14 August 2020

Marc Salit,
JIMB Director

SLAC National Lab and Stanford University

Coronavirus Standards Working Group

What should a Coronavirus Standards Working Group do?

Assure development and availability of standards, controls, interlab testing, knowledge to support successful rollout & scaling of 2019-nCoV testing

Identify and develop critical infrastructure to support…

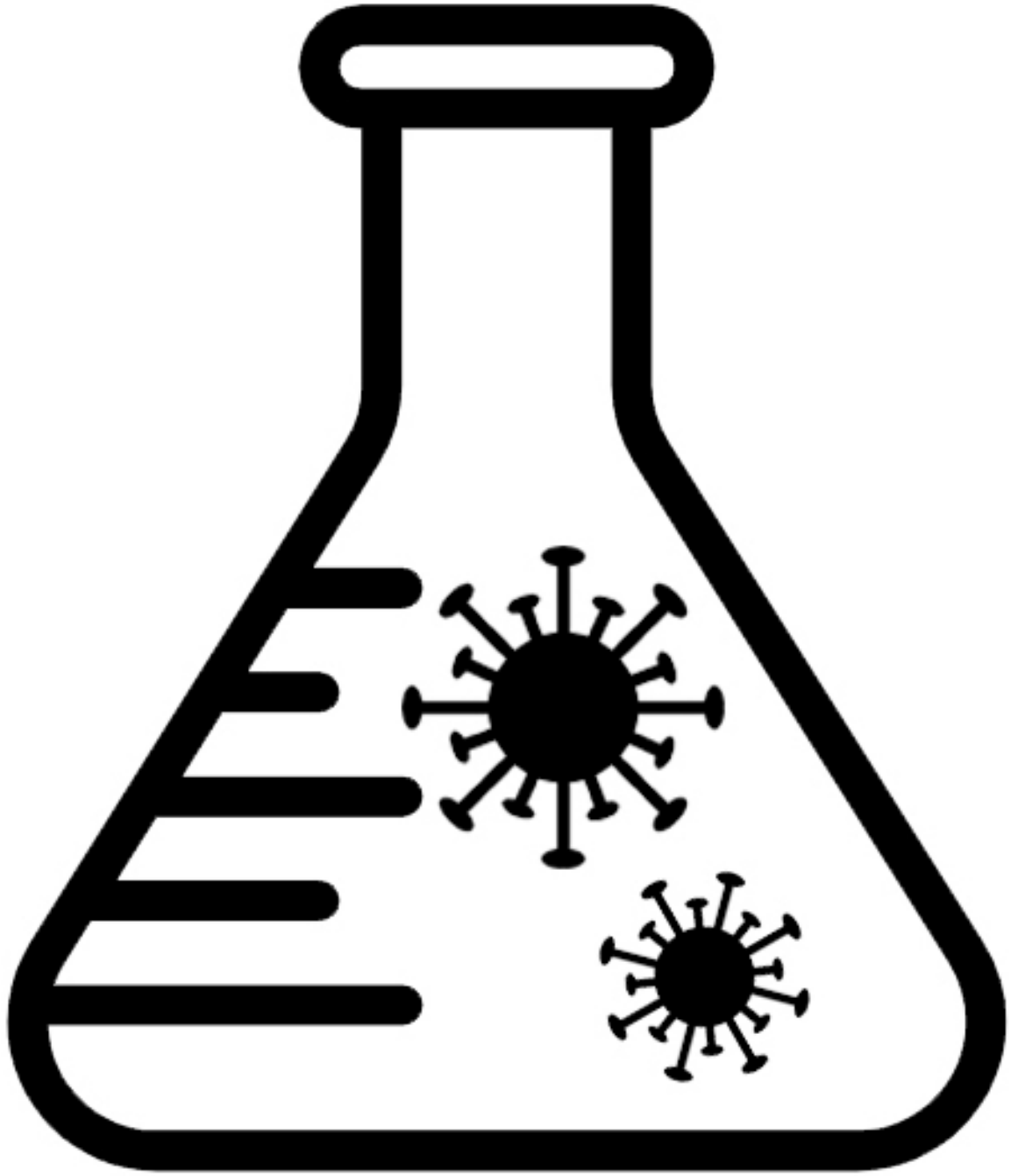
- confidence in test results
- interoperability
- scale-up
- long-term capacity

Identify best practices that should be institutionalized

Learn what we need to so next time we have a global network in place ready to make standards.

