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Nutrigenomics 2.0: The Need for Ongoing and *Independent* Evaluation and Synthesis of Commercial Nutrigenomics Tests' Scientific Knowledge Base for Responsible Innovation

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ABSTRACT

Nutrigenomics is an important strand of precision medicine that examines the bidirectional interactions of the genome and nutritional exposures, and attendant health and disease outcomes. This perspectives article presents the new concept of "Nutrigenomics 2.0," so as to cultivate and catalyse the next generation research and funding priorities for responsible and sustainable knowledge-based innovations. We further contextualize our recent study of the 38 genes included in commercially available nutrigenomics tests, and offer additional context in relation to the 2014 American Academy of Nutrition and Dietetics position. Finally, we make a call in the best interest of the nutrigenomics science community, governments, global society, and commercial nutrigenomics test providers that new evidence evaluation and synthesis platforms are created concerning nutrigenomics tests before they become commercially available. The proposed assessment and synthesis of nutrigenomics data should be carried out on an ongoing dynamic basis with periodic intervals and/or when there is a specific demand for evidence synthesis, and importantly, in ways that are transparent where conflict of interests are disclosed fully by the involved parties, be they scientists, industry, governments, citizens, social scientists, or ethicists. We submit that this will cultivate responsible innovation, and business models that are sustainable, robust, and stand the test of time and context.

NUTRIGENOMICS AND PRECISION MEDICINE

Roger J. Williams (1893–1988), who discovered pantothenic acid, has presciently observed the differences among healthy individuals in the context of nutrition and metabolism (Williams, 1956). Williams' thoughts provided the wisdom and the early hints for precision medicine, and the need to address inter-individual variability in response to foodstuff, drugs, vaccines, not to mention variability in nutrient-related disease susceptibilities.

Today, precision medicine holds the promise of tailor-made therapeutic interventions via genomic biomarker-guided patient stratification. However, before we move from promise to reality of precision medicine and healthcare, we need to cultivate evidence-based responsible innovation and thus, best serve public safety and public health.

Nutrigenomics is an important strand of precision medicine that examines the bidirectional interactions of the genome and nutritional exposures, and attendant health and disease outcomes (Ferguson et al. 2010; Patrinos et al. 2013). In the letter to the editor by Prof. Lynnette Ferguson, she first notes the value of nutrigenomics science. Second, she rightly expresses concerns on the attendant hype and in particular, public misconceptions in the field:

These are in part fostered by companies seeking to sell "health products" to the worried well. Topical in this area is "personalised nutrition", based upon diets or supplements tailored to genotype. It is essential for authors, journals, governments and the public to consider the evolving evidence base related to nutrigenomics and alleged diagnostics for personalized nutrition (Ferguson, 2016).

We shall note that as a contrast to single gene disorders or gene-drug interactions, there are also genetic tests aimed at diagnosis of complex disorders, often characterized not only by a very poor or incomplete knowledge of genotype-phenotype associations, but also with a highly complex environmental influences, e.g., nutrient uptake. In these genetic tests, different risk profiles may be generated, even for the same individual, when calculated on the basis of different risk markers, which might lack proper validation (Imai et al. 2011).

NUTRIGENOMICS 2.0

The next generation priorities for responsible and sustainable innovation

We agree with Prof. Ferguson on both counts above, and indeed applaud her plea to cultivate solid scientific evidence base and value for the nutrigenomics science broadly. We join to her plea, and wish to add that such evidence base should be cultivated in an independent manner, at arm's length from conflict of interests. Indeed, emerging fields of technology and innovation are laden with contestation and thus, synthesis of evidence or the critique of evidence base (claims over presence or absence of it) should be considered with the intent, motivation, embedded values, conflict of interests and sources of such critiques of science and innovation in a given field (De Vries 2004; Thoreau and Delvenne 2012; Petersen 2013; van Oudheusden 2014). A socio-technical history and emergence of nutrigenomics, and various omics systems science fields is available elsewhere (Ozdemir et al. 2009).

As a team of senior independent academic scientists with deep-seated experience in health products and their regulation, particularly in Europe, and importantly, with no ties with companies that offer commercial nutrigenomics tests [often provided as direct to consumer (DTC) products], we have thus aimed to independently retrieve, analyse and aggregate the evidence base associated with 38 genes included in commercially available nutrigenomics tests (Pavlidis et al. 2015). To be clearer, we posed the following fundamental question: what is the available scientific evidence base associated with commercial nutrigenomics tests related to these 38 genes? This is essential for responsible innovation with commercial nutrigenomics tests.

