

# The future of living well to 100<sup>1-3</sup>

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## INTRODUCTION

*Editor's Note: This article is based on the panel discussions at the Living Well to 100 Conference held at Tufts University. The authors were specifically asked to capture the highlights of the panel members' short statements and the audience response to what we need to know for the future in applying and disseminating this scientific knowledge responsibly to achieve healthy aging. As such, this manuscript does not lend itself to the scientific format of the other articles and should be viewed as a compilation of the discussion panels and the consistent themes emerging from the discussion.*

Healthy aging is one of the biggest challenges we face in the future, but how do we define it? Today's world of genomics has introduced the concept of molecular age; a molecular biologist might say you are as old as your transcriptome, which is one measure of an individual's genomic response to the environment. A transcriptome associated with a healthy, young macrophage or an old, diseased macrophage, and so forth, might help us conceptualize a grid for healthy aging (**Figure 1**) and ultimately move people through the grid toward an ideal endpoint: healthy aging. This assertion begs the question, what is healthy aging? It would be useful to quantify what it means. Of course the macrophage is only one of many cell types, with different transcription controls and diverse environmental influences that represent certain aspects of the biological status of the entire system. Although aging can be defined in molecular terms, we cannot neglect the broader aspects used in health care today, eg, cost-effectiveness, the effectiveness of assessing risk-benefits of medicines, and even quality-of-life years. Establishing a definition will move us toward a consensus of understanding that enables people to set clear and realistic goals. Then, future discussions should center on a life path for living well as we age.

## PREVENTION MODELS AND COMPLEX GENE-ENVIRONMENT INTERACTIONS

Currently, it is difficult to generate predictive models that allow us to think about diet as a "treatment" in the modern meaning of the word. There is no precision in dosing, and we possess surprisingly minimal knowledge of the effects of many specific nutrients on human biochemistry or of potential interactions between bioactive nutrients. Despite this knowledge deficit, we have a model of prevention that enables us to find and treat an existing high-risk patient and also to identify the potentially high-risk patient and preserve health a priori. Such a model might incorporate multiple factors, including genetic makeup, nutrition, inflammation, and lifestyle behaviors. This concept

embraces nutritional genomics. Nutrition, along with other behavior changes and, when necessary, pharmacotherapy, may permit alterations in the health trajectory to foster healthy life.

Many complex diseases involve interactions among multiple genes and multiple aspects of the environment. Genetic markers should render the effects of environment more predictable. We need to identify genetic markers that help to clarify biological responses to important environmental variables and then devise data-driven advice to harmonize the environment in persons with specific genetic predispositions. For example, if an individual is genetically at risk of a certain condition, it is reasonable to expect that diet modifications might reduce that risk in certain situations. If someone's genetic risk is already low, dietary modification might not afford risk reduction. Such consideration should inform options to modify the environment appropriately.

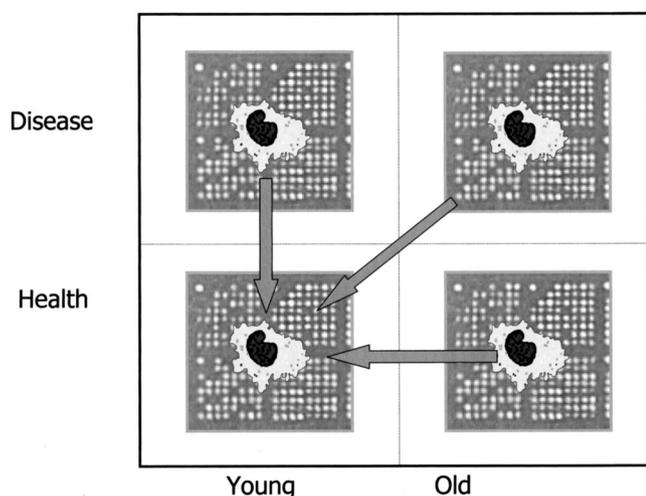
As with aging, the effect of nutritional modification on health depends on time. Available studies do not support nutritional remedy for aging, but dietary intervention may delay certain deleterious effects of time. It is very difficult to apply rigorous efficacy and safety risk-benefit analysis to interventions now, when the outcomes may not be apparent for 50–60 y. This consideration applies to nutrition and its long-term effects: the efficacy may or may not manifest itself for many years. Clearly, relevant biomarkers are needed, predictors with the highest possible fidelity based on our current understanding of the evidence that could foretell the likely long-term clinical effects of certain dietary interventions. For example, C-reactive protein (CRP) has emerged as a potentially informative biomarker for monitoring inflammatory mechanisms that bears relevance to the risk of clinical expression of chronic diseases associated with aging.

The incomplete knowledge of the biological mechanisms involved in a disease must temper expectations in the short term. It seems reasonable, however, to define genetic risk involved in specific component causes of diseases of aging. For example,

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**FIGURE 1.** Molecular age in terms of health and disease. Knowing which transcriptome associates with each state in the grid would conceptually allow strides toward the ideal endpoint of healthy aging.

apolipoprotein gene variations can affect HDL-cholesterol concentrations differently depending on the fat content of the diet (1). Reportedly, low dietary levels of *n*-3 polyunsaturated fatty acids associate with carotid artery wall thickness only in individuals with specific variations in the gene for the inflammatory molecule arachidonate 5-lipoxygenase (2). These data suggest that nutrition may modify certain genetic risks. Such epidemiologic associations require further testing in prospective randomized controlled clinical trials.

