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Multifunction Cardiogram, a.k.a. MCG

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Introduction

Coronary artery heart disease (CAD) is a major cause of death and disability in developed countries. Although CAD mortality rates worldwide have decreased over the past four decades, CAD remains the cause of about one-third of all deaths among individuals over age 35 years.[1-3] About half of all middle-aged men and one-third of middle-aged women in the United States will develop some manifestation of CAD.[4] There are several unrecognized drivers or causes of the persistence of this morbidity despite our general knowledge of major risk factors based on population data such as the Framingham Heart Study. The lack of adaptable, inexpensive, noninvasive, and accurate modalities to detect CAD in its early stages as well as the lack of effective monitoring of the effects of diet and other lifestyle intervention has been a major factor.

Electrocardiogram (ECG) stress testing, nuclear scintigraphy, stress echocardiography, and other various types of cardiac stress imaging testing are considered the standard noninvasive techniques for evaluating cardiac ischemia. Although 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 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 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.[5] At catheterization, 149,739 patients (37.6%) had obstructive coronary artery disease (70% obstruction or greater), requiring an interventional procedure. Stated bluntly, up to 62.4% of those patients could have avoided coronary angiography if more accurate noninvasive testing modalities were available. Compounding the diagnostic inadequacy of conventional testing of obstructive CAD is the emerging consensus of the role of nonobstructive coronary disease and microvascular disease in the clinical manifestation of ischemic heart disease. A review in *Circulation* 1995 by Erlin Falk demonstrated that the progression to plaque rupture and myocardial infarction (MI) over time occurs most frequently in patients with obstruction of 50% or less.[6]

It is within this context of complex and evolving concepts that Premier Heart is proud to introduce the Multifunctional Cardiogram (MCG), a noninvasive, physical-stress-free, and nonionizing diagnostic tool that can be used to quantitatively assess lesions across the very early nonobstructive to significantly obstructive spectrum and to monitor any form of therapeutic intervention.

The Purpose of This Chapter

This chapter provides an opportunity for the health professional to learn about a "new" diagnostic tool that has been more than 20 years in the making. It provides an outline as to why conventional cardiac testing is inadequate and why MCG is the ideal tool to fulfill this unmet need. There are several paradoxical or unexpected clinical developments in the management of CAD over the last several years. Although it is generally accepted that low-density lipoprotein (LDL) cholesterol plays a central role in the initiation of the coronary plaque, it is known that 50% of patients presenting with a MI have normal total cholesterol.[7] Additionally, the data from several primary and secondary prevention trials have shown that the majority of the risk of CAD still remains even after LDL reduction.[8] Perhaps the most glaring event of the inadequacy of conventional approach to the management of CAD is the 15-year outcome status report of the COURAGE trial (Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation).[9] The 15-year status of this study essentially demonstrated that

percutaneous coronary intervention (stent placement) in patients with stable CAD did not improve in mortality outcome when compared with similar patients who were treated using only optimal medical management. Perhaps related is an older but interesting piece of data from the FAME (Fractional Flow Reserve versus Angiography for Multivessel Evaluation) study.[10] The FAME study looked at 1-year outcomes (death, MI, major adverse cardiovascular event) in one group of patients whose management was guided by angiographic results versus a similar group guided by the fractional flow reserve (FFR) data. The FFR-guided group had significantly better outcome in all categories. A systems approach to address the functional aspects of this complex biological conundrum, known as the cardiovascular system, is desperately required.

What Is MCG and What Does It Measure?

