Multisystem Inflammatory Syndrome in Children (MIS-C)

Advisory Committee to the Director, NIH

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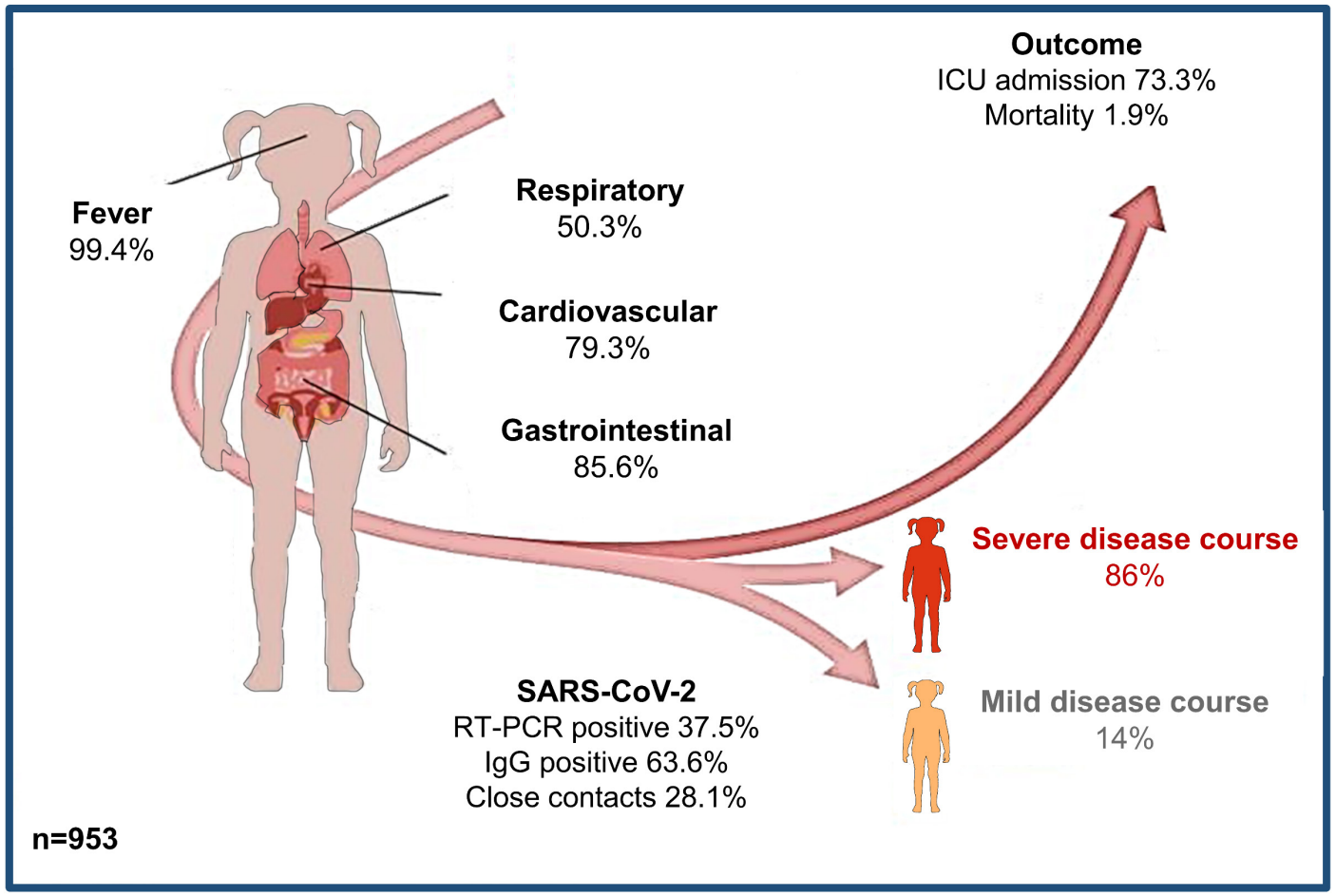
NIH *Eunice Kennedy Shriver* National Institute of Child Health and Human Development

Multisystem Inflammatory Syndrome in Children (MIS-C)

