0.885*	*0.876*	*0.821*	*0.922*
> 65	*453*	*0.492*	*0.888*	*0.942*	*0.796*	*0.817*	*0.934*
No Revasc	*827*	*0.467*	*0.868*	*0.909*	*0.832*	*0.826*	*0.913*
PCI	*188*	*0.282*	*0.888*	*0.909*	*0.832*	*0.758*	*0.952*
CABG	*61*	*0.469*	*0.918*	*1.000*	*0.881*	*0.789*	*0.961*

This performance compares favorably with other non-invasive diagnostic tests. A review of stress scintigraphy studies, for example, reported sensitivities ranging from 44%-89% and specificities of 89%-94% for 2+ vessel disease (Elhendy 2002, see reference 11). Numerous studies of exercise echocardiography as a diagnostic tool for CAD have been conducted, and reported sensitivities ranging from 31% to over 90%, while specificities range from 46% to nearly 100% (Geleijnse 2007, Marwick 2009, and Smart 2000. See references 12, 13, and 14, respectively). These studies also show that these modalities have poor sensitivity and are not applicable for the detection of single vessel CAD.

The inability of standard noninvasive diagnostic tests to accurately diagnose CAD in women has been a longstanding problem in cardiology. Importantly, in each of these trials, the sensitivity, specificity and positive and negative predictive values of MCG in predicting the existence of relevant CAS in women was just as good as it was in men. This may be because the database

against which individual patient data is compared takes into account the physiological differences between males and females as well as physiological changes due to aging. This is accomplished by populating the database with approximately half of the data coming from women (normal women and women with heart disease), and by grouping the data by age group and sex (e.g., men aged 51-60, 61-70 and women aged 51-60, 61-70, etc). In other words, MCG database design is both age and sex "normalized." In summary, these trials provide evidence that MCG is a clinically useful tool for assisting physicians in the diagnosis of CAD in women.

Strobeck et al. (2011, reference 8) have also completed a Paired Comparison of MCG with stress single photon emission computed tomography (SPECT) myocardial perfusion imaging (MPI) in 165 consecutive patients who were at intermediate risk of having CAD based on clinical findings and who agreed to undergo both MCG and stress SPECT, followed by elective angiography if SPECT was abnormal or valvular heart disease was present. They represent the diagnostic experience of a typical "real world" cardiology practice. The definition of relevant CAS was the same as that used in the other studies. Similar to the above meta-analysis, an MCG disease severity score of <4 (cutoff point) was used to indicate the absence of relevant CAD. A total of 116 patients with abnormal SPECT MPI tests, persistent chest pain or significant VHD were entered into the final analysis. The following results were reported in Table 2:

Table 2.

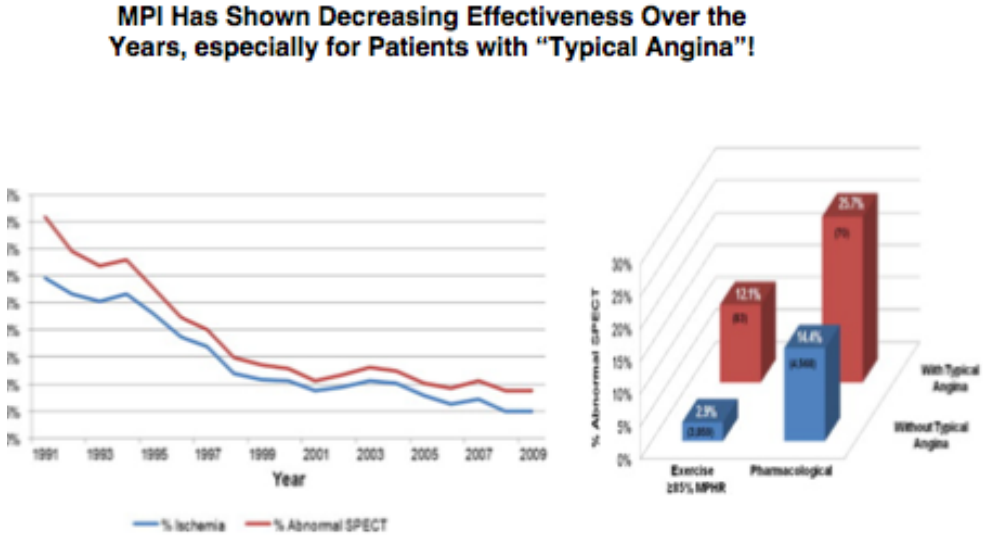
Parameter (%)	MCG	SPECT	P-Values
True positive	**48**	**45**	**< 0.02**
True negative	**55**	**9**	**< 0.01**
False positive	**8**	**54**	**< 0.02**
False negative	**5**	**8**	**< 0.01**
			Confidence Intervals
Sensitivity	**91%**	**85%**	**0.79 – 0.97**
Specificity	**87%**	**14%**	**0.76 – 0.94**
Neg. Predictive Value	**86%**	**45%**	**0.81 – 0.97**
Accuracy (%)	**92%**	**53%**	**P < .001**

