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The COVID-19 Diagnostics Odyssey:
The Achilles Heel of SARS-CoV-2 Pandemic Control Efforts

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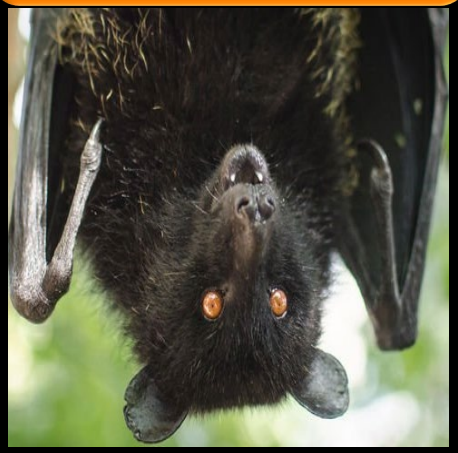
Slides available at: https://casi.asu.edu/presentations/

The 2020 COVID-19 Pandemic: The "8-D's" of Disaster

Danger (ignored)



Dispersal (global)

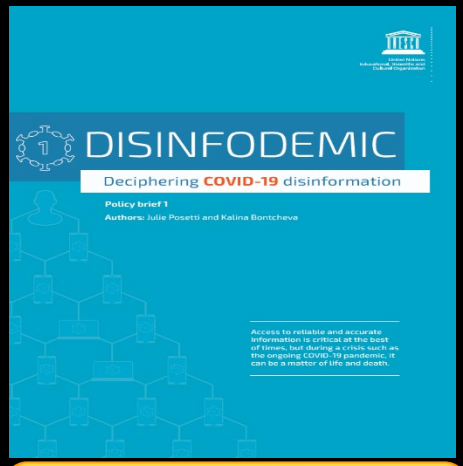
Deficient (CDC)

Disease (heterogeneity)

Disruption (socioeconomic)

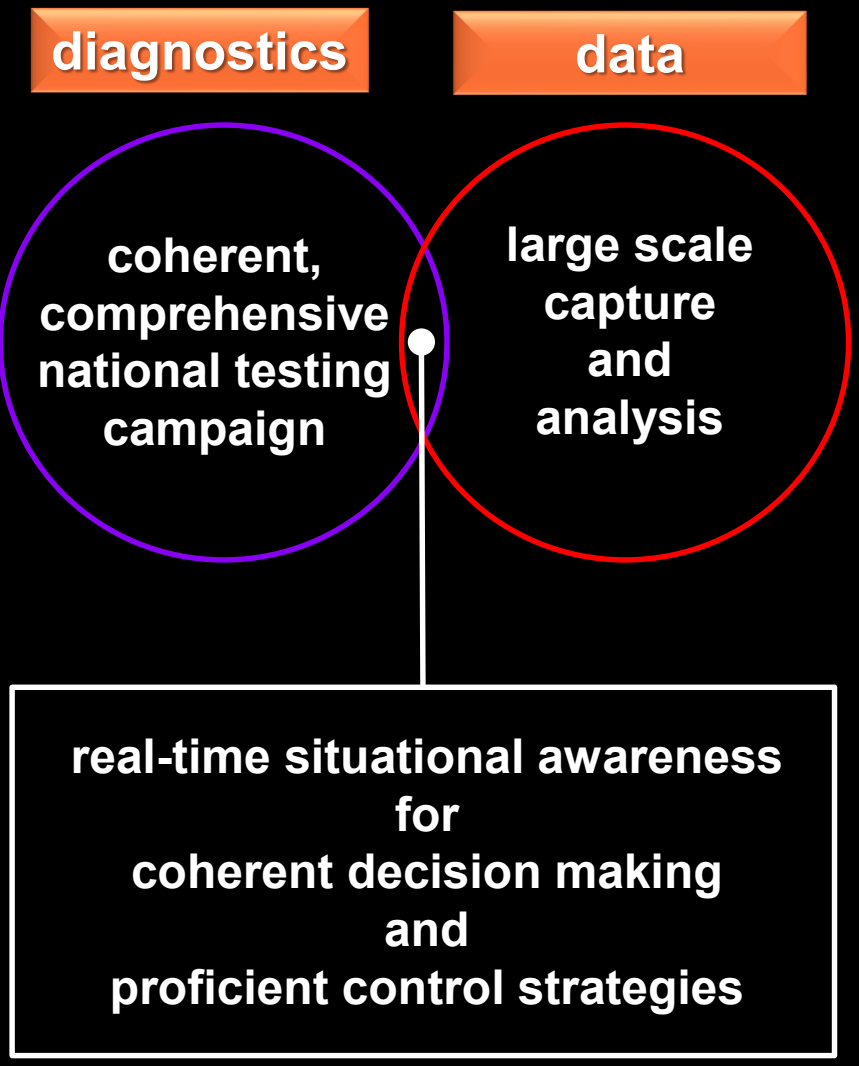
Dissent (protests)

Disinformation (distrust)

