

FROM PARASITES TO PUPPIES: TOWARDS NONINVASIVE DIAGNOSIS OF PEDIATRIC SARS-COV-2 AND MIS-C

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OUTLINE

- Case presentation
- Timeline/recognition of MIS-C
- NICHD PreVAIL klds program
- Our studies: improving diagnosis of SARS-CoV-2 and MIS-C in kids

CASE (MAY 2020)

- History: 5 yo healthy child admitted to CHOP with fever and low BP
- 4d ago - F to 104, no other symptoms
- 3d ago - rash on thighs, spreading to abdomen and soles of feet
- 2d ago - nonexudative conjunctivitis (red eyes), cracked lips, N/V/diarrhea
- in ED: ? neck stiffness, fluid-responsive hypotension (low BP)
- Admitted to intensive care unit at CHOP

- Previously healthy child
- Social history: lives in community with high levels of transmission of COVID-19, no sick contacts, "hadn't left the house in 1 month"

PHYSICAL EXAM:

Gen: fussy, consolable, asking for something to drink

HEENT: slight conjunctivitis, moderate resistance to neck flexion

LAD: no cervical, axillary, or inguinal adenopathy

Chest: clear no WOB

CV: hyperdynamic, RRR no M, well perfused

Ab: full, nontender, mild hepatomegaly, no splenomegaly

Skin: Rash, characterized by 2-3 mm erythematous blanching macules scattered on abdomen and inner thighs with larger confluent patches on thighs, decreased towards extremities, no linear areas, spares underwear area and no evidence of dermographia. No petechiae or purpura.

Neuro: normal tone, good movement of all extremities, alert and fussy but normal affect

Extrem: no joint effusions or redness



Blatz et al, OFID 2021



with parental consent



Blatz et al, OFID 2021



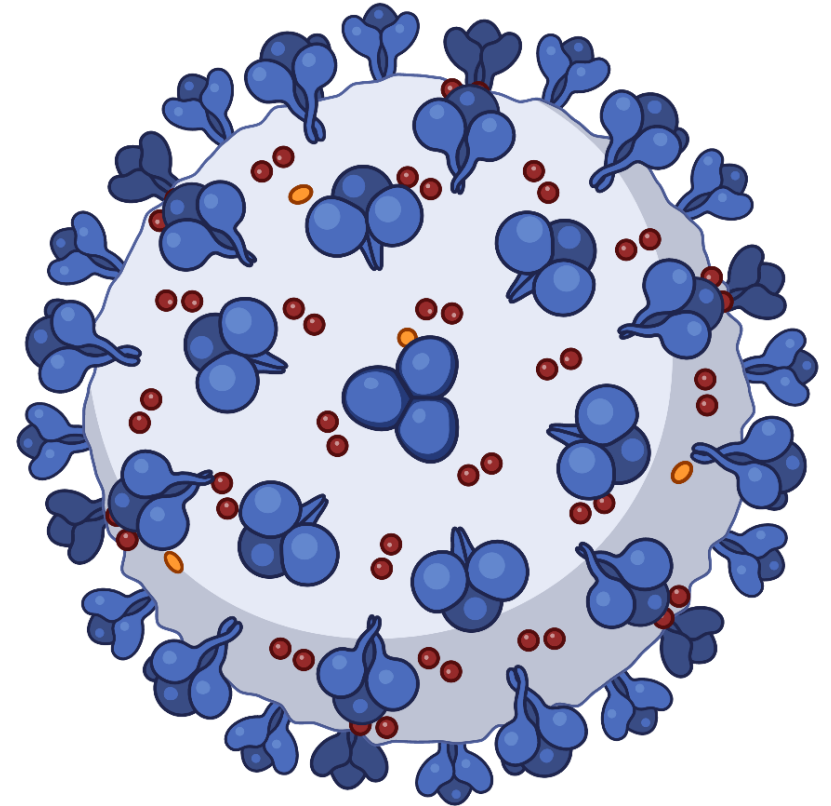
with parental consent

DIAGNOSIS: MULTISYSTEM INFLAMMATORY SYNDROME IN CHILDREN (MIS-C), ASSOCIATED WITH SARS-COV-2 INFECTION

- ECHO: normal biventricular function, trivial mitral and tricuspid regurgitation, and echo-bright coronary arteries (with normal diameter)
- Labs: Positive SARS-CoV-2 NP PCR and serology
- treatment: IVIG (X2) and methylprednisolone, ABx
- supportive care
- rapid resolution of fever, shock, rash -> rpt ECHO normal

SARS-COV-2 AND COVID-19

- 4 Jan 2020: WHO reports cluster of atypical PNA in Hubei province, China
- 12 Jan: genetic sequence of SARS-CoV-2
- 22 Jan: confirmed human-to-human transmission
- 11 Mar: WHO "global pandemic"



MAR - APRIL 2020: SARS-COV-2 IS MILD IN KIDS

- 112* positive tests of 2385 patients < 21 years tested at CHOP = 4.7%
 - 6/382 (1.6%) of pre-procedural or pre-admission testing

Clinical severity
of all positive
pediatric patients
at CHOP

Severity	N (%)
Asymptomatic	6 (5%)
Mild	97 (84%)
Moderate	1 (1%)
Severe	5 (5%)
Unknown	6 (5%)
Death	1 (1%)

**JUST WHEN YOU THOUGHT CHILDREN WERE
PRETTY SAFE...WELCOME TO 2020:**



FIRST REPORTS OF INFLAMMATORY DISEASE

April 27

WORLD NEWS APRIL 27, 2020 / 1:27 PM / A MONTH AGO

Italy, UK explore possible COVID-19 link to child inflammatory disease

Emilio Parodi, Alistair Smout

5 MIN READ

[Twitter](#) [Facebook](#)



PICS Paediatric Intensive
Care Society

27 April 2020

PICS Statement: Increased number of reported cases of novel presentation of multi-system inflammatory disease

MAY 5

Health

15 children in New York City have developed a puzzling and serious inflammatory syndrome possibly linked to covid-19

The condition is similar to what doctors have observed in Europe

**MAY 14 =
CDC
ADVISORY**

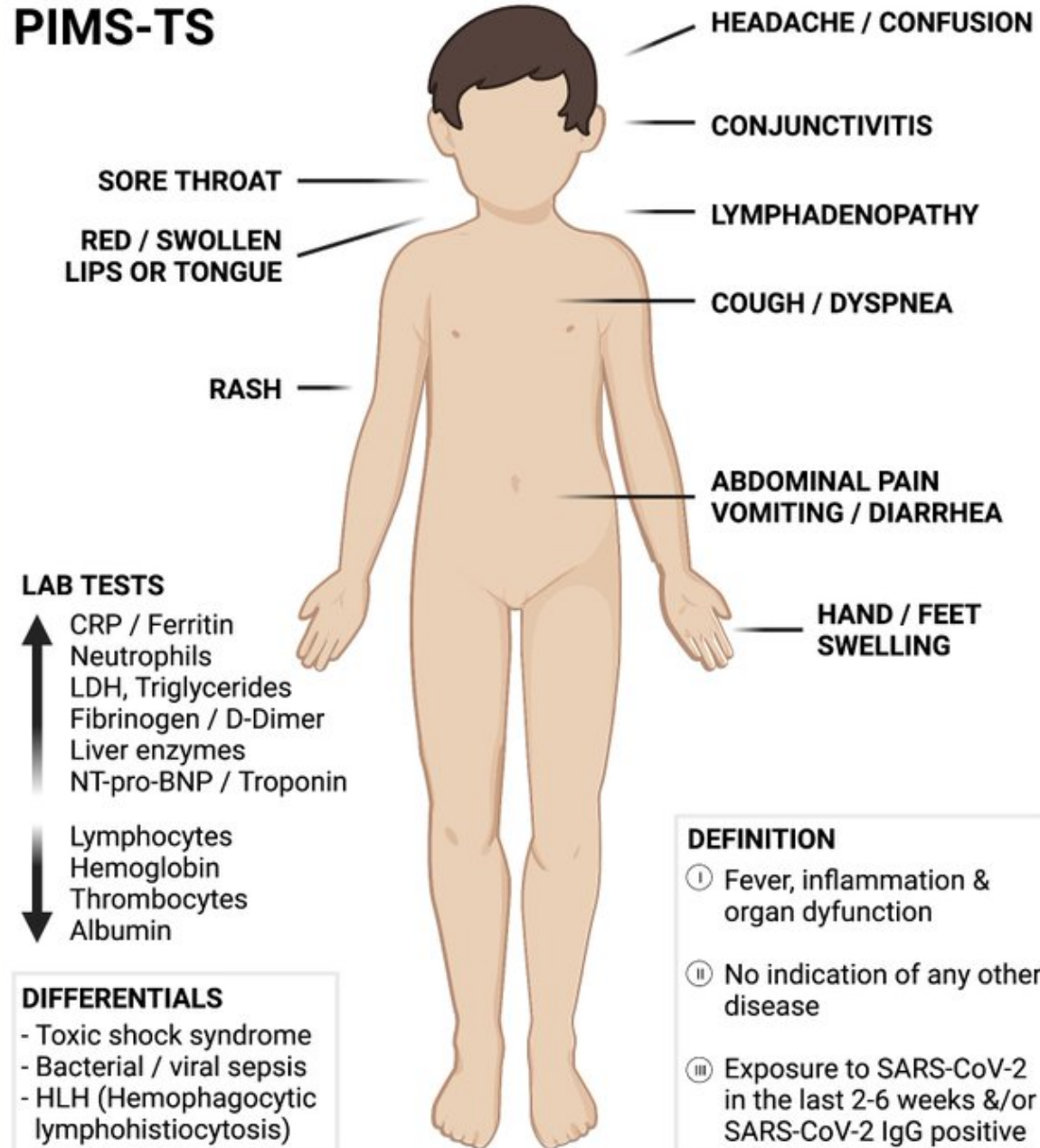
Multisystem Inflammatory Syndrome in Children (MIS-C) Associated with Coronavirus Disease 2019 (COVID-19)



