



Stakeholder Engagement and Communication Call (SEC)

September 18, 2026



Agenda

Today's Agenda

Welcome and Meeting Overview

Updates from CDC -- Joanna Regan, MD, MPH

Team Lead, Clinical Research, Epidemiology, and Outreach (CREO) Team, Chronic Viral Diseases Branch, Centers for Disease Control and Prevention

“How Progress in Long COVID is helping us understand ME/CFS”-- Nancy Klimas, MD

Professor of Medicine and Chair of the Department of Clinical Immunology; Director, Institute for Neuro-Immune Medicine (INIM), Nova Southeastern University

Question and Answer (Q&A)

CDC Updates

With Gratitude: Colleagues Who Have Moved On

Since our last Stakeholder Engagement and Communication Call

Elizabeth Unger, MD, PhD

Jin-Mann (Sally) Lin, PhD

Yang Chen, DrPH

Maung Khin

Jessica Maya, PhD

Dana Brimmer, PhD

Zachary McCann, PhD

Mangalathu Rajeevan, PhD

Val Poe

Steven Barrientos

Continuing the ME/CFS Work at CDC

Current Team Members

Joanna Regan, MD, MPH — ME/CFS Team Lead

Elizabeth Fall, MPH

Laura Eloyan, MBA — Acting Branch Chief

Stephanie Sargent Weaver, PhD, MPH

Dane Benedict, MS

Recent CDC ME/CFS Program Publications

Topics: Clinical characterization, measurement, surveillance, epidemiology, and biology

Clinical Characterization & Outcomes

1. **Post-viral infection behaviors among patients with Long COVID.** Zhang TM, et al. JMIR Form Res. 2025;9:e77644. doi:10.2196/77644
2. **Medical complexity and healthcare utilization in U.S. post-COVID clinics.** Nji MAM, et al. BMC Infect Dis. 2025;25:1145. doi:10.1186/s12879-025-11424-1
3. **Long COVID, recovered COVID, and non-COVID post-acute infection syndromes over 3 years.** Carr CR, et al. PLoS One. 2025;20:e0323104. doi:10.1371/journal.pone.0323104
4. **Long COVID as an infection-associated chronic condition.** Unger ER. Am J Health Promot. 2025;39:960–965. doi:10.1177/08901171241308066b
5. **Autonomic dysfunction in ME/CFS: findings from the MCAM Study.** Issa A, et al. J Clin Med. 2025;14:6269. doi:10.3390/jcm14176269

Measurement, Surveillance & Epidemiology

6. **Evaluation of the PROMIS Physical Function Short Form 12a in adults with ME/CFS.** Yang M, et al. Health Qual Life Outcomes. 2025;23:95. doi:10.1186/s12955-025-02431-6
7. **ME/CFS diagnostic reporting in the 2021–2023 National Health Interview Survey.** Fleig K, et al. BMC Public Health. 2026;26:1993. doi:10.1186/s12889-026-27598-5

Biology & Mechanisms

8. **Genetic insights into circulating complement proteins in ME/CFS.** Maya J, et al. Int J Mol Sci. 2026;27:1574. doi:10.3390/ijms27031574

Recent CDC ME/CFS Program Publications

Topics: Patient engagement, lived experience, education, and clinical practice

Patient Engagement & Lived Experience

9. Voice of the patient: people with ME/CFS share in their own words. Brimmer DJ, et al. *Fatigue*. 2025;13:1–11.

doi:10.1080/21641846.2024.2444826

10. Facilitators of and barriers to participation in Long COVID research. Chu L, et al. *PLoS One*. 2026;21:e0346007.

doi:10.1371/journal.pone.0346007

11. Influence of lived-experience experts on healthcare providers in a virtual community of practice. Weaver SS, et al. *Front Health Serv*. 2025;5:1562651.

doi:10.3389/frhs.2025.1562651

Education & Clinical Practice

12. Pediatric ME/CFS: a diagnostic and communication case study for healthcare providers in training. Brimmer DJ, et al. *MedEdPORTAL*.

