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Research Article

FMTVDM Study Proposal: WID2H - Breast Trial.

(Weight, Inflammation, Diet v Drug, Heart disease) – Breast Trial

Richard M Fleming[1]*, Matthew R Fleming[1] and William C Dooley[2]

[1]FHHI-OmnificImaging-Camelot, Los Angeles, CA, USA

[2]Oklahoma University Health Science Center, Oklahoma City, Oklahoma, USA

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***Corresponding author:** Richard M Fleming, PhD, MD, FHHI-OmnificImaging-Camelot, Los Angeles, CA, USA, E-mail: drrichardmfleming@gmail.com

ORCID: https://orcid.org/0000-0001-9964-1518

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Introduction

As we enter this new decade, medicine is presented with the daunting task of resolving incongruities in our existing data and the ever-increasing incidence of obesity, Coronary Artery Disease (CAD) and cancer – including but not limited to breast cancer. The consequence of our failure to quantitatively measure the impact of diets and drugs at the tissue level where the actual CAD and cancer are occurring has limited our ability to better define the dietary, lifestyle and medication changes required to limit and potentially reverse these inflammatory diseases.

This paper proposes a study which will answer these fundamental questions-a study which readers of this journal are all to familiar with the need to complete. A study, which will provide the evidence we and our patients have been looking for; defining which dietary practices are detrimental and which are clearly beneficial and it will do so quantitatively-removing any doubt about the true impact of these diets and any potential subjective interpretation of outcomes.

Inflammatory coronary artery disease [1].

It is now commonly accepted that the Fleming Unified Theory of Vascular Disease (FUTVD) [2-4], shown in Figure 1, explains the mechanisms behind the inflammatory process that is associated with the impaired physiologic response we know as Coronary Artery Disease (CAD), resulting in Angina [5] and the Major Adverse Cardiac Events (MACE) of Myocardial Infarction (MI), ischemic cardiac failure, cerebrovascular disease (CVA, RIND and TIA), claudication and cancers.

Coronary artery disease is the result of this inflammatory change within the walls of the arteries, impairing the ability of the coronary arteries to regionally deliver the amount of blood required by the heart at any moment in time [6-8]. It is this inability of the coronary arteries to relax and increase blood flow, producing regional blood flow differences-resulting in angina [5] - which we must be able to measure to accurately diagnose CAD, and it is the change in this ability over time, which we must measure, to determine if CAD is progressing, regressing or stabilizing-either naturally or as the result of a treatment process-be that dietary, medical or otherwise.

For decades it has been presumed that measureable blood (serum markers) tests associated within the various components promulgating this inflammatory proces (lipids, homocysteine, lipoprotein (a), fibrinogen, c-reactive protein, interleukin-6, and potential infectious agents), would provide useful information as to the progression, regression or stabilization of this inflammatory process.

However, these blood tests do not represent what is happening at the tissue level-the true site of the inflammatory process-raising the question as to the relationship between the serum (blood) levels of these inflammatory components and the tissue level of these inflammatory components.

As shown in Figure 2, we have known for more than a decade, that measured changes in these serum blood tests (biomarkers) considered responsible for promoting inflammatory processes does not correlate with measured changes in the actual physiologic CAD [9], yet we have continued to focus on these

