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The Evolution of Personalised Nutrition

https://doi.org/10.46756/sci.fsa.ean605

UNIVERSITY OF CAMBRIDGE
DEPARTMENT OF ENGINEERING

IfM MANAGEMENT TECHNOLOGY POLICY

FSA Contract Reference: FS900199/FS900200

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Date: 20/04/2022

University of Cambridge Reference: A24152

Release: Version 1

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Abbreviations

Acronym	Definition
AI	Artificial intelligence
B2B	Business-to-business
BMI	Body mass index
CAGR	Compound annual growth rate
CAP	Certified analytics professional
CGM	Continuous glucose monitoring
CLIA	US Clinical laboratory improvement amendment
CVD	Cardiovascular disease
DNA	Deoxyribonucleic acid
D2C	Direct-to-consumer
DBS	Dried blood spot sampling
FDA	US Food and Drug Administration
GHR	Genetic health risk
GPGRS	Genome wide polygenic risk scores
GWAS	Genome-wide association study
NCD	Non-communicable disease
PN	Personalised nutrition
RCT	Randomised controlled trial
RNA	Ribonucleic acid
SNP	Single nucleotide polymorphism
WGS	Whole genome sequencing

Executive Summary

Health and wellbeing and susceptibility to disease are causally linked to food and nutrition intake, an observation that has informed dietary advice for centuries. However, physiological response to different food types varies greatly by individual, meaning that a “one size fits all” approach to nutritional advice may be inadequate to ensure optimum health outcomes. Personalised nutrition (PN) services, operating at the intersection between health advisory, the wellness sector, and the food system, seek to address this through individualised targeted dietary advice focused on achieving lasting dietary behaviour change that is beneficial for health. In this report we specifically analyse the evolution of personalised nutrition defined as nutritional advice based on personalised analysis of scientific data obtained from the customers’ phenotype and the scientific knowledge base underpinning such advice. We will touch on technologies that enable the personalisation of food more generally only insofar as they might impact PN in the future through wider network effects within the food system.

Personalised nutrition as a clinical and academic field of study has existed for at least four decades, however recent investor interest and cheaper direct-to-consumer (D2C) testing devices have enabled a growing commercial PN sector that has evolved over the past ten years. Commercial PN services provide mostly advice, which is claimed to be based on the latest scientific evidence showing the causal connections between certain individual phenotypic traits (genes, lifestyle factors, gut microbe, blood parameters, age, sex, etc.) and the physiological response to food. In addition to advice, providers increasingly offer personalised supplements and vitamins (which are within the FSA remit) as well as personalised, tailored subscription meal plans. The sector in the UK is currently still small but represented by a number of different business models serving increasing consumer interest in health-related offerings. Moreover, there are hopes that commercial PN might, in the longer-term future, contribute to public health.

In this report we have analysed the specific input trends that have enabled the emergence of the sector with the drivers and challenges that are shaping its evolution today. This analysis included a thorough assessment of the science that underpins PN services, the role of technology trends and commercial activity

including an overview of the current global and UK markets, wider social trends that impact consumer uptake of PN, and the existing regulatory environment that surrounds PN, a currently unregulated commercial activity. The potential impact on public health, food safety and consumer choice as the industry develops over the coming decade were also assessed.

Key findings from this analysis

- Despite convincing scientific evidence that personalisation approaches work in a clinical or interventional study setting, there are still considerable knowledge gaps and new scientific developments that make the offerings on the market appear less scientifically robust than claimed by providers. In particular, the currently used genetic analysis methods seem to be questionable, given that only a very low number of genes are tested. These have been selected based on earlier studies, but their causal significance for metabolic response to food in healthy people is still unclear. Moreover, other likely more important factors for metabolic phenotype, such as epigenetic regulation, are currently not tested for. Following general well-established dietary guidelines may yield significant benefits for many without the need for tailored PN services.

- Technology push and investment, particularly in affordable Deoxyribonucleic acid (DNA) technologies and scientific data analysis software solutions have accelerated the commercialisation of science-based advice services. However, current business models are not yet commercially viable for the longer term, and a number of barriers in consumer acceptance need to be addressed first for market growth.

- Although there is a perception that consumers are becoming increasingly health-aware and understanding of the importance of healthy food choices, studies find that this is far less prevalent than thought. Consumer resistance specifically against PN services uptake is based on issues around cost of the service, the requirement for longer term commitment, lack of education to understand its benefits based on science, data privacy and security concerns, and science scepticism, among others.

- Personalised nutrition services are currently not explicitly regulated anywhere in the world. However, some existing legislation is meant to provide guidance for the sector for adhering to certain standards that should ensure quality of service and consumer protection. Currently a number of laws would impact on the sector, such as regulation for genetic testing in a healthcare setting, or GDPR for data protection, and the Food Law with associated FSA regulation in cases where supplements and vitamins and foods are sold, among others. However, it is not clear that PN providers understand the context of several regulatory agencies being responsible for different aspects of their offering, in particular, for staying within legal boundaries when making claims about their services. This situation creates considerable uncertainty not only for businesses, but also for consumers who wish to make an informed decision when choosing a PN provider.

- Wider network effects with the “personalisation of food” segment of the food system might be important to monitor, as several technological innovations enable increasing customisation of production, distribution, and consumer experience of food. This includes technologies such as food 3D printing, or tailoring shopping to very specific micro-markets with personalised delivery options. In the longer-term future, synergies between personalisation of food providers and PN providers may lead to more integrated services that may involve actual food items, which will pose food safety risks at a larger scale.

- Food safety risks of PN are difficult to assess in particular when only advice is involved as the longer-term health effects of following scientifically unsound advice will be hard to ascertain. Hence food risk is currently considered to be minimal in such cases. However, the majority of PN providers in the UK are currently offering supplements and vitamins and therefore fall within FSA remit. Food safety risks in this sector are generally well understood but might need to be re-assessed for the particulars of the PN context with regards to labelling, claims and safety of longer-term consumption.

Recommendations for the FSA

The FSA may wish to consider whether it would be appropriate to develop a broader framework that would cover all PN companies, or just the ones that also provide supplements and functional/personalised food items or vitamins, which are already within its remit.

Although explicit regulation of all PN providers may currently not fall directly under the FSA remit it is advisable that FSA collaborates with medical regulatory agencies, such as the Department of Health and Social Care in drawing up a joint framework of understanding for necessary regulation to ensure that general quality standards in the PN sector can be enforced effectively. This includes collaborating with relevant organisations that cover the data aspect of the sector, such as validation criteria for biospecimen and DNA testing, algorithm standards and data ownership and privacy rules.

Harmonising the regulatory framework for PN across agencies will enable the industry to evolve in line with consumer protection across the service offering.

Short-term FSA priorities (within 3 years)

- Establish within the FSA whether a more active role in regulating businesses that are operating at the intersection between health/wellness and the food system would be desirable for protecting consumers from low quality services linked to food, or outright fraud. This may involve changing existing remit definitions. In terms of the early developmental stage of the industry this could be an opportunity to shape its further evolution.
    - Build the necessary collaborations with other regulatory agencies that have responsibility for different areas of this multidisciplinary space.
- Ensure that the FSA has the relevant expertise required for monitoring the emerging PN sector by connecting with relevant experts. This will require maintaining networks of experts in the basic sciences who understand relevant scientific trends that may lead to applications relevant for the PN sector. Other additional expertise required would be:
    - Experts from the social sciences to provide insights into other societal trends that may be relevant for this sector.
    - Artificial intelligence (AI), privacy, and data security experts to provide a deeper understanding of how science is translated into advice and its implications for personal privacy of consumers.
- Monitor activities and connect with experts in the areas of general food personalisation, in particular where synergies with the PN sector could lead to a sudden market growth of PN services due to production capacities that may become available from different segments of the food processing sector. This is advisable as already a number of large multinational food producers are supporting the PN sector via partnerships and start-up funding.

- Explore whether existing regulation of supplements and vitamins is adequately covering the various aspects of PN services and whether a closer analysis of the sector would be required to establish to what extent existing regulation is adhered to.

Medium-term FSA priorities (3 to 5 years)

- Consider whether the FSA might be a relevant partner in potential efforts to make PN services available to larger segments of society with public health goals in mind. This may involve connecting with the NHS and the Department of Health and Social Care (DHSC) to explore to what extent such efforts are realistic.
- Consider establishing strategic partnerships with the public health, healthcare and social services regulatory bodies in order to bring food safety aspects to health regulation relevant for the PN sector.

Long-term FSA priorities (5 to 10+ years)

- It remains crucial to closely monitor the sector's evolution as novel science results from areas such as epigenetics, gut microbiome, metabolism research among others, will come to market, again at an early stage of understanding, potentially claiming to be more valid than current applications.

- Explore to what extent a growing PN market might impact the way consumers interact with the wider food system in a networked fashion, how such network effects might be utilised for achieving public health goals, and whether as a food regulator there would be opportunities for supporting such goals.

Introduction

Background

Personalised Nutrition services providers operate at the intersection between the food system and health advisory, using personal consumer data to provide highly tailored nutritional advice to optimise health and wellbeing. Start-ups active in this area have been gaining increasing media attention over the past five years, and technology push as well as investor interest are driving rapid expansion of the PN sector. Personalised nutrition is based on a scientific understanding that the specific physiological response of an individual to food intake, and certain food ingredients, is determined by genetic background, variations in certain genes, specifics of the gut microbiome, lifestyle factors, as well as phenotypic parameters, such as age, sex, and health status.

Wider uptake of PN services may affect how consumers interact with the food system in the UK, and may in the longer-term impact consumer health at the population level. Therefore, the FSA needs to understand this emerging industry to fulfil its regulatory remit, on the one hand to protect consumers from potential risks of PN services and PN-based personalised food products, and on the other to support developments that may be of benefit to society. Should a personalised food sector evolve from PN services by connecting with various food producers that would be certainly a development to closely watch with regard to FSA remit. Moreover, as PN services are based on scientific data and information personal to individual consumers, the FSA needs to gain a better understanding of how well PN providers represent the underlying science base of their offerings, and how trustworthy their interpretation of personal scientific data is in relation to advice given. This is important because PN providers base their health claims linked to foods and nutrients on scientific results that are specific to individual consumers rather than on population-based studies, and it is currently not clear to what extent their activities related to food would fall under FSA remit. For example, consideration is needed as to whether the science base of their health claims would warrant some kind of “labelling” or certification framework, so that consumers can make an informed choice of provider.

It is not only rising consumer interest in health, nutrition and wellness that drive growth of the PN sector, but also public health concerns of national healthcare providers. Currently, most countries show alarming trends of increasing disease burden through non-communicable diseases (NCDs) often linked to obesity, such as type 2 diabetes, cardiovascular disease (CVD), but also chronic lung disease, auto-immune disease, and cancer, among others. The World Health Organization estimates that NCDs account for over 70% of deaths globally with enormous costs to societies (WHO, 2021). The role of food intake in many of these diseases is considered as causal, and policy makers hope that PN could be part of a solution to these public health issues. Personalised approaches are considered in particular because several studies have shown in the past that general, “one size fits all” dietary advice has not been successful in changing food intake behaviour at the population level. In addition, NCDs are strongly correlated with low income and

poverty in all societies, and make them a social policy issue that clearly goes beyond health policy alone (WHO, 2021).

Scientific support for the PN sector came recently from “Food4Me” (www.food4me.org), an EU-funded research consortium of 25 partners from 12 European countries. The project involved a web-based randomised controlled trial of personal nutrition, to date the largest interventional trial, across eight EU countries investigating a large range of aspects of PN from the science base to specific diseases to social factors and consumer behaviour. One main result of the trial was that personalised nutritional advice might be more effective in changing food intake behaviour when based on personal, scientific information and feedback, and when achieved in a shared decision making context (Livingstone et al., 2021; Ordovas et al., 2018).

Personalisation of advice was shown to significantly increase the Healthy Eating Index (an overall measure for “healthfulness” of dietary behaviour) of participants, compared to other conventional dietary advice approaches. This effect was not however dependent on specific, more complex scientific data, such as genomics, metabolomics, or gut microbiome data – it simply reflected the individuals’ behavioural response to personalised dietary advice. In addition, within the context of this study it seemed that when participants were grouped into categories of whether their dietary intake would meet European dietary recommendations, those with the most inadequate diets benefited most from PN advice, confirming data from population studies (Livingstone et al., 2016; Trestini et al., 2021). Hence policy makers are looking toward the potential of PN to achieve public health goals, and a number of European countries support Research & Development in the PN sector with various funding schemes (Deloitte, 2021).

As there is currently no specific regulation of PN services, a dynamic start-up sector is rapidly expanding, with the US leading the trend and Europe representing 27% of the PN market growth in 2019 (ResearchAndMarkets, 2020). Increasingly, large industrial players in the food and nutrition or in the biomedical and biotechnology sector are joining the PN market, either directly or via partnerships. In addition, big data and data analytics companies are increasingly a driving force behind PN offerings creating software platforms specifically for the PN sector. They act as connectors between consumers, D2C blood, DNA or microbiome testing laboratories, or glucose monitoring services, dieticians, nutritionists, and web-based scientific information. As some of the PN providers entering the market sell food products or supplements together with their advice, either directly or through third parties, it becomes important for the FSA to understand the market dynamics with regard to PN offerings and personalised foods, types of business models, and speed of sector development, in order to anticipate any potential threats and opportunities for consumers and society at large.

Objectives

This report looks specifically at the impact of the emerging sector of Personalised Nutrition on food safety and consumer choice in the UK, provides a framework for

understanding the current state of the PN industry, and gives a forward look at how the industry might evolve over the next ten years.

This report provides an analytical framework for assessing the relevant current trends in science, consumer behaviour, economic activity, and the regulatory environment that currently shape the PN industry.

PN as a service is currently not regulated. In addition, it is ill defined in terms of regulatory responsibilities, likely because of its position somewhere between health advice/wellness, the food sector, and personal data that were so far considered to belong to the medical and healthcare domain. Hence this report aims to present a clear picture of the scientific, economic, and social foundations of PN, so that the FSA can assess to what extent certain aspects of PN might fall within its remit. This assessment should also include the possibility that FSA might wish to consider expanding current remit definitions.

This report provides an overview of the PN market globally and in the UK, its commercial players, and start-up trends, and gives an indication of the time frames within which PN services and products will impact the UK. These time frames will be presented with the intention of the FSA in mind to take an anticipatory approach to regulation.

This report will draw conclusions based on analysis of currently available data in the public domain and give recommendations where the opportunities for the FSA could lay as a regulator to act at the intersection between food and public health.

Key research questions

This report seeks to address the following research questions:

i. What does the current market for personalised nutrition look like in terms of its offerings and consumer reach?
ii. What is the current state of scientific understanding underpinning the personalised nutrition industry? For example, considering the potential for our understanding of the impact of the gut microbiome on individuals' health and nutrition - is there consensus on our understanding of its function and implications, and if not, what are the key areas of disagreement and uncertainty and their potential impact on the development of consumer products?
iii. What are the likely trends in how personalised nutrition will evolve in the next 10 years? What are the potential barriers and accelerants to its development?
iv. What are the current food safety risks (if any) from the personalised nutrition industry?
v. How might the likely changes in the personalised nutrition industry impact on food safety risk?
vi. How might the likely changes in the personalised nutrition industry affect food regulation? What steps might the FSA need to take to protect consumers, both through ensuring food safety, and supporting any positive benefits to be derived from personalised nutrition?

Methodology

This research took the form of an evidence assessment and synthesis of the available academic literature, industry reports including evidence already generated within the FSA, and a review of the personalised nutrition start-up scene. The assessment process consisted of desk-based research, and analysis and review were undertaken using standard evidence review protocols.

Academic databases were interrogated for the academic literature searches, and the research also draws on news articles, industry reports, and several food sector start-up focused databases (for example, Food Navigator, 2021; Forward Fooding, 2021). This report draws upon several decades of interest in this topic, and in particular the rapid growth in interest over the past decade. Where possible, we sought to identify multiple, most recent articles on each topic of interest to ensure a balanced perspective, and took into consideration more highly cited articles, or those from leading global institutions and research groups, and government agencies.

Definition of Key Terms

Biomarker: short for biological markers, are a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes or pharmacological responses to a therapeutic intervention. Used for clinical assessment such as blood pressure or cholesterol level and to monitor and predict health states in individuals or across populations.

Blood parameter: measurable characteristics of blood cells, such as white blood cell count, red blood cell count, hemoglobin, platelet count, etc. In a more general sense also, any other molecular parameter measured in a blood sample, such as glucose, or certain hormones.

Genotype: An organism’s complete set of genetic material or totality of all genes characteristic for an organism. The genotype is expressed when the information encoded in the genes' DNA is used to make ribonucleic acid (RNA) and protein molecules.

Metabolism: The chemical processes that occur within a living organism in order to maintain life, for example, the chemical reactions in the body's cells that change food into energy.

Personalised nutrition: (alternatively referred to as precision nutrition) is individualised dietary advice or nutrition guidelines based on a combination of an individual's genetic, environmental and lifestyle factors, including dietary habits, health status, phenotype, gut microbiome, and genotype, and focuses on health promotion.

Phenotype: set of observable characteristics of an individual resulting from the interaction of its genotype with the environment. Some traits are largely determined by the genotype, such as height, eye colour, and blood type, while other traits are largely determined by environmental factors.

Physiology: the organic biochemical processes of an organism or any of its parts or of a particular bodily process that maintain life and bodily functions of an organism.

Structure of the Report

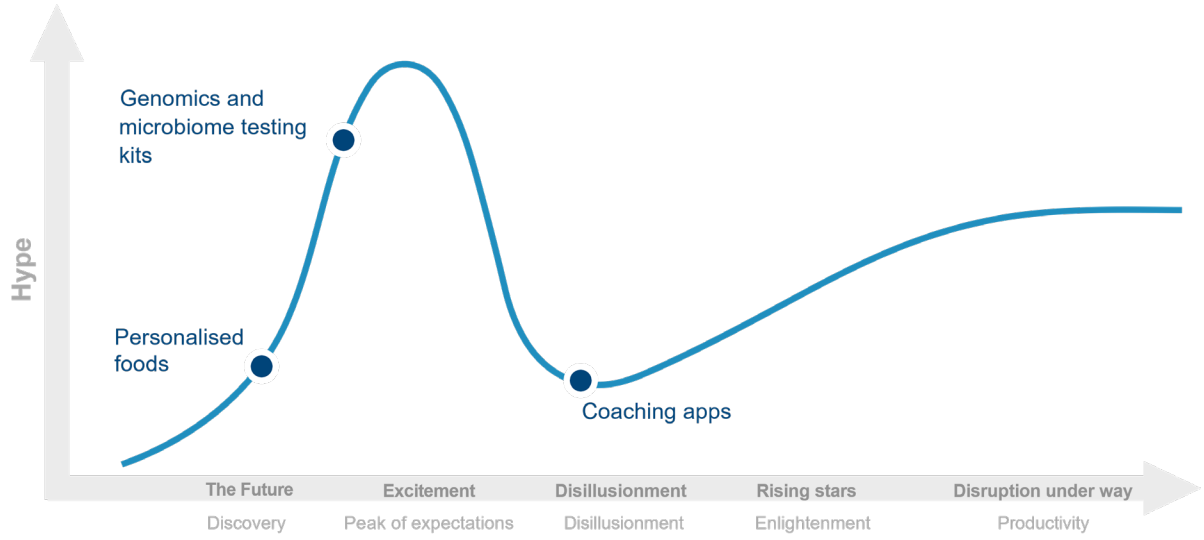
The following section (chapter 2) of this report presents an overview of the foundations of personalised nutrition, its development over the past several decades, the scientific methods underpinning PN, and the key types of PN services on offer. Chapter 3 discusses the global and UK PN market, its characteristics, business models and expected interactions with the wider food system as well as future evolution. Chapter 4 takes a thorough look at the currently used science underpinning PN services and its limitation and future developments. Chapter 5 highlights the drivers and challenges for businesses linked to technology trends and current market limitations. Chapter 6 interrogates wider societal trends that impact the evolution of PN services. Chapter 7 gives an overview of the relevant regulatory environment that may impact the currently unregulated PN sector and discusses relevant food safety issues that may arise from the sector. Chapter 8 summarises key findings. Chapter 9 draws conclusions from the research and offers recommendations for the FSA, followed by suggestions for future research.