Distributed via the CDC Health Alert Network
May 14, 2020, 4:45 PM ET
CDCHAN-00432

CLINICAL FEATURES AND DIAGNOSIS OF MIS-C

PIMS-TS



LAB TESTS

↑
CRP / Ferritin
Neutrophils
LDH, Triglycerides
Fibrinogen / D-Dimer
Liver enzymes
NT-pro-BNP / Troponin

↓
Lymphocytes
Hemoglobin
Thrombocytes
Albumin

DIFFERENTIALS

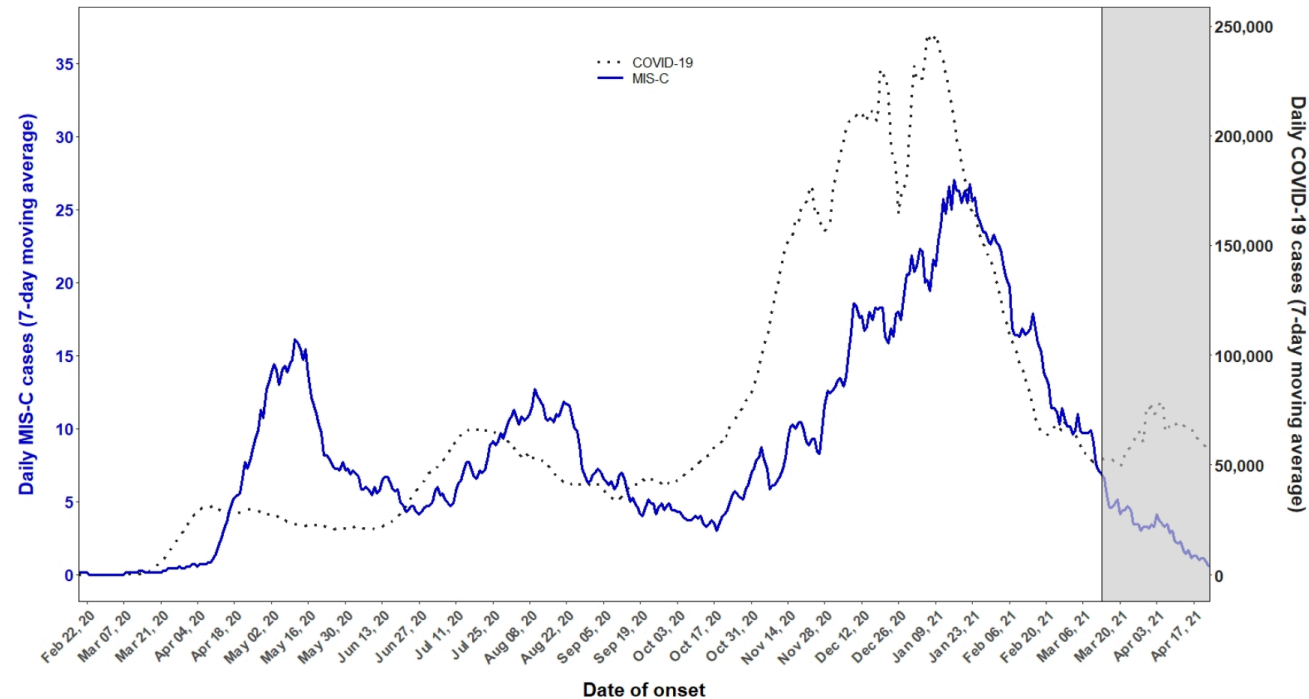
- Toxic shock syndrome
- Bacterial / viral sepsis
- HLH (Hemophagocytic lymphohistiocytosis)

DEFINITION

- ① Fever, inflammation & organ dysfunction
- ② No indication of any other disease
- ③ Exposure to SARS-CoV-2 in the last 2-6 weeks &/or SARS-CoV-2 IgG positive

MIS-C CASES IN THE US (2/2020 - PRESENT)

Daily MIS-C Cases and COVID-19 Cases Reported to CDC (7-Day Moving Average)



- >3700 cases (as of 6/01/21)
- Peak of MIS-C ~4-6 weeks from peak of COVID-19
- Rare complication (~1:10,000 or less)
- lots of unanswered questions!

The graph shows the 7-day moving average number of COVID-19 patients and MIS-C patients with date of onset between February 19, 2020 and April 23, 2021.

CARING for Children with COVID

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



- Leverages resources and networks from 3 NIH ICs to capture data from hospitalized patients with MIS-C
- Trans-NIH effort through RADx-rad to enhance diagnostic and predictive efforts



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



RADxSM 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

- ***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
- Develop translational tools to assess disease severity
- Milestone-driven award
- <https://www.nichd.nih.gov/newsroom/news/122120-prevail-kids>



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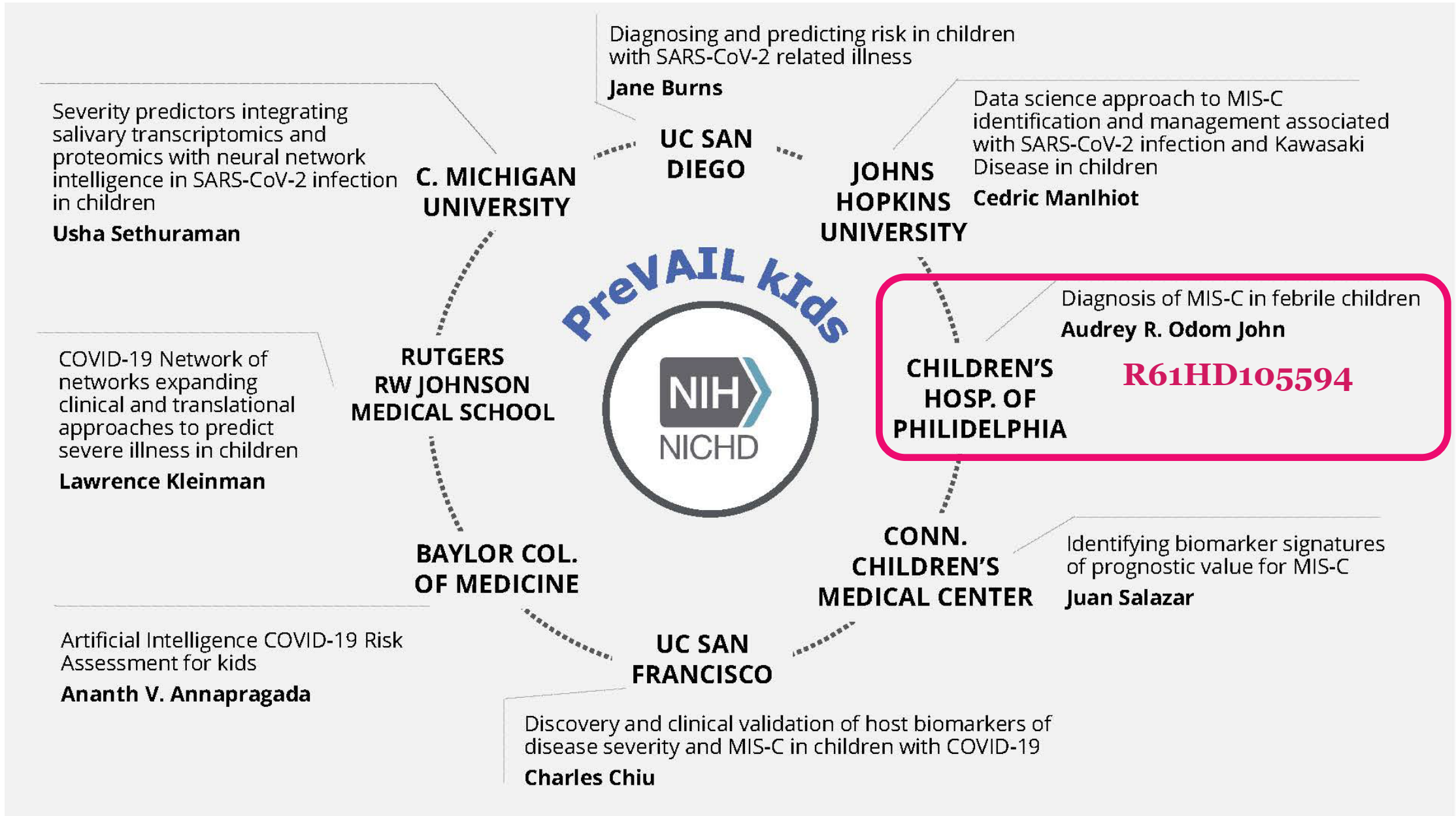