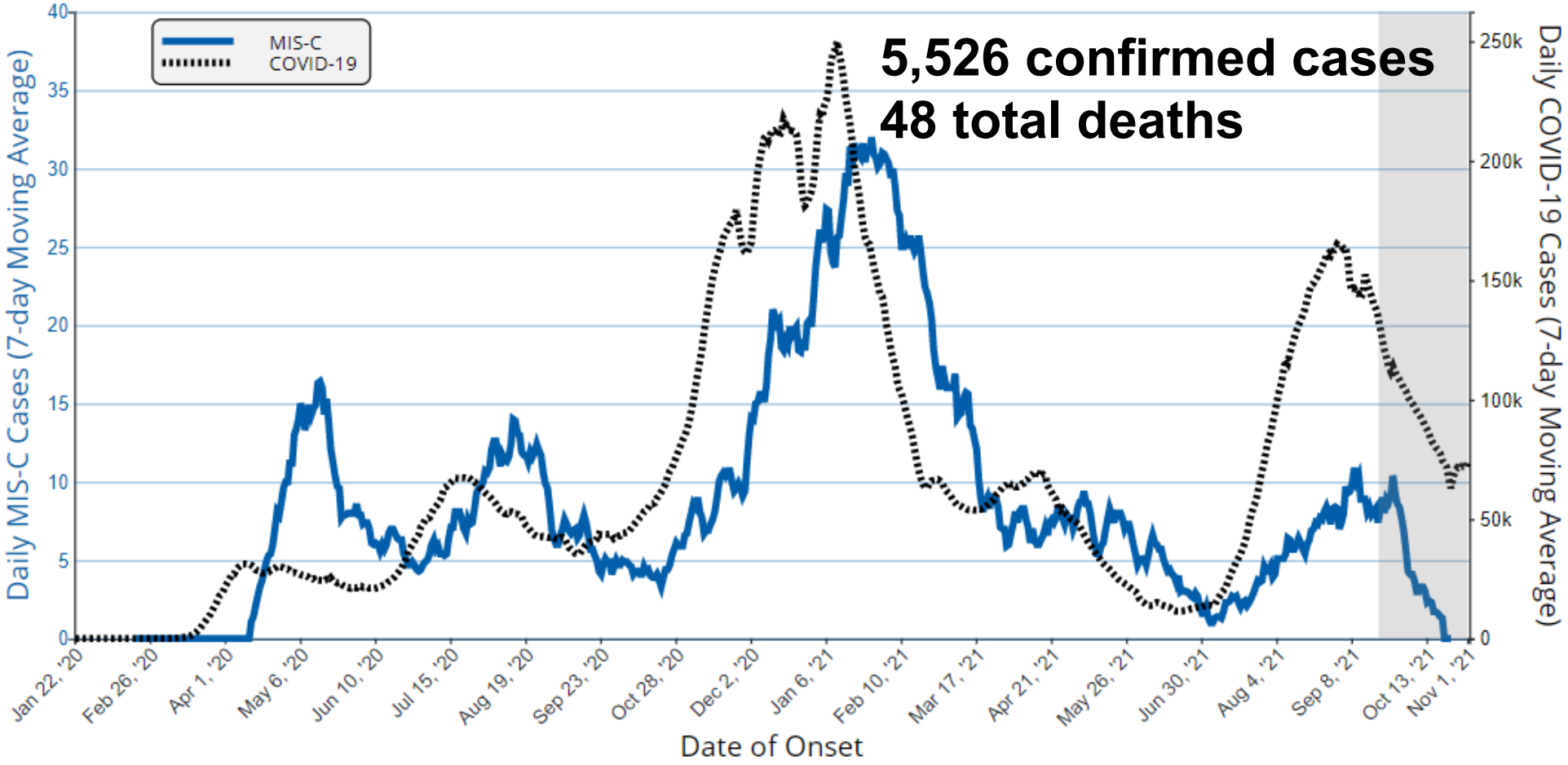
- MIS-C is characterized by fever, along with multiorgan inflammation, often with cardiovascular dysfunction
- Severe GI pain is more common in MIS-C than in related conditions
- Children become critically ill quickly, but most recover, generally within one week