Foundations of personalised nutrition

From reporting in the media, one could be under the impression that PN is a recent phenomenon of just the past five years or so. However, PN as a separate field of study, and an area that is intensely investigated and well supported by national and international funding agencies, has existed for at least over three decades with very little change in its scientific foundations and the claims being made about its benefits. What has changed however is the increasing commercialisation of the interface between scientific analysis providers and consumers, mainly driven by digital technologies and cheaper D2C testing devices for bio-specimen samples, such as blood, cells, stool, saliva etc. As we show in Figure 1, basic nutrition coaching apps are now quite well established in the market, while personalised nutrition based on genomics and the microbiome are still at a relatively early stage in their development, with the prospect of personalised foods (foods tailored to an individual's needs) only just beginning to capture investor interest at present.

Figure 1 Personal nutrition mapped onto the Gartner hype curve

Data Source: adapted from DigitalFoodLab (2021)



It appears that we are currently witnessing almost the highpoint of the hype cycle for genomics and microbiome-based personal nutrition that usually peaks when new technologies become more affordable and meet a wave of investor interest that drives growth in commercial applications. In order to be able to put such current reporting trends into context and understand PN as it presents itself today, we provide here an overview of definitions, the historical science context, and the scientific methods used in the PN sector.

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:

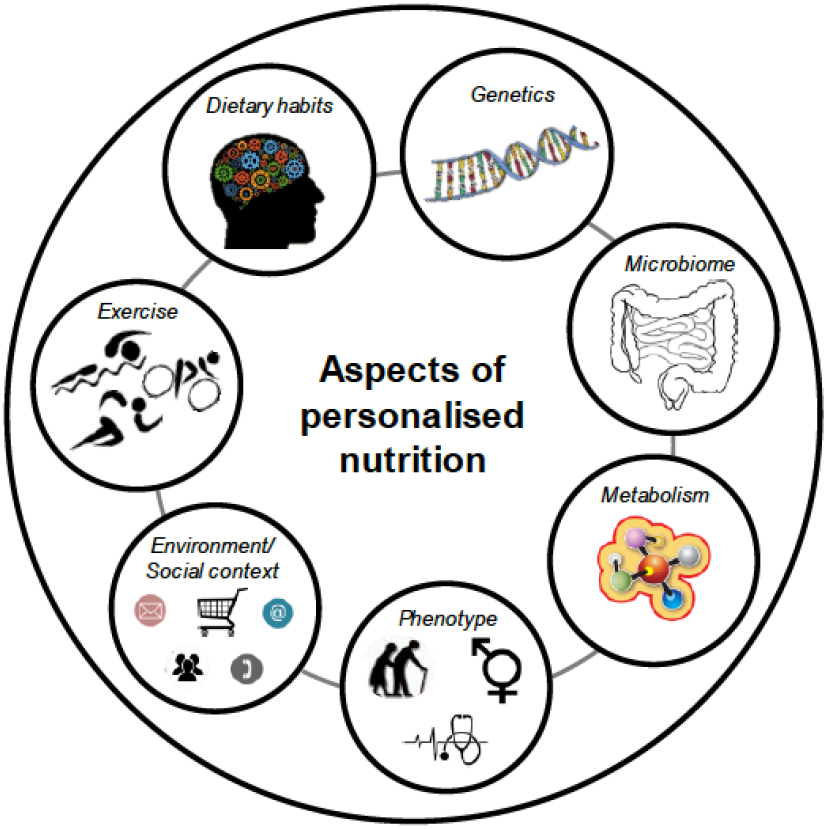
> "An approach that uses information on individual characteristics to develop targeted nutritional advice, products, or services"

> "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)

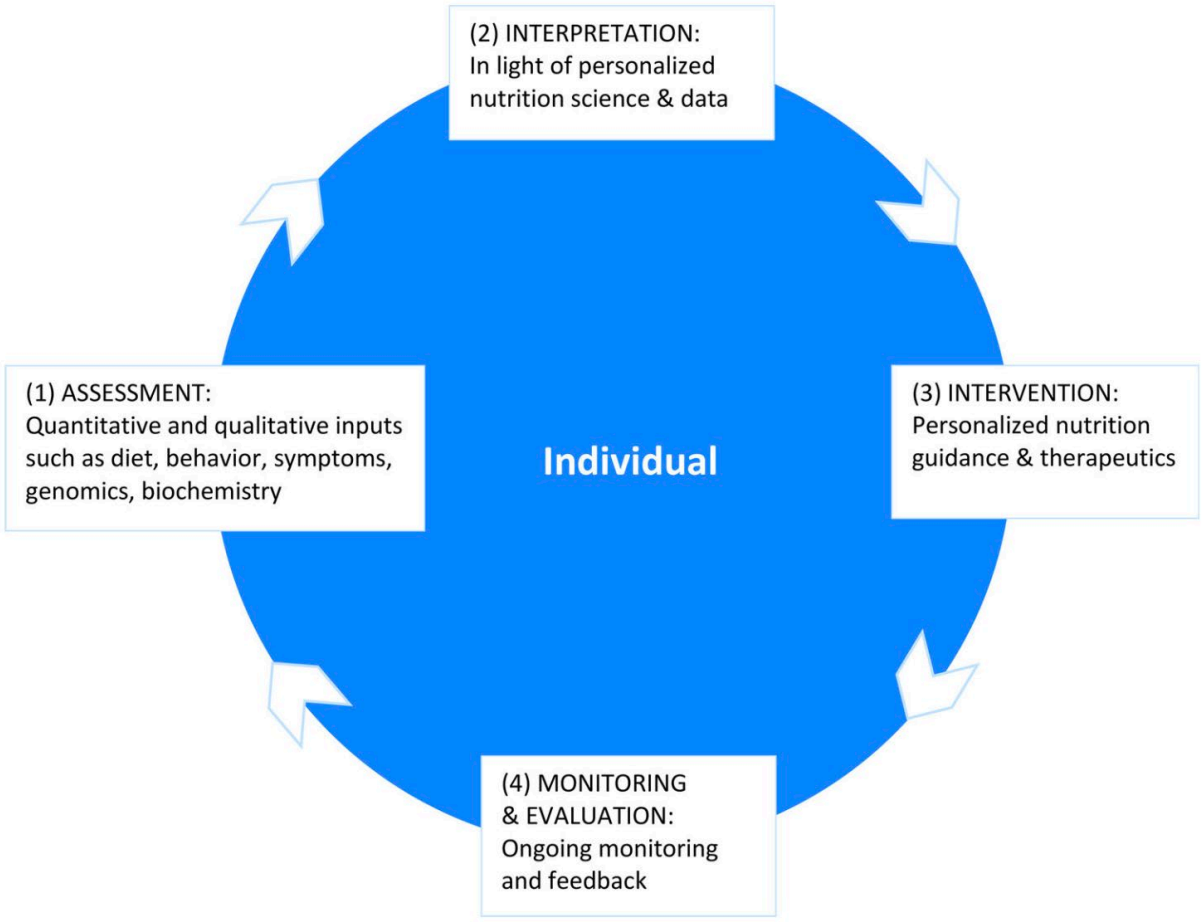


Besides phenotype data collected via questionnaires, tracker devices and software apps, blood biomarkers and metabolic parameter tracking such as continuous glucose monitoring, there is currently a strong focus by many PN providers on personal genetic or genomic information, including genetic information 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, andsector 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

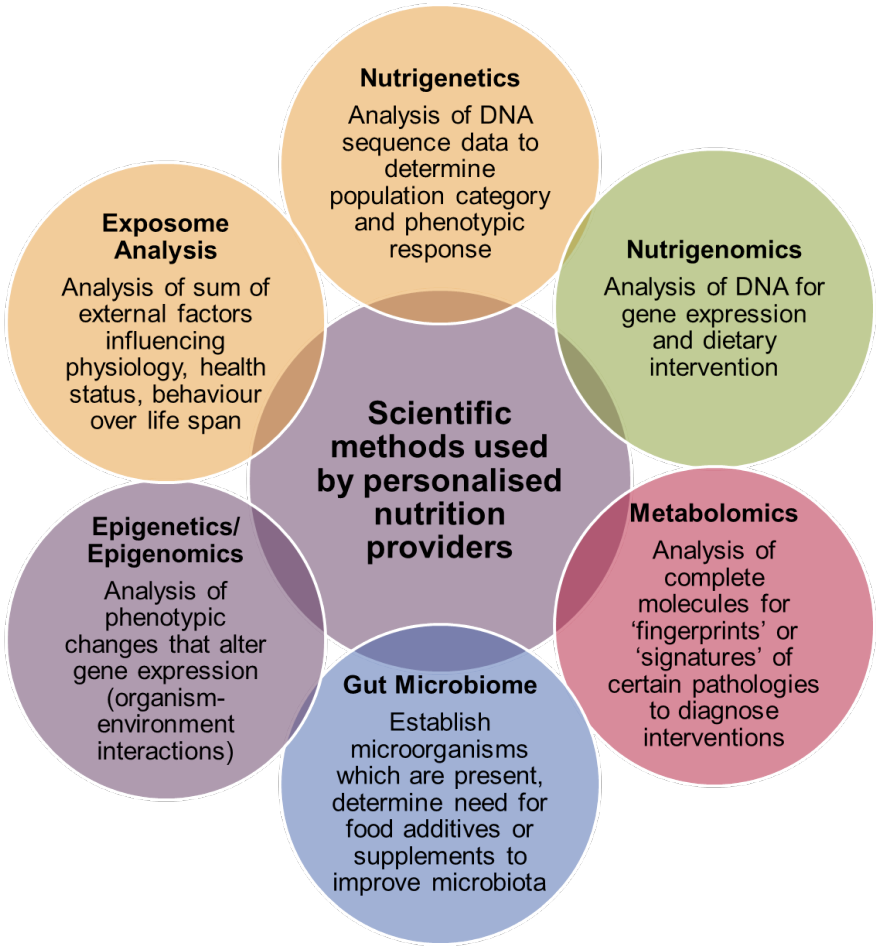
resident microbe species in a person's microbiota, usually the gut microbiota). All these technologies generate large data sets that can only be analysed with expert software and be interpreted by experienced experts. Current trends are leading to fully automated analysis and interpretation of personal 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

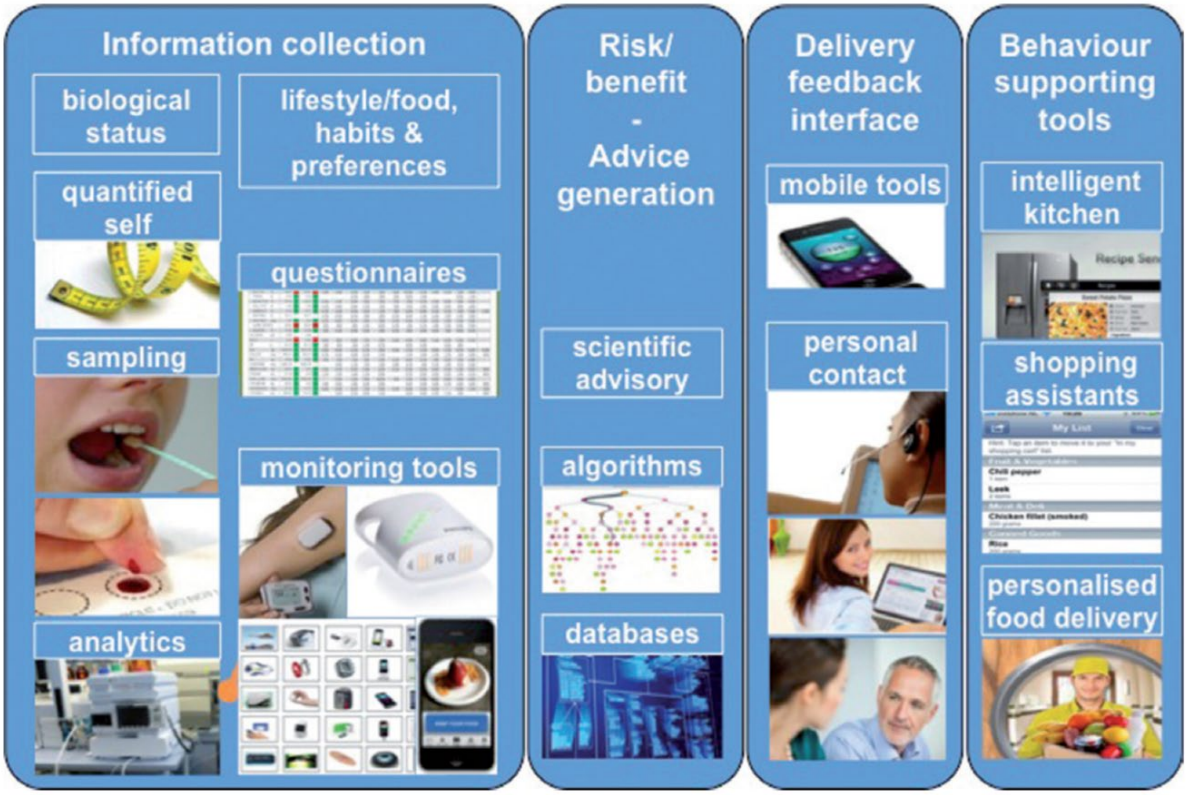
It was suggested already in 2009 to create a new term for integrating above mentioned –omics technologies as applied to the study of metabolic changes related to food intake as "foodomics", however the scientific community has been hesitant so far to adopt this term (Cifuentes, 2009; García-Cañas et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



Personalised Nutrition market and business models

Health and wellness market overview

As most PN providers position themselves within the health and wellness market, a look at the overall global wellness economy and how the wellness industry itself assesses the nutrition segment might give some indication of growth potential of PN services.

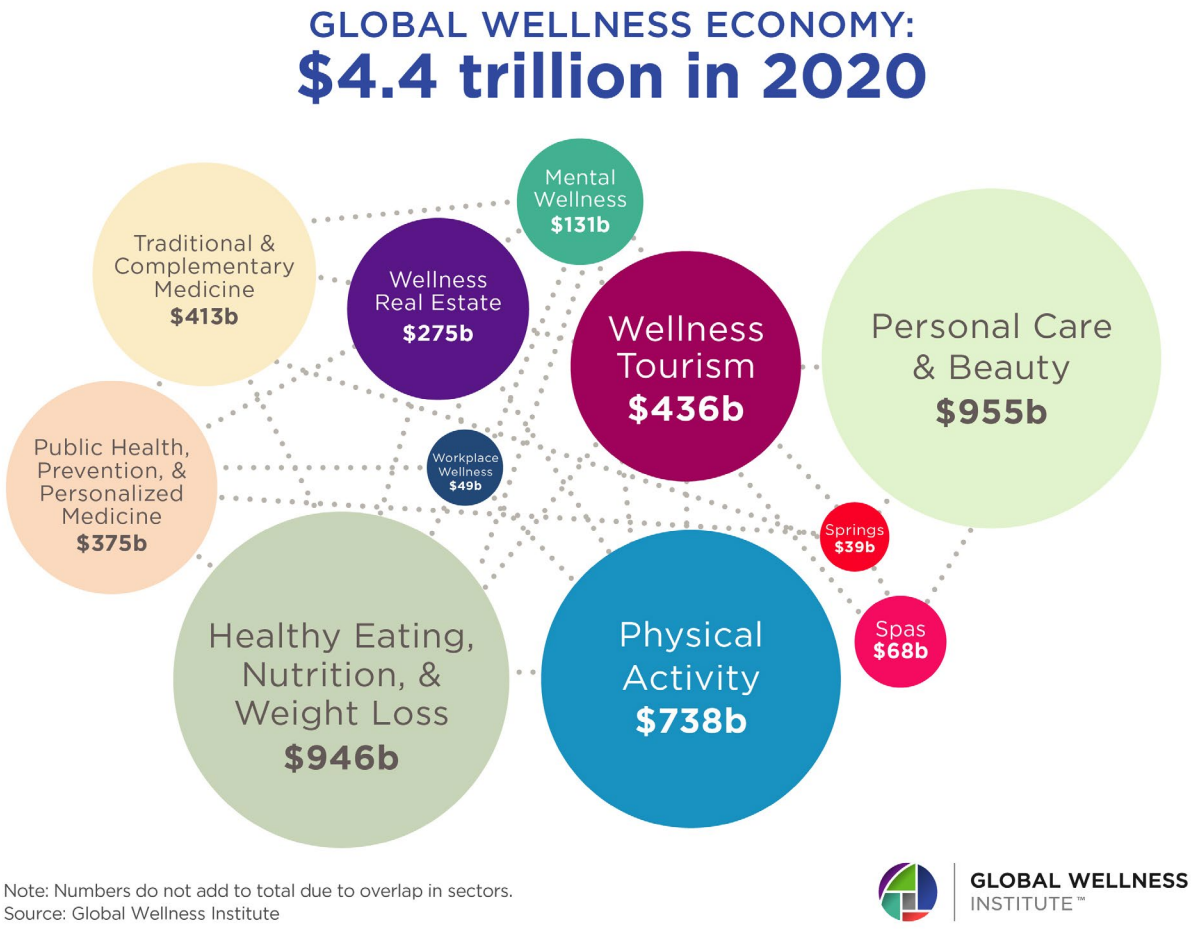
The Global Wellness Institute estimates the global wellness economy in 2020 was worth $4.4 trillion, growing at a rate of 6.6% per annum. Within this, the estimated global market segment for “healthy eating, nutrition and weight loss” is the second largest segment at $946 billion, after “personal care and beauty” at $955 billion (see Figure 6) (The Global Wellness Institute, 2021, 2022). These priorities are the same across most of the world, and consumer spending on wellness sectors is tightly correlated with GDP. More indicative than absolute market size estimates for the “healthy eating, nutrition and weight loss” category however might be its modest growth forecast of only 5.1% within the next five years, only half of the expected growth of the “physical activity” market segment (10.2%). This is in contrast to growth of other sectors of the wellness industry, such as, “wellness tourism” (growth of 20.9%), “spas” (growth of 17.2%), or “wellness real estate” (growth of 16.1%) (The Global Wellness Institute, 2021). This estimate is based on the combined projected growth of foods and beverages free from gluten, dairy, lactose, and meat as well as foods and beverages targeting weight management, which are growing rapidly,

indicating that PN seen as part of a wellness offering might be currently perceived as a service with low growth potential.

Nevertheless, Callaghan et al. (2021) suggests that within the wellness market, better nutrition has always been important, and is increasingly recognised as a key to accomplishing all other wellness goals such as better health, fitness, appearance, sleep and mindfulness. As a result, consumer interest is growing in personal nutrition apps, diet programmes, subscription food services, and so on. Moreover, there is a strong trend towards personalisation in every consumer sector, and hence demand for personalised wellbeing solutions and personalised nutrition services is anticipated to become increasingly important in the future. The Covid-19 pandemic has brought health and wellbeing to the fore for many, further stimulating demand in the sector.

Figure 6 Global wellness economy in 2020

Source: The Global Wellness Institute (2022)



Global wellness economy totals $4.4 trillion in 2020:

- personal care and beauty $955 billion
- healthy eating, nutrition and weight loss $946 billion
- physical activity $738 billion
- wellness tourism $436 billion

- traditional and complementary medicine $413 billion
- public health, prevention and personalised medicine $375 billion
- wellness real estate $275 billion
- mental wellness $131 billion
- spas $68 billion
- workplace wellness $49 billion
- springs $39 billion

Personalised Nutrition market

Companies offering personalised genomics and other biomarker testing services at an affordable price in combination with personalised behavioural change advice and feedback have created a personalised nutrition market catering to consumers who wish to tailor their nutritional intake to their physiology and disease predispositions in order to achieve health benefits and prevent disease. However, when looking into available market data there appears to still be a large discrepancy between forecast figures of the market potential for personalised nutrition and the number of companies active in this space. From an estimate in December 2020 the global market size for personalised nutrition was claimed to be worth $3.7 billion in 2019 with a forecast to grow to $16.6 billion by 2027 with a compound annual growth rate (CAGR) of 17%. This growth was predicted to be driven by consumer trends such as increasing health awareness, increasing NCDs, such as diabetes, and CVD among others. Findings, such as that in a 2017 survey of US adult consumers where 76% stated they would take dietary supplements, are interpreted as “indirect” evidence for the potential of personalised nutrition offerings.

