# Long COVID: Emerging Therapies

Steven Deeks, MD

Professor of Medicine

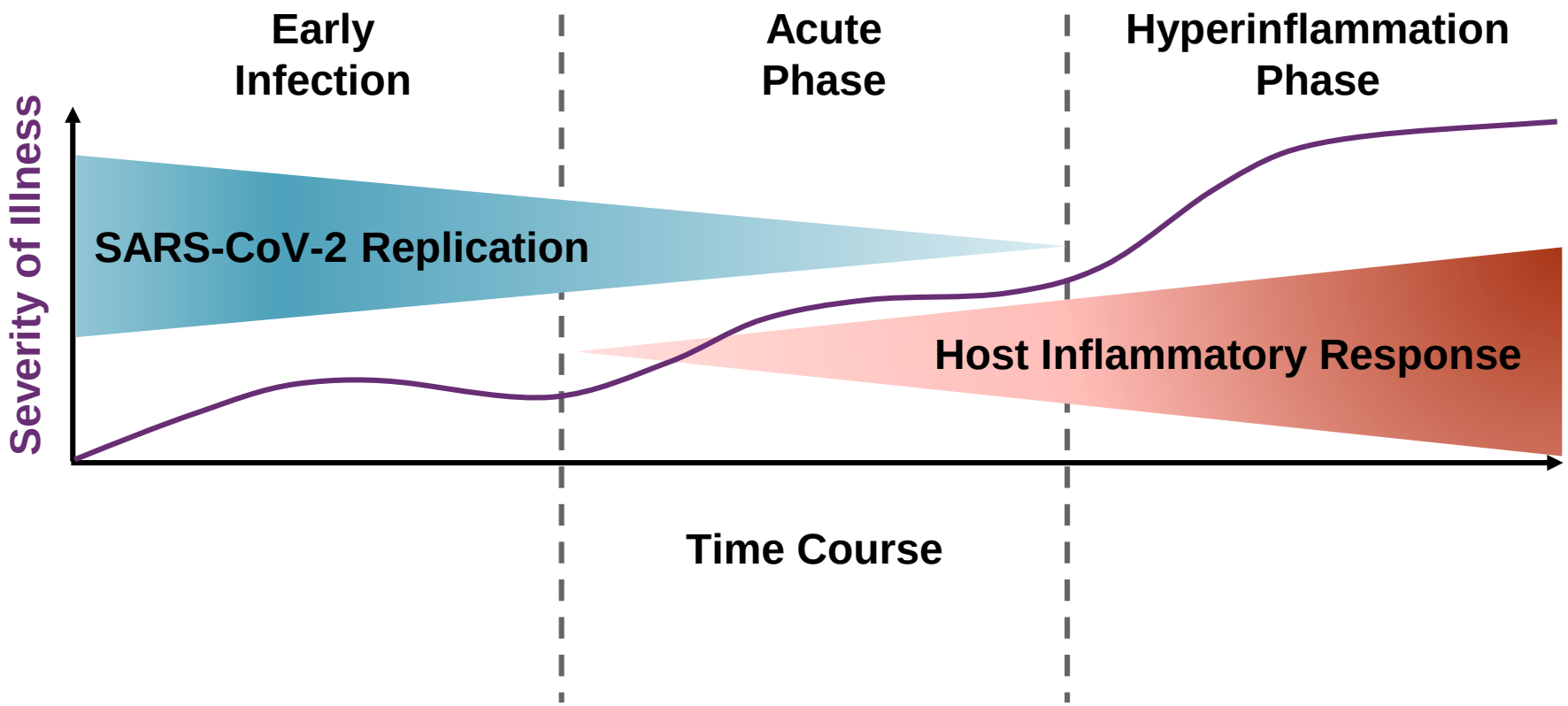
University of California, San Francisco

UCSF University of California San Francisco

RECOVER Researching COVID to Enhance Recovery

LIINC

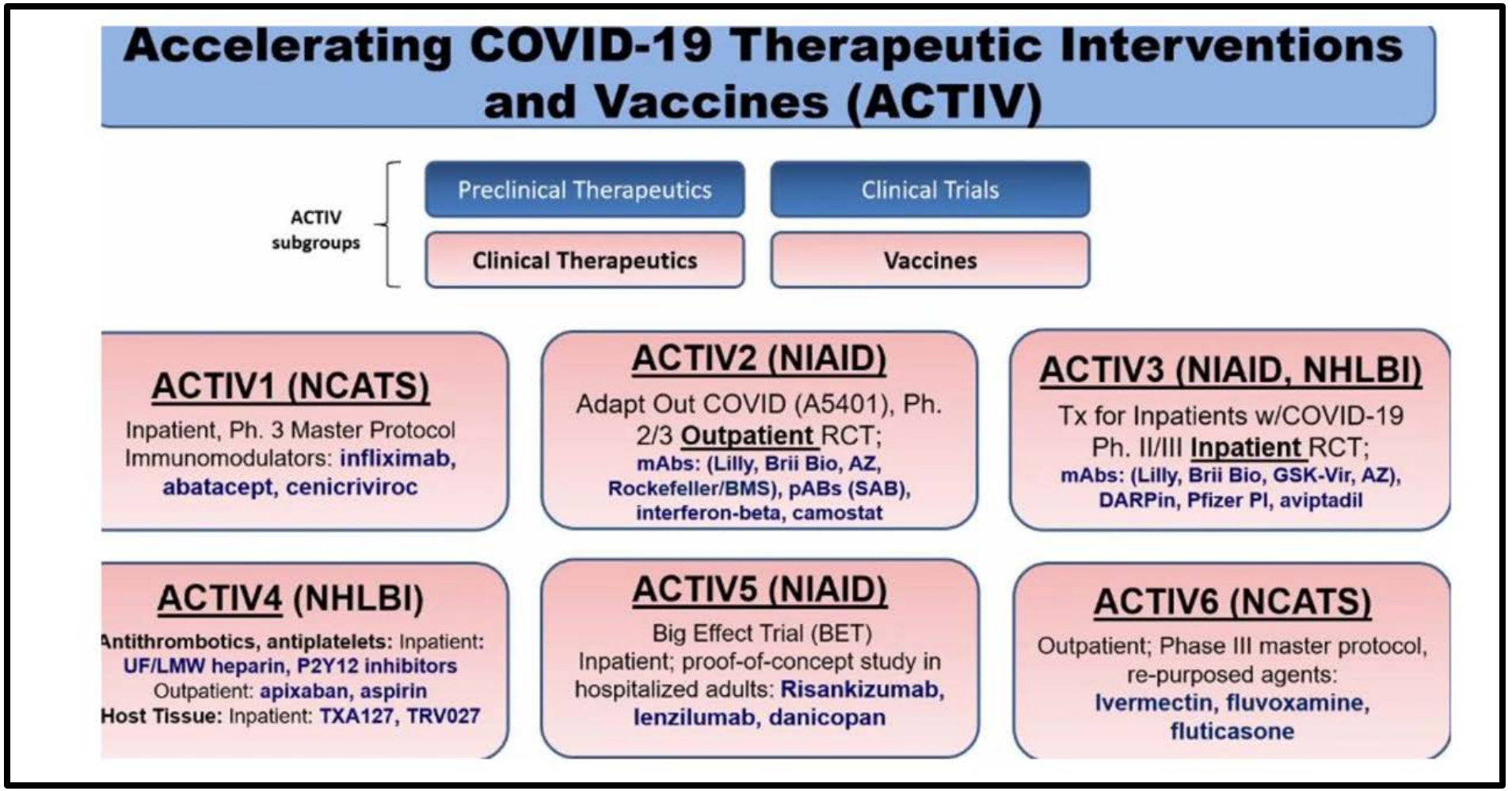
# Management of Acute COVID




| Goals | | |
|---|---|---|
| | Reduce onward transmission | Reduce progression/ hospitalization | Reduce morbidity/ mortality |
| | **Enhance immunity; use antivirals** | **Dampen immunopathogenesis, coagulation** |

*NIH COVID-19 Treatment Guidelines. J Heart Lung Transplant. 2020;39:405.*

# Development of acute COVID therapies: Public-private partnerships and adaptive platforms



# Key Therapeutic Agents Approved/Authorized or Under Evaluation for Treatment of COVID-19

## Antivirals

(Hydroxy)chloroquine
Ivermectin
Lopinavir/ritonavir
Molnupiravir
Nirmatrelvir/ritonavir
Nitazoxanide
Remdesivir