This is the first study that directly compares MCG to a standard noninvasive test for CAD. The sensitivity, specificity, negative predictive value, and overall accuracy of MCG in detecting the presence of relevant CAD in patients prior to coronary angiography is similar and reproducible to that found in other studies (References 3, 4, 5, and 6) again, independently demonstrating that MCG is a valuable aid to physicians in the diagnosis of relevant CAD (>70%). Furthermore, in this study, MCG was found to be significantly better than SPECT MPI with respect to overall

sensitivity, specificity, and negative predictive value in predicting the existence of relevant CAS. Additional analysis of the data revealed that if the MCG test result was used as the primary determinant for referral to coronary angiography, only 5/116 patients with a negative MCG score and obstructive coronary disease on angiography would not have been referred for angiography, while 55/116 patients with negative MCG scores and non-obstructive coronary disease on angiography would have been spared coronary angiography.

From our own peer reviewed literature meta-data analysis, MPI has showed decreasing effectiveness over the years (Figure 1). These findings confirm what we have found in our MCG vs. MPI/CAG trial (Strobeck 2011 Reference 8).

Figure 1.



Following the MCG peer review published clinical trials (See references 3 to 8), AMA CPT 2013 Descriptor for MCG Technology 0206T Was Released January 1, 2012 Implemented July 1, 2012. It states: "*Computerized database analysis of multiple cycles of digitized cardiac electrical data from two or more ECG leads, including transmission to a remote center, application of multiple nonlinear mathematical transformations, with coronary artery obstruction severity assessment*".

Since 2013, efforts to improve the specificity while maintaining the sensitivity have led to a new MCG session test analysis method using seven categories of severity levels (Appendix 4) (see tables 3 and 4 below). This has been validated in clinical trials comparing MCG to Functional Flow Reserve (FFR) plus Coronary Angiography, or CAG, and MCG vs. Classic Syntax Scores (SS) and Functional Syntax Scores (FSS) plus CAG as the new gold standards for the detection of functionally significant coronary artery disease.

Table 3. MCG Accuracy Validation Using FFR Cutoff Point of 0.80

Sensitivity			Specificity			PPV			NPV		
Sensitivity	LCI	UCI	Specificity	LCI	UCI	PPV	LCI	UCI	NPV	LCI	UCI
0.875	0.572	0.982	0.945	0.866	0.985	0.750	0.476	0.927	0.972	0.902	0.997

Table 4. MCG Accuracy Validation Using FFR Cutoff Point of 0.75

Sensitivity			Specificity			PPV			NPV		
Sensitivity	LCI	UCI	Specificity	LCI	UCI	PPV	LCI	UCI	NPV	LCI	UCI
0.938	0.639	0.987	0.946	0.867	0.985	0.750	0.476	0.926	0.986	0.923	0.997

