

THE IMPORTANCE OF FUNCTIONAL BIOMARKERS IN THE MANAGEMENT OF CHRONIC ILLNESS

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By the time a disease is diagnosed, significant pathology already exists. Medicine has historically focused its evolution on the refinement of the diagnosis of the specific pathology with which the patient presents. The ultimate objective of this medical paradigm is to establish a descriptive term for the pathology that we call a disease. The driving force in medicine is in establishing the differential diagnosis that then leads to an intervention or therapy acknowledged by the standard of practice to be specific to that disease. This medical model is based philosophically upon the assumption that each disease state is independent from all other diseases. This approach gives rise to the development of a medical paradigm that is dominated by subspecialties that compartmentalize diseases into different organ systems. The histopathology-based medical system has served us well for the past 80 years, during which the dominant focus of medicine has been on acute disease. This model was supported by the tremendous success in the early 20th century that resulted from breakthroughs in the understanding of the etiology of acute infectious diseases of bacterial origin. The development of antibiotic medications that were specific for the bacterial origin of disease resulted in the birth of the modern pharmaceutical industry and the use of specific medications to treat specific bacterial diseases.

This medical model was successful in managing the most significant diseases of that era. The *sine qua non* of this approach to medicine was establishing the diagnosis and its association with a specific disease. From the differential diagnosis a preferred treatment emerged. The establishment of the differential diagnosis is based on a detailed physical examination and history along with clinical laboratory tests that define the nature of the pathology. The clinical laboratory tests that are employed in leading to the establishment of the differential diagnosis are selected to reflect organ-specific pathology. In the 1950s the multi-analyte clinical chemistry screening panel was developed. This battery of serological tests was selected to reflect liver pathology (although they were termed "liver function tests," which resulted in ambiguity in their application in diagnostic medicine), diabetes, kidney disease, heart disease, and endocrine diseases. For the past 60 years, clinical chemistry has

focused its attention on refining the tests that are employed in the diagnosis of disease under the assumption that improvement in diagnosis will result in better treatment outcomes.¹

Today, however, the major health problems are chronic in nature rather than associated with acute disease pathology.² Chronic diseases such as cardiometabolic syndrome, insulin resistance and type 2 diabetes, preclinical autoimmune diseases, functional gastrointestinal dysfunctions such as irritable bowel syndrome, and chronic disorders of the nervous and musculoskeletal systems do not initially present with specific end-organ pathologies. As such, these disorders do not fit well into the dominant medical paradigm of the differential diagnosis. That said, the physician of the future who is best equipped to deal with these complex issues related to chronic illnesses might be termed the "specialty generalist" who is trained to look for patterns or networks of association among dysfunctions of different organ systems at the mechanistic level rather than focus specifically on defining the diagnosis.³

THE "NETWORK" APPROACH TO CHRONIC DISEASE MANAGEMENT

As was recently stated in *The New England Journal of Medicine*,

the network concept reveals a number of surprising connections among diseases, forcing us to rethink the way in which we classify and separate them. . . . Indeed, the fundamental question of where function lies within a cell is slowly shifting from a single-minded focus on genes to the understanding that behind each cellular function there is a discernible network module consisting of genes, transcription factors, RNAs, enzymes, and metabolites. This understanding forces us to view diseases as the breakdown of selected functional modules rather than as single or small groups of genes. Given the many components of such functional modules, there are different paths to disease-inducing systems failure; this explains why often many genes are linked to the same disease phenotype.^{3(p105)}

The theme of the changing landscape of medicine was eloquently discussed by Elias Zerhouni, MD, director of the National Institutes of Health (NIH) in his March 5, 2008, presentation to the House Subcommittee on Labor-Health and Human Services-Education. The presentation, titled, "A New Strategic Vision for Medicine," appears on the NIH website and is excerpted here.

