Cardiology Meets Personalized Lifestyle Medicine

Jeffrey S. Bland, PhD, FACN, FACB, Associate Editor

Abstract

This is a very exciting time for medicine. We are witnessing the creation of a new approach to the prevention and treatment of cardiovascular disease. It is an omnigenic approach—powered by systems biology—to assembling patient-specific information about how genes and lifestyle interact. When combined with other new technologies such as artificial intelligence and machine learning informatics, the result will be the development of a precision form of personalized lifestyle medicine applied to cardiovascular disease. This advancement will be a gateway for change throughout the entire segment of the health care system that is focused on the many complex chronic conditions affecting our world population.

Jeffrey S. Bland, ***PhD, FACN, FACB,*** *is the president and founder of the Personalized Lifestyle Medicine Institute in Seattle, Washington. He has been an internationally recognized leader in nutrition medicine for more than 25 years. Dr Bland is the cofounder of the Institute for Functional Medicine (IFM) and is chairman emeritus of IFM's Board of Directors. He is the author of the 2014 book* The Disease Delusion: Conquering the Causes of Chronic Illness for a Healthier, Longer, and Happier Life.

Many health problems that are rising in prevalence on a global scale are influenced by the interaction of a person's genes with their lifestyle, diet, social, and environmental factors.[1] Evidence has clearly demonstrated the importance of lifestyle factors in the development of cardiovascular diseases.[2] Population-based public health criteria for lifestyle interventions have had mixed success in reducing cardiovascular disease.[3] Personalized lifestyle medicine—a concept that takes into account an individual's unique response to lifestyle, diet, physical activity, stress, environmental exposures, and medications—may represent a more effective approach to the management of cardiovascular diseases.[4]

There is emerging evidence that implementation of individualized preventive health care could bend the curve of health care costs downward.[5] In the field of preventive cardiology, advancements would include integration of genomic, biometric, dietary, and lifestyle data to improve precision in both diagnosis and therapy. In an editorial titled "Introducing 'Genomics and Precision Health,'" which was published in the *Journal of the American Medical Association* in May 2017, William Feero, MD, PhD, asserted,

> This shift is inexorably moving medicine from an endeavor in which care for individual patients is driven by trial and error informed by studies designed to measure populations outcomes to one in which care is selected based on a deep understanding of health and disease attributes unique to each individual.[6]

To better appreciate how the concept of personalization is shaping the future of cardiology, we can look to a well-known and significant study from the recent past: the JUPITER trial. When the results of this study were published in 2008, a key finding was the demonstration that cardiovascular disease risk is linked to more factors than only elevated serum lipids. The JUPITER researchers found that people with low serum LDL cholesterol and elevated serum high sensitivity C-reactive protein (hs-CRP), which is an inflammatory biomarker, had a reduction in both hs-CRP and cardiovascular events when treated with the statin rosuvastatin.[7] This observation contributed to the increased recognition that cardiovascular disease results from the interaction of many variables, and some of these variables are controlled by numerous genes.[8] Cardiology is now moving toward new therapeutic frontiers based on an expanded understanding of the complexities of gene–environment interaction and its connection to health and disease.[9]

Polygenic is a word used to describe the interaction of multiple genes in a network for the regulation of physiological function.[10] According to Boyle et al, authors of an important 2017 publication called "An Expanded View of Complex Traits: From Polygenic to Omnigenic," this definition may be too limited; they write: "A central role of genetics is to understand the links between genetic variation and disease. … But for complex traits, association signals tend to be spread across most of the genome—including many genes without an obvious connection to disease."[11] These authors suggest these

gene regulatory networks are so interconnected to the etiology of complex diseases that a more appropriate characterization would be to refer to them as "omnigenic." The functional expression of omnigenic networks that are involved in the etiology of complex chronic diseases, such as cardiovascular disease, is influenced by signals derived from lifestyle, diet, and environmental exposures, including pharmaceutical drugs that are used for treatment.

How do we develop a unified conceptual approach to managing the complex interaction of gene networks and lifestyle variables? In the field of cardiac care, a systems biology approach to precision, personalized cardiology must be developed, and we are now starting to witness translation of this emerging scientific understanding. In a 2017 article I authored with my colleagues Deanna Minich, PhD, and Brent Eck, we asserted the following:

> Emerging groundbreaking research projects have given us a glimpse of how systems thinking and computational methods may lead to personalized health advice. It is important that all stakeholders work together to create the needed paradigm shift in healthcare before the rising epidemic of NCDs [noncommunicable diseases] overwhelm the society, the economy, and the dated health system.[12]

