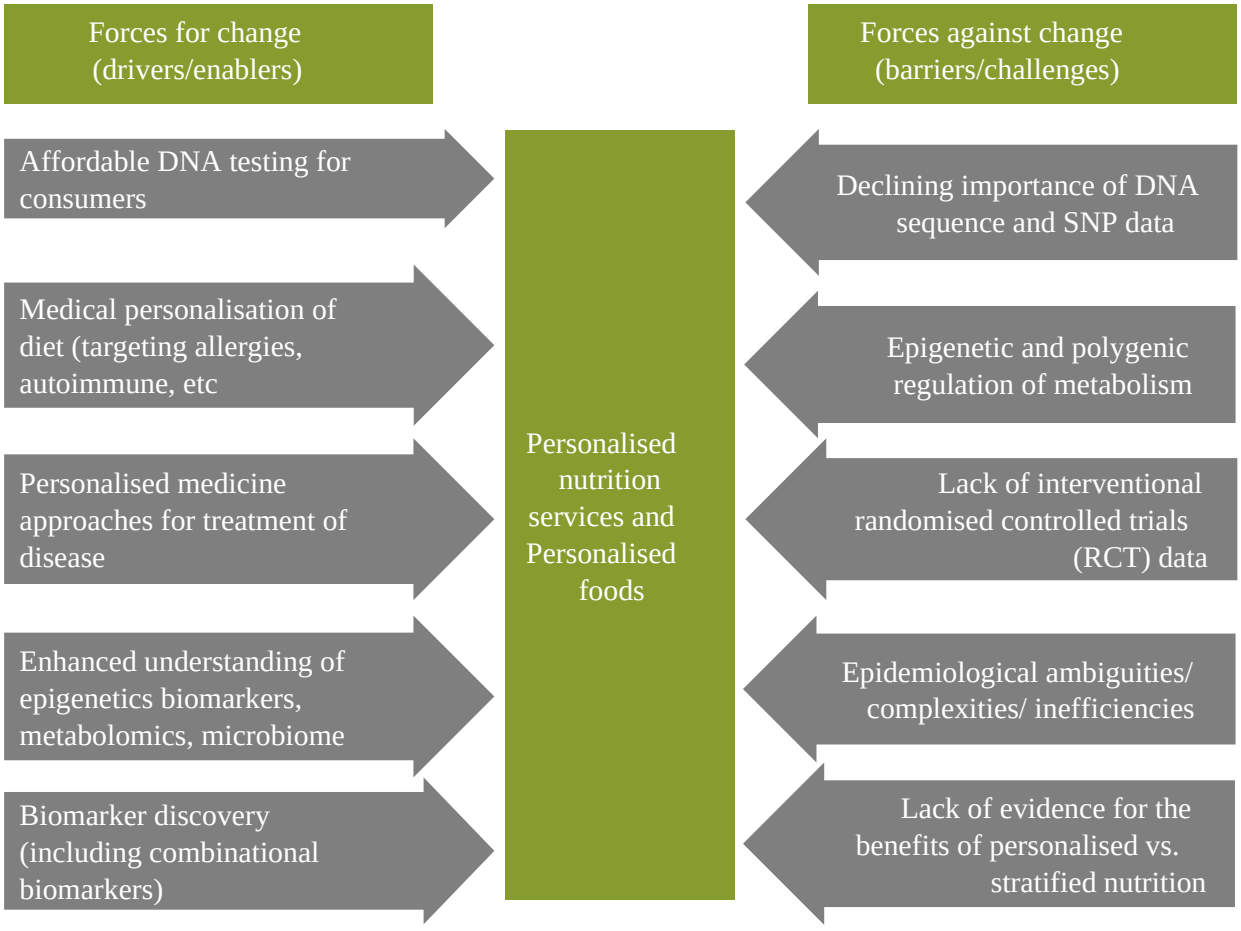
# The Evolution of Personalised Nutrition: Science and medicine – Potential and limitations

In this chapter we present an overview of the drivers and enablers in science and medicine that impact development of the PN sector, along with a critical assessment of the current state of scientific knowledge and challenges that may inhibit PN. These are summarised in figure 11 and discussed below.