2025;21:11507.

doi:10.15766/mep_2374-8265.11507

A few current projects

- **Surveillance to Optimize Protocols for Early Identification and Subgrouping of Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (STOP ME/CFS)--**
<https://divisionofresearch.kaiserpermanente.org/studies/california-emerging-infections-program-surveillance-to-optimize-protocols-for-early-identification-and-subgrouping-of-myalgic-encephalomyelitis-chronic-fatigue-syndrome-me-cfs/>
- **Medscape**—most recent spotlight course “Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS) Diagnosis and Management in the Age of COVID-19: Expert Insights” available at <https://www.medscape.org/viewarticle/995777>
- **Online Medical Education/Project ECHO**
 - Register for the Project ECHO monthly webinars--
<https://iecho.org/public/program/PRGM1699044218879IERCAXHJ8Y>
 - Register for the monthly case based virtual community of practice--
<https://docs.google.com/forms/d/e/1FAIpQLSflaUCGI7XuXxTxZ9dihW4bsh0QS56uQFAaUatamYDKSlGbZa/viewform?pli=1>

**Featured presentation—Dr. Nancy Klimas
“How Progress in Long COVID is helping us
understand ME/CFS”**

Q&A

CFS@CDC.GOV

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The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the U. S. Centers for Disease Control and Prevention.



How Progress in Long COVID Is Helping Us Understand ME/CFS

From shared post-infectious phenotypes to mechanism-informed, mediator-based intervention

Nancy Klimas, MD

Nova Southeastern University
Institute for Neuro-Immune Medicine
Miami VAMC GRECC

CDC Stakeholders Call
September 18, 2026

How Progress in Long COVID Is Helping Us Understand ME/CFS

From shared post-infectious phenotypes to mechanism-informed, mediator-based intervention

**Long COVID is a research accelerator—
not a replacement for ME/CFS science.**

ME/CFS provided decades of clinical insight. Long COVID brings scale, prospective cohorts, multi-system phenotyping, and trial infrastructure.

**Goal: identify shared biological endotypes
and treat active mediators.**

The Central Opportunity

The comparison is most useful when it advances testable biology.

1

ME/CFS contributed

- PEM as a defining illness signal
- Clinical expertise in dysautonomia, cognition, sleep, and exertional intolerance
- Early immune, autonomic, vascular, and metabolic hypotheses

2

Long COVID contributes

- Known index infection and time since onset
- Larger cohorts and serial biospecimens
- Digital phenotyping, multi-omics, imaging, and trial platforms

3

Together we can

- Replicate and refine earlier signals
- Define biology-linked subgroups
- Test mediator-based interventions across cohorts

The shared question: which mechanisms predict persistent illness and treatment response?

The Right Question Is Not “Are They the Same?”

Focus on convergence, divergence, and treatment-relevant biology.

Long COVID

Known SARS-CoV-2 trigger

Variable organ involvement

Distinct early trajectory

Many patients develop an ME/CFS-like phenotype

Shared Endotypes

PEM

Dysautonomia

Endothelial / microvascular dysfunction

Immune and mast-cell signaling

Energy and redox stress

ME/CFS

Often post-infectious

Multiple possible triggers

Frequently longer illness duration

Deeply characterized PEM phenotype

Endotype is a subtype of a disease characterized by a distinct pathophysiological mechanism, differentiating it from a **phenotype**, which refers to observable characteristics without implying a specific mechanism.

ME/CFS Identified the Clinical Problem Early

The illness is multi-system, stress-sensitive, and often invisible at rest.

1

PEM

Delayed
symptom
worsening after
exertion

2

Cognition

Brain fog and
impaired
processing
under demand

3

Autonomic

Orthostatic
intolerance,
tachycardia,
venous pooling

4

Sleep / pain

Non-restorative
sleep and
sensory
amplification

5

Energy

Reduced
reserve and
prolonged
recovery

Earlier ME/CFS studies generated important hypotheses; the limiting problem was underfunding and inadequate scale.

The ME/CFS Warning: Under-Recognition Produces Under-Research

A surveillance gap becomes a funding and intervention gap.

2-5 years

Diagnostic delay

Patients adapt

Pacing and compensation can conceal illness severity and depleted reserve.

**The
consequence**

Delayed recognition reduces access to targeted evaluation, longitudinal study, and trials.

In patient surveys, 67%–77% reported waiting more than one year for diagnosis, and approximately 29% reported waiting more than five years

COVID-UPP: A Prospective Window Into Post-Infectious Illness

Ana Palacio and Nancy Klimas, CoPIs and the CDC team: team leaders Sally Lin, Joanna Regan, Beth Unger

1,006 participants

Completed baseline assessment across six South Florida health systems.

Quarterly follow-up

Tracks clinical domains, recovery trajectory, and transition between persistent-illness states.

Direct ME/CFS comparison

COVID-UPP instruments mirror CDC MCAM measures, enabling cross-cohort comparison.

A diverse cohort: approximately 10% African American and 55% Hispanic/Latino participants.

COVID-UPP provides the longitudinal infrastructure that was often unavailable in ME/CFS.

Persistent Post-COVID Illness Is Not Binary

The “boundary” group may be especially informative for identifying transition biology.