In 2019 the US was leading the PN market with 44.56% of global market share and is predicted to be the region of major growth until 2027, while Europe in 2019 captured 27% of the market with an anticipated growth of 3% until 2027 (ResearchAndMarkets, 2020). These figures would make Europe a theoretical total addressable market of around $1billion. However, these estimates assume a homogenous market population with respect to consumer acceptance of PN across Europe, which several studies have shown is not the case. For example consumers in Greece, Ireland, Poland, Portugal and Spain, rated the general benefits of personalised nutrition highest, while in Spain and Germany respondents in a 2016 study had most reservations against commercial PN services due to low trust in data protection; even among some of the most accepting countries, such as Poland and Portugal, data protection was considered a precondition (B. J. Stewart-Knox et al., 2016). This means that within Europe the addressable market might be much smaller than estimated.

Difficulties generating realistic market data are not only due to the fact that the commercial PN sector has so far been small and slowly evolving with bigger private investments only in the past five years, but also due to its unclear positioning between health/wellness and food/nutrition. From reporting in various health/wellness and food technology media it seems that from within these industries PN is currently perceived as being more closely associated with the health/wellness sector, rather than the food sector. For example, Forward Fooding, a food technology

and innovation news platform publishes a yearly ranking of top FoodTech 500 companies in the food innovation sector including many small start-ups as well as more mature players. In their ranking of 2021 only four companies to some extent within the PN sector were included: these were Eagle Genomics, UK (www.eaglegenomics.com), a genomics services provider, ranked 59th, foodsmart, US (www.foodsmart.com), a personalised dietary advice business offering personalised meal plans without using bio-specimen data, ranked 61st, lifesum, Sweden (www.lifesum.com), a personalised weight loss platform, ranked 95th, and Nourished, UK (www.get-nourished.com), offering 3D printed personalised functional ingredients and vitamins using only questionnaire data, ranked 124th.

Not only does this reflect the small number of active companies in this space, but also the fact that from a food technology innovation perspective their impact on the global food system is perceived as rather modest from within the industry, compared for example to alternative protein producers, plant-based, or lab-grown meat companies, of which some rank among the top ten and several are represented in each category throughout the ranking table.

Personalised Nutrition examples

A study surveying genomics-based nutrition companies worldwide has found around 45 active companies in 2020, with around 20 in the US and Europe respectively and a handful in Australia and Asia (Floris et al 2020). Table 1 presents a sample of some of the companies active in the PN market, from some of the newest start-ups, to long-established market leaders. In Appendix A we present a further list of PN providers currently operating in the UK market specifically, indicating the scope and scale of their operations and specific functional areas of expertise. The appendix indicates the type of business models employed, which are discussed in the following sub-section.

Table 1 Examples of companies in Personalised Nutrition

Company	Description
Healthify Founded 2012, Singapore, Funding $100 million	Mobile-based application for tracking diet and meal planning. Offers food suggestions based on the nutritional deficiencies in the food consumption entry by the user. It also offers workout plans and expert-led guidance.
Persona Founded 2017, US Funding $4 million (acquired by Nestlé in 2019)	Provider of personalized dietary supplements, containing herbal extracts, minerals, vitamins, amino acids, probiotics, etc. The company provides supplements based on questionnaire and suggestions from nutritionists.

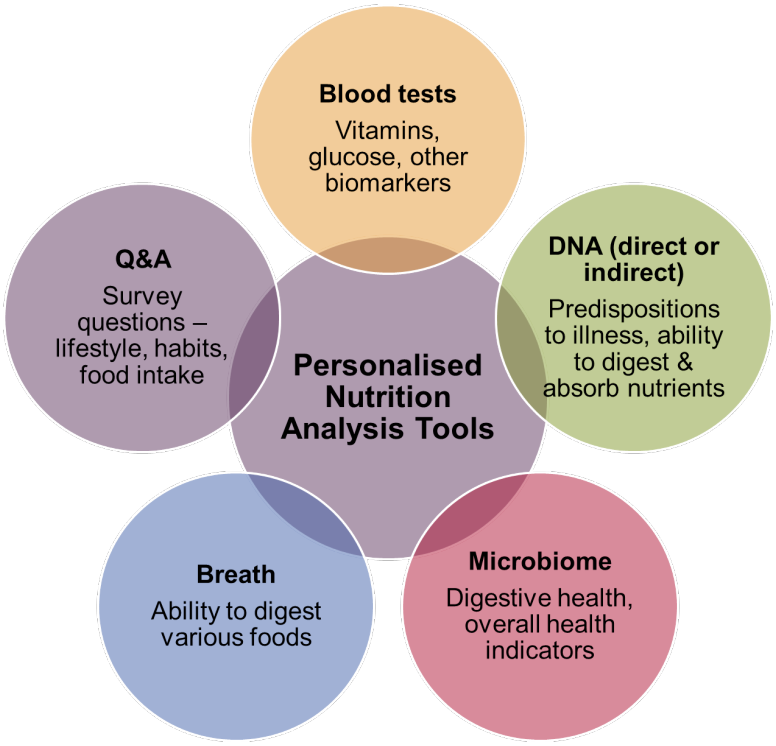
Company	Description
Care/of Founded 2016, US, Funding: $84 million	Provider of multi-category dietary supplements, such as vitamins, probiotics, herbs, minerals, and others. Allows subscribers to select the supplements they wish to receive, with filters available for supplements developed for the brain, energy, eyes, stress, heart, immunity, joints, skin, prenatal, digestion, and bones.
Clear health Founded 2021, Netherlands Funding €780,000	Participants wear a glucose monitoring patch, and log their lifestyle patterns including food, mood, exercise and sleep. The service offers its recommendations with a consultation
Lumen Founded 2020, US	Provide a breathalyser device to analyse metabolic status from exhaled air and gives users a tailored recommended diet based on the analysis.
Orig3n Founded 2014, US Funding $62 million	Provider of personalized supplements based on a genetic test. Using DNA test kits for fitness, nutrition, and performance that provide genetic data to improve health and weight. Also provides recipes, vitamins, and supplements based on DNA test.
Zoe Founded 2017, US Funding $53 million	Based on the results of ZOE's at-home gut health (microbiome), blood sugar and blood fat tests, the company creates a personalized dietary plan for its users.

Business models and types of PN services based on types of consumer data collected

PN providers differentiate themselves by their use of a limited number of scientific methods and data collection and analysis tools, which are an essential part of their business model. The exact combination for any given provider may determine whether its services would fall potentially under the FSA's remit or not. This should enable the FSA to analyse service offerings for their underlying scientific basis and types of personal data involved, as well as their relevance for the food system. Currently most providers employ five primary types of data collection and testing tools as summarised in Figure 7.

Figure 7 Five types of phenotype testing tools used for personalised nutrition applications

Source: Based on DigitalFoodLab (2021)



These tools are generally applied in the following four categories of commercial offerings (Gibney & Walsh, 2013; Ordovas et al., 2018) .

A) **Approaches collecting various kinds of personal information (longest on the market)** concerning lifestyle factors, dietary habits, demographic information, and phenotypic specifics, for example, age, sex, allergen status or physical activity etc. Information is collected via self-reported questionnaires and web interfaces. All that is provided by the consumer is personal data/information. This information then serves as input for analysis performed by the provider, presumed to be based on scientific literature or expert knowledge. Nutritional intervention advice is usually given with a nutritional goal in mind, such as weight reduction, health improvement or enhancing athletic performance among others. These forms of advice are very similar to classic dietary advice given by dieticians or nutritionists. However, most of the offerings are currently built around information and data technologies. This involves internet-based self-reporting tools, various tracker devices (fitbits, smart watches, etc.) combined with smart phone apps to generate either static or dynamic input data. To analyse these data, and to build the individualised science base applicable for individual users, the provider uses among others machine-learning and text semantics algorithms to browse vast amounts of scientific literature to automatically generate science-based advice output. Many companies in this space offer additional online support via dieticians and nutritionists, or some other form of virtual “coaching” using bots. A detailed analysis of this segment of PN services is outside the scope of this report.

B) **Approaches that use physical bio-specimen samples from customers to measure and/or quantify aspects of their phenotype**. These can be based

on blood, saliva, urine, or faecal samples, or breath, among others, to assess biochemical makers for nutritional status, or clinical parameters of health or disease risk (for example, glucose levels, cholesterol levels, metabolic enzymes, among others). Blood samples are usually collected with a certified consumer test kit method, such as Dried Blood Spot Sampling (DBS), or a microfluidic device, which do not require a nurse or phlebotomist to collect blood (fingertip prick). Direct-to-consumer DBS kits are reasonably robust, but obtainable data quality varies between manufacturers (Trifonova et al., 2019). Most consumer blood sampling kits allow only certain blood parameters to be identified, as many either would require greater blood volumes, or specific forms of blood preservation for their detection. Some of the molecules detected in blood allow classification of users into different "health/risk categories" based on clinical literature. Included in this category are offerings of continuous measurement of glucose via a D2C monitoring device that produces dynamic time-course data (well established for diabetics), which is then analysed via the provider's software. Stool samples for the assessment of the gut microbiome fall also within this category (as they are for detecting DNA of the gut microbes and not the person's DNA). Though variable for most people over time, a combination of a number of such phenotypic parameters can sufficiently identify a person's identity.

C) **Approaches using personal DNA information of customers.** DNA samples are usually collected via a consumer test kit that is sent out by the PN provider to the customer. These contain tools to swab some cells into a collection tube that is then sent back to the PN provider. (The risks of loss of personal DNA in the process are rarely discussed in the PN sector). The provider then sends the sample to a laboratory for extracting DNA and performing DNA sequencing, returning DNA sequence information to the provider. For quality assurance, ideally the laboratory is ISO 17025 certified and accredited with a body that complies with ISO/IEC 17011. Most providers test only for a very limited number of genes, or gene variants (10-30), usually the ones with a long scientific publication history and confirmed causality for disease risk or metabolic function proven to some degree at population level.

D) Approaches that use any of A, B, C, *and* sell a physical product (often described as "functional food", "personalised supplement" or similar)

A number of companies in the PN space offer services as described in A-C, and *in addition* offer branded products tailored to the results of the customer's phenotypic and genotypic data analysis results. These products often are supplements similar to "functional ingredients", "personalised vitamins", or "sports nutrition" in the form of a powder mix to be diluted and consumed as a "meal shake" (for example: www.nutri-genetix.com; or: www.foodspring.co.uk/en), bars, amino acid mixes, snacks etc. Others specialise on more traditional personalised supplements, such as personalised vitamin mixtures, including single supplements such as collagen (for example: www.personalised.co; or: www.vitl.com).

These service categories are not mutually exclusive but have historically evolved because some companies have built their offering around one novel sample analysis technology, in particular when they hold IP in that space, while more recently with reducing costs of D2C testing technologies more companies can offer increasingly a combination of these approaches. In particular, from a consumer data perspective, these categories are a good representation of how the sector is structured.

Implementation of these approaches to PN can take many forms, (Ronteltap et al., 2013) propose a categorisation of nine business model archetypes for PN:

1. Employee lifestyle guidance. Business-to-business (B2B) service where the PN provider partners with an employer to offer services to their employees.
2. “Standing strong together”. Community-level groups, including possibly NHS-funded initiatives that offer support to participants in following a PN-based programme.
3. Health club model where participants pay a membership fee that includes PN services.
4. App based self-monitoring of dietary intake using smart-devices, fitbits, web-based applications, etc.
5. “Do-it-yourself” model. After initial PN tests and guidance the participant is then left on their own to follow a dietary programme.
6. “Step-in step-out”. This model includes initial test and guidance, and then a level of optional feedback based on on-going testing and monitored progress.
7. All-in lifestyle guidance covering all aspects of health and wellbeing.
8. Traditional face-to-face dietitian advisory services.
9. Mass-media communications model – public education and awareness raising initiatives.

Business models for Personalised Food

The personalised nutrition market is primarily concerned with providing advisory services, and as discussed above, may include provision of vitamins and supplements to support a personalised diet. This is distinct from the separate category of “personalised food” businesses that offer personalisation or customisation of food, personalised food businesses already exist, albeit most are not currently based on science and PN, and in the future they could become part of a supportive ecosystem of services and hence impact or even drive the evolution and uptake of PN. For example, the PN provider tells the consumer what to eat, and the personalised food provider delivers what the consumer should be eating. Personalised food providers are likely to be the most relevant area of focus for FSA as they will fall directly within the FSA’s regulatory remit.

Personalised foods can be either pre-packaged (ready-meals, ingredient boxes, processed foods, etc), or food services (restaurants, take-aways, etc), and can be with mass-customised offering stratified product groups, or personalised for the individual consumer (Sagentia Innovation, 2021).

The literature and the start-up scene identify several potential business models offering varying degrees of personalised foods (as shown in Table 2), and new

business models can be expected to emerge as the industry evolves and leverages digitization and rapid delivery services, among other things. Figure 8 illustrates a potential schematic for an integrated personalised food system. Successful business models will need to address the following factors (Boland et al., 2019):

i. A completely connected PN/Personalised food platform, and a nutrition profile standard to create a complete value chain.
ii. Retaining the emotional aspect of food as customers mostly eat to enjoy the sensations food can bring.
iii. Consumers need to be persuaded to actively engage long-term with PN, i.e., the industry needs to create a compelling mechanism/offering to engage consumers.
iv. Consumers must have confidence that their personal genomics and other information is handled appropriately and transparently.
v. An economically viable business model based on subscription services, or other revenue streams.

Table 2 Business models for personalised foods

Source: based on Tischer et al. (2021)

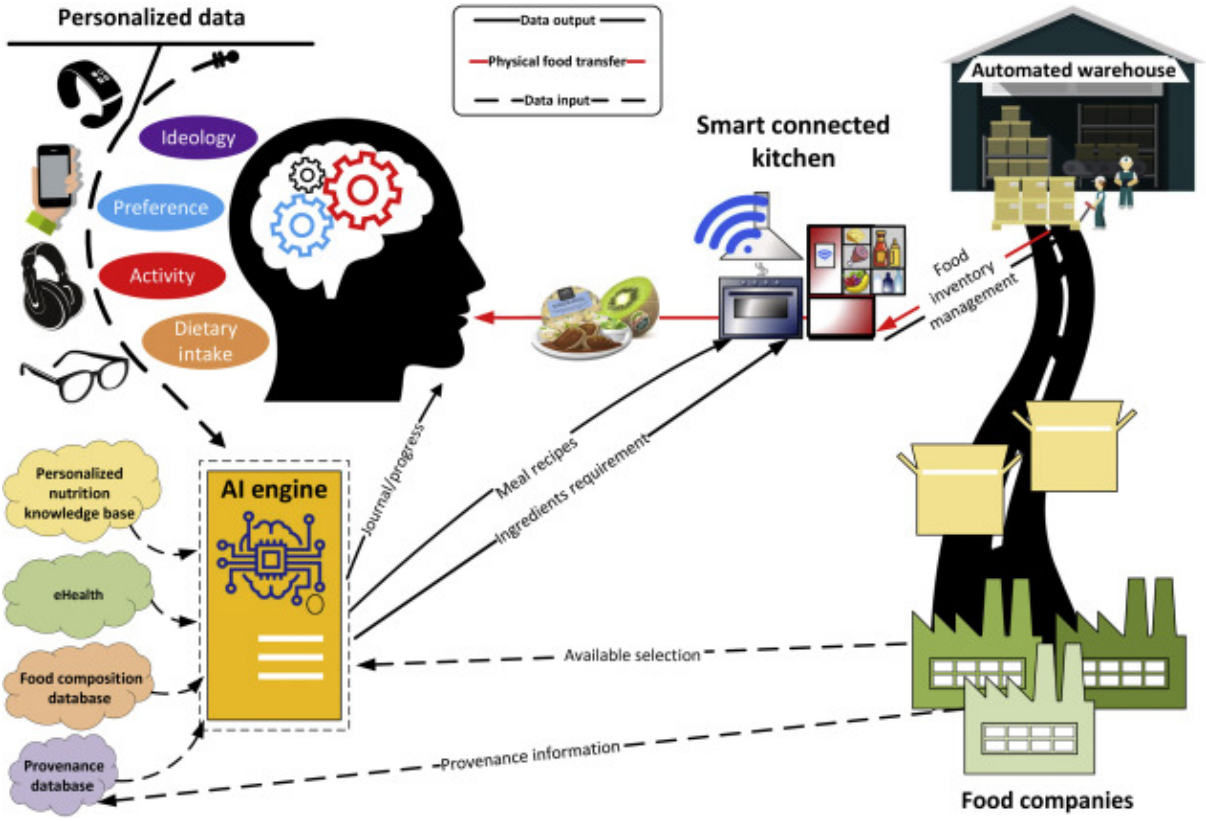
Business model	Description	Advantages	Challenges
Personalised eGrocery	Builds on existing ecommerce solutions and rapid food delivery services to offer self-segmentation. Gluten-free, organic, and so on, with potential for segments to target metabolic types, cholesterol levels, biomarkers, etc.	• Ease of use • Integrates with existing consumer routines • Consumer controls personal data • Opportunity to expose consumers to new products without significant behaviour change	• Not true personalisation • Need for consumer self-evaluation to choose products • Unsupervised health impacts • No holistic value chain – depends on consumer to do the work.

Business model	Description	Advantages	Challenges
Gastronomy	Eat-in and take-away restaurants offering meal options based on pre-defined criteria. Leverages digital technologies for menu and ordering processes, tech for in-kitchen preparation, 3D food printing, dark kitchens. Already partially seen in health-food fast-food eateries such as personalised smoothies.	• Convenience and consumer familiarity • Potentially low complexity, depending on implementation • Expand on existing fast-food franchises • Opportunity to gather data on consumer habits, needs, etc. for targeted promotion and product development	• Fragmented • Additional overhead burden for restauranteur, and runs counter to standardisation of most fast-food operations • May reduce flexibility for restaurateurs as meals must be exactly as described • Consumers may be unwilling to adopt rational PN concept in place of social aspects of dining.
Personalised nutrition platform	Two-sided marketplace, connecting consumers (and their personalised data) with retailers and restaurateurs. Revenue streams potentially related to advertising, use of consumer data for targeted offerings and for product development	• Personalised recommendations from a wider range of retailers/ manufacturers/ restaurants • Based on full PN profiling, not just self-selected categories • Convenience • Potential lock-in with consumers	• Significant investment required to build and market and establish consumer base • Data privacy concerns over how data will be used/ shared/ sold

Business model	Description	Advantages	Challenges
Subscription-based personalised meal service	Offers boxed, frozen ready to eat meals, or ingredient boxes for home preparation. These already exist, but new solutions might build on, or be closely integrated with personalised nutrition platform to provide highly tailored offerings	• Convenience for consumer • High potential impact as PN is fully integrated into diet • Extension of existing subscription services • Commitment/lock-in to subscription ensures ongoing engagement	• Variety may be challenging, and consumers may demand more choice • Depending on modularity/options may be expensive to deliver and scale • Freshness is a challenge for pre-made meals • Requires nutrition profile service

Figure 8 Schematic of a personalised food system

Source: Boland et al. (2019)



Business eco-system for personalised nutrition and personalised foods

The personalised nutrition and personalised foods business models discussed above could be vertically integrated business entities but given the specialist and diverse aspects of their operations, are much more likely to emerge through the collaboration of multiple value-chain partners. Figure 9 illustrates the potential range of actors in the eco-system, with a coordinating role for PN service integrators. The figure illustrates only PN provision, but an additional layer of personalised food providers could be added.

Figure 9 Eco-system integration of business actors and activities

Source: developed from Goossens (2015)

Growth opportunities in personalised nutrition

With rising awareness of the impact of food on our health the market potential for personalised nutrition is huge, and there are already businesses emerging offering personalised microbiome-based nutritional testing. The global nutrigenomics market size was valued at $252.20 million in 2017 and is projected to expand at a CAGR of 16.48% from 2018 to 2025. Increasing awareness among consumers along with the increased prevalence of obesity and related ailments is expected to be a key factor driving the market (Grand View Research, 2019). Epigenetic testing is still a long way off from a mass application, as epigenetics methods are still much more expensive and scientifically less proven than genomics methods. But in the same manner companies offer a complete genome analysis for a few hundred dollars, similar is expected with epigenomics in the longer-term future.

