2. SPECIFIC AIMS

Early diagnosis of Autism Spectrum Disorder (ASD) and timely intervention is widely recognized as critical for achieving improved cognitive, behavioral and social outcomes.[1] Despite a growing list of suspected risk factors,[2]–[5] the etiology of Autism is still unclear. Even with increasingly widespread adoption of screening with standardized checklists at 18 and 24 months, the median age of diagnosis for ASD remains at over 4 years. Starting with a positive initial screen, a clinical diagnosis of ASD is a frustrating multi-step process spanning 3 months to 1 year, often delaying time-critical interventions. One obvious driver for these delays is the vast number of false positives encountered in the current initial screening. For example, the M-CHAT/F, the most widely used screener,[1], [6] produces over 85 false positives out of every 100 flagged for diagnostic evaluation, significantly inflating wait times[5] especially in rural and underserved communities. Further, current screening tools are sensitive to language barriers and cultural issues, and are particularly ineffective for children with milder symptoms with average or above-average cognitive abilities until about school age,[1], [7] often due to a "wait and see" approach adopted at the primary care. The need for better screening tools is thus paramount.

In this study, we plan to develop and validate the efficacy of machine inferred **digital biomarkers** for autism, mined automatically from past medical encounters. Using individual diagnostic codes already present in individual patient files, we plan to engineer a reliable risk estimator (**ASD Co-morbid Risk: ACoR**) enabled by novel machine learning algorithms, and compare its effectiveness against existing tools such as the M-CHAT/F in a limited clinical study, with children between 16-26 months of age. Our rationale is informed by the extensively documented comorbidities of ASD ranging from dysregulation of immune pathways such as eczema, allergies, asthma, as well as ear and respiratory infections, gastrointestinal problems, developmental issues, severe headaches, migraines, and seizures.[8], [9] While ASD presentation is highly variable, sophisticated pattern recognition on the longitudinal history of diagnostic codes is expected to reveal uncharted associations that allow precise screening for at-risk patients. Orthogonal to questionnaire based detection of behavioral signals, the proposed tool potentially reduces socio-economic, ethnic and demographic biases to elicit more objective and stable results — with zero administrative burden on clinicians and parents. With a team comprising machine learning experts, pediatric clinicians and developmental experts with extensive history of research and service in the field, the ACoR score can significantly improve outcomes by either boosting sensitivity of current screening or slashing false positives by half. Thus, the principal aims this study are the following:

□ **Aim 1: Reduce false positives in current screening protocols.** The current high false positive rate exacerbates post screen wait-time, increasing diagnostic delay. To evaluate the *hypothesis: ACoR reduces up to 50% of false positives*, we will track the cases in which MCHAT-F triggers a flag, but ACoR does not. Our aim to evaluate the positive predictive value (PPV) of ACoR, under high specificity conditions ($> 95\%$). Additionally, evaluate if ACoR replicates high sensitivity observed in preliminary studies without losing specificity.

□ **Aim 2. Evaluate the statistical relationship between the ACoR score and M/CHAT-F, and formalize a joint or conditional operational protocol.** We will characterize statistical association, if any, between the test scores. *Hypothesis: The uncertainties or errors in the two tests are are statistically independent.* Additionally, we will evaluate our ability to boost performance by conditioning the sensitivity-specificity trade-offs on the M-CHAT/F score of individual patients.

□ **Aim 3. Evaluate the effectiveness of ACoR in a demographically diverse population with a range of socio-economic confounders.** *Hypothesis: A questionnaire-free approach has the potential to mitigate biases that arise from limitation of language, cultural barriers, and demographic diversity, e.g.* disproportionately failing to diagnose children with average to above-average intelligence in diverse populations,[10] and under-reporting of symptoms by parents or primary care-givers due to cultural differences.[11]

□ **Aim 4. Characterize heterogeneity of ASD presentation by relating it to patterns in medical history, and predictive co-morbidities.** Heterogeneous presentation is a key barrier in the mechanistic understanding of ASD pathobiology. *Hypothesis: We can characterize the distinct classes and/or hierarchies of co-morbidities, by leveraging our ability to disambiguate them from individual medical histories*. This will shed light into the potentially intrinsic classes of the underlying disease processes, and refine/inform intervention design.

Thus, we are proposing to exploit observed co-morbidities in children who ultimately meet the criteria for ASD to develop a risk estimation pipeline, and predict future clinical diagnosis under 2 years of age. Orthogonal to checklists, we aim to reduce the median diagnostic age for ASD, by reducing the long post-screen wait times,[5] by significant boosts in positive predictive value, reduction in false positives, and increased sensitivities at little or no loss of specificity, and at no additional administrative burden or resource utilization.