REVIEW

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Potential of multiomics technology in precision medicine

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Purpose of review
The 'precision medicine' refers to the generation of identification and classification criteria for advanced taxonomy of patients, exploiting advanced models to infer optimized clinical decisions for each disease phenotype.

Recent findings
The current article reviews new advances in the past 18 months on the microbiomics science intended as new discipline contributing to advanced 'precision medicine'. Recently published data highlight the importance of multidimensional data in the description of deep disease phenotypes, including microbiome and immune profiling, and support the efficacy of the systems medicine to better stratify patients, hence optimizing diagnostics, clinical management and response to treatments.

Summary
The articles referenced in this review help inform the reader on new decision-support systems that can be based on multiomics patients' data including microbiome and immune profiling. These harmonized and integrated data can be elaborated by artificial intelligence to generate optimized diagnostic pipelines and clinical interventions.

Keywords
artificial intelligence, decision-support systems, immunomics, microbiomics, personalized medicine

INTRODUCTION

The term 'precision medicine' refers to the new sets of methodologies and approaches able to provide optimized stratification of patients, hence generating a new 'definition' of disease phenotypes. Despite its inflated usage, the definition is still often generic although already linked to important scientific and clinical expectations and even to the possibility of developing new health policies and strategies. However, we can state that the 'precision medicine' refers more appropriately to the generation of criteria for advanced taxonomy of patients, producing models to identify and classify clinical decisions for each disease phenotype. This new perspective of patient evaluation can use both basic laboratory and clinical data (i.e. discrete variables), and omics' data (i.e. continuous variables) produced by new-generation sequencing or NGS, proteomics, metaproteomics, metabolomics, foodomics, immunomics (proteomics and integrated serology), lipidomics, microbiomics, all of them generating large-scale or *big data* (Fig. 1). These data are allowing researchers and clinicians to provide a broad spectrum of clinical, genetic, immunological information on the patient, his lifestyle (e.g. feeding, family and personal relationships and habits, sports activities, stress elements) and main interactions with the environment such as exposure to pathogens, nutrients, drugs, pollution, all variables constituting the *exposome*. These new indicators of the patient biological or clinical state may be considered, after validation processes typical of the systems medicine, biomarkers of the phenotype of the disease, and may allow to go beyond the classic semeiotics

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KEY POINTS

- By integrating structural and functional features of a biological system, it is possible to provide a complete *host-exposome* set of multidimensional data that can provide personalized information for each patient.
- When metadata on human microbiome are considered, the entire *microbiota-host-exposome* phenotype can be generated for each patient, including *microbiome profiling* that complement the phenotype of the disease (metadata or phenomics data).
- Moving from omics' or *big data* to *fused* and *small data*, the stratification of the patients can be tremendously improved, translating this process into a potential better health care.
- From integrated *microbiota-host-exposome* data it is possible to generate *decision-support systems* for optimized diagnostic pipelines and clinical interventions.
- The most recent omics sciences such as immunomics and foodomics may fulfil the best *microbiota-host-exposome* profile of a patient.

approach, overcoming signs and symptoms to decipher the disease. These 'omics data' are 'multidimensional data', exploiting numbers of patients, genomic and metagenomic sequences, metabolites, immunological profiles as whole matrices of patients' meaningful variables. Once the data are 'cataloged', that is organized in architectural systems for reading usable data, they can be harmonized and, therefore, integrated, according to univariate and multivariate statistical models, borrowed by chemometrics, which is the science of relating the measurements made on a biological system or on a chemical process with the state of the system through the precise application of statistics. By using this approach, it is possible to move from hundreds of thousands of data to a few tens through a mechanism of self-scaling (harmonization) and reduction of multidimensionality until producing a framework of both structural and functional features of the biological system. By integrating the two characteristics, it is possible to provide a complete *host-exposome* set of data that can provide personalized information for each patient, without introducing the bias of the a-priori selection of