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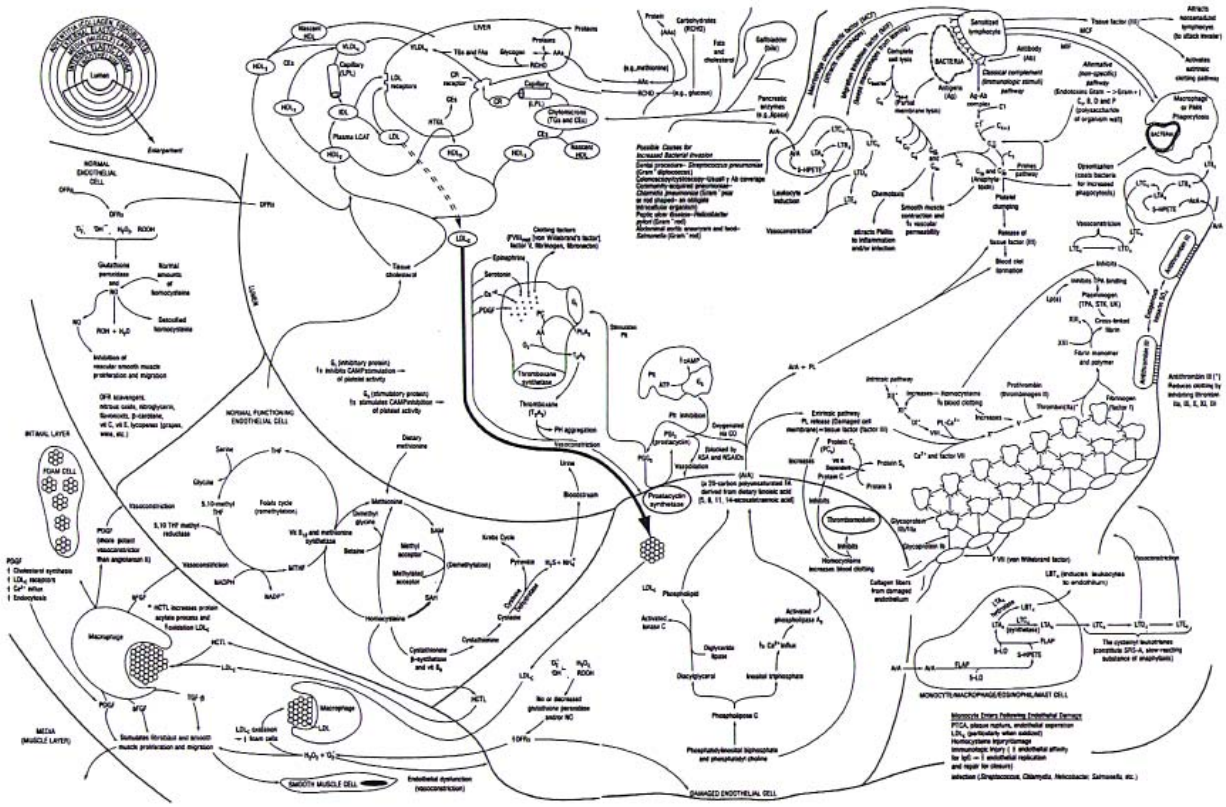

Figure 1: The *Fleming Unified Theory of Vascular Disease* (FUTVD) [2].
The detailed schematic of how multiple variables are associated with the inflammatory process impairing the function of coronary arteries – viz. Inflammatory Coronary Artery Disease – which will result in impaired regional blood flow and consequently angina.

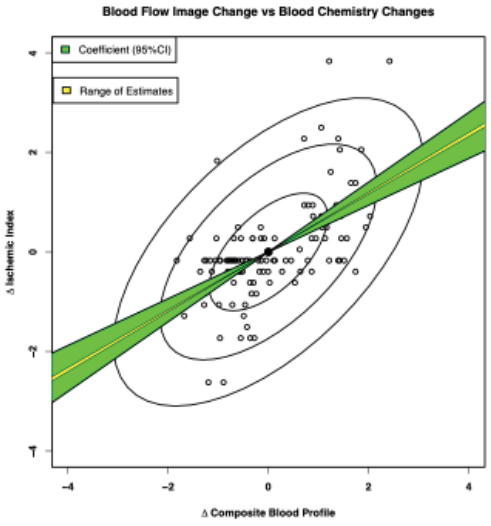

Figure 2: Standardized regression of coronary blood flow on composite blood profile [9]. The X-axis displays the composite blood profile including TC, fat, low HDL, IL-6, Lp, and Fib. The Y-axis displays changes in ischemia as measured by nuclear imaging. The standard regression analysis shows both the range of estimates (yellow) and the 95% confidence intervals (green). HDL, high-density lipoprotein; IL-6, interleukin-6; Lp-a, lipoprotein-a; Fib, fibrinogen; Tc, total cholesterol.

blood tests with their poor correlations to CAD [10], rather than measuring *true* CAD itself [11-18].

Given our improved understooding, that CAD is caused by an inflammatory buildup occuring within the walls of the arteries (Figures 3,4) resulting in impared regional blood flow (Figure 5) and only later narrowing the coronary lumen [19], the limitations in using cardiac catheterizations to measure changes in CAD, is readily apparent – coupled with the addition of other errors made with coronary arteriography [20-22].

