SARS-CoV-2 Reference Panel Comparative Data

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.

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Background

During the early months of the Coronavirus Disease 2019 (COVID-19) pandemic, clinical specimens were not readily available to developers of IVDs to detect SARS-CoV-2. Therefore, the FDA authorized IVDs based on available data from contrived samples generated from a range of SARS-CoV-2 material sources (for example, gene specific RNA, synthetic RNA, or whole genome viral RNA) for analytical and clinical performance evaluation. While validation using these contrived specimens provided a measure of confidence in test performance at the beginning of the pandemic, it is not feasible to precisely compare the performance of various tests that used contrived specimens because each test validated performance using samples

derived from different gene specific, synthetic, or genomic nucleic acid sources.

From February through the middle of May, the FDA issued a total of 59 EUAs for IVDs for the qualitative detection of nucleic acid from SARS-CoV-2 based on validation data using contrived specimens derived from SARS-CoV-2 viral RNA. As the pandemic progressed and more patient specimens became available, on May 11, 2020, the FDA recommended in the Policy for Coronavirus Disease-2019 Tests (/regulatory-information/search-fda-guidance-documents/policy-coronavirus-disease-2019-tests-during-public-health-emergency-revised)that developers obtain and use patient specimens to validate their tests.

Recognizing the value to healthcare professionals, laboratories, and patients in understanding the relative performance of NAATs for SARS-CoV-2, the FDA obtained live virus in February to develop a reference panel. Reference panels are a fundamental tool for performance assessment of molecular tests (/medical-devices/coronavirus-disease-2019-covid-19-emergency-use-authorizations-medical-devices/in-vitro-diagnostics-euas), and the use of the same reference material across different tests allows a direct comparison of analytical sensitivity performance across these tests. As was done for the evaluation of NAATs for Zika (/vaccines-blood-biologics/science-research-biologics/fda-zika-virus-reference-panel-molecular-based-diagnostic-devices-supports-product-testing-emergency), the FDA is again providing a tool for a comparative analysis of the performance of different tests. Such comparison has shown to be useful to healthcare providers and laboratories using these tests.

The FDA SARS-CoV-2 Reference Panel is shared with developers who have interacted with FDA through the review process.

Development of the FDA SARS-CoV-2 Reference Panel

To more precisely compare the performance of NAAT SARS-CoV-2 assays, through a collaboration between the Center for Devices and Radiological Health (CDRH) and the Center for Biologics Evaluation and Research (CBER), the FDA established a Reference Panel composed of standardized material, suitable for the determination and direct comparison of analytical sensitivity and cross-reactivity of nucleic acid-based SARS-CoV-2 assays.

The panel contains one heat-inactivated SARS-CoV-2 strain and one heat-inactivated MERS-CoV strain in cell culture media. The panel is composed of five tubes (T1 to T5): T1 contains the SARS-CoV-2 strain (2019-nCoV/USA-WA1/2020) at a concentration of ~1.8x108 RNA NAAT detectable units/mL (NDU/mL); T2, T3, T4, and T5 contain blinded samples, meaning that, although the FDA knows the concentration, the developer testing the samples does not. Based on a standard protocol provided by the FDA for T1, the developers are asked to perform a range finding Limit of Detection (LoD) study followed by a confirmatory study to further define and corroborate the LoD of their assay. The blinded samples (T2 to T5) are

also tested per a protocol provided by the FDA, to confirm the LoD determined for T1 and evaluate cross-reactivity with MERS-CoV virus. Depending on the test, the number of tests performed on different amounts of viral replicates can range from over 40 to over 150.

The FDA SARS-CoV-2 Reference Panel was first provided to all developers of authorized IVD EUAs that used contrived samples to validate their assay and is provided to all developers who request an EUA for SARS-CoV-2 NAATs. In general, FDA's EUAs require developers to evaluate and submit the analytical limit of detection and assess traceability of their product with any FDA-recommended reference material as a condition of the authorization. As explained above, assessment of assay performance using the FDA SARS-CoV-2 Reference Panel allows for a consistent determination of the relative sensitivity of these tests and cross-reactivity with MERS-CoV virus.

