Precision nutrition: Is tailor-made dietary intervention a reality yet? (Review)

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Abstract. Precision nutrition (PN) is an emerging field of science recognizing the variability in how individuals respond to different nutrients, driven by their unique biological makeup. The central aim of PN is to tailor dietary interventions to improve individual health, prevent disease and manage existing health conditions based on specific biological characteristics. The present review aimed to provide an overview of available multi-omics platforms that can be applied to extracting data from biological materials in the context of PN. Additionally, it proposed an updated pipeline for handling and integrating these data. A comprehensive search of academic publications was conducted across multiple databases, focusing on recent advances in PN, including its challenges and opportunities. Following this preparatory step, a data handling protocol for different omics layers was compiled to develop an up-to-date multi-omics pipeline applicable to PN. The successful implementation of PN requires a systems-level understanding of human physiological networks, their plasticity, variations in response to dietary exposures and the ability to classify population subgroups based on their nutritional needs. The realization of PN may currently seem distant due to several limitations such as the lack of ongoing large-scale epidemiological studies, challenges in database curation, the high cost of omics analysis and ethical concerns. A key advancement to this field would be the development of next-generation biomarkers connecting nutrition to chronic diseases. These biomarkers would help classify individuals at risk of diet-related conditions and quantify the dose-response relationships between individuals or groups of interacting nutrients and the onset and progression of diseases.

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Contents

1. Introduction

The role of nutrition as an integral component in human health and disease management is well established. However, dietary responses are markedly influenced by inter-individual metabolic variability which challenges the one-size-fits-all approach to dietary advice. This variability is multifactorial, influenced by genetic, epigenetic and environmental factors (1,2). The refinement of nutritional advice to meet the needs of distinct population subgroups, based on optimal patient stratification is a defining characteristic of Precision Nutrition (PN). This approach is made feasible by integrating deep molecular profiling of biological samples (for instance, whole blood, urine and saliva) from target groups with individual characteristics that contribute to heterogeneity both within and between populations. These characteristics include demographic factors (for instance, age, sex and ethnicity), psychosocial and cultural influences, health status, dietary patterns and behaviors such as adherence to or deviation from a healthy lifestyle (3,4).

Dietary interventions formulated on the principles of PN are well-suited to address metabolic perturbations associated with the onset and progression of non-communicable diseases, while illuminating diet-disease interactions (5-10). For instance, in prediabetic and diabetic subjects supplementation with inulin, a naturally occurring fiber, has been associated with improvements in clinical outcomes including reductions in blood glucose, total cholesterol and triglycerides (11). Additionally, dietary iron intake has been linked to lung cancer oncogenesis through epigenetic mechanisms (12). Moreover, proteomic and metabolomic profiling in the context of nutritional studies may assist in deciphering the molecular signatures associated with dietary patterns, providing greater insight on the onset of diet related diseases (8). In this context, the effects of precision based dietary interventions for weight loss in overweight and obese adults, were evaluated in a double blind intervention trial aiming to facilitate the adoption of health promoting behaviors (9). Therefore, PN plays a crucial role within precision health (PH), which incorporates a broader framework of disease prevention and treatment strategies. PH, which encompasses both precision medicine and PN, integrates molecular and clinical data to stratify populations, ultimately aiming to deliver targeted lifestyle and therapeutic interventions (13,14).

Aimed at deciphering the multifaceted relationship between nutrition and health at the molecular level, omics platforms represent a driving force in the development of PN. These platforms adopt a holistic approach to the precise qualitative and quantitative characterization of genes, proteins and metabolites present in biological materials (6). The integration of distinct omics layers, genomics, proteomics, transcriptomics and metabolomics, known as multi-omics, has gained prominence in PN, especially in tandem with advances in bioinformatics (15). Nevertheless, due to the elaborate nature of the raw data obtained from these technologies, significant computational power is required for their integration and interpretation, often utilizing artificial intelligence (for instance, deep learning algorithms). Despite these advancements, the availability of the necessary infrastructure is still in its early stages (16).

The aim of the present study is twofold; to provide a detailed overview of omics technologies and their application towards the realization of PN, with an emphasis on challenges and opportunities and to introduce an integrative bioinformatics pipeline for omics data analysis and interpretation within the same context.

2. Materials and methods

A literature review and computational workflow emphasizing the integration of multiple omics layers towards the realization of PN are presented.