Our study published in the September issue of OMICS, as noted in its title and throughout the manuscript and above, focused on commercially available nutrigenomics tests; it is neither a conclusion on the value of all nutrigenomics tests nor nutrigenomic science in general (Pavlidis et al. 2015). We have, in fact, wholeheartedly endorsed further investments to nutrigenomics science as a veritable field of precision medicine in the abstract and in the article. We would also like to support responsible availability of commercial nutrigenomics tests for the public and user communities - but only provided that there is sound and consistent associated evidence base.

In sum, there is no doubt whatsoever on the scientific value of nutrigenomics science. It is precisely this vision that we endorse - that good science (and good business practices) ought to rest on good, independent and pan-optic evidence base. For sustainable growth of nutrigenomics as a post-genomics scholarship and specialty, not to mention public safety and principled ethical grounds, we believe that governments, academia, publics and industry shall endorse such a vision for responsible innovation.

The study by Pavlidis et al. (2015) was conducted using a rigorous and well-defined literature search. The methodology used by Pavlidis et al. (2015) has solid precedence, rigorously peer-reviewed, and already been published in reputable forums as OMICS: A Journal of Integrative Biology as well as Human Genomics, the official journal of the Human Genome Organisation (HUGO) (Lanara et al. 2013).

In brief, Pavlidis et al. (2015) performed their analysis according to four different models due to sparse and inconsistent data available in the literature in regards to commercially available nutrigenomics tests noted in the study (page 514, Table 2 in our article). This rigorous and multi-model driven analysis informed us that a classic quantitative meta-analysis was not presently feasible – given what is available in the literature as evidence base for the 38 genes analysed, which are included in commercial nutrigenomics tests at that time. Hence, we decided that for further data aggregation and analysis, a qualitative meta-analysis was appropriate and could offer emerging insights on associations of these 38 gene-related commercially available nutrigenomics tests. For all the genomic variants considered, the nature of their link with a condition was qualified by qualitative terms, such as: ‘yes,’ ‘may,’ ‘no,’ and ‘unknown’ (Table 3 in the article by Pavlidis et al. 2015).

The objective of a meta-analysis is to generate additional or better knowledge/insight about a phenomenon by combining results from related but independent studies. When those results are quantitative, they can be analysed using a robust statistical framework, called ‘meta-analysis methodology’ which has been described in many publications (Hedges and Olkin 1985). Due to the sheer size of the literature considered - over 400 studies have been selected involving 153 different genomic variants and 89 health states - studies displayed high dimensionality and heterogeneity in the way they presented their results. Moreover, the frequent incompleteness of the available data and usage of different protocols prevented, as noted above, a quantitative meta-analysis to generate results according to a single protocol. As a consequence, the only feasible and practical way of considering them has been to record associations between genomic variants and conditions in a qualitative manner, i.e., using the terms: ‘yes’, ‘may’, ‘no’ and ‘unknown’, as clearly described in the Methods section of the article.

Similar to other peer-reviewed meta-analysis work published elsewhere (Lanara et al., 2013), profile comparison and grouping were performed using a state-of-the-art bioinformatics tool, CLUTO (Rasmussen et al., 2003). More specifically, hierarchical agglomerative clustering was carried out to produce a binary tree representing similarities between profiles and highlighting possible groupings. Finally, the most informative groups were further analysed using the STRING 9.1 (http://string-db.org) database to collect additional evidence of putative associations.

We shall note that the literature hits identified from our search of the PubMed literature database for genotype–phenotype correlation studies on these 38 genes using the terms ‘‘nutrigenomics”, ‘‘gene name”, and ‘‘disease name’’, were queried for the presence of both dietary intake and/or nutrient-related pathologies. Despite these efforts, we found that the qualitative meta-analysis of over half a million cases indicated that there are conflicting findings and a great incompatibility as far as associations between genomic variants with nutrient related pathologies and dietary intake are concerned. Hence, we wish to underscore that our study is not a traditional expert review, nor data-mining per se, and goes well beyond a systematic review in the form of a qualitative meta-analysis.

