Functional Medicine *Past, Present, and Future*

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Abstract

Embedded within the Functional Medicine model is the potential for reversibility of altered function. This perspective is inherently different from the Mendelian concept of genetics, which is grounded in the construct of dominate and recessive genetic characteristics. Mendel's work was obviously groundbreaking, but it has also contributed to a deterministic mindset about disease. Many people—even today—believe that health and disease are locked into the genes of every individual. Modern genomic research continues to reveal that the concept of genetic determinism can be (and should be) challenged. The functional interaction of our lifestyle, diet, environment, behavior, and social structure with our genome and epigenome greatly determines our health outcomes. It has been discovered that our aging epigenome can even be rejuvenated. The epigenomic structure is also a powerful predictor of disease outcome and life expectancy. As our understanding of genetic and epigenetic expression patterns grows, the implications for personalized Functional Medicine intervention programs are truly revolutionary.

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In 1990, a small group of clinicians, researchers, and health educators came together in Victoria, British Columbia, Canada. Not only did they hope to explore what an ideal healthcare system focused on the prevention and management of chronic disease might look like, they also wanted to imagine innovative ways of merging historical models of medical care with the advancing science of systems biology. They started by focusing on the fact that every patient had their own unique origin story, yet a dominant common theme would often emerge: the earliest signs of disease were associated with altered function at the physical, metabolic, cognitive, and behavioral levels.

Conceptually, alterations in function can be applied to many things beyond disease. Disturbed function can have planetary, societal, and community implications, just as it can affect health in organs and tissues, as well as performance in cellular, biochemical, and energetic processes. An ecosystem of thinking emerged among the participants at that small meeting in the Pacific Northwest, and in 1991 they established The Institute for Functional Medicine to develop a clinical model that could apply this concept of function to patient-centered health care.[1]

At the time, we obviously thought that we had developed a wholly unique and novel concept. Imagine our (delighted) surprise when—nearly two decades later—we found out that an esteemed 19th century physician named Dr. Willoughby Wade had published a clinical lecture in *Lancet* in 1871 in which asked his equally esteemed colleagues of that era to consider the concept of Functional Medicine using the language of that era.[2] He stated: "The advances of medical science have tended to produce an estrangement between scientific cultivators and the simple practice of medicine… The ideas that blend science and art may be summed up in the term 'Functional Medicine' … Because every symptom arises from the imperfect discharge of some function, hence it requires a slightly higher order of thought from that which is commonly in vogue in medicine." What's so remarkable is that the conceptual framework Dr. Wade conceived for Functional Medicine 150 years ago is as viable today as it was then. Across the centuries, the objective of Functional Medicine has steadfastly been linked to finding the root cause of alterations in physical, metabolic, cognitive, and behavioral function that later are codified as disease states. This model provides a platform from which many concerns—including planetary health—can be logically connected to personal health through a systems biological perspective.[3]

There are four guiding principles that are foundational to the development of the Functional Medicine model:[4]

- Form and function are interconnected and interdependent.
- All aspects of life can be viewed through the lens of form and function.

- We live in a hologram of interconnectedness through homeodynamic relationships (not homeostatic).
- The concept of functional systems is operative at every organizational level.

Functional Medicine, therefore, is a way of thinking about how to approach the complex diathesis of a patient. It is not a series of specific treatment protocols, but rather a way of applying a systems biology heuristic to "root cause"-focused health care.[5]

The contemporary distinguishing characteristics of Functional Medicine are embodied in the following seven core concepts:

1. The gene-environment interaction is a central feature in establishing an individual's function.
2. Function of the individual is regulated by interaction among organ systems.
3. Signals from the diet, environment, lifestyle, and social experiences are translated into clinical phenotypes.
4. Assessment of the patient is focused on an understanding of their antecedents, triggers, and mediators, and their relationship to their signs and symptoms.
5. Managing systems dysfunction requires multimodal treatment programs.
6. Each patient is unique and therefore represents an N-of-1 experience.
7. The individual's health issues must be contextualized through the perspectives of time and relationships.