Literature review. The present study conducted a comprehensive search of publications addressing advances in PN, including challenges and opportunities. An exhaustive literature search was conducted across three academic databases [PubMed (https://subread.sourceforge.net/featureCounts.html), Scopus (www.scopus.com) and Google Scholar (https://scholar.google.com/)] using the following keywords: 'Precision Nutrition', 'Precision Health', 'multi-omics', 'omics', 'Systems Biology', 'data integration' and 'personalized nutritional advice'. Among identified publications, duplicate records were manually removed and article screening was guided by consensus among all authors.

To be considered as eligible for inclusion retrieved records were required to meet specific criteria including publication in the English language and integrative use of omics technologies within the framework of PN. Articles reporting data from animal models, isolated proteomic, genomic or metabolomic and personalized nutrition studies were excluded from the review process.

Construction of an integrative multi-omic data analysis pipeline. Data handling protocols for different omics layers were compiled to develop a multi-omics pipeline applicable to PN. The proposed computational workflow represents a flexible approach for data handling and interpretation of genomics, transcriptomics, proteomics and metabolomics datasets in preparation for multi-omic integration. In detail, three modules were developed incorporating the preprocessing and analysis of raw DNA-seq, RNA-seq and liquid chromatography-mass spectrometry (LC-MS/MS) data.

Quality control and correction of genomic and transcriptomic sequencing datasets is proposed utilizing the software packages FastQC, (a specialized tool used for the detection of low quality control reads and bias in NGS data) (17) and Trimmomatic, (a flexible, pair-aware tool used for adapter sequence identification and quality filtering of NGS datasets) (18). This process is followed by DNA/RNA sequence alignment to a refence genome with advanced algorithms; for instance, Magic-BLAST (19) (a specific tool used for the alignment of RNA-seq data) and STAR (a specific tool used for the alignment of DNA-seq and RNA-seq data) (20). Thereafter, downstream analysis of genomic data incorporates advanced sequence processing) with the SAMtools toolkit (a tool used to perform variant calling, error correcting, sorting, merging and indexing) (21). Regarding transcriptomics data, the implementation of Differential Expression analysis (DEA) with R language (22) (version 4.4.1) software packages such as DESeq2 (version 1.44.0; https://bioconductor.org/packages/release/bioc/html/DESeq2.html) (23), edgeR (version 4.2.2; https://bioconductor.org/packages/release/bioc/html/edgeR.html) (24) and limma (version 3.60.6; https://bioconductor.org/packages/release/bioc/html/limma.html) (25) (all tools are used to perform Differential Expression analysis), to evaluate gene expression, is recommended.

Furthermore, for the analysis of raw proteomics and metabolomics data, several data pre-processing steps were proposed. These included dataset filtration, normalization and missing value imputation which may be conducted using standard data manipulation algorithms such as tidyverse (26), dplyr (27) and advanced modelling tools including MissForest (Random Forest algorithm) (28) and Multivariate Imputation by Chained Equations (mice) (29), respectively. Appropriate selection of imputation techniques relative to the nature of missing values present in the analyzed LC-MS/MS datasets, including values missing not at random, missing completely at random and missing at random, is critical, as this has been associated with error rate reduction and improved efficiency

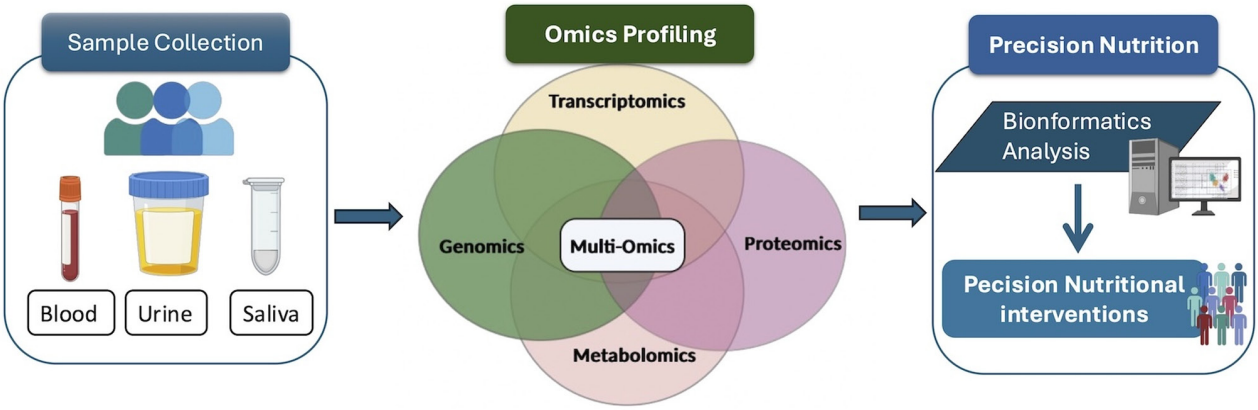

Figure 1. Conceptual workflow for the successful implementation of Precision Nutrition. Biological samples, for instance, whole blood, urine and saliva, were collected from target populations and subjected to in-depth molecular profiling using omics technologies. Multiple omics datasets were integrated with demographic and clinical data to optimize dietary recommendations.

