What is Evidence-Based Functional Medicine in the 21st Century?

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Abstract

The 21st century has already demonstrated itself to be an era of change for medicine and science. There is a new openness—to ideas, to a shift in perspectives, to a redefinition of evidence and the many ways it can be gathered. New interest in real-world data, patient-experience information has also become an increasingly important contributor to the evaluation of treatment effectiveness. It is a fertile time on many fronts, including an expanded reach for a systems biology formalism and the Functional Medicine movement.

The randomized placebo controlled trial (RCT) has achieved iconic status in the field of medical research. For many decades it has represented a scientific gold standard in which clinicians invest both their trust and confidence. The RCT model is, indeed, a useful tool for a variety of reasons, but—like most icons—it is neither perfect nor infallible.

In 2015, an article was published in Nature that invited readers to consider some powerful truths about RCTs. Written by Nicholas Schork, PhD, who is affiliated with the J. Craig Venter Institute, the University of California at San Diego, and the Translational Genomics Institute, this paper—“Personalized Medicine: Time for One-Person Trials”—raises important questions about whether we are presently using the right type of evidence to validate the effectiveness of some specific therapies. Dr Schork highlights 10 of the most commonly prescribed pharmaceutical drugs and describes RCT-derived outcomes data that indicates very limited therapeutic success (from 1-in-4 to 1-in-25 patients). Why is the translation of RCT data to patient outcome experience so poor? This is a question I examined at length in my 2014 book The Disease Delusion: Conquering the Causes of Chronic Illness for a Healthier, Longer, and Happier Life. To a large extent it is due to the fact that the common diseases these medications are designed to treat—depression, cardiovascular disease, inflammation, inflammatory bowel disease, Crohn’s disease, rheumatoid arthritis, esophageal reflux disorder, psoriasis, asthma, and schizophrenia—all have multiple triggering factors derived from the unique way that a person’s genes interact with lifestyle, diet, and environment. While symptoms related to these diseases are common in terms of presentation, the triggering events that initiate the onset of disease in each individual are highly variable. Because drug development RCTs are inherently based on a “one size fits all” approach, trials that are large in size are often necessary to demonstrate a reproducible $P < .05$ level of significance of evidence of effectiveness in an RCT.

In 2018, Dr. Schork published a follow-up paper in Social Science & Medicine in which he outlines the limitations of RCTs in the genomic age. Since it is now recognized that there is significant biological heterogeneity within any specific disease diagnostic group, he argues for the need to apply new approaches that integrate developments in biometrics, bioinformatics, and N-of-1 trial designs into criteria that we use to measure evidence of effectiveness. This approach could be described as moving from population-based data to that of individualized responses. A good example of this dynamic of generating evidence related to impact on overall health can be found in a published study describing a multi-micronutrient intervention in Brazilian children and teens that examined both physiological and psychological functional responses.

In the new trial models being explored, there are numerous ways that participant data related to physical, metabolic, cognitive, and behavioral functions could be statistically evaluated using nearest-neighbor analyses to determine which individuals share common sensitivities or responses to a given intervention or challenge. Two functional measures that can be used to stratify and study potential interventions are grip strength and male
reproductive function. Grip strength has been determined to be a highly significant variable in assessing the risk to all-cause and cardiovascular mortality in both males and females over the age of 35. Using grip strength as a marker of function, patients could be segmented into specific risk groups for evaluation of the underlying contribution to their risk profile, which could then lead to personalized interventions. In males, reproductive problems have been associated with a significant decline in both sperm count and quality that has occurred over the past 50 years. As a result, sperm count and sperm viability indices could be functional assessment measures that would be useful in individualizing interventions such as medical nutritional therapies, lifestyle modification, detoxification, or hormonal therapies.

**Evidence for Health Decision Making—Beyond RCTs**

Functional assessment in combination with new biometrics and bioinformatics tools represents a powerful step forward in the development of innovative approaches to collecting and documenting evidence in support of patient-specific interventions. In 2017, Thomas Frieden, MD, MPH, who is the former director of the US Centers for Disease Control and Prevention, published an article in the *New England Journal of Medicine* describing a number of methods outside of the traditional RCT model for obtaining evidence related to the effectiveness of individualized therapies. Such methods may be relevant not only to the study of disease, but also the evaluation of wellness. This new way of thinking about study design moves us beyond a limited focus on population risk to a higher-level, enhanced understanding of individual functional uniqueness, setting the stage for a future in which precision personalized lifestyle medicine can be successfully developed and applied to patient care.

What types of studies might one day equal—or even replace—the RCT model? Options currently include prospective cohort studies, retrospective cohort studies, pragmatic and large observational trials, nested case reports, and N-of-1 studies. Two researchers—Stacey Chang, BS, and Thomas H. Lee, MD, MSc—have introduced another concept into the mix: interpersonal medicine. In a 2018 article titled “Beyond Evidence-Based Medicine,” they describe the important context of a patient’s social experiences and preferences, influence of caregivers and other support people on the outcome, and the quality of the communication surrounding biological, social, and humanistic concerns. Furthermore, they emphasize that practitioner experience should be coupled with clinical and biological evidence in the therapeutic decision-making process.

