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Metabolomics in the clinic: A review of the shared and unique features of untargeted metabolomics for clinical research and clinical testing

By Adam D. Kennedy, Bryan M. Wittmann, Anne M. Evans, Luke A.D. Miller, Douglas R. Toal, Shaun Lonergan, Sarah H. Elsea and Kirk L. Pappan

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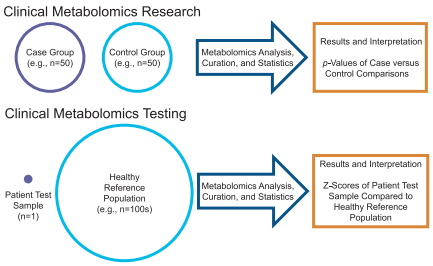

For over a decade, metabolomics has been promising to transform the practice of medicine by delivering powerful diagnostic tests. The reality, however, is that the march towards precision medicine has been slower than first anticipated because of the substantial challenges associated with the development, validation and adoption of complex multivariate testing strategies within a highly regulated environment. In this issue, Kennedy and colleagues present their vision for the future of untargeted metabolomics in clinical testing. They highlight the complexities of test design, accurate and precise data acquisition, quality control, data processing and biochemical pathway analysis when hundreds to thousands of unique metabolites are measured in a single clinical sample. The authors outline the current state of (mass spectrometry-based) metabolomics and illustrate the both the potential, and the challenges, of this rapidly evolving landscape.

Authors' biographies

Adam Kennedy is the former Director of Precision Medicine R&D at Metabolon and is currently the Director of Advanced Technology at Baebies, Inc. Dr. Kennedy earned his Ph.D. at the University of Virginia conducting research on antibody therapies to leukemia/lymphoma that culminated in a Phase III clinical trial of the antibody Rituximab. His post-doctoral studies at the National Institutes of Health focused on host-pathogen interactions specifically detailing the interaction between *Staphylococcus aureus* and human neutrophils. This research resulted in the delineation of three major clades of *S. aureus* and led to pre-clinical testing of a vaccine leading to a successful Phase I clinical trial. Dr. Kennedy's research at Metabolon included completion of over 200 metabolomics projects for biotechnology, consumer goods, animal health and nutrition, and human health companies, the development of diagnostic tests for insulin resistance and impaired glucose tolerance, and finally in the analytical and clinical development of CLIA/CAP validated tests using untargeted metabolomics for precision medicine applications such as the screening of inborn errors of metabolism. At Baebies, he is currently conducting research to develop products for newborn screening and monitoring of critical diseases. Dr. Kennedy has published widely in the areas of biochemistry, immunology, and metabolomics and has over 40 peer-reviewed scientific publications and 5 pending or awarded patents to his credit.

Bryan Wittmann is the Director of Discovery and Translational Sciences for Precision Medicine at Metabolon. Dr. Wittmann joined the Discovery and Translational Sciences group in 2011 as a Study Director for the Academic Research Services, transitioning to Associate Director for the Commercial Research Services before taking on the role of Director for Precision Medicine in 2016, where he has been involved in both the development of the clinical metabolomics products and the analysis of over 300 metabolomics datasets spanning these three sectors. Prior to joining Metabolon, Dr. Wittmann received his Ph.D. in Pharmacology at Case Western Reserve University with Dr. Monica Montano where they co-discovered and defined the role of the novel tumor suppressor HEXIM1 in steroid hormone driven cancers. He continued working in the area of transcriptional regulation and pharmacology of steroid hormones and their receptors for the development of novel SERMs and SARMs during his post-doctoral training in the department of Pharmacology and Cancer Biology at Duke University under Dr. Donald McDonnell. His work has contributed to publications and patents in the areas of metabolomics and steroid hormone nuclear receptors and their associated cancers.

Dr. Evans leads the discovery metabolomics and lipidomics profiling research and development team at Metabolon, Inc. where she has been working for 14 years. The metabolomics and lipidomics platforms developed under Dr. Evans have been the analytical basis for thousands of commercial studies from over 700 institutions since 2004. Dr. Anne Evans received her Ph.D. in chemistry from the University of Virginia where her research was focused on proteomic analysis in the areas of immuno oncology and type 1 diabetes with Dr. Donald Hunt.