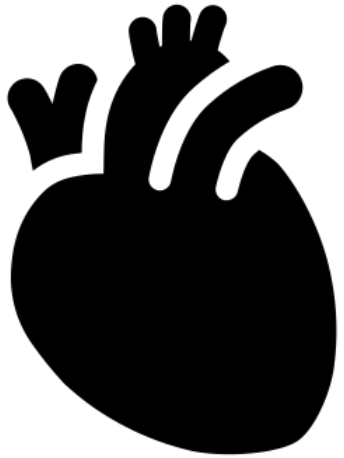
## Anti–SARS-CoV-2 mAbs

Bamlanivimab plus etesevimab
Casirivimab plus imdevimab
Sotrovimab

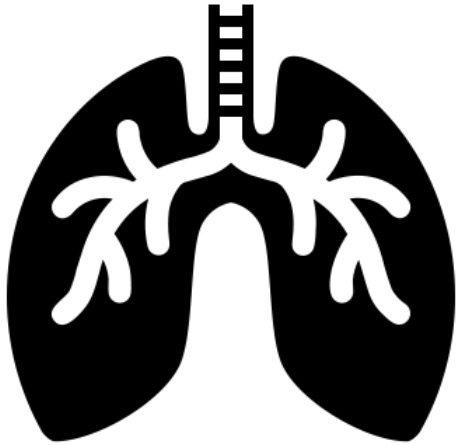
## Immunomodulators

Colchicine
Corticosteroids
Fluvoxamine
GM-CSF inhibitors
IL-1 and IL-6 inhibitors
Interferons
Kinase inhibitors
Non–SARS-CoV-2 IVIG

# PASC: Several distinct phenotypes



Cardiovascular Syndrome



Pulmonary Syndrome

Neurocognitive Syndrome

- Multiple mechanisms: Direct irreversible tissue injury, inflammation/auto-antibodies, microvascular clotting
- Multiple pathways: Vascular disease (microvascular clotting), nerve damage (dysautotomia), end-organ damage (CNS, CVS)
- Multiple outcomes: CNS, CVD, POTS, ME, MCAS
- Multiple possible treatments: anti-virals, anti-inflammatory drugs

# Lessons from the Post-ARDS Literature

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 APRIL 7, 2011 VOL. 364 NO. 14

## Functional Disability 5 Years after Acute Respiratory Distress Syndrome

Margaret S. Herridge, M.D., M.P.H., Catherine M. Tansey, M.Sc., Andrea Matté, B.Sc., George Tomlinson, Ph.D., Natalia Diaz-Granados, M.Sc., Andrew Cooper, M.D., Cameron B. Guest, M.D., C. David Mazer, M.D., Sangeeta Mehta, M.D., Thomas E. Stewart, M.D., Paul Kudlow, B.Sc., Deborah Cook, M.D., Arthur S. Slutsky, M.D., and Angela M. Cheung, M.D., Ph.D., for the Canadian Critical Care Trials Group

# Mechanism of PASC

## DRIVERS OF INCREASED SUSCEPTIBILTIY

### Racial and Ethnic Minorities

- Increased risk for exposure & severe manifestation of COVID-19
- Socioeconomic factors prevent proper self-isolation
- Less access to primary and specialty care
- Distrust of medical institutions
- Higher rate of pre-existing conditions
- Multimorbidity

### Older Population

- Increased risk for severe COVID-19
- Higher rate of pre-existing conditions
- Multimorbidity

### Clinical Complexity

- Pre-existing conditions (obesity, diabetes, heart/lung disease, etc.)
- Multimorbidity
- Severe COVID-19 manifestation
- Prior mental health history
- Women

### Rural Residents

- Increased risk for exposure to COVID-19
- Decreased healthcare infrastructure
- Older population
- Higher rate of pre-existing conditions
- Multimorbidity

David H. Jiang et al. *J Am Coll Cardiol Basic Trans Science* 2021;