PreVAIL klds: Mission and Vision

- **Overarching Goals of PreVAIL klds**
 - Address the natural history and pathobiology of the entire spectrum of SARS-CoV-2 infection in children.
 - Accurate risk stratification & prediction of health outcomes in children
- **Shared goals (and resources) across RADx**
 - RADx-Rad Programs & DCC
 - RADx-Up
 - RADx-ATP/Tech
 - Trans-NIH and HHS resources (CTSA, REACH, SEED)
- **Shared mission with trans-NIH pediatric SARS-CoV-2 agenda**
 - CARING for Children with COVID Collaborative



PreVAIL kids AWARDEES



THE CLINICAL CHALLENGE: WHICH CHILD/TEEN WITH FEVER HAS MIS-C?

- High level of concern by front-line ED clinicians
- Missed cases that return
- Anchoring bias - delayed treatment for non-MIS-C conditions
- Does early treatment help? Therapeutic study needs a clear diagnostic algorithm

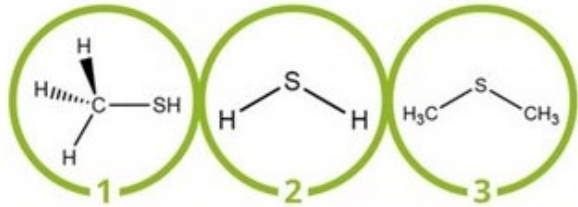


OUR SOLUTION

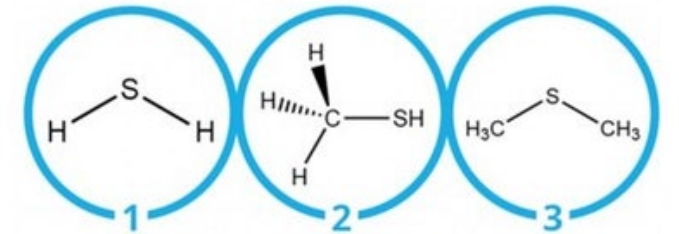


People stink

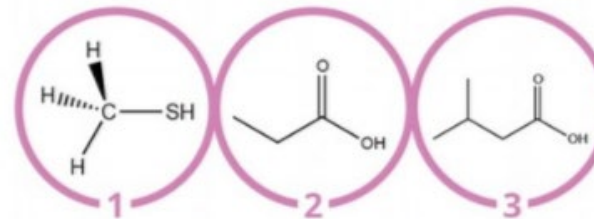
