Title Page

Title

From Personalised Nutrition to Precision Medicine: The Rise of Consumer Genomics and Digital Health

Author names

J. Bernadette Moore

Address

School of Food Science & Nutrition, University of Leeds, Leeds, West Yorkshire, LS2 9JT, UK

Corresponding author

J. Bernadette Moore,

School of Food Science and Nutrition,

University of Leeds,

Leeds,

West Yorkshire

LS2 9JT

T: +44(0)11334 39900

E: J.B.Moore@leeds.ac.uk

Running title

Consumer Genomics and Digital Health

Keywords

Precision medicine, nutrigenomics, personalised nutrition, systems biology, proteomics

Abbreviations

HGP, Human Genome Project; NGS, next-generation sequencing; SNPs, single nucleotide polymorphisms; GWAS, genome-wide association studies; WTCCC, Wellcome Trust Case Control Consortium; NHS, National Health Service; ESMO, European Society for Medical Oncology; HUPO, Human Proteome Organization; HbA1c, glycated hemoglobin; DTC, direct-to-consumer; FDA, Food and Drug Administration; GPRS, genome-wide polygenic risk scores; CGM, continuous glucose monitoring

Abstract

Advances in genomics generated the concept that a better understanding of individual characteristics, e.g. genotype, will lead to improved tailoring of pharmaceutical and nutritional therapies. Subsequent developments in proteomics and metabolomics, in addition to wearable technologies for tracking parameters such as dietary intakes, physical activity, heart rate and blood glucose, have further driven this idea. Alongside these innovations, there has been a rapid rise in companies offering direct-to-consumer genetic and/or microbiome testing, in combination with the marketing of personalised nutrition services. Key scientific questions include how disparate datasets are integrated, how accurate are current predictions, and how these may be developed in the future. In this regard, lessons can be learned from systems biology, which aims both to integrate data from different levels of organization (e.g. genomic, proteomic and metabolomic) and predict the emergent behaviours of biological systems or organisms as a whole. This paper reviews the origins and recent advancement of 'big data' and systems approaches in medicine and nutrition. Conclusions are that systems integration of multiple technologies has generated mechanistic insights and informed the evolution of 'precision' medicine and 'personalised' nutrition. Pertinent ethical issues include who is entitled to access new technologies and how commercial companies are storing, using and/or re-mining consumer data. Questions about efficacy (both long-term behavioural change and health outcomes), cost-benefit, and impacts on health inequalities remain to be fully addressed.

Genomics and the origins of 'big data' in understanding human biology

As a scientific discovery that befitted the turning of a millennium, the initial sequencing of the human genome by two independent groups was announced jointly by the president of the United States and the prime minister of the United Kingdom to much fanfare in June 2000[1]. Published the following February in tandem, in the journals Nature[2] and Science[3], these initial draft sequences were the result of several decades of technological achievements[4] and represented biomedical science's first major foray into 'big science'[5]. Multiple incremental advances in several fields, including molecular biology, chemistry, physics and robotics, led to the revolutionary innovation of capillary-based DNA sequencing instruments. These, alongside advances in computer science, ultimately permitted the reconstruction of these first draft sequences[6].

At the time of completion of the Human Genome Project (HGP), the estimated cost of sequencing a single human genome was a $100 million US dollars, and could be achieved in 9 months using 350 of the state-of-the-art capillary DNA sequencers running in parallel[7]. In the two decades since, further remarkable advances in sequencing technology have driven the cost of sequencing a human genome down exponentially, with costs approaching only a $1,000 US dollars per genome since 2015[8]. Large-scale massively parallel sequencing, or next-generation sequencing (NGS) technologies, now make possible the shotgun sequencing of several thousand human genomes a month[7]. By necessity at each stage, advances in sequencing technologies have been accompanied by advances in bioinformatics and data analysis pipelines that have inextricably linked the fields of genomics and computational biology[9]. This has permitted the identification of variation in the human genome in a variety of different contexts in an unprecedented manner.

Since the HGP, multiple large-scale genomics efforts have focused on identifying and understanding the scale of human genetic variation. The first of these, the International HapMap project begun in 2002, aimed to catalog common human genetic variants (single nucleotide polymorphisms; SNPs) and how they linked together (a haplotype). Initially focused on characterizing common SNPs, present at 5% or greater allele frequency, in four populations with ancestry from Africa, Europe and Asia[10], HapMap was subsumed into the 1,000 Genomes project begun in 2008 after the introduction of NGS, which ultimately provided much greater resolution of genetic variation in 14 populations[11]. In addition to characterizing 38 million SNPs present at 1% or greater allele frequency, the 1,000 Genomes project mapped 1.4 million short insertions and deletions (indels), and more than 14,000 larger deletions. Such mapping efforts greatly expanded our understanding of the breadth of human genetic variation and made feasible genome-wide association studies (GWAS) relating multiple genetic variants to common complex diseases.

The path towards precision medicine

Essentially large case-control cohort studies, GWAS compare the distribution of SNPs in thousands of people with and without a particular disease. The first raft of these studies were published in 2007, providing insight into multiple common chronic diseases and prompting Science magazine to declare human genetic variation the breakthrough of the year[12]. Perhaps most significant, and considered 'paper of the year' by the Lancet[13], was an unprecedented study from the Wellcome Trust Case Control Consortium (WTCCC), a group of 50 research groups across the United Kingdom. This work identified genetic associations in cohorts of 2,000 patients with one of seven chronic diseases (type 1 and type 2 diabetes, hypertension, coronary artery disease, Crohn's disease, rheumatoid arthritis and bipolar disorder) in comparison to a set of 3,000 control participants[14]. Indeed, since its participation in the international HGP, the United Kingdom has consistently remained at the forefront of large-scale efforts in genomics, with the WTCCC laying groundwork for the subsequent UK Biobank and 100,000 Genomes projects.

Initiated in 2006, the UK Biobank is a prospective population-cohort of 500,000 individuals that has gathered genome-wide genetic data along with linked detailed physical and clinical information on the participants who were aged 40-69 at recruitment[15]. Notable both for its scale and commitment to data sharing, the project follows participants through health-related records and national registries for hospital admissions, cancer diagnoses and deaths. Whereas the UK Biobank used array technology to analyse 825,927 genetic markers in healthy volunteers followed over time; the more recent 100,000 Genomes Project, begun in 2013 after significant reduction in the cost of NGS, has applied whole genome sequencing to patients with either rare diseases or cancer[16]. Rare diseases are typically Mendelian, caused by single gene defects, and manifest before the age of five. Accurate genetic diagnosis can make an enormous difference in disease management for the patient and inform families about risk of recurrence. Similarly, understanding what genomic alterations have taken place in cancer can provide diagnostic and prognostic information and has been critical in the development of targeted therapies for select epithelial malignancies[17].

Inherent in these large-scale genomics projects has been the belief that with a better understanding of genetics will come improved treatments for individuals. Therefore, a not insignificant aim of the 100,000 Genomes Project was to imbed the infrastructure required to provide a genomic medicine service within the UK's National Health Service (NHS)[16]. It has long been recognised that many chronic diseases such as cancer, which phenotypically look broadly similar, vary significantly in molecular aetiology. Consequently, the same medication given to a group of heterogeneous patients may be beneficial in some patients and not in others, and potentially also toxic for some patients and not for others. The worst-case scenario for patients would be to receive a

medicine that has no benefit and is toxic. Stratified medicine (see Table 1 for definitions) simplistically aims to subgroup and identify patients that will benefit from treatment without experiencing toxicity. Subgroups can be based on a combination of disease subtypes, clinical features, demographics, risk profiles, biomarkers or molecular assays. Possibly the best known example of stratified medicine has been the molecular subtyping of breast cancer based on hormone receptor (the estrogen and progesterone receptors) and human epidermal growth factor receptor 2 expression[18]. While the most successful applications of stratified medicines to date have largely been in cancer and genetic diseases, many others therapies with associated biomarkers are beginning to be adopted (by the UK NHS) or are in the development pipeline[19].