Key challenges for development of the sector are the high costs and long timeframes for conducting randomised control trials to develop the underlying scientific nutrition standards to support PN. This acts as a significant barrier to entrepreneurs and

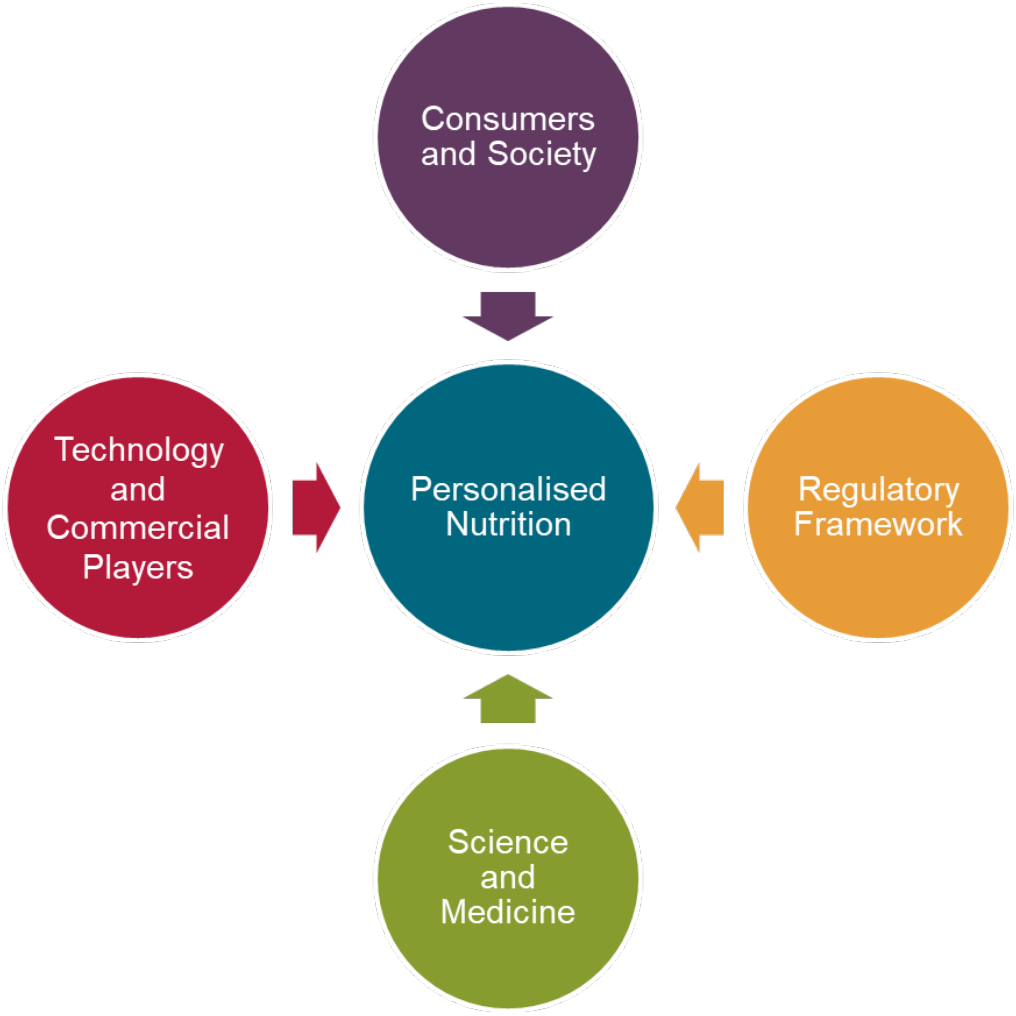
investors in the sector. To address this issue, grants and incentives to support and accelerate development of PN are available in the EU and the US. For example, the European Commission is currently offering grants to support research into microbiome composition and how this can be affected by diet, for a value of €1m per project. The Horizon Europe programme provides funding towards a molecular and neurobiological understanding of mental health and mental illness, with a budget of €10million per project (Deloitte, 2021). Tapping into these resources offers a potentially viable business model to enable new start-ups to subsidise consumer engagement in the initial phase, until such time as costs reduce and interest reaches a threshold for a sustainable economic enterprise.

Drivers and challenges for personalised nutrition

Given that PN in its current scientific understanding has been around for some decades, one might wonder why it has still not gained more traction already, either as an accessible market offering for consumers, or as a publicly supported technology for achieving public health goals. The reasons for its current state of evolution can be found in the rather complex interactions between a number of long-term input trends that have been defining PN in the past, and more recent trends of the past 5-10 years. In addition, its ill-defined position between the food and healthcare sectors will make it subordinate to trends in both these areas and their respective regulatory developments, hence it appears very unlikely that the complexity in this regard will reduce in the near future.

In order for FSA to build an analytical framework for understanding past and future evolution of PN we provide in the following chapters 4-7 an overview of important drivers and challenges that have been and will be shaping PN. It will be necessary to monitor closely this ecosystem of trends to gain some prognostic insights into likely developments of the PN industry in order to be able to design regulation proactively. We have grouped relevant trends into four categories, namely science and medicine, technology and commercial players, consumers and society, and regulation (see Figure 10). This separate grouping of trend areas may be somewhat artificial, as it is understood that these areas interact and influence each other, impacting mutually the evolution of certain trends that manifest in any given category. For the purpose of this report, we use these categories solely as a framework to support clarity of presentation of findings, and present each separately in the following chapters 4 -7.

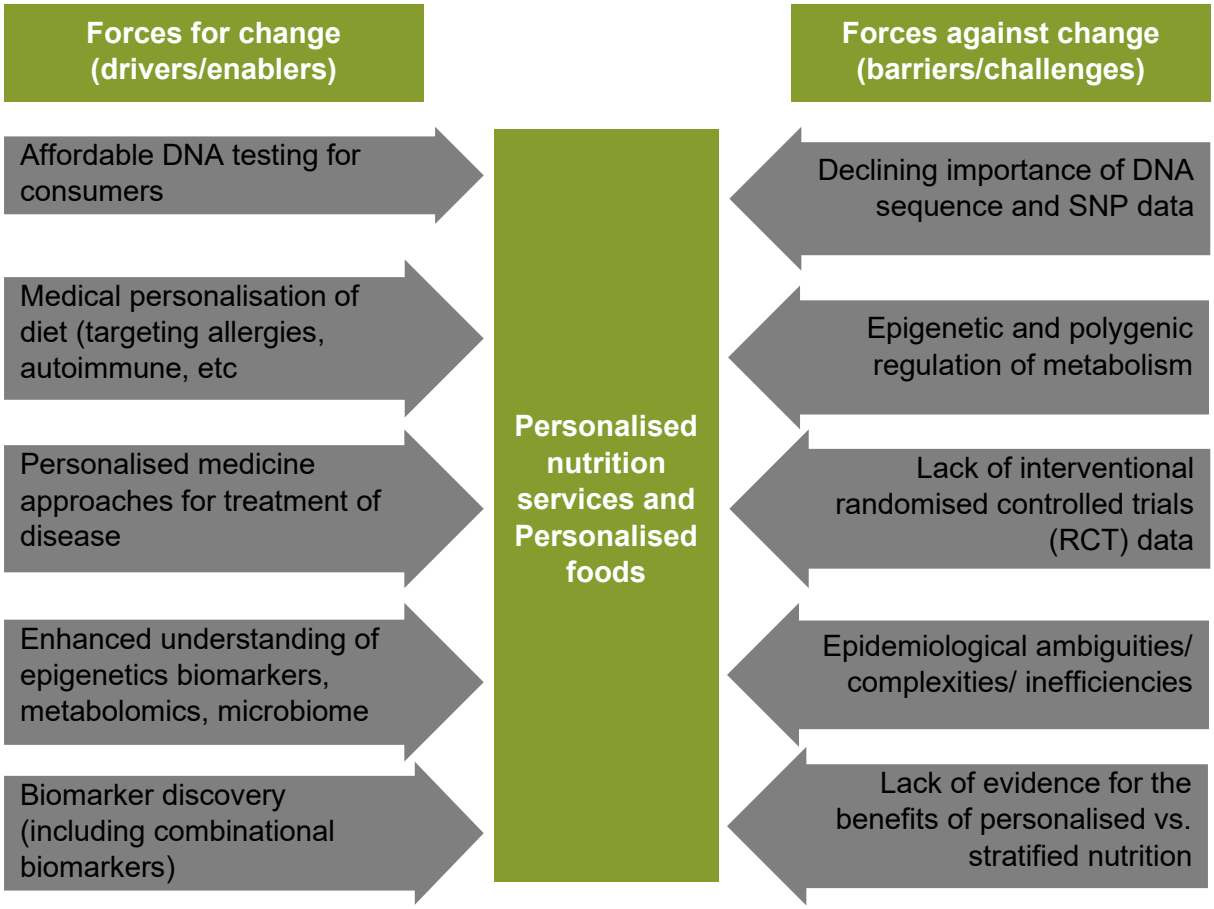
Figure 10 Input trends shaping personalised nutrition



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 (www.savorhealth.com) 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)

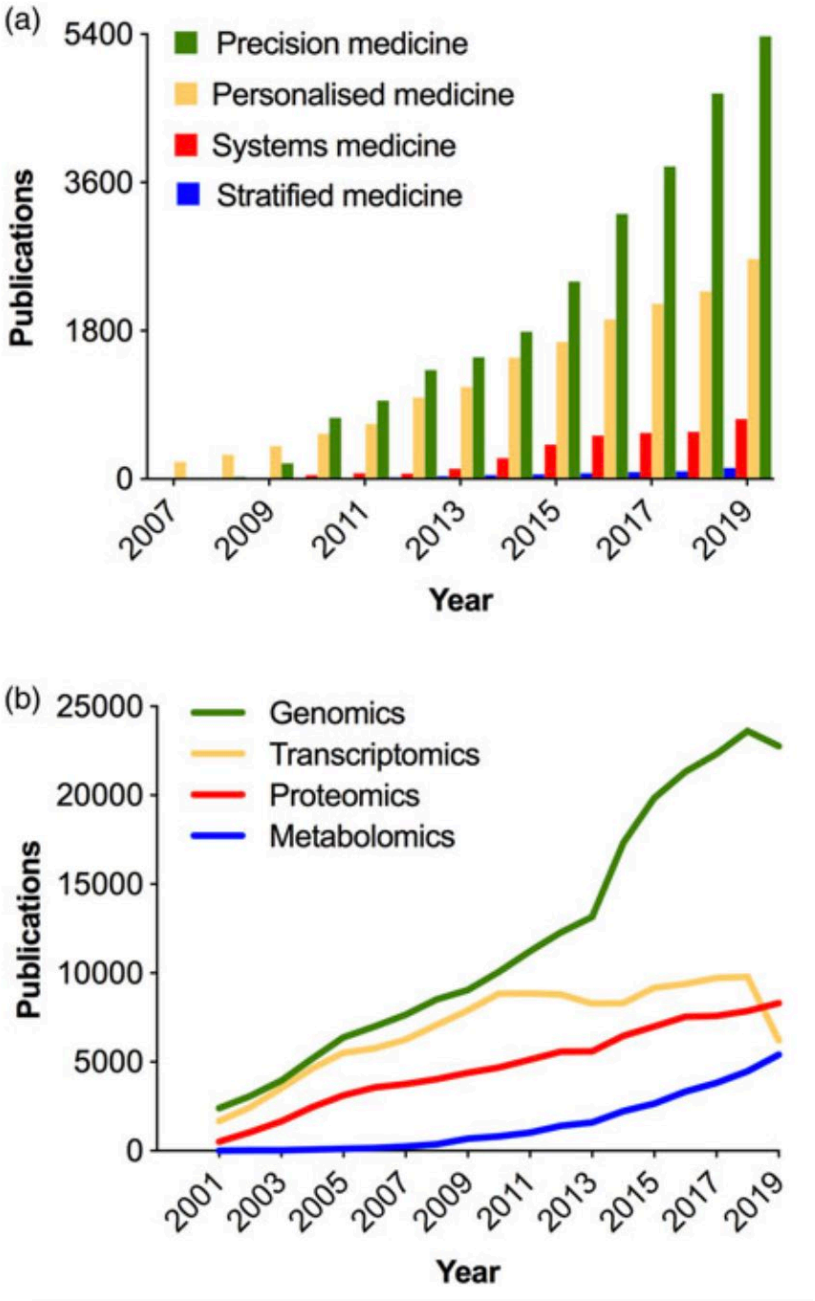
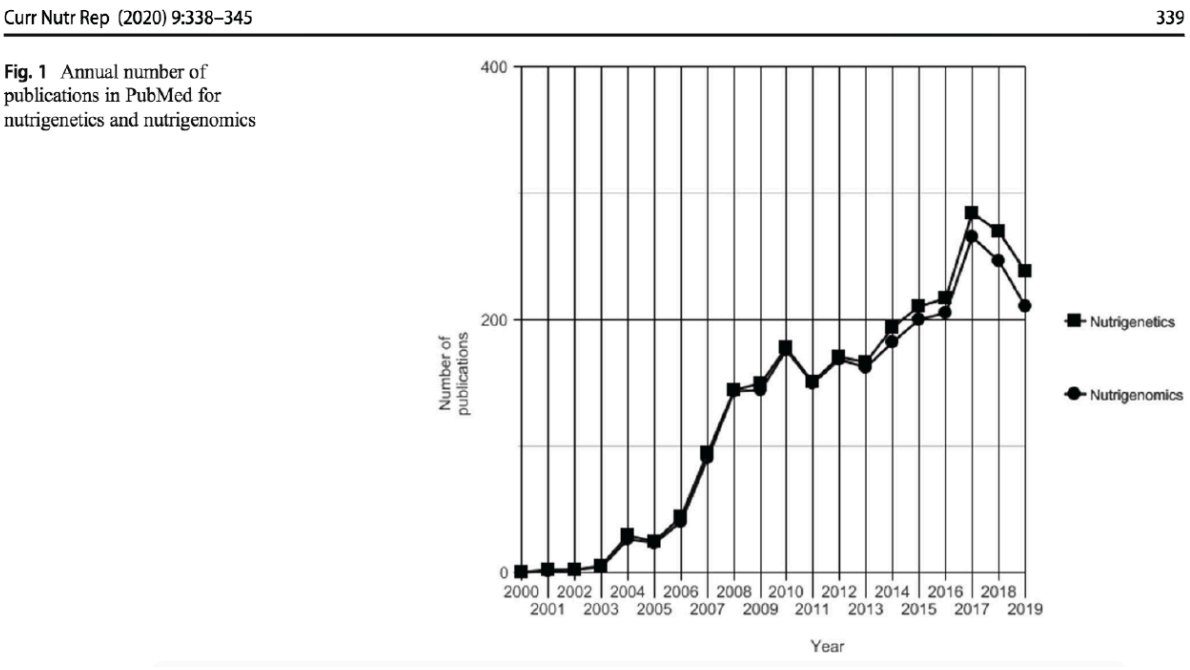


Figure 13 Publication trends - Nutrigenetics and nutrigenomics 2000 – 2019

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 (www.food4me.org) (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.

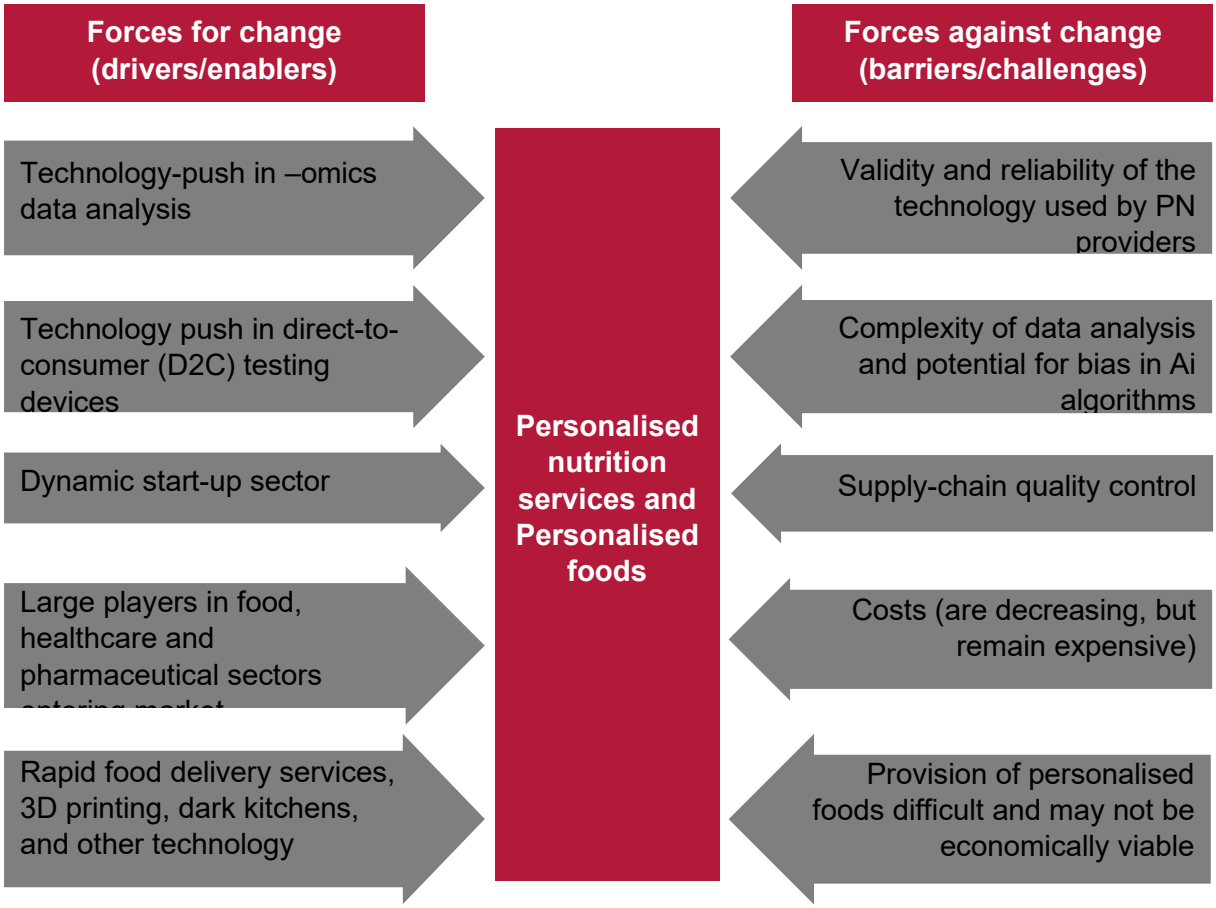
Moreover, it is a well-studied principle of epidemiology that statistically most new cases of any given disease in a population occur in parts of the population not classified as at risk. Say for example, the incidence of cases of type 2 diabetes within the general population each year is much larger 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.

Technology and commerce – Drivers and challenges

Technology and commercial players, including established food, health and pharmaceutical players and new start-ups drive PN market growth, but face a number of technological and commercial barriers to scale-up These are summarised in Figure 14 and discussed in detail below.

Figure 14 Technology and commercial players: Drivers and challenges



Technology and commercial drivers

Technology push in consumer testing devices and –omics analytics

Technology-push in –omics data analysis and D2C testing devices supported by large players are driving the current expansion of commercial PN offerings. These two longer-term trends of the past 15 years have their origins in the scientific successes of DNA technologies supported by huge investments internationally that have accelerated the growth of the wider biotech/biomed sector including PN. Genetic testing in the PN space, using D2C testing devices, was driven by companies such as 23andMe (US), offering ancestry services, as their advice was initially sold and classified. However, they also included some general health and medical information alongside. Although the US Food and Drug Administration (FDA) temporarily banned 23andMe in 2013 from offering health/medical advice, due to limited positive and negative predictive value, FDA approved in 2017 the first commercial D2C testing for genetic health risk (GHR) in the US, offered by 23andMe based on their testing technology and improved scientific foundations. The company's GHR advice is limited to 13 diseases including Parkinson's disease, Celiac disease (gluten intolerance), late onset Alzheimer's disease, and some much

rarer genetic conditions, including Factor XI deficiency, a blood clotting disorder (FDA, 2017).

