



Conference on 'Translating nutrition: integrating research, practice and policy' Symposium 2: Intervention study design and personalised nutrition

The future direction of personalised nutrition: my diet, my phenotype, my genes

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Although personalised nutrition is frequently considered in the context of diet–gene interactions, increasingly, personalised nutrition is seen to exist at three levels. The first is personalised dietary advice using Internet-delivered services, which ultimately will become automated and which will also draw on mobile phone technology. The second level of personalised dietary advice will include phenotypic information on anthropometry, physical activity, clinical parameters and biochemical markers of nutritional status. It remains possible that in addition to personalised dietary advice based on phenotypic data, advice at that group or metatype level may be offered where metatypes are defined by a common metabolic profile. The third level of personalised nutrition will involve the use of genomic data. While the genomic aspect of personalised nutrition is often considered as its main driver, there are significant challenges to translation of data on SNP and diet into personalised advice. The majority of the published data on SNP and diet emanate from observational studies and as such do not offer any cause–effect associations. To achieve this, purpose-designed dietary intervention studies will be needed with subjects recruited according to their genotype. Extensive research indicates that consumers would welcome personalised dietary advice including dietary advice based on their genotype. Unlike personalised medicine where genotype data are linked to the risk of developing a disease, in personalised nutrition the genetic data relate to the optimal diet for a given genotype to reduce disease risk factors and thus there are few ethical and legal issues in personalised nutrition.

Personalised nutrition: Genotype: Phenotype: Metatype

In 1960, over half a century ago, a paper was presented as part of the Proceedings of the Nutrition Society with the title 'Genetic determinants of nutritional requirements'⁽¹⁾. This paper referred to work at the beginning of the twentieth century on the relationship between genetics and inherited disorders of metabolism⁽²⁾. Thus, the science of human nutrition has long retained an interest in the genetic determinants of metabolism and, specifically, the manner in which that is influenced by diet. Indeed, in 1950, a review of the area of nutrition and genetics noted that: 'A genotrophic disease is one which occurs if a diet fails to provide sufficient supply of one or more nutrients required at high levels because of the characteristic genetic pattern

of the individual concerned. This concept based upon results in genetics and biochemistry is new in medical thought and is believed to be the basis for many diseases, the causation of which is now obscure. Individual patients are far from standardised specimens and medical problems should consistently be considered in terms of the genetically diverse patients, rather than in terms of an absolute normal'⁽³⁾. The first real engagement of nutrition research with a common genetic polymorphism occurred in 1977, when the effect of a common polymorphism of apoE on disorders of lipid metabolism in man was published⁽⁴⁾. As a consequence of this publication, nutrition researchers were required to take apoE polymorphisms into account in

Abbreviation: DBS, dried blood spots.

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both epidemiological and experimental studies in the interaction of diet, blood lipids and CVD⁽⁵⁾. The sequencing of the human genome just over a decade ago heralded an era wherein genetic data would begin to dominate all the biological sciences. The concept of personalised medicine, first noted in the 1970s, began to emerge and with it the concept of personalised nutrition⁽⁶⁾. Generally speaking, personalised nutrition has, alongside personalised medicine, had a gene-centric approach. However, the delivery of personalised nutrition is increasingly seen as existing at three levels: personalised nutrition advice based on personalised dietary data, personalised nutrition advice based on personalised phenotypic data and personalised nutrition advice based on personalised genomic data.

Personalised nutrition based on personalised dietary analysis

Many services presently exist that offer consumers and researchers online dietary assessment tools⁽⁷⁾. The methodologies involve both FFQ and the 24-h recall approaches. Many of these online dietary assessment tools are designed to serve the needs of large-scale dietary assessment either for the collection of national dietary intake data or for the collection of data for epidemiological studies⁽⁸⁾. For the purposes of the delivery of personalised dietary analysis, a somewhat different approach is needed. Precise and exact estimates of nutrient intakes are required for national surveys or epidemiological studies. Such a precision is most likely not necessary for personalised nutrition given that increasing the precision requires increasing the input from end-users for web-based personalised nutrition services and that the ease-of-use of such services will need to be traded against requirements for precision. For example, in a European Union Seventh Framework Programme integrated project, Food4Me, participants are recruited to receive personalised nutrition as part of an online proof-of-principle study. It is envisaged that after data entry by the user, the nutrient intake data would be compared with appropriate reference values and allocated a colour code along the lines of green for an acceptable range of intakes, orange for a range of intakes above or below this reference value and red for intakes which require urgent action⁽⁹⁾. This allows for the development of feedback on nutrient intake using simple visual tools that are more user-friendly than detailed numeric data.

