The Evolution of Personalised Nutrition: Definitions of personalised nutrition

Current definitions of PN are often used synonymously with “Precision Nutrition”, and are sometimes perceived as an extension of “Precision Medicine” and more recently, “Lifestyle Medicine” (Egger, 2017). Definitions of PN have converged over the past two decades on the following, reflecting recent scientific developments:

- “Personalised nutrition (PN) is individualised dietary advice based on dietary habits, lifestyle, health status, phenotype [an individual’s observable traits or characteristics and the influence of environmental factors] and genotype [the complete set of genetic material of the individual], and focuses on health promotion.” (Rankin et al., 2018).

This definition of PN would also include the gut microbiome (the community of microbes within the gastro-intestinal tract) as today this is considered an integral part of the human phenotype.

The above is one of many similar definitions currently in use, but in our opinion reflects well the different kinds of personal data and technologies involved, as well as its overall goal. The term, Precision Nutrition, is often deliberately used to imply that a personalisation based on genetic, genomic, metabolomic, or gut microbiome consumer data is more scientifically sound, technically precise and rigorous than personalisation that is based on general phenotype (such as body mass index (BMI) or blood type), and lifestyle information alone. This notion should suggest that science already has a sufficient quantitative understanding of the complex relationships between an individual, her/his food consumption, and his/her phenotype (including health) to offer individually beneficial nutritional intervention/advice. Other definitions, using non-technical terms to define PN, highlight rather the operational or the behavioral change aspect around food intake:

- “An approach that uses information on individual characteristics to develop targeted nutritional advice, products, or services”
- “An approach that assists individuals in achieving lasting dietary behaviour change that is beneficial for health”, discussed in: Ordovas et al (2018).

These definitions make it clear that PN is seen primarily as a form of health advice in relation to food intake behavior and health goals, similar to advice traditionally given by doctors, dietitians and nutritionists. However, the current understanding of PN implies a stronger scientific foundation behind the causal reasoning that underpins the advice given. Figure 2 summarizes the main personal input data elements based on science that are analyzed to design personalised nutrition advice.

Figure 2 Personal input data elements of personalised nutrition

Source: Holzapfel & Drabsch (2019)

Besides phenotype data collected via questionnaires, tracker devices and software apps, blood biomarkers and metabolic parameter tracking such as continuous glucose monitoring, there is currently a strong focus by many PN providers on personal genetic or genomic information, including genetic information of the gut microbiome. Efforts are currently underway to define an internationally agreed upon framework that clarifies to which extent these scientific methods should constitute an explicit part of definitions of PN (Bush et al., 2020).

Figure 3 illustrates the workflow for a typical personalized nutrition service, consisting of assessment, interpretation, intervention, and evaluation and monitoring.

Figure 3 Typical workflow of PN services

Source: Bush et al. (2020)

With decreasing costs of more complex analysis methods, “metabotyping”, which combines biomarkers, metabolism parameters, gut microbiome data, and general phenotype data, might be useful on a population level, as large pools of data will become available in the near future, to again stratify populations based on individual, personal data obtained in larger studies. This may lead to a renewed trend for population stratification according to insights gained from these data. Hence, “stratified nutrition” or “tailored nutrition” might become the more realistic option to achieve health goals at the population level in the longer-term future (Ordovas et al., 2018).

Brief history of the science context that enables PN

The concept to tailor nutrition to specific personal needs is of course not new. Aside from many traditional medicine systems, such as Ayurvedic Medicine, or Traditional Chinese Medicine among others, detailed empirical knowledge about how certain food items affect health has been studied and applied throughout most cultures for millennia. The earliest texts on European medicine clearly state the importance of food and nutrition for health and medicine, for example in his “De Alimento” (written around 400 BC) Hippocrates writes: “In food excellent medicine can be found, in food bad medicine can be found; good and bad are relative”. His pointing out the relativity of the response to food indicates that he was well aware of the fact that it might depend on the unique characteristics of each individual, as is also documented in his other writings (Dr Goodfood, 2018). In all societies certain foods have always been used to support health, for example in cases of illness, pregnancy, old age, or for enhancing athletic performance. What has changed over the centuries is the scientific evidence base that supports causal links between food, nutrients, and health.

