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"Precision Medicine is Made Possible by Metabolicomics: "A White Paper, Community Perspective"

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Abstract

Metabolomics is the extensive examination of the metabolome, which encompasses all the biochemicals or compounds found in cells. Body fluids and tissues are encompassed. The subject of global or "-omics" metabolism research is experiencing tremendous growth and has gained significant importance in recent times. The capacity to exert significant influence over medical professions. The fundamental principle underlying metabolomics is that the metabolic condition of an individual serves as a reasonably reliable indicator of their overall health to some degree. This specific metabolic state is an indication of the changes in genetic information caused by environmental variables, dietary intake, and the microorganisms residing in the gastrointestinal tract. During gene expression research, it is often unclear how the metabolic profile accurately reflects the biochemical condition, which might range from normal physiology to various pathophysiology's. Currently, medical personnel have access to only a small fraction of the vast amount of information included in the metabolome. This is because they regularly analyze a restricted range of blood chemistry analytes to assess the conditions of health and disease. Another example is the surveillance of glucose levels for individuals with diabetes. The White Paper aims to utilize metabolomics as a facilitative tool for precision medicine and to achieve anticipated treatment outcomes. In the future, we expect that the limited set of chemical tests currently used by the medical community will be substituted with studies that offer a significantly more comprehensive metabolic profile. This signature is expected to identify global biochemical abnormalities that correspond to variations in wellness states, accurately characterize specific diseases and the progression of their therapies, and significantly aid in differential diagnosis. Potentially, future metabolic signatures may offer the following benefits: (1) This study aims to identify markers that can be used to predict, diagnose, and provide information about the progression of various diseases. (2) It also aims to understand the molecular mechanisms that cause diseases. (3) By analyzing metabolic pathways, this study can help classify diseases and stratify patients based on their metabolic profiles. (4) Additionally, it can identify biomarkers that indicate how a patient will respond to a specific treatment, which is known as pharmacometabolomics. (5) This highlights the synergistic relationship between pharmacometabolomic and pharmacogenomics as potent instruments for precision medicine. They will offer valuable insights on topics such as sample acquisition and preservation, the selection of effective omics technologies, and important considerations regarding data collection, analysis, and dissemination. We strongly recommend collecting and storing samples for precision medicine studies that will address the requirement for thorough metabolic phenotyping research.

Keywords: *Metabolomics Metabonomic Pharmacometabolomic Pharmacometabolomic Precision Medicine Personalized medicine*

Introduction

The organization contends that metabolomics is an essential element of the PMI and should be integrated into all forthcoming global precision medicine initiatives. Now, it is possible to study the effects of the intricate connections between genotype, lifestyle, diet, nutrition, pharmacological therapy, environmental exposure, and gut flora on the physical characteristics of

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an organism at the molecular level (Fig. 1). This is achieved by identifying and quantifying a diverse range of naturally occurring and externally derived metabolites. Metabolic phenotyping investigations can provide new insights into the pathophysiology of diseases and the processes behind variances in medication responses in humans. These studies also contribute to predicting both the risk of toxicity and the beneficial responses to drug treatment (Beger et al. 2015; Cacciatore and Loda 2015; Everett 2015; Kaddurah-Daouk et al. 2008; Kaddurah-Daouk and Weinshilboum 2014, 2015; Kastenmu¨ller et al. 2015; Nicholson et al. 2012; Patti et al. 2012; Su et al. 2014; Suhre et al. 2016; Wilson 2009; Zamboni et al. 2015). The following provides background information on the utilization of metabolic data for disease and patient sub-classification. It also discusses available technologies for metabolic profiling, including their advantages, disadvantages, and bottlenecks. Additionally, it highlights the tools currently available for extensive research in precision medicine. This article focuses on how the metabolome can accurately reflect the real-time activities of the gut microbiota, as well as the overall impact of environmental factors on human health and individual reactions to therapy. Moreover, it has the capacity to enhance and provide information about the subsequent effects of the genome.