14 August Agenda

- Putting the ‘Standards’ in the CSWG
  - John Sninsky, Tom White, Marc Salit
- National Virtual Biotechnology Laboratory – how can they help with COVID-19 Testing R&D?
  - Pat Fitch, Los Alamos National Lab



Putting the “Standards” in the CSWG

John Sninsky, Tom White, Marc Salit

Can we do better?

The New York Times

Opinion

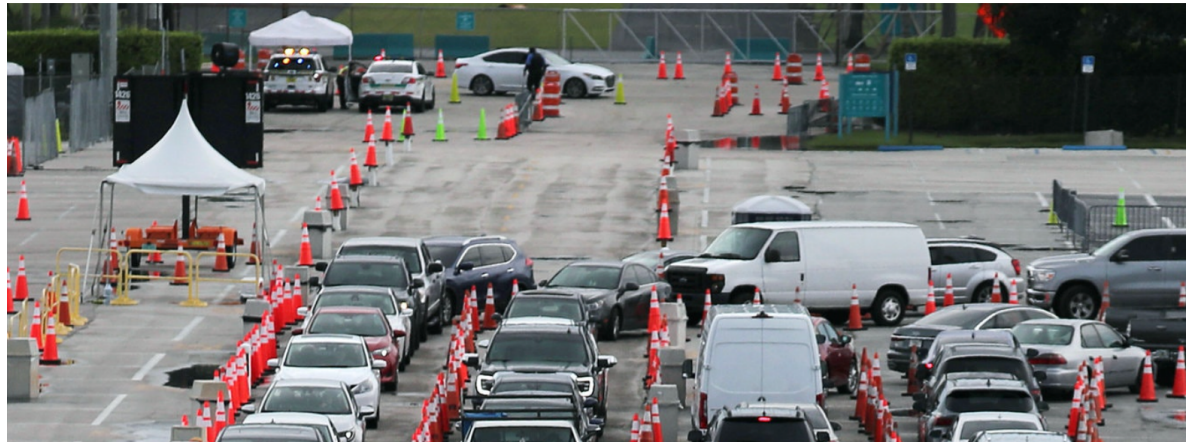
Testing Is on the Brink of Paralysis. That's Very Bad News.

Our pandemic fight requires prompt testing results — and singular cooperation among the states to achieve them.

By Margaret Bourdeaux, Beth Cameron and Jonathan Zittrain

Drs. Bourdeaux and Cameron are health policy experts. Professor Zittrain teaches law and computer science.

July 16, 2020



How we can help coordination, and how that might make a difference.

- Reference control set and performance assessment kit
  - Improve accuracy for intended use
- Testing Performance Dashboard
- Can an integrated testing performance platform inform policy?
  - Load Balancing – Smart Testing Grid
  - Integration of tacit knowledge
  - Supply Chain knowledge
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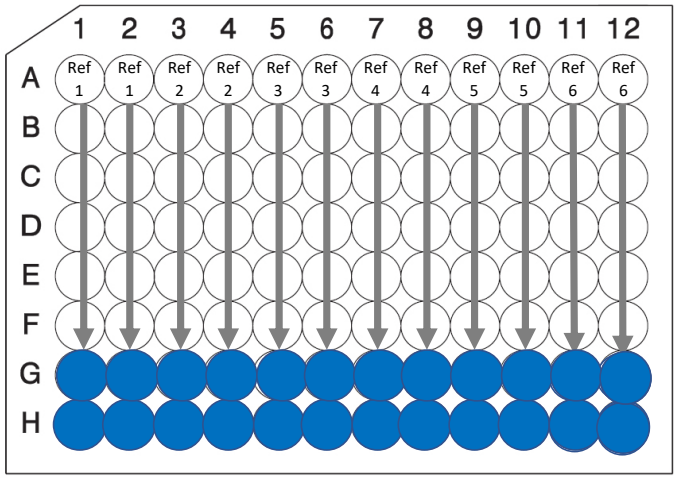