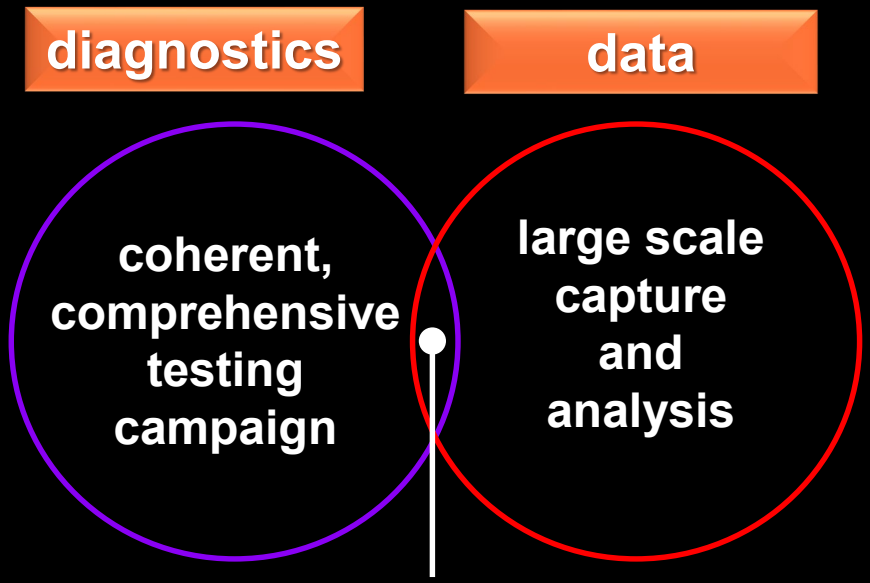


Denial (disarray)

Two Missing Critical "D's"



Two Missing Critical "D's"

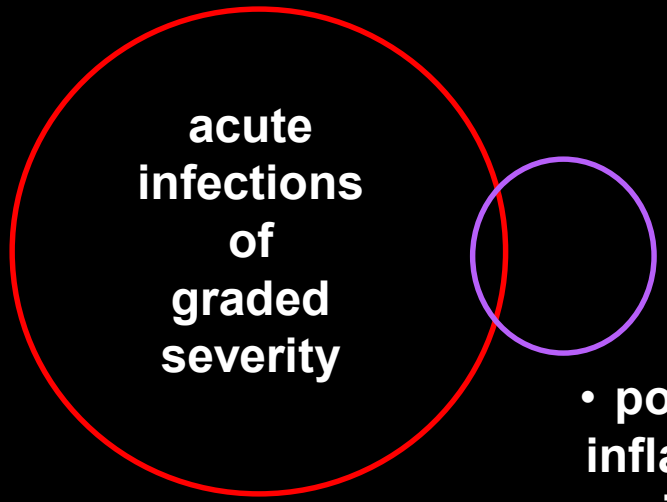


- fragmented patchwork of uncoordinated testing and control actions (federal, state, local)
- inadequate standardization (tests) and interoperability (data formats)
- Dx supply chain shortcomings
- independence of USG public health/regulatory agencies compromised by political interference

The US Diagnostic Testing Infrastructure for SARS-CoV-2: A 'F' Report Card?

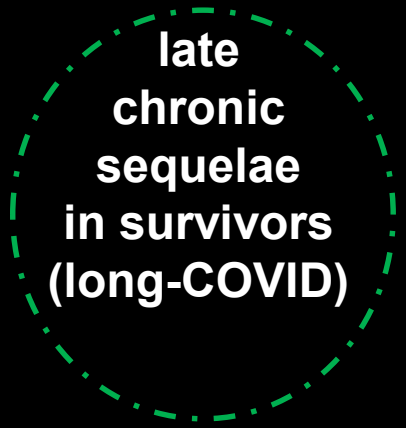
- initial CDC RT-PCR test failure (Feb 2020) and six weeks lost for critical early control
- well documented capacity limitations of State public health laboratories to conduct large scale testing
- slow action by CDC (March 2020) to engage private sector testing capacity and scalability
- fragility of supply chains for testing reagents/supplies/PPE
  - states pitted against each other in bidding wars

SARS-CoV-2 Infections:
Disease Spectrum, Prevalence and Extended Timelines



- asymptomatic vs symptomatic
- lack of biomarkers to predict disease severity
  - immunological
  - genetic
  - SDoH

- post-acute inflammatory illness
  - MIS-C
  - MIS-A



- prevalence?
- pathophysiological mechanisms?
- prognosis?
- duration?
- treatment?

The Diagnostic Landscape for SARS-CoV-2 Infections

- viral detection (RNA, antigens), exposure (serology) and contact tracing
- viral metagenomics (NGS of global viral clades and mutagenic drift)
- multiplex diagnostics
  - RT pathogen panels (22 organisms)
  - host immune and genetic factors affecting disease severity
- digital platforms
  - wearables and mobile apps for contact tracing and “immune passports”

The Diagnostic Landscape for SARS-CoV-2 Infections

- obligate foundation of real time epidemiology and effective control measures
- infection prevalence
  - geography, demographics, transmission dynamics
- validation of risk assessment models
  - guide intervention priorities and resource allocation
  - ML/AI algorithms for prognosis of disease severity in hospitalized individuals
- mapping ‘herd immunity’
  - longitudinal cumulative analysis of population exposure (natural infections and vaccination)
  - current uncertain correlates of protective immunity

Pandemic Diagnostics Suddenly Get Long Overdue Attention

- $1.5 billion investment
- test 2% US population/day
  - 6 million tests
- focus on underserved populations
- RADx-rad
  - new and repurposed HTP technologies
  - clinical prognosis makers

Categories of SAR-CoV-2 Diagnostics*

	High Vol. Reference Labs (CLIA)	Mol DX Labs (CLIA)	CLIA-waived POC	in-home	Global BSV
viral nucleic acid (NAATs)	✓	✓	✓	✓	✓
viral proteins (antigens)	✓	✓	✓	✓	✓
antibodies (serology)	✓	✓	✓	(✓)	✓
T cell responses	(✓)	✓			(✓)
inflammatory syndromes/ late chronic sequelae	(✓)	✓			(✓)
viral metagenomics and mutagenic drift		✓			✓
viral clade profiling for future potential zoonotic spillover		✓			✓
biosecurity forensics		✓			✓