Although feedback to consumers on nutrient intake based on colour-coded reference values is relatively easy, translating those data into advice on food choice poses a greater challenge. A food or food group might make a significant contribution to a nutrient intake that receives a red code, but it could also make a significant contribution to a nutrient intake receiving, for example, a green code. Correcting the intake of that food to address an unacceptably high or low intake (red code) could inadvertently cause its contribution to another nutrient to move from a satisfactory range (green) to a less satisfactory range (orange) or an unacceptable range (red). Thus, while it is tempting to consider automation of food choice advice based on apparently logical algorithms, such an approach

will require validation of the efficacy of these algorithms with expert judgement.

Traditionally, dietary advice is delivered in terms of individual foods, based on the analysis of a person's dietary patterns. These analyses are derived from the intake of the food components of a meal rather than the meal itself. If personalised nutrition moves away from the high level of precision required for epidemiological studies, then it remains probable that the analysis of an individual's dietary patterns might be based on meal intake rather than on the intakes of the individual food components of a meal. For example, if 90% of the variation of nutrient intakes in breakfasts can be explained by six broad classes of breakfasts, then these six classes of breakfasts can be visually presented to the consumer on a computer screen with a click-and-drag option to select the most appropriate choice. This can lead to a second wave of breakfast choices with the most appropriate choice finally selected again using click-and-drag technology. If, within personalised nutrition, individuals can be classified according to ranges of nutrient intakes rather than point estimates, then average values for target meals in terms of nutritional composition may make this meal-based approach possible. This is an area requiring considerable research, which again will have to be based on a multi-disciplinary approach.

Personalised dietary analysis and associated food choice will also exploit mobile phone technology. This involves the use of mobile phones to capture images of foods and beverages before and after eating. The images are then transmitted to an analytical centre charged with two key processes: the identification of each component of the meal and the volume assessment of each component before and after eating. Once the food is identified and quantified, its nutritional composition can be computed and the user can receive comprehensive feedback on nutrient intake. It has been shown that when an object of known dimension and size (a fiducial marker) is placed adjacent to the meal, the measurement of the volume of the components is greatly improved. Studies show that while adults and adolescents can easily use this technology, the adolescents are better in ensuring that all elements of the meal are captured in the mobile phone photograph⁽¹⁰⁾. The quality of the image is very important for both the identification of the food components and the estimation of volume. Thus shadows and reflections considerably reduce the accuracy of volume measurements⁽¹¹⁾. The use of mobile phone technology poses both great opportunities and significant challenges to a highly inter-disciplinary research programme, which by definition will require iterative field testing of each stage of technological development. At present, the prevailing iterative field technology is being used in studies aimed at improving the dietary habits of young adults⁽¹²⁾.

Personalised nutrition based on personalised phenotypic data

The most widely used tool for phenotypic measurements is the bathroom scale and perhaps, also, waist belts. There is, however, growing interest in the development of new portable and unobtrusive technologies, which consumers



can use to learn about many aspects of their phenotype. Although many examples exist, for the purpose of the present review, two publications that have examined the impact of phenotype monitoring devices in intervention trials will be considered. Yamasue *et al.* have developed an electronic device that allows for the measurement of the Na concentration in urine in the home or at work⁽¹³⁾. This was then used in a Na- reduction intervention study with hypertensive railway employees⁽¹⁴⁾. At the outset of the study, all the subjects participated in a group-counselling programme on salt restriction and hypertension. The electronic dietary device measured Na excretion adjusted to a 24-h output and the subjects used a home blood pressure monitoring device to record their own blood pressure on a daily basis. The subjects were then given generalised advice on ten occasions over the 4-week intervention via their mobile phone on tips to lower Na intake, on the Na content of specific foods and general encouragement to use a Na-restricted diet to reduce blood pressure. A control group received only the initial counselling advice. Daily salt excretion was significantly reduced in the intervention group, which also saw a significant reduction in morning systolic blood pressure and there was a significant relationship between these two parameters. The second study used the Internet, e-mails, a Bluetooth-enabled wrist-worn accelerometer and mobile phone technology to deliver an automated physical activity programme in a randomised control trial⁽¹⁵⁾. The 9-week intervention study showed that a significantly higher level of moderate physical activity was seen in the intervention group. These two studies illustrate the power of self-monitoring of phenotype together with personalised intervention services to improve the lifestyle of individuals. Many other phenotypic measurement devices are available, ranging from sleep monitoring devices to ambulatory glucose monitoring devices, and there exists considerable commercial interest in both the development of such devices as well as the development of commercial services to deliver personalised phenotypic advice to consumers.