Plate 0: For Collaborative Harmonization Study

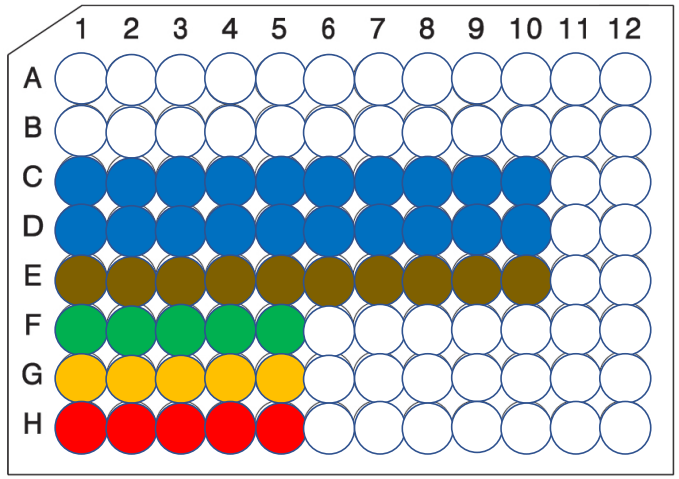


Plate 1: Analytical Sensitivity Benchmark Plate

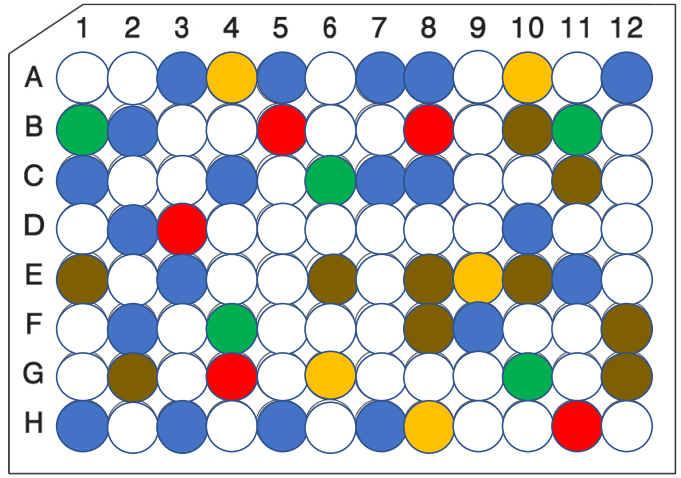
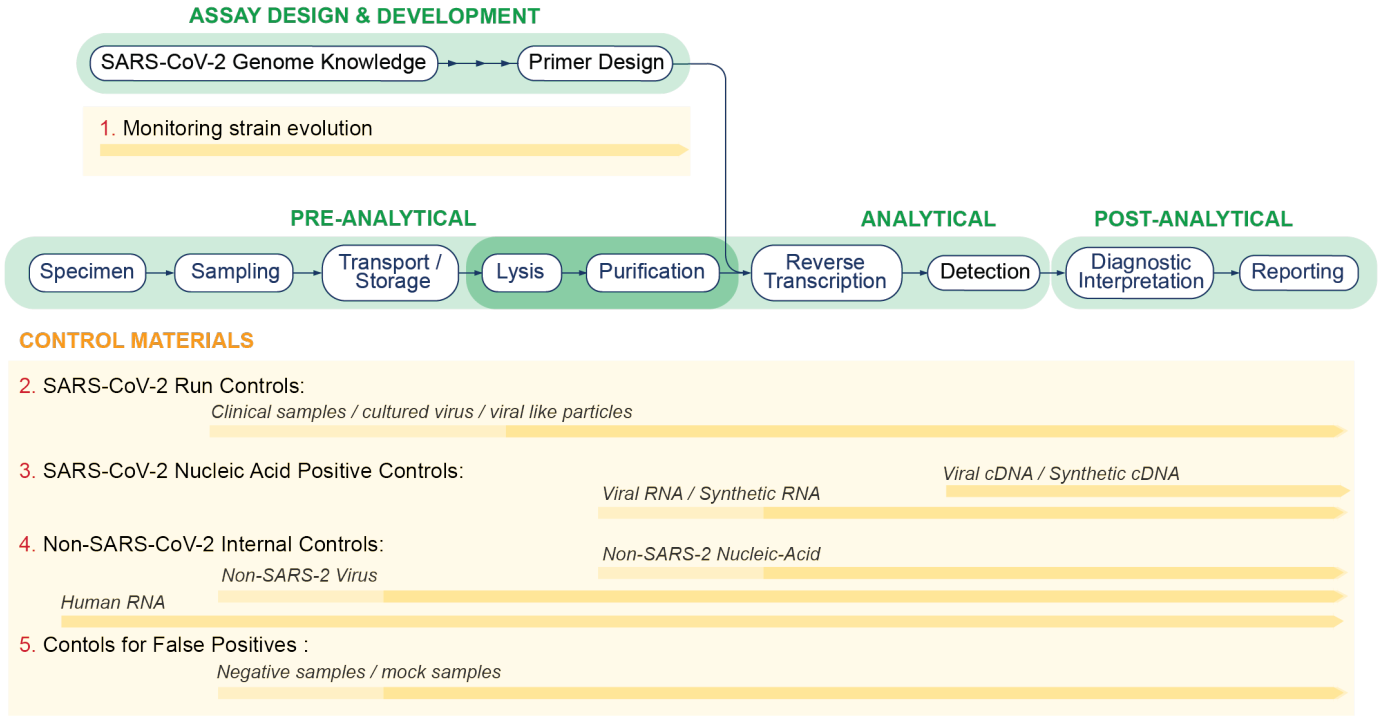


