Impact: Autism spectrum disorder (ASD) is a developmental disability associated with significant social and behavioral challenges. With ASD pathobiology still unclear, there is an immediate need for tools that help identify children with ASD as early as possible.[1], [2] Our incomplete understanding of ASD pathogenesis, and the lack of reliable biomarkers hampers early detection, intervention, and developmental trajectories.

In this study we aim to validate a new screening tool, that relies on sophisticated pattern recognition on patient medical history. With 1 in 54 children in the United States currently diagnosed with ASD, improved early screening can have immediate and significant impact in the community served by the University of Chicago, and the field of developmental pediatrics. Squarely in line with the University's mission of enabling fundamental advances in the field of medicine, this study aims a to validate a key advance in neuropsychiatric screening, where patterns in physiological co-morbidities – beyond psychosocial determinants – are effectively used to assess the risk of a future diagnosis. We aim to demonstrate that machine intelligence can discover such patterns automatically, revealing risk factors, associations, and predictive precursors not known before.

To quantify this impact, we note that even with increasingly adoption of screening with standardized checklists at 18-24 months, the median age of ASD diagnosis 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,[3], [4] produces over 85 false positives out of every 100 flagged for diagnostic evaluation, significantly inflating wait times.[5] M-CHAT/F also suffers from low sensitivity, failing to flag approximately 65 out of every 100 children who would be eventually diagnosed. This problem is exacerbated in rural and underserved communities, since access to care and resources are sparse except near urban centers. For example, only 7% of developmental pediatricians practice in rural areas, and some states do not even have a developmental pediatrician.[6], [7]

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,[4], [8] often due to a "wait and see" approach adopted at the primary care.

A screening tool that tracks the risk of an eventual ASD diagnosis, based on the information already being gathered during regular doctor's visits, and which may be implemented as a fully automated background process requiring no time commitment from providers has the potential to reduce avoidable diagnostic delays at no additional burden of time, money and personnel resources.

Thus, in this study, with UCWB's support, we plan to validate the efficacy of our risk estimator (**ASD Co-morbid Risk: ACoR**), and its effectiveness against current practice 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.[9], [10]

In our preliminary retrospective studies, ACoR identifies children at high risk with area under the receiver operating characteristic curve (AUC) exceeding 80% from shortly after two years of age for either sex, and across two large independent databases of patient records (N=4,503,584 and 37,635), conveniently outperforming M-CHAT/F.

Clarity: How will funds be used: UCWB support will be used to achieve the following specific aims:

□ **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, and the rate at which such cases are eventually determined to be M-CHAT/F false positives.

□ **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 ACoR on M-CHAT/F.

□ **Aim 3. Evaluate the effectiveness of ACoR in a demographically diverse population with a range of socio-economic confounders.** *Hypothesis: A questionnaire-free approach can mitigate biases 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]

□ **Aim 4. Characterize heterogeneity of ASD presentation from historical patterns.** Heterogeneous presentation hinders understanding of ASD pathobiology. *Hypothesis: Characterization of co-morbidity classes and hierarchies by mapping their ACoR impact*, reveal intrinsic classes of underlying disease processes.

Research Design: ACoR can screen instantaneously every child in primary care, for whom past medical history is available. To achieve the specific aims, we will gather data from both the child and the primary caregiver in the participating primary care clinic. Eligible patients at the Department of Pediatrics, University of Chicago (patients who present for a well-child visit between 16-26 months or any other non-emergency reason) will be asked for consent for access to their past medical history for carrying out the ACoR screen. If there is a flag either in M-CHAT/F or if M-CHAT/F is borderline with a flag in ACoR, the pediatrician will inform parents of a potential elevated risk of ASD, and offer to schedule for an ADOS-2 evaluation. The ADOS-2 evaluation triggered by ACoR flags will be at no cost to the patient. All study procedures and consent forms will be approved by the University of Chicago Institutional Review Board. For all assessments, basic demographic information, recruitment site, medications and diagnoses assigned by the current clinical treatment team, will be obtained from the parent/caregiver and medical record. The key steps in the study spanning 1 year are as follows (See Fig.1):

□ 1. Pediatric clinic team (led by Dr. Mitchell) will administer M-CHAT/F to incoming children with 16-26 months and procure consent

□ 2. The PI's team will compute individual ACoR (steps 1 and 2 in Fig. 6).

□ 3. If flagged by M-CHAT/F as high risk, or if the ACoR score indicates high risk and M-CHAT/F is borderline, the patients will be scheduled for ADOS-2 evaluation overseen by Dr. Smith and his team (Step 3 in Fig. 6).

□ 4. The evaluation scores will be analyzed by PI and his team.

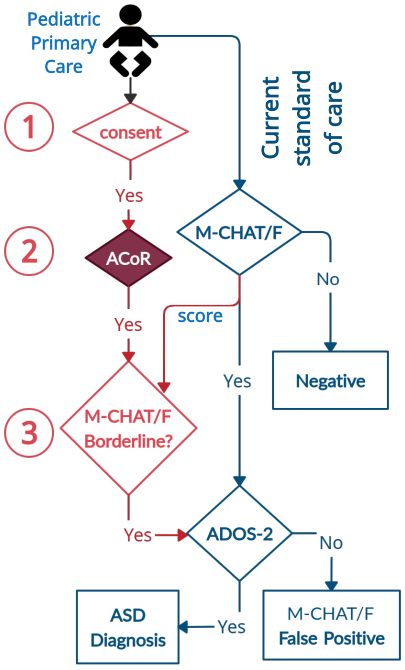

Fig. 1. **Patient processing logic**

Timeline: The study will span 1 year from the time of award. Patient recruitment will continue all throughout the project life.

Cohort Selection: Our expected cohort, drawn from UCM patient population, is diverse. Participants (16-26 months) will be approximately 5000 children per year (producing approximately 300 ADOS-2 referrals from M-CHAT/F) who will be evaluated via both MCHAT-F and ACoR. Inclusion criteria: diagnostic history on record with at least 5 codes spanning at least 10 weeks. Exclusion criteria: diagnostic history only consists of health service contact codes. Beyond the evaluation as a part of standard clinical workflow, we will carry out ADOS-2 evaluation for approximately 500 children at no cost to the patient family, to evaluate the efficacy of ACoR when M-CHAT/F is borderline (and does not trigger downstream diagnostic evaluation by itself). UCWB support will enable these evaluations and associated costs.

Study Interventions, and Patient Risk: No intervention is planned. Outcomes are efficacy and applicability of ACoR. The design of the study guarantees that patients suffer no negative impact from the added ACoR screen. Indeed, pursuant to available resources, patients might be expedited for ADOS evaluation which reduces their wait-times. For some borderline cases might be flagged due to false positives.

Need: We have applied for a NIH RO3 grant, and combined with the data generated in this study, we plan to submit a RO1 proposal within the next year. We need UCWB support to generate prospective data beyond our current preliminary results to be competitive for NIH funding. The expected impact of this study suggests potential for autonomous and sustainable funding, either through the creation of revenue (via incorporation within the standard clinical workflow), or dedicated multi-year institutional support.

Feasibility: With a team comprising machine learning experts, pediatric clinicians and developmental experts with extensive history of research and service in the field, and guided by results from our preliminary studies, we are confident that the ACoR score can significantly improve outcomes by either boosting sensitivity of current screening or slashing false positives by half. Additionally, our preliminary results with two independent and large patient databases has produced positive results.