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PROCEEDINGS

An introduction to nutrigenomics developments and trends

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Throughout our lives, we choose to a complex mixture of foods, which can have a positive or negative impact on our health. Intricate biochemical processes extract the energy and other useful components that enable us to grow and function, and many compounds, seemingly unimportant in the past, are now recognised as being beneficial. The problem, for scientists and consumers alike, is that the benefits appear not to be the same for everyone.

Individual genetic differences in response to dietary components have been evident for years, e.g. cholesterol and saturated fat intake. In the UK alone, one in three die from cardiovascular disease (CVD)—heart attack, stroke etc. High cholesterol causes a third of all CVD worldwide and by 2020 CVD will be the leading cause of death, and disability, worldwide (>20 million deaths per year rising to 24 million in 2030). A 10% reduction in blood cholesterol can halve the risk of CVD in a 40-year-old man; why 10%? Because this is about the extent to which diet alone can have an impact but even that can depend on our genetic make-up. Thus, we need to understand how what we eat interacts with our bodies—or, more specifically, our genes—to affect our health. This is the science of nutrigenomics.

The post-genomic technologies allow nutritional research to take a more holistic perspective; using new technologies provided by the sequencing of the human genome as well as adapting existing ones to measure how what we eat interacts with our genes, proteins and metabolism. The long-term aim of nutrigenomics is to understand how the whole body responds to real foods using an integrated approach termed "systems biology". The huge advantage in this approach is that the studies can examine people (i.e. populations, sub-populations—based on genes or disease—and individuals), food, life-stage and lifestyle without preconceived ideas.

Genomics seeks to understand the structure and function of our entire DNA sequence—all three billion base-pairs across 23 pairs of chromosomes. Genotyping describes the genes for a particular characteristic but cannot predict phenotype—the result—except in very simple cases, e.g. eye colour. Predictable phenotypes include those associated with disease, e.g. cystic fibrosis, but not generally diet or age-related diseases, which are controlled by many genes and external factors.

DNA codes for proteins but DNA and proteins do not "speak" the same language; their interpreter is RNA. Transcriptomics using Affymetrix GeneChip® arrays or two-colour microarrays can measure which and how often genes are actively being read. What it does not reveal is whether or not this is having any affect overall.

Proteomics is the study of proteins, their structure and their function, and metabolomics the products of our metabolism, which are affected by gene transcription and translation as well as proteins function.

Perhaps more easily understood than nutrigenomics, nutrigenetics examines single-gene/single food compound relationships. One of the best-described examples is folate and the gene for MTHFR (5,10-methylenetetrahydrofolate reductase). MTHFR has a role in supplying methionine, which is important in many metabolic pathways include production of neurotransmitters and regulation of gene expression. Folate is essential to the efficient functioning of this MTHFR. There is a common polymorphism in the gene for MTHFR that leads to two forms of protein: the

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referance (C), which functions normally, and the thermallabile version (T), which has a significantly reduced activity. People with two copies of the reference sequence gene (CC) or one copy of each (CT) appear to have normal folate metabolism. Those with two copies of the unstable version (TT) and low dietary folate accumulate homocysteine and have less methionine, which increases their risk of vascular disease and premature cognitive decline.

Supplemented with folic acid (or increased intake of folate from food sources), TT-individuals quickly metabolise excess homocysteine, restoring their methionine levels to normal. There are about 20 genes that have polymorphisms that appear to confer a significant disadvantage, which may be overcome with a specific—often single compound—dietary modification. Businesses like Sciona Inc. (http://www.sciona.com) and Genelex Inc. (http://www.genelex.com) base their services on this knowledge. There are, however, a number of wider issues to consider.

In the first place, genotypes that confer a substantial survival disadvantage are not usually preserved and those that have are shown to offer some other benefit. For example, we now know that individuals with a single copy of sickle cell or thalassemias genes have inherent protection from malaria, which is endemic in regions where these variations are most commonly found. The fact that the most common polymorphism for the MTHFR gene is present in 15–20% of European population must at least raise the question why it and the other genes have persisted. Secondly, these 15–20 genes represent 0.1% of human genes; Ensembl (http://www.ensembl.org) estimates there are 22,218 protein coding genes in the human genome. Currently, we neither know how or which of these genes interact with one another nor the consequences of modifying the response of a few on the majority or the effects of that on our immediate or long term health. Thus, while increasing your intake of folate may be beneficial in the long term, it may be shown at some point in the future that increased intake has unforeseen risks for some individuals or subpopulations.

