18 September 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.

18 September Agenda

- NEJM Perspective – final version readying to submit, some context
- FDA SARS-CoV-2 Panel LoD results
- Adding (more) signal to the (plentiful) noise: Perspectives & Communications
  - What tests, when, and for what?
  - Testing in support of Vaccine Development: Surrogate Endpoint Measures

Calibration of SARS-CoV-2 tests is vital for accurate clinical interpretation

Proposed Authorship:
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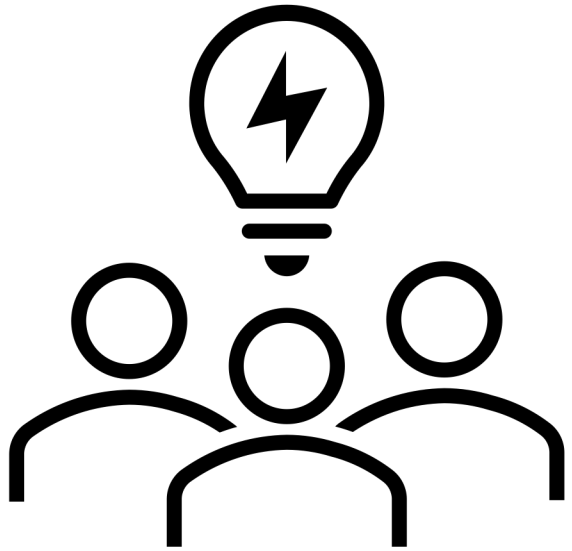
This really is a CSWG product.

- We backed off having CSWG as a signatory because there the perspective includes a policy recommendation which is awkward for some participating organizations that don't advocate policy
- This draft is MUCH improved because of CSWG membership work – thanks!
- We are grateful to our FDA colleagues who worked with us to get it right, and helped with nomenclature.
- We are allowed 1200 words, 1 figure, and 5 references.



Outline of our Perspective

- Need widely available, harmonized calibration and validation materials to meet diagnostic needs
- PPV and NPV are key, and depend on good knowledge of analytical performance
- Performance of tests does indeed vary widely
- Availability of harmonized calibration and validation materials is urgent
  - many, including us, are working on it
  - we have a useful design in development
- We recommend that harmonized calibration and validation materials be built into the regulatory apparatus now and from the start to have better results

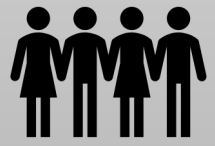
We can make the standards to make molecular testing robust, reliable, and quantitatively comparable.

‘Harmonization Kit” to establish comparability of a set of standards to put molecular testing results on a common scale

just a few labs, NMIs

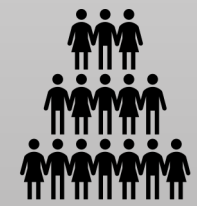
“Benchmarking Kit” for turn-key evaluation of molecular testing platforms

test developers



“Validation Kit” for blinded validation with a dashboard to form a “smart-grid” for testing

routinely measured at testing labs



Perspective from FDA CDRH Leaders

- NEJM Perspective presents the arc of the regulatory oversight response for testing
  - rapid action led to some authorization denials, confusion
  - developed FDA reference panel
  - needs for communicating PPV/NPV
- Lessons learned
  - more partnership (international)
    - shared clinical specimens early
  - focus on small number of well-developed tests suitable for high-throughput
  - need common approaches for performance assessment & validation
  - clinical test performance must be clearly articulated & understood

The NEW ENGLAND JOURNAL of MEDICINE

Perspective

Covid-19 Molecular Diagnostic Testing — Lessons Learned

Jeffrey Shuren, M.D., J.D., and Timothy Stenzel, M.D., Ph.D.

On February 4, 2020, the U.S. secretary of health and human services declared that emergency use of diagnostics for SARS-CoV-2 was justified, triggering emergency authority for the Food and Drug Administration (FDA) to grant an emergency use authorization (EUA) for a device if it reasonably believes that it may be effective, rather than waiting to grant full approval when it has reasonable assurance that the device is safe and effective. This mechanism expedites access to accurate diagnostic tests during emergencies, when information gaps and false results may adversely affect patient care and public health decision making.

The EUA process enabled molecular diagnostic tests to be developed, validated, and deployed within weeks rather than several months to over a year, as traditionally required. In January, the agency had begun engaging with commercial manufacturers of diagnostic test kits and laboratories to help foster test development. To streamline submissions, the agency developed an EUA template with recommendations on validating a molecular diagnostic test for SARS-CoV-2 and outlined the required information. By July 31, the FDA had authorized 163 Covid-19 diagnostic tests.

