



COVID-19 Evidence Accelerator Collaborative

Therapeutics & Vaccines Lab Meeting #35

Thursday, June 17th, 2021, 3-4 pm ET

Call Summary

Overview of Lab Meeting #35

During the 35th Therapeutics & Vaccines Evidence Accelerator Lab meeting we heard two presentations on the impact of long COVID in children. First, we heard from Dr. Carlos Bustamante of Stanford University who presented on post-infectious neuropsychiatric diseases, such as post-COVID neuropsychiatric disorder, and how genomic data from other areas, such as COVID swabs, can be leveraged to help better understand how these conditions arise. Second, Dr. Rohan Hazra of the National Institute of Child Health and Human Development (NICHD) provided an overview of ongoing studies at the NIH that are bringing data together to help better understand the impact long-COVID and Multi-System Inflammatory Syndrome (MIS) have on children.

Building a million-person cohort to study inflammatory brain conditions with psychiatric presentations

Dr. Carlos Bustamante, Stanford University

Post-infectious Neuropsychiatric Disease

- Inflammatory brain conditions can present with psychiatric symptoms. Examples of IBCs that present with these symptoms include Primary and Secondary CNS Vasculitis, Basal Ganglia Encephalitis +/- Vasculitis, Lupus, and post-COVID neuropsychiatric disorder.
- These sudden onset neuropsychiatric conditions may follow different types of pathogen triggers (e.g., post-COVID-19 exposure).
- Post-COVID-19 neuropsychiatric disease may present a clear and present danger to the mental health of the human population and presents a once-in-a-lifetime opportunity to study post-infectious sudden onset neuropsychiatric disease.
 - COVID-19 and Multi-Inflammatory Syndrome in Children (MIS-C) present with neuropsychiatric symptoms, could lead to massive unmet need to treat these diseases in the 2020s.
- These disorders provide opportunities to identify genetic pathways for neuroimmune modulation and modulating inflammation.
- Over the 2010s we developed 'omics and data science tools to better understand neuro-immune disorders that arise post-infection – collectively as many as 1 in 100 people may be at risk.
 - Developed the first machine learning/artificial intelligence tool for sub-setting sudden post-infectious neuropsychiatric deterioration.
 - Our project would build a one-million-person cohort using 'omics, EHR, and patient reported outcomes to help study these diseases and investigate potential business models for sustaining these efforts.
- Need to oversample population to understand these rare events.

Stanford COVID-Omics Project: Multi-omics Research Data and Analysis on COVID-19

- Nasopharyngeal (NP) swabs provide a plethora of data including HLA typing, low-pass host whole genome sequencing, host transcriptome, viral genome, etc.
- Repurposed these data for 'omics research – COVID specific and others.

Severity Scales of Patients with COVID

- Based on World Health Organization's definitions of severity, in most cases patients were "somewhat sick" with some range in more severe cases.

Polygenic Risk Score Analysis for COVID-19

- Hospitalization: Genetic predictions of BMI are a better indicator of hospitalization for COVID than actual BMI.

Population Genetics of COVID-19 at Stanford

- Examined COVID samples broken up by ancestry and saw early signals of disparities.
- Individuals with Native American and Pacific Islander ancestry were the largest group represented in the data despite less representation in the overall population studied.

Stanford HLA-COVID19 Study Experience

- Large HLA "hit" -- Protective allele in Indian-Asian Ancestry
- Likely related to why Delta broke through, some natural protection in individuals with Indian-Asian Ancestry

Medication Alignment (MedAI) Algorithm

- Use of medication history to subset patients.
- Demonstrated that subset of patients with PANDA phenotype were responding well to NSAIDs and antibiotics.

CARING for Children with COVID & the RECOVER Initiative

Dr. Rohan Hazra, National Institute of Child Health and Human Development (NICHD)

Related themes from last presentation

- Patient and family experience are critical when looking at COVID-19
- "No research about us without us" – need to involve communities affected
- COVID and Big Data will help answer a lot of questions we didn't know before.
- Need to apply things we've learned during COVID to these areas – accelerated research, public health impact of research, etc.

Emergence of a New Disease

- May 2020 – Discovered pediatric multisystem inflammatory syndrome (MIS) temporally associated with COVID-19.
- Trans-NIH taskforce established to research this syndrome.
- **Case Definition:** Children under 21 yo, fever >38 C for over 24 hours, lab evidence of inflammation, at least 2 organ system involvement, positive test or known covid exposure, no alternative plausible diagnosis, and severe illness requiring hospitalization.

MIS-C vs. Severe COVID

- Partly related to time - children not sick with initial COVID infection, develop MIS-C ~2 weeks later
- Higher level of cardiovascular involvement and mucocutaneous involvement
- Much greater need for critical care support

CARING for Children with COVID

- Studying COVID in children
- 4 aligned studies using existing programs, planning to bring the data together from separate studies:
 - Long Term Outcomes after MIS in Children (MUSIC) – NHLBI’s Pediatric Heart Network
 - Pharmacokinetics, Pharmacodynamics, and Safety Profile of Understudied Drugs Administered to Children per Standard of Care study (POPS02) – NICHD’s Pediatric Trials Network
 - Pediatric Research Immune Network on SARS-CoV-2 and MIS-C (PRISM) – NIAID
 - Predicting Viral-Associated Inflammatory disease severity in children with Laboratory diagnostics and Artificial Intelligence (pre-VAIL Kids)
 - Developing translational tools to understand the spectrum of pediatric COVID illness, rapidly diagnose and characterize MIS-C associated with COVID, and predict the longitudinal risk of disease severity after exposure and/or infection by COVID.
 - Using genetics/omics/other biomarkers, viral dynamics and immune profiling studies, digital health platforms for children, AI
- Data Flow – Sharing data from these four studies widely through three portals to make sure investigator communities can access the data.

RECOVER Initiative: Research in COVID to Enhance Recovery

- \$1.1 billion to study “long-COVID” or Post-Acute Sequelae of COVID (PASC)
 - Goal to understand, prevent, and treat PASC (adults and children)
 - PASC – new or persistent symptoms from covid
- Research Questions
 - What does recovery look like among different groups?
 - How many people continue to have symptoms after the acute infection? How many people develop new symptoms after acute infection?
 - What causes these ongoing symptoms or other health effects?
 - Why do some people develop these ongoing symptoms or other health effects while others do not?
 - Does SARS-CoV-2 infection trigger changes in the body that increase the risk of other conditions, such as chronic lung, heart, or brain disorders?