In addition to phenotypic measurements involving clinical, anthropometric and physical activity measurements, such a phenotypic profiling can be extended to blood biochemical measures of interest to nutritional assessment. In order for this to evolve into mass marketed consumer services, blood sampling has to move beyond the clinic to the home. To that end, dried blood spots (DBS) have emerged as a convenient route for home blood sampling allowing preservation of dried samples and the application on laboratory-consumer communication by postal services. DBS technology was first used in neonatal screening for inherited metabolic disorders and is extensively used in HIV studies^(16–17). The use of DBS sampling has been extended to many biochemical parameters, including hormones, cytokines, vitamins and lipids^(18–20). As with personalised dietary analysis and approaches to feedback to consumers, DBS phenotyping can be presented to the consumer as ranges from normal, to ranges that are moderately above normal, or to ranges that are very seriously outside normal. Phenotypic data on nutritional biochemistry markers can be translated into advice on modified nutrient intake, which is best delivered when

personalised dietary analysis is also available. There are, however, challenges to translation of this phenotypic advice to nutrient intake and ultimately food choice or meal pattern advice. DBS will contain a mixture of plasma and blood cells and as such will represent in certain circumstances a mixture of short-term intake (plasma levels) and longer-term intake (blood cell levels). This would certainly be the case for nutrients such as folic acid or long-chain *n*-3 PUFA. Measures of nutrient intake are subject to considerable within-person variability and this variability is greatly reduced with multiple measures of nutrient intake. In personalised nutrition, it is difficult to predict the extent to which potential users would want a once-off and quick measure or whether they would be willing to engage for a longer period within a personalised nutrition service. The former will likely lead to conflicts in the formulation of dietary advice between blood biochemistry and dietary analysis and, again, this is an area that will require considerable research.

DBS technology combined with advanced analytical chemical platforms will allow a wide range of targeted metabolites to be measured. This poses a problem for the delivery of personalised nutrition based on biochemical phenotyping. For example, if three ranges of DBS analytes are used such as high, moderately high and normal, then for five analytes, a total of 243 (3^5) combinations are possible. Some of these combinations will be frequently found in a large proportion of the population, while the others will be very infrequently found. Even allowing for a 75% attrition rate in occurrence, the number of possible combinations of analytes remains too high for the realistic delivery of personalised nutrition advice. This leads to the possibility of grouping individuals according to their metabolic profiles, an approach that is known as metabotyping. Complex datasets can be systematically studied using a wide variety of data-mining techniques⁽²¹⁾. In nutrition, the most widely used methods involve cluster analysis and this technique has been extensively used to study food intake patterns⁽²²⁾. This technique was applied to a study of the effect of vitamin D supplementation on plasma measures of the metabolic syndrome⁽²³⁾. A total of 160 subjects took part in a 4-week intervention study where one half of them received a daily dose of vitamin D and the other half received a placebo. No statistically significant difference in any of the biochemical markers of the metabolic syndrome was observed. Even when the subjects were categorised into those with adequate, sub-optimal and inadequate plasma 25-hydroxyvitamin D levels at baseline, no effect of vitamin D intervention on plasma biomarkers of the metabolic syndrome was observed. The data were then subjected to K-means cluster analysis, which is a non-supervised technique to create clusters based on input data. In this case, the cluster analysis used the thirteen biomarkers of the metabolic syndrome to create the clusters and five such were created. Of these, one showed a significant difference in the response of the markers of the metabolic syndrome with vitamin D intervention compared with controls. This cluster was characterised by low baseline levels of plasma 25-hydroxyvitamin D and higher baseline plasma levels of two adipokines, adiponectin and resistin. This is the first study to use K-means cluster

analysis to study metabolic phenotyping, but it does indicate the potential of cluster analysis in general to generate metabolotypes that, in sharing a common metabolic profile, might share a common dietary solution. However, this type of study will have to be incorporated into large epidemiological studies to discover exactly which clusters of metabolites are associated with specific chronic diseases.

Personalised nutrition based on personalised genotypic data

Following the sequencing of the human genome and advances in analytical technology, several commercial services emerged offering consumers individualised advice based on their genetic profiles and at the same time there was an enormous investment in research linking specific SNP and metabolic responsiveness to variation in diet. Typically, observational studies were used to link habitual dietary patterns with a given metabolic outcome in individuals with a varied SNP pattern of a specific gene. In general, this research has not led to any sustainable and reliable form of personalised nutrition, and even with advances in the movement from single nucleotide variation to whole genome measurements, it is difficult to see the widespread uptake of genome-based personalised nutrition. The root problem or challenge lies in the translation of observational data to data from human intervention studies. Traditionally, nutritional issues relating to health have had some initial data in animal studies which have been replicated in human epidemiological studies. That has been the pattern, for example, in the association between dietary fats, plasma lipids and CVD, which have evolved from animal studies to epidemiological studies and finally to dietary intervention studies. The latter are essential to prove cause and effect.