Consequently, coronary lumen narrowing-percent Diameter Stenosis (%DS)-occurs later in the inflammatory process, with 70% of all MIs occuring with less than 30% lumen narrowing. Interpretation using this approach to finding CAD, has resulted in errors in reading %DS, as well as the inability to determine the actual amount of inflammation (CAD) within the walls of the arteries.

Vulnerable inflammatory CAD-resulting from inflammatory damage to the wall of the coronary arteries-thus is first associated with an impairment in the ability of the arteries to dilate (relax) upon demand, to meet the increased regional blood supply required to meet cardiac demands/workload. It is now possible to quantify these changes using FMTVDM-the first utility patent capable of doing so [8,12-18].

The process of inflammatory athero-sclerotic CAD, may be associated with calcium buildup (sclerotic) or not (atheroma)-depending upon the individual. As Glagov established [19], a considerable plaque buildup is required (Figure 3) before coronary lumen narrowing can be appreciated and this need not be associated with calcification. In fact, when plaques are visualized with Intravascular Ultrasound (IVUS), clinicians

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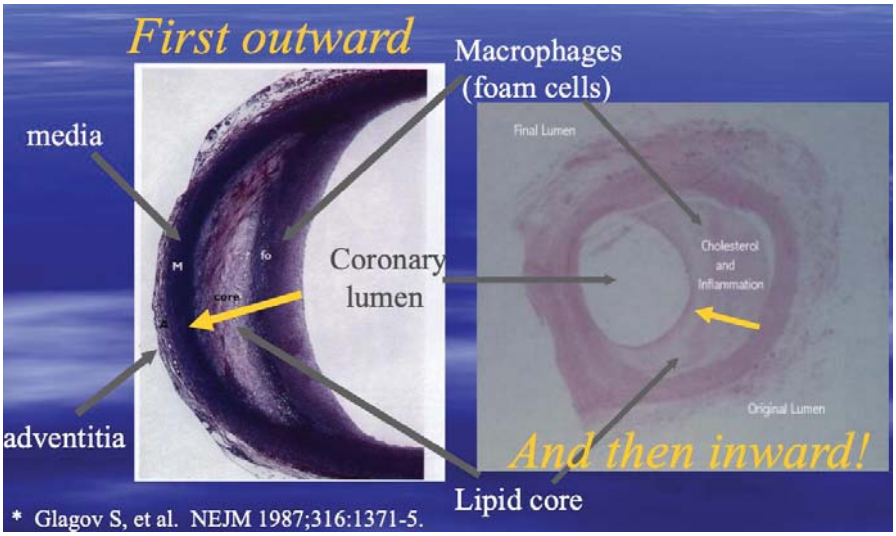

Figure 3: Fundamental demonstration of coronary arteriography limitations [19].
Post mortem demonstration that irregularities to the coronary lumen occur later in the process of CAD. Noticeable (40% diameter stenosis) did not appear until the inflammatory lesion area represented more than 40% of the internal elastic lamina area.

frequently differentiate plaques based upon visual appearance. Those lesions without sclerotic or calcific changes appear yellow in color and are more vulnerable to sudden rupture, while those with sclerosis and/or calcification have a grey or white appearance and are more stable-less likely to rupture. The presence of elevated CAC scores may provide insight into which lesions are less likely to suddenly rupture-providing insight into a subset of lesions-however, there is no information provided about lesions without calcium and no information in the literature supporting CAC use to measure regression of CAD.

Clearly once the calcium is present (Figure 6) there is demonstrable anatomic evidence of CAD; however, the use of coronary artery calcium scores (CCT/CAC) cannot be depended upon to (a) accurately diagnose non-sclerotic CAD, (b) actually measure the physiologic impact of CAD, or (c) to provide a true measure of the physiologic impact of CAD present.

Considering (1) the overall cost of CAD including the associated MACEs, (2) the lack of correlations associated with changes in blood tests and CAD, (3) the inability to accurately measure CAD using either coronary arteriography or CCT (aka CAC) scoring, (4) the tremendous costs associated with lipid reducing agents-which address only some but not all of the causes of inflammatory CAD, and (5) the ability of FMTVDM to quantitatively measure the physiologic effect of inflammatory CAD, this study is designed to determine what if any effect, lipid lowering medications, dietary and lifestyle changes have on inflammatory CAD.