The causal connection between a metabolic response to certain foods, or food ingredients, and specific genes has been established by studies of rare, sometimes detrimental human metabolic disorders, such as phenylketonuria, hereditary fructose intolerance, or galactosemia, during the second half of the 20th century (Buziau et al., 2020; Delnoy et al., 2021; Kumar Dalei & Adlakha, 2022).

In addition, more common forms of food intolerance or digestive dysfunction, such as lactose intolerance or coeliac disease, have been shown to have a genetic basis, and personalised approaches for their treatment are well established, including approaches modifying the gut microbiota to alleviate symptoms (Aboulaghras et al., 2022; Catanzaro et al., 2021; Gnodi et al., 2022; Porzi et al., 2021). Specific dietary recommendations for such patients were established based on these scientific discoveries, and when following a prescribed diet, they can lead a normal life. It was these clinical studies that demonstrated a genetic causation for some metabolic dysfunctions that have provided the paradigm for the use of personal DNA data, besides other information, to tailor PN advice.

In parallel, a body of research studying human metabolism has generated important results throughout the 20th century. These have laid the foundations for studies on large populations with the aim to understand the health impact of food ingredients and micronutrients, such as vitamins, fats, or sugars, and to tailor nutritional advice for specific purposes, including the improvement of public health. Policy makers have since used “general” or “one size fits all” advice, derived from these population studies, to guide consumers toward certain beneficial health outcomes. In the UK, The Eatwell Guide provided by the NHS, giving advice on recommended daily nutrient intake for achieving certain health goals, is one such example (NHS, 2019). It is also worth noting that such general advice regarding recommended daily intake portions of food categories such as vegetables or fruit varies between countries.

Nutritional science in the modern sense has emerged since the 1960s as a growing, independent branch of science, with at times great influence on public health debates and consumer behaviour. For example the earlier identification of well-studied diseases caused by vitamin deficiencies due to malnutrition, such as, Xerophtalmia (Vitamin A), Scurvy (Vitamin C), or Rickets (Vitamin D), established the global use of vitamin supplements by healthy, well-nourished people and a multinational, multi-£billion industry in vitamin supplements, despite the fact that scientific evidence for the benefits of vitamin supplementation for healthy individuals is still very limited, and not supported by the results of randomised controlled trials (RCT) for most of the widely consumed vitamins and supplements (Zhang et al., 2020). Several studies even indicate that long-term vitamin supplementation in healthy people may lead to increased mortality (Bjelakovic et al., 2007). Nutritional science as such has however contributed much to the visibility of science in the food sector, and sector and shaped the publicly accepted view that the human response to food can be clearly understood by science.

Personalised nutrition as a sub-field within nutritional science has been gaining increasing prominence and media attention over the past 20 years. During this period, one of the biggest drivers of growth of the commercial PN sector was the completion of the Human Genome Project in 2000/2003. The technical achievement of sequencing the complete DNA of a human was based on the scientific paradigm that any aspect of cellular life, including the treatment of disease, could be explained and manipulated ultimately by using DNA sequence information. Within the medical sciences this led to the propagation of Personalised Medicine, also called Precision Medicine, or P4 medicine (predictive, preventative, personalized, participatory), and the number of research publications on nutrigenetics and nutrigenomics as a foundation for PN increased significantly after this time (see also figs 12, 13) (Marcum, 2020). This development was spearheaded by approaches attempting to personalise cancer treatments, known as Precision Cancer Medicine. However, despite much effort and enormous investments in this field over the past 20 years, the success rates of personalised cancer treatments have been rather modest, and criticism of the validity of these precision approaches based on DNA sequence data

of cancer tissue has been mounting for over a decade (Brock & Huang, 2017; Letai, 2017; Strauss et al., 2021). It was these trends in medicine, triggered by the Human Genome Project, that have not only reinforced the public perception of DNA as the most important causal agent of life, but also have been driving several large-scale technology developments in the biomedical sciences that enable PN services today (as well as personal/precision medicine). These are:

