Opportunities and Challenges in Nutrigenetics/Nutrigenomics and Health

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Looking into the crystal ball to predict the future is always a risky operation. We are, however, confronted by this challenge when asked to provide, for others and ourselves, a vision of the evolution of a scientific area. As the essayist Jonathan Swift wrote: ‘Vision is the art of seeing things invisible.’ It is the attempt to imagine what is behind the curtain of current knowledge and wisdom. Nutrigenetics/nutrigenomics is a novel area of scientific research, its roots do not run deep in a glorious past but instead it looks towards the future. The symbol of the recently founded International Society of Nutrigenetics/Nutrigenomics (ISNN) is a tree bearing fruit, reflecting this sense of optimism. But it is a tree in springtime, when the fruits are foreseeable, but not yet within reach.

In this brief introductory chapter I will analyze some of the current needs of this new discipline. I will try to delineate the unique opportunities, and anticipate at least some of the challenges ahead.

Why Nutrigenetics/Nutrigenomics?

As living organisms, we are all the product of the interaction of our genes with our environment. Both genes and environment are essential components of life. Contrary to monogenic diseases, where a mutation in one single gene can be the sole cause and the ‘essence’ of a disease (e.g. sickle cell anemia), most global acquired diseases, such as coronary heart disease and cancer, are under the influence of a very large number of genes, and are always profoundly influenced by the environment. Therefore, acquired chronic diseases are paradigmatic examples of gene-environment interactions, where it is difficult to say which is predominant. Although family history can often be found in patients suffering an acute myocardial infarction, siblings in the same family are often unaffected, illustrating the principle that in such cases we inherit propensities, not inevitabilities.
Whatever the relative proportions of genetic and environmental factors that we may try to evaluate in such cases, the fact is that genes and environment are not entities in isolation, but they deeply interact with each other. The influence is bidirectional, in the sense that genes can affect factors that we recognize as environmentally modifiable (e.g., serum cholesterol), and environmental factors can affect gene expression. Nutrients are most likely the main environmental factors which we are exposed to, and they also interact with our genes bidirectionally. Coronary heart disease, which is now the leading cause of death and disability worldwide [1], is a case in point. In 52 countries spread across every inhabited continent, a study of the occurrence of a first myocardial infarction estimated that 9 known risk factors (smoking, history of hypertension or diabetes, waist/hip ratio, dietary patterns, physical activity, consumption of alcohol, blood apolipoproteins, and psychosocial factors) account for 90% of the population-attributable risk in men and 94% in women [2].

Three considerations appear to me extremely relevant here: (1) the above risk factors, including dietary pattern and the propensity for alcohol consumption, are all under genetic influence; (2) all these factors are modifiable, they are not at all inevitable; (3) six of these nine risk factors are influenced by the diet (or are themselves dietary patterns) and they interact with physical activity, which in the above analysis was also accounted for as an independent factor. Thus, nutritional factors, which were the first example given in molecular biology for ways to control gene expression (see the operon theory by Jacob and Monod [3]) are the best example I can give of how the environment influences our genes, and are themselves influenced by our genes. Indeed the terms ‘nutrigenetics’ (how the genetic constitution modulates the response to nutrients) and ‘nutrigenomics’ (how nutrients affect gene expression) are themselves intertwined, and are largely understandable as two faces of the same coin [4].

Opportunities

Nutrigenetics/nutrigenomics has an increasing public profile and is attracting the attention of the media. In its 2007 special report into nutrition, *The Economist*, a current affairs magazine, carried the following text:

Some people eat three-egg omelettes topped with slivers of bacon and show no sign of a spike in cholesterol. Some people indulge in one chocolate bar after another and stay as thin as a rake. Many, however, are less fortunate. Current research suggests that the culprit may be found in one's genes. Differences in genetic make-up may not only determine the ability to metabolize certain nutrients, such as fats and lactose, but also susceptibility to disease.

The good news is that, within five years or so, researchers should learn how to modify people’s diets to thereby prevent or delay the onset of a possible illness. At least, that is the goal of nutritional genomics, a new field that studies how genes and diet interact [5].

In this way, the media reflects and drives public interest in nutrigenetics/nutrigenomics, seeing it as holding the promise of personalized nutrition where each individual’s diet is devised to best interact with his or her genetic make-up. This is the
unique opportunity of this new discipline as it deepens its roots in nutrition, preventive medicine, clinical disciplines, genetics and molecular biology and systems biology. It gives rise to the possibility of exploiting subcellular, cellular and preclinical animal models and also to provide a unique way of synthesis, a unique new idea.