174

Recovered

Criteria-negative

193

Boundary

Symptoms present;
indeterminate
classification

**Recovery trajectory is
a longitudinal question.**

639

Unrecovered

Criteria-positive

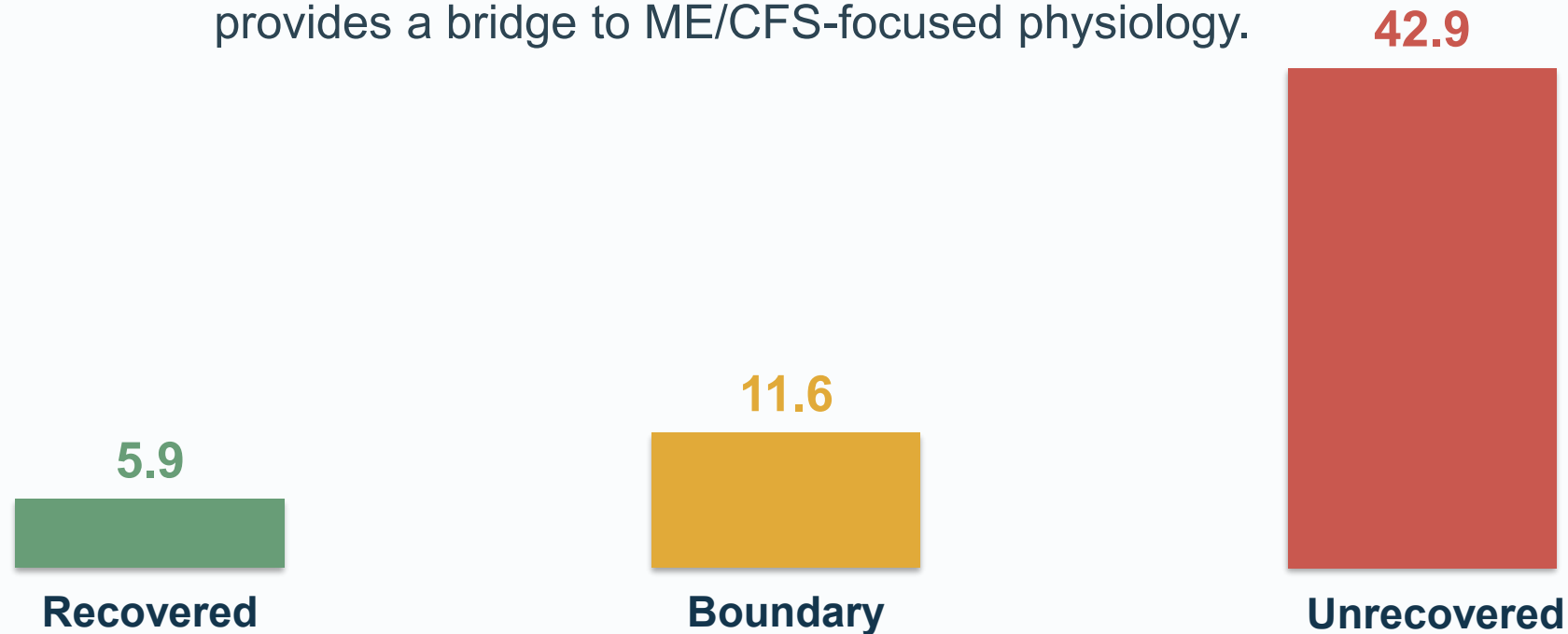
The boundary group can reveal early, fluctuating, or biologically distinct pathways into persistence.

PEM Is a Powerful Clinical Bridge

PEM burden rises sharply across COVID-UPP recovery groups.

DePaul PEM mean score

PEM distinguishes a clinically important persistent-illness phenotype and provides a bridge to ME/CFS-focused physiology.



Exertion is not merely an activity measure—it is a biologic stressor.

The Compensation Zone: Function Can Mask Reduced Reserve

Some symptomatic individuals call themselves recovered because they still maintain essential roles.

Physical function

Near-normal physical-function T-score: 49.6

Work and caregiving may continue.