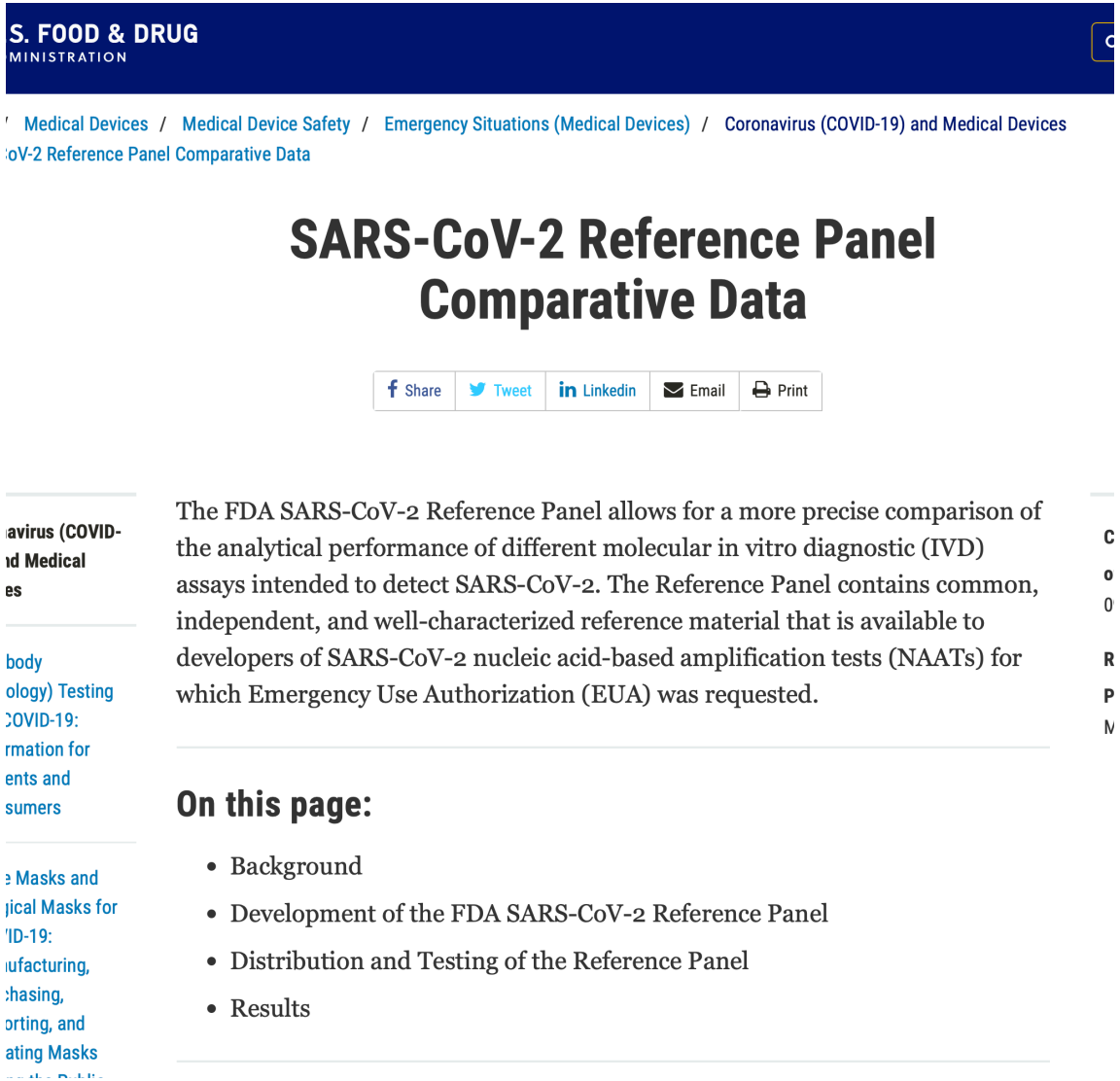
The EUA template also streamlined submission paperwork. A typical submission seeking full FDA approval for a test is about 1000 pages for laboratories and about 2000 pages for commercial manufacturers that distribute tests. The template reduced commercial manufacturers' EUA submissions to 100 to 200 pages and laboratory submissions to about 40 pages, of which only about half were generated solely to meet FDA requirements, and most of those consisted of data rather than text.

Submissions for full approval and those for EUAs differ primarily in the extent and type of evidence required. For a Covid-19 EUA, the FDA initially permitted test performance to be demonstrated by a computer analysis indicating the percentage of identity matches with publicly available SARS-CoV-2 sequences that could be detected by the proposed molecular assay and cross-reactivity with other respiratory pathogens and by testing contrived samples. Developers could "spike" human specimens, such as sputum, with different amounts of extracted SARS-CoV-2 RNA or live or inactivated virus to assess viral detection, rather than using patient specimens. Validation could thus be completed rapidly once viral RNA or virus became available. However, this approach was less likely than use of patient specimens to accurately characterize test performance.