LR+	LR-	Odd Ratio				Accuracy			a piori		
		OR (calc)	OR	LCI	UCI	Correct	LCI	UCI	a piori	LCI	UCI
17.08	0.08	103.500	1.224	0.360	4.167	0.943	0.856	0.974	0.149	0.091	0.255

Amano et al. (2014, reference 9), in 2013, completed a Paired Comparison of MCG with Functional Flow Reserve (FFR) in 100 consecutive patients who were at intermediate risk of having CAD based on clinical findings and who agreed to undergo both MCG, followed by elective angiography including FFR measurements. The article, published in BMJ's Open Heart Journal, concluded the following:

> "The predictive values of relevant ischemia were measured by MCG, standard ECG and Framingham Risk Score (FRS) and compared. Five levels of ischemia based on CAG findings adjusted by fractional flow reserve (FFR) values and three levels of MCG score of high, borderline or low were used. MCG (OR=2.67 (1.60 to 4.44), $p<0.001$) was the only test significantly associated with ischemia level. The FFR values for individual MCG scores with low, borderline and high were 0.77 (0.70 to 0.86), 0.78

(0.71 to 0.82) and 0.69 (0.65 to 0.77), respectively, p=0.042. A high MCG score had a specificity of 90.4% (87.0% to 93.9%) in model 1 adjusted by FFR≤0.8 threshold and of 87.0% (83.2% to 90.8%) in model 2 adjusted by FFR≤0.75 threshold, and a negative predictive value of 82.5% (78.3% to 86.7%) in model 1 and of 83.8% (79.6% to 87.9%) in model 2 for the prediction of severe ischemia. Conclusions: MCG showed high specificity with a high negative predictive value, suggesting that MCG could be used not only to identify functionally significant ischemia but to reduce unnecessary CAGs.

Shinoda et al. (2015, reference 10) have also completed a Paired Comparison of MCG with SS (Classic Syntax Scores) and FSS (Functional Syntax Scores), both are gold standards used to predict one year major adverse cardia event (MACE) rates. The authors concluded the following:

> " Results: The MCG was the only test significantly associated with the SS (odds ratio, 2.92 [1.60 – 5.31], P<0.001) and FSS (odds ratio, 3.66 [1.95 – 6.87], P < 0.001). A high MCG score had a specificity of 92.6% (89.0– 96.2%) and 92.3% (89.0–95.6%), and a predictive accuracy of 72.4% (67.6–77.2%) and 82.8% (78.7–86.8%) for the prediction of SS and FSS, respectively. Conclusions: The MCG showed high specificity and predictive accuracy especially for the FSS, suggesting that it is useful not only in identifying functionally significant ischemia but also in reducing unnecessary CAGs." …"Compared with the ischemia level in the previous reports [12–15], the SS and FSS in the present study have better prognostic values [1–3,11]. Therefore, the relationship between the MCG, and the SS and FSS observed in this study might contribute not only to the reduction of unnecessary CAGs but also in providing the potential risk stratification, especially in patients who are not able to exercise and have low kidney function.

Most recently, Shinoda et al. submitted an abstract (PCI/TCT 2015) to report the one-year outcome measurements in the detection of the recurrent cardiac ischemic events after successful coronary intervention using the Multifunction Cardiogram (MCG) personal monitoring device. They stated the following:

> "During the follow up period (median: 305 days), eight recurrent cardiac ischemic events occurred, 6 (out of 675 coronary segments) for events related to non-culprit lesions and 2 for events related to restenosis. Serial changes in MCG score at baseline and follow up (delta MCG) was significantly increased in patients with events compared to those without events (2.4 [1.4-2.9] vs. 0 [-0.3-0.3], p=0.016). With the Cox proportional hazard model after adjusting for confounding factors, delta MCG (OR 1.89, 95% CI 1.08-3.31, p=0.027) proved to be an independent and significant predictor for the recurrent cardiac ischemic events. The area under the receiver operating curve (ROC) analysis for delta MCG in the prediction of adverse events was 0.94(0.89-1.00), and the optimal cutoff value identified through ROC analysis was 1.0 (or 100%), with a sensitivity of 94.30% and a specificity of 97.30%."