The MCG is the first embodiment of a mathematical application of systems theory to a dynamic biological (cardiovascular) environment, which expresses the physiologic state of the heart, with a primary focus on the level of its ischemic burden. In other words, the MCG describes the dynamic functional sate of the heart, beyond relying upon anatomical status. Premier Heart's greatest priority was always the measurement of the ischemic burden, but there were additional markers that needed to be recruited to describe the heart within a functional perspective. That expression was (is) the mathematical articulation of the communication between two standard ECG leads over multiple cycles, beginning with the conversion of the signals into a frequency domain via multiple nonlinear mathematical functions, thus the use of the term "multifunction cardiography." The adaptation of systems analysis principles, combined with Lagrangian mechanics, empirical data mining, deep machine learning, and neural network development, created, to our knowledge, the first example of a commercially available information technology solution in the discipline of "Clinical Computational Electrophysiology." Following decades of research and development, through the diligent work of two generations of dedicated scientists, clinicians, and engineers, MCG technology has evolved from conceptual mathematical designs to animal testing and finally to human application. Although x-ray, computed tomography,[11] magnetic resonance (MR), or ultrasound technologies describe **spatial** anatomic separation, MCG describes **frequency** separation, whereby specific mathematical elements from the multiple functions in frequency domains via power spectra are ascribed to specific anatomical or physiologic functions of the whole cardiovascular system.[12]
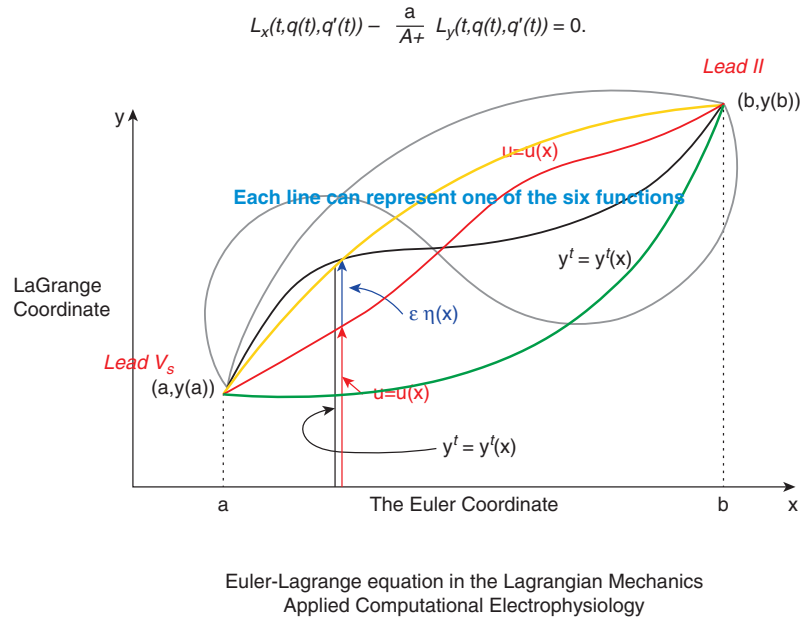
It is beyond the scope of this chapter to delve into full explanation of the applied Lagrangian mechanics used by this technology, but it is helpful to outline a few basic principles. Blood flow is a non-Newtonian fluid that is optimally assessed and reported with Euler coordinates. Cardiac tissue and brain tissue are viscoelastic

solids, and they are assessed and reported with Lagrange coordinates. Among the infinitely possible mathematical expressions within this system, we have empirically selected six dynamic and integrative mathematical functions that act as the backbone of our mathematical analysis, namely, auto power spectrum, phase angle shift, impulse response, cross correlation, coherence function, and transfer function. The Euler and Lagrange coordinates are then linked by a Laplace transformation application (see **Figure 12.1**).

The deeper questions as to what these frequency interrogations represent are issues such as:

- Quantification of the abnormal electromechanical expression patterns of stress (physical) and strain and intracardiac blood flow.
- Integration of all myocardial electrical power required to function under normal and abnormal conditions delivered by sodium (Na^+), hydrogen (H^+), potassium (K^+), calcium (Ca^{2+}), and magnesium (Mg^{2+}) channels and ATPase activities of all myocardial cells through multiple cardiac cycles.
- Oxidative stress caused by supply and demand imbalances, free radical formation, and lactic acidosis leading to ion channelopathies, particularly gradient dependent H^+ channel (a subunit of F1-F0 ATPase) in addition to chronic damage/mutation of the mitochondrial gene transcription/translation mechanics, resulting in gradual myocardial power production.