*waste water surveillance, wearables, mobile Apps and other biosensors not listed

The Covid-19 Diagnostic Landscape

COVID-19 TESTING COMMONS

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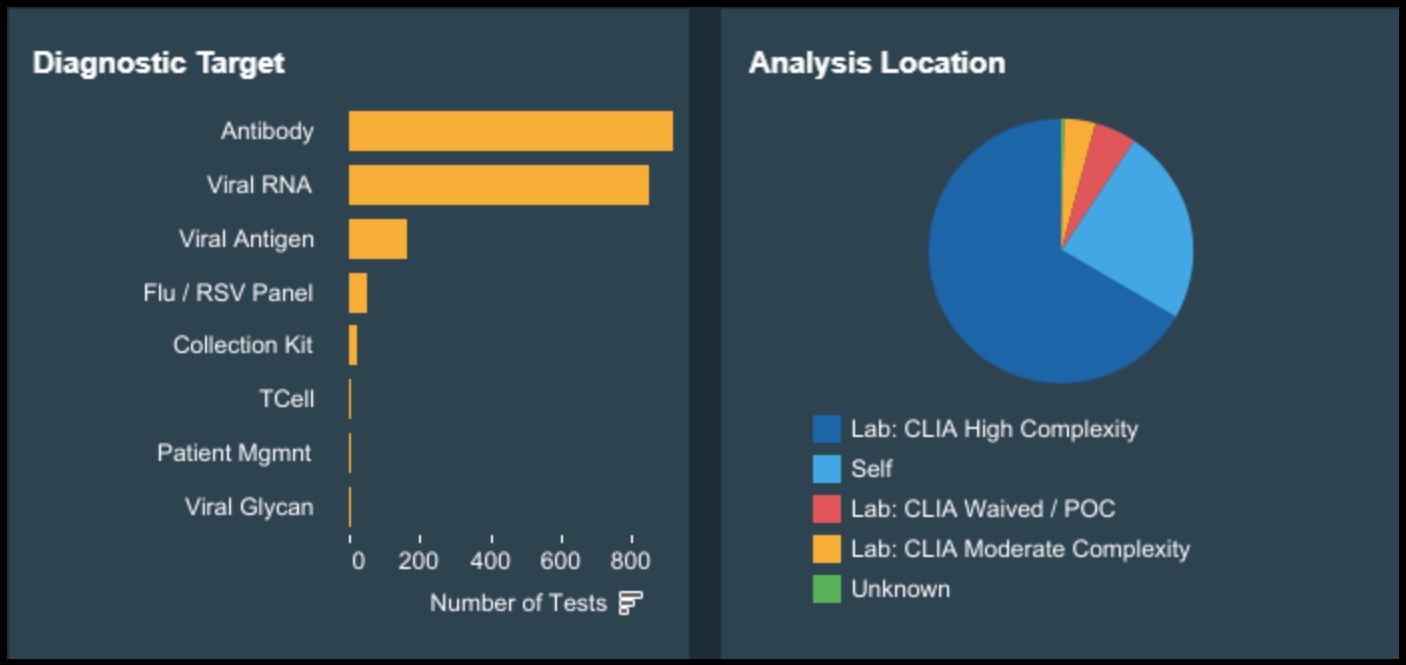
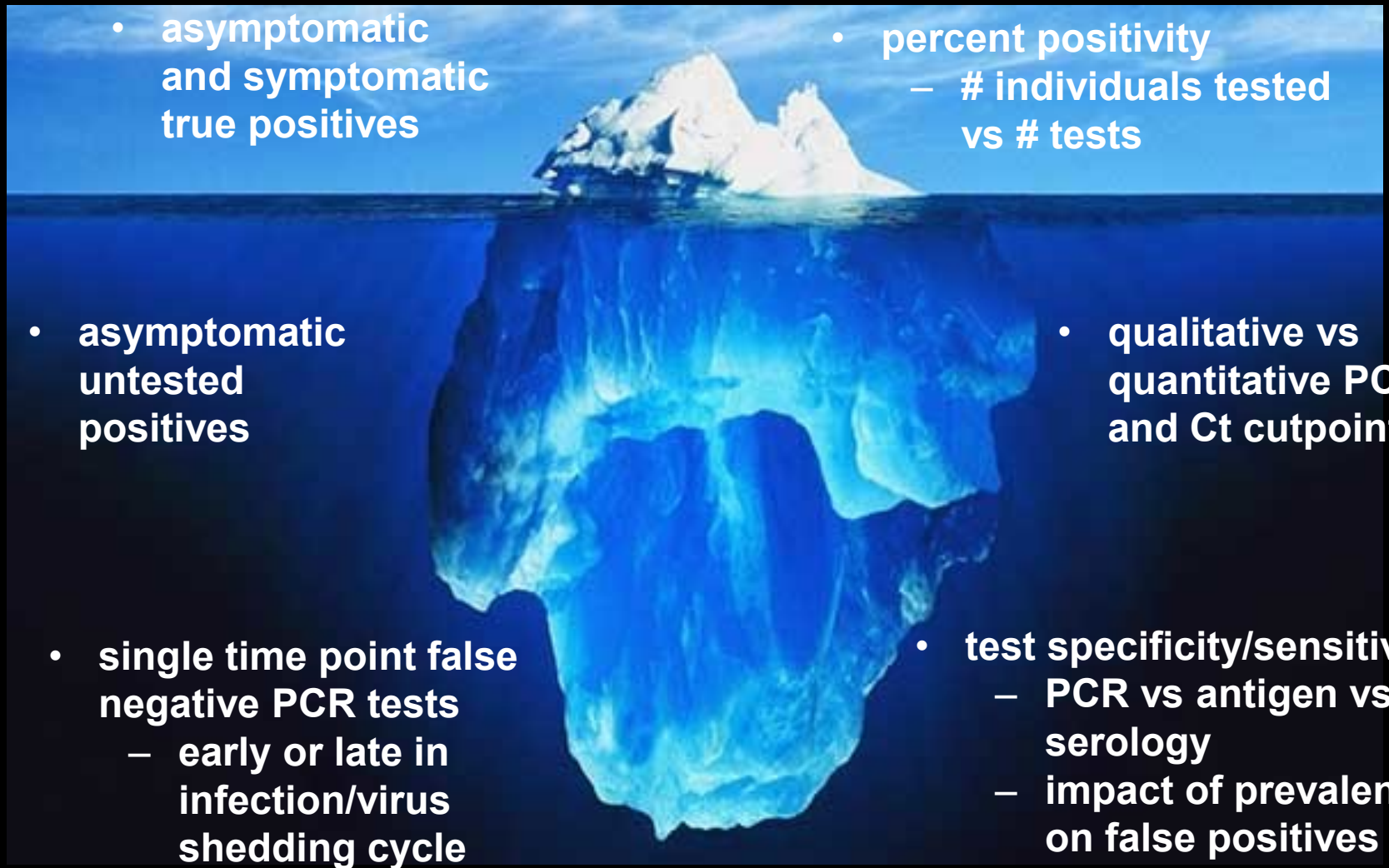