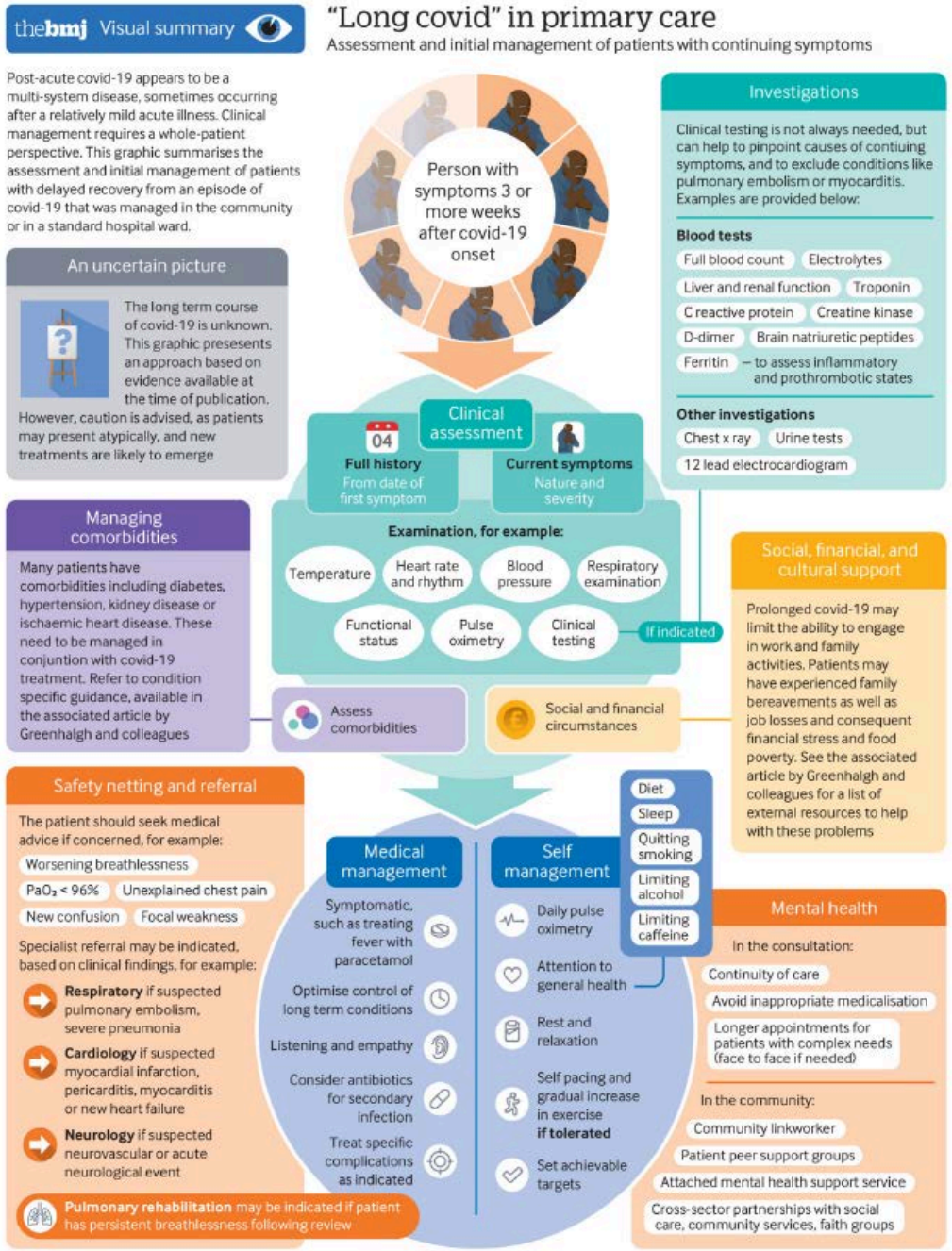
JACC Basic to Translational Science
An Open Access Journal

# Basics of clinical management: CDC

- Long COVID can be diagnosed and managed by primary care
  - Conservative approach in the first 4 to 12 weeks
  - Aggressive workup – if indicated – to begin after 12 weeks of symptoms
- Physical examination: Orthostatic vital signs, ambulatory pulse oximetry, exercise capacity (6-minute walk test)
- Laboratory testing
  - Positive COVID test not necessary
  - Tests to rule out common issues and or syndromes that present with similar symptoms (rheumatologic workup, thyroid function, cardiac enzymes) recommended
  - Inflammatory markers may be ordered despite lack of treatment
- Specialized testing: Tilt test (POTS), chest CT, brain MRI
  - Excessive testing can be harmful

# Basics of clinical management

- Goal of therapy: Improve qualify of life
  - Holistic approach is beneficial (may require referral to Long COVID clinic)
- Orthostasis and dysautonomia: compression stockings, abdominal binder, hydration, physical therapy, medications for POTS
- Post-exertional malaise and similar symptoms: Planning, Pacing, Prioritizing, and Positioning
- Flexibility exercises (yoga and tai chi) and strength exercises
- Off-label therapies: Antivirals, seroids, IVIG, others




PRACTICE POINTER

## Management of post-acute covid-19 in primary care

Trisha Greenhalgh,[1] Matthew Knight,[2] Christine A'Court,[1] Maria Buxton,[3] Laiba Husain[1]

# Long COVID clinics

- Validate experience
- Discuss uncertainty
- Rule out PASC mimickers: Usual diagnostic tests may be normal
- Rehabilitation and physical therapy
- Mental health
- Financial support
- Multidisciplinary approach is critical