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Authors' biographies

Luke Miller, PhD. V.P. of Lab Operations leads the Metabolomics, R&D, Targeted Analysis, Data Curation and Facilities Management businesses and he has management line responsibility for a group of over 60 individuals. He has a B.Sc. double honors degree in Chemistry and Management, a Ph.D in Analytical Chemistry and over 25 years' experience in small molecule analysis including over 20 years in senior management research positions. Luke joined Metabolon in March of 2013 after a 17 year career with GlaxoSmithKline where he led the Analytical Chemistry department in GSK's research organization. During his career, Luke has developed super-critical fluid instrumentation and technology for analysis and purification of small molecule drug-like compounds, designed a multiplexed UV detector and co-developed a multiplexed mass spectrometer for improved analytical throughput and co-developed a time of flight mass spectrometer to deliver higher resolution and tighter accurate mass data. Since joining Metabolon, he has isolated a novel biomarker with potential for diagnosing pre-diabetes and led the team responsible for fully characterizing that marker, leading to a patent in early 2016. He is responsible for the global metabolomics technology development, including a collaboration with Sciex to deliver a new, high throughput lipid analysis platform. His group at Metabolon works with over 700 clients and has completed over 5000 commercial studies. He speaks and publishes regularly in the field of metabolomics and health care sciences.

Douglas Toal, Ph.D. is a board-certified Diplomat of the American Board of Medical Microbiology and has broad expertise in Clinical Laboratory Operations and Assay Development. He has over 20 years of experience in diagnostic assay development and validation, quality management, talent development, and laboratory workflow efficiencies. He has completed postdoctoral-fellowship training at the Mayo Clinic and has served as Laboratory Director for multiple, high-throughput regional and global clinical reference laboratories.

In the areas of translational research and medicine, Dr. Toal led efforts to utilize multi-fluidic technologies to develop and validate clinical assays for multidrug resistant pathogens and at Metabolon, Inc., he is the Laboratory Director and a pioneer in the clinical application of metabolomics for the detection of inborn errors of metabolism and undiagnosed disease. He has developed and validated novel, small molecule biomarker assays for prediabetes, chronic kidney disease and liver disease.

Shaun Lonergan is the former Vice President, Corporate Development at Metabolon, Inc. He has extensive experience in the clinical diagnostic and life science industries, successfully introducing major research and diagnostic instrument platforms. Mr. Lonergan has held senior positions at Boehringer Mannheim (Roche), Perceptive Biosystems (Life Technologies), Third Wave Technologies (Hologic), NimbleGen (Roche), 454 Life Sciences (Roche), Ibis Biosciences (Abbott Molecular) and Seegene, Inc. He also served as CEO and President of Nerites Corporation. Prior to that, he was the Clinical Director at Oncology Laboratory, Inc. and had responsibility for the in-vitro chemosensitivity assay clinical team. Mr. Lonergan earned his Master of Science degree in microbiology from the University of Rhode Island.

Dr. Sarah H. Elsea is a Professor of Molecular and Human Genetics at Baylor College of Medicine and Senior Director of Biochemical Genetics at Baylor Genetics. Dr. Elsea received a B.S. in chemistry with a minor in biology from Missouri State University and a Ph.D. in biochemistry from Vanderbilt University. She completed postdoctoral fellowships in molecular and biochemical genetics at the Baylor College of Medicine and is a board- certified biochemical 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 100 scientific and lay articles.

Kirk Pappan is the Associate Director of Discovery and Translational Sciences – Precision Medicine at Metabolon. Dr. Pappan received a B.S. and Ph.D. in biochemistry from Kansas State University working in phospholipid metabolism and signal transduction. He completed postdoctoral training at the Washington University School of Medicine in St. Louis in the areas of islet biology and type 2 diabetes. Kirk joined Metabolon in 2011 as a Study Director in the Discovery and Translational Sciences – Academic Research Services division, where he established collaborations with academic researchers around the world and completed the analysis of over 200 research metabolomics projects spanning topics such as diabetes, nutrition, and cancer. His research is focused on developing applications of global metabolomics for clinical testing, automated analysis metabolomics results, and use of metabolomics as a functional genomics tool to elucidate the role of enzymes and variants of unknown function. He has contributed to over 50 peer-reviewed scientific publications.