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Towards utilization of the human genome and microbiome for personalized nutrition

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Generalized dietary and lifestyle guidelines have been formulated and published for decades now from a variety of relevant agencies in an attempt to guide people towards healthy choices. As the pandemic rise in metabolic diseases continues to increase, it has become clear that the one-fit-for-all diet approach does not work and that there is a significant variation in inter-individual responses to diet and lifestyle interventions. Recent technological advances have given an unprecedented insight into the sources of this variation, pointing towards our genome and microbiome as potentially and previously under-explored culprits contributing to individually unique dietary responses. Variations in our genome influence the bioavailability and metabolism of nutrients between individuals, while inter-individual compositional variation of commensal gut microbiota leads to different microbe functional potential, metabolite production and metabolism modulation. Quantifying and incorporating these factors into a comprehensive personalized nutrition approach may enable practitioners to rationally incorporate individual nutritional recommendations in combating the metabolic syndrome pandemic.

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Introduction

The past century has witnessed our modern 'developed' societies adopting dramatic changes in lifestyle and dietary habits that are characterized by limited physical activity in conjunction with over nutrition with foods high in fat, processed meat, sugars, salt and refined grains while being low in fruits and vegetables [1]. In parallel, the same societies have developed a global pandemic consisting of obesity, type 2 diabetes [2], non-alcoholic fatty liver disease and their many complications, collectively accounting for the morbidity and mortality of billions of individuals worldwide. In parallel, concerted efforts have focused on determining the components constituting a healthy and beneficial diet, and on educating the public on healthy dietary practices along generalized lines. Of note is that the US government has been publishing dietary guidelines and advice for over a century, with no less than 900 publications (guidance and educational) during that time (U.S. Department of Agriculture; URL: http://fnic.nal.usda.gov/dietary-guidance/myplate-and-historical-food-pyramid-resources). Easy to comprehend tools such as the Food Guide Pyramid and more recent MyPlate act as beacons of daily nutritional recommendation.

Despite the enormous implications of the metabolic syndrome pandemic on economy and health and widespread efforts to understand its causes and to develop effective interventions, it has not been efficiently controlled to date [2]. One possible cause of this failure relates to our poor understanding of nutritional causes contributing to the prevalence of obesity, diabetes, NAFLD and their common complications. Commonly, in the last three decades nutritional guidelines have attempted to address the epidemic by prescribing population-wide recommendations for 'healthy' versus 'unhealthy' foods [3]. These often failed, as seen by the global increase in the prevalence of obesity, a major risk factor of metabolic disease, with over 300 million adults worldwide estimated to be suffering of morbid obesity [4]. Furthermore, there has been a significant rise in the number of individuals with diabetes worldwide, from 108 million adults in 1980 to 422 million in 2014 [5]. This astounding rise in the prevalence of closely associated diseases constituting the 'metabolic syndrome' carries significant global medical and economic consequences [6].

The disappointing efficacy of dietary interventions to obesity and its complications may stem from lack of regard to inter-individual variabilities in dietary responses [7]. Indeed, a recent realization is that some of the

metabolic responses to diet differ from one individual to another, as exemplified by cholesterol metabolism and postprandial hyperglycemia, risk factors for cardiovascular disease (CVD) and type 2 diabetes [8,9], and by recent studies demonstrating that not all individuals respond in the same way to changes in lifestyle and this certainly applies to dietary changes [10,11]. Fundamental factors suggested to determine our individualized response to foods, and the biological implications of their consumption include the human genome [12], our epigenome [13], our microbiome [14••], and inter-personal variations in a variety of environmental exposures and life style factors [15]. Recent technological advances have given us an unprecedented insight into this interpersonal variability, in terms of the ability to accurately quantify genetic background and microbiome community structure, both of which modulate metabolic activity and form complex and poorly understood interactions with the components of our diet, modulating their metabolism and utilization. The genetic contribution towards disease risk has been known and studied for decades, while the commensal microbiota contribution has been ignored until recently and is being increasingly appreciated to contribute to individualized responses to food, and even link a variety of environmental factors to host physiology [16]. The inclusion of the microbiome as a necessary element explaining personal uniqueness has led to a paradigm shift in terms of our understanding of inter-individual variability and how it influences responses to environmental factors (such as diet). We are now in an era where we finally have the technologies that allow us to devise data-driven approaches to personalized diet interventions that take into account variation at the level of our genome and microbiome.

