Chemical Engineering Dissertation Defense

Development of a Novel Diagnostic Urine Screening for Autism Spectrum Disorder Using Microbially Derived Metabolites

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Abstract

There is a critical and well-recognized need for a scalable, biologically based diagnostic screening assay for children with autism spectrum disorder (ASD), as early identification has been shown to enable earlier intervention and improve developmental outcomes, and understanding the underlying causes may enable prevention of the disorder in the future. Para-cresol (p-cresol) and its primary human metabolite, p-cresolsulfate (pCS), are well-established gut-derived metabolites implicated in ASD. P-cresol is generated by bacterial metabolism of phenylalanine and tyrosine and exhibits systemic toxicity, including mitochondrial disruption, oxidative stress, immune interference, and inhibition of dopamine β-hydroxylase. To translate these biological signals into diagnostic utility, I developed the Microbially-Derived Metabolites (MDM) System™, anon-invasive urine-based screening platform leveraging targeted LC-MS quantification of specific microbially derived metabolites. In the first cohort (50 ASD, 47 TD children, ages 2–11), untargeted semi-quantitative LC-MS followed by targeted quantitation revealed significantly higher concentrations of 32 microbial metabolites in ASD participants relative to TD controls. 45 of 50 individuals with ASD exhibited at least one metabolite above the upper limit observed in TD children, and many had concentrations elevated by 100–1000-fold. I discovered that ASD participants had, on average, three elevated MDMs, while TD participants had none. I further engineered a classification model algorithm for a heterogeneous disorder, ASD. Using one or more elevated metabolites as a cutoff, the test yielded a sensitivity of 90% and specificity of 100%.Validation in an independent cohort (42 ASD, 17 TD) confirmed six significantly elevated MDMs in the ASD group, with nearly identical classification performance (90%iisensitivity and 100% specificity). This replication strengthens the evidence that elevated microbial metabolite profiles can robustly distinguish ASD from TD children using a urine sample. These findings define a reproducible biochemical sub-phenotype of ASD, to which we formally name ASD associated with Microbially-Derived Metabolites(ASD-MDM). ASD-MDM encompasses approximately 90% of ASD cases, and perhaps importantly, paves the way toward guiding earlier and more individualized treatment in a currently expensive, lifelong neurodevelopmental disability like ASD.

November 6, 2025; 2:15pm; WXLR A308

Arizona State University

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