

SPECIFIC AIMS

Early diagnosis of Autism Spectrum Disorder (ASD) and the timely intervention is widely recognized as critical for achieving improved cognitive, behavioral and social outcomes.^[1] With no laboratory tests for ASD, and despite advances from widespread adoption of screening with standardized checklists at 18 and 24 months of age, the median age of diagnosis remains 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 intervention. While a diversity of factors are implicated,^{[2]–[5]} one obvious source of these delays is the vast number of false positives encountered in the current initial screening tools. For example, the M-CHAT/F, the most widely used screen,^{[1], [6]} produces about 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.

In this study, we plan to develop and validate the efficacy of machine inferred **digital biomarkers** for autism, mined automatically from Electronic Health Record (EHR) databases. Using individual diagnostic codes already recorded during regular doctor’s visits, we plan to engineer a reliable risk estimator (**ASD Co-morbid Risk: ACoR**) enabled by novel machine learning algorithms. 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, we plan to carry out parallel tests with M-CHAT/F and ACoR in the pediatric primary care setting, and patients screening positive under either protocol will receive immediate diagnostic evaluation with Autism Diagnostic Observation Schedule, Second Edition (ADOS-2)^[1] to ascertain ASD status. In addition to direct comparison, we aim to combine the orthogonal risk estimates to substantially bring down the current false positive rates. The possibility of precise prediction of neuropsychiatric disorders from patterns in individual medical histories is supported by the high co-morbidity levels in children with ASD^[8] that span dysregulations of immune pathways such as eczema, allergies, asthma, as well as ear and respiratory infections, gastrointestinal problems, developmental issues, severe headaches, migraines, and seizures.^{[9], [10]} Thus, the principal aims this study are the following:

- **Aim 1: Evaluate how much earlier can ACoR pre-empt a clinical diagnosis.** Post screen wait-time is often the main source of diagnostic delay. To evaluate the *hypothesis: ACoR is pre-emptive (and not because of the lack of a queue under experimental conditions)*, we verify if the diagnostic evaluation is positive when our tool triggers a flag, but MCHAT-F is negative, and/or there is little concern from parents. This aim is particularly crucial for the evaluation of improved detection in borderline and/or high-functioning ASD cases.
- **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 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,^[11] and under-reporting of symptoms by parents or primary care-givers due to cultural differences.^[12]*
- **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.