# Emerging clinical trials networks

- Drugs
- Biologics
- Rehabilitation
- Behavioral
- Medical devices
- Complementary and alternative therapies

Eligilibity: Unique phenotypes

Outcomes: QOL, functional status

Adaptive platform trials likely to emerge as they did for management of acute infection

# Pharmaceutical trials for PASC

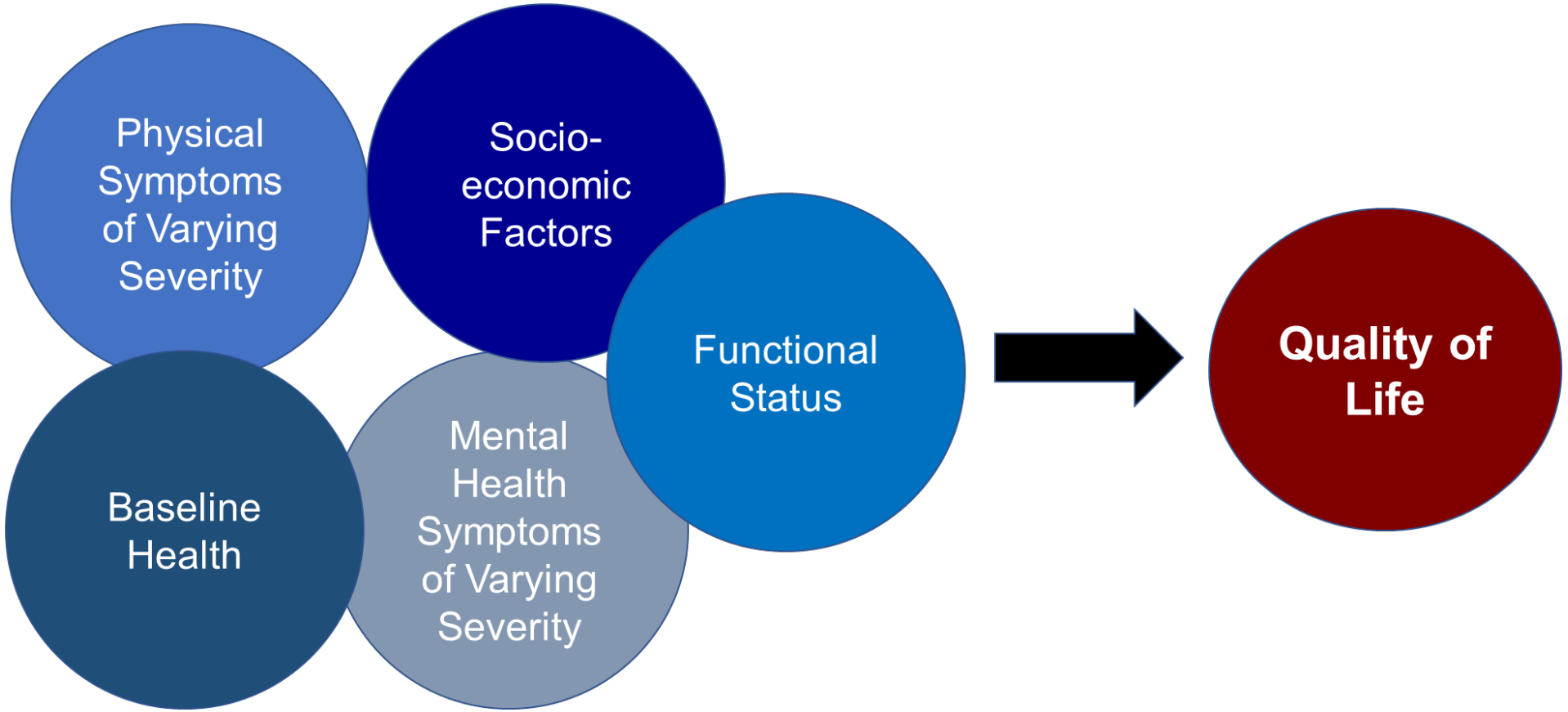
| Company | Intervention | Target |
|---|---|---|
| Amgen | Ivabradine (HCN channel blocker) | POTS |
| Ampio Pharmaceuticals | Cyclized peptide derived from aspartyl-alanyl diketopiperazine | DAMPs |
| CytoDyn | Leronlimab (CCR5 inhibitor) | Inflammation |
| GioCOV, Sorrento | Allogeneic mesenchymal stem cells | Inflammation |
| AIM ImmunoTech | Rintatolimod (poly(I):poly(C12U)) | Virus |
| PureTech | Pirfenidone | Pulmonary fibrosis |
| Synairgen | Inhaled interferon beta-1a | COPD |
| Resolve Therapeutics | RSLV-132 (ribonuclease to digest autoantibodies and immune complexes) | Autoantibodies |
| AgelessRx | Naltrexone and nicotinamide adenine dinucleotide | Fatigue |
| n/a | Montelukast | Respiratory Symptoms |
| SolAeroMed | S-1226 (inhaled surfactant) | Surfactant function |
| n/a | Sirolimus | Pulmonary fibrosis |
| n/a | Atorvastatin | Neurocognitive function |
| n/a | Metoprolol | POTS, dyspnea |
| n/a | Clopidogrel/aspirin, apixban | Amyloid microclots |