MIS-C Organ System Involvement and Disease Patterns



Hoste et al. (2021)

Daily MIS-C and COVID-19 CASES



- COVID-19 hospitalization rate increased for children and adolescents after Delta variant emerged
- Statistics are updated monthly; MIS-C numbers have not decreased

https://www.cdc.gov/mis/cases/index.html

Data as of: 11/1/21

Major Challenges in MIS-C

- How to define/diagnose MIS-C and distinguish it from similar conditions such as Kawasaki disease and severe COVID-19?
- How to predict who is at risk for MIS-C?
  - Approximately 1 in 1000-3000 children who have SARS-CoV-2 will develop MIS-C three to four weeks after the initial infection
- How to treat MIS-C?
- How should children with MIS-C be followed long-term?

How to define/diagnose MIS-C?

Predicting Viral-Associated Inflammatory disease severity in children with Laboratory diagnostics and artificial Intelligence (PreVAIL kIds)

- **Develop translational tools to understand the spectrum of pediatric SARS-CoV-2 illness, rapidly diagnose and characterize MIS-C associated with SARS-CoV-2, and predict the longitudinal risk of disease severity** after exposure to and/or infection by SARS-CoV-2
  - Genetics; omics; other biomarkers
  - Viral dynamics and immune profiling studies
  - Digital health platforms leveraged for children
  - Artificial intelligence
- Milestone-driven award (R61/R33); **up to 4 years**

RADx^{SM} Radical (RADx-rad)

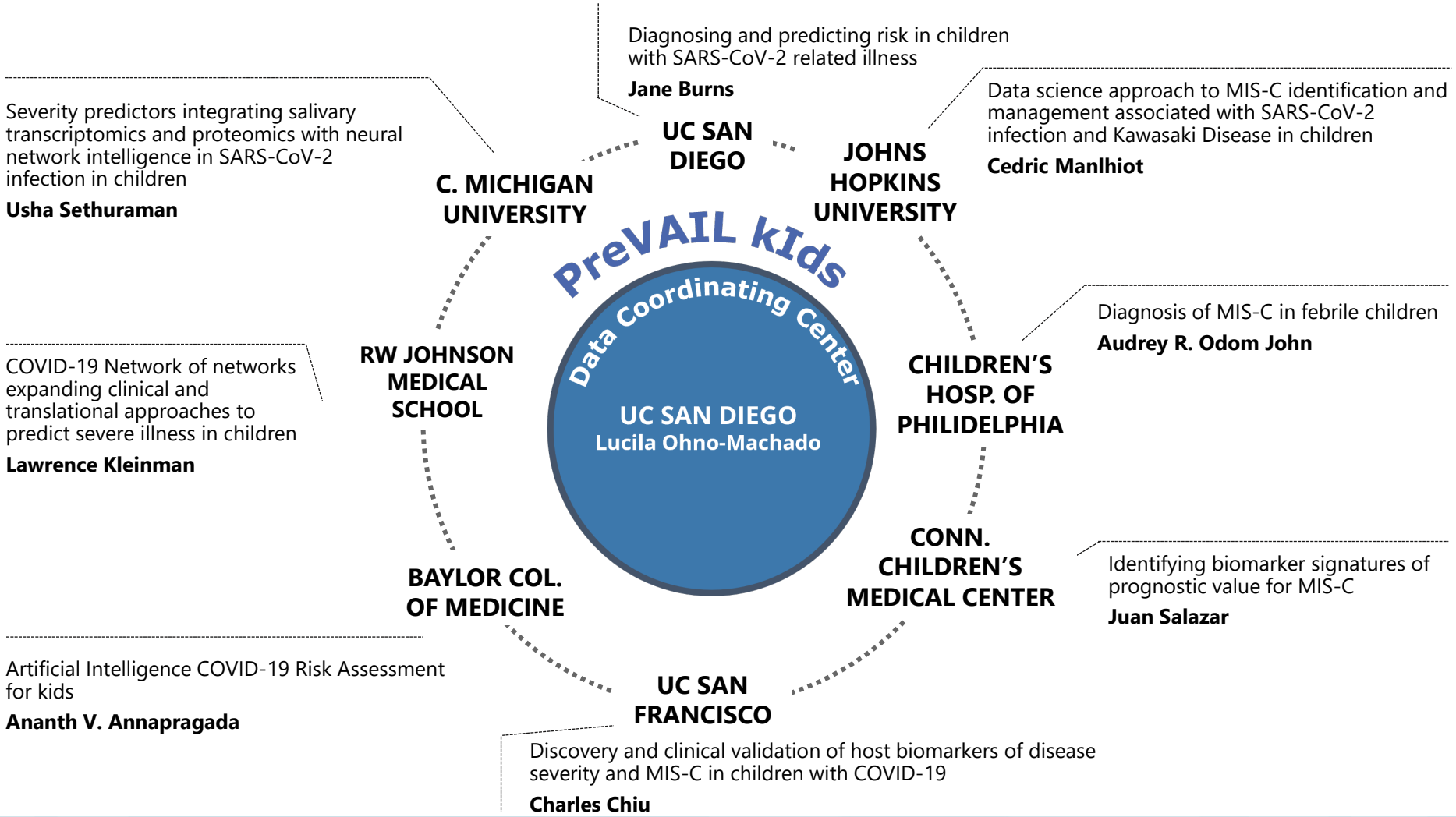
RADx-rad will support new, non-traditional approaches, including rapid detection devices and home-based testing technologies, that address current gaps in COVID-19 testing. The program will also support new or non-traditional applications of existing approaches to make them more usable, accessible, or accurate. These may lead to new ways to identify the current SARS-CoV-2 virus as well as potential future viruses.