Given the dramatic shift from acute to chronic disease, the strategies for preventing and treating diseases are beginning to shift. Today, we intervene late, when the patient exhibits symptoms of disease. Our research is changing this approach, so that we may intervene much earlier in the natural cycle of diseases, years before they strike their victims. We must now develop a much more preemptive approach that manages disease over its entire life cycle, from identifying an individual's susceptibility to a disease, to prevention, early diagnosis, reduction of complications, and smarter therapies.⁴

Patients with chronic illnesses present with a myriad of non-specific signs and symptoms that cross many diagnostic categories. As a result of the complexity of their situation, they do not fit well into the traditional diagnostic model. Early presenting signs and symptoms include fatigue, listlessness, muscle and joint pain, dyspepsia, dyslipidemias, elevated blood pressure, obesity, depression and mood swings, weakness, allergies, and frequent infections. These chronic signs and symptoms are characteristic of what is known as "functional somatic syndromes." Functional somatic syndromes include such common chronic conditions as irritable bowel syndrome, chronic fatigue syndrome, fibromyalgia syndrome, chronic immune system problems, dyslipidemias, obesity, and esophageal reflux syndrome, to name a few. Many of these chronic conditions represent the early stages of dysfunction that may later progress to a pathological state characteristic of a specific disease.⁵

THE DEVELOPMENT OF FUNCTIONAL BIOMARKERS

To assess the early stages of dysfunction associated with the emergence of chronic disease, a different assessment strategy must be implemented. The clinical laboratory tests that are used to define pathology are not well suited for the assessment of early-stage dysfunction, nor are the pharmaceuticals used to treat the pathology of disease best suited for the long-term management of chronic illnesses. A different system of assessment and intervention is required for improvement in both the prevention and treatment of chronic illness. This requires the development of functional biomarkers for defining the physiological trajectory of dysfunction that results in chronic disease. The first well accepted analyte to fulfill this criterion and to be included in the standard multi-analyte screening panel was serum cholesterol. The elevation of serum cholesterol is not associated with any specific tissue pathology but rather is a surrogate biomarker for defining the risk for chronic cardiovascular diseases. The inclusion of serum cholesterol in the standard serological panel signaled a new era in assessment moving from diagnosis to prognosis.⁶ It is now recognized that an assessment panel that is composed of functional biomarkers for chronic illnesses should include analysis of genetic and epigenetic expression, proteomic analysis, and metabolomic assessment as well as other indicators of functional status. These tests are represented in traditional biochemistry, molecular biology, and immunology as well as methods of radiology, kinesiology, and diagnostic imaging. Examples of the clinical chemistry tests that are associated with specific dysfunctions are shown in Table 1.

TABLE 1 Representative Functional Clinical Chemistry Biomarkers of Chronic Illness*

Biomarker	Type of Test	Functional Significance
Adiponectin	Plasma	Adipocyte physiology and insulin
Apo B:Apo A1 ratio	Plasma	Cardiovascular and insulin
Asymmetrical dimethyl arginine	Serum	Insulin sensitivity
Antigliadin antibody	Plasma and fecal	Gluten sensitivity
Calprotectin	Fecal and plasma	Gastrointestinal inflammation
Arachidonic: EPA ratio	Red cell	Fatty acid status
Ferritin	Serum	Oxidative stress
hs CRP	Plasma	Cardiovascular and insulin
Homocysteine	Serum	Cardiovascular and neurological
IL-6	Plasma	Cardiovascular and immune
Isoprostanes	Serum	Oxidative stress
Ghrelin	Plasma	Insulin sensitivity
Gamma glutamyl transaminase	Plasma	Liver and toxic burden, insulin sensitivity
Plasminogen activator inhibitor 1	Plasma	Insulin sensitivity
Prostate specific antigen	Plasma	Prostate function
Osteocalcin/C-telopeptide	Plasma	Bone remodeling
N-telopeptide	Urine	Bone loss
Organic acids	Urine	Metabolism
Amino acids	Urine	Metabolism
Predictive autoantibodies		
ANA	Plasma	Autoimmune
Anti-CCP	Plasma	Autoimmune
Anti-TPO	Plasma	Autoimmune
Anti-endomysial	Plasma	Autoimmune
Uric acid	Serum	Oxidative stress, insulin
8-hydroxy-d guanosine deoxyguanosine	Serum	Oxidative stress, neurology
2:16 hydroxyestrogen ratio	Serum or urine	Hormone metabolism
Glutathione:disulfide ratio	Whole blood	Oxidative stress
Neopterin	Serum	Immune, inflammatory
Phospholipase A-2	Plasma	Cardiovascular risk

*Apo indicates apolipoprotein; EPA, eicosapentaenoic acid; hs CRP, high sensitivity C-reactive protein; IL-6, interleukin-6; ANA, autoantibodies to nuclear antigens; anti-CCP, anti-cyclic citrullinated peptide; anti-TPO, anti-thyroid peroxidase.