2016 Tests (accessed 11/30/20)

Understanding the True Prevalence of SARS-CoV-2 Infections



- asymptomatic and symptomatic true positives
- percent positivity
  - # individuals tested vs # tests
- asymptomatic untested positives
- qualitative vs quantitative PCR and Ct cutpoints
- single time point false negative PCR tests
  - early or late in infection/virus shedding cycle
- test specificity/sensitivity
  - PCR vs antigen vs serology
  - impact of prevalence on false positives and negatives

Dynamics of SARS-CoV-2 Infections
M. Cevik et al. (2020) Lancet Microbe 30172-5

- meta-analysis of 98 studies
- no difference in peak load in asymptomatic vs mild symptomatic individuals but virus cleared faster in former
- significant individual variation in duration of shedding
  - URI and stool av. 17 days
  - LRI av. 14.6 days
  - serum av. 16.6 days
  - longest duration outliers: 83 days URI, 59 days LRI, 35 days in stool

Superspreading Events (SSE)

- outsized contribution to overall transmission
- analysis of 60 SSE SARS-CoV-2 episodes*
  - R_0 mean of 19.7 cases
  - extreme outlier of 187 cases in Hong Kong apartment
- logic for prevention of large gatherings of susceptible individuals and isolation/vaccination of select individuals for pandemic control

*F. Wong and J. Collins (2020) PNAS 117, 29416

The RT-PCR Bottleneck in Individual Testing and Infection Tracking

- predominant reliance on large CLIA-certified reference laboratories with high volume throughput
  - capacity outstripped by demand leading to slow TAT
- >48 hr. reporting erodes willingness of asymptomatic individuals to self-isolate
- higher cost versus other test modalities as handicap to sustained widespread use
- catalyst to develop alternative rapid CLIA-waived POC/in-home tests

Point-of-Care (POC) Antigen Testing for SARS-CoV-2

- speed: overcome TAT lag from PCR testing overloads
- comprehensive screening of large population
  - employers, schools and colleges, military
- contact tracing

Critical Dependence on Private Sector for Expanded Testing Using POC Viral Antigen Platforms

- up to 50 million BinaxNow tests/month
- USG contract to purchase/distribute 150 million tests

- 80 million tests/month by 12/20

- 12 million tests/month by 1Q/21

- additional state contracts with smaller companies/universities to expand antigen testing capacity

Pending Innovations in High Accuracy POC Tests With Rapid TAT

- CUE
- automated PCR cartridge
- 20-30 minute TAT readout
- mobile phone reporting
- $481 million HHS contract for 100,000 tests/day (3/21)
- value for POC confirmation to eliminate false positives from antigen tests

The Wild West of SARS-CoV-2 Diagnostics

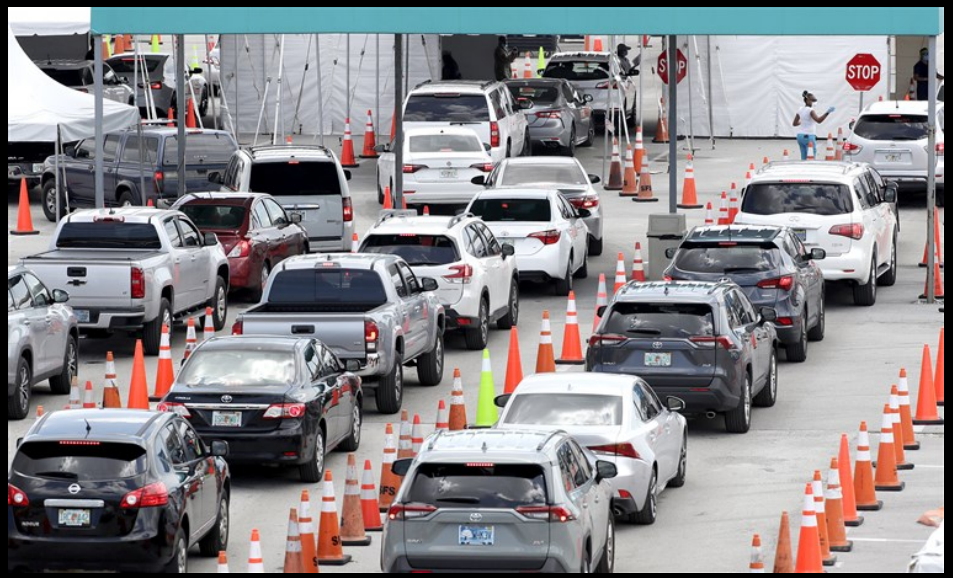
- wide variation in performance, QC/QA of EUA tests
- sensitivity span of greater than 3 log 10
- Removal Lists of Tests that Should No Longer Be Used and/or Distributed for COVID-19 Testing
  - diagnostic tests
  - serological tests