**Figure 11 Drivers and challenges: Science and medicine**




## Science enabling widespread uptake of PN

### DNA sequence information

DNA sequence information-based approaches are at present still driving the narrative that it would be the most relevant to explain metabolic status, phenotype, and be essential for health interventions. Hence affordable DNA testing for consumers is a key driver in the commercial space of PN. This narrative is based on a number of older studies that showed positive

correlations between SNP variation in genes relevant for metabolism and body weight regulation, such as the DIOGENES study, 2012 (Larsen et al., 2012). The conclusion of these studies was generally that genetic variation in nutrient-sensitive genes would affect the response to diet. Despite new insights, and criticism of these correlations based on SNP analysis (see below, challenges), a strong commercial push, making more complex and expensive DNA sequencing technologies such as WGS and SNP arrays more affordable, will continue to drive consumer DNA testing for the next decade, with WGS becoming available for under $500 possibly in the next five years (Khan & Mittelman, 2018). It is assumed that widely available WGS for consumers would allow much more accurate analysis and prediction of health status and disease risk.

## Medical personalisation of diet

Medical personalisation of diet to achieve specific health goals for patients with metabolic and other diseases including allergies, autoimmune conditions and cancer will further refine, and deliver successes in treatments of patients, which will lead to wider application of personalisation of nutrition in a clinical setting (Doets et al., 2019; Schuetz et al., 2019; Trestini et al., 2021). For example, Savor Health in partnership with Johnson & Johnson offers personalised nutrition for cancer patients. Successful personalisation solutions in medicine will further motivate commercial implementations of PN solutions for consumers.
One growth area in the sector that is currently not well developed, are novel personalisation strategies to improve food intake for people with food allergies. Although true figures for the prevalence of food allergies are currently debated (between 1% in Europe, based on meta-analysis, and 7.6% of children and 10.8% of adults in the US), globally food allergies are on the rise. Food allergies are currently mostly mitigated by following an avoidance diet, which can lead to forms of malnutrition and micronutrient deficiencies, if not complemented with the right alternative foods or supplements. Some avoidance diets can also increase disease risks as for example a gluten-free diet has been shown to increase the risk of cardiovascular disease (Lebwohl et al., 2017). A better understanding of the interactions between the immune system, its response to food, and metabolism is still required for enabling commercially available personalisation solutions (D'Auria et al., 2019).

## Personalised medicine approaches and gut microbiome research

Personalised medicine approaches for treatment of disease and drug development is itself driven currently by large international efforts to gain a better understanding of epigenetic mechanisms, novel molecular biomarkers of disease and health, metabolomics, and the gut microbiome (Matusheski et al., 2021; Spector et al., 2019). These three fast growing areas are very likely to deliver relevant findings for the foreseeable future that will open up novel approaches for personalised interventions independent from personal DNA data. However, it may take up to a decade until robust causal mechanism are identified, confirmed by interventional studies, and translated into valuable commercial offerings (Gonzalez-Covarrubias et al., 2022; Viana et al., 2021; Vicente et al., 2020). Research on gut microbiota in healthy people is currently the research area that appears most likely to deliver actionable insights in the next five years, and a number of PN providers already offer some level of gut microbiome analysis. In the following we briefly summarise main findings in this area.

### Main findings in the gut-microbiome field

Gut-microbiome analysis has recently become a robust-enough technology to be applied to faecal samples sent in by customers via a test kit. Basic discoveries in the gut microbiome field so far include the fact that most human populations globally fall into two broad "enterotypes" (ecosystems of gut microbes) usually established in early childhood and strongly influenced by dietary habits, one dominated by Prevotella the other by Bacteroides species of gut bacteria. The Prevotella enterotype is associated with a diet rich in carbohydrates and fibre, the Bacteroides

enterotype is associated with a diet low in fibre and high in sugars and fats, as often found in “western” diets. Interestingly, factors such as geography, cultural background, sex, and age have been found to have little influence on the establishment of the enterotype (Matusheski et al., 2021). Moreover, a number of studies in animals and humans could clearly demonstrate the role of gut microbiota composition in a number of health and disease aspects, including obesity and lipid metabolism, gut inflammation, insulin sensitivity, and gut infection risk among others.