Persistent symptoms

Fatigue: 54.1

Cognition: 47.5

Sleep disturbance: 53.6

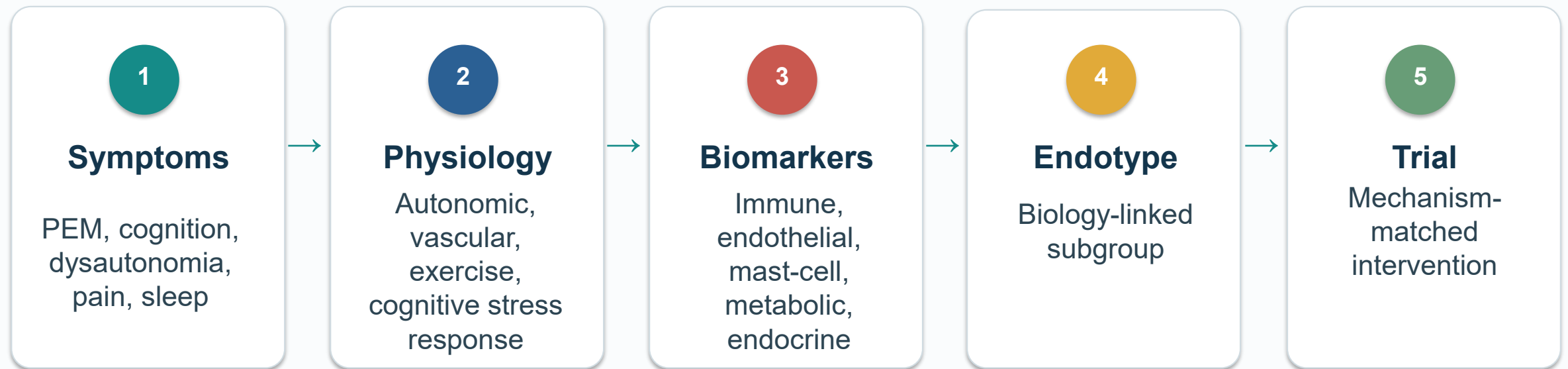
Clinical meaning

Compensation may sustain daily function while progressively exhausting physiologic reserve.

Preserved performance is not the same as restored biology.

From Clinical Phenotype to Mechanistic Endotype

Long COVID enables deeper study of trajectories, biology, and treatment response.



The target is not a diagnostic label alone; it is the active biology maintaining illness.

Mechanistic endotype? What does this mean to the patient?

What's new?

A much stronger understanding of mediators that contribute to illness persistence provide targets of intervention

Goal:

**Taking the progress in understanding pathophysiology to targeted intervention
ME/CFS**

Impaired Immune Containment

Persistent activation can coexist with ineffective antiviral surveillance , innate immune system dysfunction and/or humoral immune deficits.

1

NK-cell cytotoxic function

Reduced NK-cell cytotoxicity is a longstanding ME/CFS observation. In a subgroup, impaired killing capacity could limit control of infected or reactivated cells.

2

Cytotoxic T-cell regulation

Persistent activation, differentiation, or exhaustion-related programs may reduce effective immune resolution and sustain antigenic stimulation.

3

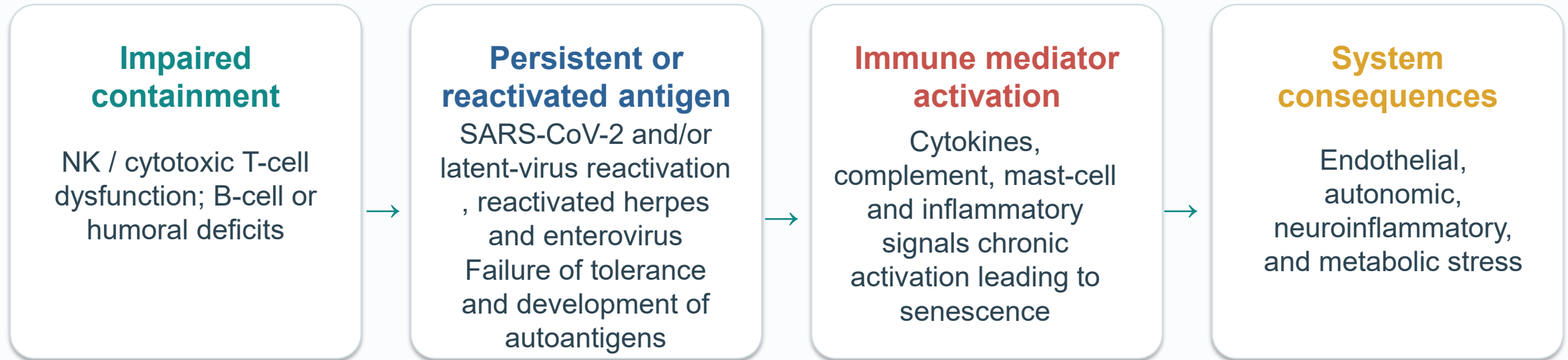
B-cell / humoral immunity

Altered B-cell regulation and, in selected patients, total IgG or IgG-subclass deficiency may reduce effective antibody-mediated containment.

Working hypothesis: impaired containment can permit intermittent viral reactivation or persistent antigenic stimulation.