Budget: $200 Million

- https://www.nichd.nih.gov/newsroom/news/122120-prevail-kids

* Note: MIS-C is one of most well-characterized forms of post-acute sequelae of SARS-CoV-2 (PASC) in children

PreVAIL kIds Investigators and Approaches

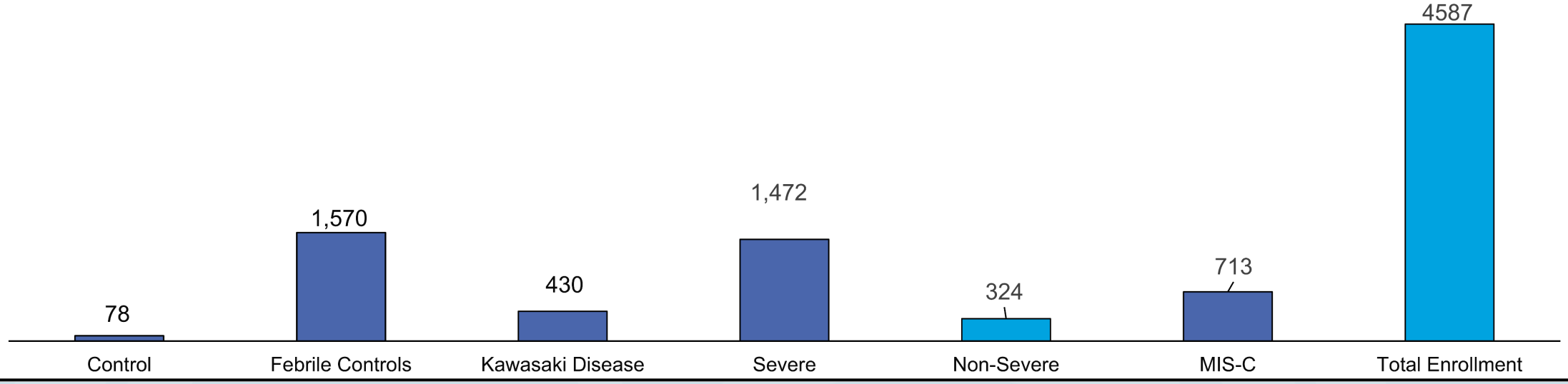


https://www.radxrad.org/awardees/prevail-kids/

PreVAIL kIds Prospective Enrollments – Ahead of Target

Prospective Enrollment Summary

Prospective Enrollment Breakdown (Actuals)



Overview of PreVAIL kIds-associated Publications and Presentations

BY THE NUMBERS

30

Published articles from the cohort

6

Presentations by PIs

Sample presentation venues include:

AAP experience VIRTUAL 2021 National Conference & Exhibition

The 13th International Kawasaki Disease Symposium

Review > Vaccine. 2021 May 21;39(22):3037-3049. doi: 10.1016/j.vaccine.2021.01.054. Epub 2021 Feb 25.