In the clinical assessment and management of patients, these core concepts translate to a Functional Medicine model that focuses on the evaluation of six core physiological processes:

1. Assimilation (digestion, absorption, microbiota)
2. Defense and Repair (immune, inflammation, cellular renewal)
3. Bioenergetics (mitochondrial function, cellular energy transport, tissue specific energetics)
4. Transport (cardiovascular, hematological, respiratory and lymphatic functions)
5. Communications (endocrine, neurotransmitters, signal transduction processes)
6. Structural Integrity (subcellular membrane barriers to musculoskeletal function)

Evidence-Based Functional Medicine

Based on this formalism of the Functional Medicine model, an evidence-based approach has been developed and applied to the management of patients with complex chronic illness and the evaluation of outcomes.[6] For a patient-specific modality like Functional Medicine, the best tool for determining outcomes in a clinical study is the validated Patient Reported Outcome Measurement Information System (PROMIS).[7]

Using PROMIS, a number of studies have been performed and published that demonstrate the clinical value of the Functional Medicine model versus a standard-of-care approach. This includes a study done at the Cleveland Clinic Center for Functional Medicine comparing outcomes and quality of life variables in patients presenting with chronic symptoms.[8] The results indicated that both treatment approaches were associated with improvements, but those patients treated at the Center for Functional Medicine had improved outcomes for a number of the PROMIS quality of life indicators that were statistically significant.

Another recent study evaluated the impact of a Functional Medicine approach to the management of inflammatory arthritis. Patients with inflammatory arthritis were treated either with standard-of-care or the Functional Medicine approach. PROMIS scores for physical health, mental health, and pain were collected at baseline and after 12 weeks of treatment. Multivariable statistical modeling was used to identify the impact of intervention on the patient-reported outcomes. This analysis revealed that patients in the Functional Medicine treatment group had statistically improved pain and physical health scores compared to those in the standard-of-care cohort.[9]

In a study of patients with Hashimoto's thyroiditis, it was found that the Functional Medicine Autoimmune Protocol resulted in directional improvement in subjective symptoms based upon PROMIS outcome variables, and a decrease in high sensitivity C-reactive protein and white blood cell count was also noted.[10] Lastly, a recent report on the outcome and costs of managing patients with complex chronic conditions was the first to provide a detailed description of a Functional Medicine-based care model in a shared medical appointment (SMA) setting. The results suggest that the SMA Functional Medicine program was both cost effective and physically beneficial to patients.[11]

Findings like this were further reinforced in a personalized lifestyle intervention and functional evaluation health outcomes survey (LIFEHOUSE) conducted in a large corporate health setting. This trial was very unique in that it used a novel, N-of-1, nested tent-umbrella-bucket design that allowed for both personalization of the program and cohort stratification of the data. There were 369 participants, and analysis of the comprehensive data collected demonstrated unique relationships between functional health problems and specific Functional Medicine interventional strategies.[12] Examination of genetic biomarkers focused on genes controlling the functional status of metabolic detoxification processes indicated that personalized diet interventions resulted in improved detoxification function.[13] As the evidence-based literature grows, we are truly witnessing the maturation and global spread of the Functional Medicine model.

Clinical Correlates of Functional Medicine Intervention

Emerging clinical evidence from multiple observational studies indicates that intervention with the Functional Medicine model has benefit across a wide-range of conditions. A recent review highlighted the benefits of the Functional Medicine approach in improving outcome in patients with Type 2 diabetes.[14] This report indicated that the application of the Functional Medicine model in these patients resulted in improved response to specific medications such as SGLT-2 inhibitors and GLP-1 receptor agonists, as well as overall better outcomes.

A very interesting review article published in 2017 discussed the application of the Functional Medicine model as an approach to the treatment of traumatic brain injuries (TBIs).[15] This review described the need for multimodal intervention approaches with individuals suffering from TBIs. A desirable aspect of the Functional Medicine model is that it provides a structured approach for the development and application of a program that is personalized to the individual's need.

Another example of the clinical implementation of a structured Functional Medicine dietary program for the management of a neurological condition associated with autoimmunity is described in a recent study by Wahls et al.[16] In this study, investigators tested a multimodal Paleolithic Diet Plan in the management of patients with multiple sclerosis. It was reported that this diet and a companion nutritional supplement plan provided intake levels of nutrients that were consistent with support of immune and neurological function, while at the same time being low in autoimmune-activating ingredients. An earlier clinical intervention trial in patients with multiple sclerosis using this dietary intervention program resulted in significant improvements in fatigue and quality of life.[17] This approach is consistent with the strategic focus of the Functional Medicine model and the seven core concepts.