All of this information and analyses are collected and collated by a bedside device within 10 minutes on the average patient, with the patient lying down (or sitting) quietly and remaining still for a few minutes. The device is the size of standard laptop. Electrocardiographic signals from two leads (II and V5) are recorded for 82 seconds per cycle and repeated for three to five times per session. Data are then uploaded and compared with the data patterns of hundreds of thousands of patients who have had the MCG test and who have had cardiac catheterization with angiogram. The database is equally male/female to eliminate gender bias, with an age range of 14 to 100 years. Every patient who has an MCG test in effect undergoes a virtual cardiac catheterization with an FFR assessment. How was this database built? The database is the end product of a laborious creation that is central to understanding MCG technology and may well be the most uniquely constructed database in all of medical data. The team, led by Dr Shen, embarked on a two-decade-long journey of research and development via digital signal processing, empirical clinical data collection, data mining, supervised machine learning, neural network development, artificial intelligence algorithm development, and countless iterations of optimization and improvement to create computer recognition of all forms of heart disease. In this endeavor, 2 million individuals were tested on MCG and more than 100,000 people with various heart diseases had their angiographic data strategically added to the system to build a production database for system software development. All the data sets used in analysis and the proposed statistical models had to satisfy the tests of

$$L_x(t,q(t),q'(t)) - \frac{a}{A+} \; L_y(t,q(t),q'(t)) = 0.$$

Euler-Lagrange equation in the Lagrangian Mechanics
Applied Computational Electrophysiology

Figure 12.1 *Graphic representation of the linkages between the Euler coordinate and Lagrange coordinate.*

both null hypothesis and alternative hypothesis. The extremely carefully verified and thoroughly validated data sets were used in the discovery of over 200 mathematical elements from the six nonlinear functions. We ensured that the development of the machine learning algorithms for the quantitative automatic heart disease pattern classification and differentiation were based purely on thoroughly vetted and trusted empirical evidence. Based on well-defined frequency and separation, the aim was to systematically explore, define, express, measure, quantify, and differentiate the hidden NORMAL and ABNORMAL electromechanical, electrostructural, electrobiochemical, electrohematologic, electroneuroendocrine, neurohormonal, and electroimmunological expressions, as well as the highly elusive, yet vitally important diverse expressions of electromyocardial perfusion pattern of the cardiovascular system. It is this kind of unique analysis, coupled with the 24/7 accessibility and reliability, that positions MCG well beyond more expensive and more cumbersome imaging and perfusion techniques.

The final report gives an overall functional severity score between 0 (totally normal) and 22 (the most severe) (see **Table 12.1**). The report also gives an assessment of secondary pathological and physiopathological conditions. These secondary conditions or markers include the following: cardiomyopathy (derangements in myocardial wall motion and/or structure), hypertrophy, arrhythmias or precipitating substrates, rheumatic pattern (LV, aortic/mitral valve derangements), pulmonary pattern (right heart, pulmonic/tricuspid valve derangements), myocardial damage (MI, contusion, etc.), congenital abnormalities, compliance changes, remodeling, energy output, ejection fraction, and angle phase shift. Although there is a generally good correlation between the severity score and the level of obstruction, there is no specific

correlation between the numerical severity score and the percentage of blockage. This fact underscores the contribution of the secondary factors to the functional assessment of the heart and highlights the difference between conventional anatomical imaging and MCG's functional physiological assessment. It also underscores the importance of the FFR information alluded to earlier in the FAME study.

The validation of MCG in the detection of myocardial ischemia caused by obstructive coronary artery disease (CAD) has been demonstrated in multiple independently conducted clinical trials in eight countries[13-23] with high sensitivity (89%-100%), specificity (83%-94%), and negative predictive values over 95%. The accuracy can be improved when the results of MCG are corelated with serum biomarkers such as abnormal fasting glucose, hemoglobin A1c, LDL cholesterol, and the heart failure marker, pro-BNP. The details of each study will not be discussed here, but there are a few that should be highlighted. The landmark clinical validation of MCG was a study by Amano, Shinoda, Kunimura et al[20] (see **Table 12.2**). The study was done in Japan but published in the *Open Heart Journal* of the *British Medical Journal*. They combined angiographic and functional flow reserve (FFR) data and demonstrated that MCG has high specificity with high negative predictive value and concluded that MCG can be used not only to identify functionally significant ischemia but also to reduce unnecessary angiograms.