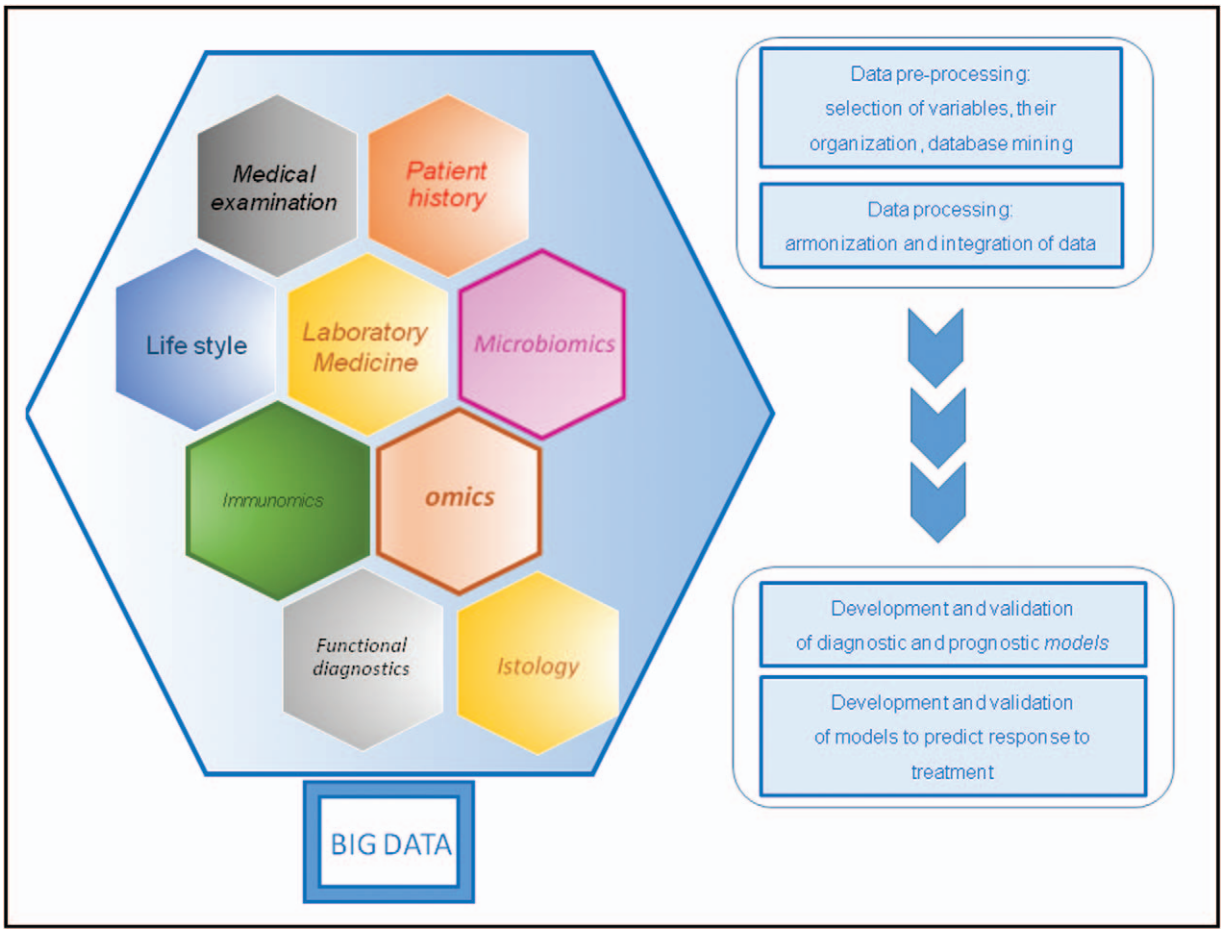

FIGURE 1. Entire set of big data that can build up a 'precise' physiopathological model in personalized medicine.