Of particular importance with regards to nutrition were a number of studies that could show that obesity is correlated with reduced diversity (dysbiosis) of gut microbiota, which was corroborated by experiments in which germ-free mice receiving faecal bacteria of obese humans gained more weight than mice on the same diet receiving bacteria from non-obese humans (Goodrich et al., 2014). In addition, some bacterial species, such as Christensenella and Akkermansia were rare in obese humans and were correlated with low visceral fat deposition and when grafted into germ-free mice could prevent weight gain. Reduced gut microbiota diversity has also been shown in human studies to be correlated with longer-term weight gain, in particular with a diet low in fiber (Menni et al., 2017). Despite these clear findings the causal mechanisms that connect microbiota diversity with obesity are complex and a number of different physiological mechanisms all play a role. Moreover, a number of diseases have been found to be linked with low microbiota diversity, such as atherosclerosis, inflammable bowel syndrome, psoriatic arthritis, type 1 and type 2 diabetes, atopic eczema, and coeliac disease, diseases that are to a large extent caused by dysregulation of the immune system leading to local or systemic inflammation.

The role of gut microbiota in general metabolic regulation in humans could be demonstrated by introducing faecal transplants from lean donors to humans with metabolic syndrome (characterised by low insulin sensitivity), which improved insulin response and led to a change in microbiota diversity, hence showing its importance in glucose metabolism (Kootte et al., 2017). In addition, microbiota composition can be a diagnostic marker for certain disease pre-conditions as has been shown for diabetes (Wu et al., 2020).

The main applicable outcomes of these studies for PN were that more diverse gut microbiota are associated with better health parameters in general, and that the main food ingredient that can change and positively influence microbiota composition is fibre. A number of studies have shown that a western low fibre diet causes degradation of the mucus barrier in the colon, which then leads to leakage of gut bacteria into the gut wall and subsequent local and systemic inflammation which might be one of the main factors of increasing NCDs in the west (Ray, 2018). In line with these findings it has been shown that prebiotics (edible carbohydrates that are not digested and absorbed in the gut), either natural or as specific dietary fibre formulations consumed as food additives or supplements, can improve microbiota composition and health. Another well-researched approach for changing gut microbiota composition is the consumption of probiotics, which are live microorganisms such as yeasts or bacteria mainly of the Bifidobacterium and Lactobacillus species. These are found in natural products such as yoghurt and are added as supplements to various food products. However, there is still debate whether consumed probiotic species can establish in the gut after digestion. The most effective way to introduce new specific gut microbes is currently still by faecal transplant, which is unlikely to become a commercial service in the PN sector any time soon. However, probiotics have been shown to have positive health effects acting directly on various physiological functions such as digestion or the immune system via the production of bioactive molecules (Kristensen et al., 2016).

With regards to the ability of certain drugs, nutrients, foods, or specific diets to change gut microbiota, several animal studies could show that for example commonly used food additives such as artificial sweeteners (aspartame, sucralose and saccharin) as well as emulsifiers (carboxymethylcellulose, polysorbate-80) reduce microbiota diversity, and increase both faecal pH and bacterial species that cause inflammation. Commonly used drugs such as proton pump inhibitors for the treatment of gastritis and reflux, and antibiotics have an effect on gut microbiota diversity, although the response is highly variable between humans. Although dietary change by

for example switching from a high fibre to a low fibre diet clearly changes microbiota composition within days, yet considerable homeostatic robustness of microbiota restores previous conditions after dietary reversion, and several studies had difficulties confirming major changes in gut microbiota in short-term feeding studies (Valdes et al., 2018).

In summary, several findings in the gut microbiome field can at present be considered more robust than others. Consensus is strong for the following main discoveries.

- Gut-microbiota composition and diversity impact energy metabolism, glucose metabolism, and other health parameters such as systemic inflammation.
- Diet and certain drugs can have a strong impact on microbiota composition and function, although these can be reversible particularly after dietary change.
- Microbiota composition and diversity affect drug response in cancer treatments such as chemotherapy or immunotherapy.
- Fibre intake is the main factor that increases microbiota diversity with multiple positive effects on health (natural fibre as well as prebiotic fibre supplements).
- Probiotic foods have positive direct health effects, although not necessarily by colonising gut-microbiota with consumed species.

Despite the fact that several actionable strategies can be derived from these insights after an analysis of gut microbiota diversity and species composition, there is also considerable natural intra-individual variation over time (Olsson et al., 2022). This can be problematic when designing intervention strategies in a commercial PN setting that are based usually on one-off testing.

So far, despite a wealth of observational data and good interventional studies on the role of gut microbiota in metabolism control, well proven robust causal links between specific food intake, metabolism and gut microbiota are still limited. Their role in PN approaches for establishing effective dietary intervention strategies is still under intense investigation, but very likely to deliver useful actionable insights in the future (Mills, Lane, et al., 2019; Mills, Stanton, et al., 2019; Valdes et al., 2018).