1. The drop in costs of DNA sequencing technologies, which have decreased over the past 20 years, from ~$100M per whole genome in 2000, to under $1000 today, outperforming Moore's law in the semiconductor sector by four orders of magnitude (NIH, 2021).
2. Much increased robustness and reliability of new types of DNA sequencing technologies with smaller instrument footprint, such as next generation sequencing (NGS), or nanopore sequencing.
3. International integration and availability of big data reference DNA sequence databases.
4. Standardised, robust DNA sequence analysis software tools, increasingly using AI.

These technological innovations in combination with computational and software innovations in the bio-informatics field enabled new big data approaches and the formation of data analysis sub-disciplines in the biomedical sciences, now known as -omics technologies, such as genomics (collects DNA sequence data of all genes of an organism), nutrigenomics (collects information of changes in gene expression in response to food intake), proteomics (protein information, using mass spectrometry), metabolomics (the quantitative measurement of proteins and small molecules of the metabolic response of organisms to food intake), microbiomics (identification of resident microbe species in a person's microbiota, usually the gut microbiota). All these technologies generate large data sets that can only be analysed with expert software and be interpreted by experienced experts. Current trends are leading to fully automated analysis and interpretation of personal DNA data without human intervention. Data interpretation also involves correlating data collected from the individual with reference data that may or may not be in the public domain.

Over the past 20 years, PN as a service offering with a scientific basis and the potential to support public health goals has become itself a well-studied subject (Joost et al., 2007). Many of the issues and concerns relating to consumers, science base, effectiveness, and regulatory uncertainties are reasonably well studied to date (Celis-Morales et al., 2015; Livingstone et al., 2020).

Scientific methods used by PN providers

Over the past decade PN providers have been offering personalised analysis of phenotype and genotype increasingly by applying methods of the following areas of science to the physical bio-specimen samples provided by the customer. It is the wider commercial availability of these methods, which have their origins in the biomedical sector that has promoted the current growth of PN services. Personalised nutrition providers may commonly employ six scientific methods for tailoring nutrition advice, as shown in Figure 4.

Figure 4 Scientific methods used by personalised nutrition providers

Nutrigenetics

Nutrigenetics is the analysis of DNA sequence data, to find either variations in certain genes that impact gene function (in the past, mostly Single Nucleotide Polymorphisms, SNPs), or to establish whether the person belongs genetically to certain population categories that have been established in the past. The results are then correlated with the different phenotypic responses of the person to a specific type of diet. These phenotypic responses can include for example weight gain/loss, change in blood pressure, plasma cholesterol, or glucose levels as a result of certain dietary habits, such as eating a high fat/low fat, vegan, or Mediterranean diet. The genes analysed can be an indicator of certain population characteristics, such as ethnic background, as well as be directly linked to known metabolic functions. However, as will be discussed in chapter 4, more recent research indicates that “classical” nutrigenetics results are less predictive in the context of dietary response in healthy subjects than was previously believed.

Samples for DNA extraction are usually collected via a D2C test kit with which cells, for example from a cheek swab, or blood, among other bio-specimens can be provided easily by customers. Most providers will screen only for a small number of selected genes they find most relevant for their offering, or their selected science base (for example, focussing more on fat metabolism, or glucose metabolism, athletic performance, etc). Such approaches use so-called gene panels that

allow rapid and cost-effective sequencing of a limited number of genes. Robustness and data quality of these panel methods have greatly improved over the past decade, but can still vary widely, and efforts to streamline standards are well recognised (Bean et al., 2020).

Although historically the terms nutrigenetics and nutrigenomics (below) have been and still are used sometimes interchangeably in the literature, the distinct definitions given here are based on a recently more widely established understanding that the former is more rooted in “classical” genetics analysis, and the latter on methods that have emerged from the human genome project in the mid-2000s, including whole genome sequencing (WGS) (Marcum, 2020).