From Immune Containment Failure to Persistent Mediator Loops

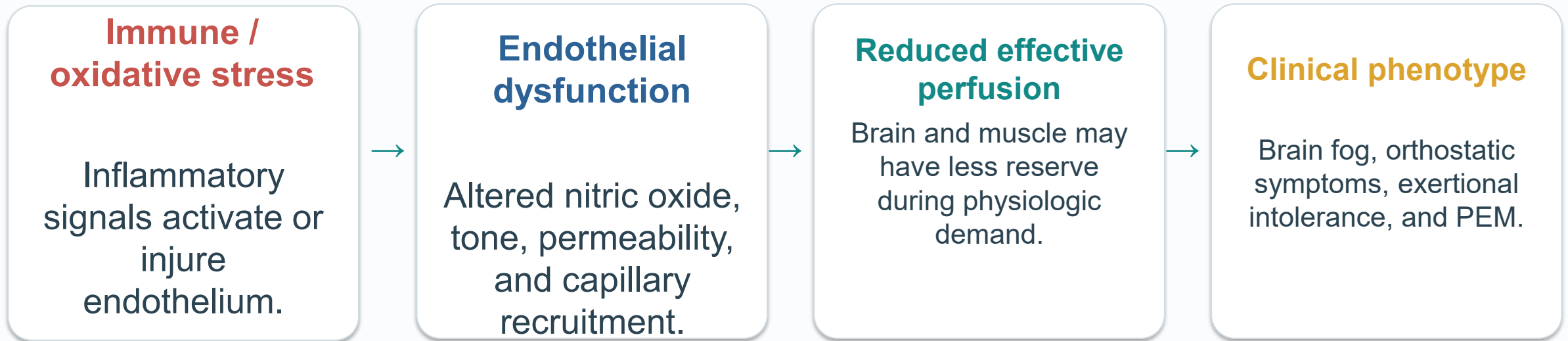
The initiating antigen and the self-sustaining response may coexist—or become partially independent over time.



This model predicts that immune and downstream mediator targets may require different treatment strategies.

Endothelium and Microcirculation Link Inflammation to Symptoms

The endothelium regulates nitric oxide, vascular tone, barrier function, coagulation, and immune-cell trafficking.



Endothelial dysfunction is a high-value shared candidate mechanism—best studied as a measurable vascular endotype.

Exertion Can Reveal Failure of Physiologic Recovery

In ME/CFS and a PEM-dominant Long COVID subgroup, exertion functions as a biologic stress test.

Before exertion

Symptoms may be partially compensated.

Resting measures can appear less abnormal than challenge-response physiology.

During / after challenge

Demand increases for circulation, oxygen extraction, autonomic adaptation, and metabolic recovery.

Clinical signal

Delayed symptom worsening, reduced reserve, and prolonged recovery are measurable treatment targets.

In plain language: Less blood may return to the heart during standing or activity, and muscles may not take up or use oxygen as efficiently when demand rises.

Systrom: Peripheral Neurovascular Dysregulation

iCPET studies support two interacting peripheral limitations in ME/CFS and Long COVID subsets.

1 Reduced venous return / preload

Lower filling pressures can limit the capacity to augment cardiac output during physiologic demand.

Potential contributors include autonomic dysregulation and venous pooling.

2 Impaired peripheral oxygen extraction

Systemic oxygen extraction can remain abnormally low despite oxygenated arterial blood.

Candidate contributors include neurovascular dysregulation, shunting, diffusion limitation, and altered oxidative capacity.

Both pathways can constrain aerobic performance during exertion.
In plain language: A normal pulse-ox reading does not guarantee that oxygen reaches and is used normally by the brain and muscles during exertion.

Oxygen Transport Is a Multi-Step Process

Normal resting oxygen saturation does not establish normal delivery, extraction, or use during exertion.



A deficit at any step can reduce aerobic reserve; multiple deficits may coexist in the same endotype.

Shared Oxygen-Extraction Abnormalities: A Testable Domain

Comparative exercise studies strengthen earlier ME/CFS observations and motivate targeted subgrouping.

Long COVID

Reduced peak aerobic capacity

Peripheral oxygen transport / extraction limitations in selected cohorts

Exercise-related symptom worsening

Shared Study Target

Impaired effective oxygen delivery, diffusion, extraction, and/or utilization during physiologic stress

ME/CFS

Reduced peak aerobic capacity

Peripheral oxygen extraction limitations in selected cohorts

PEM and delayed recovery

In plain language: After an exercise challenge, researchers found signs of muscle stress, altered energy production, and increased immune-cell activity—evidence of biology, not a lack of effort.

Wüst and Appelman: PEM Is Accompanied by Skeletal-Muscle Injury and Mitochondrial Dysfunction Biology

The muscle findings support disease-related pathology beyond a simple inactivity narrative.