- Caveat - If the investigator had adopted the seven categories while also including the impact of collateral circulation on a patient's myocardial functionality and the presence of intermediate

ischemic levels, MCG's would have reached an accuracy rating between 94% (Tables 3 and 4 above) and 100% if a new model (Table 5 below) was adopted. This model is a direct contrast to the models used in the Patel study (Reference 1) for the prediction of positive results on angiography. Our model succeeds, whereas the four models used in the Patel study failed. The investigators are considering the possibility of reanalyzing the data using the seven categories we have developed.

Table 5. New Risk assessment model combines MCG results with seven risk factors and four laboratory values produced 100% accuracy with a ROC value of 1.0.

Seven Risk Factors Included	Four Laboratory Values Included
BMI > 25	Glucose Level
History of PCI	HbA1c
History of CHF	LDL
Arterial Hypertension	hBNP
Smoking Status	Four Laboratory Values Not Included
Diabetes	Total Cholesterol
Family History	HDL
Five Risk Factors not Included	CK
Age > 75	CKMB
Gender	Other excluded Variables:
History of stroke	Ischemia Detected in resting ECG
Atrial Fibrillation	Clinical Symptoms (Yes/No)

We believe that this evidence demonstrates that MCG should precede, or in some cases replace stress testing, with or without scintigraphy, in diagnosing significant CAD. The core evidence supporting this assertion comes from the published trials described above. In the patients scheduled to undergo coronary angiography in these trials, most if not all having had preliminary stress testing, MCG has reproducibly been shown to have extremely high sensitivity, specificity and negative predictive value in predicting whether such patients will have significant CAD on coronary angiography. (See published peer review comments in Exhibits 14, 15 and 16) Notably, in the paired comparison trial of MCG with stress SPECT myocardial perfusion imaging (Strobeck et al. 2011), MCG was two times more sensitive and specific, and also had better negative predictive values than stress SPECT in determining which patients with an intermediate pre-angiography risk of significant CAD actually had significant CAD on coronary angiography. MCG has also been compared to Functional Flow Reserve or FFR (Amano at al. 2013), Classical Syntax Score or SS, and Functional Syntax Scores or FSS (Shinoda et al. 2014). Finally, MCG

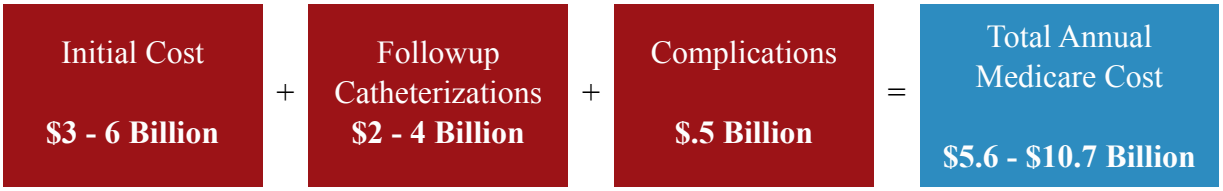
has demonstrated a perfect capability of detecting one-year outcome by reporting recurrent cardiac ischemic events post PCI/Stenting intervention, with 100% accuracy. (Shinoda et al. 2015).

Another multicenter prospective study is on the way in the near future, build to assess how to best apply MCG Technology to patients admitted to the emergency department for chest pain. The aim of the study is to determine whether an MCG test alone can accurately predict which patients presenting to the ED with chest pain symptoms and no evidence of acute coronary syndrome or myocardial infarction can be safely discharged without increasing the risk of major adverse cardiovascular events (MACE) compared to the current standard of care.