By measuring the functional (physiologic) effect of cholesterol lowering medications and/or dietary modifications designed to alter the inflammatory factors resulting in CAD, we can determine the impact of both dietary recommendations and cholesterol lowering medications at both the serum and tissue level – where the inflammatory changes have a direct effect.

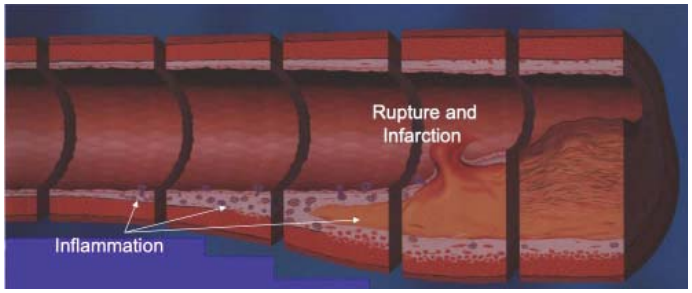

Figure 4:

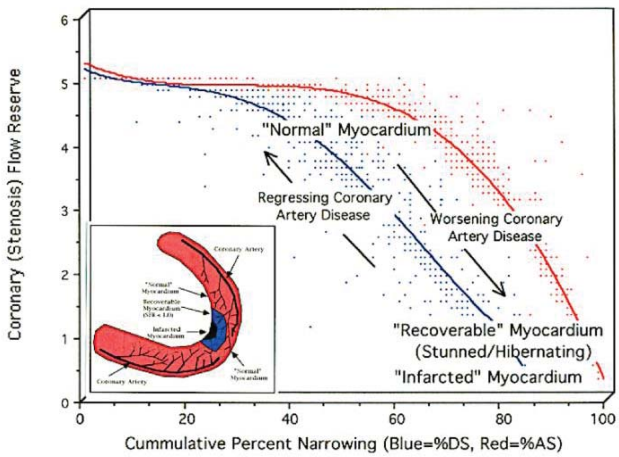

Figure 5: Relationship between inflammatory CAD and flow reserve in humans [6,7,15].
The relationship between inflammatory coronary artery disease and flow reserve is a quadratic function as graphically represented.

Breast Disease

In 2019, it was estimated that 1.8 million Americans would be diagnosed with cancer, including 268,600 women and 2,670 men with breast cancer, the most commonly diagnosed type of cancer [23].

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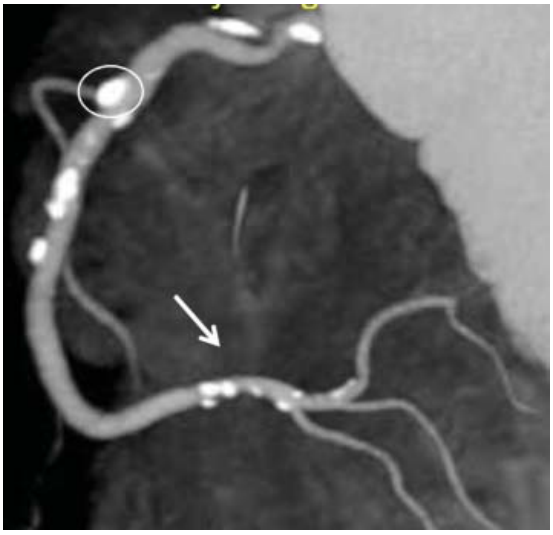

Figure 6: Presence of anatomic calcification in right coronary artery.

For decades the medical sciences have focused on the ability to find cancers, by our ability to find something abnormal, either by (A) a visual qualitative imaging test (x-rays like mammograms [24,25], CTs [26], MRI [27], etc.), or by (B) an abnormally elevated blood test-which does not actually tell us if cancer is present any more than a calcium deposit does-resulting most likely from an increased protein or molecular compound being released from cells at higher than expected levels and thus measured at higher than normal levels in the blood.

