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Prof. James S. House
Member Editor, Proceedings of the National Academy of Sciences
500 Fifth Street NW
NAS 338
Washington, DC 20001 USA

Dear Prof. House

Please find enclosed the manuscript entitled "**Reduced False Positives in Autism Screening Via Digital Bio-markers Inferred from Deep Co-morbidity Patterns**" for your consideration for publication in Proceedings of the National Academy of Sciences as a research article.

Autism spectral disorder (ASD) is currently screened for in toddlers using standard questionnaires, *.e.g.* M-CHAT/F, completed by parents at doctors' visits. The M-CHAT/F produces a notoriously high number of false positives (85%) and a low sensitivity (38%). This overwhelming number of false positives translates to long wait-times for confirmatory diagnosis ($\approx$ 1 year). Children lose crucial time within which interventions are the most effective. Additionally, questionnaires are prone to interpretive biases leading to systematic under-diagnosis in diverse communities. Finding genetic diagnostic bio-markers have been problematic due to the highly heterogeneous presentation of ASD.

Here we report an orthogonal methodology that requires **no questionnaires and no blood-work**. Using novel approaches to stochastic learning from individual diagnostic codes already recorded during past doctor's visits, we design a risk estimator significantly out-performing the state-of-the-art. WIthout manually pre-selecting co-morbid disorders, we learn hidden patterns in medical histories to enable cutting down false positives by half without losing specificity. Additionally, we get new insights into co-morbid risk that might shed light into sex differences, and ASD pathobiology, and how we can exploit subtle footprints of complex disorders in seemingly unrelated medical encounters.

We are led by a multi-disciplinary team of machine learning experts (Chattopadhyay) and clinical practioners in pediatric developmental psychology and autism: 1) Peter J. Smith, Professor of Pediatrics and **Executive Committee Chair, American Academy of Pediatrics' Section on Developmental & Behavioral Pediatrics**, and 2) Prof. Michael Msall, **Section Chief of Developmental & Behavioral Pediatrics, UChicago, and Fellow of Joseph P. Kennedy Research Center on Intellectual & Neurodevelopmental Disabilities, UChicago**.

We believe that the importance and inter-disciplinary nature of our results, with non-trivial computational modeling, merits consideration for publication in Proceedings of the National Academy of Sciences. We look forward to, and humbly hope for, your positive response.

Sincerely,

Ishanu Chattopadhyay
Chicago, IL

Tuesday 23rd June, 2020