- cease-and desist letters to 171 facilities testing without CLIA certification and/or compliance

Value of FDA Emergency Use Authorization (EUA) for SARS-CoV-2 LDTs

- Public Readiness and Emergency Preparedness (PREP) Act
  - immunity from liability claims
- Family First Coronavirus Act (FFCRA)
  - broad reimbursement including out-of-network labs
- FDA (8/15/20) action to no longer review LDTs for EUA
  - new tests blocked from these benefits
- HHS (11/17/20) directed FDA to reinstate EUA review and complete “in a timely manner’

The Nonsense of One-Time-Only Testing and the Delusion of Safety



- uncontrolled access overloads testing capacity and slows TAT
- meaningful negative status requires two negative tests 5-7 days apart
- non-quantitative PCR testing
  - useful for isolation recommendations
  - no data on viral load and potential individual infectiousness and superspreader event risks

National Reporting of Aggregated SARS-Cov-2 Testing

- patchwork of different testing platforms, instruments and data formats
- requirements to report to county, state, CDC, CMS and HHS (FEMA sometimes)
- report both positive and negative assays
- HHS/CDC guidelines inconsistent for ‘required’ vs ‘requested’ data elements and CMS non-compliance penalties
- requirement to report to state public health lab of an individual’s residence

Contact Tracing

https://freemagazines.top/bloomberg-businessweek-usa-november-23-2020/

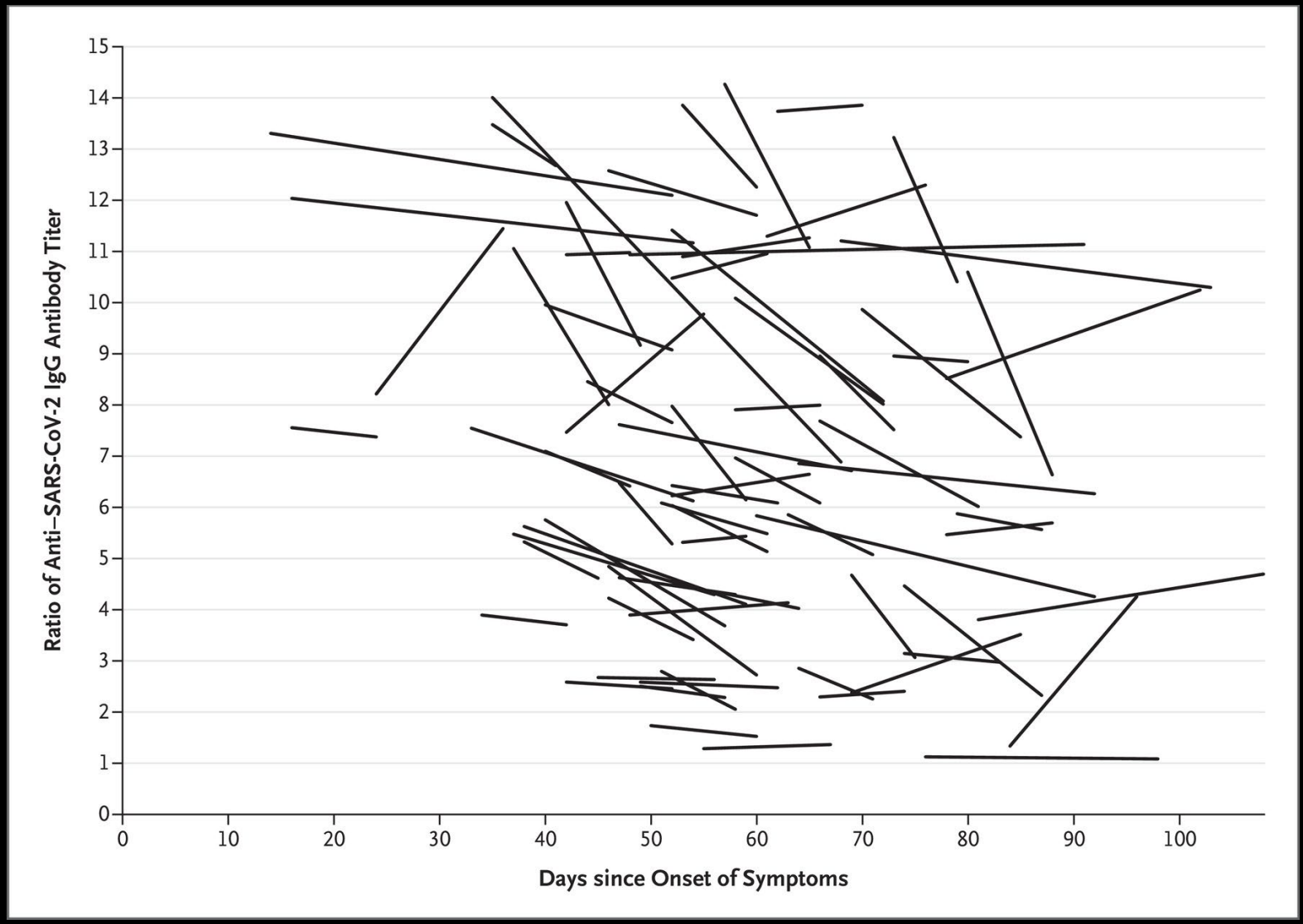
- estimated 14 million tests/day needed
- current capacity 4.5 million tests/day
- Biden proposal for 100,000 contact tracers
  current = 2000 people
- uncertain public acceptance and cooperation?
  - potential adverse effects of isolation/quarantine actions on income of many already economically compromised individuals

Mobile Phone Apps, Contact Tracing and “Immune Passports”

Immunity Passports:
A Scientifically and Ethically Questionable Concept?