Thomas Aquinas, the 13th century theologian and philosopher, stated: ‘The essence of the human being is to take two concepts which are themselves abstract, then to put them together to form a new abstract concept which is unlike the two original ones.’ This applies to the combination of the concepts that give rise to an entirely new individual entity. Nutrigenetics/nutrigenomics is indeed a single leap forward of the imagination, opening a new area of investigation with enormous potential consequences.

Although nutrition obviously predates pharmaceutics in human history, interestingly nutrigenetics is an expansion of concepts seen in pharmacogenetics: an attempt to better understand the reasons underlying variability of individual responses to the environment. Thus, nutrigenetics is an attempt to make sense of the inter-individual variation in our responses to diet – the main environmental factor – in the way that we are now approaching an understanding of why people react differently to the same antiplatelet drug [6] in terms of inhibition of platelet function and how this translates into a greater or lesser protective effect against myocardial infarction. Indeed, we now have excellent examples of genetic variants affecting the probability of a disease, and of nutrients able to modify such probability. For example, insertion/deletion gene variants in the promoter region of 5-lipoxygenase, affecting the production of leukotrienes, are related to the risk of increased intima-media thickness in the carotid arteries (a proxy for the burden of atherosclerosis), but such genetic influence can be totally abrogated by increased intake of omega-3 fatty acids, known sources of weaker leukotrienes and alternatives to the main eicosanoids derived from omega-6 fatty acids [7, 8]. And we have, likewise, examples of direct control by nutrients of gene expression, examples being – from my own personal interest – the modulation of expression of adhesion molecules and of the inflammatory enzyme cyclooxygenase-2 by omega-3 fatty acids [9, 10].

The background science is there, but how close are we to the goal of implementing personalized nutrition based on genetic knowledge? We are not there yet. I will briefly explain why.

We already now know, by-and-large, how to modify people’s diets to prevent or delay the onset of a possible illness, but we know this in terms of ‘average’ responses of groups of subjects to a given change in the diet. We also have excellent cases where dietary habits that can be good for some can be bad for others, for example, in attempts at understanding the responses of lipid metabolism to the intake of polyunsaturated fatty acids [11].

However, most such studies have not yet come full circle to establish a solid ground for health claims. The reasons are:
- Most studies performed have been either complex nutritional interventions or they isolated the effect of a single nutritional component. So far there has never been a combination of the 2 approaches with the same aim. The result is that,
with the first approach, we cannot ascribe the effect observed to one single dietary factor, and with the second, we cannot exclude the abrogation or the reversal of the effect by contrasting effects from other nutrients, due to scarce or actually absent knowledge on the effects of interactions with other dietary components.

- There is usually in such studies little or no knowledge of the overall effect on the organism. We study single outcomes, thought to be related to a more general endpoint (I use the terms ‘outcomes’ and ‘endpoint’ deliberately), but we have not proved so far the effect on the general endpoint itself.

Challenges

As researchers in a new discipline, those working in nutrigenetics/nutrigenomics are energized by the excitement of navigating uncharted waters, but we must not allow our enthusiasm to blind us to the problems. Sailors venturing into the Arctic sea know that most of the dangers lie below the surface, and because these dangers are not readily visible there is a risk of trivializing them, rendering them more insidious. It is important at the very beginning of the life of a new discipline to recognize and manage upfront these difficulties, as if they are left unchecked they may undermine the credibility of the entire field.

I see major challenges in the following areas:
- relying on surrogate/intermediate endpoints;
- issuing premature health claims;
- underestimating the financial interests involved;
- misjudging ethical and legal implications.

Surrogate Endpoints

We need surrogate endpoints. At the beginning of a clinical investigation we need readily measurable and obtainable parameters that give us a sense of where that research topic is going. In the two examples given before [7, 8], the measurement of the intima-media thickness as a proxy for atherosclerosis is logical, understandable, and supported by good evidence of its relationship to more concrete endpoints. For the relationship of polyunsaturated fatty acid intake to the blood levels of HDL cholesterol, in the other example given above [11], HDL cholesterol is a lipid parameter related to the firmer endpoint of coronary heart disease morbidity and mortality.