In the advent of the MCG Personal Monitor, early detection and prevention of sudden cardiac death (SCD) in patients with sudden increasing MCG Disease Severity Scores over a short period of time (within 24 to 72 hours) shall be made possible by establishing a network using MCG Personal Monitors to report the signs of patients with risks of SCD to save their lives with the eventual goal of either dramatically reducing or outright eliminating SCD.

MCG has immense implications for Medicare Trust Funds.

The catheterization lab is the "heart" of each hospital's reimbursement activity and profitability. Currently, an average cardiac catheterization is reimbursed at approximately $9,540, compared to a stress ECG ($77), a stress echo ($243), a nuclear stress test ($491) or even a stress MRI ($485). However, recent studies reveal that as many as 63% of all catheterization recipients reveal *no meaningful ischemia* – in other words, more than 3 out of 5 of all catheterizations are unnecessary (more than 327,000 per year in the U.S.). Beyond the immense cost this entails, 5% of all catheterizations result in complications, even loss of life totaling more than $500 million in additional annual Medicare costs. In total, cardiac catheterizations cost Medicare between $5.6 to $10.7 billion *each year.*



This is also the amount that MCG can save Medicare each year by properly stratifying chest pain hospital admissions, sending the 63% of patients home who do not need a catheterization. Alternately, MCG will increase the number of *necessary and justified* catheterizations by helping to preemptively screen and identify the thousands of individuals who die each year of undiagnosed ischemia. MCG Technology adoption will fundamentally change how catheterization labs are used.

MCG also has tremendous financial implications for hospitals.

Hospitals are under crushing pressure to reduce costs and increase revenue. Emergency Room acute chest pain admissions are the single highest source of unrecovered costs, improper charges, and lawsuit risk today because there are no fast, accurate tests that screen for myocardial ischemia or assess the proper risk-stratified response! Hospitals must implement costly "hold for observation" tactics on most patients who present with chest pain complaints. Most hospitals don't have separate observation wards, and can be reimbursed for only a fraction of the costs incurred by admitted patients in the same facilities. For many patients under the Affordable Care Act (ACA), hospitals have a hard time collecting for observation visits because they don't meet deductibles for major medical. This all adds up to significant costs to hospitals; 28% of all hospital litigation settlements are from patients who had episodes after being sent home, and Medicare/CMS is pursuing over *$37 billion in RAC audits each year* to recover hospital "improper payments" in the ER.

MCG offers hospital emergency rooms a way to quickly stratify acute chest pain admissions based on risk, quantified cardiovascular disease burden and immediacy of need, allowing hospitals to send home patients who are not in need of urgent cardiac care and to send those that need it to the catheterization lab. Based on CDC statistics and discussions with hospitals, MCG can actually *save hospitals $1,000 for each acute chest pain visit* to their emergency rooms. For a hospital with 20,000 ER chest pain visits per year, that's a savings of more than $20 million per year. Since chest pain complaints are the top category for emergency room admissions, hospitals will also be able to dramatically reduce ER congestion while improving efficiency and patient satisfaction.

MCG will save lives through mobility and complete objectivity.

MCG can be performed in patients who have contraindications to other forms of noninvasive testing. More importantly, MCG can detect full range of CAD ischemia from the very early stages (30% single vessel disease) to the late natural recovery stage due to established collateral formation. This capability is particularly relevant to patients with small vessel disease, especially women and diabetics with non-obstructive coronary artery disease (NO-CAD). Recent studies have shown the increasing burden of NO-CAD and that they have a higher risk of future events (reference 16).

MCG operates through a portable device, with all the "heavy calculations" being performed in the cloud. An MCG test can be implemented by a trained technician, and does not require a specialist or cardiologist, or special hospital facilities. This means that a comprehensive evaluation of a patient's cardiovascular system can be performed inexpensively, quickly, almost anywhere – eventually including ambulances, nursing homes, and physician's offices. However, the most important features of MCG are its *objectivity* and its *consistency.* MCG produces the *same results*

automatically and reproducibly with repeated tests, regardless of *who performs* the tests – creating a reliable and consistent standard for triaging, diagnosis and monitoring.

