SARS-CoV-2 Viral Mutations: Impact on COVID-19 Tests

The SARS-CoV-2 virus has mutated over time, resulting in genetic variation in the population of circulating viral strains over the course of the COVID-19 pandemic. Molecular, antigen, and serology tests are affected by viral mutations differently due to the inherent design differences of each test.

This page provides information regarding the impact of viral mutations on COVID-19 tests, recommendations for clinical laboratory staff and health care providers, and information about certain tests for which the FDA has identified potential impacts on performance due to SARS-CoV-2 genetic mutations. The FDA will update this page as significant new information becomes available.

On this page:

Genetic Variations: Background and Considerations

A mutation (viral mutation or genetic mutation) of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) virus is a change in the genetic sequence of the SARS-CoV-2 virus when compared with a reference sequence such as Wuhan-Hu1 (the first genetic sequence identified) or USA-WA1/2020 (the first identified in the United States). A new variant (virus variant or genetic variant) of SARS-CoV-2 may have one or more mutations that differentiate it from the reference sequence or predominant virus variants already circulating in the population. Variants of SARS-CoV-2 can have different characteristics. For example, some may spread more easily or show signs of resistance to existing treatment options (/drugs/drug-safety-and-availability/fda-authorizes-revisions-fact-sheets-address-sars-cov-2-variants-monoclonal-antibody-products-under) and some may have no impact when compared with previous and currently circulating virus.

The presence of mutations in the SARS-CoV-2 virus in a patient sample can potentially impact test performance. The impact of mutations on a test's performance is influenced by several factors, including the sequence of the variant, the design of the test, and the prevalence of the variant in the population.

The FDA has collaborated with stakeholders to better understand the public health impact of new SARS-CoV-2 variants and their impact on test performance, has been routinely monitoring publicly available databases, and has coordinated efforts to evaluate the impact of new virus variants on tests that have received Emergency Use Authorization (EUA).

In February 2021, the FDA issued the Policy for Evaluating Impact of Viral Mutations on COVID-19 Tests (/regulatory-information/search-fda-guidance-documents/policy-evaluating-impact-viral-mutations-covid-19-tests) to provide a policy and recommendations on evaluating the potential impact of emerging and future viral mutations of SARS-CoV-2 on COVID-19 tests for the duration of the COVID-19 public health emergency, including considerations for test designs to minimize the impact of viral mutations and recommendations for ongoing monitoring.

General Information for Clinical Laboratory Staff and Healthcare Providers

Clinical laboratory staff and health care providers should be aware that false negative results may occur with any molecular test for the detection of SARS-CoV-2 if a mutation occurs in the part of the virus' genome assessed by that test. The FDA first alerted clinical laboratory staff and health care providers of this issue through a January 8, 2021 safety alert: Genetic Variants of SARS-CoV-2 May Lead to False Negative Results with Molecular Tests for Detection of SARS-CoV-2 - Letter to Clinical Laboratory Staff and Health Care Providers (/medical-devices/letters-health-care-providers/genetic-variants-sars-cov-2-may-lead-false-negative-results-molecular-tests-detection-sars-cov-2).

Changes in the viral genome can result in changes to viral proteins and, therefore, can also impact the performance of an antigen or serology test.

The FDA recommends clinical laboratory staff and health care providers who use SARS-CoV-2 tests:

- Be aware that genetic variants of SARS-CoV-2 arise regularly, and false negative test results can occur.
- Be aware that molecular tests that use multiple genetic targets to determine a final result are less likely to be impacted by increased prevalence of genetic variants.
- Consider negative results in combination with clinical observations, patient history, and epidemiological information.
- Consider repeat testing with a different EUA authorized or FDA cleared molecular diagnostic test (with different genetic targets) if COVID-19 is still suspected after receiving

a negative test result.

In addition to these general recommendations, the FDA is providing recommendations for the use of specific tests impacted by genetic variation in the section below.