The number of commercially genotyped consumers has risen since 2016 exponentially, reached over 10 million in 2018 and was predicted to have risen another 10-fold by 2021, and general consumer interest is increasing further with reducing prices of these services (Khan & Mittelman, 2018; Moore, 2020). Big players in the D2C DNA testing field, such as 23andMe, supported among others by Google, are estimated to store consumer sample data in the millions. They have sold over 250,000 tests in the UK alone by 2020. Most companies using gene panel methods test for up to 50 gene variants at best, and claim that their results are obtained in certified laboratories that fulfil quality standards in the medical sector, such as in the US Clinical Laboratory Improvement Amendment (CLIA), or for analytics, Certified Analytics Professional (CAP), or ISO 17025 certification (Bean et al., 2020).

Most established companies in the PN sector using DNA data offer additional services in the health and wellness segment, such as for example: Nutrigenomix (www.nutrigenomix.com), Caligenix (www.caligenix.com), DNAFit (www.dnafit.com), GX Sciences (www.gxsciences.com), InsideTracker (www.insidetracker.com), or Day Two (www.daytwo.com) that uses gut microbiome data. More established companies usually partner with healthcare and pharmaceutical companies and show their science competence by having doctors and scientists on the board or affiliations with reputable universities. One good example is ZOE (www.joinzoe.com), based in the UK and US, focusing on gut health, blood sugar, and blood fat measurements. ZOE was involved in a series of 3 PREDICT studies since 2018 in collaboration with scientists from Massachusetts General Hospital, Stanford Medicine, Harvard T.H. Chan School of Public Health, and King's College London yielding valuable research publications (Asnicar et al., 2021; Berry et al., 2020; Spector et al., 2019). These established PN players with even a strong scientific backing keep their marketing appearance mostly somewhat undefined between health and wellness.

A similar technology push is seen with companies providing other D2C testing services, such as continuous glucose monitoring (CGM) for the purposes of personalising health and nutritional advice. Until 2017 CGM was not offered much outside of the diabetes market where continuous monitoring has been established for well over a decade in an outpatient setting for insulin dependent diabetics, with oversight by medical professionals. The recent generation of consumer devices are usually 3-4cm disks that are secured with allergen-free medical tape or glue on the rear of the upper arm after a microfluidic connection to the bloodstream was generated with an almost pain free needle mechanism. A built-in transponder then relays glucose values via a smart phone app to a data analysis platform of the provider. These devices can in ideal conditions collect data for around two weeks, and need then to be replaced with a new device. All CGM device market leaders such as Abbot Diabetes Care, FreeStyle Libre, and Dexcom reported at least 30% market growth between 2020/21, and Global Market predicts a 6.2% CAGR between now and 2030 (GlobalData Healthcare, 2021). Some of this growth is expected to

come from the PN sector where a number of start-ups are already offering PN services based on CGM data, or are at their beta stage. For example, Clear (https://www.clear.bio/) in the Netherlands with a monthly subscription model for €99 and one-off trial offers for €169, providing device, app, and advice with chat function. In addition, they offer "add-ons", such as gut microbiome testing. Other players, such as Levels (US), (www.levelshealth.com/), offer CGM device and PN advice for "eligible" consumers for $400. D2C devices, are sold usually at a premium in the PN sector and are included in the service offering, so consumers have no choice of device, even though these are often identical to what is sold in the medical diabetes healthcare market at a lower price. Recent smaller studies have tested the accuracy of algorithms predicting glycaemic responses to certain foods using either a standard carbohydrate counting method against using a CGM device and find significantly better data validity when using CGM data (Mendes-Soares et al., 2019).

Biological data analysis specialisations, now known as –omics technologies, emerged from the analysis of large DNA data sets and the framework of systems biology that integrated interdisciplinary engineering and software developments with the biosciences. A whole industry of commercial companies offering only –omics data analysis, and disease prediction and risk scoring has emerged from this field. They act as platform providers and hence the time it takes to translate scientific insights, based on complex data into a consumer offering has dramatically shortened over the past ten years to less than a year in some cases, as similar dynamics like in the general software sector are at play. For example, eagle genomics (UK) offer a broad range of data analysis, such as genomics and microbiome data, and support applications in fields such as, (in their own words): "Food & Nutrition, AgriBio, Biopharma, and Beauty/Personal Care, by extracting scientific data and delivering product claims in minutes rather than months – dramatically accelerating innovation, supporting sustainability, and reducing 'trial and error' R&D while helping drive the digital reinvention of science applications and translation" (https://www.eaglegenomics.com/). Eagle genomics is also representative in their business structure of similar software service providers in the US and Europe as it is linked to a reputable academic institution (The Wellcome Sanger Institute, University of Cambridge), is well embedded and funded in a local biotech start-up ecosystem, and partners with large consumer brands in the food and FMCG sector, such as Unilever, GSK, Reckitt, and Cargill.

However, as the data aspect of PN services is seen increasingly as a valuable source of consumer data that many companies would like to exploit, less reputable data processors may enter the market as the number of third-party raw DNA data analysis providers is rapidly increasing. This means that providers who were not involved in the consumer interaction and initial DNA extraction and sequencing of the sample, perform data analysis, which can cause quality control and oversight issues along the chain of involved entities (Moore, 2020). Rarely discussed are issues with registration and oversight jurisdiction as data analytics companies effectively operate as global "data businesses" but can affect national health sectors (see challenges, below).

Start-ups in the DNA testing and data space are globally well supported by large industry players. For example, Illumina, the world leader in DNA sequencing technology instruments and innovation runs since 2014 start-up business accelerators in the US and near Cambridge, UK, to support start-ups in the genomics space. Illumina not only provides access to capital, but also to expertise and technology within Illumina (https://emea.illumina.com/science/accelerator.html). The same DNA technology push that underpins D2C DNA testing of the human genome drives PN services based on gut microbiome analysis as it tests for DNA of microbial species.

Large players in the food and health sectors entering the PN market

Large players in the food, and health care/pharmaceutical sectors have entered the PN market over the past decade either directly or via mergers and acquisitions. Apart from software developers who offer solutions specifically for PN applications often as white label products for PN providers (example: https://suggestic.com/), multinationals in the health/pharmaceutical and food sectors are increasingly supporting start-ups in the PN space. For example, Mars Edge, the health nutrition arm of Mars, has acquired the German PN provider Food Spring (www.foodspring.co.uk) in 2019, and Nestlé, a global food and drinks processor, acquired Persona a US PN provider. In 2018, Nestlé has also supported a wellness ambassador program in Japan offering meal plans based on DNA analysis. Campbell's, a big US food and snack manufacturer, has invested in Habit (https://habit.com/), a PN provider, in 2016, which was subsequently acquired by Viome (www.viome.com) offering services based on gut microbiome analysis, claiming more than 300,000 customers. Big players in the pharmaceutical sector operating PN services either directly or via partnerships include Bayer, a large pharmaceuticals manufacturer, that offers personalised vitamins via Care/of (https://takecareof.com) and Noho, a US PN start-up. Most of the offerings from the pharmaceutical sector emerged from their expertise in supplements and nutraceutical manufacturing. However, it is estimated that uptake of these services by consumers is still moderate.

Technological and commercial challenges

The Validity and reliability of the technology

The Validity and reliability of the technology used by PN providers has been questioned by scientists for more than a decade, as there is a complete lack of published studies of the analytical and clinical/predictive validity of the specific personalisation offers on the market. A recent confirmatory study in which D2C DNA samples were sent for re-testing in a clinical laboratory found that 40% of variants detected by D2C testing were in fact false positives, also false negatives are a health risk for people in higher risk categories (Tandy-Connor et al., 2018). In addition, even advanced molecular analysis methods have certain known false positive/false negative rates, which makes it near impossible even for the provider to understand before-after changes in approaches where samples are taken repeatedly to assess the effects of dietary intervention. Findings like these raise concerns over how well algorithms that are applied to faulty raw data can deliver valuable advice. In

particular, this raises ethical issues when consumers base medical decisions on these results, and it is recognised that the medical profession needs to be appropriately trained to advise patients on these issues (Horton et al., 2019).

As personalisation in the D2C testing market is also based on predictive risk estimates based on only a small number of genes (commercial gene panels usually test for 20 to 50 genes/variants at best), genetic risk factor calculations on the market are most likely not giving a realistic assessment of disease risk, or metabolic response to food, given that large, recent genome wide association studies (GWAS) with over 100,000 participants have identified well over 150 genes relevant for dietary response, but these still can explain only less than 20% of the heritability of common diet related conditions, such as diabetes, and obesity (Horton et al., 2019; Moore, 2020). Very recent developments have led to novel, more reliable ways of estimating disease risk for diabetes and obesity, such as genome wide polygenic risk scores (GPGRS) using new algorithmic approaches, based on millions of genetic variants tested in very large GWAS including over 300,000 participants (Khera et al., 2019). These methods showed significant improvements in predictive and analytical validity and make most currently offered commercial solutions look questionable and emphasise the need for regulatory oversight of predictive health claims in relation to food intake based on DNA data.

Complexity of data analysis, supply chain quality control, and costs

Complexity of data analysis, supply chain quality control, and real cost are issues that are rarely discussed in the PN field, but impact business models and the long-term commercial viability of providers. Often the core of current PN businesses is built around algorithmic and AI based integration engines for different data inputs, such as DNA sequencing data, scientific literature data, customer phenotype data including clinical data types among others to produce the final advice output. For example, Inside Tracker describes its data integration engine in the following way: “The crowning achievement of our team is SegterraX, the patent-pending, automated algorithmic engine that runs the InsideTracker platform. It generates ultra-personalized interventions for each individual by integrating the full range of user inputs (biochemistry, demographics, profile, habits, genetics) with rules developed by our scientists based on their analysis of over 2,500 peer-reviewed scientific publications, a demographic database of over 180,000 healthy individuals, a database of over 8,000 unique foods, and the 200+ combined years of scientific experience across our team and scientific advisory board.” As is well known in the AI field, algorithms need to be trained by humans, and algorithm bias is a serious, well-recognised issue in many application areas. Quality control of all the different input data streams is expected to be very different from one provider to the next, and the inherent complexities of integrating various data streams makes the process unlikely to be error free. In particular, when providers integrate data from third party providers, such as laboratories or public databases, it is not clear how data standards are monitored and enforced along the “data supply chain” by the end-provider of PN advice. Moreover, the input data before integration needs to be initially curated by humans in some way and it is unclear what selection criteria (“rules”) are for example applied when selecting in the above example 2,500

publications (a rather low number, given the breadth of services offered) or 8,000 unique foods on which advice is based. These technical challenges will impact the quality of advice the consumer receives and currently there is no way to assess technical quality, say for example with regards to successful consumer behavioural change and achieved health goals. In the end, consumers will make their choices based on positive experience.

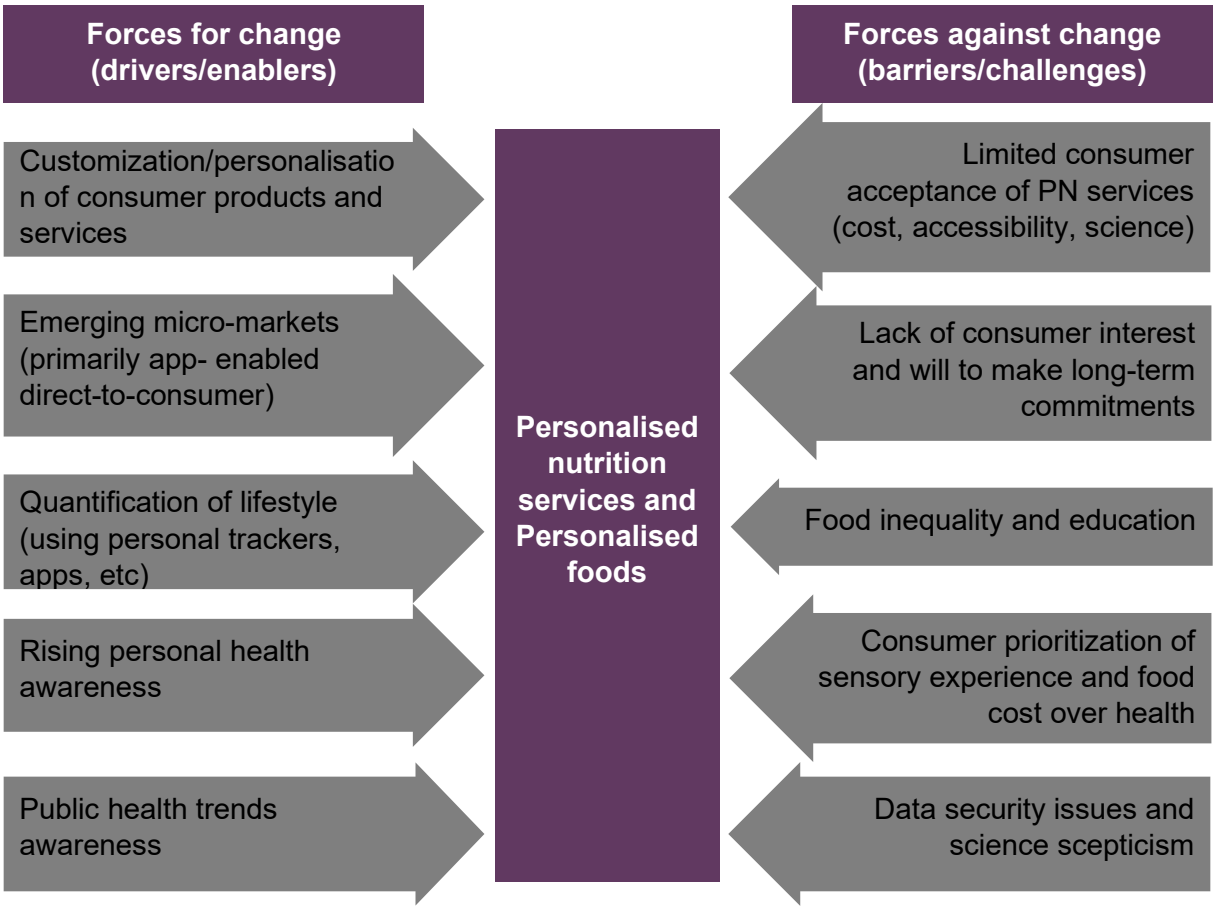
Despite decreasing costs of many now standard technologies any wet laboratory-based data input will remain fairly expensive for a consumer web offering, and once a certain customer base is reached the real costs for the business of delivering good science will become apparent, particularly once the venture capital runs low and real profits need to be made. Many early providers of personalised medicine, or wellness have failed after a few years, because they could not grow their customer base in line with a business model that generates enough profit. One prime example is Arivale, a US personalised wellness and health provider that started out in 2015 with an internationally renowned scientific founder team and world-leading facilities in the background (Bishop & Thorne, 2019). Many saw Arivale as the paradigmatic company to look up to in any area of commercial, science-based personalisation services. Five years later and after having raised $50M in capital, Arivale had to close due to high operating costs and inability to grow its customer base. The main hurdles for growth were the lack of interest by consumers in their own health and unwillingness to make longer-term commitments to provide data on a regular basis as well as the inability of Arivale to reduce prices for its services. It should also be mentioned that this happened with a customer base that comprised mostly affluent well-educated and curious people, who are also most likely to be sensitive to data security and privacy concerns or ambiguities in the science base of the offering.

Though most current PN providers are using a smaller selection of more standardised science applications, very similar dynamics are expected to be at play, challenging the long-term survival of many PN providers once they need to become profitable. Difficulties with finding the right business model for business growth have been pointed out in the academic literature almost ten years ago and are still discussed today by proponents in the sector, still highlighting issues around data quality along the “data supply chain” and finding ways to make PN offerings more experientially attractive for consumers (Ronteltap et al., 2013; Tischer et al., 2021).

Consumers and Society – Trends and implications for widespread uptake

The trends presented here briefly, summarised in Figure 15, have been recognised as specific input trends into the PN sector by a number of studies and reflect the most prevalent consumer trends that might affect uptake of PN more or less directly.

Figure 15 Trends, drivers and challenges: Consumers and society



Consumer and societal trends supporting the uptake of PN

Customisation/personalisation of consumer products and services and emerging micro-markets

Customization/personalisation of consumer products and services and emerging micro-markets are two longer-term trends that have been shaping consumer expectations and interests for at least two decades. From fashion to cars, software and financial services, to food and takeaway lattés, many product categories are now well established with myriad customisation options, either built into a stratified product range, or with customers to choose between many options. At the same time marketing has been using “individuality” as a selling point for many consumer product categories for a very long time. With digital technologies and smartphones enabling easy D2C selling, a number of micro-markets are becoming a part of the commercial ecosystem and are increasingly expected by consumers, including in the food personalisation sector. For example, Keto and Company (www.ketoand.co) is a sales and information platform offering low-carbohydrate ketogenic foods; FODmarket (www.fodmarket.co.uk), offers products for a diet rich in FODMAP ingredients (fermentable oligosaccharides, disaccharides, monosaccharides and polyols), or Beyond animal (www.beyondanimal.com), a platform for vegans, connects vegan businesses, consumers and investors in that sector. Personalisation has meanwhile also entered the restaurant space with electronic menus that allow

customers to customise a dish down to the ingredient proportions. For example, Vita Mojo (www.vitamojo.com) in the UK provides electronic solutions for the restaurant and kiosk segment that enable fast personalised ordering.

Quantification of lifestyle and rising health awareness

Quantification of lifestyle and rising health awareness are two longer–term trends, which linked by digital technologies, have enabled easy tracking of various lifestyle and health parameters via wearable devices. Initially seen as a curiosity market segment taken up early by professional athletes, it has become now a widely used way to obtain feedback about certain personal health parameters. The importance of feedback in the health-related behavioural change domain has been well researched, and measurement of status quo together with subsequent feedback after behaviour change is one of the fundamentals in this area (Macready et al., 2018). Familiarity with tracker devices and data apps for lifestyle and health analysis will further increase among consumers and will make purchasing PN services a very familiar customer experience, with the added excitement of providing samples for DNA or gut microbiome analysis. In addition, science-based web product offerings, such as ancestry services, or linked to citizen science projects will further drive increasing familiarity with certain scientific concepts. Moreover, it appears that personal scientific information, at least in the context of a large EU trial on PN nutrition (Food4Me), motivates to change behaviour around food intake (Ordovas et al., 2018).

Rising personal and public health trend awareness

Rising personal and public health trend awareness increasingly appears to be influencing consumer choices, at least in affluent strata of society. Following general media reporting, there are a number of diseases that have been reported for decades as worrying health concerns on the personal as well as public level. Among these most prominently reported are cancer, diabetes, obesity, and dementia (Alzheimer’s disease), and to a lesser extent allergies including food allergies. Due to their indeed rapidly increasing prevalence over the past two decades, many consumers will have statistically been affected by them at some point in their live. To what extent generations who have been growing up with these media reporting trends are more likely to take up PN advice is not clear, especially as the correlation between health information and healthy behavioural change does not appear to be as rational as one might think, in particular when it comes to healthy food choices. However, this awareness context somewhat prepares and possibly motivates consumers for understanding the need for personalised approaches to achieve health goals. This may become important should national health providers decide to promote PN services.

Consumer and societal barriers to widespread uptake of PN

Limited consumer acceptance of PN services

Limited consumer acceptance of PN services**,** and a number of concerns have been identified in studies carried out for over a decade to assess consumer sentiment around PN. Consumer attitudes that play a role in decision making whether to use PN services or not were concerning: willingness to undergo genetic testing (if part of

the PN offering), ease of access, willingness to pay, medical needs, and trust in provider with respect to data security and privacy. A large EU study found for example that willingness to undergo genetic testing for PN services was around 27% on average over a decade ago, but could vary considerably between countries and age groups, with older age groups being more willing to be tested if an underlying health issue was present. On average around one third to 50% of consumers would try PN services if convinced by clearly communicated science and other preconditions. Variations in willingness to pay are linked to nationality and affluence, with for example German and UK consumers less willing to pay at all, and Spanish consumers much more willing to get tested and pay for it.