The Shifting Paradigm in Medicine

These clinical studies of chronic disease management are illustrative of the transition that is occurring within pharmaceutical science. Significantly, they all represent multimodal treatment approaches rather than the one-disease/one-target/one-molecule philosophy that powered the development of the pharmaceutical industry. Historically, the pharma model was—and continues to be—very effective for the treatment of diseases that have a well-defined etiology, such as the antibiotic treatment of a specific bacterial organism associated with a well-defined infectious disease. It has been found, however, that this approach is less successful when applied to a chronic disorder resulting from multiple functional disturbances. The treatment of chronic non-communicable diseases now accounts for more than 70% of our annual health care expenditures, and this trend requires a personalized, multicomponent therapeutic system, not a one-size-fits-all protocol.[18]

In 2003, Wald and Law published a paper proposing that a "polypill" containing a statin, three blood pressure-lowering medications (each with a different target), and aspirin could reduce cardiovascular disease by 80%.[19] This suggestion shifted the discussion about the prevention and treatment of cardiovascular disease using the one-target/one-drug model to the idea of simultaneously treating multiple interacting functional disturbances. At the time, this was considered to be an example of downstream medicine because it focused on the specific biomarkers of disease risk (as opposed to a root cause treatment focused on identification and management of the origins of the multiple etiophenotypes).

In 2021, the results of a clinical prospective trial of a polypill containing these five medications in persons without cardiovascular disease reported that the polypill led to a lower incidence of cardiovascular disease in those who were at intermediate risk.[20] The study also found that there were more cases of muscle symptoms, gastrointestinal bleeding, dyspepsia, and dizziness in those who took the polypill. The one advantage of a polypill seems to be in the adherence to a multiple drug treatment regime.[21] In a recent 2022 review of the use of polypills for the prevention of cardiovascular disease, the point is made that concerns exists among specialists: "It is clear that despite the extensive evidence base, some doctors remain quite skeptical of about the benefits of a polypill-based approach compared to individualized drug selection and dosing." The authors go on to say this: "A different approach is needed to achieve a paradigm shift. We have reached a point in time where clinical guidelines need to emphatically recognize that traditional paradigms contribute to treatment gaps…."[22]

How do we best implement complex treatment programs for the management of chronic diseases? This question was explored in a landmark 2004 article published in the *British Medical Journal*: "The Polymeal: A More Natural, Safer, and Probably Tastier (Than the Polypill) Strategy to Reduce Cardiovascular Disease by More Than 75%".[23] Unlike the polypill, this strategy addresses the issue of managing chronic disease from a systems biology or root cause perspective by using a dietary approach to deliver multiple signals that influence physiological function. This concept is consistent with the Functional Medicine model, and in 2016 an article inspired by that earlier work was published in the *Journal of the American College of Lifestyle Medicine*: "Prescribing a Healthy Lifestyle Polypill with High Therapeutic Efficacy in Many Shapes and Sizes."[24]

The polypill debate continues. One key factor to consider is that prescribing a drug containing multiple medications to all people in a certain risk category is a practice that does not align with the emerging recognition that an array of functional biological disturbances contributes to the specific disease state of an individual. We know this to be true from recent studies on polygenic

risk scores for specific chronic diseases.[25] At this time, it is only through polygenic studies that evaluate many genetic variations that we gain a better understanding of the biological mechanisms associated with any one disease in any one individual. Why? Because millions of variations are encoded as single nucleotide polymorphisms (or SNPs) in the human genome, and the combined influence of these variations determine an individual's unique functional characteristics. Adding even more complexity is the impact of the epigenome. Studies show that even identical twins can have notably dissimilar epigenetic composition as a consequence of differing life exposures.[26] The interpretation of this very important research indicates that a polypill containing a limited number of bioactive ingredients that influence a few downstream physiological targets is not a viable solution for the resolution of complex chronic conditions. In fact, this type of data demonstrates that a more personalized program designed to improve functional balance of the principal upstream triggers that result in downstream effects is a more logical and effective approach.