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 (https://www.fda.gov/medical-devices/coronavirus-disease-2019-covid-19-emergency-use-authorizations-medical-devices/vitro-diagnostics-euas#covid19ivdTemplates). For example, the panel only includes one strain of SARS-CoV-2 and one cross-reactant, MERS-CoV. Recent mutations reported for SARS-CoV-2 (e.g., D614G), which may impact molecular testing, are not included.

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

The FDA began distribution of the FDA SARS-CoV-2 Reference Panel in May 2020. As of November 14, 2020, the FDA has contacted developers of 206 authorized assays for shipping information and has sent the reference panel to developers of 190 authorized assays. The FDA is reviewing results as they are returned and continues to send the reference panel out to additional developers.

As of October 9, 2020, the FDA has contacted developers of 197 authorized assays for shipping information and by October 14, 2020 sent the reference panel to developers of 181 authorized assays which are included in the tables below. Developers who received the reference panel were asked to conduct testing and return results within two weeks of receiving the panel. Many developers returned data to the FDA by October 30, 2020, but in some cases, FDA did not receive the data, or the data was uninterpretable, or is still under interactive review. All contacted developers are listed in Table 1 along with the current status of their Reference Panel testing. Confirmed results of the relative sensitivity of EUA authorized assays provided by developers as of October 30, 2020, are displayed in Tables 2A, 2B, and 2C. The results are presented in three tables according to the clinical matrix used in

the study: swab in transport media, direct swabs (dry swabs), or saliva.

Following a protocol provided by the FDA with the reference panel, developers conducted testing with 3 replicates of serial dilutions of the SARS-CoV-2 virus provided in T1 in clinical negative specimens. The studies are performed by diluting the panel material in "negative patient clinical matrix" acquired and prepared by individual developers. The developers identified a provisional LoD and then performed confirmatory testing. To corroborate the LoD identified from testing T1, developers then diluted in clinical negative specimens and tested the blinded samples (T2-T5) according to the protocol provided by the FDA.

Table 1. Status of Developers of Authorized EUAs contacted for distribution of the FDA SARS CoV 2 Reference Panel

This table lists developers who were contacted for distribution of the FDA SARS-CoV-2 Reference Panel as of 10/9/2020 for panel shipping no later than 10/14/20.

Status Notes:

- Status of "Did not provide shipping information" indicates that no shipping information was received by 10/14/2020.
- Status of "Data not returned" indicates that no data was received as of 10/30/2020.

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Developer	Authorized Test	Status
1drop Inc.	1copy COVID-19 qPCR Multi Kit	Results in Table 2A
3B Blackbio Biotech India Ltd., a subsidiary of Kilpest India Ltd.	TRUPCR SARS-CoV-2 Kit	Did not provide shipping information
Abbott Diagnostics Scarborough, Inc.	ID NOW COVID-19	Results in Table 2B
Abbott Molecular	Abbott RealTime SARS-CoV-2 assay	Results in Table 2A
Abbott Molecular Inc.	Alinity m SARS-CoV-2 assay	Under interactive review
Access Bio, Inc.	CareStart COVID-19 MDx RT-PCR	Results in Table 2A
Access Genetics, LLC	OraRisk COVID-19 RT-PCR	Data not returned
Acupath Laboratories, Inc	Acupath COVID-19 Real-Time (RT-PCR) Assay	Results in Table 2A