HALITOSIS



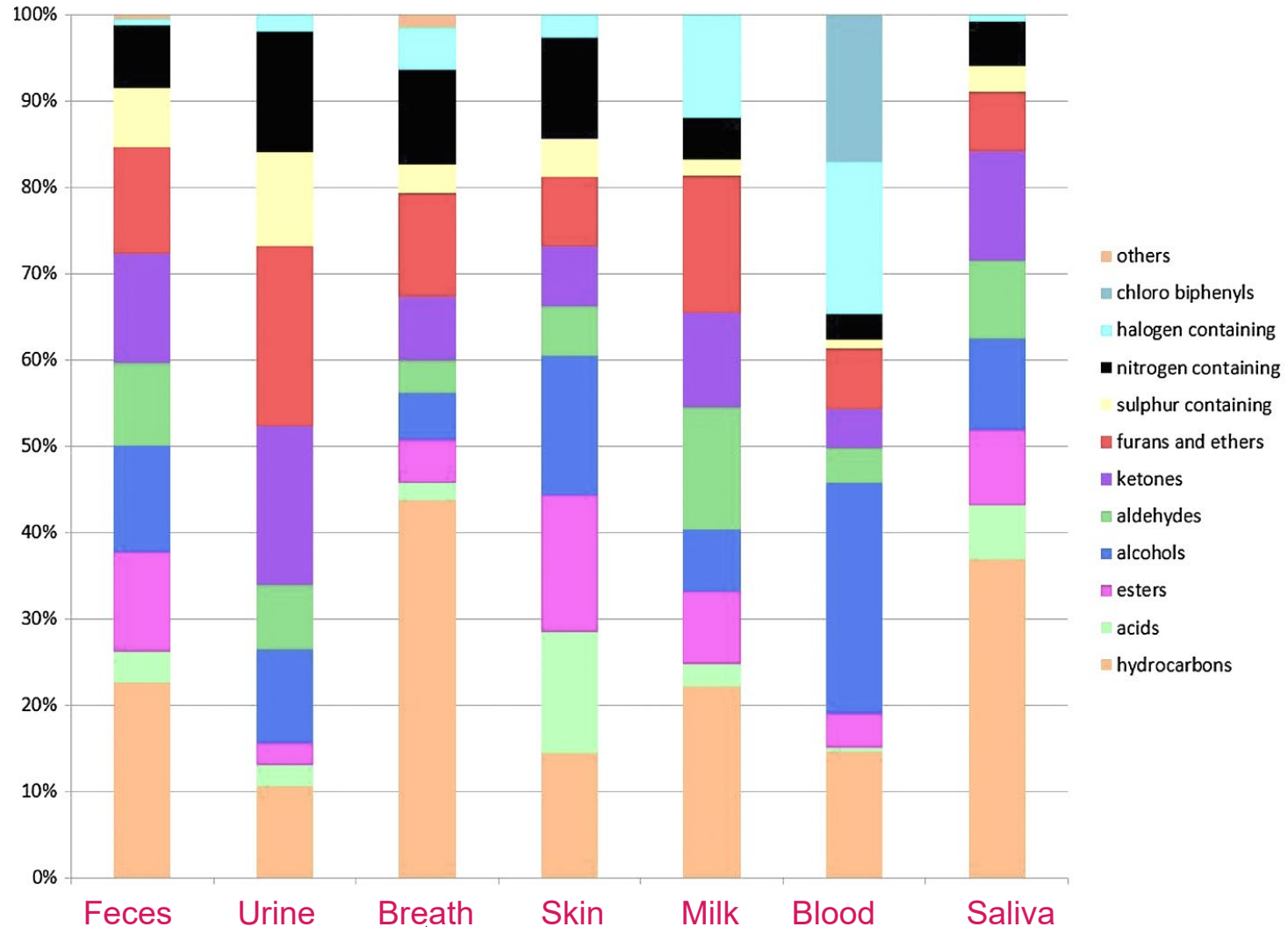
FLATULENCE



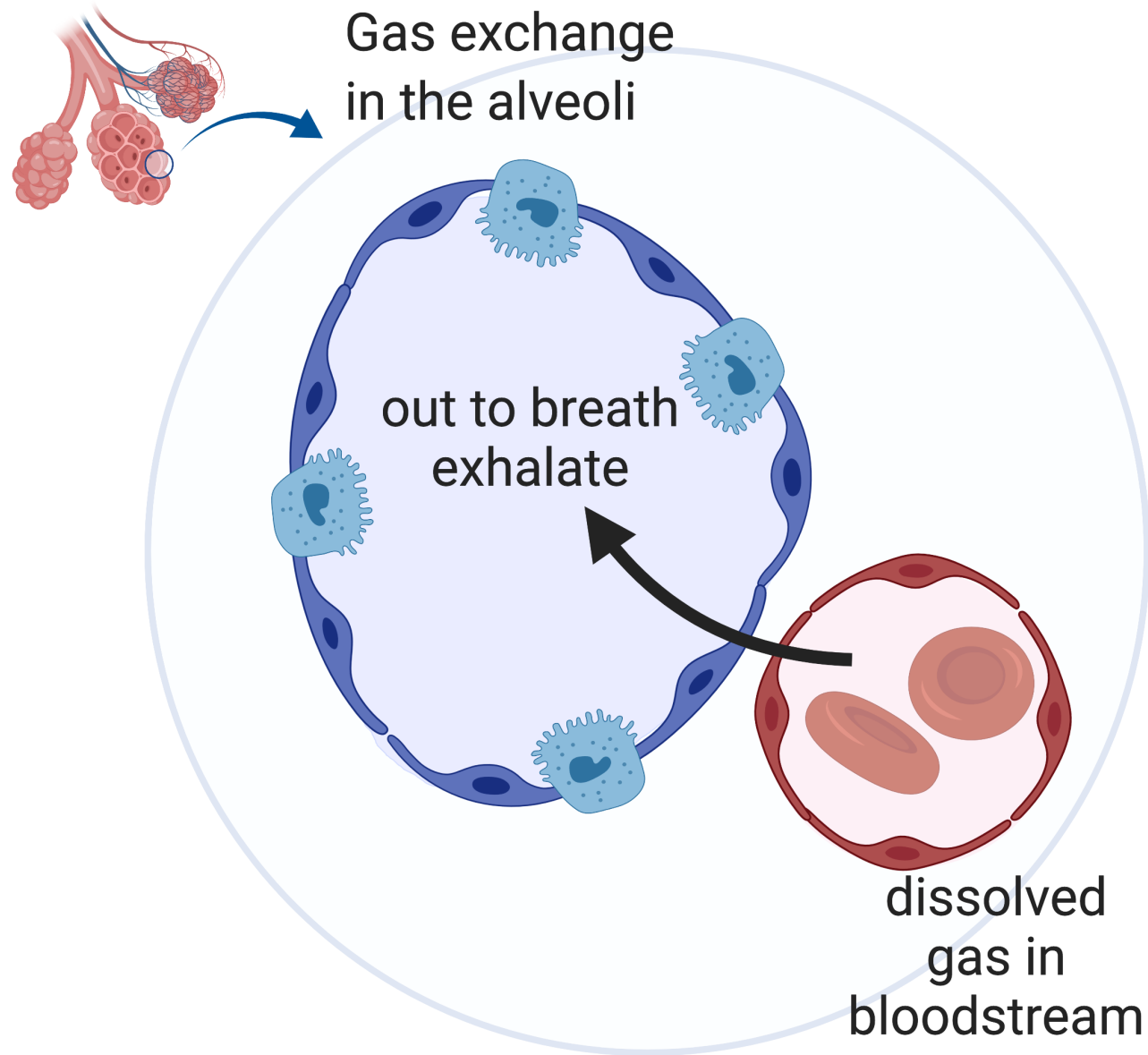
FOOT ODOUR



>1800 VOLATILES IN NORMAL HUMANS



Breath is a window to the blood

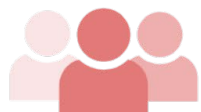


Biomarker discovery pipeline

① Study design



Healthy patients



Patients with disease

② Sample collection



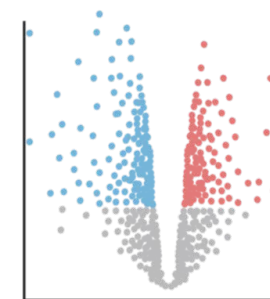
Breath,
urine, and
saliva

③ Data acquisition



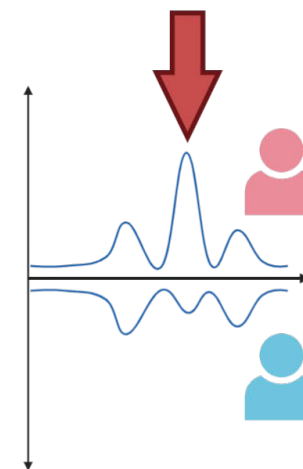
Mass
spectrometry

④ Statistical analysis

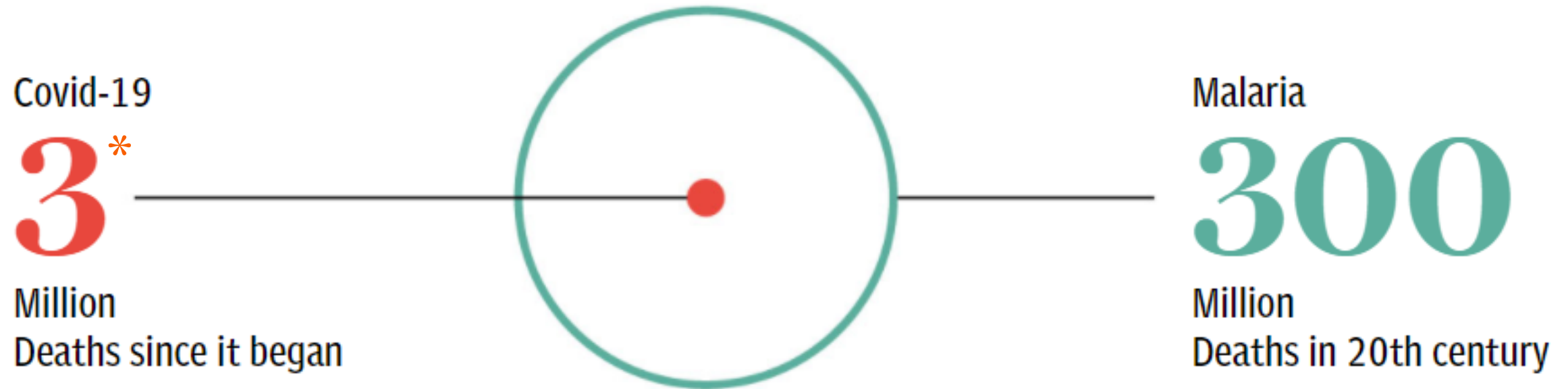


Identification of
metabolites

⑤ Biomarker identification



Covid-19 has killed roughly similar numbers in the last year as malaria killed on average every year of the last century



SOURCE: NATIONAL CENTRE FOR BIOTECHNOLOGY INFORMATION

*as of April 2021



Voluntary exhalation



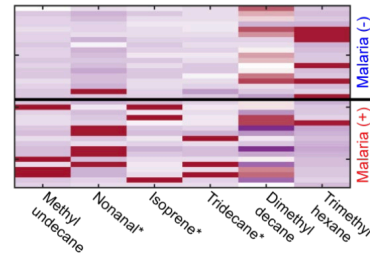
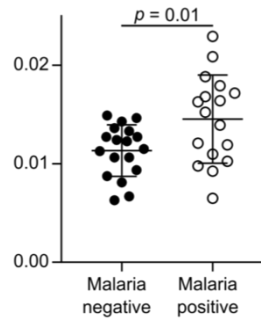
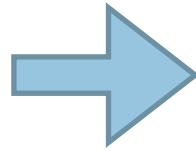
TD/GC-MS (USA)

