Defining *Function* in the Functional Medicine Model

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Abstract

In the functional medicine model, the word *function* is aligned with the evolving understanding that disease is an endpoint and function is a process. Function can move both forward and backward. The vector of change in function through time is, in part, determined by the unique interaction of an individual's genome with their environment, diet, and lifestyle. The functional medicine model for health care is concerned less with what we call the *dysfunction* or *disease*, and more about the dynamic processes that resulted in the person's dysfunction. The previous concept of functional somatic syndromes as psychosomatic in origin has now been replaced with a new concept of function that is rooted in the emerging 21st-century understanding of systems network-enabled biology.

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In 1991, the Institute for Functional Medicine was founded with 7 defining characteristics of functional medicine. These included[1]:

1. Patient centered versus disease centered.
2. Systems biology approach: web-like interconnections of physiological factors.
3. Dynamic balance of gene-environment interactions.
4. Personalized based on biochemical individuality.
5. Promotion of organ reserve and sustained health span.
6. Health as a positive vitality—not merely the absence of disease.
7. Function versus pathology focused.

During the last 2 decades, interest in functional medicine has grown dramatically. A recent Google search of the various terms describing different medical concepts produced the following data:

1. *Functional medicine*: 507 000 results.
2. *Integrative medicine*: 704 000 results.
3. *Holistic medicine*: 483 000 results.
4. *Complementary and alternative medicine* (*CAM*): 490 000 results.

Starting with publications in the mid-1980s, use of the term *functional* in medicine referred to what had been termed *functional somatic syndromes*.[2] Functional somatic syndromes are defined as related syndromes that are characterized more by complex symptoms than by disease-specific abnormalities or histopathology.[3] Conditions that fall under the functional somatic syndrome terminology have included[4]:

1. Chronic fatigue syndrome.
2. Fibromyalgia.
3. Multiple chemical sensitivity syndrome.
4. Irritable bowel syndrome.
5. Premenstrual syndrome.
6. Polycystic ovary syndrome.
7. Chronic pelvic pain syndrome.
8. Nonulcer dyspepsia.
9. Chronic pain of unknown origin.
10. Depression.
11. Minimal cognitive impairment.
12. Interstitial cystitis/painful bladder syndrome.
13. Restless leg syndrome.
14. Autistic spectrum disorder.
15. Autoimmune syndrome.

In an article published in the *Archives of General Psychiatry* in 1985, functional somatic syndromes were suggested to be associated with hypochondriasis.[5] In fact, much of the literature that has been written on the topic of functional somatic syndromes has historically been associated with the field of psychiatry, as well as with the representation that these syndromes can be "lumped" together as issues derived from psychological factors. This "lumping" assumption about the origin of these conditions has resulted in treatment options that are primarily behavioral and cognitive in nature.

For the past 20 years, however, the assumption of "lumping" all the functional somatic syndromes under the mechanistic assumption of being psychosomatic and related to hypochondriasis in origin has been challenged by those who argue these syndromes should be split into different subgroups based on their specific etiologies at the cellular/tissue level. This has resulted in a very robust debate between the "lumpers" and "splitters" as to how best to approach the management of specific conditions that fall under the term *functional somatic syndromes*.[6,7]

This debate and the resulting evolution of the medical approach to these conditions started to shift in the early 1990s toward an understanding that each of these conditions was unique in its origin. This shift in thinking was driven by the advances made in molecular and cellular understanding of the etiology of these syndromes and the resultant change in the patient's functional status. As such, each patient needs to be addressed clinically by a personalized treatment that was derived from an understanding of the etiology of their functional impairment.

This change in thinking was a result of new diagnostic tools such as radioimmune assay, computer-assisted tomography, nuclear magnetic resonance spectroscopy, positron emission tomography, and single photon emission computed tomography scans that allowed for functional characteristics of specific tissues/organs to be evaluated in real time. These new technologies supported the development and growth of functional neurology, functional immunology, functional cardiology, functional oncology, functional radiology, and functional genomics. All of these fields have seen their importance grow exponentially since the early 1990s. From 1990 to 2016, more than 31 000 papers were published in the National Library of Medicine–cited medical literature discussing aspects of functional neurology; 11 000 in functional cardiology; 76 000 in functional immunology; 89 000 in functional oncology; and 42 000 in functional radiology.