**Biomarker discovery**

Biomarker discovery itself will be shaped by a strong trend toward “combinatorial biomarkers”, as it has been recognised for well over a decade that for most phenotypic parameters of disease, single biomarkers (single gene or protein variation) are not sufficient for an understanding of phenotypic change and the design of health intervention. This means that a combination of several molecular factors in combination with lifestyle and behavioural characteristics of an individual will allow more precise and efficient personalisation (Westerman et al., 2018). This trend is driven by large international bio-banking trials which collect bio-specimen samples, including blood, serum and cells from hundreds of thousands of individuals in many countries to conduct longitudinal studies over many years or even decades to find causal links between biomarkers and disease, or disease risk. It is expected that findings resulting from these efforts will be translated rapidly into consumer applications once they are robust enough.

These developments in the bio-medical sciences are longer-term enabling/promoting trends that will sustain and extend the scientific framework that underpins PN for the foreseeable future. It is expected that as is usually the case in bio-medical discovery that novel findings relevant for PN will take up to five years or more to translate from first discovery to commercially available product offering. Although these broader trends will further support commercial PN efforts, there are a number of challenges inherent in the science base that underpins them, which may in the medium-term future lead to a considerable reassessment of what is currently believed the relevant science for PN. Several of these scientific challenges are already well understood.

# Limitations of the science

## Declining importance of DNA sequence and SNP data

Declining importance of DNA sequence and SNP data will impact PN in the mid-term future as it has been shown by a number of recent studies that currently used DNA sequence information is not able to provide strong enough causal links between gene sequence variation, function, and human metabolic response to diet. A number of recent meta-analyses of some of the largest interventional studies that investigated correlations between gene variants thought to be relevant, dietary intake, and weight change have shown that there were in fact no such correlations that could be used to tailor PN advice (Drabsch et al., 2018; Holzapfel & Drabsch, 2019). Concerns over the usefulness and scientific validity of consumer DNA testing have been raised repeatedly for over a decade (Gibney & Walsh, 2013). Moreover, recent studies agree that currently available genetic testing for consumers is not based on sufficient evidence to make health claims based on the gene variants that are tested for, and that existing validity standards and frameworks for genetic testing and nutritional advice such as, Evaluation of Genomic Applications in Practice and Prevention (EGAPP), Strengthening the Reporting of Genetic Association Studies (STREGA), Grading of Recommendations Assessment, Development and Evaluation (GRADE), European Food Safety Authority (EFSA), were insufficient to justify personalized nutritional advice based on currently used genetic information (Keith A. Grimaldi et al., 2017; Guasch-Ferré et al., 2018; Holzapfel & Drabsch, 2019). These findings, though increasingly recognized over the past decade among scientists, will impact DNA analysis-based business models currently on the market over the next five years. A decreasing number of academic publications in the areas of genomics and nutrigenetics/nutrigenomics in the past few years might indicate a shift in importance of these methods in nutrition-specific applications (see Figure 12 and Figure 13).

**Figure 12 Publication trends in personalised medicine and methods used in personalised nutrition 2007-2019**

Source: Moore (2020)

**Figure 13 Publication trends - Nutrigenetics and nutrigenomics 2000 – 2019**

Source: Marcum (2020)

## Epigenetic and polygenic regulation of metabolism

Epigenetic and polygenic regulation of metabolism is the scientific reason why the above findings were to be expected at some point. The fact that very rare monogenic metabolic diseases could be treated in the past by interventions that corrected for the one defect gene led to a paradigm that applied this notion to all of metabolism regulation. It is however now well established that most NCDs that PN approaches should help mitigate, such as diabetes, CVD, cancer, metabolic syndrome, food allergies, and obesity, are all caused by the dysregulation of a large number of genes and hence are polygenic conditions. This means that the complexities of regulatory dysfunction cannot be reduced to one or even “a handful” of “causal“ genes, and hence intervention approaches based on claims to have identified these are likely to be unsuccessful in most cases due to the unresolved complexities involved. In addition, it is now well recognised that metabolism is regulated to a large extent at the epigenetic level, for which DNA sequence information has only limited use (with very rare exceptions). This may also explain the failure of recent attempts to replicate earlier studies in the diabetes field that have reported causal connections between certain gene variants, metabolic response to food intake, and diabetes risk. Based on the earlier results, a number of widely used diabetes risk scores have been developed, but in light of the more recent findings the validity of currently used diabetes risk scores appears questionable (Li et al., 2017). Even classic textbook examples of diseases formerly considered monogenic, such as lactose intolerance have more recently been shown to be influenced to a large degree by epigenetic mechanisms (Delnoy et al., 2021; Porzi et al., 2021).