**Breath volatiles
pumped over
thermal
desorption (TD)
column**

Breath biomarker discovery/validation for pediatric malaria



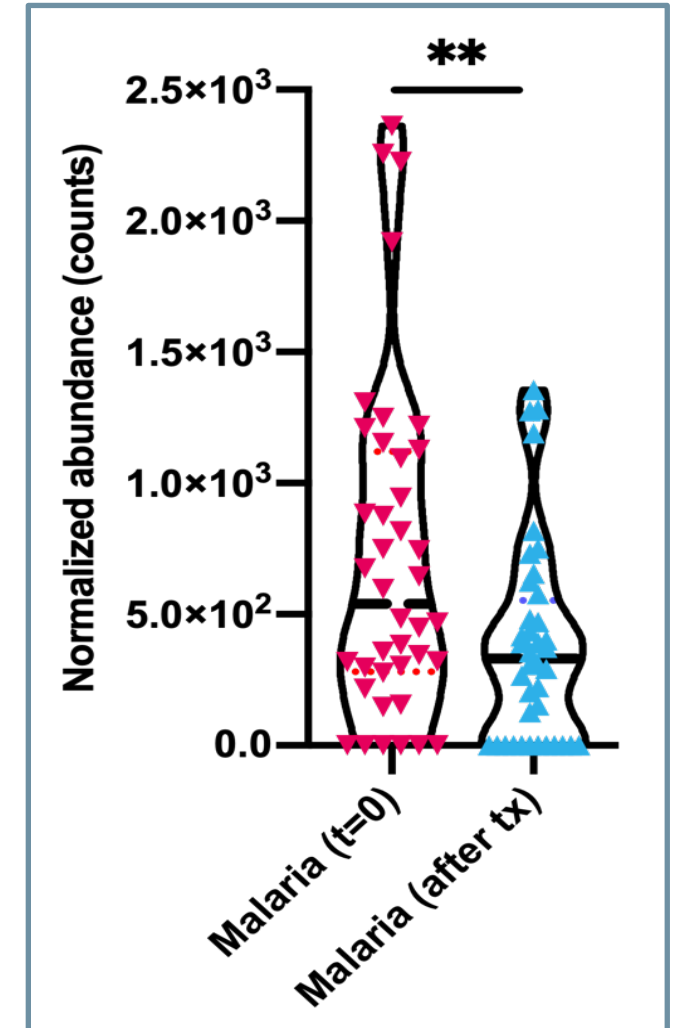
Febrile children +/- falciparum malaria



Candidate breath biomarkers



Independent validation (new cohort)



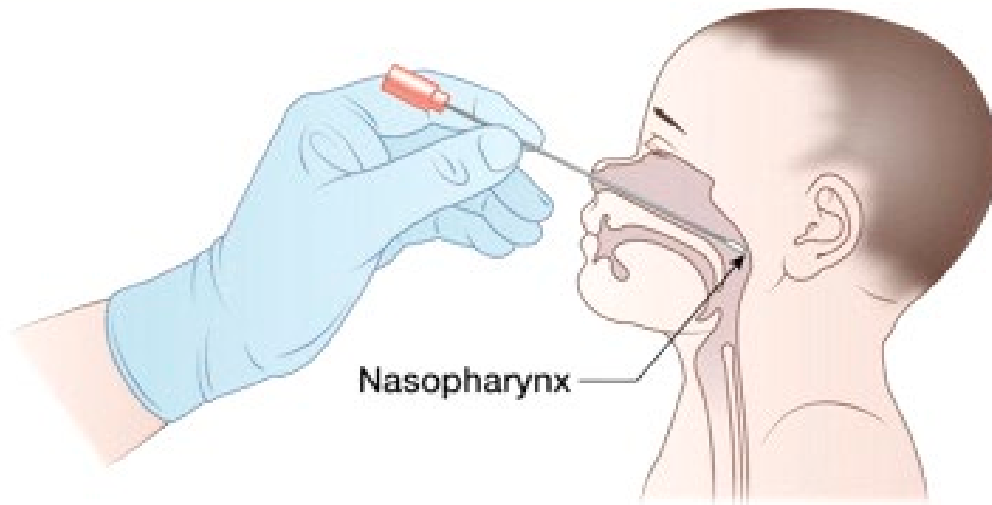
unpublished

Breath · **U**rine · **S**aliva
COVID-19 Biomarker Study



THE BUS COVID BIOMARKER STUDY

THE GOAL: RAPID, EASY, SIMPLE DIAGNOSTICS FOR SARS-COV-2 INFECTION

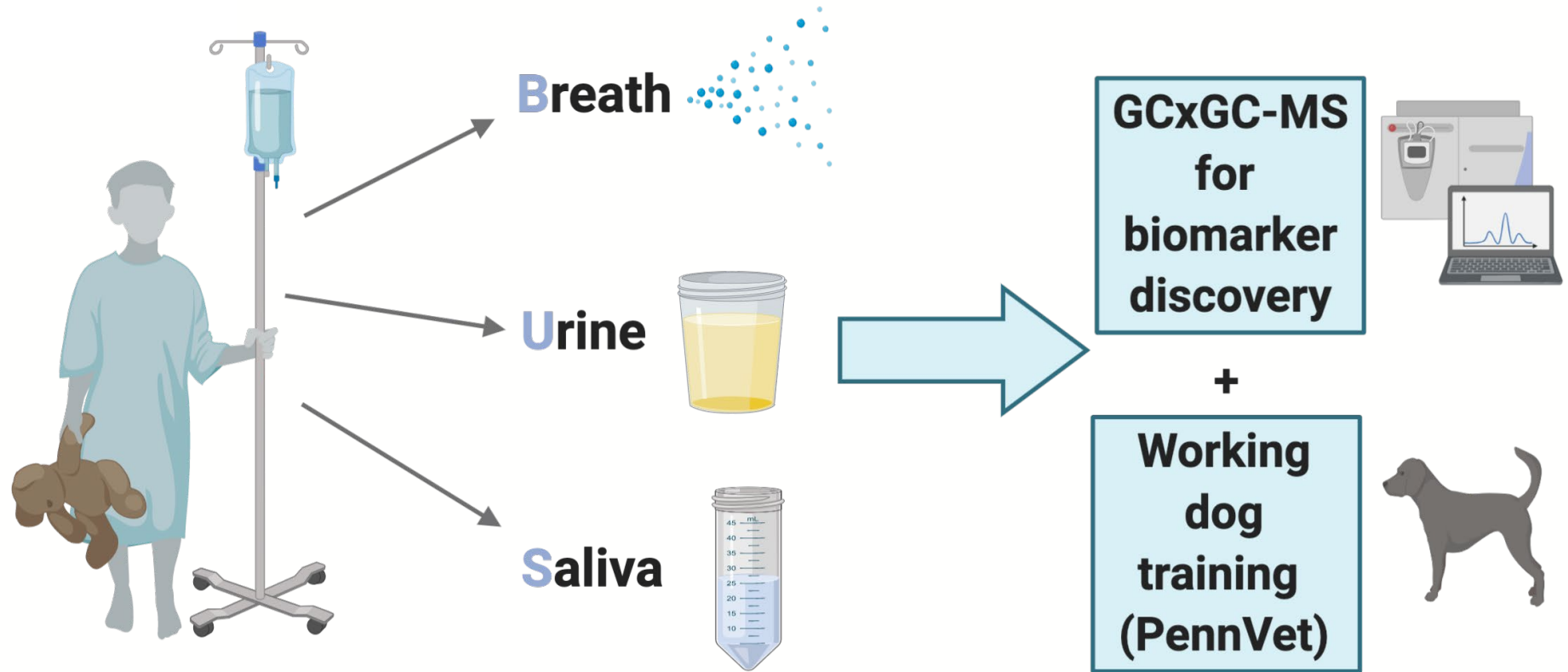


- Uncomfortable
- Time to result: 2h to days
- Special equipment and personnel needs
- Supply chains strained



- Simple, easy, noninvasive
- Fast (15 min)
- Established developmental pipeline
- Suitable for resource-limited settings
- No supply chain problem