Genetic Regulation of Cardiovascular Function: An Omnigenic Network

Cardiogenomics is a relatively new term that is being used to describe the use of genomic profiling to assess risk for cardiovascular disease. An example of the advancement in this field is the recognition that polymorphisms of specific genes such as *LDLR*, *APOB*, and *PCSK9* have been found to be important in establishing individual risk to cardiovascular disease.[13] The functional impact of these genes is known to be influenced by lifestyle, dietary, and environmental factors. For example, *PCSK9* was discovered through genetic studies documenting familial hypercholesterolemia, and PCSK9 protein, which is secreted by the liver, binds to the low-density lipoprotein (LDL) receptor and targets it for degradation; this results in alteration in LDL signaling and apoB degradation that contributes to cardiovascular disease risk.[14] Additional research has demonstrated that variations in both the *PCSK9* and hydroxymethylglutaryl CoA Reductase (*HMGCR*) genes contribute to cardiovascular disease risk.[15] Multiple single nucleotide polymorphisms (SNPs) exist for these genes and impart varying degrees of individual risk to cardiovascular disease; it is becoming recognized that SNPs with a more mild influence on the disease phenotype are more significantly influenced by lifestyle, diet, and environmental factors.[16] Clinical intervention trials in patients with existing atherosclerotic cardiovascular disease who were administered a biological drug that blocks the binding of *PCSK9* with the LDL receptor when administered along with statins demonstrated significant reduction in LDL cholesterol—beyond results that high dose statins alone can produce—and also a reduction in risk to subsequent cardiovascular events.[17]

These trials support the important understanding that variations in the *PCSK9* gene can impact vascular biology and cardiovascular risk. A complete understanding of how *PCSK9* fits into the omnigenic cardiovascular risk story is yet to be developed, but this work clearly indicates that multiple genes influence cardiovascular function, and that single nucleotide variations in these genes can result in risk that is highly personalized to the individual. Recently, a controlled animal trial demonstrated that *PCSK9* activity can be inhibited by the alkaloid berberine.[18] Berberine is found in a variety of traditional medicinal plants historically used by a number of cultures, including barberry, tree turmeric, Oregon grape, goldenseal, yellowroot, and California poppy. The results of this study indicated that with pharmacological doses of berberine (200 mg/kg by gavage in mice), the hepatocyte nuclear factor 1α, which is known to be an obligate transactivator for *PCSK9* gene expression, was inhibited, thereby reducing the genetic expression of *PCSK9* and improving LDL metabolism. This is a very interesting study in that it suggests that there are multiple ways in which a risk gene can be modulated in its expression through different environmental exposures. It is often thought that to block the effects of a risk gene, you have to directly inhibit its expression, but in fact there are many upstream and downstream events linked to lifestyle, diet, and environmental factors that can modify the expression of the genetic risk factor. This demonstrates the concept that regulatory functions can be connected to the uniqueness of an individual's gene–environment status.

Within the field of cardiology, there has been a long-standing belief that elevated serum LDL cholesterol is always a risk factor for cardiovascular disease, but recent cardiogenomic studies have found that when serum LDL is elevated but apoB is low, cardiovascular risk is low.[19] This suggests that omnigenic regulation of cardiovascular signaling processes—as reflected in the level of apoB—is more important than a single surrogate marker for cardiovascular disease, such as serum LDL.[20] Infiltration of an apoB particle into the arterial wall is the first step in initiating the atherosclerotic process. We are now learning that this process is the result of many genetically controlled functions that relate to lipid metabolism, immune function, inflammation, coagulation factors, and vascular smooth muscle cell proliferation, all of which can be influenced by lifestyle, dietary, and environmental factors.

Another example of the regulatory influence of dietary factors on risk gene expression is the variability of cardiometabolic effects of omega-3 long-chain fatty acids, such as eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA).[21] In a recent study looking at the relationship between *PCSK9* genetic variants and risk to nonfatal

myocardial infarction (MI), it was found that increased consumption of omega-3 polyunsaturated fatty acids was associated with a lower risk in C-allele carriers of *PCSK9 rs11206510*, but not in the non-C allele carriers.[22] One important implication of this study is that in designing future clinical studies to evaluate the health benefits of omega-3 fatty acid supplementation, stratification for specific genetic responders versus nonresponders might be significant.

It is important to note that agents that have weaker interaction with genomic signaling processes (which is often the case with lifestyle, diet, and environmental factors) may have more sensitivity to genetic variants than do strong interacting agents that modify omnigenic regulatory processes (such as drugs). This fact once again points to the clinical implications resulting from the intersection of cardiology and personalized lifestyle medicine.

Genetic Risk, Adherence to a Healthy Lifestyle, and Cardiovascular Disease

Data compiled from the Nurses' Health Study between 1976 and 2016 demonstrated that women who ate a diet that was low in transfat, saturated fat, refined carbohydrates, and sugar-sweetened beverages and rich in fruits and vegetables, whole grains, and sources of unsaturated fats had a reduced risk to cardiovascular disease. This reduced risk was further amplified if their lifestyle incorporated regular physical activity, maintenance of a normal body mass index, moderate alcohol intake, and no smoking. Researchers who recently reviewed this data concluded the following: "Adherence to a combination of a healthy diet and lifestyle behaviors may prevent most vascular events."[23]

Recommendations that result from large-scale, longitudinal studies are important public health messages, but it has been reported that at least 1 of every 6 people who sustain a MI have no significant risk based on traditional cardiovascular risk factors, and those with the lowest risk factors have the highest death rate after an MI.[24] These data suggest that we have much yet to learn about the etiology of cardiovascular disease and its complex relationship to individual genetics lifestyle, diet, and environment.