Main concerns that impact negatively on the uptake of PN services are around the fact that data collection and analysis is only web-based, and data security. For example, in 2020, 87% of UK NHS users declared that data privacy is of high importance to them, while they are generally trusting and appreciating the services provided by the NHS (71%) (NHS, 2020). This indicates that data security will matter a lot for UK consumers in the commercial sector. Overall, there appears to be a market segment between 30-40 % of consumers who would try PN when certain conditions are met, such as a trustworthy regulatory framework. A correlation was also found between higher trust in the national health care provider and lower willingness to use commercial PN services (Poínhos et al., 2014, 2017; B. Stewart-Knox et al., 2015). These multifactorial inputs into consumer decision-making will make it difficult to predict a clear trend for the UK. However, the fact that UK consumers were less willing to pay for PN services and generally trust the NHS (see above), points toward hesitancy to adopt commercial PN eagerly in the near future, despite much media hype around it.

Food inequality and education

Food inequality and education are two social issues that may severely affect wider uptake of PN in the UK, in particular if regulators should decide to promote it more widely. A government report on food insecurity from late 2021 finds that 15% of UK households are affected by food insecurity, which includes 2.5 million children (UK Parliament, 2021). This makes the UK one of the most food-unequal countries in the OECD and EU. If public health goals are to be pursued with PN approaches in the longer term, then considerable efforts need to go into resolving these issues around primary needs. In particular, it has been shown repeatedly that taste, texture, and cost are the leading motivators for buying a food item, despite all the media attention and advertisement around healthy food (Ignaszewski, 2022; Weinrich, 2019), and it is well established that in most countries less affluent parts of the society would benefit most from a healthier diet. Moreover, social stratification is still pronounced in the UK compared to other countries, and implementing equal educational proficiencies across social strata is still an issue. This means in the context of PN that only a very small consumer segment will currently have the required education to understand the benefits and risks of PN nutrition approaches and would therefore be able to make a reasonably “informed choice”. In this societal context ethical issues around food and educational inequality need to be considered should decision-makers want to roll out PN as a way to achieve public health goals.

Difficulties around information about food and health are generally a common problem among all consumers, also reflected in a recent US survey that asked consumers about their understanding of food related health information and find that 80% of consumers describe themselves as “being confused” by conflicting or unclear information around food-related health information (IFIC, 2018).

Data security issues and science scepticism

Data security issues and science scepticism will impact wider consumer acceptance of PN in the UK. As data protection issues have gained more public attention over the past decade and related legislation has been rolled out across the EU and UK, it is very likely that consumers will want to be able to trust in how their personal health data is handled by PN providers. However, this requires good regulatory oversight and communication by regulators on what certain data standards mean and how breaches of data regulation can be addressed. Data security, reliability of the exchange and transfer of personal data, and trust in the provider have been reported in a number of studies exploring consumer acceptance of PN as highly important when making the decision to use PN services (Poínhos et al., 2014; B. Stewart-Knox et al., 2013, 2015). Other concerns were around actual data breaches, where for example insurance companies or employers might get hold of personal information given to the provider, and about receiving “unwanted” information about health that might cause distress and anxiety (Poínhos et al., 2017).

Given that the Covid 19 pandemic has made very clear that there is approximately a persistent 15-20% segment in many European countries that rejected Covid 19 vaccines, it can be assumed that within the UK there is also a substantial minority that would not take up PN services due to various beliefs around scientific concepts. In particular, as PN lends itself for scepticism, as even for a well-informed scientist in the field the science behind PN is highly complex, and in many aspects at an early stage of understanding. Moreover, PN providers will not be able to be completely “transparent” about their technical processes, even if they wanted to, exactly because of the complexities involved (as mentioned in chapter 5: technology and commercial players). Hence it will be near impossible for the average consumer to make a “truly informed” decision when choosing a PN provider. Consumer choice will therefore have to be based mostly on trust, which makes it necessary for regulators to define and maintain standards in this sector, as well as communicate them clearly to consumers.

Regulation – Enabling and restrictive contexts and food safety

Personalised nutrition services are currently considered as “not regulated” anywhere in the world, and a number of studies have pointed this out repeatedly for over a decade. The scientific community that was driving PN science and the investigation of its merits and challenges has in the past 15 years proposed repeatedly conceptual frameworks and “guiding principles” that might be used as input for regulation of PN services (Adams et al., 2020; Grimaldi, 2019; Kohlmeier et al., 2016). However,

these efforts have to date not been taken up by regulators, and explicit regulation of the sector needs still to be implemented. However, there are other regulatory areas that “surround” the PN space and may impact its evolution. In terms of regulatory remit definitions, it is important to distinguish between a wellness and/or lifestyle offering that would maintain or improve the existing health status of a PN customer, and services that are health offerings with the explicit aim to prevent or alleviate illness. This distinction is clearly made within EU regulation and has impacted PN service offerings in some countries.

In this section we present drivers and challenges of the wider regulatory context that surrounds PN. This also means, that the effect of other regulatory frameworks with indirect impact on PN may not have clear unidirectional outcomes with respect to the evolution of a currently unregulated area of activity in the sense of “drivers” or “challenges”. Hence these terms in the regulatory domain might be better called “enabling contexts” and “restrictive contexts”. It should be noted that our interpretation of “enabling” and “restrictive” can at this stage of UK regulation only be speculative.

As PN has evolved in its current form out of the medical domain some of its aspects are already covered by some existing regulation. The main aspects of PN services that involve some form of bio-specimen testing, and therefore can be considered a health offering, are the following:

a) Analytical validity of tests (technical accuracy and robustness etc)
b) Scientific validity of analysis that is used as basis for advice
c) Utility of the advice (will it enable a beneficial outcome beyond standard advice by dieticians and nutritionists)
d) Ethical, legal, social, and data protection issues

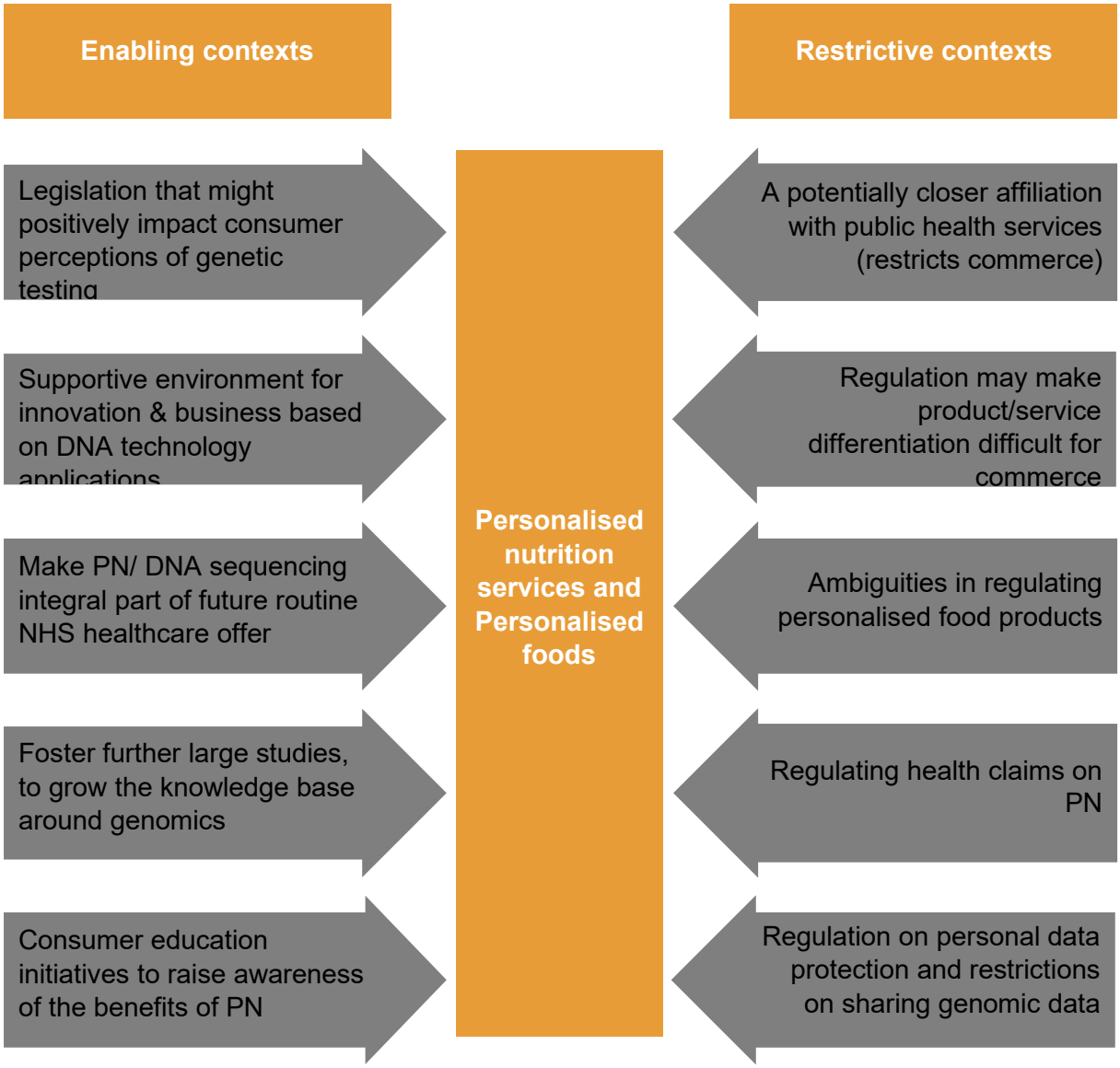
These domains are overlapping for example with existing UK regulatory frameworks that assess the validity of genetic testing in a clinical setting. The applicability and limitations of these regulatory domains for PN have been recognised for a while (Keith A. Grimaldi et al., 2017; Keith Anthony Grimaldi, 2019). In the UK, the following existing legislation would apply to most PN services, including those involving D2C testing (House of Commons Science and Technology Committee, 2021):

- the Consumer Protection Act 1987 and the Consumer Rights Act 2015 (which require products or services sold to consumers to be fit for purpose, as described, and meet certain minimum standards, covering aspects such as quality and safety)
- the UK General Data Protection Regulation (which covers the collection, storage, and use of data)
- the Human Tissue Act 2004 (which effectively bans DNA analysis without appropriate consent)

- the Advertising Codes (which ban adverts that are misleading, harmful, offensive, or irresponsible, and are enforceable under the Consumer Protection from Unfair Trading Regulations 2008 and the Business Protection from Misleading Marketing Regulations 2008)
- for commercial genomic tests with a medical purpose: the Medical Devices Regulations 2002 (which set out essential requirements for in-vitro diagnostic devices placed on the market, such as requirements on safety for users and for performance to match the manufacturers' claims).

It is currently not clear to what extent players in the UK PN market are aware of or are explicitly following existing legislation. Studies investigating current standards in the UK have to our knowledge not been undertaken.

Figure 16 Enabling and restrictive regulatory contexts for PN



Enabling regulatory contexts

Legislation that might positively impact the consumer perception of genetic testing

The UK is a world leader in DNA science and technology and Government has recently passed the strategy report “Genome UK The future of healthcare” with the aim to create a supportive environment for innovation based on DNA technologies, applications, and DNA technology businesses in the UK, and to make DNA sequencing an integral part of future routine healthcare offerings of the NHS. In addition the framework should foster further large studies, such as sequencing all 500,000 individual samples of the UK biobank, to grow the knowledge base around genomics for the benefit of human health (HM Government, 2020). The importance of public trust in genomics was recognised and expressed by the pledge to: “establish a gold standard UK model for how to apply strong and consistent ethical and regulatory standards”. A major goal of the proposal was to implement personalisation of medicine across the NHS. In parallel, large public engagement and information initiatives are promised to educate the public about the benefits of genomics applications. Implementation steps were published in the following year (UK Government, 2021). The role of commercial players in the genomics space was only mentioned in passing by expressing the intention to enable industry growth through start-up support. Overall, it is expected that these efforts might lead to increased public awareness of personalisation approaches based on genetic analysis, and hence might have a positive effect on commercial PN providers.

Specific concerns related to commercial D2C genomic testing have been raised by a House of Commons Science and Technology Committee report published in 2021 (House of Commons Science and Technology Committee, 2021). This is important, because D2C testing involves medical devices that are used for collecting, extracting, and sequencing DNA. As Government has after the Brexit transition period decided to not implement new EU regulation due to be implemented in 2022, currently the UK legal framework for commercial D2C testing is unchanged and based on earlier legislation as outlined above, with the Medicines and Healthcare products Regulatory Agency (MHRA) considered the responsible regulator for devices used in the PN sector. In this context, the report by the UK House of Commons Science and Technology Committee identified a number of problematic areas that needed addressing in order to progress beyond the currently ill-defined legal situation, and the following recommendations were made:

- D2C tests should be required to be subject to greater pre-market assessment by an external body to assess clinical and analytical performance of the tests. Currently most providers can self-declare whether they believe their product meets standards within current legislation.
- Technical standards for D2C tests should be defined in collaboration with Genomics England and the NHS. Ideally, test providers should then voluntarily meet such standards in order to reduce false positive/false negative rates, and gain trust by consumers.

- Obligatory information about different kinds of consequences of test results, not necessarily linked to the specific service offering, should be provided, as well as support in cases of “unwanted” or distressing results. This includes for example potential consequences for family members, or the need for some results to be assessed under medical supervision.
- The UK’s current data protection framework needs to be re-assessed whether it is fit for dealing with a growing market of confidential health related consumer data, including looking into risks and opportunities presented by novel technological developments.
- It should be considered whether there should be restrictions on the use of D2C tests for testing asymptomatic children or for prenatal testing.
- The scope of regulation needs to be re-assessed in particular for companies that sell products in the UK, but conduct testing and analysis outside of the UK, and companies offering analysis of genomics data obtained from third parties.

These recommendations correspond very well with what has been recommended in the academic literature for over a decade. Should Government decide to act upon these recommendations then this might lead to a more trustworthy commercial environment for genetic testing with better quality products for consumers. In addition, a clear regulatory environment might encourage further commercial activity in this sector. However, given the usual time frames in politics and legislation, this may be at least five to ten years away.

Restrictive regulatory contexts

Potentially closer affiliation with public health services

A potentially closer affiliation with public health services in the UK could emerge from above outlined regulatory intentions, which might create a regulatory environment that could make it more cumbersome for PN businesses to enter the market. Moreover, as all potential providers will need to adhere to the same science base it will be difficult to differentiate from other providers and create a distinct offering. Developments in EU countries might be instructive for possible future outcomes in the UK. The current EU frameworks impacting PN are fragmented and no EU-wide piece of legislation to regulate PN exists. Genetic testing and medical devices for genetic and other bio-specimen testing are regulated in the EU by the Medical Device Regulation, and the *In vitro* Diagnostic Medical Device Regulation (IVDD/IVDDR), with the latter differentiating between testing for medical purposes (health offerings) and testing *outside of traditional healthcare settings* for the purpose of providing information on disease disposition. While the device aspect of PN is covered by this legislation throughout the EU the ways genetic testing can be offered and by whom is not, as issues of “medical supervision” and “informed consent” are subject to national legislation and hardly harmonised across the EU. Direct-to-consumer testing is regulated quite differently across the EU and has to do with public sentiment around genetics and trust in science in general as well as with different cultural norms around medicine and health. For example, France and

Germany have restricted all genetic testing for health purposes to “medically supervised use”, which in effect prohibits D2C testing in a commercial setting (Röttger-Wirtz & De Boer, 2021).

Ambiguities in regulating personalised food products

Ambiguities in regulating personalised food products that are associated with health claims might lead to a persistent regulatory vacuum that might have a negative impact on consumer trust in PN products as well as on businesses due to regulatory uncertainty. Currently, PN providers either do not offer personalised food at all, or do so by selling personalised vitamin formulations and supplements. Although supplements do not need to be licensed or registered in the UK, they need to comply with the General Food Law and are subject to the provisions of the Food Safety Act (FSA remit) as well as the Food Information Regulation 2014 and the Food Supplements (England) Regulation 2003. Companies selling supplements need to register as a Food Business Operator (FBO). In the context of PN it is important to point out that within UK law, supplements are defined as ‘any food the purpose of which is to supplement the normal diet and which is a concentrated source of a vitamin or mineral or other substance with a nutritional or physiological effect, alone or in combination and is sold in dose form' and ‘they are not medicinal products and as such cannot exert a pharmacological, immunological or metabolic action. Therefore, *their use is not intended to treat or prevent diseases in humans or to modify physiological functions’* (our emphasis). This latter definition makes explicit that supplements are not supposed to be sold with the intention to act on the body in similar ways like a medicine. Most PN providers however make claims regarding disease prevention, or effects on immune and metabolic function, placing these at the core of the PN offering. This discrepancy would need to be addressed by regulators such as the FSA in order to provide clearer guidance for the PN sector on how to stay within legal boundaries when making claims.

Existing EU legislation can give a good illustration of the issues involved and might be seen as instructive for the UK context. The main ambiguity arises from the blurred boundary between food and medicine in the case of a personalised food offering with claimed health benefits. The EU General Food Law (GFL) defines as food: “any substance or product, whether processed, partially processed or unprocessed, intended to be, or reasonably expected to be ingested by humans”. This has to be contrasted with nutrition that is associated with claims that make its effect on health so prominent that it would fulfil the definition of a medicinal product. According to article 1(2) of Directive 2001/83/EC medicinal products are defined as: “any substance or combination of substances that either *is presented as having properties for treating or preventing disease in human beings*, or that may be used in or administered to human beings, either with a view to restoring, correcting or modifying physiological functions by exerting a pharmacological, immunological or metabolic action, or to making a medical diagnosis” (Röttger-Wirtz & De Boer, 2021) (our emphasis).

Thus, the classification as medicinal product either follows from the *presentation* of the product or from its *function*. In cases where it is unclear whether a product might

be qualified as a medicinal product or as another regulated product (e.g., a food product), then the application of the pharmaceutical legislation takes precedence in EU law. This hierarchy of regulatory frameworks within the EU is also confirmed in the GFL, which in Article 2(d) excludes the application of the GFL to medicinal products (Röttger-Wirtz & De Boer, 2021). Should the UK wish to regulate personalised food products then very different regulatory frameworks need to be considered in the cases of medicine or food, but more importantly a clear stance needs to be taken on how to make this distinction for PN products in the context of UK law.

Existing UK food safety regulation and standards defined by FSA would apply to PN products that can be classified as foods, such as supplements. However, this regulatory framework is usually applied to food items that are sold to larger populations, and not to foods in effect sold to one person. Hence food safety issues for the wider public should not arise, as in theory only the person for whom it was personalised should eat it with the expectation that it will positively impact that person's health. Potentially other people with very similar personalisation parameters might eat the same formulation of food item with similar benefits. In contrast, there could be situations in which a personalised food item consumed by a person for whom it was not tailored for might suffer immediate or short-term negative health effects. It is understood that any food product, personalised or not, coming to the UK market needs to comply with regulatory standards for any food product first. What is not clear however is to what extent PN providers would classify their products in the current regulatory situation as foods or as supplements. This situation might cause confusion not only among potential customers, but also among providers, who will probably tend to choose the easier regulatory framework to follow, or will avoid offering food products altogether because of these ambiguities.

Regulating health claims on PN

Regulating health claims on PN may be attempted by future UK legislation and would affect the way PN services are offered and how providers can operate. In the UK, as in the EU, consumers should be protected from false and unsubstantiated claims about a product. As with other products the legal requirement that advertisement, labelling, presentation including packaging and given information shall not be misleading applies certainly to PN offerings. This can be considered particularly important in this sector because consumers cannot be expected to have the required scientific expertise to make a truly informed choice. Clarification on permitted claims for the PN sector would be helpful to build trust with consumers and enable confident decision making for businesses.