As positive patient samples became more readily available, the FDA transitioned to requiring the

FDA Reference Panel results: 15 September

- 5 sample panel
  - Tube 1
    - heat-inactivated cultured SARS-CoV-2 strain (2019-nCoV/USA-WA1/2020)
    - ~$1.8x10^8$ RNA NAAT detectable units/mL (NDU/mL)
  - Tubes 2, 3, 4, 5 blinded
    - MERS-CoV strain as cross-reactivity control included in the set
- Standard protocol to do range-finding LOD w/Tube 1, w/ confirmatory experiment
- Tubes 2-5 measured to back up LOD and evaluate cross-reactivity
- Takes between 40 to > 150 tests



S. FOOD & DRUG
MINISTRATION

Medical Devices / Medical Device Safety / Emergency Situations (Medical Devices) / Coronavirus (COVID-19) and Medical Devices
oV-2 Reference Panel Comparative Data

SARS-CoV-2 Reference Panel Comparative Data

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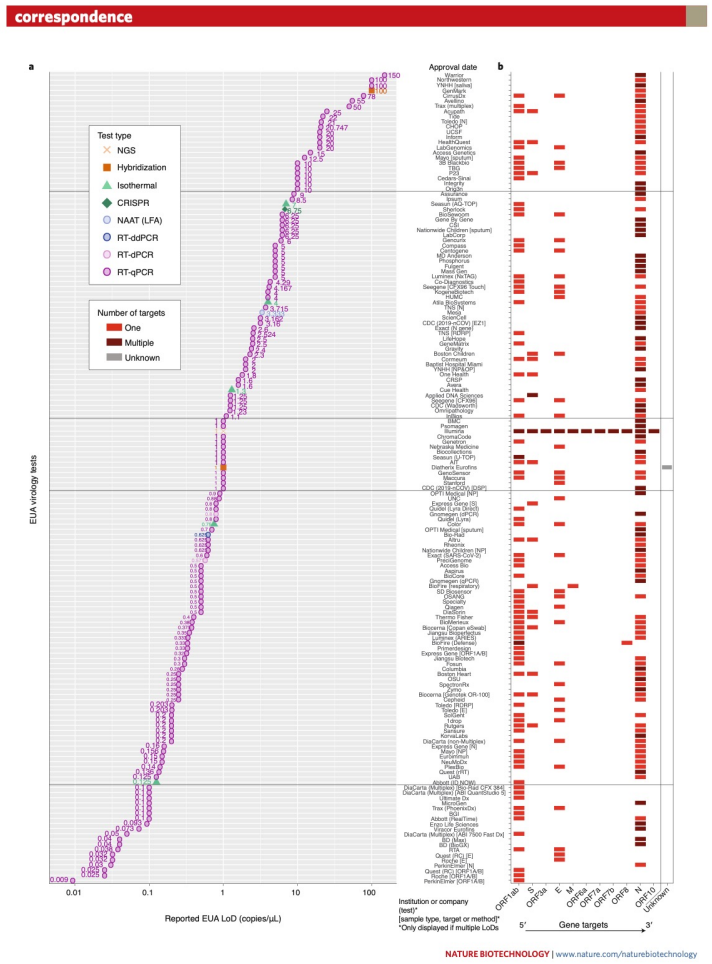
The FDA SARS-CoV-2 Reference Panel allows for a more precise comparison of the analytical performance of different molecular in vitro diagnostic (IVD) assays intended to detect SARS-CoV-2. The Reference Panel contains common, independent, and well-characterized reference material that is available to developers of SARS-CoV-2 nucleic acid-based amplification tests (NAATs) for which Emergency Use Authorization (EUA) was requested.

On this page:

- Background
- Development of the FDA SARS-CoV-2 Reference Panel
- Distribution and Testing of the Reference Panel
- Results

1000-fold range of LODs reported

"While the FDA SARS-CoV-2 Reference Panel helps determine the comparative performance among authorized tests, the panel is not a replacement for the analytical and clinical validation recommendations the FDA has provided in the EUA templates."