Multisystem inflammatory syndrome in children and adults (MIS-C/A): Case definition & guidelines for data collection, analysis, and presentation of immunization safety data

Tiphanie P Vogel [1], Ka
Pamela Moceri [6], Lisa
Nicola P Klein [10], Eliza

> Sci Immunol. 2021 Mar 2;6(57):eabf7570. doi: 10.1126/sciimmunol.abf7570.

Deep immune profiling of MIS-C demonstrates marked but transient immune activation compared to adult and pediatric COVID-19

ge [2 5 6],
Pampena [2 9],
nderson [2 9],

> Clin Chim Acta. 2020 Nov;510:790-795. doi: 10.1016/j.cca.2020.09.023. Epub 2020 Sep 19.

Clinical performance of a semi-quantitative assay for SARS-CoV2 IgG and SARS-CoV2 IgM antibodies

Joanna Jung [1], Emily G
Eduardo Benzi [3], Nive

> Data Min Knowl Discov. 2021 May;35(3):1134-1161. doi: 10.1007/s10618-021-00746-8. Epub 2021 Mar 23.

Tackling Ordinal Regression Problem for Heterogeneous Data: Sparse and Deep Multi-Task

> Eur J Immunol. 2021 Oct 2. doi: 10.1002/eji.202149556. Online ahead of print.

Characterization of SARS-CoV-2 and common cold coronavirus-specific T-cell responses in MIS-C and Kawasaki disease children

Li-En Hsieh [1], Alba Grifoni [2], John Sidney [2], Chisato Shimizu [1], Hiroko Shike [3], Nanda Ramchandar [1], Elizabeth Moreno [1], Adriana H Tremoulet [1], Jane C Burns [1], Alessandra Franco [1]

How to predict who is at risk for MIS-C?

PreVAIL kIds Progress To Date

- In addition to the prospective cohort, five of the groups have enrolled 21,651 patients retrospectively across all clinical phenotypes, from mild to severe COVID-19 and MIS-C
- Early results have identified:
  - Potential signatures of 4 genes that distinguish MIS-C from Kawasaki disease, bacterial and other viral infections
  - Specific cytokines in saliva that may predict disease severity
- Four projects have initiated discussions with company partners for commercialization support

NIH Intramural MIS-C Research (NIAID)

- Longitudinal, multi-institutional study used multi-omics to identify novel time- and treatment-related immunopathological signatures in children with COVID-19 and MIS-C
  - Differentiated immune responses for pediatric COVID-19 compared to MIS-C
  - Association of MIS-C with certain HLA alleles suggests genetic susceptibility