We have also come to depend upon (C) biomarkers (e.g. BRCA1/2) suggestive of the potential for cellular and tissue change-but not determinant of change. Finally, we have come to depend upon our ability to diagnose cancer based upon our ability to find something (D) microscopically-including biomarkers (HER2, ER+, PR+) and abnormal cellular details as noted above. However, even this *gold standard* requires human qualitative interpretation with associated errors [28-30].

The changes that occur as *normal* cells respond to environmental insults resulting in a series of possible transformative changes, which may or may not result in cancer, can be measured from beginning to end as shown in Figure 7 [30-34].

Like inflammatory CAD, the transitional changes from "normal" breast tissue through the inflammatory changes into cancerous tissue, can be quantitatively measured (FMTVDM) using the same methods used to quantify physiologic inflammatory CAD.

Like CAD, measuring the consequential changes in regional blood flow and metabolism, that occur either naturally or as the result of treatment, is now possible using FMTVDM.

Rather than thinking about patients as a collection of diseases, a model promulgated by DRG and *current procedural terminology* (CPT) codes, the physician goal, pursuant to the *Hippocratic Oath* and the *Declaration of Geneva*, is to think in terms of the health of the patient [35]-viz. the patient's *health-spectrum*.

As explained in detail elsewhere [34], the transitional changes associated with the potential development of cancer is the result of (A) enhanced genetic metabolic activity, which results in (1) the release of chemical mediators responding to the environmental factors-both positive and negative-and (2) augmentation of regional blood flow [36-39].

Nuclear imaging provides the only physiologic tool available for medical imaging of the body. As such, nuclear imaging provides the only true, real time, in vivo method for analyzing physiologic changes occurring within the patient.

While prior nuclear imaging procedures addressed qualitative imaging controls, they did not take into account quantitative imaging controls, leaving the interpretation of diagnostic studies flawed and without the accuracy, consistency and reliability required to (A) measure transitional changes in tissue or (B) the ability to measure the true impact of treatment upon cancer or other diseases such as coronary artery disease [40]. This has only recently been made possible [12,32].

Cancer has now become the number one killer of people worldwide. This fact alone should emphasize the importance of how we approach this global health problem. Cancer is no longer limited to industrialized countries, the poor or even the affluent. Cancer knows no geographic or socioeconomic barriers.

It is impossible to intelligently approach cancer from an absence of knowledge or limited approaches to finding, monitoring and determining the treatment response of a cancer. That which makes cancer, cancer, and that, which makes transitional changes in cells/tissue different from cancer and *normal* tissue, is what we must be able to measure if we are to address the health risk associated with the number one cause of morbidity and mortality worldwide. We cannot address cancer or its treatment, without the ability to measure these changes [41-44].

Study Design

The study will include: Initial and Final FMTVDM measurements of both the Heart and Breast.

Serum blood tests routinely used to compare with FMTVDM outcomes, and Dietary Treatments.

Treatments

While there are differing opinions, most agree that dietary and lifestyle factors play a MAJOR contributing role in the development and progression of inflammatory CAD. Absent a prior quantitative study measuring the physiologic outcome (FMTVDM), there is no clear consenses as to which dietary and lifestyle factors are most influential.

Prior studies conducted by the Principle Investigator have demonstrated that for three different treatment arms, a study of 120 individuals is sufficient to demonstrate statistical