Therefore, the vision of personalised or precision medicine in most areas of medicine is arguably still aspirational. Precision medicine aims ultimately to tailor treatments to an individual based on molecular features (plus lifestyle and environment) of a patient and/or their disease; ideally also using companion diagnostics to determine responders and non-responders to the therapy. While the terms stratified, systems, personalised and precision (Table 1) have been used interchangeably, and in some cases fiercely debated[20], the term precision medicine is now preferred and has been more commonly used in the medical literature since 2010 (Fig. 1a). In calling for a new (molecular) taxonomy of disease towards precision medicine, concerns outlined by the US National Research Council were that the term personalised could be "misinterpreted as implying that unique treatments can be designed for each individual", in part because it had been widely used in advertisements for commercial products[21]. These concerns were echoed by the European Society for Medical Oncology (ESMO) in their Precision Medicine Glossary[22]. Additional reasons outlined by the ESMO were that precision medicine "better reflects the highly accurate nature of new technologies that permit base pair resolution dissection of cancer genomes". Whereas personalised medicine "could describe all modern oncology practice that takes into account patient factors such as personal preference, cognitive aspects and co-morbidities in addition to treatment and disease factors"[22].

Functional genomics

As the HGP was drawing to completion, came the goals of functional genomics. Namely applying high-throughput genome-wide approaches to studying gene transcription, translation and protein-protein interactions. Along with the over use of the suffixes '-ome' and '-omics'[23], emerged research efforts in transcriptomics, proteomics and metabolomics. There was early recognition that ultimately if viewed together, comprehensive datasets along the entire 'omics cascade' would provide significant insights into the response of biological systems to genetic, environmental or disease-mediated perturbations[24]. Initial functional genomic insights came from transcriptome profiling experiments, with early applications in the nutritional sciences including the identification of genes

regulated by dietary zinc[25,26]. The genomic sequence information from the HGP in combination with advances in lithography led to high-density DNA arrays that made it possible to measure levels of gene expression for tens of thousands of genes simultaneously; superseding the more laborious and technically challenging differential display approach[27].

However, while an individual's genome and transcriptome yield insight into 'what can happen', critical to precision medicine are clinical biomarkers, which are most commonly proteins or metabolites and speak to 'what is happening'[24]. Proteins and metabolites are chemically much more complex and heterogeneous than nucleic acids; and therefore, much more challenging to isolate, identify and measure. Consequently, publications in the fields of proteomics and metabolomics have risen subsequent to, and at a lower rate than, those in genomics and transcriptomics (Fig. 1(b)). Unsurprisingly then, the human proteome, the functional compartment encoded by the genome, emerged as a next logical biological challenge to be tackled internationally after completion of the HGP[28]. The Human Proteome Organization (HUPO) was founded in 2001 in large part to promote and coordinate open access initiatives in this field[29]. With recognition of the critical role of small-molecule (<1500 Da) metabolites in clinical diagnostics and as pharmaceutical agents, complementary efforts in metabolomics followed in short order[30].

Whereas sequencing an entire genome is now relatively inexpensive and technologically feasible by NGS within a few hours, measuring a proteome or metabolome in its entirety is still not possible from a single experimental approach. Nonetheless, advances in mass spectrometry and nuclear magnetic resonance spectroscopy, along with bioinformatics, databases and annotation, mean that we can now measure many, many more proteins and metabolites in 'single runs' than two decades ago. Building on early tissue-specific (plasma, liver, brain), antibody and data standard development initiatives, the Human Proteome Project was formally launched by HUPO in 2010[31]. The work of 50 international collaborating research teams is organized by chromosome, biological processes and disease categories and has since been reported collectively yearly. As of 2019, robust mass spectrometry data has been reported for 89% of the 19,823 predicted coding genes, and separate antibody-based histochemical evidence exists for the expression of 17,000 proteins[32]. While such cataloging efforts are not without their detractors[33], the efforts of 'discovery science' clearly can and have fostered hypothesis-driven approaches[34]. In the context of the Human Proteome Project, multiple strands of research have identified biomarkers and characterized molecular mechanisms of human disease, contributing to efforts towards precision medicine[32].

Systems biology

Systems biology as a discipline, although proposed as early as 1966[35], became truly established in the aftermath of the HGP[36,37]. Representing the antithesis of reductionism, systems

biology combines molecular and computational approaches to understand highly complex interactions within, and ultimately predict the behavior of, biological systems as a whole[38,39]. From early in its conceptualization, both the generation and the integration of different levels of biological information (e.g. genomic, transcriptomic, proteomic, metabolomic) in order to yield predictive mathematical models, was articulated as fundamental to systems biology[36]. Therefore, whereas the high throughput datasets of genomics and proteomics provide the foundation for the 'reconstruction' of biological networks at the genome-scale; it is computational simulation that yields insights into the systems structure and dynamics, and predicts biological outcomes[39,40].

The first Institute for Systems Biology was founded in 1999 in the United States by Leroy Hood, whose early work had made seminal contributions to the fields of genomics and proteomics through the development of high throughput instrumentation for DNA and protein sequencing; in addition to this, he led significant sequencing efforts that contributed to the HGP[41]. Undoubtedly a visionary, who viewed continued advances in high-throughput measurement technologies, databases and tools for integrating the various levels of biological information, essential to systems biology[36]; Hood's Institute radically brought together biologists, chemists, computer scientists, engineers, mathematicians, physicists, and physicians; and has continued to pioneer new technologies (including single cell microfluidics) and new computational platforms in the ensuing decades[42]. Perhaps most revolutionary however, was Hood's early vision for what he first termed "predictive, preventive, and personalised medicine" and later renamed "P4 medicine: predictive, preventive, personalised and participatory medicine"[43,44]. Relevant to the concept of personalised nutrition discussed below, there was early recognition in the systems biology field that nutrition is a critical environmental factor that interacts with genetics (and metabolism) to determine health or disease, particularly later in life[45,46].

From the systems biology perspective, disease is viewed as arising from either genetically and/or environmentally perturbed networks in the affected organ. Computational modelling allows the determination of how systemic networks are changing in individual cells, tissues or organisms, dynamically influencing pathophysiology of the disease. Systems medicine and systems pharmacology, considered the subfields of systems biology underpinning precision medicine[47], aim to integrate genetic, clinical and 'omic' data into network models, representing an *in silico* human that can yield emergent insights (Fig. 2)[48]. Systems pharmacology is a logical extension of physiologically-based pharmacokinetic modelling, offering methods to account for genetic variation impacting whole-cell metabolism and the regulation of key drug metabolism enzymes[49].Whereas applications in pharmacology may be aimed at predicting responders/non-responders to a drug or identifying mechanisms of action underpinning drug off-target effects; equally systems approaches

may be applied to predicting the response to dietary intervention given an individual's background genetics, microbiome, life stage and/or disease state (Fig. 2)[38,48,50].