Another Japanese study by Takeshita and Shinoda[21] (see **Table 12.3**) compared classic syntax scores (SS) with functional syntax scores (FSS). The SS is derived purely from anatomical analysis of angiographic data. The FSS is derived from the addition of fractional flow reserve (FFR) information to the analysis. FFR is the percentage of reduction in pressure recordings across both obvious obstructive lesions

Table 12.1

8 CATEGORIES OF DISEASE SEVERITY

7	Extremely High Myocardial Dysfunction	Minimum MCG Severity Scores ≥ 15, *oscillating between 15 and ≤22*
6	Very High Myocardial Dysfunction	Maximum MCG Severity Score ≥ 15 and a minimum of 7.0 *oscillating between 7 and ≤15*
5	High Myocardial Dysfunction	Minimum MCG Severity Scores ≥ 3.5 and maximum score 7.0, and *oscillating between 3.5 and ≤7*
4	Intermediate Myocardial Dysfunction	All MCG Severity Scores fluctuating above or below 3.5, ie, any score lower or higher than 3.5 appearing in the same session; *oscillating between 0 and ≤X*
3	Collateral Circulation Group	Any MCG Severity Scores ≥ or ≤ 2.0 with or without significant pathological and physiopathological conditions
2	*Low Myocardial Dysfunction*	*Maximum MCG Severity Scores ≤ 3.5, or session scores oscillating between 0 and ≤3.5*
1	*Clinically normal*	*Maximum MCG Severity Scores ≤ 2.0 in a session, including 0, oscillating between 0 and ≤ 2.0;*
0	True Normal	MCG Score a "Zero"

and not-so-obvious nonobstructive lesions. They concluded that MCG showed high specificity and predictive accuracy especially for FSS, again supporting MCG's usefulness in identifying functionally significant ischemia and potentially its role in reducing unnecessary catheterizations.

A poster presentation at the Transcatheter Cardiovascular Therapeutics (TCT) 2015 meeting in San Francisco: TCT is a prestigious professional society that focuses on interventional cardiology. The poster by T. Amano et al[22] showed that MCG correctly identified all six restenosis and two new blockages among 45 patients who were followed 1 year post placement of coronary stents. With a sensitivity of 94.3% and a specificity of 97.3% among 720 epicardial coronary artery segments, 16 per patient, MCG delivered a 0.94 (0.89-1.0) in the area under the receiver operating curve (ROC) analysis for the prediction of adverse events.

Finally, a word on the only outlier (negative) among these trials: Kawaji et al[23] published a study allegedly showing poor correlation between angiographic with FFR and MCG. However, there were several problems including a significant deviation from the original protocol.[24] They did not consider collateralization as a cause of false-negative results. Also, the decision not to perform FFRs on many diabetic patients with nonobstructive disease inserted a significant degree of bias. The authors, subsequently, reanalyzed the same data and retracted their initial position at a later date, in a Japanese language journal.

Table 12.2

MCG VERSUS CORONARY ANGIOGRAPHY (CAG)/FRACTIONAL FLOW RESERVE (FFR)

Predictive power of spectral ECG components stenosis through mathematical analysis of spectral ECG components

Conclusions: The MCG showed high specificity and predictive accuracy especially for the FRR + CAG, suggesting that it is useful not only in identifying functionally significant ischemia but also in reducing unnecessary CAGs.

- A high MCG score had a specificity of 90.4% (87.0%-93.9%) in model 1 adjusted by FFR≤0.8 threshold and of 87.0% (83.2%-90.8%) in model 2 adjusted by FFR ≤0.75 threshold, and a negative predictive value of 82.5% (78.3%-86.7%) in model 1 and of 83.8% (79.6%-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.
- 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% and 100% if a new model was adopted. The investigators are considering the possibility of reanalyzing the data using the seven categories we have developed.

BMJ Open Heart. 2014;1. doi:10.1136/openhrt-2014-000144.