Plate 2: Validation Plate and Dashboard

3 Plates for SARS-CoV-2 Viral Standards



Molecular Testing is a Measurement Process

Standards and controls work in different parts of the process

Quality requires controls for each process element

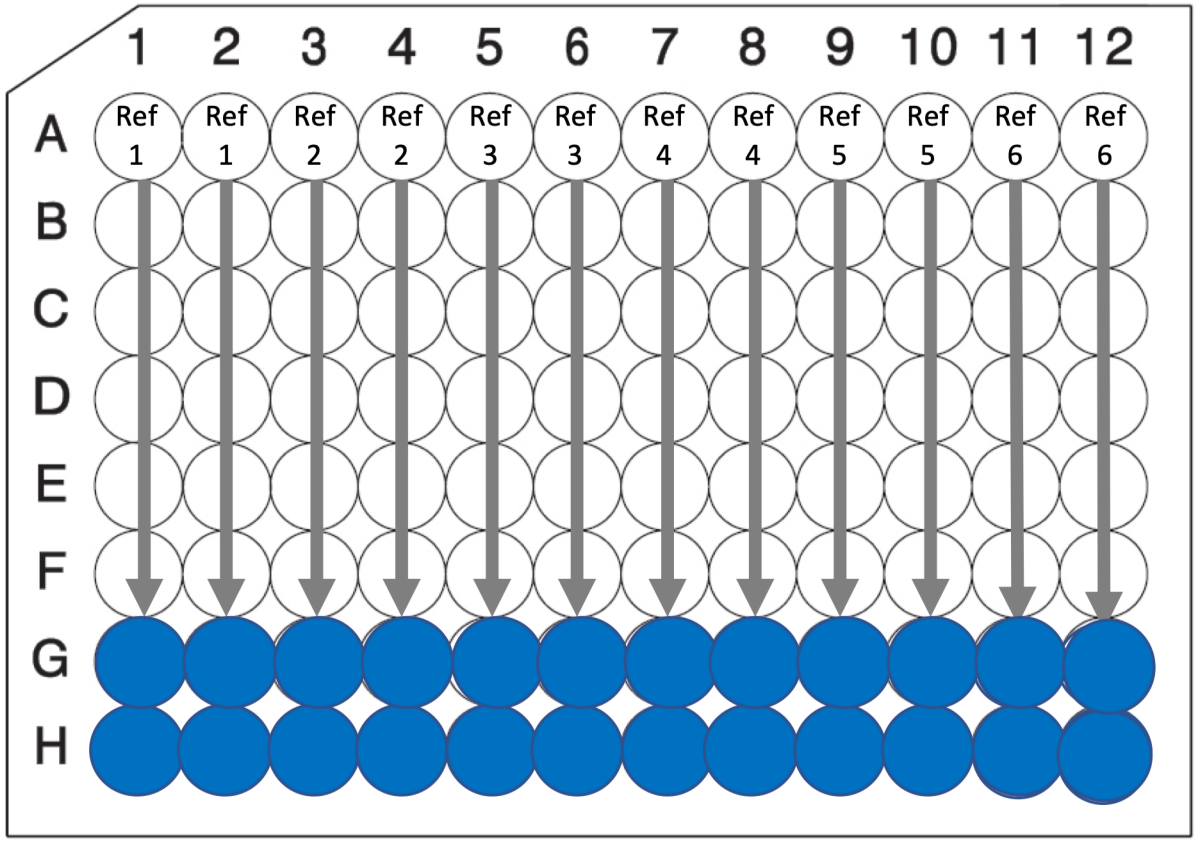
Thoughts on a CSWG Harmonization Study

Get the controls on the same measurement scale

- Harmonization by value assignment
  - convene control producers to contribute materials to a panel
  - conduct collaborative study to establish copy concentration of SARS-CoV-2 targets in panel
- Workplan
  - obtain, aliquot and distribute sample panel
  - blind replicates of each control material
  - appropriate negative controls?
  - appropriate calibration molecules?
  - probably about 50 samples
- National Measurement Institutes and experienced diagnostic labs