Background

Metabolomics and the Central Dogma

After the Central Dogma of molecular biology was acknowledged, there was a significant transformation in the field of biological sciences. Indeed, the origins of life can be elucidated by understanding that chromosomal DNA is transcribed into RNA, which is then translated into functional proteins. Furthermore, it offered scientific knowledge regarding the inherent diversity in human susceptibility to illness and the differences in the efficacy of specific therapeutic drugs for each particular patient. However, the Central Dogma fails to consider the active involvement of genes, transcripts, and proteins in the regulation of the cellular composition of small molecules. These little molecules play a crucial role in carrying out most of the necessary processes for cell operation. This includes controlling the activity of large molecules through intricate feedback systems (Fig. 1). The interplay between the macromolecular constituents and the smaller molecules within the cell is the main determinant of the cell's function and dysfunction.

It is crucial to understand that our own gene-encoded proteins only generate a small portion of the intricate and constantly evolving metabolome. Furthermore, it originates from the air we inhale, the food we consume, the water we drink, and the metabolic waste products generated by the bacteria residing in our bodies (Nicholson et al. 2004; Goodacre 2007; Scalbert et al. 2009; Lindon and Nicholson 2014). Due to this limitation, the human transcriptome, proteome, and genome alone cannot provide a complete understanding of the metabolome. Therefore, they cannot be used to make accurate predictions about it. However, we contend that the metabolome provides the most enlightening and immediate understanding of the diversity of human diseases and the differences in how individuals respond to treatment, and it does so by considering the entire system. Despite the intricate nature of the metabolome and the associated

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technical difficulties in accurately measuring it, this remains the case. Regarding human health, significant non-genomic factors are considered.

Advancements in technology have enabled the accurate and thorough measurement of numerous metabolites, including the relative concentrations of thousands of distinct metabolites, in complex biological mixes like blood and urine. This is a substantial advancement in the realm of biochemistry. This feature enhances the untargeted metabolite profiling methodology, turning it into a very effective and advanced analytical method. Complete metabolite profiling, when used on samples from large-scale initiatives like the National Institutes of Health Precision Medicine Initiative Cohort (PMI), is expected to be an extremely valuable tool for categorizing patients, thus advancing the potential of precision medicine. This is attributed to the ongoing expansion of existing technology, with the likelihood of forthcoming technical advancements. Therefore, the use of metabolomic analysis in extensive precision medicine projects is imperative to maximize the return on investment. Although the process of incorporating metabolomics may occur in stages over time, such as sample collection, preparation, and storage, we kindly ask that samples for the current investigations be gathered in a way that meets the criteria for metabolomic profiling.

Metabotyping is currently used to screen for inborn errors of metabolism

A multitude of inborn errors of metabolism, referred to as IEMs, have been identified due to the accumulation of metabolic data and the inclusion of a certain metabolic profile in blood. If IEMs, which are monogenetic metabolic abnormalities, are not promptly identified and treated, they can be fatal for newborns or result in permanent organ damage. However, numerous inflammatory bowel disorders (IEMs) can be managed with dietary modifications and the use of nutritional supplements, which can be life-saving if detected through early screening. By utilizing current metabolite profiling platforms, which can analyze numerous metabolites in small amounts of neonatal blood, we expect that in the near future, the range of diagnosable inborn errors of metabolism (IEM) will greatly increase. This advancement will enable us to identify genetic disorders that have not been previously recognized.

Metabotypes for genotypes—the metabolome provides a readout for functions of genetic variants

More than a hundred years ago, Archibald Garrod suggested that "inborn errors of metabolism" are simply extreme instances of variances in chemical behavior that likely exist to a lesser extent worldwide. He also suggested that this "chemical individuality predisposes individuals to certain diseases and provides them with immunities against various mishaps that are commonly referred to as diseases." Garrod's proposal posited that these variances likely exist universally, but to a lesser extent. Currently, researchers are analyzing stored samples of blood, urine, and other bodily fluids using advanced technologies such as genomics, transcriptomics, proteomics, metabolomics, and other large-scale omics techniques (Kastenmu¨ller et al. 2015; Sanseau et al. 2012; Shin et al. 2014; Suhre et al. 2011a, b, 2016; Suhre and Gieger 2012). Population-based study involved surveying thousands of individuals from the general population to gather data on their demographics, health, and lifestyle choices.