Table 12.3
PREDICTING ONE- YEAR OUTCOMES TARGETING MCG RESULTS VERSUS SS/FSS
Predicting one-year outcomes targeting MCG results versus SS/FSS a.k.a. syntax score and functional syntax scores, the platinum standards for one-year mace outcome measures used by interventional cardiologists
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. MCG was the only test significantly associated with the SS (odds ratio, 2.92 [1.60-5.31], P < .001) and FSS (odds ratio, 3.66 [1.95-6.87], P < .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 90% (89%-100%) and 94% (89%-100%) for the prediction of SS and FSS, respectively.
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It is clearly evident that MCG's capabilities for the detection of early, intermediate-, and late-stage myocardial ischemia and natural recovery stages go far beyond conventional diagnostic stratagem and are of special value in women or individuals with microvascular or nonobstructive diseases, such as diabetes mellitus. MCG has also been demonstrated to have a direct and close correlation with the physiologic FFR measurement. MCG provides a uniquely positioned high-quality diagnostic tool to clinicians for making critical diagnostic and clinical management decisions in a timely, affordable, and dependable manner at the patient's bedside in real time.

Clinical Applications

MCG can be used in a number of clinically appropriate situations. It may be used in any situation wherein there is a clinical suspicion of CAD based on signs or symptoms. These signs or symptoms may be typical but may also be atypical, especially in women. Metabolic disorders such as diabetes mellitus, metabolic syndrome, and obesity have particularly striking features in MCG's capability of unmasking underlying CAD. The MCG may be used before or after conventional testing such as myocardial perfusion stress test. Although data have suggested that inappropriate coronary angiograms may be avoided by MCG testing, the reverse is also true—MCG may dictate coronary angiogram by uncovering severe CAD in unsuspecting patients. Then, as shown earlier, the technology can be used to assess the effectiveness of any form of intervention, conventional or lifestyle.

Case Studies

The following three case studies are illustrative of MCG's clinical utility.

SG is a 54-year-old woman with a history of dextrocardia who was concerned about a calcium score of 75 and a family history of CAD (her father died of an MI before age 60 years). She had atypical pains (neck, upper back). Her MCG scores were 4, 7, 7, 7, and 9 with indications of predominantly local (focal) ischemia. The secondary markers were positive for cardiomyopathy (wall motion dysfunction), atrial fibrillation, myocardial damage, and myocardial inflammation. Compliance abnormalities were absent. The study was interpreted as consistent with probably nonobstructive disease, predominantly in the left anterior descending (LAD)/circumflex (LCx) distribution (localization based on the dextrocardia) but could not exclude diffuse (global) disease. A cardiac magnetic resonance (MR) perfusion test was done as the next step. The cardiac MR report showed "decreased sub-endocardial signal in all three coronary territories. Differential diagnosis includes reversible ischemic disease versus 3-vessel obstructive disease." A cardiac angiogram was suggested. Subsequent catheterization report showed proximal LAD 30% to 40%, proximal LCx 30% to 40% lesion, and right coronary artery dominant, with luminal irregularities (small nonobstructive lesions). Intensive dietary and lifestyle intervention was begun. MCG correctly identified a pattern that more expensive and invasive techniques subsequently verified.

JR is 43-year-old man with a body mass index greater than 25 with poorly controlled type 2 diabetes, high cholesterol, recurrent chest pains, and a family history of early MI affecting his father, uncles, and brother. He presented to the emergency departments multiple times complaining of chest pains. His ECG readings, blood tests, and stress tests were all interpreted as "normal." However, MCG detected global ischemia with a severity score between 8.5 and 9.5. At one of his emergency room visits, a coronary angiogram was done and it showed no coronary obstruction but narrowed distal arteries showing TIMI II flow, indicating possible small vessel disease. He was subsequently managed with aggressive lifestyle changes and medication. In 60 days, he lost 35 pounds and was asymptomatic. His MCG severity scores fell to less

than four, and the MCG functional expressions showed gradual normalization. At his request, he is now being monitored quarterly by MCG.