Structural and metabolic change

Lower exercise capacity with skeletal-muscle structural alterations, local and systemic metabolic disturbances, and lower energy production.

Post-exertional worsening

After PEM induction, muscle abnormalities worsened, including features interpreted as exercise-induced myopathy and amyloid-containing deposits.

Immune-cell signal

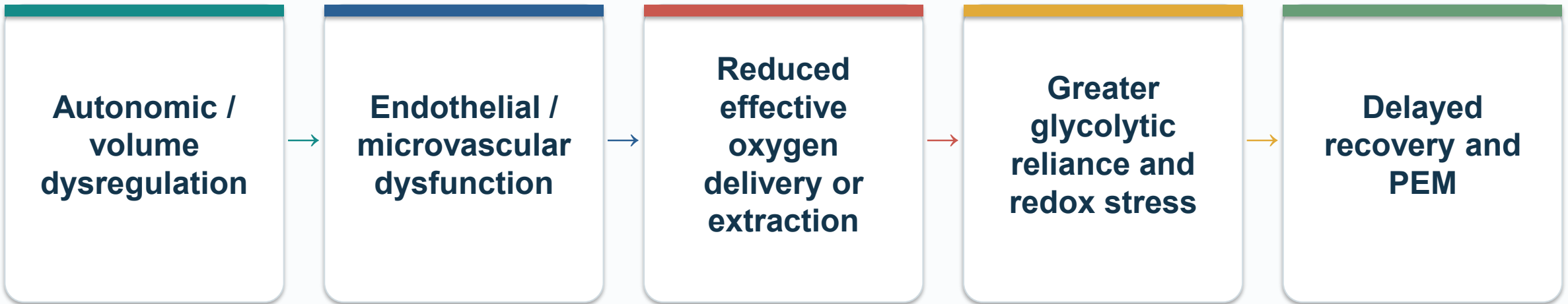
Reported skeletal-muscle infiltration included increased T cells and macrophages, but not B cells, in the source presentation.

Interpretation: exertion can expose active peripheral biology—not merely reduced fitness.

In plain language: A feedback loop can develop: circulation and oxygen-use problems increase energy stress, which can worsen delayed recovery after activity.

Integrated Interpretation: A Perfusion–Metabolism Stress Loop

A working model for a subgroup—not a single explanation for every patient.



Therapeutic implication: identify the dominant breakpoints in the loop and measure target engagement.

In plain language: The lining of blood vessels can become inflamed or less responsive, making it harder to adjust blood flow when the brain or muscles need more oxygen.

Endothelial Dysfunction: A Shared, Actionable Candidate Mediator

The endothelium links immune signaling, vascular regulation, and tissue perfusion.

Endothelial activation

Inflammation, oxidative stress, immune-cell trafficking, and barrier signaling.

Vascular consequence

Altered nitric-oxide signaling, tone, capillary recruitment, and permeability.