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The investigations have confirmed that there are multiple instances where genetic predisposition combines with environmental influences and lifestyle choices, mediated by metabolic phenotypes, in the development of complex illnesses. This supports Garrod's hypothesis. Figure 2 portrays a genetically influenced metabotype (GIM), serving as a visual representation of the notion. Currently, approximately 150 genetically modified organisms (GMOs) have been identified (Kastenmu¨ller et al. 2015). The GIMs are presently being used to analyze the genetic and environmental variables that contribute to the development of complicated disorders (Fig. 3). The Deep metabolic phenotyping, conducted as part of the Precision Medicine Initiative Cohort Program along with other projects in precision medicine, is expected to discover novel targets for clinical intervention, new biomarkers, and definitively identify crucial components in the development of major diseases. The community of systems biology has generated a comprehensive blueprint of human metabolic pathways and its connection to genes and their expression. The blueprint is commonly known as the global human metabolic network (Thiele et al. 2013). Based on the results of a recent genome-wide association study (GWAS) conducted by Sanseau et al. in 2012, this blueprint would provide guidance for the development of strategies to accurately and specifically regulate metabolites that are not functioning properly. These solutions may involve using existing and safe medications. In summary, the metabolome serves as a means to understand the impact of genetic variations on human diseases, while also offering valuable insights on disease pathways, heterogeneity, progression, and treatment-related variations.

Pharmacometabolomics: a detailed biochemical roadmap for defining disease heterogeneity and drug response variation

The Pharmacometabolomics Research Network (PGRN) and the Pharmacogenomics Research Network (PMRN) have collaborated extensively over the past eight years in their research projects, with substantial funding from the National Institute of General Medical Sciences (NIGMS). These networks have made a substantial contribution by identifying how genetic and metabolic data, either separately or together, can offer insights into treatment outcomes and the mechanisms that cause variation in response to medicines. To demonstrate the applicability of the precision medicine approach in human research, a study was conducted on over 10 distinct categories of drugs in patients. This study, along with several others, played a key role in creating the structure and establishing the essential concepts for this emerging field of research. Alternative terms for this discipline are pharmacometabolomics and pharmacometabonomics.

The initial table. Based on the results of a significant study conducted by researchers from Imperial College and its pharmaceutical consortium (Clayton et al. 2006), the initial metabolomics data acquired in the study can offer valuable information and understanding regarding the metabolism and toxicity of medicines in animals. The discipline of pharmacometabolomics has emerged to study how individuals respond to medication and get a deeper knowledge of treatment outcomes. It aims to identify an individual's "metabotype," which refers to their metabolic state, influenced by environmental, genetic, and enteric microbiome

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factors (Fig. 1). Previous research has shown that baseline metabolic profiles, collected before to treatment, can offer insights into treatment success and the variability of the condition. The metabolic profiles also serve as valuable tools for mapping the worldwide effects of medications on metabolism. They also aid in the identification of networks and pathways related to a drug's mechanisms of action and the factors contributing to variations in drug responses. Furthermore, metabolic profiles can be employed to delineate the overall impact of medications on metabolism.

Kaddurah-Daouk and Weinshilboum (2014) and Weinshilboum (2015) have recently published reviews that have emphasized exceptional findings about the factors influencing the variability in response to drugs used for treating neuropsychiatric and cardiovascular illnesses. Metabolic profiles have been found to offer insights into the occurrence of therapeutic side effects and variations in the response to medications such as antipsychotics, statins, antidepressants, antihypertensives, and antiplatelet treatments. The metabolic profiles of patients can provide this information through testing. In the initial human validation trial, three antipsychotics were administered to individuals with schizophrenia to investigate their effects on metabolism. The study also identified a baseline signature that is associated with treatment outcomes (Kaddurah-Daouk et al., 2007). The purpose of this inquiry was to authenticate the efficacy of the treatments for schizophrenia. Subsequent to that period, the process of identifying the different metabolic profiles of individuals with depression and understanding the sequence of biochemical changes caused by SSRI antidepressants (specifically serotonin reuptake inhibitors) has commenced to elucidate the biochemical basis for delayed response, placebo effects, and resistance to treatment in cases of major depression.