medRχiv

THE PREPRINT SERVER FOR HEALTH SCIENCES

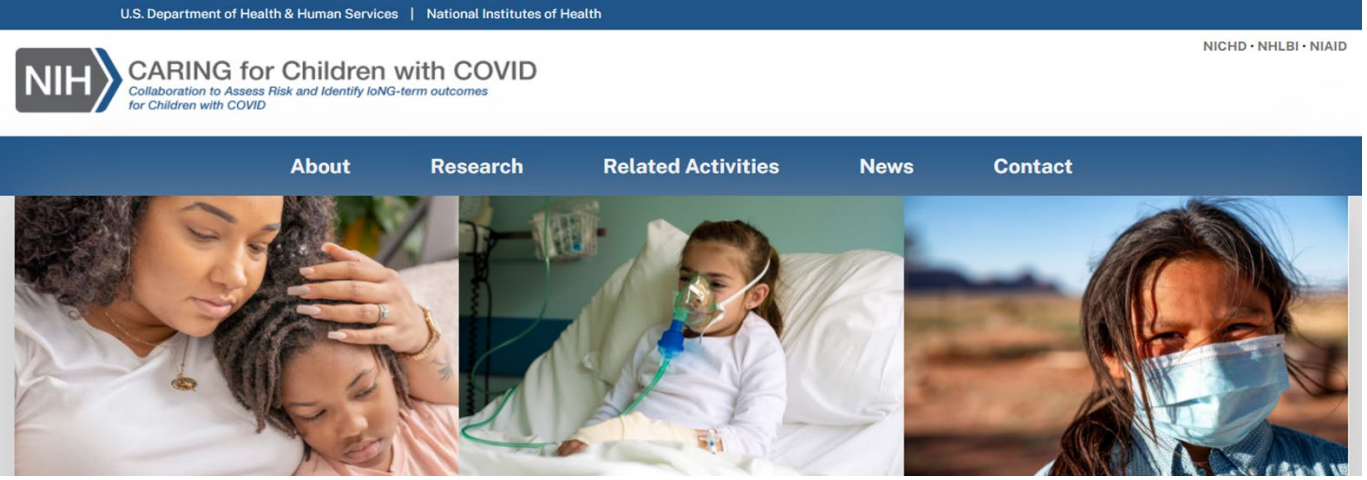
Cold Spring Harbor Laboratory BMJ Yale

Comment on this paper

Multi-omics approach identifies novel age-, time- and treatment-related immunopathological signatures in MIS-C and pediatric COVID-19

Sacco K et al. September 27, 2021

How to treat MIS-C?



PEDIATRIC TRIALS NETWORK

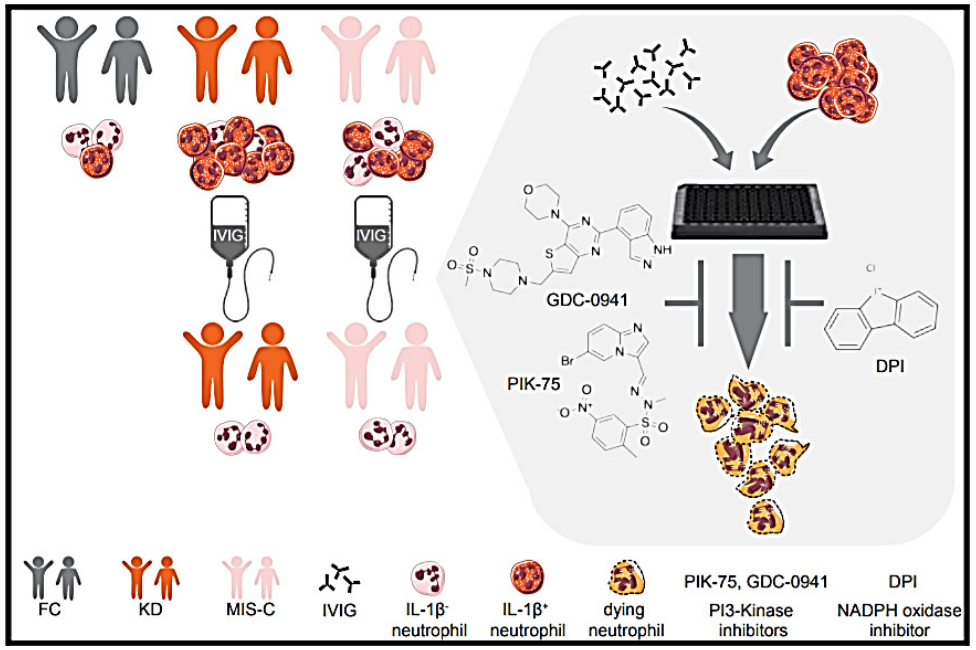
Making drugs safer & more effective for use in the youngest patients

NIH NICHD

- Pharmacokinetics of drugs used to treat COVID-19 in children, expanded to study MIS-C
- Observational study, MIS-C and pediatric COVID, currently at 33 sites
  - Approximately 420 SARS-CoV-2 positive
  - ~100 with MIS-C
- 102 treated with remdesivir; approved for treatment down to age 12
  - ~40 participants less than 12 years
  - Pharmacokinetic data pending; could lead to label change