Historically, RCTs have been built around population statistics derived from parametric Gaussian distribution analyses, and this is now recognized to be a serious limitation. In most types of biological research, the data from humans is nonparametric and may be multimodal. It also has a long tail due to significant genomic variation. Often, biological functions or biometrics evaluated in a clinical study are the result of many contributing effects, and therefore these represent isolated components that are part of a much larger biological network. In order to understand the presence of a specific biomarker in an individual, it is necessary to also understand the status of the biological network that regulates that biomarker—a concept that is often referred to as systems biology. The field of network medicine has emerged to address complex data analysis derived from systems biology. A foundational tenet that underlies network medicine is the recognition that conditions identified as “comorbidities” or “disease adjacencies” may actually be functional perturbations of the same underlying biological network expressed in different cells, tissues, or organs. The network medicine model has already been successfully applied. One well-known example is the revelation that type 2 diabetes is not one disease, but rather at least three different subtypes that are distinguished by unique functional changes in metabolism. In the near future, treatment of type 2 diabetes will likely become very personalized, with less focus on the disease itself and more emphasis on evidence related to the unique functional metabolic disturbance in the patient. In a similar fashion, noted neurologist and author Dale Bredesen, MD, has reported that Alzheimer’s disease exists in at least three different subtypes involving functional disturbances in brain metabolism, each of which requires personalization of therapy. Both of these conditions—type 2 diabetes and Alzheimer’s disease—affect millions of people every year, and yet they serve as excellent examples of the need to gather evidence focused on the individual versus the group.

The growth of personalized medicine as a field has intersected with significant advancements in personal technology, especially the growing interest in and use of wearable medical devices. Michael Snyder, PhD, who is director of the Center for Genomics and Personalized Medicine at Stanford University, has emerged to be a leading expert on this topic. In various publications, Dr Snyder and his team describe front-edge biometric devices that can continuously measure a range of personalized data points in real time: sleep quality and duration, heart rate, blood oxygen levels, blood sugar, blood pressure, and body composition. As the technology marketplace continues to evolve and grow, so too will the ability to assess individual functional capabilities both at rest and under stress, which will further inform and guide the personalization of therapies.

**The Precision Cancer Treatment Movement: What Has Been Learned?**

The age of personalization really began with the precision cancer movement. A diagnosis of cancer is traditionally defined by the anatomical site of origin, but in 2017 we witnessed regulatory approval of the first
cancer drug focused on disturbed cellular function, with the identification of the cancer type linked to a specific mutation of the cancer cell rather than to an organ. As recently as the 1990s, treatment for many cancer patients came in the form of relatively ineffective toxic chemotherapy because “evidence”—as it was defined in that era—supported the use of these medications. Today, the field of oncology has significantly evolved as a result of the advancement in understanding of the molecular etiology of cancer, which in turn has made it possible to personalize therapeutic interventions in a manner that is more efficient for both physicians and patients. New clinical trial designs were instrumental in forging this new era of cancer treatment. One—an adaptive study design that features “umbrellas” and “baskets”—allows for the stratification of patients into various cohorts that are assigned treatments based on personalized genetic information. This type of protocol assists researchers in collecting evidence of a drug's effectiveness in terms of unique patient sensitivity and response to an intervention. Stratifying a study population according to specific biomarkers and then using combined cellular and biochemical profiling to identify predictive responses to specific therapies is a pioneering approach. The increased use of genomic sequencing and profiling has fundamentally changed the nature of diagnosis from that of the population to that of the individual. It is a logical and needed next step for clinical trial design to change in a responsive manner, and for the parameters that guide how evidence in support of therapy is defined to be reexamined as well.

Diet studies related to cancer therapy have proven to be difficult in terms of demonstrating evidence of effectiveness. There are various reasons for this, including the significant heterogeneity of responses to nutrient signals, as well as the low signal strength of nutritionally derived, biological, response-modifying substances. Siddhartha Mukherjee, MD, PhD, and Lewis C. Cantley, PhD, both highly respected researchers, have recently announced a collaboration among Weill Cornell Medical College, Columbia University Medical Center, and New York-Presbyterian to evaluate specific dietary interventions in cancer. Previous work done in tumor models in mice revealed key findings about the role of glucose and fructose in enhancing the tumor-promoting effects of insulin through the PI3 kinase signaling network. Earlier this year—in 2019—a group led by Dr Cantley reported that high-fructose corn syrup enhances intestinal tumor growth in mice. This animal work, in combination with clinical observations that low-sugar diets appear to be helpful in reducing the progression of a number of types of cancer, has culminated in a crowdsourcing initiative to fund a human clinical trial. Engaging the public in the support and execution of research has been described as “leveraging the citizen scientist.” It is a novel model—one that highlights a new kind of transparency and openness—and it is being now being applied not only to cancer research, but also to the study of diseases such as rheumatoid arthritis, amyotrophic lateral sclerosis, and multiple sclerosis.