clinical and laboratory data (*'targeted' approach*). When metadata on human microbiome are also considered, the entire *microbiota-host-exposome* phenotype can be generated for each patient, including *microbiome profiling* as *enterophenotype* that can complement the classical phenotype of the disease (metadata or phenomics data). At individual level *microbiota-host-exposome* data may act as diagnostic and prognostic tool, while at population level they can generate baseline profiling acting as prediction factor of disease. With this approach, the description of a pathophysiological state by representative variables is performed by an '*untargeted*' approach, without any selection *a priori*. This allows researchers to consider the disease as a 'system' represented by as many variables or 'features' as possible that can be collocated in a 'precise' or 'personalized' picture of the clinical history of the patient, in the context of the 'strict' observed disease phenotype. Moving from omics' or *big data* to precision medicine, through a process of *fused data* down to *small data*, the stratification of the patients can be tremendously improved, translating this process into a potential better health care.

GUT MICROBIOME, CAUSE AND DISEASE PROFILING

In a recent Nature article [1▪▪], the major modulating variables of a healthy human microbiota have been reported, showing that host genetics acts only in negligible quantity with respect to external stimuli and to modifications induced by environment (exposome). The growing availability of systems biology approaches to study intestinal microbiome has provided powerful and sophisticated analytical tools, allowing to produce multidimensional omics data (big data) able to describe without a-priori constraints a human microbiome, including variables associated with food [2▪]. The prediction of modulating effects on the symbiotic and dysbiotic state of the microbial ecosystem, through patterns of trajectories of microbial evolution, is now possible [3▪]. Therefore, the intestinal microbiota can be analysed nowadays in its ecological complexity of microbial organ within the host organism (superorganism or holobiont), characterized by continuous dynamic interactions with host, food and environment. The exhaustive description of an intestinal microbiota in the early stages of life, immediately after birth and during childhood, when the so-called *physiological programming* is carried out, has an important impact on neonatology and paediatrics, as it provides nutraceutical indications for the entire process of the growth [4▪▪]. Moreover, it is known that some diseases, expressed at extraintestinal level, such as allergies, are associated with perturbations of the gastrointestinal microbial ecosystem, starting since birth [5▪]. Obesity and metabolic diseases associated with obesity, such as the metabolic syndrome and type 2 diabetes, have also been linked to structural and functional characteristics of the intestinal microbiota [6▪], the last also induced by antibiotic treatments, as shown in mouse models [7▪▪]. Based on these studies, it seems plausible that the ability of the intestinal microbiota to regulate the inflammatory response is critical in the complex mechanisms related to obesity and metabolic syndrome, and even to the risk of developing some adult diseases, such as cardiovascular diseases [8▪]. In addition, for mendelian diseases, such as cystic fibrosis (CF), chronic inflammation and hence derived recurrent respiratory infections, appear to have substantial effects on the intestinal microbiota, through dynamic correlations associated with its dysbiosis [9▪]. As it is known, mutations in the Cystic Fibrosis Transmembrane conductance Regulator (CFTR) gene alter the physiology of the ion channel of the apical membranes of epithelial cells, deregulating exocrine production, with consequent malabsorption, obstruction and nutritional deficiency of the intestine. Indeed, in patients with CF the role of the intestinal bacterial proliferation and the implications of the gene defect remain controversial in endogenous inflammation and in the alteration of immunological homeostasis. A recent study produced by our group [10▪▪] has highlighted the main players of the intestinal microbiota that correlate with the gut functional alterations but also with the host's metabolism typical of CF patients. Particularly, 31 CF naïve patients were studied under clinical stability in a case–control modality, hence compared with age-matched healthy patients (1–6 years).

