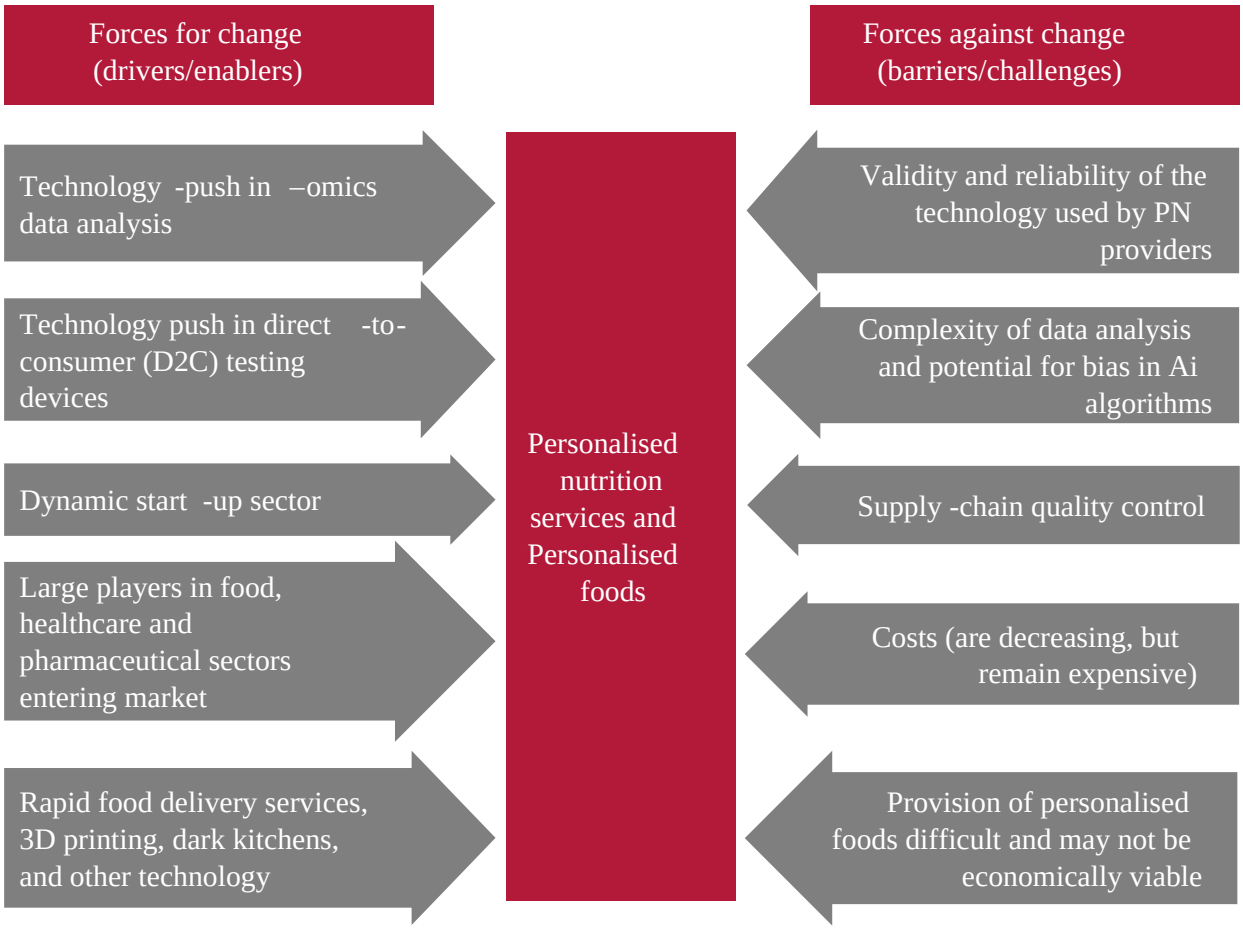
The Evolution of Personalised Nutrition: Technology and commerce – Drivers and challenges

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, Caligenix, DNAFit, GX Sciences, InsideTracker, or Day Two 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, 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 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), 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”. 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. 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: Suggestic), 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 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, a PN provider, in 2016, which was subsequently acquired by Viome 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 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).