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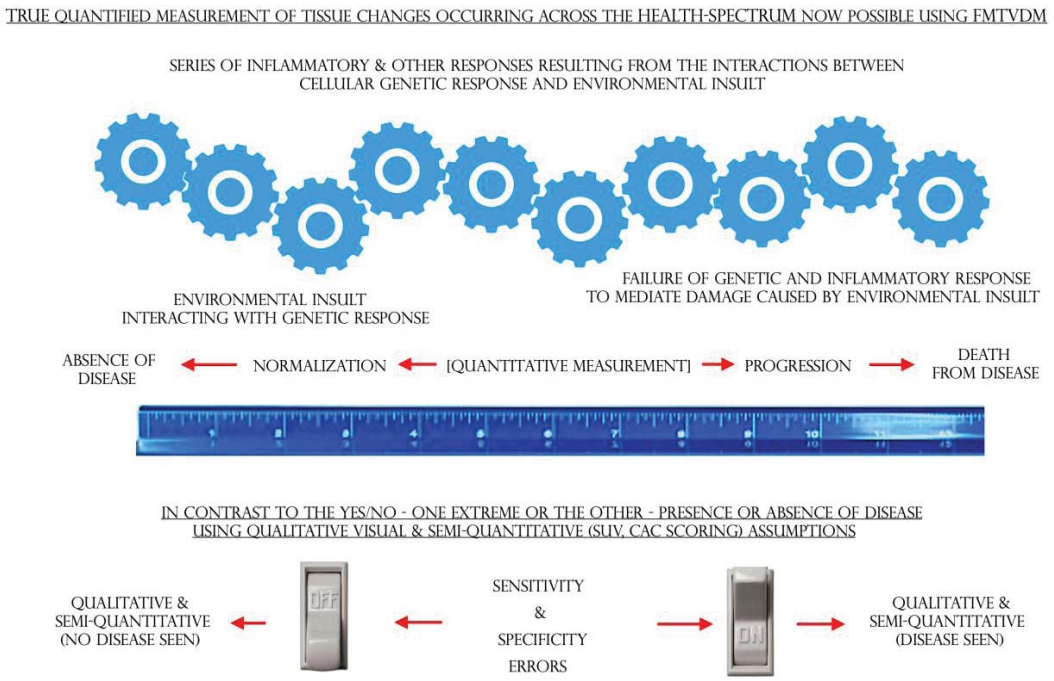

Figure 7: Quantification of changes in the cellular *Health-Spectrum* [34].
Cellular changes resulting from genomic-environmental-treatment (part of the cellular environment) interactions can be measured across the Health-Spectrum.

differences between groups. Thus, the proposed study would include 40 individuals per treatment arm of the study. These prior studies have also demonstrated statistical differences after 1-year of treatment.

To maximize the benefits of each treatment arm, sites will be selected, where the investigators (a) agree as to the specifics of the treatment approach and (b) do not deviate from the proposed protocol.

Participants should include men and women 21 plus years of age, non-pregnant, on no vitamins, minerals or medications. Non-smokers (including cigarettes, cigars, pipes, marijuana, vaping products, etc.), with investigator agreed to limits on alcohol consumption. They must agree not to become pregnant during the study.

Proposed Treatment Arms (n=40 per arm) of the study

1) Dietary and lifestyle.

A) Low Carbohydrate

B) Vegan

C) American Heart Association, or

D) another as of yet unidentified diet

2) Lipid Lowering medications.

A) Statin #1

B) Statin #2

C)PCSK9-Inhibitor

If further groups are added (e.g. a diet and drug combination, a diet and vitamin combination, etc.), this will become an independent "arm" of the study with an "n" of 40 participants.

Measured outcomes.

1) FMTVDM (Heart & Breast).

A) As this is an absolute quantifiable value, and cannot be altered, it will become the final deteminant of the physiologic impact of treatment upon inflammatory CAD.

B) Measurement will be at the beginning and end of the treatment period.

If participants drop out prior to completion of the 1-year of treatment, FMTVDM will be obtained at the time of drop out AND at the completion of 1-year-as this reflects real world outcomes.

2) Simultaneous Breast Cancer-Disease Imaging will be acquired per FMTVDM.

Measured Surrogate Blood Tests and Weight.

1) Measured at entry, 6-weeks, 3-mo Association nths, 6-months, 9-months - exit and 1-year from beginning of study.

Weight/ height/BMI	Total Cholesterol	LDL Cholesterol	HDL Cholesterol	Triglycerides
TC/HDL	Fasting Glucose	Hb A1C	C-reactive protein	Homocysteine
Fibrinogen	Lipoprotein (a)	CBC	Interleukin-6	CK-MM
Urine with ketones	ß-HCG	LFTs	Renal Function	Electrolytes

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The quantification of changes in both coronary artery disease and breast disease as measured by FMTVDM, will provide answers to the fundamental questions surrounding the impact of current dietary practices and medical regimens.

This knowledge will allow us to scientifically make recommendations to patients based upon measured outcomes and become the foundation for further research and understanding of individuals with heart disease and cancer

Acknowledgments

FMTVDM is issued to first author. First author, authored the "Inflammation and Heart Disease" and "Angina" Theories.

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