Immune response to intravenous immunoglobulin in patients with Kawasaki disease and MIS-C

Yanfang P. Zhu,[1] Isaac Shamie,[2] Jamie C. Lee,[1,2] Cameron J. Nowell,[3] Weiqi Peng,[1,4] Shiela Angulo,[1] Linh N.N. Le,[1,2] Yushan Liu,[1,5] Huilai Miao,[1] Hainan Xiong,[1] Cathleen J. Pena,[1] Elizabeth Moreno,[1] Eric Griffis,[6] Stephanie G. Labou,[7] Alessandra Franco,[1] Lori Broderick,[1,8] Hal M. Hoffman,[1,8] Chisato Shimizu,[1] Nathan E. Lewis,[1,2] John T. Kanegaye,[1,8] Adriana H. Tremoulet,[1,8] Jane C. Burns,[1,8] Ben A. Croker,[1] and the Pediatric Emergency Medicine Kawasaki Disease Research Group Consortium[8,9]



Effects of intravenous immunoglobulin treatment for MIS-C

Works by reducing activated IL-1β+ neutrophils

Second line drugs include steroids, immunosuppressive drugs such as anakinra (anti IL-1) and infliximab (TNF blocker)

J Clin Invest. 2021 Oct 15;131(20)

How should children with MIS-C be followed long-term?

CARING for Children with COVID

(Collaboration to Assess Risk and Identify loNG-term outcomes for Children with COVID)

- Leverages networks from NICHD, NHLBI, NIAID to study MIS-C
  - Capitalizes on strengths of each network: immune profiling (NIAID); long-term cardiac effects (NHLBI); PK/PD of drugs used to treat COVID-19 but not labeled for children (NICHD)
  - Aim to follow children for five years through longitudinal protocol
  - Currently >1200 children enrolled across three protocols (>20% of MIS-C cases in the U.S)
  - Broad geographic reach; 20-30 sites for each protocol (limited overlap)

COVID MUSIC STUDY
Understanding MIS-C

PEDIATRIC HEART NETWORK

PRISM

PEDIATRIC TRIALS NETWORK
Making drugs safer & more effective for use in the youngest patients

CARING for Children with COVID

- **Long-Term Outcomes after the MUltisystem Inflammatory Syndrome In Children (MUSIC)** *(MIS-C patients)*
  - **Primary aim:** Characterize coronary artery abnormalities and left ventricular dysfunction
  - **Biorepository:** Includes 477 samples; 49 complete trios; more than 1000 cardiac echos
  - Enrolling both retrospectively and prospectively; 4 sites in IDeA states
  - Design paper in American Heart Journal; 3-5 manuscripts planned for next few months
- **Pediatric Research Immune Network on SARS-CoV-2 and MIS-C (PRISM)** *(MIS-C and acute COVID-19 patients)*
  - 1-year observational study of **clinical outcomes** and **immunophenotyping**
  - Includes pre-treatment and immediate post-treatment biospecimens for analysis
  - First release of clinical results expected in Q1 2022

