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A multi-omics precision medicine approach for diagnosis of inborn errors of metabolism

Metabolomics is the study of the distinctive chemical fingerprint produced by specific cellular processes. Untargeted mass spectrometry-based metabolomic profiling for small molecules in body fluids is an emerging technique used to produce and analyze this chemical fingerprint. This technology holds the promise of providing new insights into human disease states and serving as a primary diagnostic tool for novel and previously characterized inborn errors of metabolism (IEM), as well as for the identification of biomarkers of disease and treatment. Clinical metabolomic profiling allows for parallel screening of hundreds of metabolites in a single biological specimen. On average, ~900 small molecules are detected in a given plasma sample with a core group of ~350 analytes found in all specimens tested to date. The analytes detected encompass numerous classes of small molecule biomarkers including acylcarnitine's, amino acids, bile acids, carbohydrates, lipids, and nucleotides. In addition, metabolomic data in many cases affords a much richer view of a patient's metabolic disturbance by identifying: (1) elevated metabolites located far upstream of the genetic defect, (2) treatment related compounds, including commonly tested therapeutic drug monitoring analytes, and (3) spectrally unique analytes that are not yet associated with a biochemical phenotype. In our clinical experience, the integration of whole exome sequencing data with the metabolomics profile has improved the interpretation of genetic variants, including ruling out the diagnosis of IEMs, as well as supporting a specific diagnosis, and for the identification of new disease and/or treatment biomarkers. For undifferentiated clinical phenotypes such as intellectual disability, hypotonia, autism, or seizures, many different tests involving different sample types are often needed for diagnosis. This can lead to prohibitive costs and ongoing diagnostic odysseys. Data will be presented on genomic and metabolomic profiling of previously non-diagnostic cases which pointed to genetic disorders such as aromatic amino acid decarboxylase deficiency, GABA transaminase deficiency, adenylosuccinate lyase deficiency, and peroxisome biogenesis disorders, illustrating the powerful synergy of genomic and metabolomic analysis in determining the pathogenicity of variants of uncertain significance. Ultimately, a clinical systems biology approach to the integration clinical data with genomic, transcriptomic, epigenomic, proteomic, and metabolomics data will provide a comprehensive precision medicine approach to improve understanding of natural biological variation and to improve diagnosis and management of disease.

Biography

Sarah H Elsea is a Professor of Molecular and Human Genetics at Baylor College of Medicine and the Senior Director of Biochemical Genetics at Baylor Genetics. She has received her BS in Chemistry with a minor in Biology from Missouri State University and a PhD in Biochemistry from Vanderbilt University. She has completed her Postdoctoral Fellowships in Molecular and Biochemical Genetics at the Baylor College of Medicine and is a Board-Certified Geneticist through the American Board of Medical Genetics and Genomics. She held Faculty appointments at Michigan State University and the Medical College of Virginia at Virginia Commonwealth University prior to returning to Baylor College of Medicine. Her research is focused on the discovery, pathomechanisms, diagnosis, and treatment of rare disease, particularly neurodevelopmental and neurometabolic disorders. She is a Member of several professional societies and has authored more than 90 scientific and lay articles.

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