regarding downstream data analysis (30-32). To evaluate disparities in protein/metabolite expression, DEA outputs can be generated using advanced models including limma (25) and non-parametric statistical tests (for instance, Mann-Whitney test).

Finally, to aid the process of data interpretation, functional annotation by means of enrichment analysis, is suggested. To this end several core analyses may be employed towards the identification of key biological processes, molecular functions, topology and molecular pathways (33), including Gene Ontology (34,35) analysis, Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway enrichment (36) and Gene Set Enrichment analysis (37). A core component of all aforementioned steps is data visualization, which can be achieved with data visualization software packages available through the R language (for instance, ggplot2 and lattice) (38,39).

3. Results and discussion

The currently available PN pipelines consist of multiple tandem bioanalytical steps. Specifically, following sample collection, biological materials are analyzed using omics approaches, resulting in the production of large data arrays, which are subsequently processed using relevant computational tools (Fig. 1). Data analysis and interpretation using bioinformatics delivers key information pertaining to the exact molecular profile of examined samples (whole blood, urine and saliva) (40). This procedure aims to stratify the populations under study into appropriate clusters based their distinct molecular profile and ultimately deliver tailor-made dietary interventions adjusted to their characteristics (41).

For PN datasets to be populated, efficient analytical handling, adjusted to the nature of biological samples under investigation, is required. Genomic and transcriptomic analytical workflows encompass the preparation of DNA and RNA libraries for sequencing, using advanced NGS platforms. In addition, proteomic and metabolomic pipelines involve the analysis of tissues and other biological samples using LC-MS/MS. For proteomics, prior to LC-MS/MS analysis, protein extraction and peptide generation steps are required, while appropriate metabolite extraction is an essential component in metabolic profiling. The generated omics data are analyzed using bioinformatics algorithms in order to achieve multi-omic data integration and ultimately create predictive models capable of delivering dietary advice based on the principles of PN. For this purpose, raw data is processed using algorithms, including machine-learning models and statistical tools, such as STAR aligner for sequence alignment of RNA-seq data, DESeq2 for differential expression analysis in transcriptomics and proteomics and mice for the imputation of missing values in proteomics and metabolomics (42).

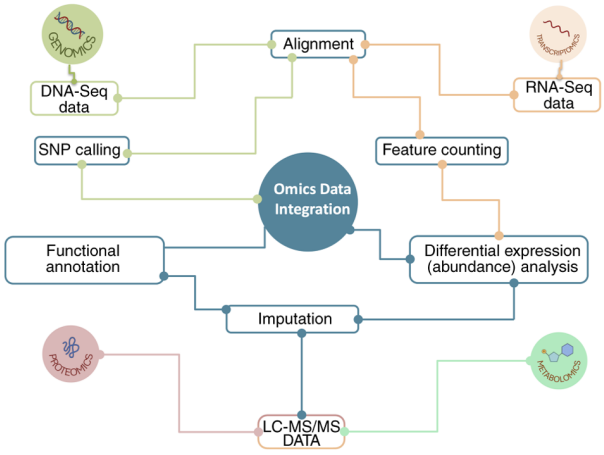

Figure 2. Proposed pipeline for the analysis of multiple omics datasets (genomics, transcriptomics, proteomics and metabolomics) in preparation for data integration. This workflow consisted of multiple pre-processing and analysis steps either unique to or shared between the different omics layers. -Seq, sequencing; SNP, single-nucleotide polymorphism; LC-MS/MS, liquid chromatography-mass spectrometry.