In 2000, the application of these technologies in nutrition was relatively untried and untested. They were clearly powerful tools with enormous potential, but there was a need for standardisation in approach both in terms of the logistics and study design as well as many other issues that prevented their use. Such is the complexity of nutrigenomics that it is not possible for nutritional researchers to work alone. Expertise in a wide variety of different areas—molecular and cell biology, mathematics and statistics, nutrition and diet, food chemistry, and social science—are fundamental to progress. To this end, 22 leading groups in Europe have united to create The European Nutrigenomics Organisation, or NuGO (23 w.e.f. 2006).

Funded by the European Commission for 6 years, NuGO gives scientists, from organisations that usually compete for funding and the best researchers, their first real opportunity to work together to advance nutrigenomics research. Difficulties stemming from professional jargon, organisational structure, and distance are more than offset by the benefits of integrating nutrigenomics facilities and expertise to ensure cooperative use of knowledge and its application in nutritional research.

The post-genomics technologies are still an enormous challenge in humans. Much of the work already in the literature is in animal or cell models, not free-living humans, but this is changing. And research projects, like Diogenes and Lipgene, are capitalising on these and other advances, e.g. better food composition tables from EuroFIR (European Food Information Resource Network).

The ethical, legal and societal aspects of nutrigenomics are as complex as the technical difficulties. Some of the information emerging from nutrigenomics research is difficult to handle. For example, a mutation in the apolipoprotein E protein (e4/e4) is associated with increased risk of early CVD. Changes in the intake of dietary fats are successful in reducing this risk but, the individual may or may not become ill in the future. He or she is only more likely to experience CVD at an earlier age than someone without this mutation; when and in what form remains uncertain. However, this genotype is also linked with a 60% increased risk of developing Alzheimer's disease. Currently, there is no means of preventing or curing Alzheimer's disease, and it is not clear whether reduced risk of CVD, following modification of an individual's dietary lipid intake, is concomitant with reduced risk of Alzheimer's disease. And, here again, it is only a 60% increased chance, not a certainty. Just as with genetic diseases, nutrigenomics must allow choice; the right to opt out of knowing whether you are a carrier of a particular genotype, and the right to employment and insurance benefits regardless of whether you choose to access that information, and the right to ignore dietary and lifestyle advice albeit that this is not without some penalty. The pharmaceutical industry has much to offer nutritional science in trial design, and understanding of risk-benefit. It also has much to teach us about economic access to "treatment" and the right not to be discriminated against.

Promotion of healthy patterns of nutrition and lifestyle are paramount and key messages on a healthy diet are well established. We should not risk diluting these messages with premature speculation about what nutrigenomics can achieve or raise unrealistic expectations. It would also be unfortunately to scare people about increased risk of age-related disease unnecessarily. The reality is, however, that poor dietary choice within a sedentary lifestyle is contributing to chronic ill health. The "one-size-fitsall" strategies in public health have not always been delivered consistently,

which may be why they do not appear to be working to be changing people's dietary habits, and personalising nutrition may be more effective in achieving the desired long-term change. Nutrigenomics is not an alternative to public health policies but it does have much to contribute to the discussion and perhaps some solutions.

Industry needs strong examples with clear benefits to put nutrigenomics products on supermarket shelves. But, it might be argued that these products are already there.

Lifestyle products such as organic and free-range demonstrate consumers' desire for personalised products that suit their ethical consciousness as well as their perceived dietary needs such as lowfat alternatives and GI (glucose index). Phenotypic products (anticholesterol, blood pressure reducing and "friendly bacteria"), which are clinically proven to different extents, are targeted those consumers that know they are at risk or think they might be because family history or a less than ideal lifestyle. The challenge here is to ensure that such products do not harm those who choose to self-medicate unnecessarily.

Life-stage products already exist—folic acids supplements for women thinking about getting pregnant, kids and older agegroups vitamins supplements, and if seeking an example that is real food then consider milk; full fat milk for under fives, semiskimmed for older children and young adults, and skimmed for adults. Genotypic products will follow, starting with "medical groups" (e.g. diabetics) and formalising the existing phenotypic products.

In the end, humans are complex and so too are their diets; these make nutrition science and the questions it must address fiendishly difficult. Although they still seem impossibly complicated, nutrigenomics and systems biology are the ideal, and perhaps, only tools able to answer the question—what should we be eating?

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