This has been achieved by identifying the fundamental biological pathways. Metabolomics data combined with genetic data can provide initial insights into the factors that contribute to variation in treatment response. For instance, it can help identify gender differences in response to antiplatelet therapies like aspirin, as well as the ethnic factors that contribute to variation in response to antihypertensives such as beta blockers and thiazide. Both of these cases were presented within the framework of the therapeutic response. The contrasting responses to acetaminophen (Clayton et al. 2006, 2009; Winnike et al. 2010) and statins (Kaddurah-Daouk et al. 2011b) emphasized the significant influence of gut flora on the body. Metabolomics data provides insights into factors that affect human health beyond genetics. Several studies, including those focused on cancer chemotherapies, as well as pharmacometabonomics, all emphasize the significance of incorporating this data into precision medicine initiatives.

Metabolomics is an important tool for analyzing and categorizing patients, and it has the potential to be seamlessly incorporated into therapeutic practice. This integration would enable the anticipation of treatment outcomes. This may lead to the creation of decision support systems that will aid medical professionals and patients in choosing or suggesting the most suitable treatment option (including lifestyle modifications) in a comprehensive manner. By using "personalized profiles," we want to avoid the commonly used treatment-failure approach, leading to better patient outcomes.

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The gut microflora influence human metabolism and a metabolic profile informs about gut microbiome activity

The metabolic activity of the microbiome residing in the human intestine is widely recognized to be similar to that of the liver's blood. The gut microbiome's composition has many consequences, both locally and systemically. Therefore, it has been linked to several systemic conditions, including but not limited to neurological, cardiovascular, and immunological difficulties, as well as local disorders such inflammatory bowel disorders (Table 2). Microbiome-associated metabolomics has allowed for the exploration and definition of numerous therapeutically relevant aspects. Examining the composition of the stool/gut metabolome and microbiome, together with analyzing the systemic metabolome of the host using biofluids such blood, urine, and saliva, is generally seen as beneficial in this context. Table 2 presents a concise overview of important and medically significant uses of metabolomics in relation to the functions of the gut microbiota. Hence, to assess the metabolic activity of the gut microbiome, the metabolomics task group suggests collecting at least one urine sample and one fecal sample from a subset of individuals included in the PMI Cohort and related research endeavors. Following a complete 24-hour period of fasting, it is recommended to collect these samples. In order to monitor the body's response to environmental shocks, such as the impact of pharmacological therapies on the gut microbiota, it would be highly beneficial to collect more samples from a specific subset of the population at regular intervals.

Nutrition-associated metabolic phenotyping

The metabolic phenotype has been extensively analyzed and characterized utilizing metabolomics in the field of nutrition. Moreover, it is crucial to examine the impact of food as a prominent environmental factor in comprehending its association with disease and to develop a concise and conclusive public health communication on disease prevention. Metabolomics is the scientific discipline that investigates the interrelationships of disease, diet, and pathology. This research not only improves our understanding of pathology but also clarifies how understanding of metabolism can be used to increase human function and performance, as well as play a vital role in disease prevention. Accurately assessing food intake is challenging because most research relies on proxy approaches, such as questionnaires, which are known for their inaccuracy (Dhurandhar et al., 2015).

In addition, analyzing the metabolic composition of blood and urine can offer biomarker data that can rectify inaccuracies in questionnaires and significantly enhance the precision of estimating dietary consumption. Analyzing the blood and urine can provide this information. Nutrition has been well established to have a substantial impact on both health and illness. Obesity and adiposity, along with cardiovascular disease and some malignancies, are linked to various additional negative health consequences. For example, the probability of males having colon cancer is greater than that of females, and food also plays a key role as a risk factor for this disease. Consuming diets that contain a significant amount of red or processed meats is linked to a higher likelihood of developing colon cancer. The main experimental categories that can be

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identified in nutritional metabolomics research are: (A) the use of dietary biomarkers; (B) the study of metabolic reactions to dietary treatments; and (C) the investigation of disorders associated with food. Each of these applications can provide further information about the impacts of food, which is a crucial environmental factor that can be changed.