The profile of the intestinal microbiota obtained from the fusion of metagenomic and metabolomic data identified bacterial preponderance and deficits, with high abundances of *Propionibacterium*, *Staphylococcus* and Clostridiaceae, *including Clostridium difficile*, and poor presence of *Eggerthella*, *Eubacterium*, *Ruminococcus*, *Dorea*, *Faecalibacterium prausnitzii*, associated with over-expression of 4-aminobutyrate [gamma-aminobutyric acid (GABA)], choline, ethanol, propylbutyrate and pyridine and low levels of sarcosine, 4-methylphenol, uracil, glucose, acetate, phenol, benzaldehyde and methyl acetate [10▪▪]. These correlations represent an absolute novelty with respect to the previous acquired knowledge on intestinal microbiota profiling in paediatric disease, since induced to define as prevalent driver of intestinal microbiota dysbiosis its genetic deficit. The study demonstrated two fundamental and innovative aspects: first, the intestinal microbiota milieu is primarily modulated and induced

by the alteration of the CFTR function of the host; hence the GABA and choline molecules, as they directly reflect the alterations of the intestinal transport of water and of the components regulating the intestinal osmosis, can be considered specific biomarkers of CF microbiome, while alcohols, esters cobiomarkers of the altered microbial activity, providing a new idea of disease-predicting metabolites to be investigated in the future; second, the intestinal microbiota is only secondarily modulated by patient's age, disease phenotype, colonization/infection of the pulmonary microbiota and by the chronic antibiotic treatment regime. Both evidences are extraordinary considerations if compared with what is known on intestinal microbiota/health/disease. In CF, the increase in intestinal inflammation has been repeatedly reported, possibly triggering intestinal bacterial proliferation, otherwise called blooming, favoured by the sticky material that hinders the transport of antimicrobials [11▪,12▪]. However, in naïve CF paediatric patient, our work has shown an almost independent microbiome profile from the chronic antibiotic regimen, which could be explained by the ceramide effect [10▪▪].

When different disease phenotypes, even including those associated with a single genetic modification, are catalogued and associated with microbial enterotypes, the set of phenotypic profiles becomes pleiotropic, and instead of organism we speak of a *superorganism*, which implies the direct or indirect role of the microbiota on human diseases. For this reason, advanced tools of genomics are needed (i.e. NGS), capable of performing optimal studies of highly complex microbial communities. In addition to metagenomics, the microbiota is currently analysed by metabolomics. Through the production of antimicrobial compounds, volatile fatty acids and chemically modified bile acids, the intestinal microbiota creates a metabolically very reactive environment, often described as a bi-reactor. Recent studies, including those of our group, have shown that 1H-NMR, gas chromatography-mass spectrometry (GC-MS) metabolic analyses of faecal extracts can provide important clarifications on the interspecies metabolic differences of the components of the microbiota. Metabolomics may produce important diagnostic information for the main intestinal diseases, to examine metabolic cooperation host/microbiota with respect to phenotype, pathology and diet [13▪▪]. Indeed, in colon rectal cancer (CRC) patients, a GC–MS-based approach allowed to identify 17 metabolites associated with Asp metabolism, ammonia recycling, protein biosynthesis, and Trp metabolism, which are involved in tumorigenesis (i.e. Lys, heptanedioic acid, norvaline), while 42 metabolites, involved in Asp, Ala metabolism and protein biosynthesis, were not detectable in the CRC group. Targeted-metagenomics identified 76 bacteria, including Proteobacteria, Enterobacteriaceae and Fusobacteria as key discriminants of CRC, whereas Firmicutes, Clostridiales, Clostridia, Lachnospiraceae, Ruminococcaceae and *Faecalibacterium* were only ascribed to healthy patients considered as controls (CTRLs). Integrated analysis correlated CRC-associated microbes with metabolites, such as polyamines (cadaverine and putrescine), producing more functional insights than single datasets.

In general, mutualistic relationships in the intestinal microbiota influence metabolic health, regulate energy balance, xenobiotic metabolism, resistance to pathogen colonization, immunological maturation in children and nutritional health. On this basis, biomarker design associated with microbiota dysbiosis for specific diseases can have a direct diagnostic relapse. Applying highly performing and processive metaproteomic technologies, based on Triple-TOF mass spectrometry, Sequential Windows Acquisition of all Theoretical Precursors technology, orbitrap fusion pipelines, additional analytes from faeces or blood can produce qualitative and quantitative profiles of differentially expressed proteins/metabolites, capable of providing large in-silico reservoir of information for each individual patient [14▪▪].