In the UK, health claims related to nutrition are regulated by the Nutrition and Health Claims (England) Regulations 2007 and Regulation (EC) 1924/2006, updated following Brexit on 1 January 2021 with 'The Nutrition (Amendment etc.) (EU Exit) Regulations 2019' and 'The Nutrition (Amendment etc.) (EU Exit) Regulations 2020'. After Brexit the responsibilities for the risk assessment and risk management processes covered by nutrition legislation were transferred to bodies in Great Britain. As regulatory oversight over nutrition legislation is a devolved responsibility in the

UK, the Department of Health and Social Care is responsible in England, the Welsh Government in Wales, Foods Standards Scotland in Scotland, and the FSA in Northern Ireland. This regulatory framework also covers claims to reduction of disease risk and claims based on newly developed scientific evidence. Although UK Government stated in above post-Brexit amendments to be committed to upholding EU and international standards, it might be useful to look at what EU legislation already covers in the PN space as this might inform future regulatory decision-making in the UK.

The EU Food Information to Consumers (FIC) Regulation would cover any food product sold by a PN provider and not only prohibits any misleading information about contents and quantity, but also explicitly prohibits "attributing to food any effects and properties it does not possess" and "*to attribute to any food the property of preventing, treating or curing a human disease, nor refer to such properties*". This distinction again reinforces the boundary between food and medicine and will basically prevent marketing of food products personalised via genetic testing as "reducing disease risk".

The second piece of EU legislation relevant to health claims is the Nutrition and Health Claims Regulation issued in 2000 with the rise of "functional foods" and food supplements. The regulation distinguishes between nutrition claims (such as ingredients, calorific value etc) and health claims that link a food or food ingredient to health. Health claims on the health promoting activity of certain foods or ingredients need to be "authorised health claims" that are specified by the legislation and their health effects need to have been proven by prior generally accepted scientific evidence. As "promotion of health" is an integral aspect of PN it matters which kind of claims can be legally made, as this affects the core value proposition of the PN offering. The legislation specifies three categories of health claims, namely functional claims, disease risk reduction claims and children's development claims. Under functional claims fall claims that refer to: a) development, growth, and functions of the human body; b) psychological and behavioural functions of the human body; c) reducing or controlling body weight or suppressing/reducing hunger as well as reducing calorie intake. Again, these claims can only be legally made when they are listed authorised claims backed up by scientific evidence.

Disease risk reduction claims for personalised food items need to be carefully crafted within these regulatory boundaries so as not to transgress the food/medicine boundary. For example if claims are made that the disease risk reduction would be an immediate effect of consuming the personalised food (after disease risk was first established by a genetic test), then the food would be seen as being presented as a medicine. In this context the disease risk reduction claim needs to specifically state whether the disease risk is multi-factorial, and if so whether influencing one factor with a given personalised food or ingredient will change the overall risk. In addition, it is forbidden: to imply that *not* eating the personalised foods in question will negatively impact health; to state specific amounts of "expected" or "predicted" weight loss; to make claims based on statements of individual doctors or other health professionals, such as dieticians. Other requirements for making legal health claims

include additional statements that must be made together with the main claim. This includes the reference on the importance of a varied and balanced diet, how often and how much of the food item in question needs to be consumed to achieve the claimed health effect, as well as any safety warnings who should not consume the food, for example in relation to allergies, or small children etc. Any claim that certain personalised food items would be “generally healthy”, or “health promoting” in a general sense can only be made when this claim in relation to that food is on the list of authorised health claims.

In particular, in a PN context disease risk reduction claims are usually made via complex analysis of many phenotypic variables specific to the consumer, and hence are based on a multi-factorial analysis. As currently health/disease risk reduction claims can only be made one ingredient or nutrient at a time by specifically showing scientific evidence for one causal nutrient-health interaction, it is problematic how health or disease risk reduction claims can be formulated in simple claim statements for consumers. So far no listed authorised claim has been submitted that would make it a legal statement that a certain nutrient can affect the genetic predisposition for certain diseases. Again, for most PN providers that is seen as a fundamental aspect of their offering.

One way to market PN products could be via catering to micro-markets of consumers who share certain phenotypic characteristics as defined by PN data analysis. This would mean that a claim would be applied only to a specific sub-population, as is currently regulated for example when making claims specific to children, pregnant women, the elderly etc. In such an approach the claim needs to be based on scientific evidence specific for that sub-population and given that the difference between such sub-populations and the general population can only be defined in terms of subtle genetic and other phenotypic differences, it is currently questionable whether these would be considered by legislators as sufficient to warrant definition of novel sub-populations. EU regulation related to such an approach would be Regulation 609/2013 that specifically deals with targeting of food products to specific groups with special dietary needs, such as foods for infants and children, for specific medial purposes (for example in an intensive care setting), or intended for weight loss in cases where it can replace a normal varied diet. This regulation applies mostly to clinical settings or the care home sector when people cannot consume normal food due to their medical conditions and the specified foods are usually consumed under medical supervision. It is therefore unlikely that regulators will consider defining sub-groups of healthy people sharing similar characteristics as defined by a PN provider. Moreover, professional athletes and diabetics have so far been explicitly excluded from this regulation for sub-populations with special dietary needs (Röttger-Wirtz & De Boer, 2021).

This overview of regulatory issues was intended to demonstrate the areas of regulatory intervention that would need a clear resolution with regards to existing UK and EU legislation, should UK legislators want to decide to support commercial PN efforts in the longer term. Given the above complexities, any intention to impact the evolution of the commercial PN market needs to be taken up immediately as it may

take considerable time to find simple actionable regulatory solutions. In the meantime, the current regulatory situation might lead on the one hand to a proliferation of over-promising providers making possibly even unintentionally, illegal claims about their offerings, while consumer trust and interest in such offerings may erode, and new businesses in the sector will not be able to grow because of regulatory uncertainties.

Personalised nutrition and food safety

Given its current state of evolution PN may pose food safety risks in two areas, one still hypothetical und unexplored, and the other related to better understood issues to do with the longer-term consumption of supplements. As PN is currently to a large extent nutritional advice it may appear that there are no safety risks involved beyond the risks of following advice given by nutritionists or dieticians. It is assumed that such advice is based on scientific evidence from large population studies, so it is always likely to have some margin of error when applied to individuals.

However, what is hard to assess at present is whether longer-term negative health impacts may arise from adhering to advice that is generated by complex PN analysis and supposed to be more suitable for a specific individual, in cases when the advice given by PN providers is in fact based on unintentionally faulty scientific analysis. This situation is not unlikely given the complexities around the scientific foundations and data integration of PN as discussed in chapter 4. As consumers will have generally limited knowledge around the science, and few possibilities to evaluate the information they pay for, it will be important to define what might constitute fraud in this area. These considerations are currently not within FSA remit, but the FSA might wish to consider whether it would be worthwhile, in collaboration with other regulators such as the Department of Health and Social Care, to establish certain standards at the advice level for an emerging industry that is associated with food.

In cases where providers sell supplements and vitamins in addition to personalised advice certain well understood risks for consumers may exist. These can arise from low quality of source materials, inappropriate storage or packaging, contamination during production, erroneous or fraudulent labelling etc. all of which are within FSA remit and are covered by existing legislation.

Key findings

Despite several decades of scientific progress underpinning personalised nutrition, scientific uncertainties remain.

Although at least 40 years of bio-medical research have generated a convincing scientific evidence base for the proof of principle that dietary personalisation approaches can be effective by using personal genetic, microbiome, and blood biomarkers, at least in a clinical or interventional study setting, considerable uncertainties remain. These arise from the vast complexity of the human physiological responses to food intake. Simple correlations between single genes or biomarkers, or even “a handful” of them as reported in earlier studies, are not sufficient for creating robust and scientifically valid tests. Even most recent products

on the market that offer algorithm-based analysis of a few dozen genes are not considered scientifically valid enough to justify personalised interventional advice.

Uncertainties emerge in particular due to the fact that genetic variation at the genome level might only play a very minor role in metabolic response to food intake (with rare exceptions) as more recent results indicate that epigenetic regulation is much more important, but is currently not well enough understood to enable affordable commercial testing. Despite much media attention around recent findings in the gut microbiome field, actionable scientific understanding is at an early stage and advice given does not go much beyond earlier recommendations, such as eating more fibre being beneficial for gut health. The most robust parameters to test for are well-established clinical parameters, such as blood glucose/insulin levels, or lipids in a weight loss setting, but these would not require additional personalisation to be actionable.

However, it is expected that the rapidly growing scientific fields of epigenetics, metabolomics, biomarker discovery, and more affordable WGS, may deliver new results in the coming decade that will not only change the current science base of PN, but will also strengthen its validity to enable better commercial applications. The speed with which these new discoveries may emerge will depend greatly on investment into the basic science of these sectors to be able to lead up to large interventional studies. Large investments are needed as these are areas of science that are far more complex than DNA-based research, and technologies required are still less robust and much more expensive than most recent DNA sequencing and analysis approaches.

Technology and investor push drive a growing PN start-up sector, but technical and commercial challenges limit longer-term growth

A strong technology push in the areas of DNA sequencing and D2C testing devices, such as for at home blood and DNA testing kits, as well as commercial big data analysis solutions has been driven by increasing investor interest in the bio-medical sector for the past two decades. In addition, large players in the food processing and pharmaceutical sectors are supporting the PN start-up sector more recently. This has enabled PN providers to offer affordable (but still expensive for most) testing for biomarkers and nutritional advice based on advanced software solutions for data analysis and interpretation, easily accessible for consumers via smartphone apps.

However, PN companies face a number of technical as well as business challenges that appear currently hard to solve in the near future. To provide high quality services the underlying science base is complex and involves integrating large data streams from DNA, biomarker, and personal lifestyle information into scientifically sound advice. Although many providers involve nutritionists most of the advice is generated by algorithms which raises technical issues with quality control along the “data supply chain” from different test laboratories to the “rules” that underpin algorithm design, all affecting scientific validity. For PN providers using wet lab tests, such as for DNA and blood, the logistics and laboratory services are still expensive and costs to grow laboratory capacity with growing customer numbers are considerable even when outsourced to third parties abroad.

Currently business models are converging on very similar solutions that can offer services from £100 upwards either via subscription models or more expensive one-off solutions, but consumers need still to be convinced to make longer-term commitments. To grow beyond the curiosity market segment and reach larger market shares has been difficult for all providers that have been on the market so far. If claims made by companies can be believed, they reach a few thousand to just over 100,000 customers within a few years. A study surveying genomics based nutrition companies worldwide has found around 45 active companies in 2020, with around 20 in the US and Europe respectively and a handful in Australia and Asia (Floris et al., 2020). This compares with for example DNA based ancestry services, which could sell up to a few million one-off tests in over five years globally.

Selling actual personalised food products is currently not commercially viable, which is the reason why PN providers that offer personalised products do so in the form of vitamins and supplements. However, future integration with a growing food personalisation industry could lead to synergies supporting growth of the PN sector.

Consumers are becoming more receptive to PN services but are far from convinced

A number of consumer trends align well with the offerings of PN. Increasing customisation of consumer products and services as well as food has been shaping many industries over the past two decades. In addition, health awareness in relation to food has been increasing for decades despite also increasing obesity in most countries. Several sub-markets for vegans and vegetarians, or consumers with certain allergies are increasingly well established and in many countries growing, which might prime consumer interest further for more individual customisation of nutrition. Consumer acceptance (of possibly 30% willing to try PN services in some countries) has been studied in the past decade and has been found stagnant, due to a number of reasons. These include a lack of motivation to commit longer-term to health interventions, prioritising taste and texture as well as price in food choices, a lack of education to understand the benefits of a commercial health offering based on complex science, current costs of PN services, as well as scepticism around science and data security and privacy issues. Moreover, should PN be promoted by regulators in the future, considerable social barriers exist in the context of current food inequalities in the UK.

Regulatory uncertainty might slow growth of a trustworthy personalised nutrition sector

Personalised nutrition services are currently not explicitly regulated anywhere in the world. However, a number of existing regulatory frameworks in the UK apply already to some aspects of the PN services and may affect their evolution. These include regulation for genetic testing in a healthcare setting, GDPR concerning data handling, and if providers sell supplements or vitamins all legislation under the General Food Law, the Food Safety Act (FSA remit) as well as the Food Information Regulation 2014 and the Food Supplements (England) Regulation 2003. In addition, the UK government has committed to a supportive regulatory environment for DNA technologies for the benefit of public health, which may lead to quicker translation of

DNA based findings into applications. Despite a favourable environment for such technologies in the UK, challenges remain for commercial providers to create viable businesses.

In order to increase consumer trust and to guide companies' decision-making, clear guidelines would be helpful for the PN context regarding certification standards for the validity of laboratory test results, data analysis, and personal data encryption, privacy and security. Currently it is up to providers to self-assess whether they believe their tests meet certification criteria, they can choose which ISO laboratory or data encryption standards they wish to implement, and have no clear instructions on how to communicate personal DNA and biomarker-based results to customers. Although some providers do explain which certifications they adhere to, and most declare to comply with GDPR, consumers have no way of understanding whether these are legally appropriate or binding.

In addition, regulatory responsibilities are currently unclear for the sector as PN operates in between the health/wellness and food sectors and different regulators would be responsible for different aspects of a PN offering. This affects for example definitions of food vs. medicine, or various claims being made by providers regarding health benefits of certain foods, ingredients, or supplements. The currently uncertain regulatory situation may lead to low quality service offerings for consumers and difficult decision making among businesses, which may slow, or prevent growth of a high quality PN sector.

The most likely science trends to shape the PN sector over the coming decade are glucose monitoring and gut microbiome analysis

Among currently used technologies possibly advice based on glucose monitoring and gut microbiome analysis may prove to become more robust and actionable than advice based on other current technologies. The former is based on several weeks of 24/7 glucose monitoring in the blood, which can give a good indication how the daily dynamics of the metabolism function, and then advice can be tailored around when during the day best to eat certain foods, the response to which can then again be monitored and efficient strategies for weight reduction or improvement of athletic performance can be developed. Despite delivering relevant personal data many consumers will be hesitant to wear a monitoring device that may be inconvenient in everyday life. Smaller, less invasive devices may help growth in that market.

Results from the gut microbiome field will become more robust, but even current fundamental insights, such as that consuming more fibre will lead to many health benefits are clearly actionable and relatively easy to implement, which will be important for wider consumer uptake.

Personalised nutrition is likely to remain niche for the foreseeable future, limiting the potential for broad impact on public health

Although PN holds the promise of transforming the food system towards highly tailored diets optimised for the individual to deliver consumer and public health

benefits, the scientific challenges, costs, limited consumer interest, and other factors identified in this report are likely to inhibit widespread adoption, at least in the short to medium term. PN and personalised foods will likely remain niche, catering to an affluent, educated minority for the foreseeable future, and as such will have limited impact on the wider society and broader public health agenda. Moreover, the benefits of PN seem somewhat marginal when compared to what is already understood about a healthy diet. Simply following existing guidelines on fruit, vegetables, fibre, red meat and alcohol consumption, and the acknowledged benefits of prebiotics and probiotics would achieve significant improvements in health and disease reduction for many. Furthermore, the segment of society that could most benefit from personalised nutritional advice, those in lower income brackets, is the least able to afford such PN services or quality personalised foods. Therefore, it could be argued that rather than focusing on PN, the more important and expedient approach for policymakers would be to focus on addressing income inequality and poverty, consumer education on what constitutes a healthy diet, improved access to quality wholesome food, restrictions on access to foods that are known to be detrimental to health and encouraging and facilitating more active lifestyles.

The larger objective of a personalised foods sector presents much greater potential for impact, but is counter to the current food system

Personalised foods, such as personalised ready-made meals, meal kits, and personalised restaurant and take-away meals offer consumers the opportunity to more easily integrate PN advisory services into their daily diet and meal routines, and are more likely to lock consumers into extended programmes so improving the potential for successful health changes. However, a fundamental barrier to production of personalised foods is the structure of the current food system which is built on mass production, designed to deliver food products at high rates of productivity and economies of scale, offering convenience with enhanced shelf-life, and often largely indifferent to regional context and cultural tradition. It is possibly the very opposite of the system required to deliver personalised foods. Process modifications and novel food technologies are proposed as potentially holding the key to the needed transformation towards mass-customisation and personalisation of foods. However, the extent to which this can be achieved and the costs of delivering highly personalised products is unclear at present. While niche providers offering premium personalised food services already exist and can be expected to grow, wide-spread adoption may be quite limited.

Food safety and food fraud risks associated with PN

Assessing the food safety and public health risk of PN is complicated. Most PN providers are not subject to FSA or Department of Health and Social Care regulation, so their services and the scientific basis and quality of advice are not monitored or controlled. This may present some risk where extreme advice is offered (recommending excessive quantities of certain nutrients for example), but like most common dietary advice, seems unlikely to present serious risks for consumers at large. Where PN is combined with a functional food, vitamin, or other food

supplement offering, these are covered by food standards regulation, so again risk should be minimal. The more likely outcome, if negative, is that the proposed benefits of a recommended diet simply do not materialise. This latter issue may relate to misleading advice and potentially fraudulent claims of science-based advice.

Personalised foods on the other hand do potentially represent a food safety and food fraud risk that may need to be considered by FSA. One of the benefits of the current mass-production-based food system is that product composition, production hygiene, labelling, and other factors are well defined and relatively easily monitored for compliance. With a shift towards ever more personalised food offerings, possibly with highly localised production and using novel on-demand production systems such as 3D printing, compliance monitoring, validation of ingredient lists, control for allergens and contamination, etc becomes far more complicated for the regulator.

Stratified nutrition may become more relevant than personalised solutions

As discussed above there are significant challenges to introducing PN and personalised foods, and the potential for broad uptake and hence broad impact on public health is therefore limited. However, one potential outcome of development in the PN sector is a far more comprehensive understanding of dietary response in populations and sub-populations. This knowledge may enable the Department of Health and Social Care to offer better guidance at the population level on diet, and enable food manufacturers to offer a wider selection of stratified nutrition products, similar to current gluten-free, vegan, lactose-free and other such offerings, targeting particular sub-groups of the population based on broad phenotype or genotype characteristics. Enhanced stratified nutrition may therefore ultimately be the main outcome of the current PN initiatives.

Industry pressure to monetise personal PN data

A variety of business models are emerging in the personalised nutrition and personalised food sectors, but few are profitable, and even the largest and best-funded operations struggle to survive once the initial venture funding is exhausted. Identifying an economically viable business model is challenging because of the high upfront costs associated with establishing a PN system and creating the underpinning datasets, the value proposition to the consumer is still not very clear, high prices discourage consumer engagement, and difficulty in retaining consumers for the long-term as results may not be readily apparent.

One potential solution is to attempt to monetise consumer personal data, as is the standard model in much of the digital economy, and increasingly being deployed in food rapid delivery services to subsidise the customer experience. Such two-sided models have consumers paying for PN advice on one side, and buyers/users of personal data including advertisers and food/wellness/lifestyle providers on the other side. The highly personalised type of data that PN services gather, covering all aspects of lifestyle, health, diet, physical activity, habits, genetic makeup, etc. could be significantly more valuable than data currently gathered through social media and

other channels, and hence highly lucrative for targeted advertising and for example to support product development initiatives, tailored subscription offerings, insurance, etc.

The grey area in which PN operates, outside of the food sector regulation and outside health and medical regulation may enable such business models to be pursued, but raises significant privacy and ethical issues. Consumer resistance and regulatory intervention may be anticipated to prohibit such use of personal data, but there is likely to be significant pressure from the industry, justified based on contribution to societal and public health objectives, to try to pursue such business models.

A potential role for the NHS in provision of PN services

One of the identified barriers to adoption of PN services is a lack of trust in private sector enterprise for delivery of such services and protection of personal data. Delivering PN services within the National Health Service, through local GP clinics may address these consumer issues, and at the same time enable access for those unable to afford private services. If and when the benefits of PN are more clearly defined, the NHS may prove to be the most expedient vehicle to deliver on large-scale public health goals in the UK. As always with the NHS, funding would be a challenge, and it may be that the private sector would need to be involved as a partner, but the long-term benefits of PN interventions for society and the cost savings associated with reduced incidences of diet-related disease may offer economic justification.