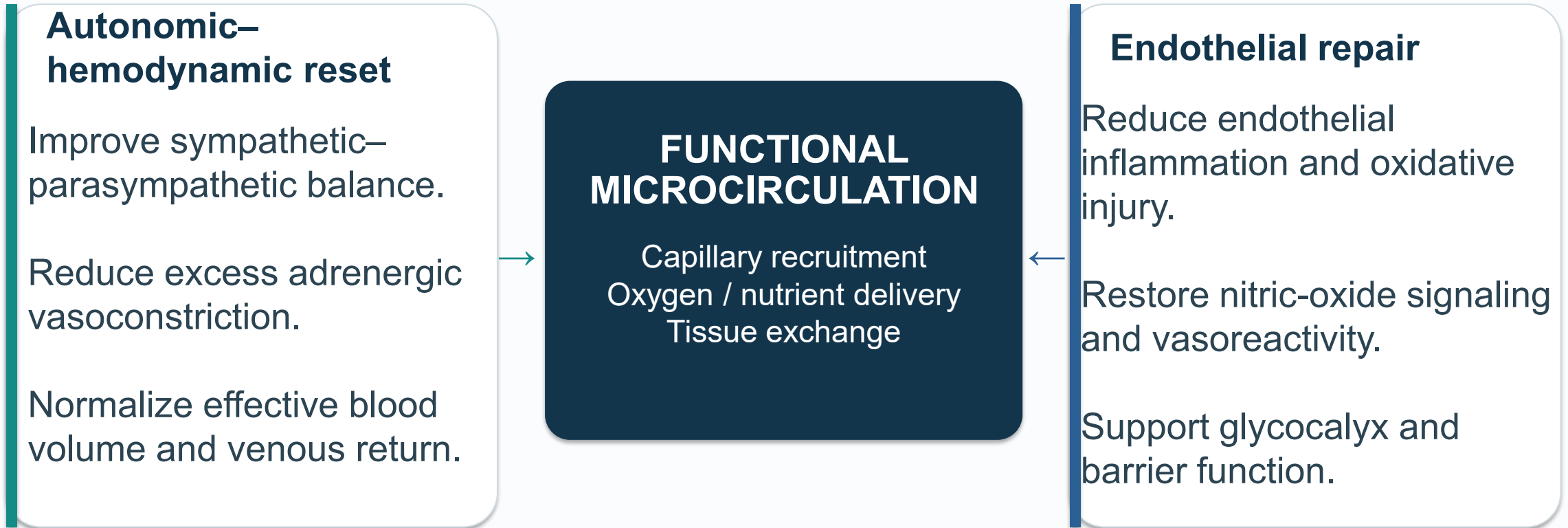
Clinical consequence

Impaired perfusion to brain and muscle; amplified autonomic and exertional symptoms.

Study it as an endotype: vascular measures + symptom phenotype + physiologic response.

In plain language: Autonomic nerves, blood volume, and the smallest blood vessels must work together to deliver oxygen and nutrients where they are needed.

Autonomic–Vascular Coupling Determines Effective Tissue Perfusion



Autonomic balance, circulating volume, and endothelial responsiveness converge at the capillary bed.

In plain language: Brain and muscle depend on oxygen to make energy. When delivery or use is limited during demand, cells rely more on less-efficient energy pathways.

Brain and Muscle Require Effective Oxygen Delivery

When oxygen delivery, extraction, or utilization is constrained during demand, aerobic reserve falls.

Brain

High, continuous energy demand

Potential consequence: cognitive slowing, sensory overload, and cognitive exertional intolerance.

AEROBIC ATP

Effective delivery
+ extraction
+ mitochondrial use

Skeletal muscle

High demand during activity

Potential consequence: early fatigability, reduced exertional capacity, and delayed recovery.

A shift toward glycolytic compensation may increase lactate burden, redox stress, inflammatory signaling and symptom amplification .

In plain language: Mast cells release chemical signals that can affect blood vessels, nerves, the gut, skin, and immune responses in a subset of patients.

Systems Biology:

A Therapeutic “Reset” May Require More Than One Lever

Persistent illness can represent an abnormal but stable regulatory state.



Mediator-Focused Management: Autonomic–Hemodynamic Dysfunction

Clinical goal: improve effective perfusion, upright tolerance, and physiologic reserve—not heart-rate control alone.

Clinical pattern to identify

- Orthostatic intolerance, POTS-like tachycardia, hypotension, or venous pooling
- Temperature dysregulation, postprandial symptoms, and impaired upright tolerance
- Low circulating volume, impaired venous return, sympathetic overdrive, or abnormal vascular tone

Management targets

- Improve circulating volume and venous return when clinically appropriate
- Reduce excess adrenergic drive without worsening hypotension or fatigue
- Improve vascular tone, upright tolerance, and autonomic stability
- Treat sleep, GI dysmotility, migraine, and pain that amplify autonomic instability

Studies needed

- Physiology-informed trials using autonomic and preload patterns
- Test whether therapy improves perfusion, oxygen use, PEM, and durable function

Clinical principle: restore effective tissue perfusion and physiologic reserve.

Mediator-Focused Management: Endothelial and Microvascular Dysfunction

Clinical goal: identify vascular stress patterns and test whether vascular target engagement changes function.

Clinical pattern to identify

- Exertional intolerance, cognitive dysfunction, orthostatic worsening, temperature/color change, or vascular lability
- Evidence of impaired vascular reactivity or perfusion where validated measures are available
- Coexisting autonomic, inflammatory, and mast-cell mediator patterns

Management targets

- Reduce modifiable endothelial injury and oxidative stress
- Optimize autonomic and hemodynamic drivers of capillary recruitment
- Treat documented cardiovascular, thrombotic, pulmonary, hematologic, and endocrine conditions by standard indications
- Avoid presenting anticoagulation or “microclot” regimens as universal established care

Studies needed

- Trials of nitric-oxide, endothelial, glycocalyx/barrier, and capillary-recruitment targets
- Pair vascular measures with cognition, exertional physiology, PEM, and function

The critical question: does vascular target engagement produce meaningful clinical recovery?

Mediator-Focused Management: Antigenic Drive, Immune Activation, and Senescence

Clinical goal: distinguish an ongoing stimulus from a self-sustaining immune–metabolic persistence state.