- ill-defined determinants of true immune protection
  - antibodies (neutralizing (N) vs non-N; titers), T cell responses?
  - duration of immune protection (natural vs vaccine)?
- risk from tests with inadequate specificity (false positives) and low sensitivity tests (false negatives with low antibody titer)
- discrimination risks for employment and travel?

Individual Heterogeneity in Antibody Responses to SARS-CoV-2

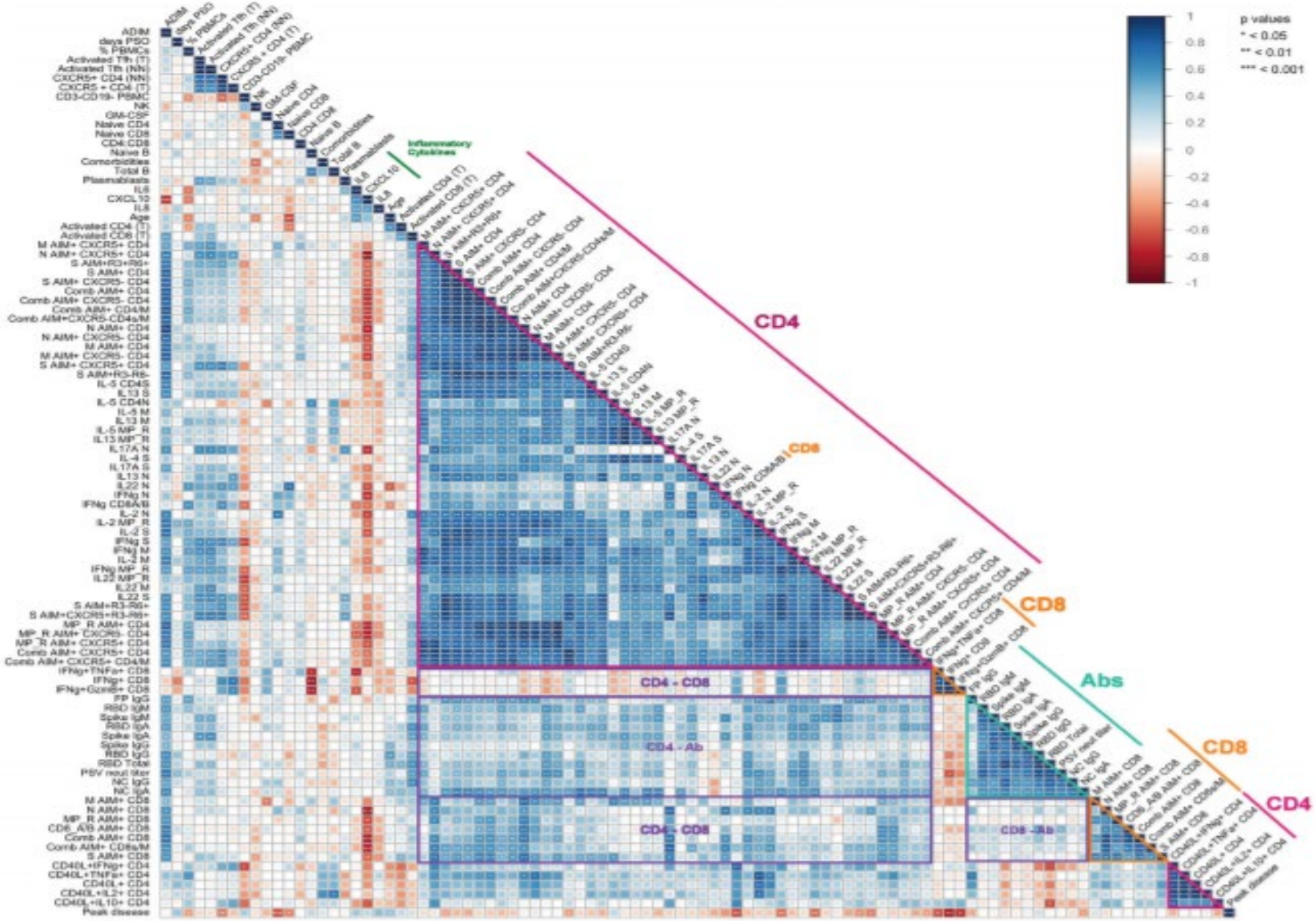


https://www.nejm.org/doi/10.1056/NEJMc2027051

Host Inflammatory and Immune Biomarkers and Prediction of Clinical Deterioration in Hospitalized COVID-19 Patients

- multiparameter clinical risk algorithms
- cytokine storms
- autoantibodies to IFN-I
- decoupling of CD4/CD8 T-Cell responses
- genetics
  - hypo-and hyper-inflammatory response genes
  - ACE2 receptor polymorphism
  - HLA genotypes
  - chromosome 3 Vindija 3.3.19 Neanderthal alleles?

