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THE KEY TO PRECISION MEDICINE IS A BLUEPRINT OF INDIVIDUAL HEALTH

Precision medicine is at the heart of health care providers' goals to improve health, diagnoses and treatment for their patients. The key to advancing precision medicine lies in first creating a blueprint of human health. This will require collecting and analyzing massive amounts of data to build an expansive toolbox of recommendations about wellness and treatment for individuals.

Many organizations, including Metabolon, have embraced this challenge as interest in precision medicine continues to grow. Several partnerships aim to unlock understanding of health and disease so they can develop better treatments. Examples include Amgen's acquisition of deCODE Genetics, 23andMe's agreements with pharmaceutical companies like Genentech and Pfizer, and Geisinger Health System's collaboration with Regeneron.

Then there's the personal health and wellness side of the equation, where Metabolon is collaborating with Craig Venter's Human Longevity, Inc. and Lee Hood's Arivale. These organizations aim to understand the blueprint for health and aging to favorably alter these states. Even Apple is in the game with their ResearchKit for iPhones and its potential to enable personal health and precision medicine.

A Data Conundrum

While genomics is undeniably important in creating the precision medicine blueprint, most of these initiatives recognize the need to include other types of data, in addition to medical records and standard clinical assessment. This is because the last decade of genomics research has revealed higher than anticipated individual genetic variation. In addition, most traits of interest involve a combination of many genes[1,2]; and the majority of mutations reside in non-coding regions of the genome, where we have a very poor understanding of the function[3]. It cannot be ignored that massive amounts of data must be managed before consensus and actionable data can be effectively mined, as illustrated by a recent whole genome sequencing initiative published in *JAMA*[5,6].

Add to the above the fact that elusive influences such as the microbiome[4] and epigenetics are clearly important, and it is evident why many genomics investigators seek additional data types in their efforts to contend with this overwhelmingly complex picture.

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The Missing Link in Precision Medicine

Metabolomics is becoming a core element in defining the blueprint of human health. The reason for its inclusion is simple. Metabolites are central to the health state, and they reflect the role of factors such as genetics and external influences like diet and lifestyle. An individual's metabolic state offers an intimate assessment of their state of health ***as it is*** at the time a sample is provided. Recall, many metabolites such as glucose and cholesterol are already the staples in clinical assessment today.

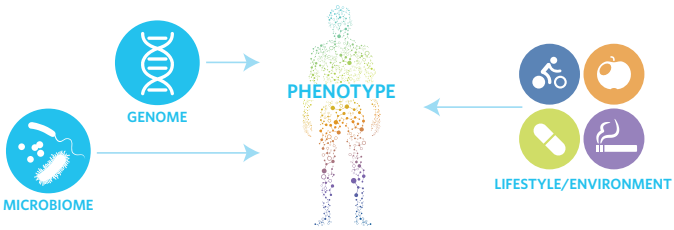
Metabolic pathways are more completely understood than almost any other aspect of human biology. They have been integral for mapping many complex physiological processes like muscle and cancer metabolism. Metabolomics measures all of the metabolites within these pathways. This is a critical reason why a growing number of large precision medicine and next-generation sequencing (NGS) initiatives have adopted metabolomics as a cornerstone of their programs to link genetics and metabolic profiles to phenotypes or health states.

Metabolomics alleviates some of the challenges of genomics by identifying genes that are effectively "active" and then creating a functional connection between the gene and the health state. This has been demonstrated for a variety of traits in fairly healthy populations[7,8] and profoundly illustrated in more severe genetic states[9,10].

In work done in collaboration with HLI and King's College, low frequency and rare variants identified by whole genome sequencing were queried by metabolomics to reveal a host of important insights. Arguably, the most important insight was that rare heterozygous variants were associated with significant deviations of various metabolites, even though they are only associated with diseases in homozygous cases.[11] This work echoes the growing list of publications that illustrate the value of adding metabolomics for informing on genetics and human health.

There is growing appreciation that complex illnesses such as diabetes, cancer, cardiovascular and neurological diseases are caused by a combination of genetic and non-genetic factors.

Clinicians must take into account the impact of these factors to make an informed diagnosis. Metabolomics reflects the influences of genes, diet, lifestyle, environment and xenobiotics to aid in understanding gene function and how diseases originate. It also provides the biomarkers for health assessment and customized therapy.



NGS & Population Health Studies Have Tapped into Metabolomics

Large-cohort population health studies will fill the precision medicine toolbox with more information, leading to far more options for health care and precision medicine. Not surprisingly, metabolomics is routinely being used to augment and highlight important genomic data in these health initiatives. But more broadly, metabolomic profiling is an ideal way to phenotype individuals and establish a beachhead from which to integrate genomics and other types of data. This framework ultimately provides a gateway for deriving the blueprint of individual health. The basis of achieving better individual health by any means, including precision medicine, is to map this blueprint completely and accurately.

Metabolomics has emerged as a powerful technology for precision medicine by dissecting underlying disease processes. This may set the stage for new ways to diagnose, monitor and provide guidance for treatment. Metabolon is participating in many of these efforts to map human health, while also capitalizing on the biomarkers and signatures already derived to assess individual health right now. Whether used for routine health assessment or in conjunction with genetic sequencing, metabolomics must play a vital role in precision medicine.

Supporting References

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