Metabolic profiling technologies

In the last 15 years, there has been a significant transformation in the investigation of metabolites, resulting in the growth of the metabolomics field. This transformation has been facilitated by pioneering advancements in scientific instruments and computational resources. Thanks to the continuous advancements in chromatography combined with mass spectrometry (MS) and nuclear magnetic resonance (NMR) spectroscopy, we can now effectively measure hundreds to thousands of metabolites in a biological sample within a short analytical time of less than twenty minutes. This has enabled us to achieve this. Previously, our ability to monitor metabolites throughout a typical hypothesis-testing inquiry was restricted to a small number (Cajka and Fiehn 2014; Fiehn 2016). Dunn et al. (2011) assert that the significant increase in analytical capability has led to the emergence of unforeseen opportunities. In other words, it has successfully illuminated regions that were previously overlooked. The term "metabotyping," also referred to as metabolic phenotyping, is used to characterize this non-targeted approach. Metabotyping plays a crucial role in revealing the molecular interactions that facilitate metabo-regulatory processes in cells and tissues, as well as identifying the metabolites present in a complicated biological mixture.

Only by employing holistic methodologies can we accurately describe the complete biological interactome in respect to human phenotypes. Once certain metabolic indicators have been found, further investigation can be carried out using personalized testing to confirm the findings and examine newly developed ideas. The latest translational study (Gooding et al. 2015; Tannahill 2013) indicates that metabotyping has the capacity to lead to the identification of novel and important biomedical findings. Methods such as nuclear magnetic resonance (NMR) spectroscopy, gas and liquid chromatography linked to mass spectrometry (GC–MS and LC–MS), and other techniques are currently available for doing thorough metabolic profiling. Recent studies have demonstrated the feasibility of gathering data that is both dependable and of high quality (Draisma et al., 2015; Dunn et al., 2015). This breakthrough is important since large-scale cohort studies rely heavily on the reliability and consistency of these systems. By utilizing this method, we have successfully shifted from performing research on a limited scale to conducting comprehensive studies that may encompass thousands of samples.

In point of fact, a number of "Phenome Centers" are currently being established in order to provide the infrastructure and resources that are required to support large-scale studies. These centers include the National Phenome Centre in London, the Phenome Centre in Birmingham, United Kingdom, the six NIH Regional Comprehensive Metabolomics Resource Cores in the United States of America, and large consortia such as Alzheimer Disease Metabolomics. It is crucial to standardize the studies conducted at many sites to ensure that the data can be compared

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and integrated. This is due to the absence of a single facility with the capacity to support investigations of the scale envisioned for the PMI Cohort. Moreover, this could prove to be a challenging endeavor. In the absence of standards, it will be impossible to collect data from other sites and compare or combine it between them. These new endeavors have made it possible to apply the expertise of metabolic profiling studies to investigations in which only genomic and transcriptome data were previously accessible in a manner that is synergistic.

A reliable method for absolute quantification of a smaller number of metabolite panels (hundreds, rather than thousands) can be achieved through the utilization of numerous (semi)-targeted assays for each individual sample. In order to improve metabolic phenotyping in a holistic manner, this combined omics technique is being utilized, and relative quantification data is being generated. As an illustration, the company Biocrates engages in the sale of kits that are designed for the analytical research of certain metabolic zones. In addition to measuring amino acids, biogenic amines, and 150 lipids, the Biocrates p180 kit has been shown to be useful for evaluating dry blood spots (Biocrates Life Sciences 2016). This has been proved through a number of studies. With the help of the Biocrates bile acid kit, it is possible to precisely quantify each of the sixteen bile acids that are found in human beings. In the last 15 years, there has been a significant transformation in the investigation of metabolites, resulting in the growth of the metabolomics field. This transformation has been facilitated by pioneering advancements in scientific instruments and computational resources. Thanks to the continuous advancements in chromatography combined with mass spectrometry (MS) and nuclear magnetic resonance (NMR) spectroscopy, we can now effectively measure hundreds to thousands of metabolites in a biological sample within a short analytical time of less than twenty minutes.