Proving that systems level integration of genetic data with clinical and multiple omic datasets is feasible and can yield personalised predictive insights and facilitate a preventative health intervention (involving nutrition!), was a landmark study published in 2012[51], led by Michael Snyder, another pioneering leader in developing systems approaches to functional genomics and proteomics[52]. The study combined whole genome sequencing with transcriptomic, proteomic, metabolomic and autoantibody profiles in blood from a single individual—Professor Snyder himself—measured sequentially over a 24 month period. Apart from the signficant computational feat in terms of data integration, this work was fascinating in monitoring Snyder's dynamic response to two viral infections, as well as his onset of type 2 diabetes and response to dietary and lifestyle intervention. While Snyder's elevated risk for diabetes was predicted by genome sequence analysis, the onset of a frank high glucose and elevated glycated hemoglobin (HbA1c) phenotype occurred about 10 months into the study and appeared to have been triggered by infection with respiratory syncytial virus. Choosing to implement "a dramatic change in diet, exercise and ingestion of low doses of acetylsalicylic acid", over the course of the following eight months Snyder was able to reduce his glucose and HbA1c levels to normal[51]. The work uniquely characterized molecular pathways involved in both onset and resolution of viral infections and diabetes at extraordinary depth, with unique insights provided by the combination of transcriptomic, proteomic and metabolomic profiling. Other examples of multi-omic data integration in this way that have informed cancer as well as rare and common diseases have recently been reviewed[53].

Personalised nutrition and consumer genomics

As in medicine, the meaning of 'personalised' in the context of nutrition has been deliberated[54-56]; and terminology (Table 1) continues to evolve with the more recent use of the term 'precision' emerging in the scientific literature in the last five years (Fig. 3). Analogous to the ambitions of precision medicine, the aim of personalised or precision nutrition is to tailor nutritional advice/diets to optimize health based on an individual's characteristics[55]. For a nutritionist or clinical dietitian, these characteristics have long included anthropometry, dietary history and preferences, information on lifestyle and physical activity, along with clinical parameters and biochemical markers of nutritional status. But after the sequencing of the human genome came an era of increasing research interest in nutrigenomics and nutrigenetics (Table 1 and Fig. 3), and the accompanied vision of providing personalised dietary advice to prevent diet-related diseases based on genetic differences and the predicted response to nutrients derived from genetic profiling[57,58]. Notably, while scientists have remained largely circumspect about clinical utility and the extent to which genetic or polygenic

risk scores can explain overall risk for common, multifactorial diseases (e.g. obesity, diabetes, fatty liver) or micronutrient status[59,60]; an astonishing number of direct-to-consumer (DTC) genetic testing companies have proliferated offering personalised nutrition advice to individuals based on nutrigenetic testing via the internet[61].

Public interest in these commercial genetic services has rapidly grown in the last five years. The number of genotyped consumers started rising exponentially in 2016 and surpassed 10 million worldwide at the beginning of 2018[62]. The notorious, ultimately temporary, US Food and Drug Administration (FDA) ban of medically-relevant testing by 23andMe in 2013, means the majority of DTC genomic tests sold to date were marketed and sold as ancestry services[59,62]. In addition to raising a host of ethical questions around data privacy, forensic genealogy, personal identity and race[63,64], this prompted a very market-based work around the regulatory legislation for health-based genetic testing[65]. Specifically, a crop of third-party interpretation services have arisen that will interpret raw genotyping data that is provided to consumers by many DTC ancestry genetic services without having done the testing per se[65,66]. Separately, in a much criticized reversal, in 2017 the US FDA approved a 23andMe genetic health risk test of limited clinical sensitivity (limited positive and negative predictive values)[67]. Moreover, a significant number of companies are marketing 'health and wellness insights' that are largely unregulated and relate to common (nutrition-related) disease risk[61,68]. In a survey of 246 companies offering online DNA testing, done in 2016, a majority (136) offered some form of health-related testing service[61]. Seventy four companies offered nutrigenetic testing, many of which also offer tailored diet services, food supplements and/or meal plans; and 38 companies offered tests for athletic ability.

There are multiple scientific concerns with the personalised nutrition promises offered by DTC nutrigenetic testing companies, given the marked absence of published studies assessing either analytical or clinical/predictive validity of these tests. A merely analytical concern is the reliability of the sequence data in the first instance. A concerning study of confirmatory testing in referrals to a clinical diagnostic laboratory, found 40% of variants in a variety of genes reported in DTC raw data to be false positives[66]. In terms of predictive validity, the majority of genetic risk estimates returned by DTC companies are based on only a select number of genetic variants. This is in contrast to the numerous (>100) genetic loci identified by the largest (>100,000 individuals) GWAS done to date, which still only explain a fraction (20% or less) of the heritability of common diet-related chronic diseases such as obesity and type 2 diabetes[69,70]. Moreover, very recently, completely novel genome-wide polygenic risk scores (GPRS) have been developed for obesity, type 2 diabetes and other common diseases; facilitated by improved algorithms and very large GWAS studies[71,72]. In the case of obesity, the GPRS was comprised of *2.1 million* common genetic variants and significantly

outperformed a score that incorporated only the 141 independent variants that had reached genome-wide levels of statistical significance in the prior GWAS[69,72]. A 13 kg gradient in weight and a 25-fold gradient in risk of severe obesity was observed in adults across GPRS deciles. Although practical considerations on how such a GPRS might be implemented and inform interventions for obesity prevention remain[73]; and methodological and clinical utility questions have been raised[74] about an equally novel GPRS for coronary artery disease[71]. Nonetheless these GPRS studies call into question any DTC genetic test and personalised nutrition advice around body weight made on a handful of SNPs.

Related to nutrition status, and equally suspect in terms of predictive validity, is personalised nutrition advice from multiple companies claiming to help consumers "maintain healthy levels of vitamins, antioxidants & minerals" on the basis of a handful of genetic variants. In contrast to obesity and type 2 diabetes, to date much fewer loci have been associated with biomarkers of micronutrient status[60]. These explain only a small fraction of variance in micronutrient status. Moreover, not all vitamins and minerals have been studied, and there are no data examining 'response' to intake/supplementation. Perhaps even more relevant for the concept of personalised nutrition beyond the much debated 'missing heritability'[75], is that both micronutrient status and the risk for many common diseases is only partially determined by genetics; with environment playing a critical and often dominant role. Similar to the heterogeneity observed in response to pharmaceutical agents in clinical trials, humans are inherently variable in their responses to food and nutrient/dietary interventions[56,76,77]. Beyond genetics, inter-individual variation in a host of factors (sex, habitual dietary habits, physical activity, epigenetics, gut microbiome) effect an individual's absorption, distribution, metabolism and excretion of dietary compounds and metabolites[78].

Wearables and digital health

In addition to advances in multi-omic technologies, the miniaturization of electronic devices in the last decade in particular has heralded tremendous innovation in, and adoption of, mobile technologies, sensors and wearable devices. Globally, smartphone (considered mobile computing devices) usage increased by 40% between 2016 and 2020, and an estimated 45% of the world's population now owns one[79]. Worldwide revenue for the wearable tech industry was estimated at $23 billion dollars in 2018 and is anticipated to reach $54 billion by 2023[80]. So-called 'wearables' now permit individuals to track a multitude of parameters including diet, physical activity and sleep; and physiological measurements such as heart rate, body temperature, blood pressure, oxygen saturation and glucose levels[81]. Although heartrate monitors for exercise have existed since the early eighties, the first clip-on accelerometer activity tracker, the Fitbit, appeared on the market in 2007. By 2013 Fitbit (and other companies) had released a wristband tracker capable of measuring sleep as well as activity.