Because MCG Testing can be performed for a fraction of the cost of an angiogram or stress test, this can move *the highest level of cardiac diagnostics to the first point of care.* This will effectively enable it as a triaging tool, helping to identify thousands of individuals who would have otherwise suffered from death or heart attack, or helping thousands more receive the appropriate level care they would not have received through misdiagnosis from current tools. MCG will eventually find further use as a monitoring tool, tracking and alerting on minute changes in patients' health.

Conclusion

From 2002 to 2015, MCG has been directly compared to the gold standard diagnostic tools used in clinical cardiology, namely, MCG vs CAG, MCG vs. MPI, MCG vs FFR/CAG, and MCG vs. SS/FSS/CAG under the investigation of highly skeptical independent investigators, interventional cardiologists from the seven countries, without quid pro quo, to demonstrate its capabilities reproducibly and consistently. MCG has improved accuracy since 2013 software upgrading by adopting the seven categories of disease severity (Appendix 4). In patients referred for elective coronary angiography, MCG can assist in identifying those patients with relevant CAS objectively and automatically. As such, MCG has the ability to assist in improving patient selection for diagnostic angiography and reduce the number of angiographies in patients without relevant CAS before or after coronary intervention. MCG can be performed at the point of care and produce results within minutes, thereby enabling physicians to make management decisions quickly. Moreover, MCG can be performed in patients who have contraindications to other forms of non-invasive stress imaging testing. More importantly, MCG can detect full range of CAD ischemia from the very early stages (30% single vessel disease) to the late natural recovery stage due to established collateral formation. This feature allows early detection and prevention to potentially reduce sudden cardiac deaths and save lives, especially for women with CAD, in an effective and timely manner in any clinical setting. This capability is particularly relevant to patients with small vessel disease, especially women and diabetics with non-obstructive coronary artery disease (NO-CAD). Recent studies have shown the increasing burden of NO-CAD and that they have a higher risk of future events (See reference 16). These attributes, among others, make MCG an important diagnostic tool for detecting myocardial ischemia and relevant CAS that, in certain clinical situations, may have advantages over other currently used non-invasive tests, and therefore, it should be strongly considered for wider use.

Premier Heart's MCG Technology is designed based on the principals of systems engineering in physiology. It applies mathematical transformations of the electrical signals of the heart, combined with empirical digital database mining and machine learning to make automatic diagnosis objectively, rapidly, and accurately 24/7/365 without the need for an expert to read the digital output and produce reports. It represents the future of *Digital Medicine,* where an "Internet of Things" replaces subjective decision making by the human medical experts. Tomorrow has arrived with MCG leading the way.

Things to remember about MCG

MCG Technology leverages a combination of the best technology disciplines currently available to healthcare enterprise or individuals and

- Offers ease of use and diagnostic **accuracy**
- **Is equally as accurate for women as it is for men,**
- **Is** meeting **the urgent unmet clinical needs**
- Offers early detection and enables disease prevention to save lives
- Is accessible anywhere with Internet or Cellular network available 24/7/365
- Produces completely **objective and consistent** reproducible robust results automatically
- Delivers Results **before** the physician leaves the patient's bedside
- Reduces unnecessary tests and resulting complications
- Reduces disallowed hospital charges via *RAC audits*
- Increases hospital efficiency
- Will save Medicare $5.6-$10.7 Billion annually