Plate 0 – for our harmonization study

- Build panel of ~6 SARS-CoV-2 viral particle surrogate "Run Controls"
  - NIBSC/WHO, SeraCare, BEI, FDA, Imperial College, EVA
- Standard plate as reservoir
  - 6 different reference materials in duplicate
    - serial 3x dilutions in white (729-fold range)
  - 1/4 plate negatives (blue)



Harmonization Plate 0

Discussion

- Develop materials to use for calibration of RT-qPCR
  - Results that can be compared improve test interpretation
  - Harmonize viral concentrations of multiple materials
    - Establish a common calibrated scale

- Develop knowledge of how different materials perform in multiple expert labs
  - is there a “best” run control?
- Open transparent process
  - no data embargo, once data are verified, they’re made available
- Are you willing to contribute a candidate material?
- Are you willing to measure the panel?

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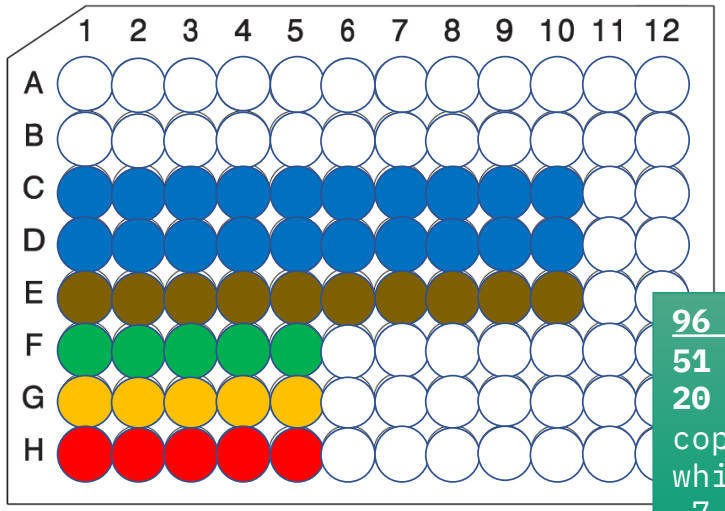
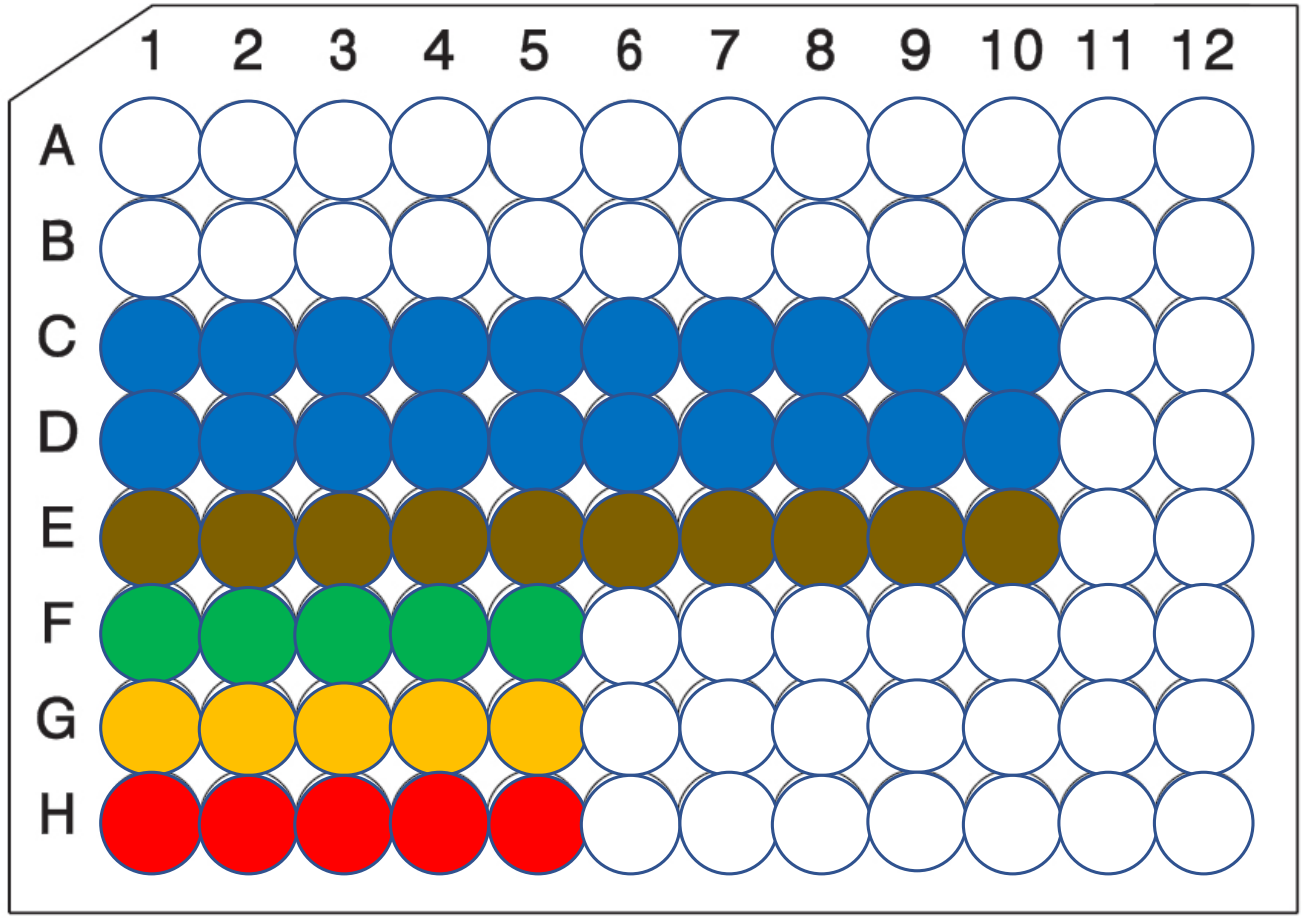