The Epigenome and the Future of Functional Medicine

Embedded within the Functional Medicine model is the potential for reversibility of altered function. This perspective is inherently different from the Mendelian concept of genetics, which is grounded in the construct of dominate and recessive genetic characteristics. Mendel's work was obviously groundbreaking, but it has also contributed to a deterministic mindset about disease. Many people—even today—believe that health and disease are locked into the genes of every individual. Modern genomic research continues to reveal that the concept of genetic determinism can be (and should be) challenged.

It is now recognized that as we grow older, approximately 20% of our health is determined by the hardwiring of our genes, while the remaining 80% is influenced by the ways our lifestyle choices and our physical and social environment contribute to the expression of our genes. It has been said and even published that this concept of epigenetic remodeling represents the biology of hope.[27] There is a notable group of scientists—Randy Jirtle, Michael Skinner, Moshe Szyf, and Michael Meaney, to name a few—who are creating the fields of nutritional, environmental, and behavioral epigenetics, and helping to transform our view of the future of health care.[28] The functional interaction of our lifestyle, diet, environment, behavior, and social structure with our genome and epigenome greatly determines our health outcomes. It has been discovered that our aging epigenome can even be rejuvenated.[29] The epigenomic structure is also a powerful predictor of disease outcome and life expectancy.[30] As our understanding of genetic and epigenetic expression patterns grows, the implications for personalized Functional Medicine intervention programs are truly revolutionary.

What's ahead? We are witnessing the development of technologies that will eventually allow for the measurement of alterations in the epigenome and impact on the phenotype. We will soon be able to measure and analyze the complex patterns that are associated with functional changes in our health, and this information will allow us to intervene at the earlies stages of dysfunction, which will in turn have the greatest impact on long-term health outcomes. We will even be able to assess the state of our epigenetic imprintome, and therefore follow the success of interventions designed to increase resilience and organ reserve.[31] These discoveries will light the way for the future evolution of the Functional Medicine model. We will see medicine transform into a humanistic art that utilizes advances in science to create a system that sustainably supports functional health at the planetary, social, personal, organ, tissue, cell, biomolecule, and energetic levels.

References

1. Bland JS. The Natural Roots of Functional Medicine. *Integr Med (Encinitas).* 2018 Feb;17(1):12-17. PMID: 30962772; PMCID: PMC6380987.
2. Wade WF. Clinical Lecture on Functional Medicine. *Lancet*. 1871 Jul 1.
3. Bland J. Functional Medicine: An Operating System for Integrative Medicine. *Integr Med (Encinitas).* 2015 Oct;14(5):18-20. PMID: 26770161; PMCID: PMC4712869.
4. Bland J. Defining *Function in the Functional Medicine Model. Integr Med (Encinitas). 2017 Feb;16(1):22-25. PMID: 28223904; PMCID: PMC5312741.*
5. Hanaway P. Form Follows Function: A Functional Medicine Overview. *Perm J.* 2016 Fall;20(4):16-109. doi: 10.7812/TPP/16-109. Epub 2016 Oct 14. PMID: 27768567; PMCID: PMC5101104.
6. Bland JS. What is Evidence-Based Functional Medicine in the 21st Century? *Integr Med (Encinitas).* 2019 Jun;18(3):14-18. PMID: 32549804; PMCID: PMC7217393.
7. Bland JS. What is the Best Way to Assess Functional Health?: The History of the Development and Application of the Patient Reported Outcome Measurement Information System (PROMIS). *Integr Med (Encinitas).* 2020 Feb;19(1):8-11. PMID: 32549858; PMCID: PMC7238913.
8. Beidelschies M, Alejandro-Rodriguez M, Ji X, Lapin B, Hanaway P, Rothberg MB. Association of the Functional Medicine Model of Care With Patient-Reported Health-Related Quality-of-Life Outcomes. *JAMA Netw Open*. 2019 Oct 2;2(10):e1914017. doi: 10.1001/jamanetworkopen.2019.14017. PMID: 31651966; PMCID: PMC6822085.
9. Droz N, Hanaway P, Hyman M, Jin Y, Beidelschies M, Husni ME. The impact of functional medicine on patient-reported outcomes in inflammatory arthritis: A retrospective study. *PLoS One*. 2020 Oct 8;15(10):e0240416. doi: 10.1371/journal.pone.0240416. PMID: 33031458; PMCID: PMC7544031.
10. Abbott RD, Sadowski A, Alt AG. Efficacy of the Autoimmune Protocol Diet as Part of a Multi-disciplinary, Supported Lifestyle Intervention for Hashimoto's Thyroiditis. *Cureus*. 2019 Apr 27;11(4):e4556. doi: 10.7759/cureus.4556. PMID: 31275780; PMCID: PMC6592837.
11. Beidelschies M, Alejandro-Rodriguez M, Guo N, Postan A, Jones T, Bradley E, Hyman M, Rothberg MB. Patient outcomes and costs associated with functional medicine-based care in a shared versus individual setting for patients with chronic conditions: a retrospective cohort study. *BMJ Open*. 2021 Apr 13;11(4):e048294. doi: 10.1136/bmjopen-2020-048294. PMID: 33849860; PMCID: PMC8051390.
12. Lamb JJ, Stone M, D'Adamo CR, Volkov A, Metti D, Aronica L, Minich D, Leary M, Class M, Carullo M, Ryan JJ, Larson IA, Lundquist E, Contractor N, Eck B, Ordovas JM, Bland JS. Personalized Lifestyle Intervention and Functional Evaluation Health Outcomes SurvEy: Presentation of the LIFEHOUSE Study Using N-of-One Tent-Umbrella-Bucket Design. *J Pers Med*. 2022 Jan 15;12(1):115. doi: 10.3390/jpm12010115. PMID: 35055430; PMCID: PMC8779079.
13. Aronica L, Ordovas JM, Volkov A, Lamb JJ, Stone PM, Minich D, Leary M, Class M, Metti D, Larson IA, Contractor N, Eck B, Bland JS. Genetic Biomarkers of Metabolic Detoxification for Personalized Lifestyle Medicine. *Nutrients*. 2022 Feb 11;14(4):768. doi: 10.3390/nu14040768. PMID: 35215417; PMCID: PMC8876337.