COVID MUSIC STUDY
Understanding MIS-C

PEDIATRIC HEART NETWORK

PRISM

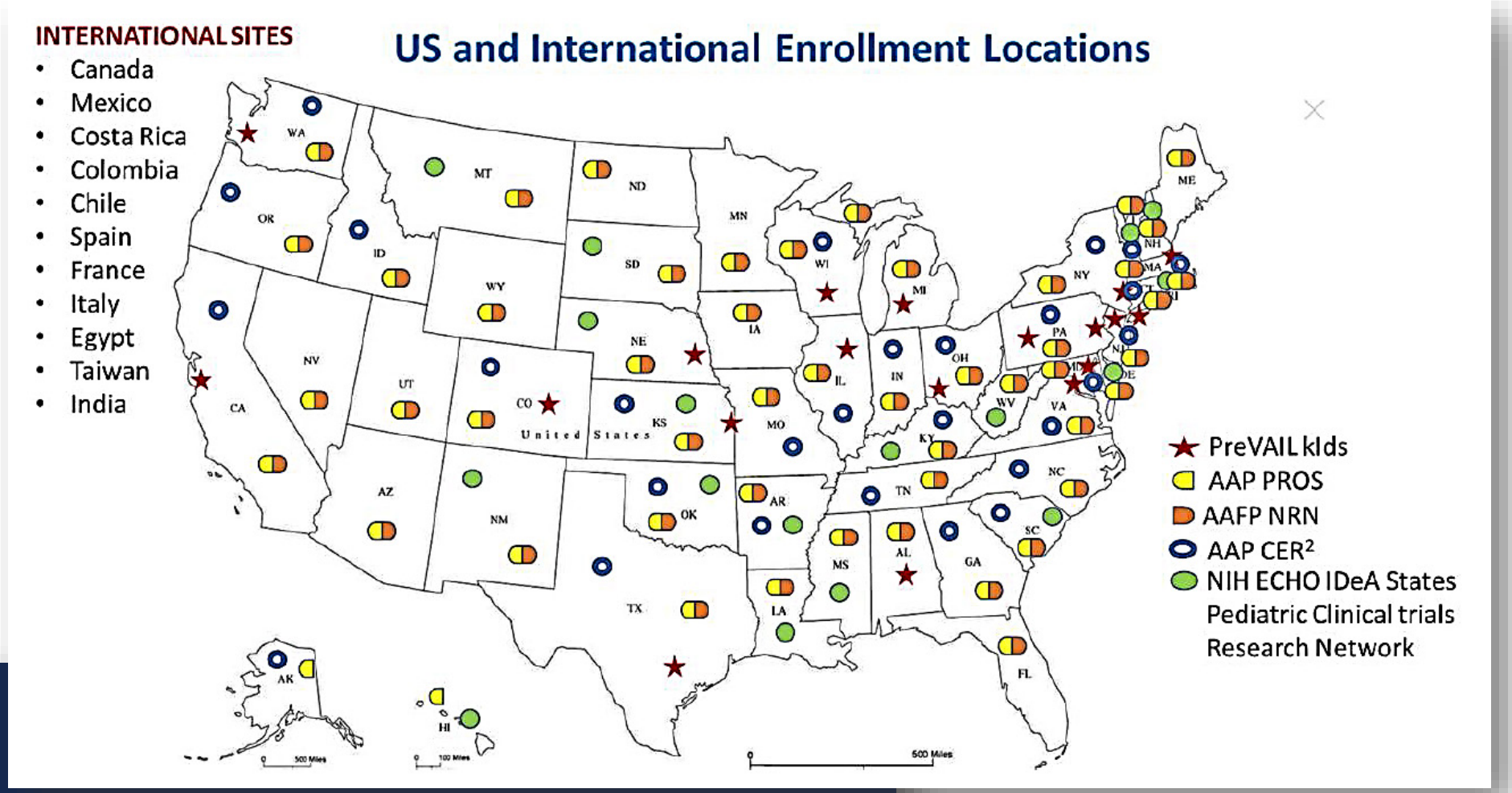
Data Interoperability is Vital to Maximize Understanding of COVID-19 Infection and MIS-C in Children

- A searchable data set for **interoperable sharing across different platforms**
  - Data platforms maximize data sharing & FAIRness *(Findability, Accessibility, Interoperability, and Reusability)*
  - First data released from the NICHD POPS study (~50 patients) in October 2021; larger batch of data under curation for release in the next couple months
  - Using HL7® FHIR® as an interoperability framework, facilitating data sharing with intent for iterative & continued collaboration
    - FHIR is the bridge from hospital-based data to research
- NICHD has led development of pediatric Common Data Elements that can be used across COVID-19 research projects (https://tools.niehs.nih.gov/dr2/index.cfm/resource/24250)

Successful multi-PI PreVAIL kIds Collaboration

MPIs: *Kleinman, Annapragada, Chiu, Manlhiot, Salazar & Sethuraman*

CLOCK
(Collaborative Long-term study of Outcomes of COVID-19 in Kids)



RECOVER
Researching COVID to Enhance Recovery

RECOVER is Powered by Collaboration

Thank you!

Questions?