Breath · **U**rine · **S**aliva
COVID-19 Biomarker Study



Patients aged 4-20y
Admitted to CHOP
SARS-CoV-2 positive/negative



Cindy Otto DVM PhD
Director, PennVet Working Dog Center

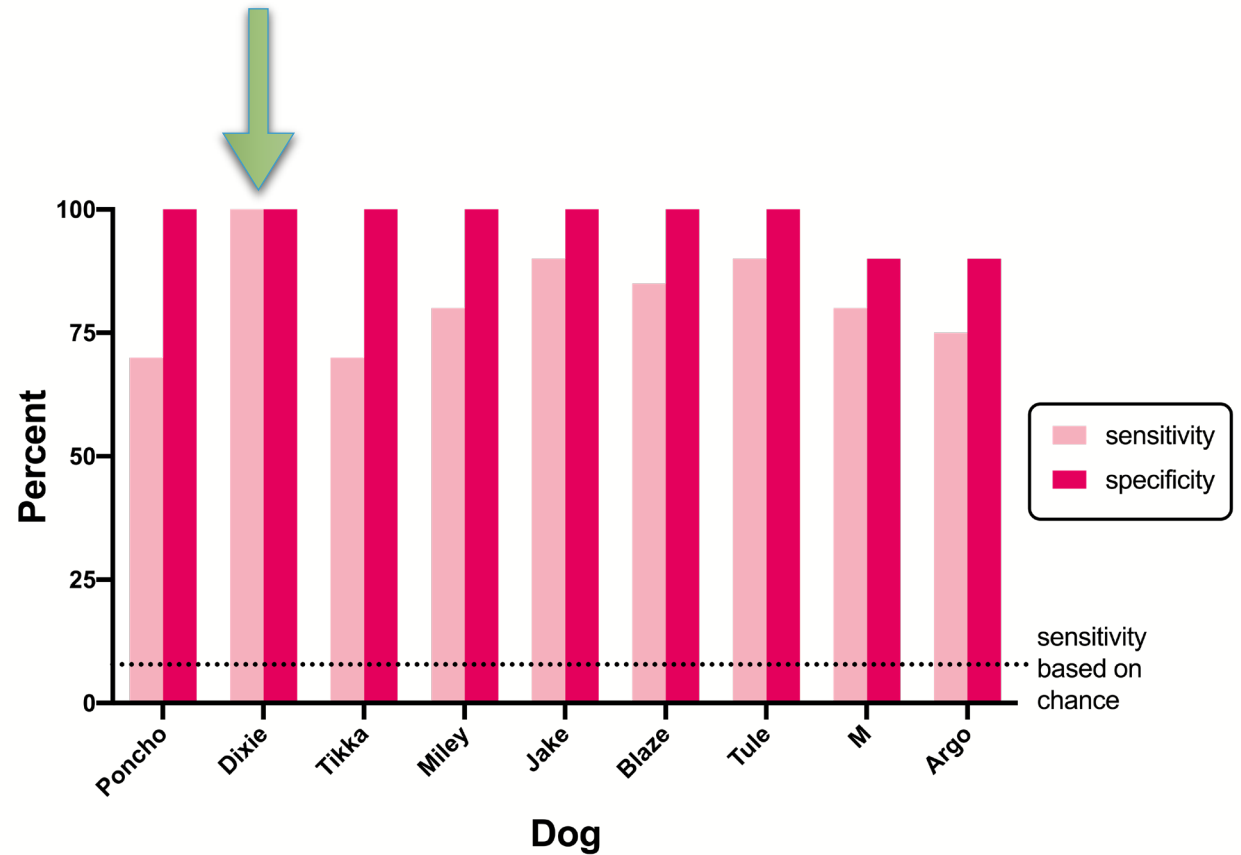


PennVet
UNIVERSITY of PENNSYLVANIA

VERY GOOD DOGS!



<https://www.washingtonpost.com/science/2020/08/18/dogs-sniff-coronavirus-detection>



AVG SENSITIVITY = 82.2 +/- 10.0%
AVG SPECIFICITY = 97.8 +/- 4.4%

GROWING EVIDENCE FOR DISTINCT ODORS OF SARS-COV-2



Dubai

CORONAVIRUS | Feb 8, 2021, 07:08am EST | 551 views

Are Covid-Sniffing Dogs The Miami Heat's New MVPs?



Robert Glatter, MD Contributor 

Healthcare

I cover breaking news in medicine, med tech and public health

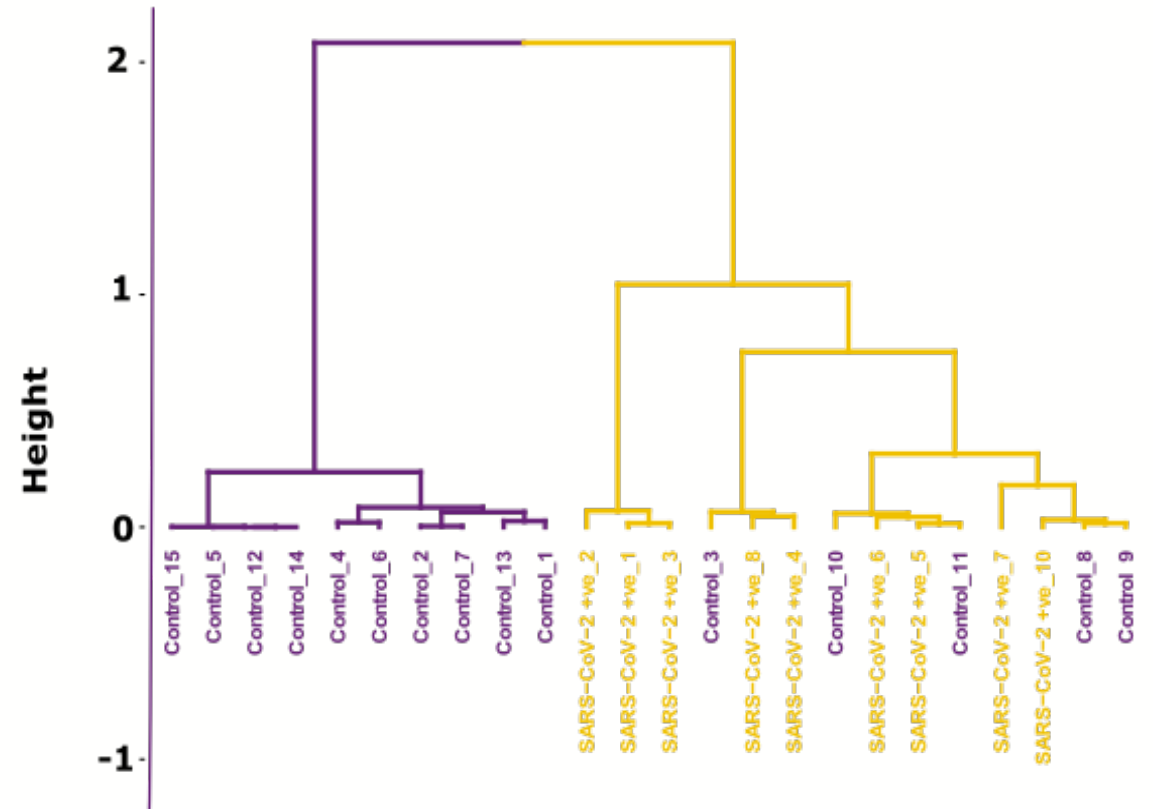
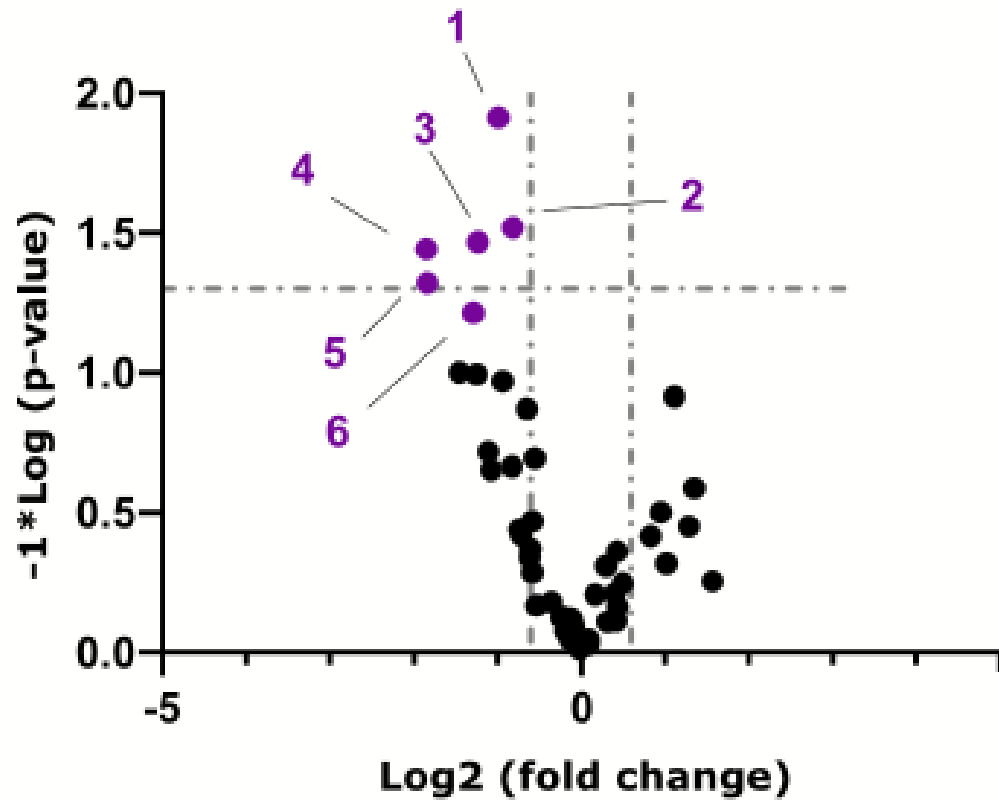
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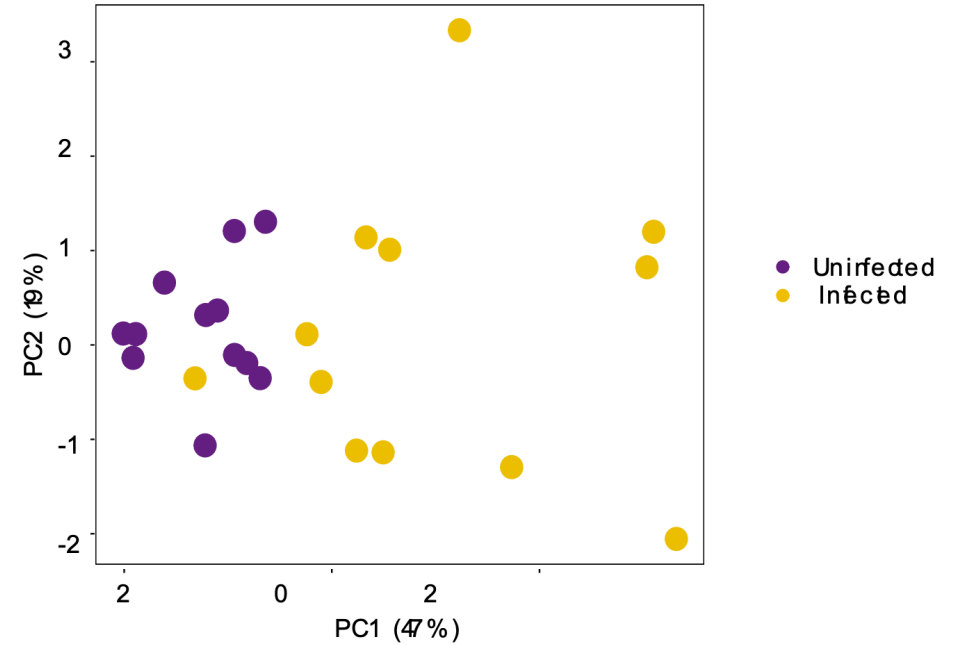
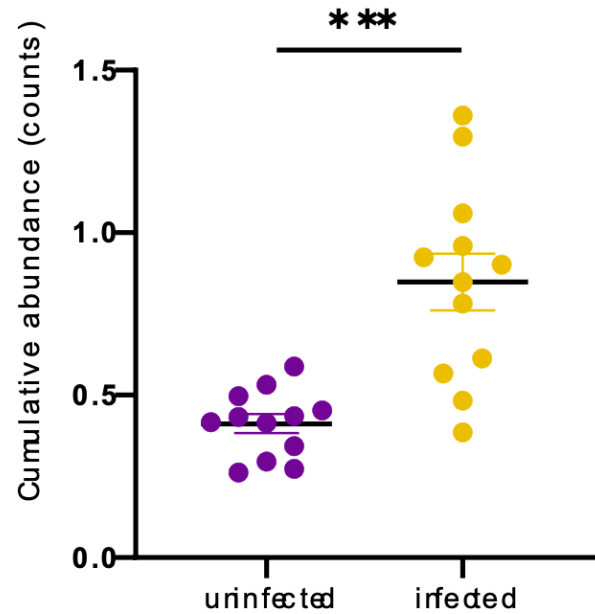
MIAMI, FLORIDA - JANUARY 28: Miami Heat K-9 handler Wayne Weseman walks Happy, a COVID-19 detection ... [\[+\]](#) GETTY IMAGES

