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.
24 April Agenda

• Manuscript Overview
• Structure
• Figures
• Table(s)
• Draft Minimum Information Standard
• 1st Complete Database of Controls
Our paper describes the technical and operational needs for a coordinated global project assuring the availability of standards (documentary and control materials) and standardization efforts for coronavirus testing.

- Process analysis to identify sources of bias and variability
- Role of standards to mitigate
- Minimum Information About...
  - Standards
  - Assays
- Inventory of available control materials/standards
• Abstract
• Introduction
• Testing as a Measurement Process and roles of standards, validation studies and Standardization practices (interlab and proficiency testing)
  • Molecular testing (virus)
  • Serological testing (host response)
• Analysis and Interpretation of test results for SARS-CoV2 (what are we doing well, and what are we missing?)
  • Molecular testing (virus)
  • Serological testing (host response)
• Minimum Information Standards to report attributes
  • Standards/Controls
  • Assays
• Immediate gaps and Recommendations to fill them
• Resources
  • dynamic, web-hosted standards inventory
  • Assay surveys
• Roadmap
  • Resource maintenance
  • Maintain gap analysis
  • Standards development
Figure 1 - Emergence of diagnostic signal though clinical course of SARS-CoV-2.

- This Figure is intended to support the narrative of what testing is appropriate for what clinical purpose, and consideration for interpretation.
Figure 2 - Nucleic Acid Testing

Molecular Test Measurement Process

Experimental factors:
- Nasal
- Blood
- Throat
- Saliva
- Speculum
- Naso/opharyngeal
- Bronchoalveolar lavage
- Dry swab
- Wet swab
- Liquid
- Viral RNA stabilization buffer
- Viral inactivation solution
- Buffered solution
- Viral transport medium
- Osmotic Physical Chemical Thermal
- Concentration
- Co-purified matrices
- Priming
- Gene Assay / method Units
- Pass / fail
- Performance
- Threshold setting
- Format
- Protocol
- Standardized reporting formats?
- Proficiency testing schemes:
- Interlaboratory studies
- (Inter-comparability of operators, platforms, reagents, assays)

Best practices:
- Sample collection, transport, and storage (see Supplementary Materials for example document)
- SOPs for validation, Limit of detection, repeatability, reproducibility [Degree of validation; full or truncated LLOQ (extraction through interpretation)]
- ISO docs e.g. ISO 20395 (Biotechnology — Requirements for evaluating the performance of quantification methods for nucleic acid target sequences — qPCR and ePCR)

Controls:
1. Patient Samples
   - Positive and negative test controls
2. Synthetic virus-like:
   - Virus Culture, Packaged Viral RNA
3. SARS nucleic acid:
   - Viral RNA, Synthetic RNA
4. Non-SARS-CoV-2:
   - Human RNA
   - Non-SARS-2 Virus
   - Non-SARS-2 Nucleic Acid
   - Non-SARS-2 cDNA

Fig 2—Molecular Test Measurement Process
Figure 2 - Nucleic Acid Testing

**Assay Design & Development**: Reference Genome → Primer Design → Validation

**Pre-analytical**: Specimen → Sampling → Transport/Storage → Lysis → Purification

**Experimental factors**:
- Nasal
- Blood
- Throat
- Saliva
- Sputum
- Nasopharyngeal
- Bronchoalveolar lavage
- Dry swab
- Wet swab
- Liquid
- Water
- RNA stabilisation buffer
- Viral inactivation solution
- Buffered solution
- Viral transport medium
- Osmotic
- Physical
- Chemical
- Thermal
- Concentration
- Co-purified matrices
- Priming
- Gene
- Assay/method
- Units
- Threshold setting
- Format protocol

**Reverse Transcription** → **Detection** → **Diagnostic Interpretation** → **Quality Control** → **Reporting**

**Best practices & documentary standards**
- Standardised
- Reporting formats?
- RT-qPCR assay design and validation; optimal primer/probes
- Standardisation
- Transport, and storage (see Supplementary Materials for example document)
Fig 3 – Serological Test Measurement Process
Figure 3 – Serological Test Measurement Process
### Table I – Molecular Process Annotation

- Deeper annotation of measurement process figures: including element description, effect on performance, gaps, relative influence

| Phase  | Element               | Action                                                                 | Experimental Factors                                                                 | Effect of poor performance                                                                 | Standards & Validation Approaches (how does std help?) | Gaps                                                                                             | Influence of Element on diagnostic performance |
|--------|-----------------------|------------------------------------------------------------------------|---------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------|
| Pre-analytical | Specimen Type | Specify patient sample to collect                                      | Significant uncertainty in diagnostic comparability and performance                   | Mock sample to evaluate whole process                                                    | No authoritative knowledge of viral distribution in different fluids                               | Imperfect understanding of sampling biases from different fluids/locations                       | +++                                                |
|        | Sampling              | Specify sample collection device                                       | Spike-in positive and negative controls                                               | Performance differences between sampling devices in efficiency and RNA degradation        | Variability in collection substrate (collect and release)                                       | PCR inhibitors in collection substrate                                                          | ++                                                 |
|        | Sampling              | To obtain an accurate sampling from the patient/subject that represents their current health status | Sample collection method Substrate used for collection Interim storage (time/temp)    | False negatives Underestimation of viral load Perceived variability in NA assay performance |                                                                                                   |                                                                                                  |                                                    |
# Table I – Molecular Process Annotation

- **Phase**
  - Assay Design, Pre-analytical, Analysis, Post-analytical

- **Element**
  - Specimen type, Sampling, Transport/Storage, Processing, Assay, Interpretation

- **Action**
  - functional description

- **Experimental Factors**
  - influential factors (swab type...)

- **Effect of poor performance**
  - what breaks

- **Standards & Validation Approaches**
  - what standardization can bring confidence

- **Gaps**
  - what don’t we have

- **Influence on diagnostic performance**
  - +, ++, +++
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<th>Minimum Information Standard: Standards and Controls</th>
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<td>Controls for Specimen taking</td>
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Standards Inventory

- Compiled by Alexandra Whale, Megan Cleveland, Jim Huggett, Pete Vallone
- Uses the Minimum Information About a Control Material draft standard
- Will be web-hosted, searchable
- 41 materials in current inventory
All other business

Mailing list – converting to Google Groups (MailChimp too much work)
Communications, planning, engagement, process, operations?
Discussion