Beyond the evaluation of specific analytes that are related to physiological status at rest there is the need to assess functional reserve of various organ systems that relate to the patient's ability to maintain homeostasis during times of physiological stress. This has resulted in the development of specific challenge or stress tests to examine "physiological reserve." These functional biomarkers include information from physiological stress tests such as the exercise electrocardiogram and the oral glucose/insulin tolerance tests that evaluate physiological organ reserve under the stress of exercise or an oral glucose challenge, respectively. Compromised organ reserve represents one of the principle causes of declining function associated with chronic illness, and it can be assessed when an individual is placed under a specific controlled physiological stress.⁷ Examples of physiological challenge biomarker tests are as shown in Table 2.

TABLE 2 Representative Functional Biomarker Challenge Tests*

Test	Clinical Implication
Oral glucose and insulin tolerance	Insulin sensitivity
Oral fatty acid tolerance	Insulin sensitivity
Exercise electrocardiogram	Cardiovascular reserve
Oral methionine challenge	Folate/homocysteine metabolism
Oral acetaminophen challenge	Hepatic detoxification function
Oral lactulose/mannitol challenge	Gastrointestinal mucosal integrity
Oral vitamin B ₆ challenge	Pyridoxine functional status
Oral thiamine EGOT challenge	Thiamine functional status
DMPS challenge	Heavy metal toxicity
Flow-mediated dilation	Vascular endothelial function

*EGOT indicates erythrocyte glutamic oxalacetic transaminase; DMPS, sodium 2,3-dimercapto-1-propane sulfonate.

The underlying strategy of the use of functional biomarker evaluation is to employ a panel of tests that enables understanding of the patient's unique physiological pattern. Such a panel includes not only biochemical markers and the results of specific challenge tests but also indicators of physiological function as measured through new noninvasive technologies, as described in Table 3. The integration of information from the patient's physical and history along with functional biomarkers results in a pattern-recognition approach to the development of a personalized intervention program.⁸ No one test can provide a definitive evaluation of a patient's "physiological map," but an appropriate battery of functional biomarkers can provide the data set necessary to better understand the unique dysfunctional pattern contributing to a patient's chronic illness. The development of increased computational capability in the form of the microcomputer coupled with bioinformatics software has allowed for large data sets from multi-analyte profiles made up of functional biomarkers to be analyzed routinely. The ability to recognize patterns of altered physiological function provides a significantly different approach to laboratory assessment than the traditional model of the clinical laboratory focused on pathological assess-

TABLE 3 Representative Functional Physiological Biomarker Tests

Test	Clinical Implication
Mammography	Breast cancer risk
Colonoscopy	Colon cancer risk
Carotid intimal-medial thickness	Vascular endothelial function
Coronary artery calcium score	Vascular disease risk
Bioimpedance analysis	Body composition
Functional magnetic resonance	Bioenergetics, intramyocellular lipotoxicity
Gnomic stability	Functional nutritional status
Heart rate variability	Cardiovascular stress and insulin function

ment and diagnosis, looking at each test result as an independent diagnostic marker. This concept results in the development of a systems biology approach to medicine in which patterns of altered functional status are evaluated and then analyzed as a network pointing toward the mechanistic origin of the signs and symptoms associated with the dysfunction.⁹