To illustrate the research pipeline that is needed to move from observational studies to public health nutrition policies, the example of the C677T variant in the gene encoding the enzyme methylenetetrahydrofolate reductase in hypertension is worth considering. In a case-control study comparing hypertensives with controls, conditional logistic regression analysis controlling for body weight showed a significant association of the T allele of this SNP with essential hypertension⁽²⁴⁾. This was followed by a meta-analysis of the literature for studies in subjects of Chinese origin which affirmed the observations among Caucasians that the TT allele of the methylenetetrahydrofolate reductase gene is associated with an increased risk of hypertension⁽²⁵⁾. The TT genotype is known to be associated with a reduced activity of methylenetetrahydrofolate reductase which is linked to a reduction of the FAD co-factor⁽²⁶⁾. The vitamin B, riboflavin, is an integral element of FAD and human intervention studies showed that in subjects with the TT variant of methylenetetrahydrofolate reductase, riboflavin lowered homocysteine⁽²⁶⁾. Extending this to CVD (subjects), riboflavin intervention over 16 weeks was found to modify blood pressure in those subjects with the TT variant, but not in those carrying the C allele of C677T genotype⁽²⁷⁾. In a follow-up study focusing on the TT genotypes, riboflavin intervention again

was shown to significantly reduce hypertension in CVD patients⁽²⁸⁾. It should be pointed out that both of the riboflavin intervention studies involved patients with hypertension who were being treated for this condition using a variety of hypertensive drugs. It is therefore clear that the move from a simple observational study of a diet-gene interaction to data that unreservedly show a diet-gene interaction in intervention studies requires quite a high research investment.

Consumer aspects of personalised nutrition

Regardless of advances in the technologies and improved scientific understanding of nutrigenomics, the key factor for the successful implementation of personalised nutrition is consumer acceptance. Before a consumer can be enticed to use any new product or service they must first be convinced of its value that it can provide some benefit and that it can be trusted. In the case of personalised nutrition, the consumer can be viewed as the individual who chooses it independently as a direct-to-consumer service or as the health-care provider who utilises it in health promotion. A pan-European survey of almost 6000 individuals found that willingness to undertake genetic testing for the purpose of personalised nutrition was 27%, but varied according to the country and age group⁽²⁹⁾. In those aged >65 years 55% were willing to undergo a genetic test for general interest. The study also showed that individuals who were aware that they had a health problem were more favourable towards personalised nutrition. Data from the USA indicate that 21% of consumers would be opposed to engaging in genetic testing for any reason⁽³⁰⁾. A later survey of consumers in Germany indicated that 45% would agree to nutrigenomics testing and that 40% would be willing to buy a proposed functional food product for the purpose of following personalised nutrition advice⁽³¹⁾. Such findings suggest promising potential for the personalised nutrition market and are encouraging for advancement in the area.

A large-scale consumer study in the Netherlands investigated the effects of consumer perception on personalised nutrition and found that the key determinants of acceptance by consumers were clear customer benefits at a reasonable cost, ease of implementation including peer support and, most importantly, freedom of choice regarding the uptake of such a service⁽³²⁾. In addition, the study also identified agreement among expert stakeholders as a key component for acceptance by consumers. It is inevitable that disagreement among scientists and health-care providers regarding the validity of personalised nutrition will lead to suspicion and a lack of trust among the public. It is the responsibility of providers and regulators to ensure that there is a code of practice in personalised nutrition that can be trusted. This is particularly challenging when many services are Internet-delivered, making it more difficult to legislate according to jurisdiction.

Advances in nutrigenomics and Internet-delivered nutritional assessment will contribute to a consumer-driven health-care market, where users can be empowered by initiating their own tests outside the traditional clinical



setting. Many providers of personalised nutrition fall into the category of direct-to-consumer genetic testing where the sale and use of genetic tests exclude the involvement of a health-care provider⁽³³⁾. In an inventory of direct-to-consumer genetic tests sold on the Internet, Goddard *et al.* identified a lack of accountability and consensus in recommendations among the service providers. In addition, health-care providers can be fraught with the task of explaining such test results to confused consumers when they themselves have a lack of resources for interpretation of results⁽³³⁾. Clearly, there is a need for safeguarding the delivery and interpretation of personalised nutrition for consumer protection.