In the future, large randomized controlled trials (RCTs) or similar well-designed studies of commercial nutrigenomics tests' associations with nutrient-related pathologies and/or dietary intake would lend themselves to quantitative meta-analysis. As things stand, however, and based on the 38 commercially available gene list, our conclusion is that a quantitative meta-analysis is not feasible with the data available, nor a qualitative meta-analysis to aggregate the attendant data from over half a million cases resulted in a sound evidence base supporting specifically these 38 gene list included in commercially available nutrigenomics tests. We welcome future analyses of commercial nutrigenomics tests that might have become available since 2013.

At this stage, we shall return to our original question and intent, and further contextualize these observations in a scientific and ethical context: That a solid and consistent aggregate association evidence base could not be produced for the 38 gene list in our study, is an evidence itself that this particular set of genes are not yet ready to be offered as a commercial genetic testing service. To us, this is an important consideration for responsible innovation (Guston 2015), public safety and interest, and cultivating successful and sustainable business models that are consistently and strongly supported by evidence and thus, stand the test of time and context in a sustainable manner for the stakeholders.

POSITION BY THE ACADEMY OF NUTRITION

In a 2014 position article, the American Academy of Nutrition and Dietetics indicated that “It is the position of the Academy of Nutrition and Dietetics that nutritional genomics provides insight into how diet and genotype interactions affect phenotype” (Camp and Trujillo, 2014). They further observed that

The knowledge gained from nutritional genomics requires an evidence-based approach to validate that personalized recommendations result in health benefits to individuals and do not cause harm.

Whether or not the knowledge gained from nutritional genomics can be integrated into the everyday lives of consumers is yet unknown (Camp and Trujillo, 2014).

Taken together, and in an effort to address the nutrigenomics hype, public interest, expectations and misconceptions, the intent and conclusions of the work by Pavlidis et al. (2015) are fully aligned with the conclusions of the position paper by the American Academy of Nutrition and Dietetics (Camp and Trujillo, 2014). We shall note that our results concerns the PubMed data entries from 1995 to 2012 due to data complexity and the time needed for their subsequent input, analysis and interpretation as well as the numerous points that appeared to demand discussion and contextualization.

As such, our findings do not counteract the well-established genome-diet interactions in disease nor raise distrust in the nutrigenomics field. On the contrary, efforts to gather and synthesize data by independent groups without conflict of interests can only boost confidence in the field and help define the future research and practice targets for the next generation nutrigenomics science. We encourage multi-omics strategies to delineate data complexity towards responsible innovation. According to the Society for Nutrition Education, personalized nutrition will become more of a reality, when it will be integrated into science-based dietary guidelines, directly aligned with the conclusions of the Pavlidis et al. (2015) study.

A CALL FOR SUSTAINABLE AND INDEPENDENT NUTRIGENOMICS SCIENCE PLATFORMS

Finally, we shall make a call, in the best interest of the nutrigenomics science community, governments, citizens and commercial nutrigenomics test providers that new evidence evaluation and synthesis platforms are created not only concerning nutrigenomics tests before they become commercially available, but also those that are already commercially available in the market place. The proposed assessment and synthesis of data should be carried out on an ongoing dynamic basis with periodic intervals and/or when there is a specific demand for evidence synthesis, and importantly, in ways that are transparent where conflict of interests are disclosed fully by the involved parties, be they scientists, industry, governments, citizens, social scientists and ethicists (Petersen 2013; De Vries 2004). That would best serve our community of nutrigenomics science and help capture the lowest hanging fruits that are ready for commercial nutrigenomics testing. Such evidentiary platforms should question issues such as “whose evidence/”, “produced by whom/”, “under what conflict of interests?” and so on, as evidence is not a value-neutral construct and is influenced by the value systems of those who create and examine them.

The insurance coverage of genetic services is changing continuously as increasing numbers of genetic services are being covered by insurers. Today, nutrigenomics tests may be reimbursable by insurance companies or the Medicare in the US, if the clinical geneticist or laboratory is an approved provider (http://ghr.nlm.nih.gov/handbook/testing/insurancecoverage). At the same time, some people may choose to pay for testing themselves, in case their person’s health insurance coverage might be affected. It is timely and responsible that such decisions are informed by an ongoing evaluation and synthesis of the available evidence on commercial nutrigenomics tests.

Conflict of Interests

The authors declare no conflict of interests.

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