Since then there has been a market explosion of DTC wearables and medical devices, along with associated apps, aimed at encouraging individuals to actively participate in their own health/wellness behaviour change or disease management[81,82]. These have included most recently, smartwatches capable of taking an electrocardiogram reading with an accompanying app running an FDA approved algorithm for recognition of atrial fibrillation[83]. By 2015, there were more than 500 different health care-related wearables available facilitating real-time data collection of lifestyle and physiological measurements both by individuals and for research[84,85]. In addition to the application of new technologies for dietary assessment[86], of particular relevance to personalised nutrition and the goal of prevention of diet-related diseases, has been the improvements in wearable devices for continuous glucose monitoring (CGM). In DTC fashion, data may now be released to a user's phone and sensors can now be worn for up to two weeks. This lengthening of sensor life has greatly facilitating recent research efforts using CGM, which have underscored the remarkable high level of variability between people in response to the same meals[76,87].

In a notable study for computationally driven personalised nutrition, Zeevi and coworkers, developed a predictive algorithm for postprandial glycemic response through profiling an 800-person Israeli cohort without diabetes who underwent CGM for 7 days, while recording food intake, activity and sleep in real-time via their mobile devices[76]. The machine learning algorithm integrated gut microbiome data derived from 16S rRNA metagenomics profiling, as well as blood parameters, anthropometrics, dietary intakes, activity, and CGM data profiled over the week in the development cohort and first validated in an independent cohort of 100 individuals. The algorithm's predictions for glycemic responses correlated significantly better to the CGM measured responses than 'carbohydrate counting' (R. 0.71 vs. 0.38) or caloric counting (R. 0.33) models often utilized; a result that has now been replicated in independent American populations[88,89]. Lastly, in a smaller randomized trial in 26 individuals, it was shown that the algorithm could accurately predict 'good' and 'bad' diets. In a one-week crossover design participants had lower glycemic responses and favourable changes in the composition of their gut microbiomes in response to their predicted 'good diet' in comparison to a week on the 'bad diet'.

Although the interpretation of the high interindividual variability in glycemic response observed by Zeevi et al. has been criticized[90], multiple research studies since have also concluded that there is both high intraindividual and interindividual variation in glycemic response to both standardized meals and mixed diets[87,91,92]; with implications for the often debated concepts of glycemic index and glycemic load[93,94]. Notably, the work by Hall and colleagues also applied a data driven approach to CGM defining 'glucotypes' based on how variable the glycemic responses were in aggregate overtime for 57 healthy participants with no diagnosis of diabetes (on screening 5 met

criteria for type 2 diabetes and 14 had prediabetes). They show a relationship between their novel machine learning classification (low, moderate, severe) of glucose variability and clinical measures of aberrant glucose metabolism. Where severe glycemic variability correlated with higher values for fasting glucose, oral glucose tolerance test HbA1c and the steady-state plasma glucose test for insulin resistance. Similar to the work by Zeevi, they also demonstrated tremendous heterogeneity in the glycemic responses to three standardized meals of either bread and peanut butter, a protein bar or cornflakes and milk. While the expected relationship between carbohydrate/fiber content of the meals and severity of glycemic response was observed (cornflakes conspicuously producing a 'severe' response for 80% of participants), for each meal there were high and low responders in terms of blood glucose spikes. The authors show that even among their normoglycemic participants, those classed with a 'severe glucotype' had glycemic responses in prediabetic and diabetic ranges 15% and 2% of the time. However, whether these individuals are at increased risk for developing diabetes or other metabolic diseases requires long-term follow up studies, as does investigation of the utility of CGM for early risk detection.

A critical question for public health is whether or not insights from 'big data' generated from wearables and multi-omic profiling can empower individuals to behavioural change. Two other recent studies, remarkable for their scope of phenotyping and big data analyses orchestrated, suggest that, at least in an intervention setting, changes with health benefits can be motivated[95,96]. The first of these, the Pioneer 100 Wellness Project, was the realization of Leroy Hood's aforementioned vision of P4 medicine[95]. Here, 108 individuals had their whole genomes sequencing and were followed for a 9-month period with daily activity tracking and extensive clinical testing along with analyses of their metabolomes, proteomes, and microbiomes. Significantly, participants also received monthly behavioural coaching on 'actionable possibilities' based on their profiles to improve their individual health via diet, exercise, stress management, dietary supplements, or doctor referral as necessary. Longitudinal improvement in a host of clinical analytes related to nutrition, diabetes, cardiovascular disease and inflammation were observed. The second study, was an extension of Michael Snyder's self-piloted systems approach to 109 individuals at risk for type 2 diabetes.[96]. Participants' genomes were whole exome sequenced and participants were followed prospectively with multi-omic profiling done quarterly for up to 8 years (median, 2.8 years) along with CGM and activity monitoring. Again, unique insights into temporal changes in molecular physiology were made along with 'actionable health discoveries' for participants, and 81% reported some change in their diet and exercise habits.

Conclusions and future directions

The last two decades have brought unprecedented advances in omics, wearables, and digital technologies. Undoubtedly, systems integration of multiple technologies has generated mechanistic

insights and informed the evolution of precision medicine and personalised nutrition. These have prompted the recent launching of the most ambitious precision medicine cohort study to date, the All of Us Research Program, which aims to collect genetic and health data (utilising electronic health records, digital health technology), along with biospecimens for biomarker analyses, from at least one million diverse individuals in the United States[97]. Nonetheless, work to date has been limited to the ground-breaking discovery studies led by a few elite research groups, and significant research and societal challenges yet need to be overcome prior to widespread adoption in clinical and public health settings[98,99]. Considerable data integration and methodological issues in study design must be addressed. In addition to issues around data dimensionality reduction, data storage, handling and sharing, there are are complex challenges regarding study design, analytical assumptions and statistical validation[100]. Prediction modelling is suspect to algorithmic bias, black box issues, confounders and the fundamental problem of causal inference[98].

In addition, pertinent ethical issues involve who can access new technologies, and how commercial companies are storing, using and/or re-mining consumer data. Substantial questions about efficacy in terms of long-term behavioural change and health outcomes remain. Related concerns are those of overdiagnosis in healthy individuals[101], cost-benefit and impacts on health inequalities. Dietary and lifestyle choices are influenced by a broad range of socioeconomic factors including income, education, social networks and the built environment[102]. Tackling diet related disease requires close scrutiny of the social determinants of food environments and population-wide, public health policies aimed at reducing health inequalities[103]. Ultimately, financial investment in the future of precision medicine and digital health must be balanced with limited resources available for public health initiatives.

Acknowledgements

The author would like to dedicate this manuscript to Professor Robert J Cousins who was at the forefront of early applications of functional genomics in the Nutritional Sciences[104], and fostered her early fascination in nutrigenomics. He has remained a source of scientific inspiration and mentorship in the decades since. The author is also grateful to Professor John Blundell for critical reading of the manuscript in its final stages. Lastly, the author would like to thank her students past, present and future, for whom she wrote this manuscript.

Financial Support

Some of the work reviewed here from JBM was made possible through funding from the UK Biotechnology and Biological Sciences Research Council, including a studentship grant (BB/J014451/1 for Dr. Elaina Maldonado) and the project grant (BB/I008195/1). The support of both the University of Surrey and the University of Leeds is also acknowledged.

Conflict of Interest

None.

Authorship

JBM had sole responsibility for all aspects of the preparation of this manuscript.