Nutrigenomics

Nutrigenomics is the analysis of DNA sequence data of all or most genes, and in particular is looking for gene expression differences after dietary intervention. Gene expression information is related to the level of activity, or transcription, of certain genes (hence this aspect of genomics is also called transcriptomics, as only active genes are analysed). Usually, a profile of gene activity is established before intervening with food intake behaviour, and then again sometime after the intervention and change of diet. This kind of analysis is more elaborate and often requires better sample quality, or more sample material, as well as more sophisticated DNA sequencing equipment and software analysis tools. Often the gene activity information is accompanied in parallel by other non-DNA biomarker measurements, such as blood glucose or cholesterol levels or other metabolic markers etc.

As will be discussed in more detail in chapter 4, WGS is still not easily available for commercial applications at an affordable price, but it is likely that results from studies of large numbers of complete individual genomes will provide better actionable genetic data with regards to correlations between certain genetic traits and metabolic response to food.

Metabolomics

Metabolomics is the analysis of ideally the complete set of molecules representing the substrates, intermediates, and products of the metabolism of an organism as a whole, or of specific tissues (such as, liver metabolism, gut metabolism, etc.). These molecules are mostly smaller proteins, such as hormones, and signalling molecules that affect physiology more globally, and intermediary products of complex physiological processes, by definition smaller than 1.5 kDa (a unit of molecular size/weight).

Metabolomics research attempts to find metabolic “fingerprints” or “signatures” for certain pathologies that should help with their diagnosis and therapeutic intervention. Currently, obesity, diabetes, CVD, cancer as well as neurodegenerative diseases are intensely studied with respect to their metabolic characteristics (Gonzalez-Covarrubias et al., 2022). Moreover, earlier large trials, such as the EU funded LIPIGENE trial, found that so called “metabotypes”, which correspond to a person’s individual metabolic response to dietary intervention are good predictors of intervention outcomes. Metabotyping was also shown to become more robust when including other data types into the signature, such as genotype and cytokine profile (a marker for inflammatory and immune system status) (O’Sullivan et al., 2011).

Proteins are detected and quantified by protein isolation and detection methods, such as liquid and gas chromatography and/or together with different mass spectrometry methods. The general field of protein analysis that uses in particular mass spectrometry methods is called Proteomics, hence a large proportion of Metabolomics is Proteomics applied to certain kinds of proteins relevant for metabolism. These methods are technically more elaborate as different classes of proteins can have very different biochemical properties. Therefore, protein analysis is still less robust, and more expensive than DNA sequencing technologies. Moreover, sample collection, preservation and processing are more error- and contamination-prone and require well-trained

technical staff for sample handling. Bio-specimen samples provided by customers include saliva, urine, plasma, faeces, exhaled breath, or sweat, among others, and different metabolic molecules can be enriched in each of these. Currently, it appears that only very few PN providers offer serious metabolic profiling, likely due to the more diverse and complex biochemical analyses required.

Microbiomics

(Gut-)microbiomics is the analysis of the communities of microorganisms called microbiota that live on and within organisms. These include symbiotic, commensal, as well as pathogenic microorganisms, such as bacteria, archaea, and fungi. These microorganisms are considered today an integral part of an organism's phenotype, as they are essential for some physiological functions of the organism (for example synthesis of vitamins B and K in humans by gut bacteria). In particular, the gut microbiota (in the past, somewhat incorrectly, also called gut flora) have been shown to have wide-ranging systemic effects, not only on metabolic digestive functions within the digestive tract, but also on immune function, hormone regulation, or neurophysiology and mood (the gut-brain axis) as well as on various disease risks.

