Editorial

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Personalized Medicine

Could food act as personalized medicine for chronic disease?

"An interesting question is whether participants of the PREDIMED study would have achieved similar outcomes by following one-size-fits-all government-endorsed dietary guidelines."

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Introduction

Based on recent conflicting views on nutritional approaches, are nutrition health professionals meant to wait until key long-term human randomized controlled trials of good methodological quality are published on UK-type populations, a process that could take decades at the current rate. Instead, they could embrace the new 'omic' technologies as innovative tools to help personalized nutrition. Based on current findings, a single microbiome test can provide more reliable information about a person's health than a genome screen and major disruptions are seen in allergy, obesity, colitis and irritable bowel syndrome, diabetes or even cancer. While treating every patient as a research subject, health professionals should see every meal as an opportunity, and every food as a potential drug.

Food is our main source of nutrients, defined as constituents of a diet, natural or designed, that play a unique biochemical or structural role in a function [1]. Nutrients in food serve as energy-yielding substrates. They also serve as precursors for the synthesis of macromolecules as well as other components needed for normal cell differentiation, growth, renewal, repair, defense and maintenance. They are involved in cell signaling, and work as cofactors and determinants of normal molecular structure and function, as well as promoters of cell and organ integrity.

The fact that nutrients are much more than a source of fuel has become increasingly apparent since the completion of the Human Genome Project in 2003. Scientists now have the ability to identify and measure genome-wide influences of individual nutrients and dietary patterns on the transcriptome, proteome and metabolome of cells, tissues and organisms. This means that we are able to assess the relationship between human genotypes at a population level and the risk of developing diet-related phenotypes, such as obesity, Type II diabetes, cardiovascular disease (CVD) and cancer.

While for decades observational studies full of biases have been giving us misleading or conflicting information about the role of foods and disease – such as coffee or soy causing cancer or dairy eating causing heart disease, few studies performed proper long-term trials of foods. One exception is the PREDIMED (PREvención con Dieta MEDiterránea – literally 'Prevention with a Mediterranean Diet' in Spanish) was a large multicenter, randomized, primary prevention trial designed to assess the long-term effects of the Mediterranean diet (MeDiet) on markers of cardiovascular risk such as altered lipid profiles, increased inflammation and carotid atherosclerosis [2]. The study

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ran for 5 years and recruited 7447 mildly unhealthy men and women with a mean age of 67 years and a mean BMI of 30 kg/m^2 and risk factors for CVD, and nearly half of them had Type II diabetes. The aim was to compare a low dairy, low-fat diet with a high-fat MeDiet. Simple dietary changes involving supplementation of a vegetable-rich MeDiet with either extra virgin olive oil (EVOO) or mixed nuts versus a standard low-fat regime. The study was stopped early by the ethical committee because of a clear difference, but not in the way predicted. The intervention resulted in a 30% reduction in CVD risk, metabolic syndrome and Type II diabetes as well as breast cancer. The CVD risk reduction experienced in either EVOO or nut arms was comparable to that reported in statin clinical trials, demonstrating that food can truly act as personalized medicine [3].

Public health versus individualized health nutrition

An interesting question is whether participants of the PREDIMED study would have achieved similar outcomes by following one-size-fits-all government-endorsed dietary guidelines. Increasingly modern science is showing the extent of interindividual variation in physiological demand for and response to nutrients such that lean healthy students on identical diets and exercise will gain weight at very different rate ranging from 4 to 13 kg over 8 weeks and gene variations have a lot to do with this – as being a twin reduced the variation dramatically [4]. Other human genetic work has shown big genetic variations between people in energy expenditure [5], antioxidant vitamin levels in blood [6], chemical metabolites [7,8], fat deposition [9] and even the normal immune system [10].

This fundamentally challenges the foundations on which population guidelines have been based, such that the message may be disadvantageous for some. This is clearly illustrated by the official dietary guidelines issued by Public Health England, known as 'The Eatwell Guide' [11], which promote the idea that a diet that is high in carbohydrates (at least 50% of total) and low in fat is 'healthy and balanced', a phrase that is repeated throughout textbooks in nutrition and dietetic practice.

Increasingly, this rather dogmatic simplistic advice is being challenged particularly given the increasing rates of diabetes and prediabetes in the population. For example, reviews of the same literature [12] suggest that a lower carbohydrate diet achieves significant reductions and even cessation of diabetic medication and that it is possible that the current dietary advice – that is, embedded in the Eatwell Guide, may actually be accelerating β-cell exhaustion. Type II diabetics have been led to believe that government-endorsed advice to eat 'plenty of starchy foods such as rice, bread, pasta and potatoes (choosing whole-grain varieties when possible)' [11] is based on clear evidence and applicable to the whole population. In fact, neither are correct.

