18 September 2020

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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 do 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: John Sninsky, Marc Salit
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
- ‘Benchmarking Kit’ for turn-key evaluation of molecular testing platforms
- ‘Validation Kit’ for blinded validation with a dashboard to form a “smart-grid” for testing

just a few labs, NMI

routinely measured at testing labs

test developers
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

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.

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 vital 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
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.

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

Mayra García,* Rafaela Fares-Gusman, Kim Sapphord, Karen Chancey, Andriyan Grinev, Stephen Lovell,* Uwe Scherf,* and Maria Rest

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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 test (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 ZIKV 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 static two different heat-inactivated ZIKV strains (PENNSYR and FS131225) in concentrated stocks and three blinded concentrations prepared from these 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% (21/25) of the NAT assays had analytical sensitivities between 400 and 10,000 RNA NAT-detectable units/mL (NDUs/mL). One device showed better performance (10,000 to 30,000 NDUs/mL), and another one showed lower performance (1,000 to 30,000 NDUs/mL). Results of the Zika FDA-RP are available on request to developers who have interacted with the FDA through the review process.

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?

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<th>Test Attributes</th>
<th>Sick person Urgent Care</th>
<th>Routine testing for Healthcare Workers</th>
<th>Essential Workers</th>
<th>School/College Screening</th>
<th>Travel</th>
<th>Return to work</th>
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<td>Establishes prior exposure. Lab-based, moderate</td>
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Discussion