Gut microbiome analysis tries to establish which species of microorganisms are present in the gut by screening for the presence of short, microbe species-specific DNA sequences for ribosomal 16s, or 18s RNA. This is necessary, because most microorganism species that are adapted for the digestive tract environment cannot be isolated and kept alive in a laboratory outside of the gut, hence they can only be detected indirectly via the presence or absence of their respective DNA that encodes their 16s or 18s RNA genes. This method of surveying an ecosystem of microorganism species by testing for highly conserved, short species-specific DNA sequences is called Metagenomics, which can also be used for the detection of pathogenic contaminants and spoilage in food among other applications. An ideally complete set of DNA data representing all species within microbiota of the gut is then called the gut microbiome (a brief summary of main recent results is given in 4.1.3).

Epigenetics/Epigenomics

Epigenetics/Epigenomics is the analysis of stable phenotypic changes that alter gene expression without a change in the DNA sequence of genes. These changes are often the result of organism-environment interactions, can be adaptive to environmental stimuli, and can be heritable over several generations without a "genetic", heritable change in DNA sequence. The gene regulatory effect of epigenetic mechanisms is often exerted through the modification of proteins that interact directly with DNA in a regulatory fashion, such as through methylation/de-methylation of histone proteins. These protein modifications can then either increase or decrease the activity/expression of certain genes, or even switch genes on or off without any change in DNA sequence.

It is now increasingly acknowledged that metabolism is regulated to a large extent by epigenetic mechanisms, hence interest in that area for PN approaches will increase over the coming years. For example, transgenerational inheritance of obesity has been linked to high fat diets, malnutrition, and environmental toxin exposure of previous generations, as well as to early intrauterine exposure to obesity triggers either via the mother or environmental factors. Epigenetic effects on metabolism can be stably inherited in humans for up to three generations, without any change in DNA sequence (King & Skinner, 2020). To date, epigenetic analysis, and its methods for consumer applications are still in development, and commercially available offerings are still limited as epigenetic data collected from large populations is still much more complex and less available than DNA sequence data (de Luca et al., 2017).

Exposome analysis

Analyses the sum of external environmental factors that influence an organism's physiology, health status, and behaviour over longer periods of time, or throughout its entire life span. This term is a relatively new coinage to summarise all the data that can be gathered about an individual that do not require a bio-specimen sample, but often include quantifiable parameters, such as stress levels, physical activity, dietary habits, working and sleeping patterns, etc. In particular, since these kinds of data have become more easily quantifiable via digital technologies, such as smart watches, fitbits, tracker devices, and smartphone apps, they can then be analysed via algorithms to categorise individuals, and have become an essential data source for tailoring advice around food intake behaviour and health more generally. It is this data category that has been longest in use to assess an individual's status with respect to food intake and health outcomes. These were collected in the past through paper questionnaires and in-person assessment and anamnesis interviews with doctors, dieticians, and nutritionists. This initial personal data collection is still the most important interaction between health service providers and customers today, but take place increasingly online and via apps, often replacing the human expert with bots and other "virtual experts" for giving advice. In addition, recent attempts to include molecular measurements of the impact of various environmental factors have added a whole new dimension of complexity to this concept and it is recognised within the scientific community that unified standards and technologies are required to deliver better actionable results (Zhang et al., 2021).

Foodomics

It was suggested already in 2009 to create a new term for integrating above mentioned –omics technologies as applied to the study of metabolic changes related to food intake as "foodomics", however the scientific community has been hesitant so far to adopt this term (Cifuentes, 2009; García-Cañas et al., 2012).

Digital technologies supporting PN

A range of evolving digital technologies is underpinning the above scientific methods to integrate various data streams into personalised advice. Figure 5 presents an overview of the elements and activities that constitute a full personalised nutrition service, from the use of various technologies for information collection as discussed above, processing of the data to provide nutrition advice using big data analytics, algorithms and artificial intelligence, through to providing feedback to the consumer, and ongoing support mechanisms to monitor and encourage behaviour change towards positive health outcomes. Behavioural change is arguably the most critical point of the process, and various technologies are emerging to facilitate this including digital shopping assistants, intelligent kitchens and 3D printing on demand, and personalised food delivery services, to name just a few.

Figure 5 Overview of the elements and activities that constitute a fully integrated, personalised nutrition service

Source: Goossens (2016)