# THE HARTWELL FOUNDATION

## 2023 Nominee Individual Biomedical Research Award

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### Neonatal Asthma Risk Prediction with Genetic Models to Improve Detection, Monitoring, and Treatment

Asthma is a chronic immune-mediated disease characterized by difficulty breathing. The onset of asthma can take place in childhood or adulthood and is associated with other comorbidities such as sleep apnea, pneumonia, and chronic inflammation. With child-onset asthma as the leading cause of emergency hospital visits, prolonged hospitalizations, and the leading cause of school absences, the CDC reports that approximately 6 million children in the U.S. have the disease. Childhood asthma has a strong genetic component, with 25%-82% of risk due to genetic factors estimated from common variants in genome-wide association and twin studies. However, there is little knowledge about the risk alleles and risk genes that could enable predictive measures to initiate secondary prevention, and/or inform treatment. Because current clinical asthma tests are not accurate until about three years of age, asthma risk prediction remains an unmet healthcare need. Therefore, understanding the factors that determine the probability a patient is experiencing asthma could help clinicians triage the cause of wheezing (i.e., bronchiolitis, asthma, or simply small airways); providing critical information to enable a treatment plan for affected children, parents, and healthcare workers, alike. Unfortunately, existing clinical risk models use a small number of predictive features, such as family history, recurrent episodes, wheeze type, and pulmonary function, and suffer from highly variable performance across cohorts. By contrast, current genetic models consider more features but have low accuracies, e.g., <10%. To address the existing need for improvement, I propose to identify genetic and clinical risk factors of pediatric asthma to construct a clinical risk model that can predict asthma risk even before overt symptoms appear. I will exploit the identification of gene expression risk factors from causal cell types, modeling the combined risk of genetic, transcriptomic, and non-genetic risk factors. Using cutting-edge statistical genetics to identify genes conferring asthma risk, I will leverage single cell gene expression data in cell types that are causal for asthma. To understand how genetic and non-genetic components interact to confer asthma risk, I will then construct genetic risk scores for child-onset asthma using inferred risk genes and variants from genome-wide association studies across ancestrally diverse cohorts, which will enable evaluation of the predictive value of non-genetic risk factors. A genetic test informed by the transcriptome should also help identify key drivers of asthma pathways, which will inform new approaches that improve detection, monitoring, and treatment, as well as secondary prevention. If I am successful, accurate risk stratification in affected children should be possible during the critical window before lung function tests are conclusive, which will reduce emergency doctor visits, hospitalization, and improve school attendance, leading to the overall improved mental health and wellbeing of all affected children.