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Use of metabotyping for optimal nutrition

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In recent years there has been general agreement that dietary advice needs to be tailored to the individual and that we need to move from a one size fits all approach. Evidence has emerged that personalising dietary advice results in improved dietary behaviours. Concomitant with this there has been an increase in the application of developing technologies such as metabolomics to nutrition studies. The concept of the metabotype has emerged and set to play a key role in the development and delivery or personalised nutrition. The term metabotype refers to a group of individuals with similar metabolic profiles. This review gives an overview of the potential role of this approach in delivering optimal nutrition advice.

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Personalised nutrition

In the 1970s the concept of personalised nutrition emerged in the context that nutritional recommendations need to be refined for specific subgroups of the population [1]. It is well established that the nutritional needs of individuals vary according to age, gender and physiological status such as pregnancy. Furthermore in recent years, through analysing the responses to dietary interventions it has become evident that there is substantial inter-individual variation in the response to diet [2]. Considering this it has now become evident that the time has come to initiate the tailoring of dietary advice to the individual level. In more recent years a comprehensive definition of personalised nutrition emerged which describes a three level approach: level 1 describes the delivery of dietary advice following assessment of the individual's dietary intake; level 2 refers to the delivery of personalised advice following assessment of the individual's diet and phenotypic measures (such as blood pressure and clinical chemistry parameters); level 3 refers to the delivery of advice taking into account the individuals diet, phenotypic measures and genetic profile [3,4].

The Food4me project examined various aspects of personalised nutrition and performed a large scale randomised control trial to determine if personalised dietary advice resulted in improved dietary intakes compared to general population based guidelines [4,5••]. A total of 1269 participants completed the 6 month intervention: participants randomised to receive personalised nutrition consumed less red meat, salt and saturated fat compared to the conventional dietary advice arm. Overall, they also had higher Healthy Eating Scores demonstrating that the delivery of personalised nutrition advice induced larger and more appropriate changes in dietary behaviour.

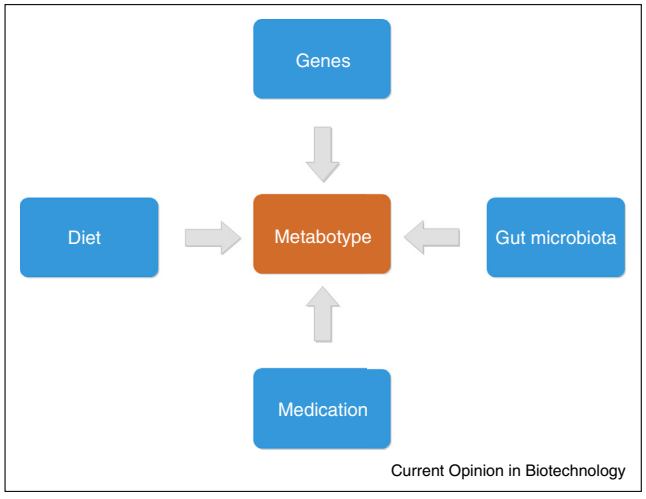
Although the outcomes from the Food4me study and the observation of high inter-individual response to dietary interventions support the concept and need for personalised nutrition it is clear that we will not reach a truly personalised level where specific foods will be created for individuals. A more realistic version is similar to the concept developed within Food4me where personalised advice is delivered by assessment of the individual on a number of levels. From a public health viewpoint this is still not easy to scale to the population level and as a result the concept of delivery of nutrition advice to groups of individuals has emerged [6••,7,8••]. Classification of individuals into groups can be achieved through analysis of their metabolic/phenotypic profile. Indeed, this concept is more advanced in the medical field and currently gaining momentum in terms of grouping individuals based on prediction of their drug response [9]. This approach of grouping subjects based on their metabolic phenotype was coined 'metabotyping' and has been used in a number of studies [10,11•]. This review will examine this concept in terms of moving towards delivery of personalised nutrition.