A recent study that shines a particularly bright light on the future of precision cardiology framed within a personalized lifestyle medicine context is the work of Sekar Kathiresan, MD, at the Center for Human Genetic Research and Cardiology, Massachusetts General Hospital, and his collaborators at Massachusetts General Hospital, Brigham and Women's Hospital, the Broad Institute, Mount Sinai Medical Center, Lund University Department of Clinical Sciences, Perelman School of Medicine, and the University of Texas Health Sciences Center. This study, which was published in *The New England Journal of Medicine* in 2016, used a polygenic score of DNA sequence polymorphisms of 50 genes identified from Genome Wide Association (GWAS) studies in 3 prospective studies: 7814 participants in the Atherosclerosis Risk in Communities Study, 21 222 in the Women's Genome Health Study, and 22 389 in the Malmo Diet and Cancer Study, and also in 4260 participants in the cross-sectional BioImage Study for whom genotype and covariate data were available. All of the participants in these studies also had the quality of their lifestyle evaluated using a scoring system consisting of four factors: smoking status, physical activity index, body mass index, and diet.[25]

The objective of the study, which included data collected since 1987, was to determine whether there was a correlation between the polygenic cardiovascular risk score and the aggregate lifestyle score in cardiovascular disease outcome in people enrolled in the studies. The results were very instructive about the nature of the interaction between various risk genotypes and modifiable lifestyle factors. The relative risk of incident cardiovascular events was 91% higher in the participants in the highest genetic risk group than those of the lowest genetic risk, indicating that genetics does play a role in cardiovascular disease. This research team also found that a favorable lifestyle was associated with a substantially lower risk of cardiovascular events than an unfavorable lifestyle, regardless of the genetic risk category. Most important, among participants at the highest genetic risk, a favorable lifestyle was associated with a 46% lower risk of cardiovascular events than those with an unfavorable lifestyle. The authors suggest this finding translates to a reduction in the standardized 10-year incidence of coronary events from approximately 10% for an unfavorable lifestyle to 5% risk for a favorable lifestyle in the high genetic risk category. They also reported that in the BioImage Study participants, a favorable lifestyle score was associated with a significant reduction in coronary artery calcification in each genetic risk category.

The conclusions of this study were truly frameshifting in terms of increasing the understanding of the nature of the interaction of genes with lifestyle in the etiology cardiovascular disease. The findings were summarized with the following statement:

> Across four studies involving 55 685 participants, genetic and lifestyle factors were independently associated with susceptibility to coronary artery disease. Among participants at high genetic risk, a favorable lifestyle was associated with a nearly 50% lower relative risk of coronary artery disease than was an unfavorable lifestyle.

What were the 50 genes identified by GWAS to be associated with cardiovascular disease risk that were included in the study? The study authors provide supplemental materials for anyone wishing to dive more deeply into the parameters used for interpretation. My review and analysis indicate that 29 of the 50 could be

functionally linked to 5 different physiological processes. Here is the breakdown I created:

Inflammation-related Genes

- *MRAS*
- *SCL22A4*
- *TRB1B1*
- *ADAMT*
- *BCAP29*
- *GGCX*

Lipid Metabolism-related Genes

- *LIPA*
- *SH2B3*
- *HHIPL1*
- *UBE2Z*
- *SMG6*

Vascular Endothelial Biology-related Genes

- *SORT1*
- *MIA3*
- *EDNRA*
- *GUCY1A3*
- *PDGFD*
- *FLT1*
- *COL4A1*
- *KCNK5*

Vascular Smooth Muscle Proliferation-related Genes

- *RASD1*
- *CYP17A1*
- *ZC3HC1*
- *TCF21*
- *ANKS1A*
- *WOR12*

Coagulation-related Genes

- *ZEB2*
- *PLG*
- *ABO*
- *DHACTR1*

It is my belief that by grouping the patients' individual risk genes into 5 functional assessment areas, a model for personalized recommendations with regard to lifestyle, diet, environment, and medical therapy could be developed based on the identified function related to the specific gene network. Recent studies linking each of these 5 functional areas to specific lifestyle factors, diet, nutrient, botanical medicine, physical activity, stress, sleep, environment exposures, and medication have been published. Consolidation of this information could serve as the framework for a new personalized lifestyle medicine approach to precision preventive cardiology. By using information contained within a whole genome sequence and pairing it with information about the impact of specific SNPs on function, a clinician would have new tools for applying a systems biology approach to clinical decision making.

Summary

This is a very exciting time for medicine. We are witnessing the creation of a new approach to the prevention and treatment of cardiovascular disease. It is an omnigenic approach—powered by systems biology—to assembling patient-specific information about how genes and lifestyle interact. When combined with other new technologies such as artificial intelligence and machine learning informatics, the result will be the development of a precision form of personalized lifestyle medicine applied to cardiovascular disease. This advancement will be a gateway for change throughout the entire segment of the health care system that is focused on the many complex chronic conditions affecting our world population.

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