Developer	Authorized Test	Status
Agena Bioscience, Inc.	MassARRAY SARS-CoV-2 Panel	Under interactive review
AIT Laboratories	SARS-CoV-2 Assay	Results in Table 2A
Alpha Genomix Laboratories	Alpha Genomix TaqPath SARS-CoV-2 Combo Assay	Results in Table 2A
altona Diagnostics GmbH	RealStar SARS-CoV-2 RT-PCR Kit U.S.	Data uninterpretable*
Altru Diagnostics, Inc.	Altru Dx SARS-CoV-2 RT-PCR assay	Results in Table 2A
Applied BioCode, Inc.	BioCode SARS-CoV-2 Assay	Results in Table 2A
Applied DNA Sciences, Inc.	Linea COVID-19 Assay Kit	Results in Table 2A
Aspirus Reference Laboratory	Aspirus SARS-CoV rRT Assay	Data not returned
Assurance Scientific Laboratories	Assurance SARS-CoV-2 Panel	Results in Table 2A
Atila BioSystems, Inc.	iAMP COVID-19 Detection Kit	Results in Table 2B
Avellino Lab USA, Inc.	AvellinoCoV2 test	Results in Table 2A
BayCare SARS-CoV-2 RT PCR Assay	BayCare SARS-CoV-2 RT PCR Assay	Results in Table 2A
Becton, Dickinson & Company	BD SARS-CoV-2 Reagents for BD MAX System	Results in Table 2A
Becton, Dickinson & Company (BD)	BioGX SARS-CoV-2 Reagents for BD MAX System	Results in Table 2A
Beijing Wantai Biological Pharmacy Enterprise Co., Ltd.	Wantai SARS-CoV-2 RT-PCR Kit	Did not provide shipping information
BGI Genomics Co. Ltd	Real-Time Fluorescent RT-PCR Kit for Detecting SARS-CoV-2	Results in Table 2A
BillionToOne, Inc.	qSanger-COVID-19 Assay	Data not returned

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* No patient matrix was used

** Test performed with nasopharyngeal swab and saliva, but data uninterpretable

FDA SARS-CoV-2 Reference Panel Results

Confirmed results from reference data sets received as of October 30, 2020, are shown in Table 2. No cross-reactivity with MERS-CoV has been observed unless otherwise specified.

Note: In the data in Table 2, a lower LoD represents a test's ability to detect a smaller amount of viral material in a given sample, signaling a more sensitive test. The FDA will continue to update the table as it receives results to provide laboratories, healthcare providers, and patients with a resource they can use to better inform which tests they select to use.

Table 2. Sensitivity Mean Estimates of the EUA authorized SARS-CoV-2 molecular diagnostic tests using the FDA SARS CoV-2 Reference Panel

Note: The current performance reflects the extraction/ instrument combination with the least sensitive LoD. For additional information please refer to the Instructions for Use of the assay.

Table 2A - Swabs in Transport Media

Swabs are collected and transported in media as per the Instructions for Use of each EUA. If several specimen types are authorized, nasopharyngeal (NP) swabs were recommended to use. The clinical matrix is spiked following the FDA-proposed dilution protocol and tested.

Notes:

- Nasopharyngeal swabs, unless otherwise noted. Transport media refers to Viral Transport Media (VTM), Universal Transport Media (UTM), phosphate-buffered saline (PBS), saline, etc.
- NDU/mL = NAAT Detectable Units/mL

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Product LoD (NDU/mL)	Developer	Test	Comments
180	PerkinElmer, Inc.	PerkinElmer New Coronavirus Nucleic Acid Detection Kit	
180	Viracor Eurofins Clinical Diagnostics	Viracor SARS-CoV-2 assay	
450	Zymo Research Corporation[1]	Quick SARS-CoV-2rRT-PCR Kit	