In this mini-review we discuss the current state of play with regards to personalized nutrition and highlight the main factors modulating individual responses to nutritional interventions.

Source of human variation modulating responses to diet

The main sources of human variation that modulate responses to diet include the genome and microbiome. While both may be used for a person-specific diagnosis and stratification of dietary responses and recommendations, the microbiome is also amenable to modulation by approaches such as pro-biotics, pre-biotics, antibiotic treatment, and recently post-biotic intervention, thereby representing an exciting new potential for preventive and interventional modification of personalized dietary responses.

Human genome
Successful full genome characterization by the Human Genome project [17] was followed by additional large collaborative efforts to characterize human genetic

variation, including the International HapMap consortium [18], the Human Variome Project [19] and the 1000 Genomes Project Consortium [20]. Large scale genetic variation information has facilitated population based studies such as genome-wide association studies (GWAS) to determine genetic influences on disease risk [21]. It is now accepted that genetic variations influence the bioavailability and metabolism of nutrients between individuals but also between ethnic groups. This notion has revolutionized the field of nutritional sciences and has paved the way for personalized nutrition approaches.

Propagated by rampant advances in genomics technologies, an unprecedented volume of data on genetic variations throughout the genome has been acquired and characterized [19,20]. Epidemiological nutritional studies have suggested an association between diet and chronic diseases, revolutionizing the field of nutritional research by incorporating individual genetic information (Figure 1) and giving rise to a new area of study, namely nutrigenomics that is the study of how our genes influence dietary intake. Understanding these underlying interactions can translate into individual specific nutritional interventions based on their genetic characteristics and result in the identification of positive and negative responders or those that do not respond at all to diet interventions.

The neutrigenomics approach was best exemplified in rare monogenic disorders such as phenylketonuria (PKU). PKU patients have mutations in the *PAH* gene (encodes the enzyme that converts phenylalanine to tyrosine) resulting in an accumulation of phenylalanine and its toxic metabolites, leading to mental retardation and delayed development. Nutritional intervention (restricted in phenylalanine and supplemented in tyrosine) is currently regarded as the only available treatment, which, when properly followed, prevents the deleterious life-risking complications of PKU. Another example of neutrigenomics interventional approaches in a monogenic disease can be seen in the case of Galactosemia, a metabolic disease resulting in the inability to metabolism galactose. It represents a group of three metabolic diseases (Type I, Type II and Type III galactosemia caused by mutations in the genes GALT, GALK1, GALE respectively) with deficiencies in enzymes from the Leloir pathway of galactose catabolism [22]. Currently, the only form of effective treatment for galactosemia is galactose restriction.

Despite the efficiency exemplified in the above monogenic disorders in using genomics for dietary recommendations, adaptation of genomic diagnostics and stratification tools in tailoring diets for the prevention and treatment of chronic polygenic complex diseases such as cancer, CVD, obesity and type 2 diabetes has proven much more complicated and of limited value. Examples