427 **Table 1.** Terminology

Term	Definition
Stratified medicine	Defines current practice in pharmaceutical medicine of identifying and subgrouping patients for optimal treatment with least toxicity. Subgroups can be based on a combination of disease subtypes, clinical features, demographics, risk profiles, biomarkers or molecular assays.
Precision medicine	Goes beyond stratification to tailoring treatments to individuals based on molecular features of the patient and the disease. Implies use of multi-omics data in assessing molecular features and companion diagnostic/prognostic indicators to predict toxicity and likely responders and non-responders. Preferred term over personalised medicine[21,22].
Personalised medicine	Taken and used by many to mean the same thing as precision medicine. No longer preferred because of its widespread commercial use and concerns it implies unique treatments can be designed for individuals[21].
Systems biology	An interdisciplinary field that combines molecular and computational approaches to study systemic network behaviours and predict the behavior of biological systems (cells, tissues, organisms) as a whole.
Systems medicine	Subfield of systems biology underpinning precision medicine and the integration of clinical and multi-omic data into predictive models.
Systems pharmacology	Subfield of systems biology focused on characterising mechanisms of drug actions, interactions and off-target effects at a systems level. Extends physiologically based pharmacokinetic-pharmacodynamic modelling, incorporating genetic variation and whole-cell metabolism.
Nutrigenomics	In broadest sense the study of any interactions between nutrition and the genome; implies use of high-throughput tools of functional genomics[105]. While often used interchangeably with nutrigenetics, can be differentiated as the study of the effect of nutrients/diet on gene expression and, consequently, the proteome and the metabolome[106,107].
Nutrigenetics	The study of how genetic variation influences differential response to nutrients/diet and risk of nutrition-related disease.
Stratified nutrition	Nutrition advice/intervention given to groups of individuals based on shared characteristics. For example, population-level dietary guidelines are stratified accounting for sex, age, pregnancy/breastfeeding; and dietetic/clinical nutrition tailors on phenotypic and disease information.
Personalised nutrition	The tailoring of nutritional advice/diets to optimize health based on an individual's characteristics. At increasing depths of personalization may include dietary, phenotypic and genotypic information[56]. Commercially infers nutrigenetic profiling.
Precision nutrition	More recent term, used interchangeably with personalised nutrition but implying an in-depth quantitative level of understanding[55] from genetic and digital health profiling (e.g. dietary, physical activity, glucose).

428

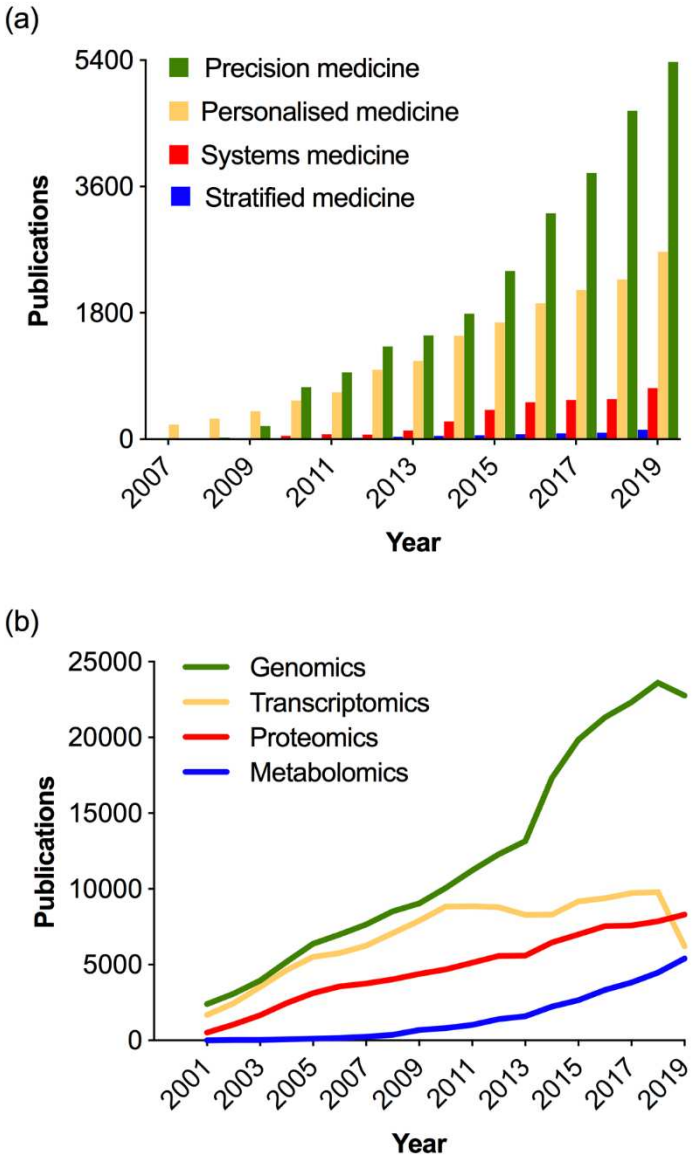

Fig 1. Recent growth in publications in PubMed database using specified terms. (a) Number of publications using adjectives "precision", "personalised", "systems" or "stratified" in conjunction with medicine since 2007. Data were generated by performing a PubMed [All Fields] search with terms searched in quotes e.g "precision medicine". Personalised medicine was searched as: "personalised medicine" OR "personalized medicine". (b) Growth in publications in genomics, transcriptomics, proteomics and metabolomics since 2001. Genomics, proteomics and metabolomics were searched as: "genomics"[MeSH] OR "genomics"[All Fields]. Transcriptomics was searched as: "gene expression profiling"[MeSH] OR "transcriptomics"[All Fields].

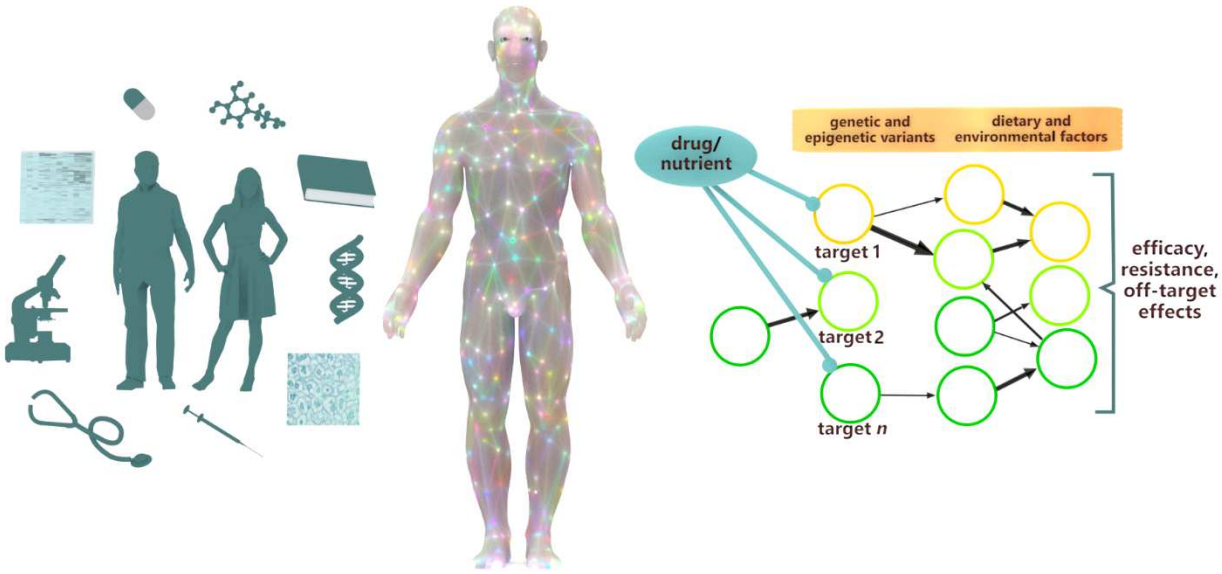

Fig 2. Systems approaches integrate genetic, clinical and 'omic' data into *in silico* models. Simulations aim to understand network dynamics and predict the response to dietary or pharmaceutical intervention accounting for an individual's genetics, lifestyle, life stage, health and/or disease state. Reprinted with permission[47].