This has enabled us to achieve this. Previously, our ability to monitor metabolites throughout a typical hypothesis-testing inquiry was restricted to a small number (Cajka and Fiehn 2014; Fiehn 2016). Dunn et al. (2011) assert that the significant increase in analytical capability has led to the emergence of unforeseen opportunities. In other words, it has successfully illuminated regions that were previously overlooked. The term "metabotyping," also referred to as metabolic phenotyping, is used to characterize this non-targeted approach. Metabotyping plays a crucial role in revealing the molecular interactions that facilitate metabo-regulatory processes in cells and tissues, as well as identifying the metabolites present in a complicated biological mixture.

Only by employing holistic methodologies can we accurately describe the complete biological interactome in respect to human phenotypes. Once certain metabolic indicators have been found, further investigation can be carried out using personalized testing to confirm the findings and examine newly developed ideas. The latest translational study (Gooding et al. 2015; Tannahill 2013) indicates that metabotyping has the capacity to lead to the identification of novel and important biomedical findings. Currently, there are various methods available for doing comprehensive metabolic profile, including nuclear magnetic resonance (NMR) spectroscopy, gas and liquid chromatography coupled with mass spectrometry (GC–MS and LC–MS), and

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other approaches. Recent studies have demonstrated the feasibility of gathering data that is both dependable and of high quality (Draisma et al., 2015; Dunn et al., 2015). This breakthrough is important since large-scale cohort studies rely heavily on the reliability and consistency of these systems. By utilizing this method, we have successfully shifted from performing research on a limited scale to conducting comprehensive studies that may encompass thousands of samples. Several "Phenome Centers" are currently being built to provide the necessary infrastructure and resources for large-scale studies.

The centers mentioned are the National Phenome Centre in London, the Phenome Centre in Birmingham, United Kingdom, the six NIH Regional Comprehensive Metabolomics Resource Cores in the United States of America, and the Alzheimer Disease Metabolomics consortium. It is crucial to standardize the studies conducted at many sites to ensure that the data can be compared and integrated. This is due to the absence of a single facility with the capacity to support investigations of the scale envisioned for the PMI Cohort. Moreover, this could prove to be a challenging endeavor. Without established standards, it will be unfeasible to gather data from different sites and make meaningful comparisons or merge it together. These recent initiatives have enabled the utilization of metabolic profiling studies in investigations that previously only had access to genomic and transcriptome data, resulting in a synergistic approach. To accurately measure the exact amount of a smaller set of metabolite panels (hundreds, not thousands), one can use multiple (semi)-targeted assays for each sample.

To enhance comprehensive metabolic phenotyping, researchers are employing a combined omics method to obtain relative quantification data. For example, Biocrates is involved in selling specialized kits that are specifically developed for the analytical investigation of specific metabolic areas. The Biocrates p180 kit has demonstrated utility in assessing dry blood spots, as it can measure amino acids, biogenic amines, and 150 lipids (Biocrates Life Sciences 2016). This has been substantiated by a multitude of investigations. The Biocrates bile acid kit enables accurate quantification of all sixteen bile acids present in humans.

Stable isotope tracing in mechanism-based human health

Conducting a large-scale inquiry employing tracer techniques is not feasible, even though these methods offer more interpretability and effectiveness compared to profiling (Fan et al., 2012). However, it is possible to envision carrying out research on a specific subgroup, such as cancer, by utilizing tissue samples and liquid biopsies (leukocytes). During these types of research, the sample is exposed to a suitable tracer, and the investigation focuses on the metabolic activity of the tissue or cells. Thanks to the advancements in mass spectrometry, it is now feasible to analyze very tiny quantities of tissue using this technique. Long-term research, encompassing trials conducted both before and after therapy, demonstrates the efficacy of these techniques. In summary, significant advancements have been made during the past fifteen years, enabling thorough research on the presence of metabolites in individuals. The PMI Cohort and other extensive programs are currently striving to achieve the objective of conducting comprehensive and replicable large-scale investigations on the role of metabolites in predicting variations among

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human subjects. This research are becoming viable. Due to our integration of several platforms and approaches, we are currently capable of offering extensive coverage of the organism's metabolome. We expect that standardized methodologies will be implemented in upcoming high-throughput metabolite profiling facilities worldwide. New technological advancements are expected to enable the following: enhanced detection of metabolites, increased efficiency in processing samples, establishment of normal ranges for various metabolites found in blood, and simplified transportation of samples from home to the clinic.