***Adapted from Schmidt, Nature Biotechnology (2021); updated via ClinicalTrials.gov***

# Phase II studies now maturing

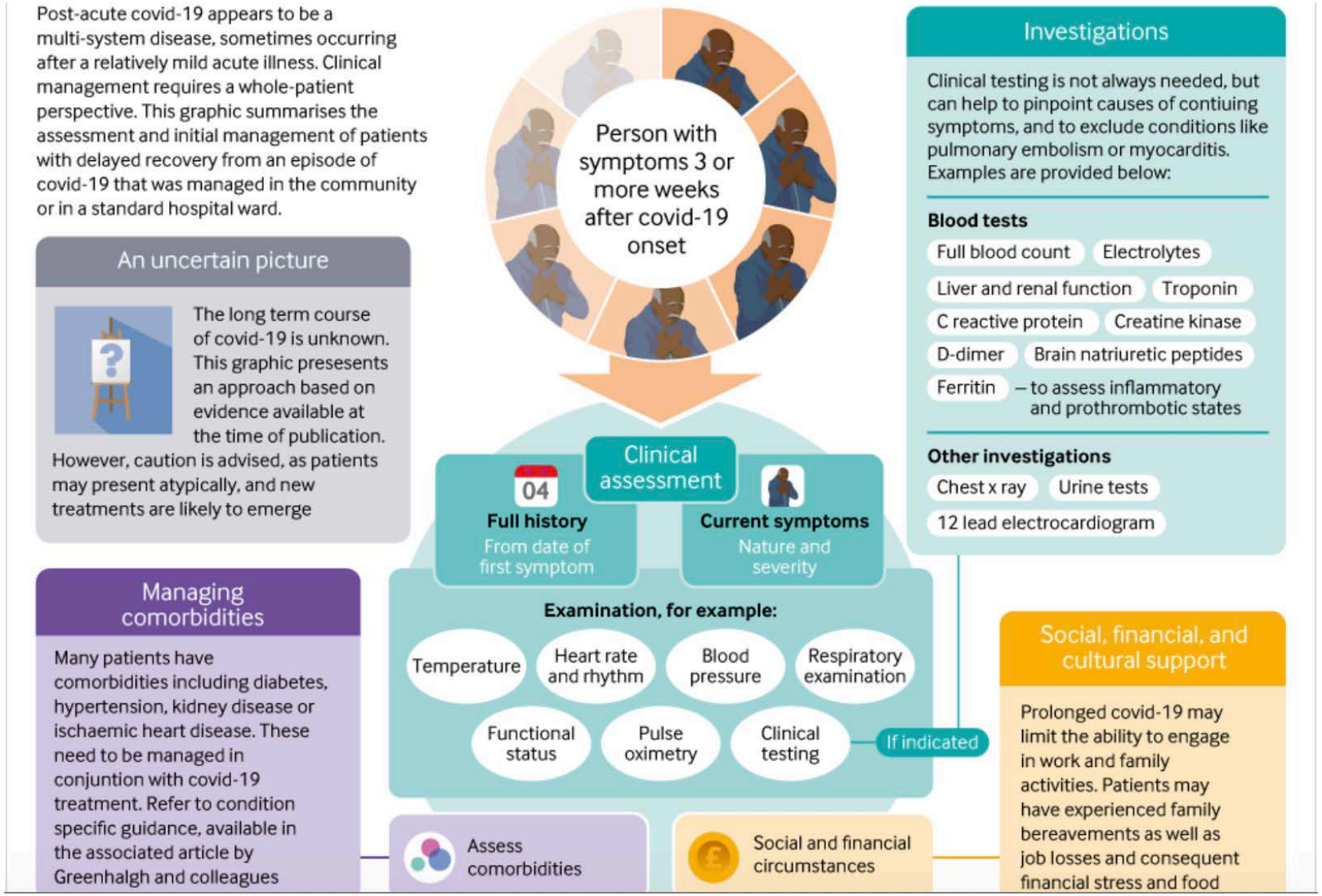
- LYT-100: deuterated form of pirfenidone (PureTech, NCT04652518)
  - Post-hospitalization with long-term respiratory complications stemming from a prior hospitalisation due to Covid-19 (N=168)
  - Outcome: 6-minute walk test
- AXZ1125: amino acids that can improve mitochondrial function (Axcella, NCT05152849)
  - Population: Long COVID (=40)
  - Outcome: Mitochondrial tests (phosphocreatine recovery rate following moderate exercise)
- AT1001: larazotide acetate, CD163 antagonist/zonulin antagonist (Mass General Hospital, NCT05022303)
  - Population: MIS-C (n=20)
  - Outcome: GI symptoms
- RSLV-132: RNase fused to a human IgG1 Fc domain (RESOLVE, NCT04944121)
  - Population: PASC (n=70)
  - Outcome: Symptoms