96 well plate layout:
51 no-template controls (white)
20 samples with an average of 1 copy of template/reaction, of which you would expect 37%, or ~7, to be negative (blue)
10 of 10 copies (brown)
5 of 100 copies (green)
5 of 1000 copies (orange)
5 of 10000 copies (red)

- Reagent to measure/assess limit of detection (analytical sensitivity) and identify lab-associated contamination in standard plate format
- Put LOD measurements on a common scale
  - use harmonized standards from collaborative study to calibrate
    - absent calibration, can assess LOD dilution level
- Design features:
  - Large number of negatives (53% plate)
  - Larger number (20) of on average 1 copy to accommodate Poisson distributed expected negatives
  - Increased number (10) of an average 10 copies
  - 5 replicates each for 100, 1000 and 10,000 copies
- Use this plate in a process control mode by…
  - combining with negative clinical samples
    - add negative clinical sample to each well
    - or directly add the contents of Plate 1 to negative clinical samples or just buffer-dilute into a plate of clinical samples
  - may be able to combine before ***or*** after extraction/purification

Analytical Sensitivity Benchmark Plate Discussion

- Does this design work to give a good measure of LOD?
- Does this design inform the absence of contamination?
- Can we disseminate this plate as a useful reference reagent for test development and improvement?

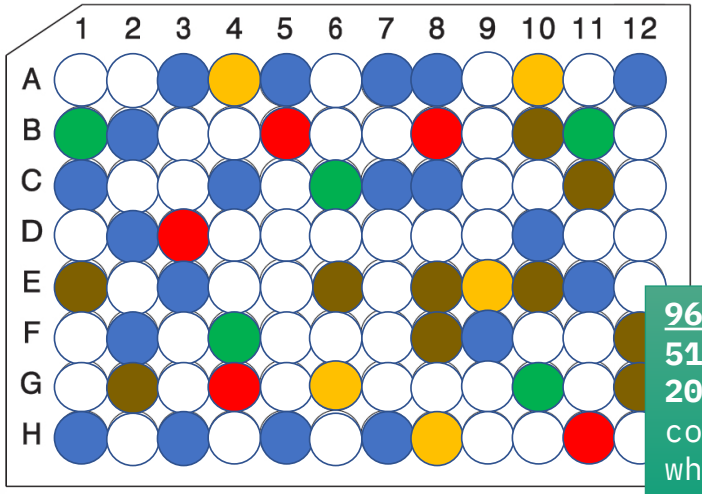


precisionFDA

- Provides a private area where participants (individuals or organizations) can conduct analysis and comparisons, and a community area where they can publish and share results
- Cloud-based platform where participants can access and share datasets, analysis pipelines, and bioinformatics tools, in order to benchmark their approaches