Appendix 1

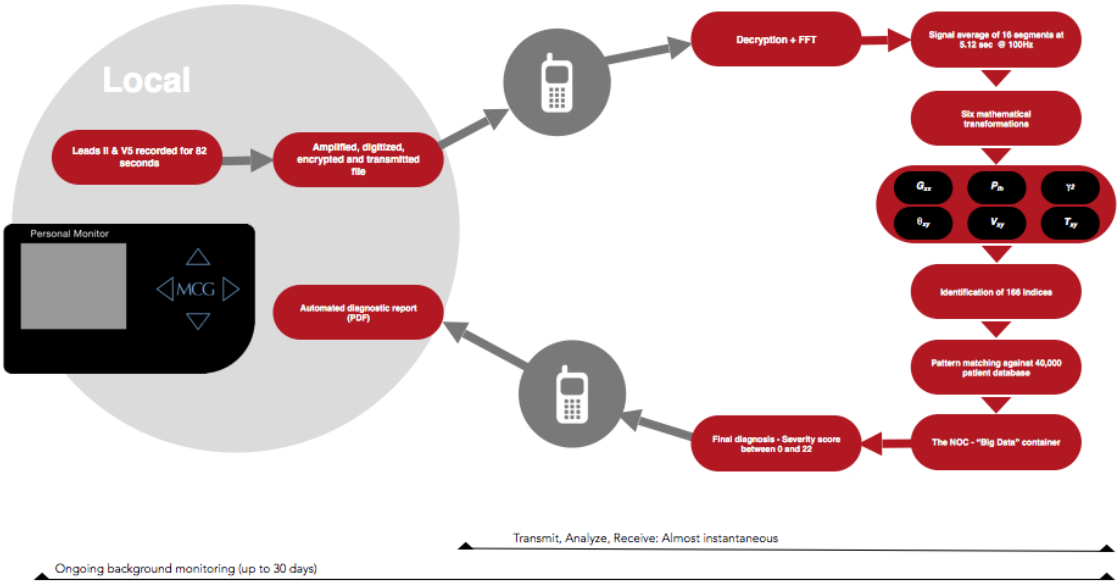
	ECG	MCG
Heart attack right now	✔ (with poor accuracy)	✔
Heart attack in past	✔ (with poor accuracy)	✔
STEMI	✔	✔
NSTEMI		✔
Early warning of heart attacks		✔
Quantified severity of cardiovascular disease burden		✔
Reversible CAD Stages		✔
Local and Global Ischemia		✔
Ventricular Hypertrophy	✔ (with poor accuracy)	✔
Atrial Fibrillation	✔ (with reasonable accuracy)	✔
Ventricular arrhythmia	✔	✔
Cardiomyopathy		✔
Pulmonary Heart Disease		✔
Myocarditis or Myocardial Inflammation		✔
Rheumatic Heart Disease or remnants thereof		✔
Congenital Heart Disease or remnants thereof		✔
Myocardial Damage		✔
Bradycardia	✔	✔
Tachycardia	✔	✔
Myocardial remodeling		✔
Decreased myocardial compliance		✔
Increased myocardial compliance		✔
Decreased cardiac output by decreased ejection fraction		✔
Acute Power Failure		✔
Global asynchrony		✔
Regional or localized asynchrony		✔

Appendix 2

MCG compares to the conventional ECG

Reductionist - ECG			**MCG - Systems Theory**
Theoretical single dipole plotted on Einthoven Model (T / V)			**Multiple functions based on LaGrange-Euler Model and Systems Theory**
System as parts - vectors have no connection with each other			**Integrates organ's various functions into a whole system digitally**
Single cycle, single lead; segments of separate waveforms			**Dual leads across multiple cycles to extract multiple non-linear functions between leads**
Does not detect ischemia well, or STEMI vs NSTEMI			**Detects myocardial ischemia severity caused by anatomic coronary obstruction**
Requires on-site specialized clinician; rarely available 24-7			**Automated, empirical clinical database driven reporting available 24-7 without human expert factor**
Accuracy impaired by BBBs, arrhythmias, etc.			**Accuracy unaffected by ECG wave morphologies**
Subjective expert interpretation / opinion			**100% objective, machine learning through data-mining of large empirical database**
Dependent on risk factors, presentation, previous events			**Independent of risk factors, clinical presentation, patient history**
No evidence of accuracy compared to CAG since 1949			**High documented accuracy compared to CAG, FFR and Nuclear Stress**