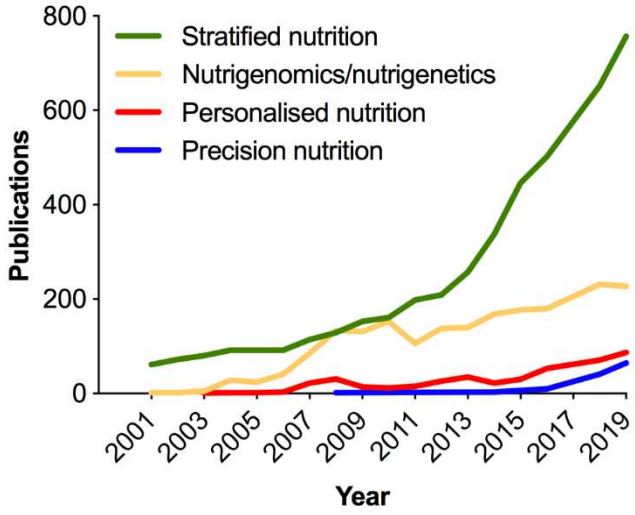

Fig 3. Increase in publications in PubMed database related to nutrigenomics and stratified, personalised, or precision nutrition. In the cases of stratified, personalised and precision nutrition, terms were searched in quotes e.g "precision nutrition"[All fields]. Personalised nutrition was searched as: "personalised nutrition" OR "personalized nutrition". Nutrigenomics/nutrigenetics was searched as: "nutrigenomics"[MeSH] OR "nutrigenomics"[All Fields] OR "nutrigenetics"[All Fields].

Figure Legends

Fig 1. Recent growth in publications in PubMed database using specified terms. (a) Number of publications using adjectives “precision”, “personalised”, “systems” or “stratified” in conjunction with medicine since 2007. Data were generated by performing a PubMed [All Fields] search with terms searched in quotes e.g “precision medicine”. Personalised medicine was searched as: “personalised medicine” OR “personalized medicine”. (b) Growth in publications in genomics, transcriptomics, proteomics and metabolomics since 2001. Genomics, proteomics and metabolomics were searched as: “genomics”[MeSH] OR “genomics”[All Fields]. Transcriptomics was searched as: “gene expression profiling”[MeSH] OR “transcriptomics”[All Fields].

Fig 2. Systems approaches integrate genetic, clinical and ‘omic’ data into *in silico* models. Simulations aim to understand network dynamics and predict the response to dietary or pharmaceutical intervention accounting for an individual’s genetics, lifestyle, life stage, health and/or disease state. Reprinted with permission[48].

Fig 3. Increase in publications in PubMed database related to nutrigenomics and stratified, personalised, or precision nutrition. In the cases of stratified, personalised and precision nutrition, terms were searched in quotes e.g “precision nutrition”[All fields]. Personalised nutrition was searched as: “personalised nutrition” OR “personalized nutrition”. Nutrigenomics/nutrigenetics was searched as: “nutrigenomics”[MeSH] OR "nutrigenomics"[All Fields] OR "nutrigenetics"[All Fields].

References

1. The White House: Office of the Press Secretary (2000) President Clinton announces the completion of the first survey of the entire human genome. Available online: https://clintonwhitehouse3.archives.gov/WH/New/html/20000626.html Accessed on December 30 2019
2. Lander ES, Linton LM, Birren B *et al.* (2001) Initial sequencing and analysis of the human genome. *Nature* **409**, 860-921.
3. Venter JC, Adams MD, Myers EW *et al.* (2001) The sequence of the human genome. *Science* **291**, 1304-1351.
4. Roberts L, Davenport RJ, Pennisi E *et al.* (2001) A history of the Human Genome Project. *Science* **291**, 1195.
5. Collins FS, Morgan M& Patrinos A (2003) The Human Genome Project: lessons from large-scale biology. *Science* **300**, 286-290.
6. Green ED, Watson JD& Collins FS (2015) Human Genome Project: Twenty-five years of big biology. *Nature* **526**, 29-31.
7. Venter JC, Smith HO& Adams MD (2015) The Sequence of the Human Genome. *Clin Chem* **61**, 1207-1208.
8. Wetterstrand KA DNA Sequencing Costs: Data from the NHGRI Genome Sequencing Program (GSP) Available at: www.genome.gov/sequencingcostsdata Accessed [October 14 2019]
9. Mardis ER (2011) A decade's perspective on DNA sequencing technology. *Nature* **470**, 198-203.
10. The International HapMap Consortium (2005) A haplotype map of the human genome. *Nature* **437**, 1299-1320.
11. Abecasis GR, Auton A, Brooks LD *et al.* (2012) An integrated map of genetic variation from 1,092 human genomes. *Nature* **491**, 56-65.
12. Pennisi E (2007) Breakthrough of the year. Human genetic variation. *Science* **318**, 1842-1843.
13. Summerskill W (2008) Paper of the year 2007. *The Lancet* **371**, 370-371.
14. Wellcome Trust Case Control Consortium (2007) Genome-wide association study of 14,000 cases of seven common diseases and 3,000 shared controls. *Nature* **447**, 661-678.
15. Bycroft C, Freeman C, Petkova D *et al.* (2018) The UK Biobank resource with deep phenotyping and genomic data. *Nature* **562**, 203-209.
16. Turnbull C, Scott RH, Thomas E *et al.* (2018) The 100 000 Genomes Project: bringing whole genome sequencing to the NHS. *BMJ* **361**, k1687.
17. Stevens EA& Rodriguez CP (2015) Genomic medicine and targeted therapy for solid tumors. *J Surg Oncol* **111**, 38-42.
18. Prat A, Pineda E, Adamo B *et al.* (2015) Clinical implications of the intrinsic molecular subtypes of breast cancer. *Breast* **24 Suppl 2**, S26-35.
19. Association of the British Pharmaceutical Industry (2014) Stratified medicine in the NHS: An assessment of the current landscape and implementation challenges for non-cancer applications. Available online: https://www.abpi.org.uk/publications/stratified-medicine-in-the-nhs/ Accessed on October 14 2019.
20. Erikainen S& Chan S (2019) Contested futures: envisioning "Personalized," "Stratified," and "Precision" medicine. *New Genet Soc* **38**, 308-330.
21. National Research Council (US) Committee on A Framework for Developing a New Taxonomy of Disease (2011) *Toward Precision Medicine: Building a Knowledge Network for Biomedical Research and a New Taxonomy of Disease.* Washington (DC): National Academies Press (US) National Academy of Sciences.
22. Yates LR, Seoane J, Le Tourneau C *et al.* (2018) The European Society for Medical Oncology (ESMO) Precision Medicine Glossary. *Ann Oncol* **29**, 30-35.
23. Lederberg J& McCray AT (2001) 'Ome Sweet 'Omics--A Genealogical Treasury of Words. *Scientist* **15[7]**, 8.