Conclusions

Summary of the personalised nutrition landscape

Personalised nutrition in its current implementations has had a slow evolution so far for well over two decades. Although largely convincing in clinical settings, the underlying science base of PN and related software technologies still need to improve significantly in a commercial consumer context. Providers on the market are still developing and testing commercially viable business models to be able to offer trustworthy and scientifically valid services at an affordable price. The number of providers of genomics based PN is small globally (around 50, with around 15 in the UK), and served markets are still mostly curiosity customers who make one-off purchases or subscribe for a few months. The PN providers offering a personalised food product are doing so either in the form of personalised vitamin formulations or supplement mixtures to be consumed as meal shakes or snack bars/cookies, which are regulated by the UK food law. Consequently, these businesses need to be registered as a Food Business Operator (FBO).

Despite its slow evolution as a separate offering outside of traditional healthcare, growth might accelerate in the longer-term future through network effects with other recent trends in the food sector, and food related regulation might then begin to play more of a role. One of these trends is general food customisation via software enabled means to personalise meals, food shopping, and cooking, or via food

processing technologies, such as 3D printing, and local small to medium-scale speciality food producers catering to niche markets.

Once the science base of PN becomes more robust and trusted by consumers, ecosystem effects such as partnering between food producers and PN service providers would enable a seamless personalised food service in which the PN providers inform consumers what food and how they should consume their food, and food producers might be technically equipped to provide actual personalised food products to match that advice. Proponents envisage a world of restaurants providing customised menus, personalised meal delivery services, and mass-customisation. However, this is currently still speculative as the existing food system is built to provide standardised mass-produced food at affordable prices, which runs counter the idea of producing individualised food items with limited editions. However, should small to medium scale food production processes become viable locally then personalisation might become a specialist production mode for such food processors that could link up with PN service providers and create submarkets for personalised food items.

Implications and recommendations for FSA

The current PN market in the UK is still limited and most active companies are at an early stage in their development, mainly small start-ups in their first or second funding round having raised a few £100,000 to a few million pounds, mainly in the past five years. However, 9 out of 13 surveyed active companies in the UK offer personalised vitamins or supplements, which may indicate that this is the direction into which PN providers will be going in the medium-term future (see Appendix A). As PN is still a curiosity market with mostly one-off purchases or subscriptions for a few months the total market coverage of these UK companies at any given time may currently be in the range of thousands up to the lower hundreds of thousands of customers, based on their self-reported customer figures, with a potential temporary peak during the height of the Covid-19 pandemic during which consumers tended to seek out heath improvement offerings.

With regards to FSA regulatory remit two aspects of PN services might be of relevance for considerations to what extent FSA might be able to contribute in a positive manner to the development of the sector. First, given existing FSA leverage in the supplements and vitamin sector and therefore also their labelling within a PN context, it might be straightforward to achieve regulatory impact by making sure that personalised products are not labelled and presented as a medicine. Second, enforcing registration as a food business when selling supplements might also help PN businesses understand that the health claims made in their personalised advice based on biomarker and DNA data may not be translated into health claims on their supplements. For the food and labelling regulators (including the FSA, Department of Health and Social Care, DEFRA) to take a clear stance on food related health claims in general might also help with generating a more trustworthy business culture that will help build consumer trust in the sector. The specifics of how PN offerings are presented, and which services and products are sold depends on the individual

business model of each company, hence the degree to which their activities fall within the FSA's remit might need to be assessed on a case-by-case basis.

Summary of emerging personalised nutrition approaches and implications for FSA

Based on the definition of personalised nutrition given in this report (section 2.1) a number of business models can be found implemented by currently active PN providers. In addition, there are other on-going activities in the food sector that can be called "personalisation of food", which are different from personalised nutrition as discussed in this report. Personalisation of food services range from shopping platforms tailored to specific dietary needs/preferences, such as for vegans, vegetarians or food intolerant consumers, to personalised dining experiences in restaurants, or personalised modes of production of certain foods, for example via 3D printing among others. Although these activities within the food sector are potentially relevant in the future for enabling an ecosystem of interlinked customisation/personalisation technologies that might connect in the longer-term future with PN providers in the stricter sense to provide integrated services, these are not discussed here as they are already within FSA remit. The following types of PN services currently implemented on the market have different implications for consumers and FSA regulatory remit.

A) Services based only on personal data on phenotype, lifestyle dietary habits, and physical activity patterns etc. Currently not within FSA remit as it is advice only that can be seen equivalent to general advice by nutritionists and dieticians.

B) Services based on personal data and bio-specimen test results (including from blood, saliva, stool, breath, and sweat among others, but excluding personal DNA)**.** Here the FSA may wish to consider taking on responsibilities at the intersection between health claims on foods or supplements that are made with an understanding of addressing specific health issues identified by personal phenotype data using scientific methods. There could be an opportunity for setting standards for a certain level of required scientific validity and robustness of test results before health claims on advised foods can be made. A stricter regulation of claims concerning this relationship between personal health requirements and food claims might be justified on the basis that this relationship is presumed to be specific to the customer receiving personalised nutrition advice, and hence can be different to claims that have their origins in large population studies. A clearer language in this respect may help with building a framework of trust between providers, consumers and regulators.

C) Services based on personal DNA sample test results and analysis. As in B, FSA may wish to take a stronger position at the interface between claims on food and the scientific justifications for the effectiveness of certain foods in addressing health issues identified through DNA analysis in individual customers.

D) Services based on any of, or, a combination of A-C, *and* offering a food product such as supplements, functional foods, or vitamins. This segment already falls within FSA remit, however as discussed in section 7 it is currently

unclear whether the PN sector has sufficient awareness of existing regulation, and it certainly appears that claims are made that are questionable with regards to vitamins and supplements sold in combination with personalised advice based on individual scientific results and analysis. In particular, the distinction between food and medicine needs to be upheld by making sure that the presentation of sold food items such as supplements does not blur that line deliberately, and that all other relevant regulation for supplements is adhered to, including food safety aspects, labelling, allergen advice etc. to avoid consumers being misled to believe that supplements offered by a PN provider are qualitatively different from other supplements.

General recommendations for consideration

Given that business models in the sector currently vary and whether the PN provider would sell personalised supplements and functional foods, FSA may wish to make a decision whether it would be appropriate to develop a broader framework that would cover any PN companies, or just the ones that would also provide supplements and functional/personalised food items or vitamins.

Although explicit regulation of all PN providers may currently not fall directly under FSA remit it is advisable that FSA directly collaborates with medical regulatory agencies in drawing up a framework of understanding for necessary regulation to ensure general quality standards in the PN sector can be enforced effectively. This includes collaborating with relevant organisations that cover the data aspect of the sector to such as validation criteria for biospecimen and DNA testing, algorithm standards and data ownership and privacy rules. Harmonising the regulatory framework for PN across agencies will enable the industry to evolve in line with consumer protection across the service offering. In such an effort decision on the following areas need to be made in collaboration with other regulatory bodies:

- Analytical validity of tests: requiring analytical tests to be carried out by certified laboratories in the UK. In case of test samples being sent to other countries due to perceived or real economic advantages, the overseas laboratories need to comply with UK validation standards in order to be able to process samples from UK consumers.
- Scientific validity of analysis: science in this field is still evolving and new findings are emerging that may impact the nature of analysis of data and how the algorithms used by PN providers are designed. This in turn will impact the nature of advice given to certain individuals or subpopulations. Therefore, it would be advisable that regulation would require PN companies to update their algorithms based on the latest relevant scientific findings.
    - For the FSA and other regulatory bodies working on this issue it would be advisable to aim for harmonisation of validation requirements for algorithm certifications with highest clinical standards. This can be addressed by working with a science advisory board to be able to 1) keep up with the latest scientific breakthroughs 2) translate the latest scientific findings into validation parameters that need to be considered for algorithm certifications.

This is important, because the advice PN companies offer is not based on human judgement but rather is the result of a chain of software automated decisions that underpin the AI that is used for final advice given. In cases of automated advice causing harm to consumers the question of legal responsibility needs to be traceable to the technologies involved. Therefore, the parameters that the algorithms are trained on need to be accessible for external validation and need to reflect latest scientific findings as the field progresses.

- Utility of advice: considering that at the current state of the industry the algorithms that underpin automated advice are trained and built upon the individual knowledge and experience of dietician/s or scientists working with each start-up. Therefore, the previous point on scientific guidelines on validation parameters of algorithms will be a key point for harmonising rules that are being used to train algorithms.
    - At the same time as the PN sector grows and increases its customer base to the millions, feedback and data regarding how different individuals responded to these new dietary interventions and their impact on their health outcomes, will become a very valuable source of empirical data for research. Owning this data can become a monetisable and valuable source of competitive advantage depending on how this information is used.
- Ethical, legal and data protection issues need to be covered by collaborating with relevant regulatory agencies.

Short-term FSA priorities (within 3 years)

- Establish within the FSA whether a more active role in regulating businesses that are operating at the intersection between health/wellness and the food system would be desirable for protecting consumers from low quality services linked to food, or outright fraud. This may involve changing existing remit definitions. In terms of the early developmental stage of the industry this could be an opportunity to shape its further evolution.
    - Build the necessary collaborations with other regulatory agencies that have responsibility for different areas of this multidisciplinary space.
- Ensure that the FSA has the relevant expertise required for monitoring the emerging PN sector by connecting with relevant experts. This will require maintaining networks of experts in the basic sciences who understand relevant scientific trends that may lead to applications relevant for the PN sector. Other additional expertise required would be:
    - Experts from the social sciences to provide insights into other societal trends that may be relevant for this sector.
    - AI, privacy, and data security experts to provide a deeper understanding of how science is translated into advice and its implications for personal privacy of consumers.

- Monitor activities and connect with experts in the areas of general food personalisation, in particular where synergies with the PN sector could lead to a sudden market growth of PN services due to production capacities that may become available from different segments of the food processing sector. This is advisable as already a number of large multinational food producers are supporting the PN sector via partnerships and start-up funding.
- Explore whether existing regulation of supplements and vitamins is adequately covering the various aspects of PN services and whether a closer analysis of the sector would be required to establish to what extent existing regulation is adhered to.

Medium-term FSA priorities (3 to 5 years)

- Consider whether the FSA might be a relevant partner in potential efforts to make PN services available to larger segments of society with public health goals in mind. This may involve connecting with the NHS and the Department of Health and Social Care to explore to what extent such efforts are realistic.
- Consider establishing strategic partnerships with the public health, healthcare and social services regulatory bodies in order to bring food safety aspects to health regulation relevant for the PN sector.

Long-term FSA priorities (5 to 10+ years)

- It remains crucial to closely monitor the sector's evolution as novel science results from areas such as epigenetics, gut microbiome, metabolism research among others, will come to market, again at an early stage of understanding, potentially claiming to be more valid than current applications.
- Explore to what extent a growing PN market might impact the way how consumers interact with the wider food system in a networked fashion, how such network effects might be utilised for achieving public health goals, and whether as a food regulator there would be opportunities for supporting such goals.

Limitations of study

This report is believed to have captured the most salient science, technologies, services and trends immediately relevant to the evolution of the PN sector. As PN is a fairly well researched and studied subject in its own right we believe the most relevant findings from the academic and grey literature in the public domain are captured in this report. However, for giving a more detailed account of the current impact of PN providers on consumers, a more detailed analysis of the currently active commercial players would be required. More in-depth commercial information is however often not available either due to the short period of commercial activity of companies, or not made available due to issues around IP or confidentiality. Though

care was taken to report on most relevant trends impacting the evolution of PN, no attempt was made to quantify them in terms of size of potential impact, as this would have required additional research and methods beyond the scope of this report.

Recommendations for future research and analysis

- To get a clearer understanding of the current state of adherence to existing legislation in the PN sector a study should be carried out to establish such information from existing providers.
- For anticipating synergistic effects between PN and existing “personalisation of food” activities in the food processing industry, a study of currently existing food personalisation technologies and trends within this segment should be conducted.

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Appendix A: Personalised nutrition companies in the UK

This appendix presents details of personalised nutrition companies currently active in the UK, and relates their business models to the categories identified in section 3.4 of this report:

A. Approaches collecting various kinds of personal information, for example, through a questionnaire or app/web interface
B. Approaches that use physical bio-specimen samples from customers to measure and/or quantify aspects of their phenotype, including breath tests, blood tests, and gut-microbiome.
C. Approaches using personal DNA information of customers
D. Approaches that use any of A, B, C, *and* sell a physical product (often described as “functional food”, “personalised supplement” or similar)

Table 3 Companies active in the UK

Company, UK	Science/Data used	Services/Products	Claims
Atlas Biomed Active: 2016-, Series B funding $21 million	**(Combination of business model B & C)** • **DNA test** (£99). • **Microbiome test** (£159).	• Dietary advice based on DNA/microbiome test. • New offer: image recognition app that gives dietary recommendations on pictures taken of meals and food items • Carrier status, risk for hereditary diseases, impact on vitamins, nutrients and predisposition to nutrient intolerances, DNA ancestry. • Carrier status, child risk for hereditary diseases • Impact on vitamins, nutrients and predisposition to gluten, lactose, caffeine and alcohol intolerances • Athletic predisposition to performance and injury • DNA ancestry, origins, and Neanderthal genes • Unique personal traits determined by genes • Personalised food recommendations • Probiotics and beneficial bacteria report • Lactose and gluten metabolism • Anti-inflammatory potential	• User Data are securely stored on certified servers located within the European Union • SHA-256 with RSA Encryption • Full UK GDPR and EU GDPR compliance • Registered with Information Commissioner's Office • The technologies used in the Atlas DNA Test are 99.9% accurate. • ISO 13485:2016 accreditation for medical device quality management systems. • DNA sample is analysed using DNA microarray technology from Illumina in a certified EU lab.

Company, UK	Science/Data used	Services/Products	Claims
Bioniq balance Active: 2012-; Raised in 2020 $7.8M for US and ME expansion.	**(Business model B)** 35 parameter **blood test** from a partner laboratory. Includes testing for lipids such as cholesterol, ions such as Calcium, Potassium, Sodium, and microelements such as copper, zinc, selenium among others, and vitamins B9, B12, D, E, and basic haematology parameters.	• Personalised vitamins of up to 34 vitamins and minerals in special slow-release capsules by Swiss manufacturer. • Subscription for £99 or £200, with bespoke vitamins for 3 months from £300, with health monitoring and health advice from £500. • Access to a personal dashboard or the bioniq app to monitor progress • Home visit from a qualified nurse for blood testing - £50 one-off payment. • Consultation with dietician (£250)	• Health monitoring and advice algorithm based on 30,000 blood results. • Conducted 24 small-scale clinical studies to validate their approach since 2012.
Dnafit Active 2013-, was in 2018 acquired by Prenetics, a Hong Kong based DNA testing company backed by Alibaba.	**(Business model C)** **DNA test**	• DNA test and analysis with multiple reports on health/disease risks including cancer, diet/nutrition, sport/fitness, stress and ancestry. • Three levels of DNA tests: “Diet Fit” (£111.75), “Health Fit” (£149.25), and “Circle Premium” (most extensive version on the market, for £374.25). • Free nutritionist support, training for using meal planning app live chat.	• Have sold 100,00 tests by 2018. • Analysis compatible with 23andMe data. • Most extensive DNA test on the market. • 99.9% technical accuracy, externally verified • ISO 27001 data security, data not sold or shared

Company, UK	Science/Data used	Services/Products	Claims
GetNourished (Remedyhealth), Active: May 2019- venture funding round 1, undisclosed.	**(Business model D based on A)** • **Questionnaire**-based personalisation of vitamins/ micronutrients. • 2-minute consultation questionnaire and **proprietary algorithm** will recommend 7 nutrients. • No disclosure of science.	• 3D printed gummy vitamin "stacks" (cookies).	Data stored on "our secure systems" and customers can request a data update, a copy of their information, and that their account or data held by Remedy Health is deleted permanently, in line with the 2018 General Data Protection Regulation
Everlywellness: also known as Vive wellness; Active: 2019-	**(Business model D based on A)** In-house **nutritionists** select supplements that "are effective". Online questionnaire, focus on themes, such as digestion, skin, hair & nails, immunity etc.	• Packaged vitamins/supplements from Cultech and Eurocaps (soft gel manufacturer), leading manufacturers in the supplement industry. • Products only include what "your body can absorb safely, and are free from unnecessary bulking agents, fillers, colours and preservatives".	Vitamin manufacturer Cultech and Eurocaps are GMP (Good Manufacturing Practice) certified, and MHRA the (Medicines and Healthcare products Regulatory Agency) accredited.
Fitness Genes: Active: 2013-, series A funding 2017: $6.6M	**(Business model C)** **DNA test** report on 42 genes.	• DNA analysis report on genes impacting on appetite, eating behaviour, oxygen levels when exercising, fat burning, sleep cycle, nutrient metabolism, muscle strength, insulin function, post-	• DNA reports created by using proprietary TrueTrait™ algorithm. • Certifications for: ISO 9001 for business processes, ISO 17025 for laboratory testing and calibration services, compliance with Good Laboratory Practice (GLP), Good

Company, UK	Science/Data used	Services/Products	Claims
		workout recovery, muscle fibre composition, among others. • Nutrition guide. • Workout plans.	Clinical Practice (GCP) and current Good Manufacturing Practice (cGMP) for pharmaceutical studies and accreditation to ISO 17043 for the operation and management of proficiency testing schemes. • Safe storage of DNA samples. • GDPR compliant. • No data sharing with third parties.
GP Nutrition Active 2016-, founder Gabriela Peacock, nutritionist, declared £2 million revenue in 2019. Products stocked at Harrods, and Browns & Rocco Forte Hotels, and online sales.	**(Business model D based on A)** **Nutritionist** advice	• Nutrient blends and vitamin mixes	• Selling to aristocracy and stars.
Karmacist: UK, pre-seed funded £700,000; Active: 2021-	**(Supplements only)** Call themselves a nutrigenomics company, but offer **no tests, no questionnaires**	• Pre-assembled supplement mixtures to enhance immunity, mood, energy, relaxation. • Monthly subscription model for re-fill packs.	• Supplements made in the UK, no animal products, no allergens. • Supported by US based nutritional psychologist Dr Uma Naidoo, (Harvard General Hospital) and Prof Vittorio Sebastiano, epigenetics researcher at Stanford School of Medicine, US.

Company, UK	Science/Data used	Services/Products	Claims
Lumen US, launched in 2020 in the UK,	**(Business model B)** CO2 analysis with a **breath analysis device** for metabolic status and **app** for data readout.	• Personalised meal recommendations. • Real-time metabolic insights. • Tailored eating plans. • Six-month track from £249. • C02 measurement device.	• Natural weight loss. • Improved overall health. • Boosted energy.
NGX: UK, raised over £800,000 via crowd funding platform Crowdcube. Active: 2017-	**(Business model D based on C)** **DNA test** of 14 genes (£99).	• DNA test analysis. • Pre-prepared meal shake powder sachets according to DNA test result. Two weeks Starter pack (£129.99). • 15 minute consultation with nutritionist.	• Ingredients naturally sourced, vegan-friendly containing no artificial sweeteners, flavours or colours. They are also free from soy, lactose, gluten and genetically modified organisms (GMO). • Products help to improve mental motivation and drive, with weight loss, and increase athletic performance. • DNA sample is securely destroyed after obtaining results.
Personalised Co. Raised £492,800 via equity crowd funding platform Crowdcube; Active: 2018-	**(Business model D based on A)** Provide **rating of scientific evidence** on their products. Product design based on science. Online **questionnaire**.	• Personalised vitamins monthly supplies. • Collagen/hyaluronic acid Biotin A/B vitamin formulation for hair growth; monthly plan £25, 3-month plan £57. • Free consultation with nutritionist.	• Personalisation based on algorithm. • Formulations based on in-house nutritionists. • Over thousand subscribers.
Vitamin Buddy no disclosed funding; Active 2016-	**(Business model D based on A)** **Questionnaire**	• Personalisation of monthly vitamin packages based on questionnaire results. • Single vitamins.	• Vegan-friendly, gluten-free, pharmaceutical grade and made in the UK.

Company, UK	Science/Data used	Services/Products	Claims
Vitl £6.2 million funding, partially by equity crowd funding; Active: 2015-	**(Business model D based on A, B and C)** • **DNA test** with over 40 reports (£119). • **Blood test** for vitamin and cholesterol levels (£49.99). • **Questionnaire**	• Personalised advice by nutritionist based on blood and DNA tests. • Personalised monthly vitamin packs. • Single general multivitamins for men and women.	• No specific claims beyond offering.

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