Ethical considerations

Central to the ethical debate surrounding personalised nutrition is whether it is simply another useful tool for the preservation of health in modern society or whether it contributes to the medicalisation of food and an over-emphasis on health as the sole marker of well-being. Although there is an undoubted benefit to freedom of choice by consumers, voluntary genetic testing for personalised nutrition can carry an unfavourable outcome when the results reveal an increased risk of disease or ill health. Opportunistic screening could result in an unexpected burden or a worry and therefore there is an ethical responsibility for counselling and support to be included in such services for the protection of vulnerable consumers⁽³⁴⁾.

The handling of personal data also raises several ethical issues, particularly in relation to data sharing and sample identity. Consumers have expressed concern over misuse of genetic information⁽³⁵⁾. In addition, sensitive information regarding disease risk has the potential for discrimination with respect to insurance and employment⁽³⁶⁾. In 2008, the Genetic Information Non-discrimination Act was signed into law in the USA to protect its citizens against discrimination by health insurers and employers in relation to their genetic information⁽³⁷⁾. Such measures are vital for consumer protection if personalised nutrition is to become widespread practice in public health. Conversely, those individuals who receive information on 'low risk' may feel that it is unfair if this is not taken into consideration to lower the cost of their health insurance.

Dietary restrictions can have societal and cultural implications if individuals are advised to refrain from particular eating practices that are central to their identity because the role of food can extend beyond nutritional aspects. Therefore, it is particularly important that personalised nutrition advice is valid and is based on adequate scientific evidence in order to avoid unnecessary changes to lifestyle. An audit of genetic testing services was conducted by the US Government Accountability Office and it reported that the predictions made by such tests can be misleading to consumers, and may lead to needless preventative actions in the avoidance of illness or impervious behaviour when disease risk is believed to be low⁽³⁸⁾.

As the field of nutrigenomics is still in its infancy, the ethical issues concerned are related to the introduction of

personalised nutrition not only to the general public, but particularly to participants of clinical research⁽³⁴⁾. The European Nutrigenomics Organisation has produced a set of guidelines to assist stakeholders in this area⁽³⁹⁾. Much work is still needed to ensure adequate education and communication to consumers, particularly in the area of informed consent.

Future direction for personalised nutrition

Although personalised nutrition appears to be both logical and attractive to researchers, ultimately its future uptake depends on consumer demand. The area most likely to first benefit from personalised nutrition is the area of weight management. At present, this is the only area where consumers purchase nutritional services and where the food industry provides specific food products for consumers. One leading weight loss company offers personalised dietary advice on weight reduction together with personalised phenotypic measurement of energy expenditure⁽⁴⁰⁾. In the course of time, it is likely that genotypic data will become available that will allow consumers to be allocated to a weight-loss programme most suited to their genotype. A second possible early market might lie in food supplements. At present, such supplements are formulated for the general market or for a segment of the general market with a keen interest in the use of supplements, for example the older segment of the population. Although it is impossible to envisage how food companies could manufacture brands to different nutritional standards for different segments of the market, it is possible to envisage the provision of multiple formulations of food supplements for such purposes. This would require the analysis of large-scale databases of plasma micronutrient status to create clusters of common micronutrient phenotypes, together with the use of DBS technology to subsequently assign potential customers to the appropriate cluster and to provide them with the optimal nutritional supplement for their metabolic profile.

At present, a number of retailers offer personalised dietary analysis online, mainly with weight loss as their focus. However, it is possible to envisage extending this to personalised healthy eating plans. Consumers would input their dietary data and, as previously described, receive visual feedback on the nutritional quality of their diet. If one or more nutritional inadequacies are initially targeted, a food-based set of dietary feedback could be generated. In the event that meal-based food coding can be developed, this feedback can evolve into advice at meal-menu level. With online supermarket shopping in the UK set to grow at an annual rate of 14.6% between 2012 and 2017, the potential to engage the grocery retail sector in the delivery of personalised nutrition remains an attractive possibility⁽⁴¹⁾. This survey also revealed that 44% of subjects expect to use the Internet to buy their groceries in the next 5–10 years.

The future direction of personalised nutrition remains unclear, but the conclusion of the European Union Seventh Framework Programme integrated project, Food4Me, will develop detailed reports on consumer attitudes to

personalised nutrition options for the development of business models, ethical and consumer aspects as well as a proof-of-principle study of the efficacy of delivery of personalised nutrition at dietary, phenotype and genotype levels in eight European Union countries.

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