24. Dettmer K, Aronov PA& Hammock BD (2007) Mass spectrometry-based metabolomics. *Mass Spectrom Rev* **26**, 51-78.
25. Cousins RJ, Blanchard RK, Popp MP *et al.* (2003) A global view of the selectivity of zinc deprivation and excess on genes expressed in human THP-1 mononuclear cells. *Proc Natl Acad Sci U S A* **100**, 6952-6957.
26. Moore JB, Blanchard RK& Cousins RJ (2003) Dietary zinc modulates gene expression in murine thymus: results from a comprehensive differential display screening. *Proc Natl Acad Sci U S A* **100**, 3883-3888.
27. Cousins RJ, Blanchard RK, Moore JB *et al.* (2003) Regulation of zinc metabolism and genomic outcomes. *J Nutr* **133**, 1521s-1526s.
28. Abbott A (2001) Workshop prepares ground for human proteome project. *Nature* **413**, 763.
29. Hanash S& Celis JE (2002) The Human Proteome Organization: a mission to advance proteome knowledge. *Mol Cell Proteomics* **1**, 413-414.
30. Wishart DS (2007) Proteomics and the human metabolome project. *Expert Rev Proteomics* **4**, 333-335.
31. HUPO--the Human Proteome organization (2010) A gene-centric human proteome project. *Mol Cell Proteomics* **9**, 427-429.
32. Omenn GS, Lane L, Overall CM *et al.* (2019) Progress on Identifying and Characterizing the Human Proteome: 2019 Metrics from the HUPO Human Proteome Project. *J Proteome Res* **18**, 4098-4107.
33. Stern CD (2019) The 'Omics Revolution: How an Obsession with Compiling Lists Is Threatening the Ancient Art of Experimental Design. *Bioessays* **41**, e1900168.
34. Spanos C, Maldonado EM, Fisher CP *et al.* (2018) Proteomic identification and characterization of hepatic glyoxalase 1 dysregulation in non-alcoholic fatty liver disease. *Proteome Sci* **16**, 4.
35. Rosen R (1968) Systems Theory and Biology. Proceedings of the 3rd Systems Symposium, Cleveland, Ohio, Oct. 1966. M. D. Mesarović, Ed. Springer-Verlag, New York, 1968. xii + 403 pp., illus. $16. *Science* **161**, 34-35.
36. Ideker T, Galitski T& Hood L (2001) A new approach to decoding life: systems biology. *Annu Rev Genomics Hum Genet* **2**, 343-372.
37. Kitano H (2002) Systems biology: a brief overview. *Science* **295**, 1662-1664.
38. Moore JB& Weeks ME (2011) Proteomics and systems biology: current and future applications in the nutritional sciences. *Adv Nutr* **2**, 355-364.
39. Fisher CP, Kierzek AM, Plant NJ *et al.* (2014) Systems biology approaches for studying the pathogenesis of non-alcoholic fatty liver disease. *World J Gastroenterol* **20**, 15070-15078.
40. Kitano H (2002) Computational systems biology. *Nature* **420**, 206-210.
41. Agrawal A (1999) New institute to study systems biology. *Nat Biotechnol* **17**, 743-744.
42. Hood LE (2018) Lessons Learned as President of the Institute for Systems Biology (2000-2018). *Genom Proteom Bioinf* **16**, 1-9.
43. Hood L, Heath JR, Phelps ME *et al.* (2004) Systems biology and new technologies enable predictive and preventative medicine. *Science* **306**, 640-643.
44. Hood L (2008) A personal journey of discovery: developing technology and changing biology. *Annu Rev Anal Chem* **1**, 1-43.
45. Desiere F (2004) Towards a systems biology understanding of human health: interplay between genotype, environment and nutrition. *Biotechnol Annu Rev* **10**, 51-84.
46. van Ommen B& Stierum R (2002) Nutrigenomics: exploiting systems biology in the nutrition and health arena. *Curr Opin Biotechnol* **13**, 517-521.
47. Stephanou A, Fanchon E, Innominato PF *et al.* (2018) Systems Biology, Systems Medicine, Systems Pharmacology: The What and The Why. *Acta Biotheor*.
48. Moore JB (2019) From sugar to liver fat and public health: systems biology driven studies in understanding non-alcoholic fatty liver disease pathogenesis. *Proc Nutr Soc* **78**, 290-304.

576 49. Maldonado EM, Leoncikas V, Fisher CP *et al.* (2017) Integration of Genome Scale Metabolic
577 Networks and gene regulation of metabolic enzymes with Physiologically Based
578 Pharmacokinetics. *CPT: Pharmacometrics Sys Pharmacol*.
579 50. Maldonado EM, Fisher CP, Mazzatti DJ *et al.* (2018) Multi-scale, whole-system models of liver
580 metabolic adaptation to fat and sugar in non-alcoholic fatty liver disease. *NPJ Syst Biol Appl*
581 **4**, 33.
582 51. Chen R, Mias GI, Li-Pook-Than J *et al.* (2012) Personal omics profiling reveals dynamic
583 molecular and medical phenotypes. *Cell* **148**, 1293-1307.
584 52. Schmidt S (2019) Congratulations to Michael Snyder for receiving the 2019 George W. Beadle
585 Award! *Genes to Genomes*. Available online: http://genestogenomes.org/snyder-beadle/
586 Accessed January 22 2020
587 53. Karczewski KJ& Snyder MP (2018) Integrative omics for health and disease. *Nat Rev Genet* **19**,
588 299-310.
589 54. Gibney MJ& Walsh MC (2013) The future direction of personalised nutrition: my diet, my
590 phenotype, my genes. *Proc Nutr Soc* **72**, 219-225.
591 55. Ordovas JM, Ferguson LR, Tai ES *et al.* (2018) Personalised nutrition and health. *BMJ* **361**,
592 bmj.k2173.
593 56. Gibney ER (2019) Personalised nutrition - phenotypic and genetic variation in response to dietary
594 intervention. *Proc Nutr Soc*, 1-10.
595 57. Muller M& Kersten S (2003) Nutrigenomics: goals and strategies. *Nat Rev Genet* **4**, 315-322.
596 58. Trayhurn P (2003) Nutritional genomics - "Nutrigenomics". *Br J Nutr* **89**, 1-2.
597 59. Torkamani A, Wineinger NE& Topol EJ (2018) The personal and clinical utility of polygenic risk
598 scores. *Nat Rev Genet* **19**, 581-590.
599 60. Dib MJ, Elliott R& Ahmadi KR (2019) A critical evaluation of results from genome-wide
600 association studies of micronutrient status and their utility in the practice of precision
601 nutrition. *Br J Nutr* **122**, 121-130.
602 61. Phillips AM (2016) 'Only a click away - DTC genetics for ancestry, health, love...and more: A
603 view of the business and regulatory landscape'. *Appl Transl Genom* **8**, 16-22.
604 62. Khan R& Mittelman D (2018) Consumer genomics will change your life, whether you get tested
605 or not. *Genome Biol* **19**, 120.
606 63. Blell M& Hunter MA (2019) Direct-to-Consumer Genetic Testing's Red Herring: "Genetic
607 Ancestry" and Personalized Medicine. *Front Med* **6**, 48.
608 64. Aldous P (2019) 10 Years Ago, DNA Tests Were The Future Of Medicine. Now They're A Social
609 Network — And A Data Privacy Mess. Available online:
610 https://www.buzzfeednews.com/article/peteraldhous/10-years-ago-dna-tests-were-the-
611 future-of-medicine-now Accesed on January 11 2020
612 65. Saey TH (2018) What consumer DNA data can and can't tell you about your risk for certain
613 diseases. *Science News*. Available at: https://www.sciencenews.org/article/health-dna-
614 genetic-testing-disease Accessed January 20 2020.
615 66. Tandy-Connor S, Guiltinan J, Krempely K *et al.* (2018) False-positive results released by direct-
616 to-consumer genetic tests highlight the importance of clinical confirmation testing for
617 appropriate patient care. *Genet Med* **20**, 1515-1521.
618 67. Wynn J& Chung WK (2017) 23andMe Paves the Way for Direct-to-Consumer Genetic Health
619 Risk Tests of Limited Clinical Utility. *Ann Intern Med* **167**, 125-126.
620 68. Kalokairinou L, Howard HC, Slokenberga S *et al.* (2018) Legislation of direct-to-consumer
621 genetic testing in Europe: a fragmented regulatory landscape. *J Community Genet* **9**, 117-132.
622 69. Locke AE, Kahali B, Berndt SI *et al.* (2015) Genetic studies of body mass index yield new insights
623 for obesity biology. *Nature* **518**, 197-206.
624 70. Fuchsberger C, Flannick J, Teslovich TM *et al.* (2016) The genetic architecture of type 2 diabetes.
625 *Nature* **536**, 41-47.