Figure 1
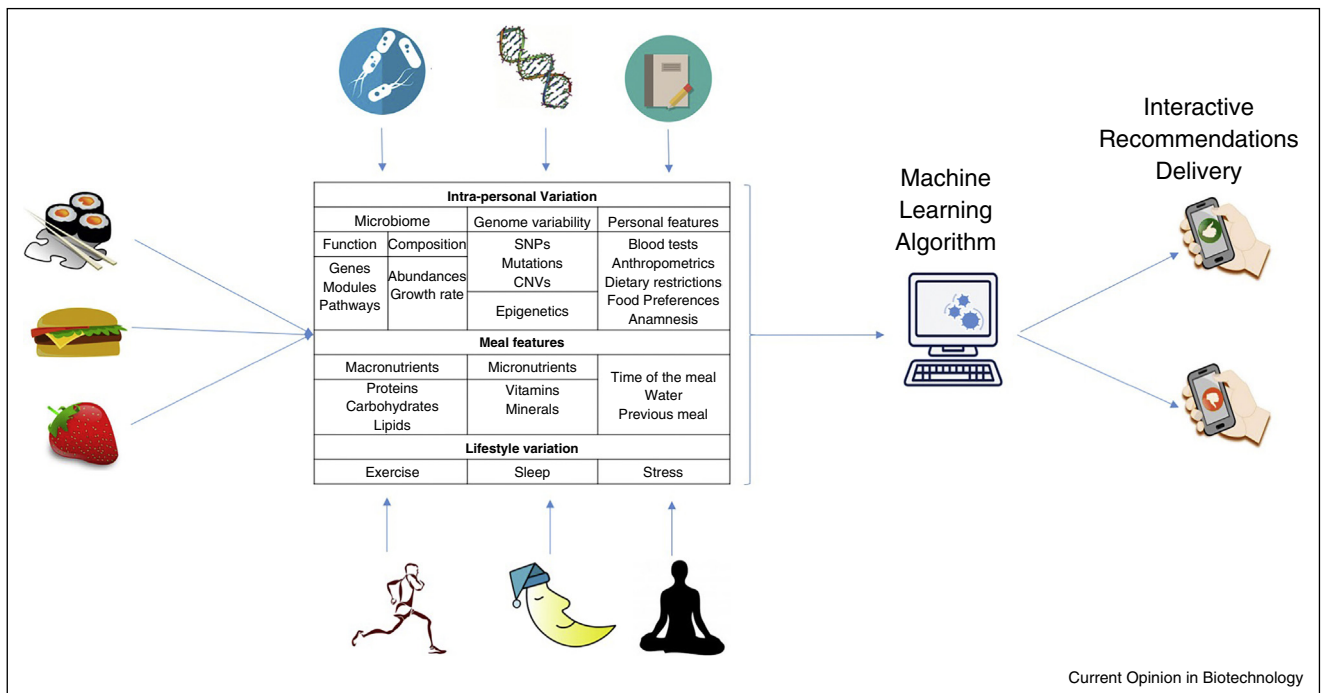
Rationally designed personalized dietary approaches determine the effects of numerous parameters on diet response (e.g. microbiome composition, genome variability, personal lifestyle, medical metadata). Machine learning algorithms utilize these comprehensive data sets to deliver dietary recommendations.

of genomic contribution to dietary planning in the context of multi-factorial diseases are sparse and include enhanced benefits of Mediterranean diet in preventing breast cancer risks in patients carrying SNPs in GST1 (glutathione S-transferase 1) and Nat2 (N-acetyltransferase 2) of the xenobiotic metabolism pathway [23]. Another example relates to individuals with the APOA2 CC genotype who are found to feature a greater susceptibility to increased BMI and obesity upon consumption of a diet that is abundant in high-saturated fat [24]. These individuals with the APOA2 CC genotype may therefore benefit from following a diet regiment with reduced saturated fat intake. Furthermore, transcription factor 7-like 2 gene (*TCF7L2*) polymorphism rs7903146 (C>T) has been associated with type 2 diabetes [24]. A randomized trial following 7018 participants found Mediterranean diet to decrease fasting glucose and lipids and reduced the incidence of stroke in TT homozygote individuals [25].

However, the many other claimed nutrigenomics approaches of effectively influencing dietary choices among the general population at risk have mostly proven to be non-evidence based. For example, Pavlides *et al.* [26••] show this in a meta-analysis focusing on 38 genes that are included in commercially available nutrigenomics tests and are commonly analyzed. They found

inconsistencies and conflicting results with regards to gene–diet associations, as well as a lack of significant association for these 38 genes [26••]. Apart from indicating the need for a solid scientific basis in the implementation of neutrigenomics, it also highlights the fact that these are still early days and the field is in need of further development. Furthermore, a meta-analysis of thirteen observational studies reporting gene–macronutrient interactions and Type 2 diabetes [27••] showed that none of the eight unique interactions reported to be significant between macronutrients and genetic variants in or near *TCF7L2*, *GIPR*, *CAV2* and *PEPD* were replicated.

Furthermore, the added value of providing elaborate genetic information to individuals undergoing personalized nutrition (PN) advice should be considered. It is indicative that the largest intervention study to date comparing the effect of PN on health related dietary behavior showed the advantage of PN advice based on individual baseline diet and lifestyle over a conventional approach. However, no additional advantage was found by basing PN advice on individual baseline diet and phenotype (anthropometry and medical metadata), or individual baseline diet plus phenotype plus genotype (five diet responsive genetic variants) [28]. It should be noted however that the baseline diets, lifestyle and phenotypes were self-reported by participants,

potentially introducing a bias and in turn reducing the benefits of including genetic information.