Inspiration for a COVID-testing dashboard

Plate 2: Validation Plate & Dashboard



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- Validation reagent that randomly interleaves samples from “Analytical Sensitivity Benchmark Plate” (Plate 1)
- Cloud-hosted dashboard for performance assessment
  - think precisionFDA
  - randomized plate designs are decoded on data upload
- Private spaces, public spaces, analysis tools, useful for optimization and process monitoring
  - common analytical tools for uniform assessment
  - supports regulatory oversight

Validation Plate Discussion

- Confidential blinding of materials in wells supports validation of full process, including interpretation and reporting
  - cloud-hosted, private analysis dashboard (inspired by pFDA) unblinds plate and reports confidentially to laboratory
    - lab can see their performance in the population
  - opt-in to openly disclose

- Knowledge of (even anonymized) testing performance across participating labs will support public confidence in test enterprise

- Systematic observation of validation data can inform testing coordination at scale

How we can help coordination, and how that might make a difference.

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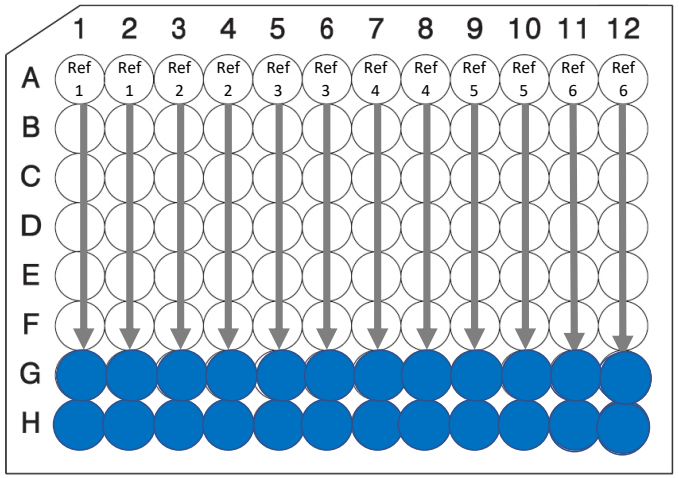

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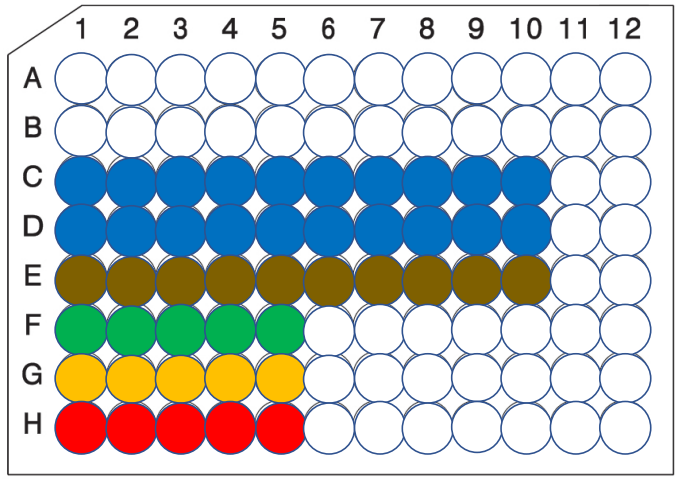