71. Khera AV, Chaffin M, Aragam KG *et al.* (2018) Genome-wide polygenic scores for common diseases identify individuals with risk equivalent to monogenic mutations. *Nat Genet* **50**, 1219-1224.
72. Khera AV, Chaffin M, Wade KH *et al.* (2019) Polygenic Prediction of Weight and Obesity Trajectories from Birth to Adulthood. *Cell* **177**, 587-596.e589.
73. Torkamani A& Topol E (2019) Polygenic Risk Scores Expand to Obesity. *Cell* **177**, 518-520.
74. Curtis D (2019) Clinical relevance of genome-wide polygenic score may be less than claimed. *Ann Hum Genet* **83**, 274-277.
75. Genin E (2020) Missing heritability of complex diseases: case solved? *Hum Genet* **139**, 103-113.
76. Zeevi D, Korem T, Zmora N *et al.* (2015) Personalized Nutrition by Prediction of Glycemic Responses. *Cell* **163**, 1079-1094.
77. Drew JE (2019) Challenges of the heterogeneous nutrition response: interpreting the group mean. *Proc Nutr Soc*, 1-10.
78. de Roos B& Brennan L (2017) Personalised Interventions-A Precision Approach for the Next Generation of Dietary Intervention Studies. *Nutrients* **9**.
79. Turner A (2020) How many smartphones are in the world? Available online: https://www.bankmycell.com/blog/how-many-phones-are-in-the-world Accessed January 23 2020.
80. Globaldata (2019) Wearable Tech – Thematic Research. Available at: https://store.globaldata.com/report/gdtmt-tr-s219--wearable-tech-thematic-research/ Accessed January 20 2020
81. Yetisen AK, Martinez-Hurtado JL, Unal B *et al.* (2018) Wearables in Medicine. *Adv Mater*, e1706910.
82. Dias D& Paulo Silva Cunha J (2018) Wearable Health Devices-Vital Sign Monitoring, Systems and Technologies. *Sensors* **18**.
83. Isakadze N& Martin SS (2019) How useful is the smartwatch ECG? *Trends Cardiovasc Med*.
84. Li X, Dunn J, Salins D *et al.* (2017) Digital Health: Tracking Physiomes and Activity Using Wearable Biosensors Reveals Useful Health-Related Information. *PLoS Biol* **15**, e2001402.
85. Witt D, Kellogg R, Snyder M *et al.* (2019) Windows Into Human Health Through Wearables Data Analytics. *Curr Opin Biomed Eng* **9**, 28-46.
86. Forster H, Walsh MC, Gibney MJ *et al.* (2016) Personalised nutrition: the role of new dietary assessment methods. *Proc Nutr Soc* **75**, 96-105.
87. Hall H, Perelman D, Breschi A *et al.* (2018) Glucotypes reveal new patterns of glucose dysregulation. *PLoS Biol* **16**, e2005143.
88. Mendes-Soares H, Raveh-Sadka T, Azulay S *et al.* (2019) Model of personalized postprandial glycemic response to food developed for an Israeli cohort predicts responses in Midwestern American individuals. *Am J Clin Nutr* **110**, 63-75.
89. Mendes-Soares H, Raveh-Sadka T, Azulay S *et al.* (2019) Assessment of a Personalized Approach to Predicting Postprandial Glycemic Responses to Food Among Individuals Without Diabetes. *JAMA Netw Open* **2**, e188102.
90. Wolever TM (2016) Personalized nutrition by prediction of glycaemic responses: fact or fantasy? *Eur J Clin Nutr* **70**, 411-413.
91. Matthan NR, Ausman LM, Meng H *et al.* (2016) Estimating the reliability of glycemic index values and potential sources of methodological and biological variability. *Am J Clin Nutr* **104**, 1004-1013.
92. Meng H, Matthan NR, Ausman LM *et al.* (2017) Effect of macronutrients and fiber on postprandial glycemic responses and meal glycemic index and glycemic load value determinations. *Am J Clin Nutr* **105**, 842-853.
93. Meng H, Matthan NR& Lichtenstein AH (2018) Reply to Brighenti F et al. *Am J Clin Nutr* **107**, 846-847.
94. Vega-Lopez S, Venn BJ& Slavin JL (2018) Relevance of the Glycemic Index and Glycemic Load for Body Weight, Diabetes, and Cardiovascular Disease. *Nutrients* **10**.

95. Price ND, Magis AT, Earls JC *et al.* (2017) A wellness study of 108 individuals using personal, dense, dynamic data clouds. *Nat Biotechnol* **35**, 747-756.
96. Schussler-Fiorenza Rose SM, Contrepois K, Moneghetti KJ *et al.* (2019) A longitudinal big data approach for precision health. *Nat Med* **25**, 792-804.
97. The All of Us Research Program Investigators (2019) The "All of Us" Research Program. *NEJM* **381**, 668-676.
98. Prosperi M, Min JS, Bian J *et al.* (2018) Big data hurdles in precision medicine and precision public health. *BMC Med Inform Decis Mak* **18**, 139.
99. Wang DD& Hu FB (2018) Precision nutrition for prevention and management of type 2 diabetes. *Lancet Diabetes Endocrinol* **6**, 416-426.
100. Misra BB, Langefeld CD, Olivier M *et al.* (2018) Integrated Omics: Tools, Advances, and Future Approaches. *J Mol Endocrinol*.
101. Vogt H, Green S, Ekstrom CT *et al.* (2019) How precision medicine and screening with big data could increase overdiagnosis. *BMJ* **366**, l5270.
102. Moore JB& Boesch C (2019) Getting energy balance right in an obesogenic world. *Proc Nutr Soc* **78**, 259-261.
103. Moore JB& Fielding BA (2019) Taxing confectionery, biscuits, and cakes to control obesity. *BMJ* **366**, l5298.
104. Cousins RJ (2016) Driving Along the Zinc Road. *Annu Rev Nutr* **36**, 1-15.
105. Mathers JC (2017) Nutrigenomics in the modern era. *Proc Nutr Soc* **76**, 265-275.
106. Mutch DM, Wahli W& Williamson G (2005) Nutrigenomics and nutrigenetics: the emerging faces of nutrition. *FASEB J* **19**, 1602-1616.
107. Ferguson LR, De Caterina R, Gorman U *et al.* (2016) Guide and Position of the International Society of Nutrigenetics/Nutrigenomics on Personalised Nutrition: Part 1 - Fields of Precision Nutrition. *J Nutrigenet Nutrigenomics* **9**, 12-27.