Product LoD (NDU/mL)	Developer	Test	Comments
540	ScienCell Research Laboratories	ScienCell SARS-CoV-2 Coronavirus Real-time RT-PCR (RT-qPCR) Detection Kit	
540	Fast Track Diagnostics Luxembourg S.á.r.l. (a Siemens Healthineers Company)	FTD SARS-COV-2	
600	BioCore Co., Ltd.	BioCore 2019-nCoV Real Time PCR Kit	
600	Bio-Rad Laboratories, Inc	Bio-Rad SARS-CoV-2 ddPCR Test	
600	DiaCarta, Inc	QuantiVirus SARS-CoV-2 Test kit	Results were obtained with the version of the test authorized on 4/08/2020
600	DiaCarta, Inc	QuantiVirus SARS-CoV-2 Multiplex Test Kit	
600	Hologic, Inc.	Panther Fusion SARS-CoV-2 Assay	
600	Hologic, Inc.	Aptima SARS-CoV-2 assay	
600	SEASUN BIOMATERIALS	U-TOP COVID-19 Detection Kit	
720	PrivaPath Diagnostics, Inc.[2]	LetsGetChecked Coronavirus (COVID-19) Test	
1800	Altru Diagnostics, Inc.	Altru Dx SARS-CoV-2 RT-PCR assay	
1800	Becton, Dickinson & Company (BD)	BioGX SARS-CoV-2 Reagents for BD MAX System	
1800	CirrusDx Laboratories	CirrusDx SARS-CoV-2 Assay	
1800	Euroimmun US, Inc.	EURORealTime SARS-Cov-2	
1800	Helix OpCo LLC (dba Helix)	Helix COVID-19 Test	
1800	LabGenomics Co., Ltd.	LabGun COVID-19 RT-PCR Kit	

Product LoD (NDU/mL)	Developer	Test	Comments
1800	OPTI Medical Systems, Inc.	OPTI SARS-COV-2 RT PCR Test	
1800	Quest Diagnostics Infectious Disease, Inc.	Quest SARS-CoV-2 rRT-PCR	
1800	Rheonix, Inc.	Rheonix COVID-19 MDx Assay	
1800	Roche Molecular Systems, Inc.	cobas SARS-CoV-2 & Influenza A/B	
1800	Roche Molecular Systems, Inc. (RMS)	cobas SARS-CoV-2	
1800	UMass Memorial Medical Center	UMass Molecular Virology Laboratory 2019-nCoV rRT-PCR Dx Panel	

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[1] Sputum
[2] Nasal swabs
[3] Oropharyngeal swabs
[4] Cross-reactivity with MERS-CoV was observed

Table 2B-Direct Swabs (Dry Swabs)

For devices authorized for use with dry swab specimens only, mock swabs are prepared by pipetting 50 µL of each diluted virus stock onto a swab. Dry swabs are let to dry for a minimum of 20 minutes, and the swab is tested following the Instructions for Use for the device.

Notes:

- Nasopharyngeal swabs, unless otherwise noted.
- NDU/mL = NAAT Detectable Units/mL

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Product LoD (NDU/mL)	Developer	Test
60000	Cue Health Inc.[a]	Cue COVID-19 Test

Product LoD (NDU/mL)	Developer	Test
180000	Atila BioSystems, Inc.	iAMP COVID-19 Detection Kit
300000	Abbott Diagnostics Scarborough, Inc.	ID NOW COVID-19
540000	Quidel Corporation	Lyra Direct SARS-CoV-2 Assay

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[a] Nasal swab

Table 2C-Saliva

Corroborated negative saliva is pooled. The volume of saliva that goes into the collection device is then spiked with the material at the same dilution as indicated for NP swabs (considering the replicates needed and an excess volume for the serial dilution). If the collection device is a dry container with nothing in it, the saliva is spiked and tested. However, if the collection device contains liquid, the saliva is mixed with virus and then the normal volume of collected saliva is added to the container to mimic the workflow. The volumes in the FDA-proposed dilution protocol may need to be adjusted to follow the device Instructions for Use.

Note: NDU/mL = NAAT Detectable Units/mL

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Product LoD (NDU/mL)	Developer	Test
600	Quadrant Biosciences Inc.	Clarifi COVID-19 Test Kit
3600	DxTerity Diagnostics, Inc.	DxTerity SARS-CoV-2 RT-PCR Test
5400	Clinical Reference Laboratory, Inc.	CRL Rapid Response
18000	Yale School of Public Health, Department of Epidemiology of Microbial Diseases	SalivaDirect
18000	Phosphorus Diagnostics LLC	Phosphorus COVID-19 RT-qPCR Test
54000	Fluidigm Corporation	Advanta Dx SARS-CoV-2 RT-PCR Assay
180000	Express Gene LLC, DBA: Express Gene Molecular Diagnostics Laboratory	Express Gene 2019-nCoV RT-PCR Diagnostic Panel

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