# Quality of life and functional status are the outcomes that will shape drug development, which poses regulatory challenges



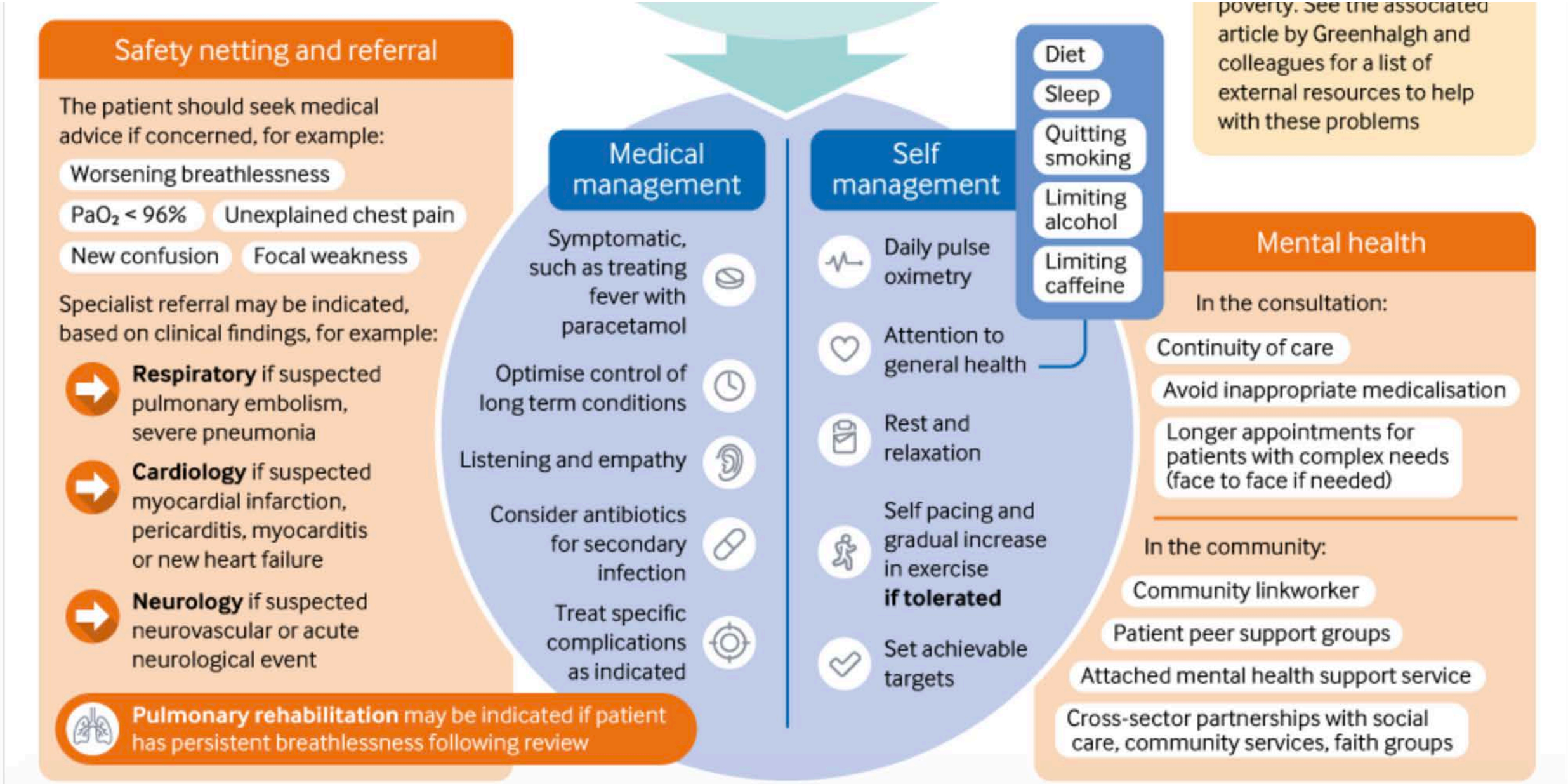

- Multiple biologic mechanisms and hard-to-define clinical outcomes that wax and wane will make drug development challenging
- Limited industry engagement remains a major barrier