Appendix 3


Local
Leads II & V5 recorded for 82 seconds
Amplified, digitized, encrypted and transmitted file
Personal Monitor
MCG
Automated diagnostic report (PDF)
Decryption + FFT
Signal average of 16 segments at 5.12 sec @ 100Hz
Six mathematical transformations
Identification of 166 indices
Pattern matching against 40,000 patient database
The NOC - "Big Data" container
Final diagnosis - Severity score between 0 and 22
Transmit, Analyze, Receive: Almost instantaneous
Ongoing background monitoring (up to 30 days)

Appendix 4

MCG Criteria for Myocardial Ischemia Severity

7	Gravely High Myocardial Ischemic Burden	Minimum MCG Severity Scores ≥ 15 with the presence of local or global myocardial ischemia
6	Extremely High Myocardial Ischemic Burden	Minimum MCG Severity Scores ≥ 7.5 but ≤ 15 with the presence of local or global myocardial ischemia
5	High Myocardial Ischemic Burden	Minimum MCG Severity Scores ≥3.5 with the presence of local or global myocardial ischemia
4	Intermediate Myocardial Ischemic Burden	All MCG Severity Scores fluctuating above or below 3.5 i.e. any score lower or higher than 3.5 appearing in the same session; and there are simultaneous fluctuating myocardial ischemia patterns represented by either local, global myocardial ischemia or occasional myocardial ischemia altogether absent in the same session
3	Collateral Circulation Group Various degrees of reduced Myocardial Ischemic Burden, but signs of functional changes due to chronic exposures remain	Any MCG Severity Scores ≥ or ≤ 2.0 with significant Pathological and Physiopathological conditions related to long-term exposures to myocardial ischemia as results of obstructive coronary artery disease, i.e. myocardial remodeling, asynchronization, decreased myocardial compliance, etc., per MCG reporting standards.
2	Low Myocardial Ischemic Burden	Maximum MCG Severity Scores ≤ 3.5 but ≥ 2.0; there are fluctuating myocardial ischemia patterns represented by either occasional local, global myocardial ischemia, or with myocardial ischemia altogether absent in test(s) in the same session
1	Normal	Any MCG Severity Scores < 2.0 without local or global ischemia and minimum Pathological and Physiopathological conditions reported

Appendix 5 (Trial Monitor Dr. Alan Berson Letter)

Bioresearch Funding Group

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Novato, CA 94949

Phone/Fax: 415 883 3773

February 21, 2006

Joseph Shen, MD
Premier Heart, LLC
14 Vanderventer Avenue
Port Washington, NY 11050-3757

Dear Dr. Shen:

This is to summarize my role in clinical trials that were conducted in Germany and in several countries in Asia. The purpose of the trials was to determine the accuracy of diagnosis of regional or global ischemic heart disease due to coronary artery disease using 3DMP interpretations, a Premier Heart diagnostic program of 3DMP digital ECG data, by comparing them to clinical catheterization (angiogram) results.

The 3DMP diagnoses performed at Premier Heart were blinded to responsible physicians until coronary angiographic reports were sent to me. Conversely, angiographic reports were blinded to Dr. Shen and to staff at Premier Heart until I received and verified that matching 3DMP reports existed. The comparative analyses are based on the results obtained from Premier Heart and the participating physicians prior to the data exchange.

The 3DMP results for any patient were not seen by the responsible physician nor were catheterization reports seen by Dr. Shen or any Premier Heart staff until I performed this verification. I certify that these trials were conducted in a strictly double-blind manner.

Sincerely,

Alan Berson

Alan Berson, PhD

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