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Editorial

What Makes Personalized Nutrition Clinically Useful?

Andrea Maugeri

Department of Medical and Surgical Sciences and Advanced Technologies "G.F. Ingrassia", University of Catania, 95123 Catania, Italy; andrea.maugeri@unict.it

1. Introduction

Noncommunicable diseases caused at least 43 million deaths in 2021, representing 75% of deaths unrelated to the pandemic, according to the World Health Organization [1]. Dietary risks accounted for an estimated 7.22 million deaths among adults aged ≥25 years, highlighting the scope for improving dietary prevention [2]. Personalized nutrition seeks to translate this population-level need into advice informed by individual biology, behavior, and circumstances. Its biological rationale is supported by substantial variation in responses to identical meals, documented by Zeevi and colleagues in 800 participants [3] and extended to postprandial glucose, insulin, and triglyceride responses in 1002 adults in PREDICT 1 [4]. Yet measurable differences do not necessarily identify better treatments. In Food4Me, personalized advice improved dietary behavior, but adding the phenotypic and genotypic information tested provided no further benefit in the principal analysis [5]. Similarly, among 609 adults in DIETFITS, neither the prespecified genotype pattern nor baseline insulin secretion significantly modified the comparative effects of healthy low-fat and healthy low-carbohydrate diets on weight loss at 12 months [6].

The Special Issue "The Impact of Nutrigenomics and Personalized Nutrition on Non-Infectious Disease" examines this gap between individual variation and clinical usefulness. Its methodological and original research contributions explore how dietary exposures interact with genetic susceptibility, metabolic responses, and behavior, and what these relationships might mean for disease prevention and management. This Editorial considers their findings within the broader evidence, assessing the methodological and translational work needed before differences in dietary response can reliably guide practice. The central question is when, for whom, and under what conditions personalization improves nutritional care sufficiently to justify the information and resources it requires.

2. Interpreting Biological Variation

The review by Maugeri (contribution 1) provides a methodological framework for assessing when gene–diet findings can inform nutritional care. Across classical interaction models, causal inference, multi-omics, and machine learning, their interpretation depends on reliable dietary measurement, clearly defined interactions, and validation across populations. These concerns recur in the original contributions. Hrncir and colleagues (contribution 2) show how dietary combinations may influence metabolic outcomes through interconnected microbial and host responses. Their experimental findings on fructose and preservatives highlight the complexity of dietary exposure, while the absence of preservative-only groups and the preclinical setting limit conclusions about specific interactions and their relevance to human diets.

The studies by Lee and colleagues (contribution 3) and Liu and colleagues (contribution 4) examine how genetic variation may inform dietary strategies for cardiovascular

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and metabolic health. Lee and colleagues identify associations between HDL-related variants, dietary intake, and cardiovascular outcomes, but their cross-sectional design leaves temporality unresolved, and broad nutrient categories require translation into specific, testable dietary changes. Liu and colleagues integrate genetic and lifestyle analyses with molecular docking to generate hypotheses for further investigation. Functional validation, bioavailability studies, and prospective evaluation remain necessary before these findings can guide care. Across both studies, clinical value will depend on whether genetic information improves dietary decisions and outcomes beyond what established clinical assessments already provide.

3. Adherence and Physiological Context

Behavior and physiological state introduce further dimensions of personalization. Yatsuda and colleagues (contribution 5) report associations between serotonin transporter genotype and selected outcomes during a diet and exercise program. However, defining adherence through body-fat reduction makes it difficult to distinguish following advice from responding biologically to it. This distinction matters clinically: difficulty sustaining a dietary change and limited benefit despite adherence call for different approaches to care.

Safari and colleagues (contribution 6) explore whether responses to short-term dark chocolate supplementation vary across menstrual phases in female athletes. Their findings raise the possibility that nutritional advice may benefit from adaptation to changing physiological states. The small, specialized sample and functional outcomes limit broader inference; larger studies with hormonal verification are needed to establish whether such adjustments offer reproducible benefits.

4. Establishing Clinical Benefit

Before differences in dietary response can guide care, their sources and clinical importance must be established. Dietary composition, genetic susceptibility, behavior, and physiological state require distinct measurements and comparisons. As Maugeri discusses (contribution 1), statistical interaction depends on the analytical scale, and relative effects should be accompanied by absolute estimates of expected benefit. The studies in this Special Issue point to specific priorities: separating the effects of dietary components, prospectively replicating genetic associations, and measuring adherence directly (contribution 2–4). Prespecified analyses and transparent reporting of unsuccessful replication are essential. Structured tools such as ICEMAN can further support assessment of the credibility of apparent differences in treatment response [7].

A marker's intended use should determine how it is evaluated. Identifying people at higher risk does not establish which diet will benefit them most; treatment selection requires evidence that the marker modifies the comparative effects of alternative interventions. Multiomics and repeated sampling could help explain these differences and distinguish predictors of response from consequences of dietary change. Prediction models should demonstrate calibration, independent validity, and added value over readily available clinical and dietary information (contribution 1). TRIPOD+AI provides a framework for transparent reporting of models developed using regression or machine learning [8].

Intervention evidence offers cautious encouragement. In the METHOD randomized trial, a personalized dietary program improved triglycerides and several secondary outcomes, but not LDL-cholesterol, relative to standard advice [9]. The contribution of biological information remained difficult to separate from that of dietary support. Trials assessing a marker's added value should therefore provide comparable professional contact and behavioral support across groups. Outcomes and follow-up must match the intended claim, distinguishing improvements in dietary behavior from benefits in disease prevention or

treatment. Longer-term and pragmatic studies will be needed to establish whether benefits persist and justify the resources required in routine care.

5. Adapting Care and Widening Access

Nutritional advice may need to evolve as physiological circumstances and engagement change, as the studies of menstrual phases (contribution 6) and behavioral responses (contribution 5) suggest. Future interventions could begin with routine clinical and dietary assessments, monitor outcomes, and add targeted measurements when these could change management. Adaptive trials and, where appropriate, N-of-1 designs could evaluate such approaches, provided they distinguish meaningful responses from everyday variation and account for carryover effects.

Access will shape their population impact. With 82% of premature deaths from non-communicable diseases occurring in low- and middle-income countries [1], research must extend across diverse dietary, cultural, and healthcare settings. Evaluation should consider affordability, professional workload, equitable benefit, and responsible data use. Additional testing should demonstrate sufficient value to justify its cost while preserving access to dietary counseling. Its usefulness will also depend on whether people can obtain and afford the foods recommended.

6. Conclusions

The six contributions in this Special Issue address different parts of the evidence needed for personalized nutritional care. Experimental findings suggest mechanisms to investigate, population studies identify associations to test, and intervention studies examine response under defined conditions. The included methodological review helps distinguish what each design can establish and what must be learned next. Connecting these forms of evidence will require studies whose results can alter a specified clinical decision.

For some patients, assessment of diet, metabolic status, preferences, and practical constraints may provide enough information to choose an effective intervention. For others, a validated biological marker or repeated measurement of response may support a different choice. Establishing those indications is a realistic and clinically useful goal for the field. Success should be judged by sustained improvements in health and by whether the resulting care reaches the people who need it. Individual differences in response to a meal are a compelling observation. Their importance to medicine will depend on what we can reliably do with that knowledge.

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