With this high interdisciplinary impact and with a work at the interface between research and clinic, microbiologists and specialists in-omics sciences can now understand the role of the intestinal microbiota in physiological and pathological states, and can assign characteristics (fingerprints), able to define human endophenotypes (Fig. 2). What is already clear is that the role of the microbiota in human health is much more important than previously thought: understanding the dynamics of bacterial populations and governing them, instead of attacking them with antibiotics, could represent the correct strategy in the next future to defeat numerous diseases and the growing phenomenon of antimicrobial resistance. Microbial communities could therefore be managed in terms of their content and metabolic balance rather than in term of their removal. The classic concept of infection associated with a single organism that invades our body and reproduces itself by inducing a series of alterations is no longer acceptable. In fact, it has been discovered that some diseases appear to be caused by imbalances of microorganisms' populations rather than by a single pathogen [15▪]. This new model can be extended to various diseases and not only be confined to infectious processes.

Research currently hypothesizes that gut microbiota alterations are the basis of many chronic

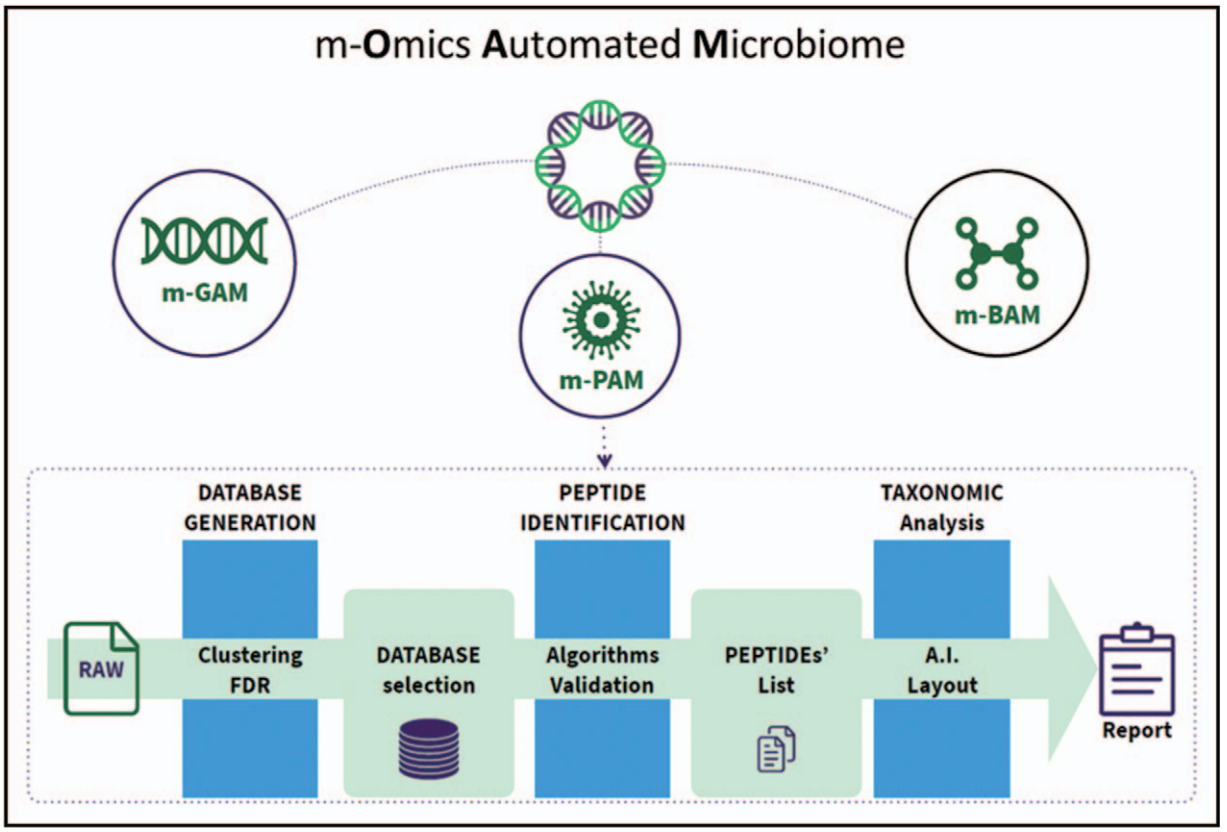

FIGURE 2. Metagenomics, metaproteomics and metabolomics platforms, interpreted by artificial intelligence, may provide automated microbiome models in health and disease. m-BAM, meta-bolomics Automated Microbiome; m-GAM, meta-Genomics Automated Microbiome; m-PAM, meta-Proteomics Automated Microbiome.

inflammatory diseases, allergies, diabetes, obesity. The higher is the diversity, the less likely it is the possibility that external pathogens can invade and settle inside the human body. In fact, if all the niches are occupied, it becomes difficult for the invaders to invade places and become operative. However, the role of the gut microbiota in the human pathogenesis does not rely on exclusive competition: indeed, our microbiome interacts with the environment that dominates the genetic make-up [1▪▪].

PRECISION MEDICINE AND MICROBIOMICS

Researches on microbiome are increasingly exploiting omic and metaomic pipelines and algorithms that allow microbiomics researchers to characterize the gut and other districts' human microbiomes in the most variable physiopathological conditions almost reaching the description of the *gradient* laying between eubiotic and dysbiotic landscapes of gut microbiome. In particular, our research group has focused its activity on the production of