Computational medicine

Metabolic phenotyping has the capacity to provide a significant volume of intricate spectrum data owing to its intricacy. To effectively utilize this data in the medical field, whether for patient classification, diagnosis, or mechanistic study, a substantial amount of computational power and expertise is necessary. Currently, the metabolomics community uses several computational frameworks. However, none of these frameworks are specifically designed to suit the requirements of precision medicine, as stated by Xia et al. in 2013. Large-scale metabolic modeling enables the integration and simulation of many types of omics data with metabolic networks (Aurich and Thiele 2016). In addition, it enables the integration of genetic and nutritional data alongside metabolomic data (Heinken and Thiele 2015). The metabolic models (Aurich and Thiele 2016) establish the molecular connections between proteins, genes, and metabolites. These models are based on human biochemistry, enabling them to provide this information.

Recent research have shown that metabolic modeling, when used in conjunction with personalized metabolic data, has the potential to advance precision medicine (Yizhak et al. 2014). In a study conducted by Aurich et al. in 2016, the potential of metabolic modeling was highlighted. In the near future, computational medicine is expected to make significant progress by integrating the flexibility of advanced "big data" machine learning methods with the strict limitations of conventional epidemiology. This will be achieved by integrating the two methodologies. To advance the development of future clinical expert systems, it is imperative to establish a comprehensive understanding of the intricate interconnections among metabolomic, genomic, and other omic data. Furthermore, the profiles that are produced from this mapping procedure must be connected with clinical metadata obtained at the patient's bedside.

One of the major obstacles in developing omic precision medicine will be the compression of large amounts of high-throughput data into instruments that are relevant to clinical practice. The inclusion of an omic-based prognostic/diagnostic signature in a "test" relies on the existence of a corresponding precise computational model. An omic test, as defined in the report "Evolution of Translational Omics" published by the Institute of Medicine (IOM) in 2012, refers to an assay that consists of multiple molecular measurements and is interpreted by a fully specified computational model to generate a clinically actionable result. Put simply, an omic test is a test that assesses the outcomes of several molecular measurements.

Consequently, the advancement of rigorous statistical techniques and specialized computational models is just as crucial to this field of study as managing the rapid progress in technology.

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Recommendations for precision medicine initiatives

1. When obtaining biofluids, adhere to the accepted standard operating procedures (SOPs) established by the metabolomics community. Formulate collaborative teams of people from the metabolomics community to develop optimal protocols for sample collection, sample preservation, sample processing, data collection, and omics analysis.
2. To ensure the long-term storage of samples, it is necessary to build a dependable and strong biobanking system that involves meticulous inventory control. It is advisable to include samples that contain serum or samples that have been rapidly frozen, in addition to plasma (EDTA or heparin). It is advisable to gather additional samples of urine and feces in order to conduct follow-up research on topics such as the microbiota in the gastrointestinal tract, diet, and other scientifically significant subjects.
3. It is crucial to establish funding options to address challenges in personalized medicine by using biobanked samples and conducting extensive metabolic phenotyping studies using targeted and untargeted techniques.
4. In order to ensure consistency and quality in plasma metabolomics studies conducted at different analytical locations across time, it is recommended to use plasma samples obtained from the NIST Standard Reference material (SRM1950) for standardization purposes.
5. It is necessary to provide a NIST Standard Reference material for urine and serum to simplify the process of standardizing and controlling the quality of research related to urine and serum metabolomics. Expanding the quantity of shared reference resources will provide individuals more choices.
6. It is crucial to create rigorous statistical and epidemiological methodologies with the advancement of computational medical tools for future generations.