CLINICAL APPLICATION OF THE FUNCTIONAL BIOMARKER CONCEPT

The 26th Annual JP Morgan Healthcare Conference held in January 2008 focused much of its attention on the development of new methods applied to the evolution of personalized medicine. The concept of personalized medicine emerged in the 1990s, when new databases were being developed by such companies as Incyte Pharmaceuticals (Wilmington, Delaware) and Human Genome Sciences (Rockville, Maryland) that made differences in the genome among individuals due to the presence of single nucleotide polymorphisms (SNPs) well recognized. Up to this time the development of drugs that achieved blockbuster status was built upon the concept that all people would respond to the agent similarly. When one considers the therapeutic index for a drug that is now recognized to have significant variability in the individual manner with which it is used, metabolized, and excreted, it has become clear that only 50% of patients actually receive the most benefit with the fewest side effects for a particular disease-focused medication at a specific dose. The interest at the JP Morgan Conference was in new diagnostic/prognostic tests that would allow for early intervention and personalization of therapy. Many new biomarkers for chronic illness and later disease were described at the conference, including test kits such as those offered by Myriad Genetics (Salt Lake City Utah), to screen for the presence of oncogenes such as BRCA1 to determine a woman's predisposition to breast cancer. From this analysis a preventive intervention strategy for breast cancer can be developed.¹⁰ This is just the tip of the iceberg relative to the development of new biomarker technologies that will move the clinical laboratory from a primary focus on diagnosis to that of balance with prognosis and the support of the development of personalized medicine.

Most analysts in the laboratory sector see this as the next major growth opportunity for the clinical laboratory business.

The application of this concept extends far beyond cancer prevention to the prevention of virtually all chronic diseases, including cardiovascular disease, stroke, type 2 diabetes, and autoimmune diseases. All of these conditions share common features of alterations in systems biology that can be analyzed through the use of appropriate validated biomarkers. Robert Eckel, MD, in his presidential address at the 2005 American Heart Association Scientific Session, commented that preventive cardiology associated with lifestyle and pharmacological therapy was dependent upon the development of better biomarkers for establishing personalized risk for cardiovascular disease and providing objective markers for following the success of early intervention. The traditional Framingham Risk Factors for coronary heart disease are of great value, but as all physicians learn in practice, there are patients who suffer a cardiovascular event who have none of the traditional Framingham Risk Factors.¹¹ This has resulted in the development of new biomarkers that extend beyond the traditional risk factors, such as homocysteine, high sensitivity C-reactive protein, and phospholipase A-2 to define individual risk and to follow the success of early intervention. The US Food and Drug Administration and insurance providers are seeking new methods for assessing targeted biomarkers for the early assessment of risk. Gordon Mills, MD, chairman of the Department of Systems Biology at the M.D. Anderson Cancer Center in Houston, recently said, "The key right now is the concurrent development of biomarkers and therapeutics." John Sninsky, vice president of discovery research at Celera (Rockville, Maryland) has said that with the development of new predictive biomarkers a shift is emerging in the approach to complex chronic conditions such as cardiovascular disease, Alzheimer's disease, rheumatoid arthritis, and cancer. "These are catch-all diseases that all look the same," he said in a presentation in January 2008, "but when you scratch below the surface, you begin to understand that the underlying physiology of similar phenotypes can be fundamentally different." This observation makes the concept of disease diagnosis much less important and raises the importance of understanding the individual alterations in function of the specific patient that result in the presenting signs of illness.

The need for the development of validated functional biomarkers presently represents the limiting factor in the evolution of this approach to the early recognition of dysfunction and management of chronic illness.¹² The development of successful patient-individualized intervention programs to meet the needs of patients with various chronic illnesses is dependent upon the evolution of the field of functional biomarkers. In the absence of aligning the clinical laboratory with these objectives, medicine will have limited success in managing the rise in prevalence of chronic diseases that is occurring as a result of the aging baby boomer generation and the increase in chronic dysfunctions in children and adolescents, such as autistic spectrum disorders and atopic and attention disorders.^{13,14} The medical laboratories that provide panels of validated functional biomarkers and the

analytical ability to interpret physiological patterns that allow for improved patient outcomes at earlier stages of dysfunction, before the onset of overt pathology, will emerge as leading laboratory businesses in the development of 21st-century medicine.

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