Miami

BREATH-BASED DIAGNOSIS OF SARS-COV-2 IN CHILDREN BIOMARKER DISCOVERY (N=25)



BREATH-BASED DIAGNOSIS OF SARS-COV-2 IN CHILDREN INDEPENDENT VALIDATION (N=24)

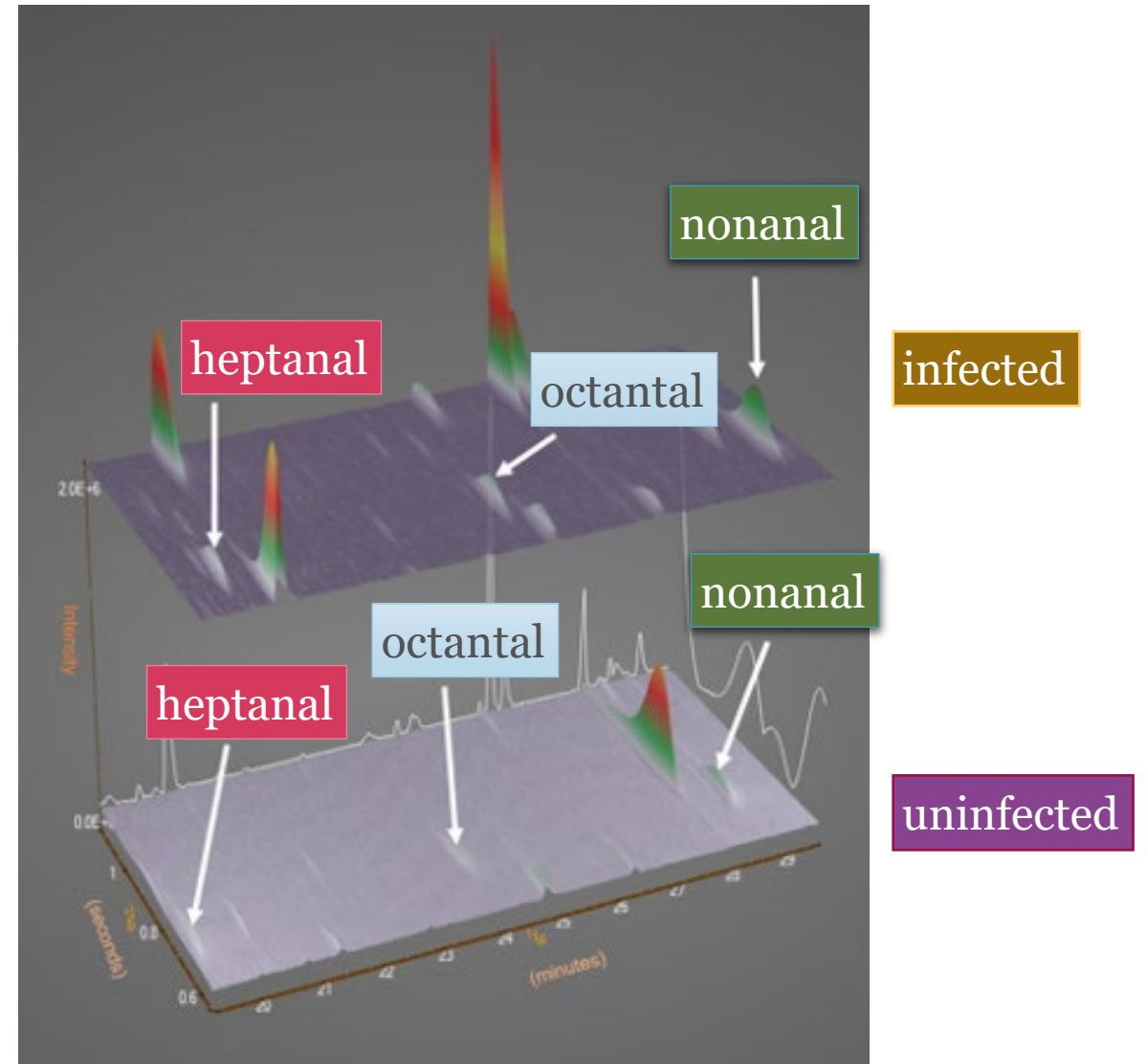


84% OVERALL ACCURACY
91% SENSITIVITY

BREATH BIOMARKERS OF ADULT COVID-19

Most discriminatory breath volatiles in adults:

M1	Ethanal
M2	Acetone
M3	Acetone/2-Butanone cluster
M4	2-Butanone
M5	Methanol Monomer Methanol Dimer
M6	Octanal
M7	Feature 144
M8	Isoprene
M9	Heptanal
M10*	Propanol
M11*	Propanal



global change in breath aldehydes

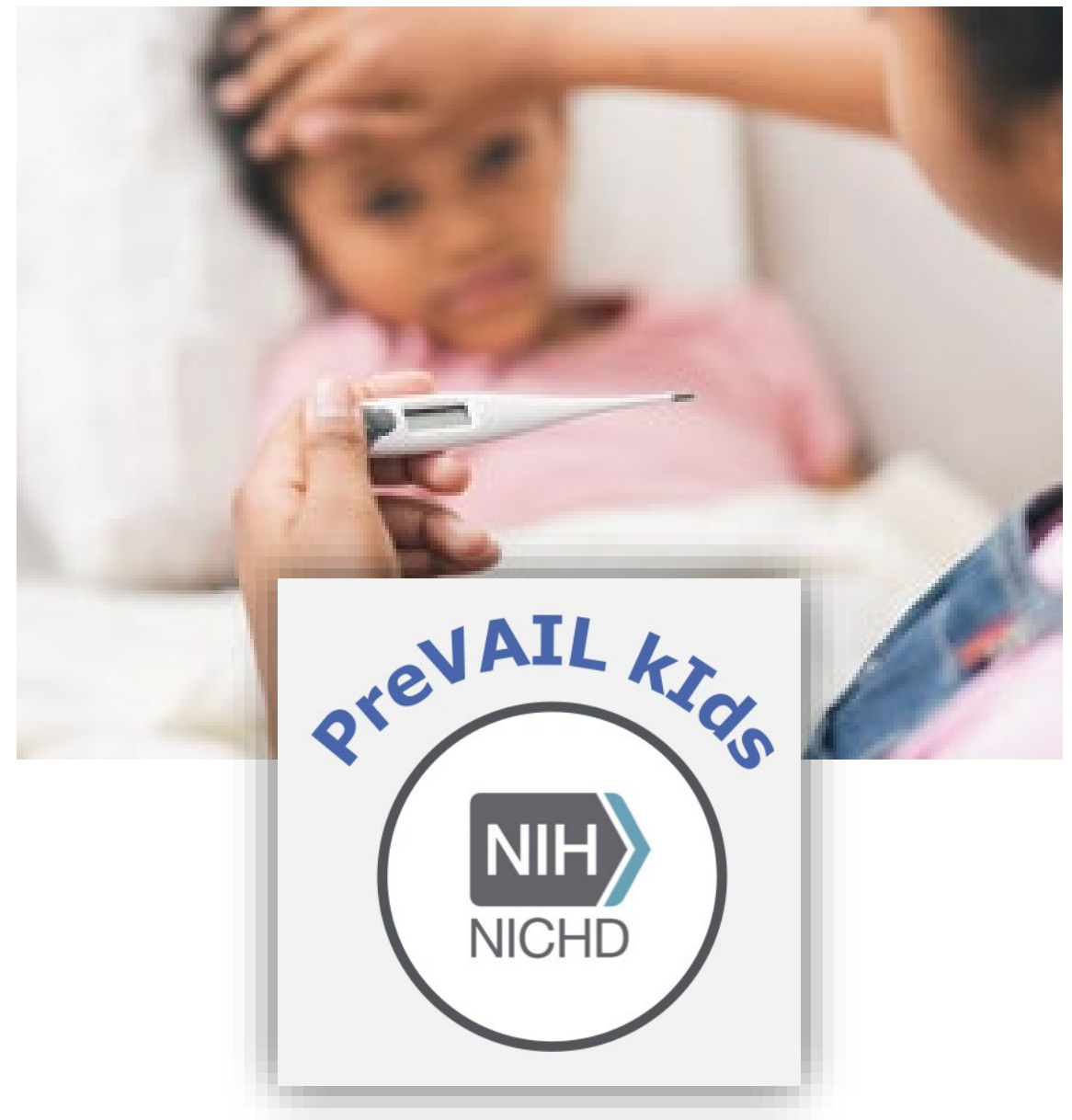
THE GOAL: RAPID, EASY, SIMPLE DIAGNOSTICS FOR PEDIATRIC INFECTION

- Breath volatiles = a reliable non-invasive window to health and disease
- Validated biomarkers for malaria
- Proof-of-concept for SARS-CoV-2 infection



ONGOING WORK

- Specificity (once respiratory viruses are back...)
- Biological origin of SARS-CoV-2-generated metabolites?
- PreVAIL kids study for diagnosis of post-SARS-CoV-2 MIS-C



CHOP PREVAIL KIDS: ONGOING STUDY



Inclusion criteria:
Children > 2 yr (4+ for breath)
T >38.0° C for 3+ days
2+ clinical/historical features
suggestive of MIS-C

Clinical screening labs
(per CHOP MIS-C pathway):
CBC, CMP, CRP, ESR
(clinically indicated)

Metabolomics of
non-invasive clinical
samples (breath, urine,
saliva)

Immunoprofiling
(cytokine profiling,
flow cytometry,
SARS-CoV-2 serology,
banked specimen)

*continued clinical
suspicion for
MIS-C?*

YES

NO

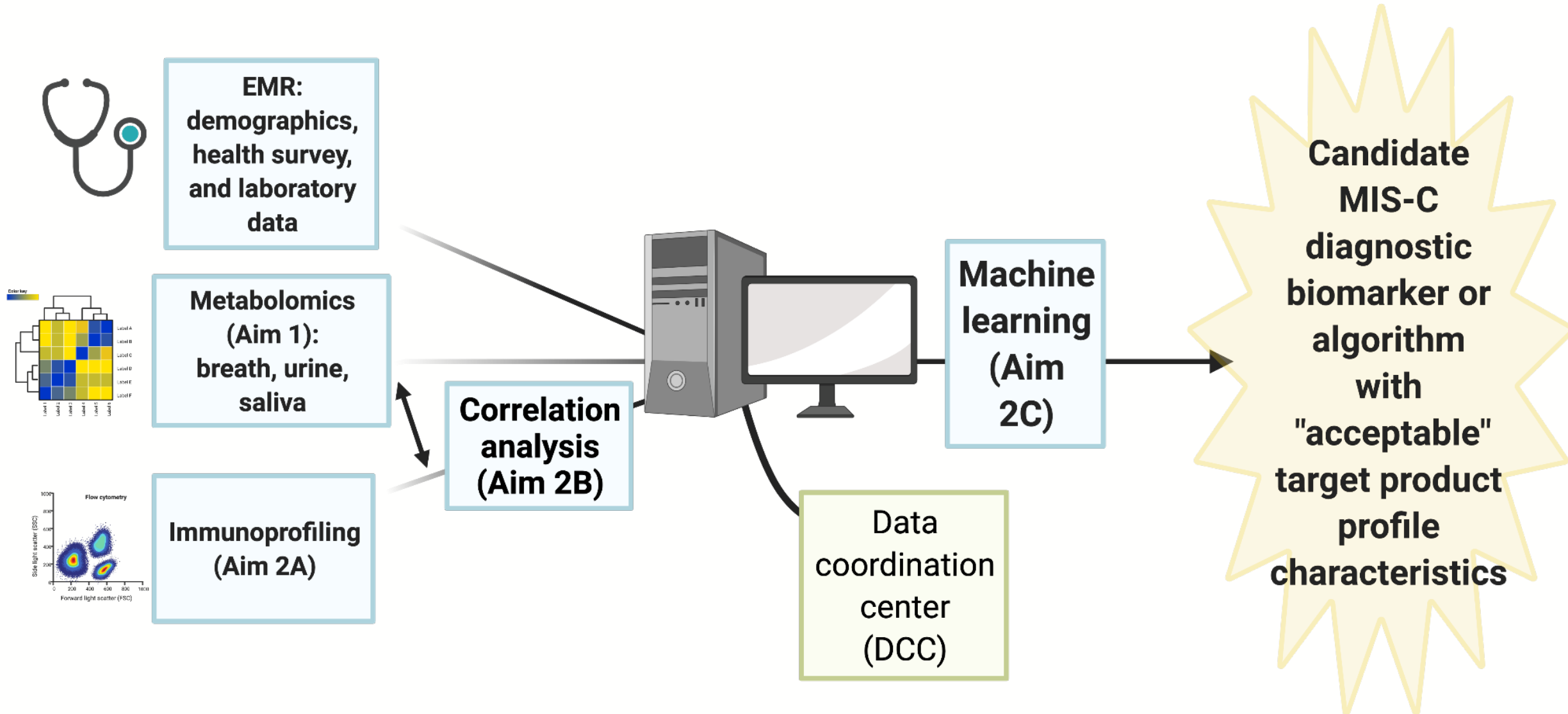
-additional testing
-admission
-multi-disciplinary consultation for
MIS-C diagnosis (current gold
standard)

Diagnosis:
not MIS-C
(n=150)

Diagnosis:
MIS-C
(n=30)

**Single enrollment site:
CHOP Emergency Department**

PROJECT OVERVIEW: PREVAIL KIDS





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**Children's Hospital
of Philadelphia®**

Division of Infectious Diseases