microbiome maps (profiles) associated with various pathological conditions such as CF, fatty liver, obesity, multidrug-resistant germ infections, autism, inflammatory bowel diseases, intestinal bowel syndromes, cancer, mental retardation, idiopathic arthritis, allergy, dermatitis, HIV, trying to address dysbiome features through dysbiosis tracking indexes (Patent ITUA20164448: *Metagenomic method for in vitro diagnosis of gut dysbiosis*) and integrated meta-omics data [16▪–18▪,19▪▪,20▪▪,21▪–24▪,25▪▪,26▪,27▪▪].

An interesting area of research regards microbiomics and carcinogenesis. In the study by Ponziani *et al.* [20▪▪], gut microbiota features associated with hepatocellular carcinoma (HCC) in patients with complex phenotypes, such as cirrhosis and nonalcoholic fatty liver disease (NAFLD), were investigated. Microbiota profile, intestinal permeability, inflammatory status and circulating mononuclear cells were considered 'features' to construct a correlation model in hepatocarcinogenesis. Patients with HCC showed increased levels of fecal calprotectin, while intestinal permeability was similar to patients with cirrhosis but without HCC. Plasma levels of IL8, IL13, chemokine ligand (CCL) 3, CCL4 and CCL5 were higher in the HCC group and associated with activated circulating

monocytes. The fecal microbiota of patients with cirrhosis showed higher abundance of Enterobacteriaceae and *Streptococcus* and a reduction in *Akkermansia*. *Bacteroides* and Ruminococcaceae resulted increased in the HCC group, while *Bifidobacterium* was reduced. *Akkermansia* and *Bifidobacterium* were inversely correlated with calprotectin concentration, which conversely was associated with humoral and cellular inflammatory markers. This study highlighted that in patients with cirrhosis and NAFLD the gut microbiota profile and systemic inflammation are significantly correlated concurring in hepatocarcinogenesis processes [20▪▪]. Remarkably, inflammation status was found to be not correlated to microbiota profiling in juvenile idiopathic arthritis (JIA) [25▪▪]. A recent large multicenter, prospective, observational cohort study included Italian and Dutch paediatric patients affected by JIA at baseline, with inactive disease, and with persistent activity compared with healthy CTRLs [25▪▪]. Random forest models distinguished between Italian patient baseline samples and healthy CTRLs and suggested differences between Dutch patient samples and healthy CTRLs. The article showed strong evidence for dysbiosis in JIA patients. Only patient/CTRL status, age and geographic origin appear to be drivers of the microbiota profiles, regardless of disease activity stage, inflammation and markers of autoimmunity.