Based on these recent conflicting views, what are nutrition health professionals meant to do? One option is to wait until key long-term human randomized controlled trials of good methodological quality like the PREDIMED study are published on UK-type populations, a process that could take decades at the current rate.

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Another, more appealing option for the demanding 21st century patient is to engage in 'one-person trials' [13] that move away from the concept of 'the average person'. Instead, individualized medicine takes personalization to the next level, making healthcare participative by involving their patients in the process of their own care, accounting for differences in their patient's genes, environments and lifestyles. Instead of waiting for years for science to make it from bench to bedside, clinicians should run n = 1 PREDIMED-style trials with their patients, watching closely the impact of – for example, an energy-unrestricted Mediterranean-type diet that is high in unsaturated fat and rich in antioxidant nutrients from EVOO and nuts, on metabolic factors such as abdominal obesity, hypertriglyceridemia, low HDL cholesterol, elevated fasting blood glucose and elevated blood pressure. As long as they are monitored – there is much more to gain healthwise than there is for them to lose, particularly when the key foods recommended are core to ancient dietary patterns, just as EVOO is to the MeDiet.

Food as personalized medicine: a growing demand

An ever-growing number of nonscientists are taking advantage of open-access databases and peer-reviewed journals to realize that they can very soon become more well-read than their doctors, and the ability to share content easily by means of social networking means scientific findings and debates can be disseminated rapidly. Combine this context with growing interest in 'omics' assays that expose people's unique characteristics at the molecular level and one can start to understand how these individuals, avid for knowledge about their health and how to improve it, are pushing for a dramatic reduction in the time it takes for a discovery made in a laboratory to turn into a public

health recommendation. The Genome revolution has allowed nearly a million people to test their own DNA via the internet on sites like 23andme.com avoiding doctors. However, gene testing has so-far failed to accurately predict for an individual the optimal diets or risk of common diseases despite exaggerated or misleading claims about the potential benefits of direct-to-consumer genetic testing companies, mostly because genetic data only provides part-answers to the complex jigsaw that is health. More powerful tools to help personalized nutrition are likely to come from other directions.

The last 5 years has seen an explosion of research in the gut microbiome brought about by gene testing of the microbes using a small stool samples to assess the thousands of different species [14]. These microbes collectively called a microbiome vary between individuals far more than our genes do and are influenced by our health and our diet. Increasingly, it looks like you can assess a person's health far better by a single microbiome test than a genome screen and major disruptions are seen in allergy, obesity, colitis and irritable bowel syndrome, diabetes or even cancer. The 'Western diet', rich in animal protein, fats and artificial additives, and lacking in fiber, beneficial microbes, plant phytochemicals, vitamins and minerals, is thought to drive these conditions by encouraging gut dysbiosis [15]. While these tests are not diagnostic in nature, and can vary from day to day, the reports and accuracy will continue to improve with time and larger datasets. Importantly, they are useful in motivating the patient and providing a holistic snapshot of gut health and diversity.

Emphasizing the forgotten role of fiber is another key element [8], but the health professional who helps the individual understand what the results mean for them in their particular context – for example, depending on their family medical history, age, lifestyle and dietary habits. For someone with low microbial diversity and a few 'microbial quirks' that make them more prone to obesity and metabolic disease, recommendations could be made to increase certain high-fiber foods, along with polyphenol-rich fruits and vegetables – to help boost certain bacteria. For example, someone with deranged markers of inflammation, glucose and lipid metabolism is likely to benefit from including whole-grain barley and brown rice in their diet, as this tends to result in an increase in the number of microbes of the *Roseburia*, *Bifidobacterium* and *Dialister genera*, leading to improvements in metabolic dysfunction in humans [16]. Blueberries may also be an appropriate food for someone with high oxidative stress [17] as excess free radical formation increases the risk of cardiovascular disease. This polyphenol-rich fruit is known to significantly increase numbers of the probiotic Bifidobacteria, *Longum infantis*, which is known to possess immunomodulatory and anti-inflammatory activity [18].

Akkermansia muciniphila is seen in higher numbers in lean people [19]. Recent human evidence points to ellagic acid, a polyphenol in pomegranates, as having the ability to increase Akkermansia red grapes contributing to an increase in the abundance of this beneficial bacterium [20]. A group in Israel has recently developed an algorithm [21] to personalize your optimal diabetic diet based on your gut microbes. They found that even for measuring glucose spikes – the gut microbe composition was far more important than the calories or glycemic index score of the food.

With growing amount of omics research being conducted, there is an obvious translational bridge to cross between research and clinical practice, which demands continuing professional development to remain up-to-date. People want to work with health professionals who involve them in their care, giving them, individualized health advice that makes sense to them.

The future of nutrition could look very different. We should be tearing up the old text books – cautiously embracing the new omic technologies and the Internet – but above all treating every patient as a research subject, every meal as an opportunity and every food as a potential drug.

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