From a historical context, the definition of *functional somatic syndromes* is changing in response to this new definition of *function* at the organ system, organ, tissue, cellular, and subcellular levels. This transition in the definition of *function* is driven by the influence of the introduction of newer assessment tools for evaluating functional changes at different organizational levels. The use of noninvasive testing methods and many new biomarkers of physiological function have all combined to provide a much greater understanding of the functional status of the individual. A demonstration of the emerging importance in the changing context in health care of the definition of *function* was demonstrated in 1994 with the approval by the US Congress of the Dietary Supplement and Health Education Act, which was passed to regulate claims for dietary supplement products. This act defined allowable label claims for dietary supplements to be based on structure-function criteria. Under this act, structure/function claims may describe the role of a nutrient or dietary ingredient intended to affect the normal structure or function of the human body—for example, "Calcium builds strong bones." In addition, they may characterize the means by which a nutrient or dietary ingredient acts to maintain such structure or function—for example, "Fiber maintains bowel regularity," or "Antioxidants maintain cell integrity." The concept of structure and function being related is a perspective that can be applied at many levels from that of the whole organism to that of the subcellular effect of a substance on the function of specific molecular networks.

It was the recognition in 1991 that the definition of *functional* in medicine was changing from a singular focus on psychosomatic to an integrated focus including the whole biological system that led to the founding of the Institute for Functional Medicine. It was believed by the founding members of the Institute for Functional Medicine that the information that would emerge from completion of the Human Genome Project would revolutionize medicine by creating a framework for the understanding that the origin of disease in the individual resulted from the interaction of their unique genome/epigenome with their environment, diet, and lifestyle. It was forecast that during the next few decades this new genomic information coupled with new technologies that allow for the evaluation of the physiological, cognitive, emotional, and physical function of the individual would redefine the use of the word *functional* in medicine and open a new era of precision, personalized, participatory, and eventually predictive health care. It was the understanding of this revised definition of *function* in medicine that resulted in the founding of the Institute for Functional Medicine. The functional medicine model was based on the recognition of the dynamic interplay between the individual's genetic template and his or her environment that results in an outcome manifested in their functional capabilities. It was believed that the future of the medical diagnostics would not be based solely on the diagnosis of disease, but rather in detecting early changes in function that would allow successful intervention with personalized therapies that used tools with more favorable risk profiles than the therapeutics needed to treat more advanced stages of disease.

The early 1990s were also the time when many of the now common syndromes started to gain better understanding and prominence in medicine. Syndromes that grew to be seen as major medical issues during this time included the following:

1. Metabolic syndrome and obesity-related health issues.
2. Fibromyalgia syndrome.
3. Chronic fatigue syndrome.
4. Polycystic ovary syndrome.
5. Obstructive sleep apnea syndrome.
6. Irritable bowel syndrome.

7. Esophageal reflux disorder syndrome.
8. Erectile dysfunction syndrome.
9. Attention deficit disorder syndrome.
10. Depression syndrome.
11. Chronic pain syndrome.
12. Cognitive dysfunction syndrome.
13. Autistic spectrum disorder syndrome.

Since the early 1990s, these syndromes have become recognized as some of the most common disorders for which people seek medical attention. We have witnessed a transition in medicine from the singular focus on disease to that of the age of the complex chronic syndrome. Many of the most financially successful pharmaceuticals approved during the past 20 years are for syndromes rather than diseases including equine hormones for menopausal syndrome, statins for elevated cholesterol syndrome, sildenafil for erectile dysfunction syndrome, pregabalin for fibromyalgia syndrome, and celecoxib for arthralgia syndrome.