However, in addition to often being of little importance to patients, surrogates may lead to misleading and erroneous conclusions [12]. Endpoints are indeed a first approximation to the disease we are trying to prevent, but they must be substantiated at some point with firmer evaluations. The history of clinical pharmacology is replete with examples of drugs found to be effective in large-scale trials on some intermediate outcome and then proven in the end to cause harm rather than benefit on the same disease process that is known to be related to the intermediate outcome investigated.
An example is hormone replacement therapy, which was found to favorably affect atherosclerosis progression and yet caused increased – rather than decreased – cardiovascular deaths because of an unexpectedly high excess risk of thrombosis [13]. There is also the more recent unfortunate story of the cholesterol ester transfer protein inhibitor torcetrapib, found to be very effective in raising HDL-cholesterol, and yet causing more harm than benefit in treated patients, likely due to some unanticipated off-target detrimental effect of the specific drug used [14]. How much of the currently performed nutrigenetic/nutrigenomic research goes down the road to the point of showing the ultimate health consequences of personalized nutrition? I would assert that no such examples yet exist. There must be a way to come to full circle to demonstrate the clinical relevance of operating differentially in different patient categories. Until this process is completed, it is premature to make health claims.

Premature Health Claims
As a consequence of the current weaknesses in evidence, most of the other challenges come from the temptation to rapidly exploit the burgeoning amount of knowledge being acquired for rushed, unwarranted health claims, linked immediately to financial interests. While industrial interests can help the development of sound scientific research, they can also thwart it, ultimately discrediting it. It is easy to understand the willingness of manufacturers to sell their genetic tests even if doctors do not know what to do with them [15]. Similarly, it is easy to anticipate (actually, to witness) the creation of companies wishing to ride the horse of the trendy business of personalized nutrition, selling recipes claiming to be ‘good for you’ and ‘based on the latest scientific developments’. This is a huge problem that has to be faced properly.

Ethical and Legal Implications
Last, but not least, there are ethical and legal implications in the area of genetic testing [16] and of nutrigenetics [17] that need to be known and carefully approached. These involve:

– the management of genetic information;
– consent, confidentiality, familial consequences, testing children;
– non-medical uses of information by employers and insurers.

The handling of genetic information is an area fraught with difficulty. For example, we know that a mutation in apolipoprotein E (e4/e4) that is found in 14% of the UK and US populations is linked to an increased risk of early cardiovascular disease, and such risk can be modified with diet. This genotype is, however, also linked with a 60% increased risk of developing Alzheimer’s disease, where it is not clear whether changing dietary fat intake favorably or unfavorably affects the risk of Alzheimer’s disease.

We must also consider the fact that, in general, it is well established that having a healthy diet and lifestyle are of paramount importance. We should therefore not risk diluting these messages with premature speculation and resist the temptation to raise expectations that may later prove unrealistic. It is also important not to frighten...
people with results of genetic tests showing they have increased risk for a condition that could be modifiable with an expensive and at this time still unproven ‘personalized’ diet. In other words, we should continue looking at what we have already on our shelves, where there are already dietary choices known to be healthier than others, independent of any knowledge of individuals’ genetic constitution. These include foods derived from organic and free-range animal farming (which not just affect our genes, but also involve ethical choices), low-fat products, products with a low glycemic index, increased intake of fish, fruits and vegetables, friendly bacteria products, folic acid to prevent neural tube defects and severe cases of hyperhomocysteinemia, vitamins for children and older age groups to combat absolute or relative deficiencies.

How to Deal with the Challenges

Meeting these challenges is a daunting prospect and fighting this battle will be difficult, more so if those in the field act only individually. It is for this reason that there is a great need for a scientific society with the mission to select and give voice to sound scientific information in an extremely complex, crowded and ‘polluted’ arena. The ISNN aims to act as a clearing house for media and scientific information, and place itself in an intermediate position between investigators and industry. In his welcome note on the organization’s website, society president Dr. Artemis P. Simopoulos wrote that the purpose of the ISNN is to ‘increase understanding through research and education of professionals and the general public of the role of genetic variation and dietary response and the role of nutrients in gene expression’ [18]. Dr. Simopoulos continued that important aims of the ISNN include serving as a clearing-house for the media in disseminating facts regarding the role of genetic variation and dietary response and the role of nutrients in gene expression, assisting in interpreting the new facts into sound nutritional advice for the public, and establishing science and education committees. The ISNN provides an opportunity for an ethical alliance of scientists motivated by genuine science to advance knowledge, but also to act as a transmission chain to the public.

We are humbled by the magnitude of the task, but also proud and thrilled by the opportunities and the challenges ahead.

References