Our current understanding of epigenetic mechanisms and their role in nutrition is at an early stage but new findings may deliver important insights with respect to diet and health in the near to medium term future. However, compared to DNA sequence analysis methods, our basic understanding and methodologies of epigenetic analysis are lagging behind DNA analysis at least a decade. Hence, reliable consumer testing products and data analysis are currently still not available due to the early stage of the technology and its science base. It is expected that with the

declining importance of DNA testing in the nutritional advice sector that epigenetic methods will enter that space together with novel metabolomics, gut microbiome, and biomarker applications, however it will likely take up to a decade until new findings in these areas will be tested in interventional studies and translated into sound commercial offerings.

## A lack of interventional, randomised controlled trials

A lack of interventional, RCTs is currently stated as the main reason for considerable uncertainties with respect to clear causal links between molecular and other phenotype data analysed, and physiological response to diet in humans, despite myriad observational studies. Due to their large costs, most RCTs focus on the most prevalent conditions in western countries, such as CVD, diabetes, cancer, and obesity, hence study humans mostly within a disease context. Current interventional studies that investigate general metabolic response to dietary interventions in healthy people are still rare, although some have delivered a wealth of useful insights, in particular around consumer behaviour, and the behavioural change aspects around food intake, such as the Food4Me study (Macready et al., 2018). A series of PREDICT studies currently carried out in the US and UK as a collaboration between commercial PN provider ZOE and academics to elucidate diet metabolism interactions including the role of the gut microbiome, might deliver important results for the PN field (Spector et al., 2019; ZOE, 2020). ZOE launched in the UK in April 2022, positioning itself as a “program” to achieve health goals by offering PN services, including coaching, based on gut microbiome analysis, blood sugar, and blood fat measurements. These are then used as input for AI that then generates a personal ZOE score for any food or meal. However, advances in finding reliable and robust phenotypic and molecular parameters that would allow easy personalisation of diet based on glucose or lipid response have been modest so far, given that they have been studied for decades.

## Epidemiological ambiguities/complexities/inefficiencies

Epidemiological ambiguities/complexities/inefficiencies that are inherent in any attempts to achieve health goals at a population level are also affecting the scientific foundations of personalisation approaches. Most insights into metabolic response to diet have been gained in the past from observational studies and animal experiments, and the basic causal relationships were then confirmed in large population studies. The difficulty of translating these insights based on large “averages” to specific interventional studies, which are essential to prove causality and can be conducted for cost reasons only on smaller sample populations, remains an issue, as these may not show “expected” “average” metabolic behaviour. In addition, when findings should then be applied to advice at the population level to achieve public health goals, phenomena such as the prevention paradox, or Rose paradox play statistically an important role in the actual efficacy of the intervention for the individual (Rose, 1981). The prevention paradox states that an intervention that appears to support positive health outcomes according to a population study might not have the expected effect at all in any given individual. Specific individual differences between humans, including lifestyle factors, can explain this, but the reverse is true for personalisation approaches, namely interventions that appear successful in small, personalised interventional studies may be difficult to translate into scientifically sound advice for further personalisation strategies of larger sub-populations.

Moreover, it is a well-studied principle of epidemiology that statistically most new cases of any given disease in a population occur in parts of the population not classified as at risk. Say for example, the incidence of cases of type 2 diabetes within the general population each year is much larger than the incidence among people classified as at risk to develop diabetes. These issues have been considered relevant for the PN field for at least a decade and are unlikely to be resolved easily in the near future (De Roos, 2013; Gibney & Walsh, 2013).

The challenges presented here are understood as challenges to the scientific basis of currently promoted implementations of PN. They will change over the coming decade our causal

understanding of how human metabolism responds to food in relationship to human phenotypic characteristics. This will most likely not lead to a fundamental shift in the overall structure of personalisation approaches, however it will affect commercial players and business models, depending on how quickly investor interest in commercialising novel scientific findings in these new trends will lead to new players in the field using a different science base compared to current offerings. Overall, shifts in the science base might slow down evolution of the field more generally.