Correlograms of Adaptive Immunophenotypes in COVID-19 Patients

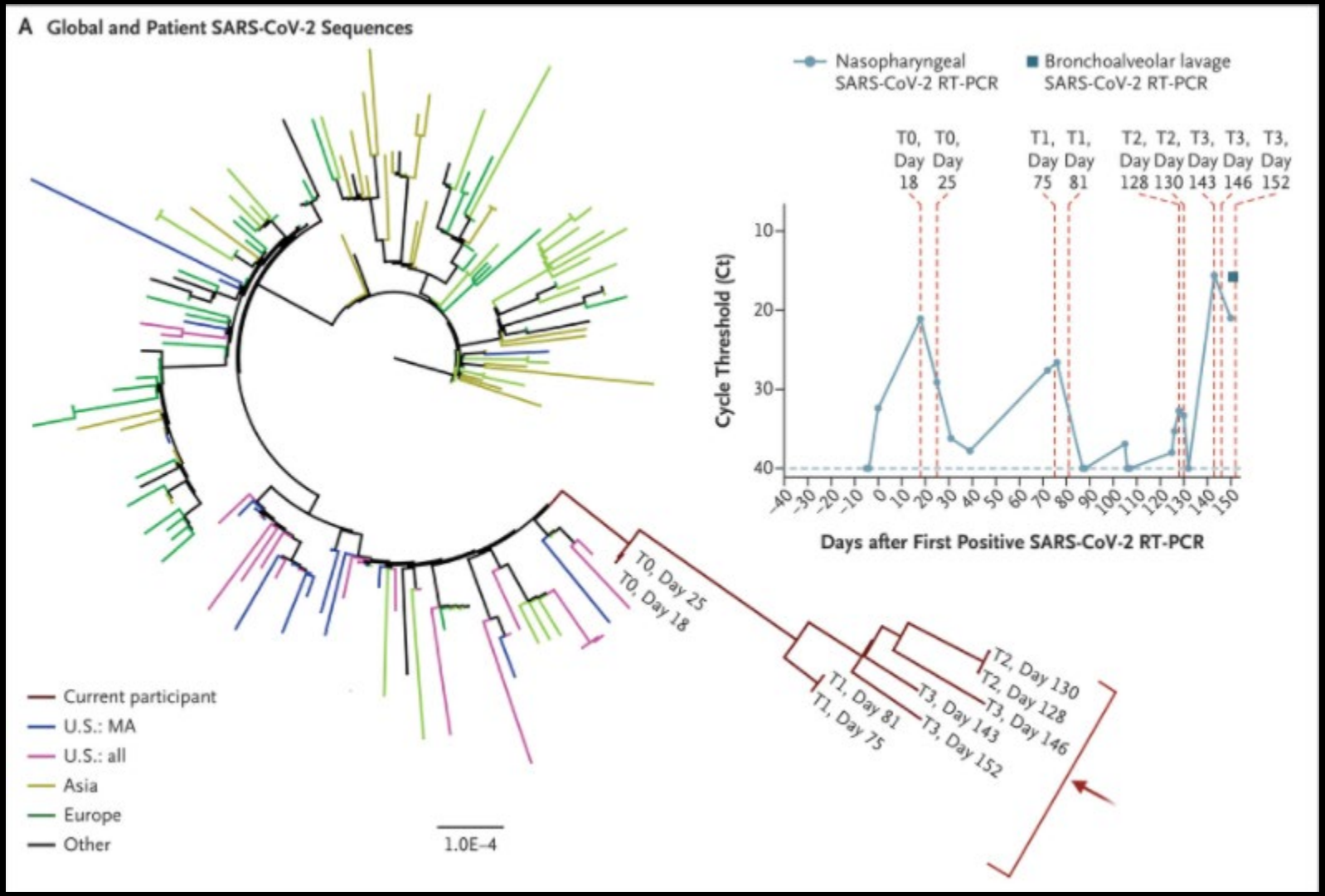


C. Rydyznski et al. (2020) Cell 183, 996 https://www.sciencedirect.com/science/article/pii/S0092867420312356?via%3Dihub

Comprehensive Biosurveillance of Potential New Zoonotic SARS-CoV-2 Reservoirs and Novel Mutational Drift