The emergence of the following triad has fueled the interest in functional medicine that is rooted in this newer definition of *function*: new diagnostic/prognostic tools that allow assessment of function, genomic understanding of individual differences in response to the environment and lifestyle, and the increasing understanding of the cellular etiology of complex chronic disease. Functional genomics is the application of omics technologies to the discovery of how biological systems are regulated. Since 2000, there have been more than 32 000 articles published in the peer-reviewed medical literature on this topic. This work has allowed for an understanding of what previously were "lumped" under the term *functional somatic syndromes* to now be "split" into conditions with different origins that require precision, personalized care for their successful management.

In 2013, an important study was published with the title, "Functional Somatic Syndromes: One or Many? An Answer by Cluster Analysis."[8] The conclusions from this detailed analysis in 394 patients with functional somatic syndrome symptoms, which were evaluated on the basis of 47 somatic symptoms, was that the clusters could not be defined by increasing symptom scores alone. This argues for the "splitters" claim that each of these conditions is unique in its etiology and requires personalized intervention.

In 2015, Williams and Moore[9] from the Perelman School of Medicine at the University of Pennsylvania authored the paper "Lumping versus Splitting: The Need for Biological Data Mining in Precision Medicine."They point out that the mining of data from the recent spectrum of biological and biomedical research is revealing broad implications for medicine as it moves toward a more precision, personalized form of delivery. Until recently, it was not possible to accurately quantitate changes in an individual's functional status before the onset of recognizable disease. The ability we now have to detect early changes in function is a disruptive influence on the health care system that creates the context for delivering a more precise form of personalized medicine. New functional assessment tools are being developed in every specialty area of medicine by using the new biomedical information that is becoming available in this postgenomics era. These tools will allow for the assessment of complex chronic health problems that were in the past considered as functional somatic syndromes to be understood at the systems biology level. This approach will allow the patient to be managed by application of the functional medicine operating system at the systems biology level that treats the cause and not just the symptoms of their condition and moves closer to achieving a predictive medical care system.

Schadt and Björkegren[10] described the development of a systems biology approach to health care as the foundation of the new biology that will provide medical solutions to complex health problems that have been resistant to the 20th-century approach to disease treatment. They pointed out that health and disease patterns are governed by the complex network of interaction among genes, environment, diet, lifestyle, and social environment. Moreover, they argued that these interactions determine both individual health and in the collective societal health. All of this new biology and network-enabled wisdom about health and disease is driven by a much more precise understanding of function and what it means at every level of organization.

In retrospect, it is remarkable how the concepts that became the founding principles for the definition of *functional medicine* and the Institute for Functional Medicine in 1991 track with the development of biomedicine during the past 25 years. In the past 2 decades, we have witnessed medicine responding to the remarkable discoveries that have been made in understanding of the effect that genes and environment have on health and disease. The health care industry is showing changes in response to the transformative effects of this new biology that is focused more on defining individual function/dysfunction and less on the lumping of individuals into specific disease categories.

Functional medicine has evolved to be a clinical operating system for the application of a patient-centered, systems biology approach to health care. Its focus is on understanding an individual's physiological, cognitive, emotional, and physical function, as well as on the design and implementation of a therapeutic program that is personalized to the functional needs of the patient. The functional assessment can be applied at many organizational levels derived from a systems network biology perspective ranging from the patient's social and spiritual functions to organ system, organ, tissue, cellular, or subcellular functional levels. Functional medicine practitioners are trained to think in terms of function

derived from biological and social systems and network biology. They become skilled in looking at the patient simultaneously from the frame of reference of both a telescope and microscope—the macroscopic and the microscopic holograph.

In the functional medicine model, the word *function* is aligned with the evolving understanding that disease is an endpoint and function is a process. Function can move both forward and backward. The vector of change in function through time is, in part, determined by the unique interaction of an individual's genome with their environment, diet, and lifestyle. The functional medicine model for health care is concerned less with what we call the dysfunction or disease, and more about the dynamic processes that resulted in the person's dysfunction. The previous concept of functional somatic syndromes as psychosomatic in origin has now been replaced with a new concept of function that is rooted in the emerging 21st-century understanding of systems network-enabled biology.

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