10x smaller variability using shared material

Comparison to MacKay, M.J., Hooker, A.C., Afshinnekoo, E. *et al.* The COVID-19 XPRIZE and the need for scalable, fast, and widespread testing. *Nat Biotechnol* **38,** 1021–1024 (2020). https://doi.org/10.1038/s41587-020-0655-4

The Journal of Molecular Diagnostics, Vol. 21, No. 6, November 2019

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A Zika Reference Panel for Molecular-Based Diagnostic Devices as a US Food and Drug Administration Response Tool to a Public Health Emergency

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In 2015, Zika virus (ZIKV) appeared as an emerging pathogen, generating a global and urgent need for accurate diagnostic devices. During this public health crisis, several nucleic acid testing (NAT)—based Zika assays were submitted to the US Food and Drug Administration (FDA) for Emergency Use Authorization. The FDA's Center for Devices and Radiological Health, in collaboration with the FDA's Center for Biologics Evaluation and Research, responded to this Zika emergency by developing and producing a reference panel (RP) for Zika RNA (Zika FDA-RP) suitable for performance assessment of ZIKV NAT-based *in vitro* diagnostic devices. Reference panels are a fundamental tool for performance assessment of molecular tests. The panel is composed of five vials: two different heat-inactivated ZIKV strains (PRVABC59 and FSS13025) in concentrated stocks and three blinded concentrations prepared from those strains. The Zika FDA-RP was shared with developers who had devices in the final stages of validation. *In vitro* diagnostic developers tested the Zika FDA-RP using the FDA-provided protocol. Depending on sample type, 85% (12/14) of the NAT assays had analytical sensitivities between 500 and 5000 RNA NAT-detectable units/mL (NDUs/mL). One device showed better performance (100 NDUs/mL), and another one showed lower performance (10,000 to 30,000 NDUs/mL). Vials of the Zika FDA-RP are available on request to developers who have interacted with the FDA through the review process. *(J Mol Diagn 2019, 21: 1025—1033; https://doi.org/10.1016/j.jmoldx.2019.06.004)*

On February 26, 2016, the Secretary of Health and Human Services declared that circumstances existed justifying the authorization of the emergency use of *in vitro* diagnostics (IVDs) for detection of Zika virus (ZIKV) and/or diagnosis of ZIKV infection.

ZIKV is an arbovirus member of the *Flaviviridae* family, transmitted to individuals primarily through the bite of an infected *Aedes* mosquito. In 2015, ZIKV first appeared outside of Africa and Asia when it was isolated in Brazil,[1,2] causing an outbreak that likely originated from an infected traveler from French Polynesia. From there, the virus spread through South, Central, and North America, reaching the Caribbean in the beginning of 2016.[3,4] Although it often causes only arthralgia, myalgia, headache, conjunctivitis, mild rashes, and fever,[5] or no symptoms at all, severe neurologic manifestations, including Guillain-Barré syndrome and congenital microcephaly, have been associated with ZIKV infection.[6,7] Early and correct diagnosis of ZIKV infection in pregnant women is critically important to identify babies with a potential risk of microcephaly and other brain anomalies, which is complicated by the fact that 80% of ZIKV infections are asymptomatic. Problems from microcephaly can range from mild to severe, are often lifelong, and, in some cases, can be life threatening

Supported by US Food and Drug Administration (FDA) Medical Countermeasure Initiative grant OCET 2016-331 (M.R.). This project was supported in part by an appointment to the Research Participation Program at the Office of Blood Research and Review/Center for Biologics Evaluation and Research, FDA, administered by the Oak Ridge Institute for Science and Education through an interagency agreement between the US Department of Energy and the FDA.

Disclosures: None declared.

https://doi.org/10.1016/j.jmoldx.2019.06.004

Zika Reference Panel is a model

- similar approach, similar design
- well-posed probit model for LOD
- unclear how calibrant is value-assigned, method not specified

Here are other papers or letters we've discussed as CSWG products

- Infrastructure for now, and for the next time
  - EUA for calibration materials
    - *to be submitted Monday*
- Testing – what kind? where do we use it? how good is it? and... what can it make possible?
  - technical note connecting characteristics of the tests to the application needs
- Testing – what kind? where do we use it? how good is it? and... what can it make possible?
  - note for lay audience focused on the consequences and tradeoffs of testing modes
- Vaccine Roadmap – "How can we be sure we have a vaccine?"
  - level-headed "what can we know, when, and what does that mean for safety and efficacy"

What tests do we use for what scenarios?

Consider a CSWG publication to help interpret the utility, application, and interpretation of different tests.

- many different approaches being advocated
- can we add objective and experienced knowledge of testing and interpretation to help?

	Test Attributes	Sick person Urgent Care	Routine testing for Healthcare Workers	Essential Workers	School/College Screening	Travel	Return to work	Movie Theatre Screening
RT-qPCR	clinical diagnostic, centralized	+++	+++	++	+		+	
LAMP	innovative, cheap, rapid, decentralized	++	++	++	++	+	+	+/-
Antigen	cheapest, rapid, home-use	+	++	++	++	+	+	+/-
Antibody ELISA	Establishes prior exposure. Lab-based, moderate			+	+			
Antibody Lateral Flow	Cheap and informs on exposure			+	+	+?		

Discussion