What do we measure to get the maximum information for the least amount of trouble? It depends on what we are trying to achieve. Even validated biomarkers, eg, CRP or carotid intima-media thickness in the cardiovascular arena, do not predict disease perfectly, and many biomarkers require rigorous validation (eg, coronary calcium score).

### MULTISYSTEM DISEASES REQUIRE A MULTIDISCIPLINARY APPROACH

The diseases of aging often affect multiple organ systems and have multifactorial causes (eg, obesity), yet can involve common biological mechanisms (eg, inflammation). Traditionally, we have dealt with isolated systems and organs. Instead, we should seek integration across disciplines to collaborate in promotion of healthy aging. We should strive to integrate thinking about nutrition in the context of multisystem diseases. We need to harness every aspect of the current advances in biological sciences to achieve this goal and avoid narrow study of only one aspect of disease. The tools we have today offer us the opportunity to examine these complex interactions. We can now think about nutrition not just in the context of sustenance, but in terms of prevention and therapy, to move forward and combat the challenges we face. Personalized medicine should aim to involve the use of genetics and other risk factors to identify individuals at risk while they are still healthy. We must not wait for persons at risk to develop disease, but rather should seek effective and selective nutritional interventions to preserve health in individuals on the basis of their risk factor profile and genetic makeup.

As reflected in the National Institutes of Health roadmap, consortia of partnerships should prove increasingly important in

the future. We should move beyond the model of the single laboratory thriving in its area of research to optimize our understanding of a process as complicated as aging. To isolate one discipline of science and focus exclusively on one aspect is not only shortsighted but also incomplete. Partnerships should lead to greater opportunities. Interdisciplinary gatherings such as this meeting provide a starting point to determine the best way of achieving healthy aging among different population groups. A multiplicity of perspectives can overcome obstacles and speed success. For example, pharmacologists may identify agents, medicinal chemists can optimize them, toxicologists can evaluate them, and finally, clinicians can test efficacy. Nutritionists need to capitalize on this model and learn from it. Formalizing partnerships and encouraging nutritionists to work with other disciplines can accelerate understanding of the clinical implications of nutrition.

### PERSONALIZED MEDICINE

Optimal nutrition differs among individuals: one size does not fit all. Individuals respond differently to nutrients and to drugs. What determines this heterogeneity? How do we construct predictive models that may permit use of nutrients as a precise and personalized treatment? Nutrition may modify disease risk, but barriers prevent practical implementation of dietary change. Success in this regard requires not only identification of effective lifestyle interventions but also strategies for their maximal adoption.

### EDUCATION

Knowledge of genetics has increased dramatically, but a lag in public understanding creates a disconnect that may only increase in the future. As important as our current knowledge is, we are looking only at the surface. "Until we achieve the ultimate goal of genotype-based medicine, drug developers and healthcare providers will struggle with how to interpret differential drug response by groups when group definition is imprecise, fluid and time-dependent" (3). We can substitute *genotype-based nutrition* for *genotype-based medicine* and *nutrients* for the word *drug* in the statement above to furnish a concise statement of the challenge that confronts the subject of nutritional genomics.

Scientists and physicians must learn to convey knowledge about nutrition and genetic research more effectively. A disease treatment industry exists that includes a health care delivery system, but we lack a wellness industry per se. Society rewards primary prevention insufficiently in the current health care system. We certainly need to invest in research that targets effective means of changing behaviors of the public and professionals alike in adoption of preventive measures.

What measures will help prepare the next generation of nutritional scientists to operate in this arena? How do we educate future nutritionists to have not only the breadth needed in nutrition but also the depth required by contemporary science and medicine? A fundamental grounding in basic science coupled with a multidisciplinary exposure to pathology would help to achieve this goal.

## DRIVERS

What will drive nutritional genomics in the years to come? The private sector? Health care professionals? The media? Will consideration of liability, ethics, confidentiality or other issues slow progress in this area? Likely, all of the above matters will influence the development and adoption of nutritional genomics. Ultimately, public acceptance in the quest for healthy aging may speed the development and practical adoption of nutritional intervention based on genetic information. Strong drivers appear to exist for adoption of a wellness model that incorporates genetics and nutrition as integral components in healthy aging. These drivers could include a strong science foundation to support the clinical value of genetic risk factors and the effects of specific nutrients in targeted individuals, biomarkers that allow prediction and monitoring of beneficial biological responses to the nutrients, a regulatory environment that encourages consumers to differentiate products on the basis of science, and credible and respected information delivery to consumers.

## CONCLUSIONS

Healthy aging presents an enormous challenge, but advances in biological sciences may provide the knowledge and tools needed to understand nutrition at genetic and molecular levels and elevate the scientific basis underlying nutritional recommendations. Understanding the roles of nutrition, genetics, and inflammation clearly requires interdisciplinary cooperation. Developing partnerships among specialties should promote the goal of healthy aging. We need to come together as a science community and generate the evidence base to influence public policy and recommendations. Although the challenges are real, we are

approaching a time when we should seek to broaden our understanding of the potential value of nutrition and genetics in achieving healthy aging. 

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PR is a full-time employee, shareholder, and board member of Interleukin Genetics Inc. GWD is a consultant to Interleukin Genetics Inc and owns shares in the company. Interleukin Genetics has patents issued and pending on the use of interleukin 1 and tumor necrosis factor  $\alpha$  genetics as risk factor tests for various diseases with inflammatory components. The other authors had no conflicts of interest to report.

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