Clinical pattern to identify

- Persistent antigen or latent-virus reactivation hypothesis; recurrent infections; autoantibody-associated biology
- Impaired immune containment: NK / cytotoxic T-cell dysfunction, altered B-cell regulation, or clinically meaningful IgG / subclass deficiency
- Chronic inflammatory / senescent pattern: oxidative stress, impaired autophagy, and metabolic inflexibility

Management targets

- Evaluate and manage documented immune deficiency, recurrent infection, autoimmune disease, and actionable reactivation
- Distinguish pathogen antigen, latent reactivation, and autoreactive signaling
- Reduce chronic inflammatory load without indiscriminate immunosuppression
- Treat senescence, autophagy, and mTOR biology as investigational targets

Studies needed

- Antigen-targeted trials in antigen-positive groups
- Immune modulation in defined immune patterns
- Senomorphic / mTOR studies with autophagy, metabolic, and functional measures

Therapeutic objective: remove the sustaining driver when present and restore immune flexibility and cellular resolution.

Mediator-Focused Management: Mast-Cell and Neuroimmune–Endocrine Networks

Clinical goal: interrupt cross-system amplification affecting vessels, nerves, endocrine control, and energy regulation.

Clinical pattern to identify

- Mediator-reactive pattern: flushing, urticaria-like symptoms, wheeze, diarrhea, reactivity, or postprandial tachycardia
- Neuroimmune pattern: brain fog, sensory hypersensitivity, headache, pain amplification, sleep disruption, and stress-provoked worsening
- Neuroendocrine / matrix patterns: circadian disruption, HPA/HPG-axis concerns, and hypermobility features where relevant

Management targets

- Evaluate allergy, autonomic, endocrine, medication, GI, migraine, sleep, and other mimics before assigning mast-cell biology
- Treat documented comorbidities and reduce reproducible triggers
- Use stepwise mediator-directed approaches only in selected patients
- Correct measurable endocrine disease; do not equate HPA research with adrenal insufficiency

Studies needed

- Biomarker-informed mast-cell and neuroimmune–endocrine studies

Mast cell mediators and the collagen matrix connection – are there ways to stop the breakdown and rebuild the matrix?

- Pair mediator change with autonomic, vascular, cognitive, sleep, pain, PEM, and functional outcomes

The therapeutic objective is to interrupt cross-system amplification—not simply suppress one symptom.

What Long COVID Is Teaching Us About More Effective Treatment

Clinical experience in ME/CFS helped define the problems; Long COVID studies are helping identify measurable targets.

What patients and clinicians learned through experience helped shape the questions now being tested in Long COVID.

ME/CFS clinical experience

Recognized PEM, dysautonomia, brain fog, immune symptoms, and illness persistence long before COVID.

Long COVID research

Adds larger cohorts, known onset, longitudinal samples, and more opportunities to test mechanisms.

New treatment targets

Systrom and Wüst support investigation of circulation, oxygen-use, muscle biology, and recovery after exertion.

The next step: test treatments that target the active mediators—and validate them in both Long COVID and ME/CFS.

Conclusion: From Persistent Symptoms to Treatable Mediators

Long COVID can help move the field from descriptive syndromes to biologically informed intervention.

**Long COVID has supplied scale and urgency.
ME/CFS research has already taught us where to look.**

**Do not force diagnostic
equivalence**

Respect heterogeneity,
trigger, and disease-duration
effects.

**Do identify mechanistic
convergence**

Use shared clinical and
biological endotypes.

**Do test mediator-
matched interventions**

**Include parallel Long
COVID and ME/CFS
treatment cohorts.**

**Precision treatment of illness persistence turns complexity into actionable
therapeutic opportunity.**

Thank You

Questions and discussion

**From experience to evidence—
from persistent symptoms to measurable treatment
targets.**

With gratitude to patients, families, collaborators, and the Long COVID and
ME/CFS research communities.

**Nancy G. Klimas, MD • Institute for Neuro-Immune
Medicine**



The INIM Team thanks our sponsors
and our participants
With gratitude:



Study participants! Thank you!

INIM CDC COVID UPP team: Nancy Klimas, MD, Ana Palacio, MD, MPH, Leo Tamariz, MD, MPH, Kristina Aenlle, PhD, David Quesada, PhD, Korrine Rodrigue PhD, Devra Cohen, MPH, Juanita Reyes, MD, Nicole Velasquez, Baian Khanjar, Yang Chen, DrPH, Sashah Damier, PhD, Max Mendoza, PhD, McHenry Mauger, Sylvia Garay, Kim Gale

CDC COVID UPP team: Sally Lin, PhD, Joanna Regan MD MPH, Beth Unger, MD PhD, Elizabeth Fall, MPH

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