

“Translating global metabolomic profiling by LC-HRMS to a clinical diagnostic assay”

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Abstract – Metabolomics is a routine clinical diagnostic approach to understanding patient disorders. Clinically available metabolic tests have measured compounds of a single class such as amino acids, organic acids or acylcarnitines as small panels of metabolites or as individual compounds. These tests were made possible by the use of mass spectrometry and a colleague once said that “we are approaching a near zero false discovery rate” when discussing how fundamental mass spectrometry is to clinical diagnostics. Global metabolomic profiling (including lipidomics) is an attempt to measure metabolism in a new way by finding patterns or key sets of metabolites that correlate to a disease or disorder. This is made possible by utilizing high resolution/high mass accuracy mass spectrometry to measure thousands of metabolites from a small drop of blood. However, global metabolomic profiling is limited to research only projects because of the nature by which we measure the metabolome.

Currently, measuring the metabolome requires batching of controls with the set of samples from the experimental group and measuring them as a set. This is typical for any research type project as it helps to reduce error from day-to-day fluctuations of the instrument, column, or lab area, which then aids in finding the metabolites that describe the disorder not the day of analysis. This batch-mode approach limits translation to clinical diagnostics. In a clinical lab, the samples must be run as they come in not when we have a set of samples from a group of like individuals. Several groups have tried normalization approaches such as LOESS to help reduce day-to-day differences in large metabolomic projects, which has shown some success. This approach still relies on running groups of samples from the same project rather than samples from any project (or patient).

At UF, I am working with the Clinical and Translational Science Institute (CTSI) to translate Global Metabolomic profiling to clinical diagnostics. Our plan is to develop a library of clinical normals that will become the basis of clinical diagnostics. This clinical normal library will be curated to include a detailed clinical history attached to the global profile (metabolomic and lipidomic) obtained from LC-HRMS. While mass spectrometry is the basis of data collection, informatics is the basis of diagnosis, so a key aspect is our partnership with the Informatics Institute at UF in developing a decision making system using patterns compared to controls that will enable diagnosis.

I believe the incorporating quantitation as a part of a global profile will provide a better step forward not only for reducing day-to-day variability, but also providing a means to qualify the instrument for each sample, which is a necessity in clinical diagnostics. We plan to quantify several metabolites as part of the same analytical run for global metabolomic profiling as a better measure of data quality and specific variation in quality control specimens and therefore in patient samples.

Bio – Timothy J. Garrett earned his Bachelor's in Chemistry from the University of Georgia (Athens, GA) in 1999. After working in industry for a couple of years, he returned to school for graduate study at the University of Florida (Gainesville, FL) where he earned a Doctor of Philosophy in 2006. Dr. Garrett then translated to an assistant professor position in the College of Medicine at the University of Florida, and assumed operation of the Biomedical Mass Spectrometry facility. He has focused his work on expanding the use of MS in clinical sciences through education, analysis, and collaboration. At present, Dr. Garrett has collaborated with over 30 faculty members at the University of Florida. Dr. Garrett is currently a Research Assistant Professor in the Department of Pathology, Immunology and Laboratory Medicine at the University of Florida. He is Director of the high-throughput MS metabolomics core of the Southeast Center for Integrated Metabolomics (SECIM). Dr. Garrett is also working closely with the University of Florida Clinical and Translational Science Institute as well as UF Clinical Toxicology to grow and expand MS services for diagnostics.