The concept of the metabotype

Metabolomics has emerged as a tool for determining metabotypes: metabolomic profiles or combinations of specific metabolites can be used for classification of individuals into groups or clusters. Application of a cluster analysis statistical tool such as *k*-means can result in grouping individuals based on similar metabolic profiles. Using this approach a group of *n* individuals is classed into *k* clusters in which each individual belongs to one cluster only. Hierarchical clustering is another approach often used. In the metabolomics field, principal component

analysis (PCA) is one of the most commonly used data analysis tools. Although PCA is useful in analysing trends in the data, however, it is not a clustering technique itself. Work in our research group led to the development of an approach based on PCA to allow group identification: the mixture of probabilistic PCA [12] establishes the number of inherent groups in metabolomic data. More recently, a statistical health monitoring approach has been described where the metabotype of an individual is compared to healthy metabotypes using a multivariate approach with the aim to classify the metabotype as health or abnormal [13]. As mentioned earlier, the concept has been previously developed in the medical field and in particular in terms of drug response to therapy. In the literature the term pharmacometabolomics has emerged for the specific application to drug response; the approach has helped identify potential responders to specific drugs but also aids in understanding the underlying mechanism of action of the drug. A recent review of the field gives an elegant overview of the role of pharmacometabolomics in personalised medicine [9].

Figure 1



An overview of the some of the factors that influence the metabotype.

With respect to nutrition our previous work demonstrated the use of the metabotype approach in response to a vitamin D intervention: a metabotype characterised by low concentrations of vitamin D and higher concentrations of adipokines was responsive to vitamin D supplementation [14]. In a separate study we used a similar concept to identify differential response to an oral glucose tolerance test: a total of four distinct metabolic responses were identified and the approach led to the identification of an at 'risk' metabolic group [15]. In another example the authors applied *k*-means clustering to lipoprotein profiles and identified three clusters two of which had a positive response to fenofibrate. The subjects ($n = 775$) underwent a three week treatment of fenofibrate and lipoprotein profiling was performed on baseline samples. This approach was more effective in identifying responders compared to traditional approaches based on baseline HDL-c and triglycerides cutoffs and nicely illustrates how we could match patients with appropriate treatments [16•].

The success of the metabotype approach is partly due to the fact that the metabotype is influenced by a combination of genetic and environmental factors such as diet and the gut microflora and therefore encompasses a multitude of important biological processes (see Figure 1). A careful selection of the metabolites used to perform the metabotyping can render more or less important the different factors in determining the metabotype. Suhre and colleagues have demonstrated elegantly that genotype influences the metabolomic profile and have performed a number of genome wide association studies with metabolic traits (mGWAS) [17–20]. Furthermore, in recent years a number of studies have linked specific metabolite levels in urine and faecal water with the gut microbiota [21–24]. Thus if metabotyping is performed using these metabolites then the influence of the gut microflora will be inherent in defining the groups. With the emergence of a number of biomarkers that reflect dietary intake there is also the potential to tailor the selection of metabolites to include specific biomarkers of certain foods. Careful selection of biomarkers can lead to the identification of metabotypes that are relevant to nutrition and tailored dietary advice can be delivered to each of these groups. Thus as our ability to measure accurately more metabolites that reflect factors such as diet and gut microbiota we will have a better ability to define metabotypes that are relevant for the delivery of nutrition advice.

Application of the metabotype approach in delivery of personalised nutrition

Our previous work has demonstrated the use of a metabotype based framework for delivery of optimal nutrition at a group level. An overview of the concept is given in Figure 2. Using four commonly measured markers of metabolic health (cholesterol, HDL-cholesterol, glucose and triacylglcerols) we classified individuals into one of 3 possible metaboptyes [6••] using a *k*-means clustering approach. Metabotype 1 was characterised by higher concentrations of cholesterol whereas metabotype 2 was characterised by low concentrations of cholesterol, triacylglycerols and glucose. Metabotype 3 participants were the most metabolically unfavourable with higher circulating concentrations of cholesterol, triacylglycerols and glucose. Additionally, this group also has the highest prevalence of the metabolic syndrome. A framework was then established for the delivery of nutrition advice to each metabotype group. A decision tree approach was implemented which further captured anthropometric data and blood pressure. Testing of the approach revealed

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