The present study constructed a pipeline consisting of multiple bioinformatic analysis steps/nodes for the processing of multi-modal omics data with a view to their integration (Fig. 2). The following bioinformatic steps were introduced: i) Alignment of DNA- and RNA- seq data (for instance, utilizing BWA or Bowtie2 and Magic, BLAST, STAR and HISAT2 respectively). ii) Determination of polymorphism topology in genomics data using single nucleotide polymorphism calling [SAMtools (version 1.21; https://github.com/samtools/

samtools/releases/tag/1.21), BCFtools (version 1.21; https://github.com/samtools/bcftools/releases/tag/1.21)]. iii) Gene quantification/gene expression count generation (feature counting) from RNA-Seq data using tools such as HT-Seq count (version 2.0; https://htseq.readthedocs.io/en/latest/) and featureCounts (version 2.20.0; https://subread.sourceforge.net/featureCounts.html). iv) Imputation of missing values in LC-MS/MS data derived from proteomics and metabolomics. v) Differential expression (abundance) analysis to discern expression patterns in transcriptomics, proteomics and metabolomics data (DESeq2, limma and SDAMS) (43-45). vi) Functional annotation of proteomics and transcriptomics data (for instance, KEGG pathway, Gene Ontology analysis, Gene Set Enrichment Analysis). The integration of data generated by the aforementioned procedures was achieved using artificial intelligence based models, for instance, machine learning tools based on multivariate techniques, such as the mixOmics framework (46) and deep-learning approaches including large language models, convolutional neural networks.

Nevertheless, despite the rapid technological advancements supporting progress in the biomedical field, a number of critical gaps need to be bridged before PN is realized (47-49). Crucially, the creation of relevant repositories enriched with data from additional nutritional epidemiological studies will play a pivotal role towards the realization of PN. Efficient adoption of such strategies must be based upon sound study design, encompassing sample size among other parameters (50). Furthermore, harmonization of data storage and retrieval protocols should be prioritized in parallel with the much-needed enrichment of publicly available omics data repositories (51,52).

Breakthroughs achieved by artificial intelligence can be leveraged to address limitations across the entire PN pipeline (53). When implemented under human supervision, artificial intelligence can be leveraged towards efficient study design and subsequent data gathering and processing. As such, use of artificial intelligence models as catalysts for the development of predictive models adapted to PN (16). Finally, active learning based models use feedback to refine their predictive accuracy, thus facilitating patient guided study design and data interpretation (54).

Overall, the process leading up to the adoption of PN gives rise to several practical and ethical concerns. The large-scale analytical accumulation of molecular, personal data requires that an adequate degree of data protection is ensured to maintain patient privacy and reduce healthcare disparities (55). Moreover, firm understanding of PN and omics concepts by targeted groups should be ensured prior to recruitment in nutritional epidemiological studies so that informed consent is obtained (56).Thus, the necessary regulatory framework for the protection of patient rights must be established (57-59), taking present legislature such as the General Data Protection Regulation into account.

While valuable insights have been gained by the progress achieved in the field of PN through the application of omics technologies, its widespread implementation may currently seem far-fetched due to existing limitations with regard to the organization of such efforts at a global scale. To this end, further nutritional epidemiological studies in tandem with standardization of omics pipelines, including analytical and bioinformatics workflows, are required (15,58,60,61). Furthermore, the capacity to integrate epigenetic omics datasets in future PN multi-omics workflows is something to be taken under consideration. The lack of its integration is a limitation of the present work. The establishment of international networks fostering cross-disciplinary collaboration will facilitate the gradual creation of new and enrichment of existing biological databases, whilst addressing ethical concerns.

4. Conclusion

Individual responses to dietary exposures are characterized by a high degree of heterogeneity driven by demographic, nutritional and psychosocial factors (1,62). PN is an emerging discipline aiming to provide optimized dietary advice to relevant population subgroups in the context of disease prevention and management (6). The successful realization of PN requires a systems-level understanding of human physiology and individual characteristics associated with metabolic variability.

To this end, the present review offered for the first time, to the best of the authors' knowledge, a detailed overview of omics technologies and their application towards the realization of PN. Furthermore, an integrative bioinformatics pipeline that can be used as a model for omics data analysis and interpretation was introduced in the present study. The holistic adoption of omics technologies in parallel with large scale epidemiological studies is anticipated to give rise to molecular biomarkers linking nutrition to the onset and/or progression of chronic diseases. Embracing such efforts will bring us one step closer to bridging the gap between PN and its implementation in clinical practice within the broader framework of precision health (63-65).

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Availability of data and materials

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Authors' contributions

Conceptualization was by AA and investigation by MP, HT, AP, OM, MK, IV and IG. MP, HT, AP, OM, MK, IV, IG and AA were responsible for writing the original draft of the manuscript and AA and KS for writing, review and editing the manuscript. All authors read and approved the final manuscript. Data authentication is not applicable.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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