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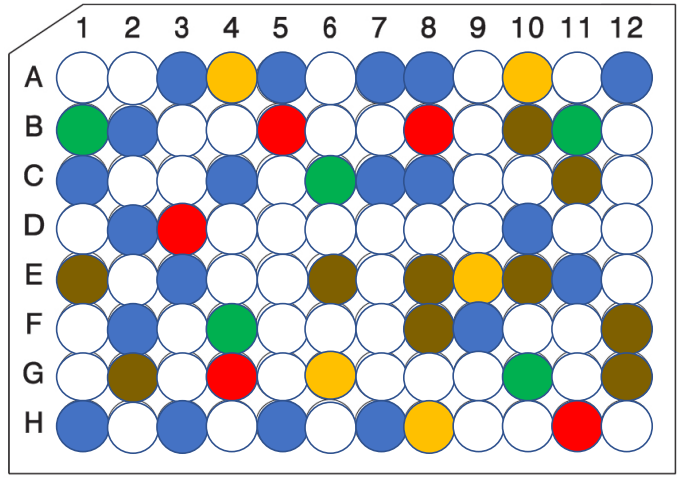

Plate 2: Validation Plate and Dashboard

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COVID-19 Testing R&D
DOE National Virtual Biotechnology Laboratory (NVBL)

Coronavirus Standards Working Group

Pat Fitch
Associate Laboratory Director
Chemical, Earth, & Life Sciences
August 14, 2020

NVBL COVID-19 Testing R&D Team of National Laboratories:
Ames, Argonne, Lawrence Berkeley, Lawrence Livermore, Los Alamos, Renewable Energy, Oak Ridge, Pacific Northwest, Sandia, SLAC

Research was supported by the DOE Office of Science through the National Virtual Biotechnology Laboratory, a consortium of DOE national laboratories focused on response to COVID-19, with funding provided by the Coronavirus CARES Act.

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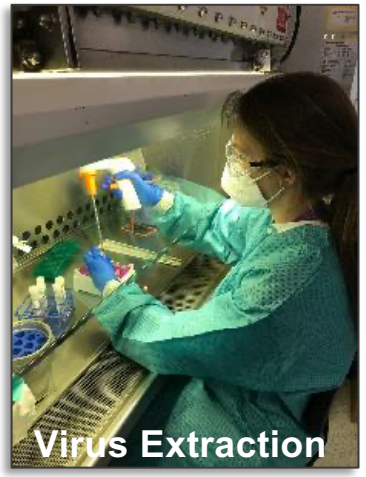
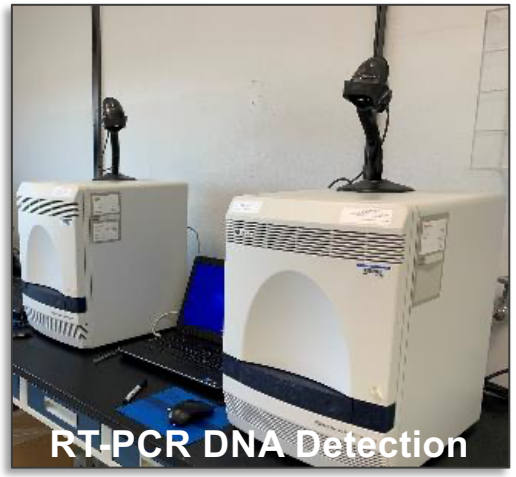
National Nuclear Security Administration
Managed by Triad National Security, LLC for the U.S. Department of Energy's NNSA

Approach: Increase Availability of Existing / Develop and Demonstrate New Protocols and Instruments, and Support Collaborating Stakeholders

Canonical nucleic acid testing protocol





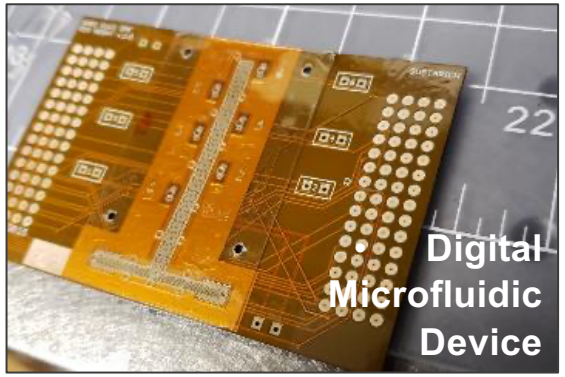
Alternatives

- Nasopharyngeal swabs
- Sputum
- Breath
- Viral transport media (4)
- Inactivation efficiency

- Pooling studies
- Automation
- Extraction (3)

- New RNA targets
- Target erosion
- Isothermal amplification
- Digital Microfluidic Device for droplet PCR assays

Seeking input to update gaps and requirements



Engage with the DOE National Virtual Biotechnology Laboratory (NVBL)

COVID-19 Testing Gaps and Requirements