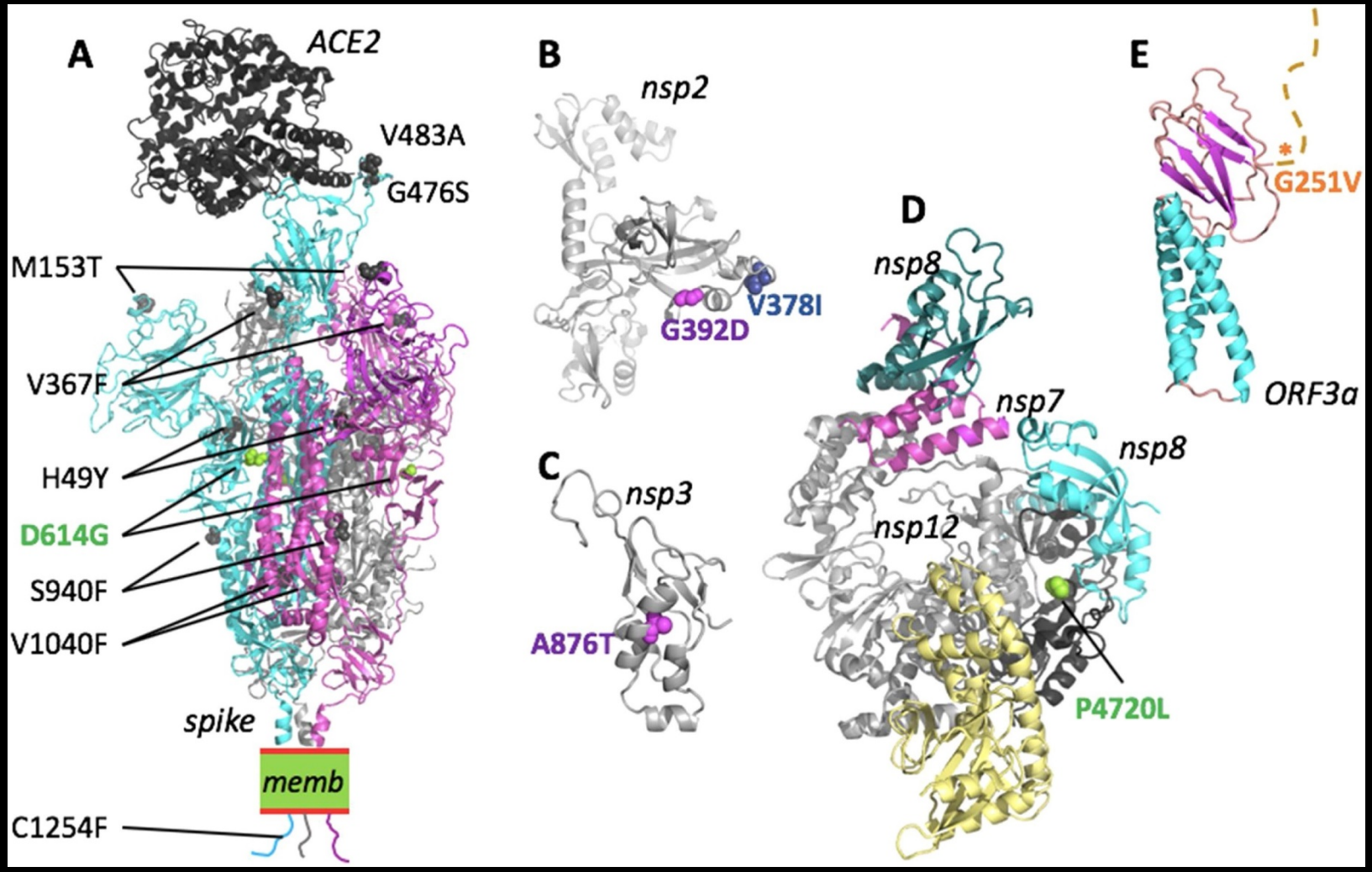
- cull of 17 million mink (Denmark) due to emergence of new SARS-CoV-2 variant ("cluster 5")
  - suspected human to mink transmission (spill-back)
- six countries (5EU, USA) reported mink infections to WHO

Global SARS-CoV-2 Phylogenetic Trees and Rapid Evolution in an Immunocompromised Patient *



B. Choi et al (2020) NEJM 383, 2291

Global Biosurveillance of Protein Mutations in SARS-CoV-2 Clades: Implications for Vaccine Efficacy



International Journal of Infectious Diseases Volume 100, November 2020, Pages 216-223

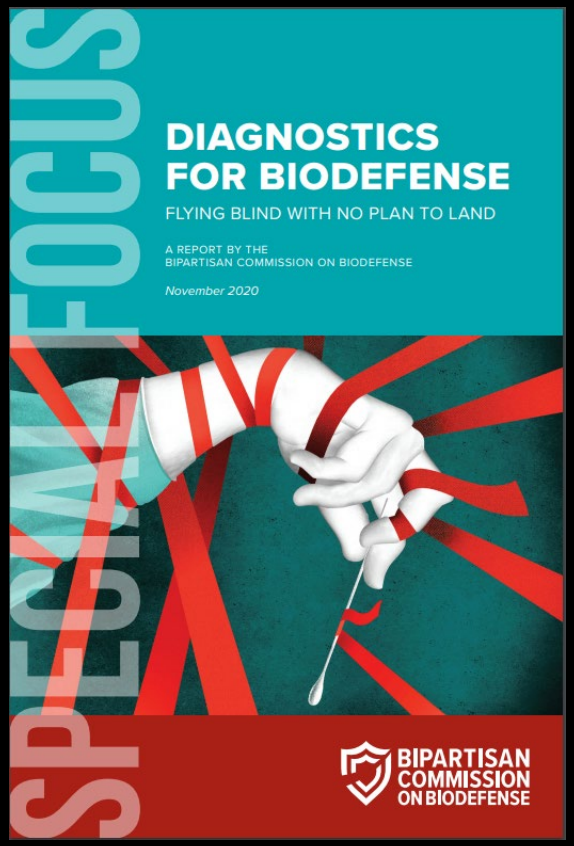
Evolution or Deliberate Design of SARS-CoV-2 Variants: Challenges for Future Vaccine Design and an Expanded Bioterrorism Threat

Increased Dual-use Risk from Open Literature Publications?

Rapid reconstruction of SARS-CoV-2 using a synthetic genomics platform

Tran Thi Nhu Thao, Fabien Labroussaa, […], Volker Thiel *Nature* **582**, 561–565(2020)

Pandemic Control:
The Need for a Systems-Based End-to-End Preparedness



- diagnostics: too long ignored and under-invested as a critical component of biosurveillance, bioincident management and national security
- pandemics are complex, multi-dimensional dynamic (adaptive) systems
- unidimensional control responses are futile
- robust preparedness requires integrated system-based adaptive strategies to match this multi-dimensionality complexity
  - public and private sector collaboration
  - domestic and international coordination
- proactive sustained investment to limit impact of future pandemics

Happy Holidays

Stay Safe and Hoping for a Less Challenging 2021

https://www.theatlantic.com/magazine/

Slides available at: https://casi.asu.edu/presentations/