14. Valencia WM, Botros D, Vera-Nunez M, Dang S. Diabetes Treatment in the Elderly: Incorporating Geriatrics, Technology, and Functional Medicine. *Curr Diab Rep*. 2018 Sep 5;18(10):95. doi: 10.1007/s11892-018-1052-y. PMID: 30187176.
15. Richer AC. Functional Medicine Approach to Traumatic Brain Injury. *Med Acupunct*. 2017 Aug 1;29(4):206-214. doi: 10.1089/acu.2017.1217. PMID: 28874921; PMCID: PMC5580364.
16. Titcomb TJ, Bisht B, Moore DD 3rd, Chhonker YS, Murry DJ, Snetselaar LG, Wahls TL. Eating Pattern and Nutritional Risks among People with Multiple Sclerosis Following a Modified Paleolithic Diet. *Nutrients*. 2020 Jun 20;12(6):1844. doi: 10.3390/nu12061844. PMID: 32575774; PMCID: PMC7353368.
17. Wahls TL, Titcomb TJ, Bisht B, Eyck PT, Rubenstein LM, Carr LJ, Darling WG, Hoth KF, Kamholz J, Snetselaar LG. Impact of the Swank and Wahls elimination dietary interventions on fatigue and quality of life in relapsing-remitting multiple sclerosis: The WAVES randomized parallel-arm clinical trial. *Mult Scler J Exp Transl Clin*. 2021 Jul 31;7(3):20552173211035399. doi: 10.1177/20552173211035399. PMID: 34377527; PMCID: PMC8326636.
18. Bland JS, Minich DM, Eck BM. A Systems Medicine Approach: Translating Emerging Science into Individualized Wellness. *Adv Med*. 2017;2017:1718957. doi: 10.1155/2017/1718957. Epub 2017 Oct 15. PMID: 29164177; PMCID: PMC5661085.
19. Wald NJ, Law MR. A strategy to reduce cardiovascular disease by more than 80%. BMJ. 2003 Jun 28;326(7404):1419. doi: 10.1136/bmj.326.7404.1419. Erratum in: *BMJ*. 2003 Sep 13;327(7415):586. Erratum in: *BMJ*. 2006 Sep;60(9):823. PMID: 12829553; PMCID: PMC162259.
20. Yusuf S, Joseph P, Dans A, Gao P, Teo K, Xavier D, López-Jaramillo P, Yusoff K, Santoso A, Gamra H, Talukder S, Christou C, Girish P, Yeates K, Xavier F, Dagenais G, Rocha C, McCready T, Tyrwhitt J, Bosch J, Pais P; International Polycap Study 3 Investigators. Polypill with or without Aspirin in Persons without Cardiovascular Disease. *N Engl J Med*. 2021 Jan 21;384(3):216-228. doi: 10.1056/NEJMoa2028220. Epub 2020 Nov 13. PMID: 33186492; PMCID: PMC7116860.
21. Baumgartner A, Drame K, Geutjens S, Airaksinen M. Does the Polypill Improve Patient Adherence Compared to Its Individual Formulations? A Systematic Review. *Pharmaceutics*. 2020 Feb 22;12(2):190. doi: 10.3390/pharmaceutics12020190. PMID: 32098393; PMCID: PMC7076630.