# UK Guidelines

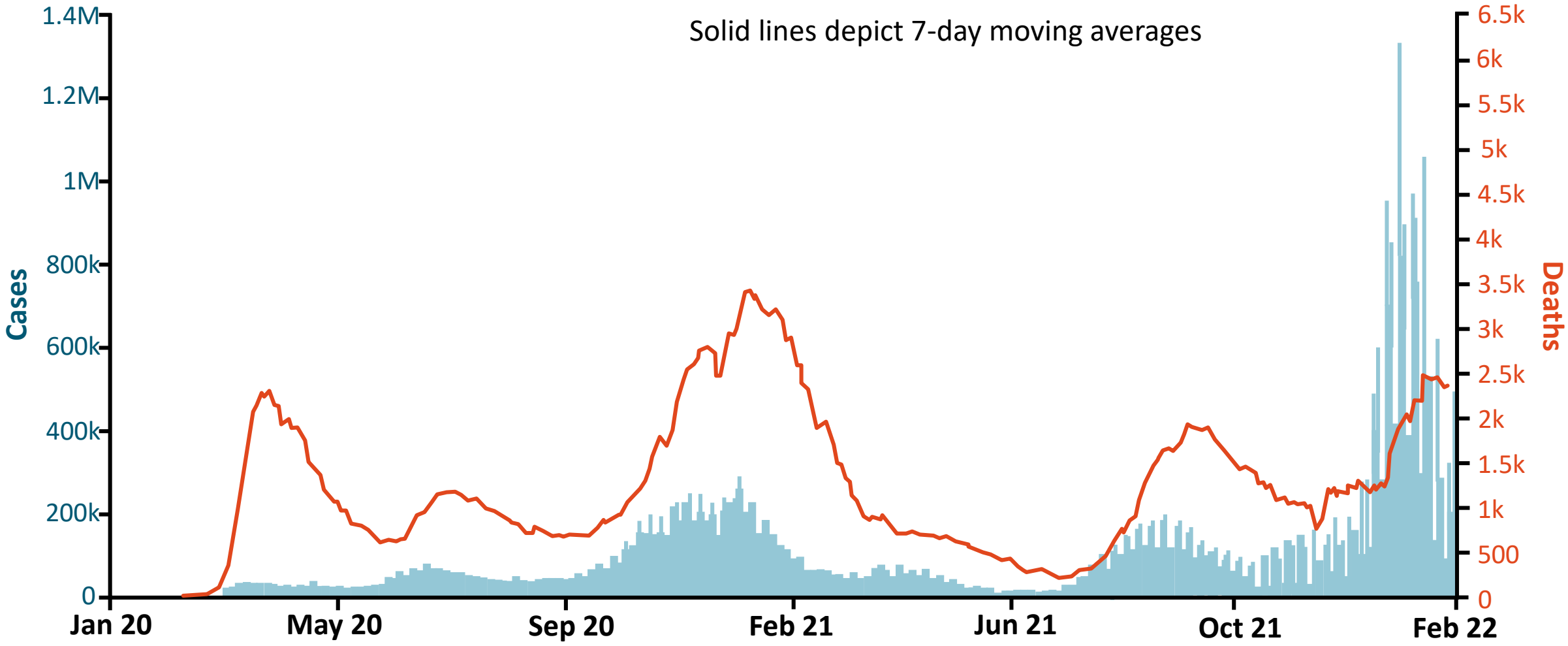



Greenhalgh BMJ 2020

# UK Guidelines



# CDC: COVID-19 Reported Cases and Mortality




cdc.gov/coronavirus/2019-ncov/covid-data/covidview/index.html

# UCSF OPTIMAL Approach to Diagnostics

- Pulmonary Function Tests
  - I like to include 6MWT
- If DLCO is low, consider CT chest
- Also consider TTE
- Labs:
  - CBC diff, ESR/CRP, Thyroid, +/- CPK