In addition, the modulation of the intestinal microbiome following administration of pre, probiotics, nutritional modulation and resetting due to intestinal microbiota transplantation have been investigated. This massive microbiome profiling has generated more than 7000 paediatric and adult microbiota maps, generating a very advanced database of microbiome biobank (https://www.bbmri.it/nodo-nazionale/gruppi-di-lavoro/microbiota-umano-e-biobanking/) and microbiome resources (Fig. 2) that can contribute to the best definitions or taxonomy of the disease. Based on microbiomics algorithms, our group is developing the following decision-support systems (DSS) as diagnostic-clinical tools: first, dysbiosis profiles of intestinal microbiota based on targeted-metagenomics; second, identification of microbial markers and molecular biomarkers of health and disease, directly related to alterations of the intestinal microbiota; third, production of *host-microbiome* integrated omics data profiles; fourth, faecal microbiota transplant programs; fifth, design of computer applications, based on artificial intelligence to manage omics data and dietary profiles with the purpose to translate microbiota profiling into a score-based system for intestinal dysbiosis diagnosis and clinical-nutraceutical interventions.

CONCLUSION ON ADVANTAGES OF PRECISION MEDICINE AND ROLE OF MICROBIOMICS

The advantages of precision medicine are innumerable. First of all, we can contribute with this approach to clarify unknown etiopathogenetic mechanisms of disease; we can identify several diagnostic and prognostic biomarkers in different patients, within the framework of the same pathology, and the reason for their variability; we can understand in different individuals a differential response to the same pharmacological treatment, despite affected by the same disease.

As limitations, we have to consider the design of the study. As reported in several studies [1▪▪,6▪,18▪,25▪▪] identifying specific biomarkers for disease prediction in a global population may not be straightforward. It is extremely important to consider optimal population CTRL groups to avoid bias linked to environment, food, ethnic-specific features which can affect reproducibility of case–control studies. In addition, appropriate stratification of disease is extremely important [6▪,11▪,18▪]. Moreover, technological platforms, experimental procedures and computational algorithms need to be standardised by performing experimental settings in multiple collaborative sites including large sample sizes to avoid 'batch effects' and minimize biological variabilities.

However, regardless limits, precision medicine can be considered a new tool for evaluating the parameters of efficiency and effectiveness in the management of health policies. In this context, microbiomics complement deep phenotyping, providing enterophenotypes features and relationship with host genetics, metabolism, immunology, overcoming the host genetics [28▪]. As new laboratory medicine, data from microbiomics integrated with patient metadata and other omics data may provide advanced DSS. We are entering the new era of artificial intelligence that can harmonize, integrate, but especially learn from single omics models to provide new combined models of fused phenotypes/enterophenotypes associated with disease profiling. The aim is that artificial intelligence in DSSs may provide advanced taxonomy of disease phenotype to improve response to treatment through diagnostic and prognostic models of response prediction, based on score-based systems (Fig. 3). We would basically have two genomes: the human genome and the microbiome; therefore, the fluctuations in the microbial population of the microbiota would result in the manifestation of dysbiosis and, therefore, in the subsequent onset or flare-up of diseases. The ability to govern these fluctuations can represent the