22. Patel A, Ojji D, de Silva HA, MacMahon S, Rodgers A. Polypills for the prevention of cardiovascular disease: a framework for wider use. *Nat Med*. 2022 Feb;28(2):226-229. doi: 10.1038/s41591-021-01635-9. PMID: 35102336.
23. Franco OH, Bonneux L, de Laet C, Peeters A, Steyerberg EW, Mackenbach JP. The Polymeal: a more natural, safer, and probably tastier (than the Polypill) strategy to reduce cardiovascular disease by more than 75%. *BMJ*. 2004 Dec 18;329(7480):1447-50. doi: 10.1136/bmj.329.7480.1447. PMID: 15604180; PMCID: PMC535974.
24. Arena R, Lavie CJ, Guazzi M. Prescribing a Healthy Lifestyle Polypill With High Therapeutic Efficacy in Many Shapes and Sizes. *Am J Lifestyle Med*. 2015 Nov 30;11(6):476-478. doi: 10.1177/1559827615619341. PMID: 30202373; PMCID: PMC6125003.
25. Mars N, Koskela JT, Ripatti P, Kiiskinen TTJ, Havulinna AS, Lindbohm JV, Ahola-Olli A, Kurki M, Karjalainen J, Palta P; FinnGen, Neale BM, Daly M, Salomaa V, Palotie A, Widén E, Ripatti S. Polygenic and clinical risk scores and their impact on age at onset and prediction of cardiometabolic diseases and common cancers. *Nat Med*. 2020 Apr;26(4):549-557. doi: 10.1038/s41591-020-0800-0. Epub 2020 Apr 7. PMID: 32273609.
26. Polygenic Risk Score Task Force of the International Common Disease Alliance. Responsible use of polygenic risk scores in the clinic: potential benefits, risks and gaps. *Nat Med*. 2021 Nov;27(11):1876-1884. doi: 10.1038/s41591-021-01549-6. Epub 2021 Nov 15. PMID: 34782789.
27. Jirtle RL. The science of hope: an interview with Randy Jirtle. *Epigenomics*. 2022 Mar;14(6):299-302. doi: 10.2217/epi-2022-0048. Epub 2022 Mar 10. PMID: 35264021.
28. Szyf M. The epigenetics of early life adversity and trauma inheritance: an interview with Moshe Szyf. *Epigenomics*. 2022 Mar;14(6):309-314. doi: 10.2217/epi-2021-0483. Epub 2021 Dec 8. PMID: 34877868.
29. Zhang W, Qu J, Liu GH, Belmonte JCI. The ageing epigenome and its rejuvenation. *Nat Rev Mol Cell Biol*. 2020 Mar;21(3):137-150. doi: 10.1038/s41580-019-0204-5. Epub 2020 Feb 4. PMID: 32020082.
30. Gadd DA, Hillary RF, McCatney DL, Evans KL, McIntosh AM, Suhre K, Marioni RE. Epigenetic scores for the circulating proteome as tools for disease prediction. *eLife* 2022;11:e71802
31. Bland JS. A Discovery that Reframes the Whole of Global Healthcare in the 21st Century: The Importance of the Imprintome. *Integr Med (Encinitas)*. 2021 Aug;20(4):18-22. PMID: 34602872; PMCID: PMC8483255.