In another case, RR is a 77-year-old with known severe obstructive coronary artery disease and high MCG scores, with high cholesterol, LDL, and a history of prostate cancer with radical prostatectomy. He refused to undergo any revascularization procedure. He decided to try a ketogenic diet to lose weight and hopefully to improve his cardiovascular function. MCG overtime demonstrated steady improvement, as his scores fell from a range of 7.5 to 10 down to a range of 4 to 7. The elements of his mathematical matrix also showed functional improvements. This demonstrates that the metabolic component of a patient with severe ischemia can be reversed and that reversal can be measured and monitored by using MCG.

Summary

- The Multifunction Cardiogram (MCG) is the first purpose-built artificial intelligence cardiac disease diagnostic tool that utilizes systems theory within a biological context to give a functional analysis of the heart.
- It is a physiological test, not an anatomical imaging test, but the severity of ischemic score and the presence/absence of certain secondary factors (eg, phase shift) give its users actionable anatomical and functional information.
- MCG is capable of identifying CAD in its early stages long before it is demonstrable by more conventional testing. It is particularly powerful when combined with biomarkers such as B-type natriuretic peptide, myeloperoxidase, asymmetric dimethyl arginine or measures of oxidative stress. Thus early detection and primary prevention can be measured and monitored objectively and qualitatively based on functional outcome.
- It is an excellent tool for assesing subsets of patients whose anatomic features elude accurate diagnostic testing by conventional imaging methods. These include women (also men) with small vessel disease and patients with microvascular or non-obstructive disease seen in conditions such as diabetes and the metabolic syndrome.
- MCG is more accurate in the detection of myocardial ischemia caused by obstructive coronary artery disease than conventional tests, such as nuclear stress tests and echocardiography. Thus MCG should be provided BEFORE the stress imaging tests are used. This recommendation is consistent with the independent decision by Highmark Medicare contractor medical directors in a local coverage determination draft policy (LCD) in 2012-2013.
- MCG should be used as the first line tool for patients presenting to the emergency room for chest pain to reduce false negative discharges and false positive admissions, which would lead to effective resource allocations and value based care delivery.

- MCG is also an excellent tool for pre-surgical cardiac clearance, since it is more sensitive and specific for the detection of obstructive coronary artery disease.
- For patient safety, MCG should be utilized especially when the stress imaging tests are relatively contraindicated, eg, elderly patients who may be incapable of undergoing the demands of a stress imaging test session; and for patients with end stage renal diseases, since intravenous contrast agents applied in computed tomographic or magnetic resonance angiographic imaging may hasten the deterioration of renal function.
- MCG is the ideal, convenient, and flexible tool to measure the real-time outcome of lifestyle or other therapeutic interventions.

Future Challenges and Opportunities

- Medicare and commercial insurance coverage is needed for easier access to patients in the provider community. A forthcoming publication on MCG's utility as a triage tool in the assessment of emergency department patients with chest pain here in the United States will be extremely useful in the quest for insurance coverage.
- Premier Heart is actively working on developing a robust graphic interpretation report that captures and illustrates all the important variables that are measured in a study.
- One of the weaknesses of an MCG is its requirement for the patient to be still and for the environment to have minimum electrical interference. The technology is evolving so that devices will be wearable for remote personal use and can be adapted for a true exercise stress test.
- The technology and adaptability of MCG open paths for assessments in complex and difficult situations. The detection and monitoring of CAD in patients with the clonal hematopoiesis of indeterminate potential (CHIP) mutations and the monitoring of CAD in patients who are treated for elevated levels of trimethylamine-*N*-oxide are two areas of tremendous interest.
- Analysis of hundreds of MCG data has revealed a unique pattern of infiltrative disease correlating with possible chemotherapy induced cardiomyopathy and cardiac amyloidosis. These observations provide another opportunity for early recognition of two vexing clinical entities. Future studies need to be done to establish clinical utility.
- Since MCG represents an individual's phenotypic expressions, the information can be combined with genotypes to establish a unique MCG + Genomic database for studying clinical, pharmaceutical and medical/surgical treatments at an unprecedented depth to customize better personalized drugs and devices, and create outcome/evidence based management modalities.

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