N-of-1 Trials and Personalized Evidence

Stratified trial designs using new biometric and genomic tools are now being applied to the evaluation of epigenetic effects related to a range of interventions, including physical exercise, Ayurvedic practices, and meditation. Progress has been made in the documentation of individualized responses, which has resulted in the codification of specific procedures for N-of-1 study designs. Factors that have been linked to the usefulness of this type of study include the following: the mechanism of action of the treatment is pleomorphic; the study population is heterogeneous; and the clinical endpoints variable in type, duration, frequency, and intensity. Multi-person N-of-1 trials can be designed and effectively executed if the objectives, functional variables, reasons for stratifying the cohorts, and specific intervention rationale are clearly defined.

There is evidence that single-subject N-of-1 studies can be useful in establishing evidence of effectiveness in translational nutrition research. Optimally, these N-of-1 designs should employ integrated use of multiple functional assessments, in combination with biometric assays and omics tools, to identify individual metabolic phenotypes. Using this array of assessment tools to identify the functional status of the individual before and after nutritional intervention allows for the development of valid evidence. Multiple individual N-of-1 studies using the same assessment tools and outcome measures can provide additional evidentiary support for use of the intervention in patients who share similar metabolic phenotypes.

Obesity is a condition marked by complex physiology and psychology. As such, the application of gene-based personalization of dietary advice for nutritional weight management in patients with this condition has historically resulted in only limited success. This field of studying the relationship between genes and weight, which is now commonly referred to as nutrigenomics, recently took a major step forward. Amit Khera, MD, and Sekar Kathiresan, MD, who are both affiliated with the Center for Genomic Medicine at Massachusetts General Hospital, the Broad Institute at MIT, and Harvard Medical School, have worked with a team of collaborators to create a polygenic prediction algorithm to track weight and obesity trajectories from birth to adulthood based on the analysis of 2.1 million common genetic variants. This work is truly groundbreaking because it relates to establishing specific genetically determined risk categories for complex health issues such as obesity. Interestingly, when the number of genetic variants in the computational algorithm only included those that had been identified by GWAS studies on obesity, no significant predictive ability...
was noted. However, when the larger set of 2.1 million common variants was used, the predictive ability of the algorithm became significant, even though most of the genes had not been identified as being associated with obesity. This fact demonstrates the high level of biological heterogeneity that exists in an individual’s response to diet. Ali Torkamani, PhD, and Eric Topol, MD, of the Scripps Research Translational Institute, jointly authored a commentary about the work of Khera et al and suggest it is an important illustration of why nutritional intervention trials often fail to produce clear evidence of improved outcome.40 In the future, use of the polygenic risk score in combination with biometric information, functional data related to the impact of the gut microbiome on metabolism, and lifestyle and dietary factors may frame the design of N-of-1 approaches that will provide us with evidence about the relationship between a personalized diet and health outcomes.

The Nested Case Report as a Source of Evidence

N-of-1 studies provide information from which a nested series of case reports can be developed to serve as additional supporting evidence for defining outcome. There is now an established format for publishing case reports under consensus-based guidelines called the CARE REport (CARE) Statement and Checklist.41 The CARE approach includes the following: development of an appropriate abstract; an introduction; patient information; assessment criteria; therapeutic intervention; outcomes; discussion of strengths and weaknesses of the report; patient perspectives on their experience with the intervention; and informed consent.42

Empirical evaluations have indicated that important treatment effects are often revealed through well-designed small studies that are properly stratified for participants within specific functional categories.43 It is well understood that population-based RCTs have value in identifying specific, single-agent effects in acute disease states, but have limited application to personalized interventions in complex chronic disease. There are now a number of study designs available to assess the impact of personalized interventions and provide the evidence necessary to support the use of systems biology precepts and the application of Functional Medicine approaches to chronic disease management.44

The April 9, 2019 issue of the Journal of the American Medical Association features an editorial titled “The Evolving Uses of ‘Real-World’ Data.” As the article outlines, real-world data (RWD) and real-world evidence (RWE) constitutes information that is not derived from RCTs or similar experiments. And yet—the authors point out—such information is now considered to have value in establishing the landscape related to the effectiveness of specific clinical interventions. They write: “The frenzy of interest in RWD has also been fueled by the Food and Drug Administration (FDA) signaling receptiveness to consider these data sources in regulatory review, and recent publication of a framework for doing so.”45

In addition to this new interest in real-world data, patient-experience information has also become an increasingly important contributor to the evaluation of treatment effectiveness.46 In a recently published editorial about evidence supporting cardiovascular clinical guidelines, authors Robert O. Bonow, MD, MS, and Eugene Braunwald, MD, state: “There will never be enough time, effort, or funding to implement RCTs to address all clinical scenarios that confront physicians. Moreover, RCTs are usually confined to patients of specific ages with single conditions. … Individual patients are unique and many differ from those enrolled in RCTs on which the guidelines are based.” They continue: “This results in the common need to extrapolate guideline recommendations built upon ideal patients to the real patients seen in practice…”47 The 21st century has already demonstrated itself to be an era of change for medicine and science. There is a new openness—to ideas, to a shift in perspectives, to a redefinition of evidence and the many ways it can be gathered. It is a fertile time on many fronts, including an expanded reach for a systems biology formalism and the Functional Medicine movement.

References