Gut microbiome

A recently appreciated factor that greatly contributes to our understanding of inter-individual human variability is the enormous micro-organismal ecosystem and its gene pool that are integrated into all mucosal surfaces of the human body, collectively termed the microbiome. The most heavily colonized and studied ecosystem, the gut microbiome, contains a heavy population of bacteria of equal numbers as our own cells [29] and as many as 100 times more genes as the human genome, and is considered to be our 'second genome' [30]. In addition to bacteria, the gut microbiome contains a plethora of viruses [31], achaea [32], fungi [33] and parasites [34], collectively forming a large ecosystem that is increasingly recognized to impact multiple facets of human physiology [35]. Among others, our microbiome modulates our metabolism and disease risk [36]. The inter-individual microbiota community structure of healthy individuals differs significantly in colonized sites such as gut and skin [37–39]. Furthermore, inter-individual variation in gene content of microbiota species leads to differences in their functional potential [40].

Commensal microbionts have a deeply symbiotic relationship with their human host, providing it with many essential functions [41]. It is now established that microbiota, along with other important factors such as lifestyle and genetics, can modulate responses to diet. Changes in diet can modulate host physiology and disease through commensal microbiota. For example, elevated levels of Trimethylamine-N-oxide (TMAO) and other choline metabolites are associated with greater risks of adverse cardiovascular events and are dependent on gut microbiome metabolism [42]. Plasma levels of TMAO in patients were significantly suppressed after the intake of antibiotics and reappeared after cessation of antibiotics [42]. The intra-personal difference in the circulation of TMAO when consuming TMAO precursors is a function of gut microbiome, with people who showed greater TMAO response having the higher ratio of *Firmicutes* to *Bacteroidetes* [43].

Another example is of flavonoids, polyphenolic compounds found in numerous dietary components including vegetables and fruits. Several subclasses of flavonoids have been suggested to play a role in human physiology affecting for example cardiometabolic health as well as cognitive function [44]. A large amount of ingested flavonoids reach the colon and undergo hydrolysis and fermentation by commensal microbiota. A high level of variability in flavonoid bioconversion occurs as a result of variability in microbiome composition with some individuals having a greater ability to convert flavonoids [45] that

can result in the production of metabolites with greater biological activity.

In addition to the above examples demonstrating how the microbiome responds to diet and utilizes dietary compounds in its interactions with the host, diet is also a crucial component in shaping the microbial environment [46]. Following some types of dietary interventions, the microbiome may undergo changes in less than a week, and these changes occur at both taxonomic and bacterial gene expression levels [47]. Importantly, community changes imposed by diet can be predicted, with important ramifications on the prospect of dietary interventions [48•]. It is however relevant to point out that although dramatic dietary alterations indeed impact the microbiome structure, more subtle changes may not [49], demonstrating potential microbiome resilience to some less dramatic dietary changes, as indicated by Korem *et al.* [48•]. Furthermore, changes conferred to the microbiome structure can be direct, and be mediated through diet composition, for example high protein and animal fat as opposed to carbohydrates that can each drive the abundance of particular bacteria such as *Bacteroides* and *Prevotella* respectively [50]. Changes conferred can also be indirect via microbiota-associated metabolites innate immune modulation, whereby microbiota metabolites modulate NLRP6 inflammasome signaling and the resulting microbiome-host interactions can influence community stability [51].

Towards individualized dietary approaches

Moving towards rationally designing personalized dietary approaches must take into account the intricacies of the microbiome and its effects on human physiology, as well as details on person specific life style and medical metadata. Exemplifying the use of personalized nutritional intervention to lower postprandial glycemic response, Zeevi *et al.* [14••] developed a machine-learning algorithm integrating numerous clinical blood parameters and gut microbiota data to accurately predict postprandial blood glucose responses to meals on a personal level. Diet intervention based on these predictions proved to be successful in lowering postprandial responses [14••]. The benefits of improved glucose metabolism through consumption of barley kernel-based bread display substantial inter-individual variability with responders having a gut microbiota enriched in *Prevotella copri* that may be contributing by potentially promoting glucose storage [52]. The effects of eating traditionally prepared artisanal sourdough bread (coveted for its health benefits) compared to industrially made white bread, were found to be highly personal to each type of bread [49]. Interestingly, machine-learning algorithms predicted the type of bread inducing a lower glycemic response in each person based on gut microbiome compositional data [49].