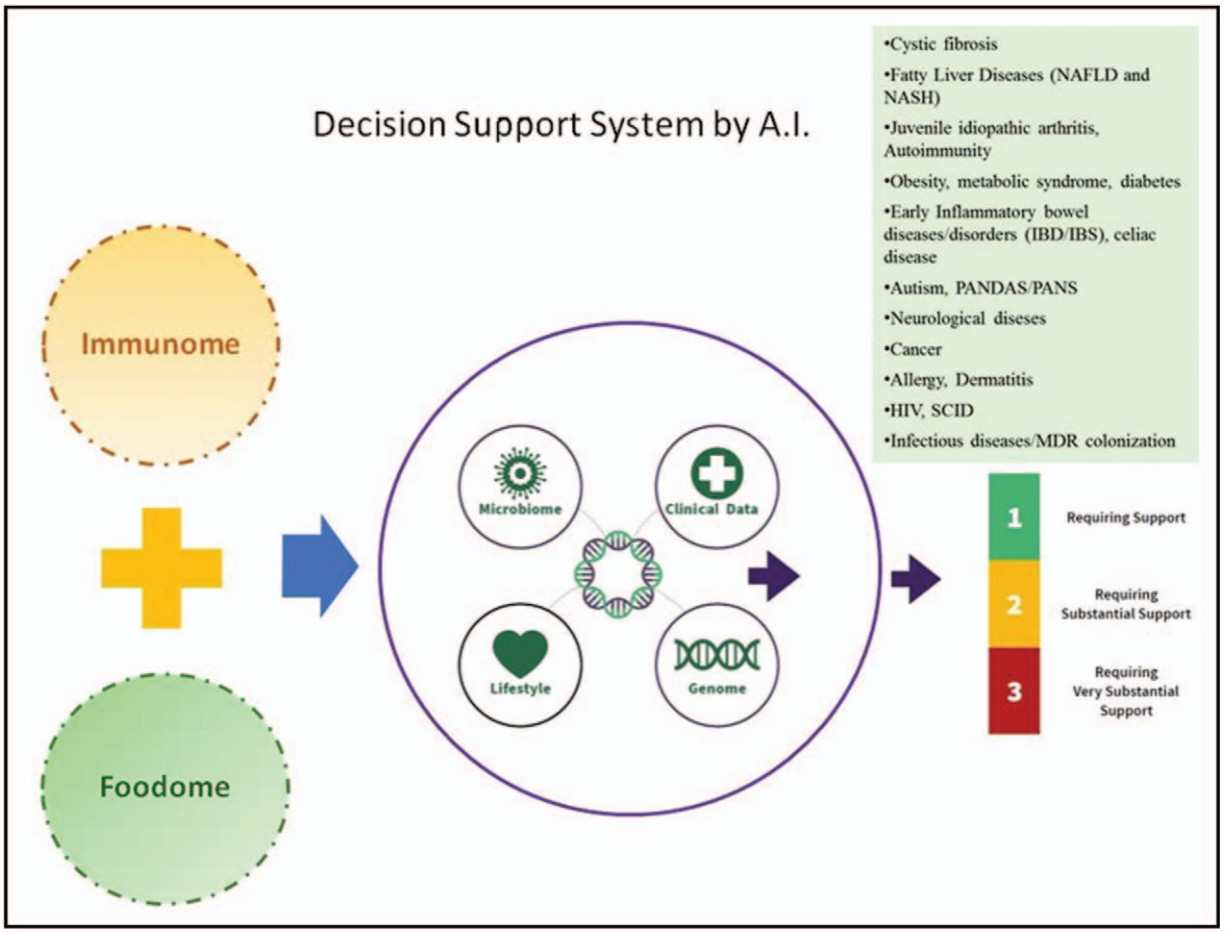

FIGURE 3. Framework of omics integration, including immunomics and foodomics, diseases and artificial intelligence to generate optimized diagnostic pipelines and clinical interventions. hiv, Human Immunodeficiency Virus; MDR, multi-drug-resistant germs; scid, severe combined immunodeficiency.

medicine of the future, acting on entities that can be modified, contrarily to what happens for the human genome, whose gene content cannot be modified.

The future of microbiota is already present in current diagnostics and clinical practice and, therefore, it is already precision medicine.

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Conflicts of interest

There are no conflicts of interest.

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- ■ of special interest
- ■■ of outstanding interest

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Microbiome data can better predict many disease-related human traits than models that use only host genetic. The gut microbiome 'beats two to zero' host genome to interpret host phenotype; exposome definitely dominates over host genetics in modulating gut microbiota.