In a further display of inter individual variation through gut microbiome involvement, dysbiosis resulting by the intake of non-caloric artificial sweeteners (NAS) can lead to induction of glucose intolerance. The response of the individuals to the consumption of NAS is highly variable and gut microbial composition related [53•]. At a time of obesity reaching pandemic proportions and diet interventions to reduce weight are on the rise but generally fail in the long run, in another recent study we showed that the microbiome is implicated in what is termed the 'yo-yo' effect, defined as accumulation of excessive weight gain when undergoing weight gain-and-loss cycles [54•]. It was found that the microbiome of normal weight mice with a history of obesity have a microbiome composition different to that of normal mice (without part obesity), that drives the 'yo-yo' effect. Furthermore, transferring the microbiome of ex-obese mice to germ free (GF) normal weight mice results in excessive weight gain and other unfavorable metabolic syndrome effects when given a high fat diet (HFD). The weight gain of the mice was predicted with high accuracy using only microbial taxa abundances and the top ranked bacteria in predicting weight gain are bacteria capable of breaking flavanoids and Lactobacillus. Furthermore, the mechanism underlying the yo-yo effect is that the energy expenditure of ex-obese mice is lower compared to normal mice when both are fed a HFD, and when supplementing ex-obese mice with Apigenin or Naringenin (plant derived substances belonging to the Flavanoid family), the energy expenditure increases and the 'yo-yo' effect is gone [54•]. Another study discovered a positive feedback loop between gut microbiota and the central nervous system, that promotes hyperphagia and increased energy storage as fat [55]. It was shown that acetate production increases due to a gut microbiota–nutrient interaction in HFD-fed rodents, which in-turn results in parasympathetic nervous system activation and increased ghrelin (the hormone which regulates appetite) and glucose stimulated insulin secretion. Collectively, these studies demonstrate the capacity of massive quantification of person-specific data in contributing to a heightened capability to utilize computational platforms in predicting clinical outcomes.

Conclusion

As in the emerging field of personalized medicine, there are increasing efforts to go beyond the one-fit-for-all diet approaches [3]. Driven by technological advances, our insights into human variation (with all that it encompasses) and its effect on disease risk are steadily increasing. Our inherited genome and our microbial 'second genome' both intricately modulate our response to diet; this has been studied and established. There is now a need for developing new tools that will allow using the whole potential of individual microbiome and genetic fingerprints for the benefit of PN. This is no easy feat and requires new approaches in analysis of the ever expanding data being accumulated. The instruments from the emerging field of machine learning and big data were successfully implemented in a series of studies [49,54•,55,56,57], and with more data available the proper utilization of information will become a crucial point (Figure 1). Public acceptance of genetic testing and microbiome characterization towards implementing PN in disease prevention is a predominant factor along with user participation and involvement, as well as their nutrient environment that all play an important role since diet compliance is crucial [58]. Moreover, the long term efficacy of PN and its advantages over customary population based dietary recommendations in preventing, ameliorating and treating metabolic syndrome-associated disorders remain to be determined. Of note, smartphones are becoming a universal accessory with the number of smartphone users estimated to reach 2.5 billion by 2018 (Statistica; URL: https://www.statista.com/statistics/330695/number-of-smartphone-users-worldwide/) and can be utilized as a tool in the implementation of PN regiments through the use of interactive diet related applications for monitoring nutrient consumption (Figure 1) [59,60]. These can aid in improving long-term compliance, considered by many in the field to co-constitute the biggest hurdle in integrating 'healthier' dietary habits in large populations. Another important challenge, as a more refined understanding of how variability influences disease risk is achieved, relates to ethical issues concerning the safeguarding of delicate individual-specific information as well as who can access this data and for what reason. With these limitations and challenges notwithstanding, integrating 'big data' including genomic and microbiome data into personalized nutrition and personalized medicine constitutes one of the most exciting and promising approaches in tackling common human metabolic disorders.

Conflict of interest statement

Eran Elinav & Eran Segal are payed consultants to Daytwo.

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