Molecular Tests Impacted by SARS-CoV-2 Mutations

The FDA's analysis to date has identified the following EUA-authorized molecular tests whose performance could be impacted by SARS-CoV-2 viral mutations:

- Accula SARS-CoV-2 Test (Mesa Biotech Inc.)
- Linea COVID-19 Assay Kit (Applied DNA Sciences, Inc.)
- TaqPath COVID-19 Combo Kit (Thermo Fisher Scientific, Inc.)
- Xpert Xpress SARS-CoV-2, Xpert Xpress SARS-CoV-2 DoD, Xpert Omni SARS-CoV-2 (Cepheid)

Accula SARS-CoV-2 Test

- **Test Name (Link to EUA):** Accula SARS-CoV-2 Test (/media/136345/download)
- **Manufacturer:** Mesa Biotech Inc.
- **The FDA's Analysis:** Performance may be impacted when a SARS-CoV-2 patient sample having certain viral mutations is tested. The FDA previously alerted health care providers (/medical-devices/letters-health-care-providers/genetic-variants-sars-cov-2-may-lead-false-negative-results-molecular-tests-detection-sars-cov-2) about a potential performance impact due to a genetic mutation at positions 28881-28883 (GGG to AAC). In addition, there is potential impact on performance of the test due to a genetic mutation at positions 28877-28878 (AG to TC) in patient samples.
- **Potential Impact:** While the impact does not appear to be significant, the FDA is providing this information out of an abundance of caution.
- **Notes:** The FDA's analysis included information provided by the manufacturer.

  Recommendations for Clinical Laboratory Staff and Health Care Providers Using This Test

  Be aware that the current instructions for use for the Accula SARS-CoV-2 Test include the exact variant location, *in silico* analysis of the primer binding, and observed performance impact due to genetic mutation at positions 28881-28883 (GGG to AAC) when compared

with the perfect match target, but do not yet include specific information about impact from a genetic mutation at positions 28877-28878 (AG to TC).

Linea COVID-19 Assay Kit

- **Test Name (Link to EUA):** Linea COVID-19 Assay Kit (/media/138060/download)
- **Manufacturer:** Applied DNA Sciences, Inc.
- **The FDA's Analysis:** One of the two targets of the test has significantly reduced sensitivity due to certain mutations, including one of the mutations in the B.1.1.7 variant (UK VOC-202012/01).
- **Potential Impact:** Since this test is designed to detect multiple genetic targets, the overall test sensitivity should not be impacted. The pattern of detection when certain mutations are present may help with early identification of new variants in patients to reduce further spread of infection.
- **Notes:** The FDA's analysis included information provided by the manufacturer.

Recommendations for Clinical Laboratory Staff and Health Care Providers Using This Test

Be aware that one positive target and one negative target showing the S-gene drop out (reduced sensitivity with the S-gene target) when using the Linea COVID-19 Assay Kit is consistent with certain mutations, including those in the B.1.1.7 variant. If local or state clinical laboratories have access to quick turnaround whole genome sequencing services, such as those using the EUA-authorized Illumina COVIDSeq Test (/media/138778/download), these labs should consider further characterizing the specimen with genetic sequencing when this pattern is identified. If such services are not readily available, local or state clinical laboratories should consider reaching out to the Centers for Disease Control and Prevention at EOCenter177@cdc.gov (mailto:EOCenter177@cdc.gov) for additional information.

TaqPath COVID-19 Combo Kit

- **Test Name (Link to EUA):** TaqPath COVID-19 Combo Kit (/media/136113/download) (may also be labeled as the TaqPath COVID-19 Combo Kit Advanced)
- **Manufacturer:** Thermo Fisher Scientific, Inc.
- **The FDA's Analysis:** One of three targets of the test has significantly reduced sensitivity due to certain mutations, including one of the mutations in the B.1.1.7 variant (UK VOC-202012/01).

- **Potential Impact:** Since this test is designed to detect multiple genetic targets, the overall test sensitivity should not be impacted. The pattern of detection when certain mutations are present may help with early identification of new variants in patients to reduce further spread of infection.
- **Notes:** The FDA's analysis included information provided by the manufacturer and multiple reports from clinical laboratories.

Recommendations for Clinical Laboratory Staff and Health Care Providers Using This Test

Be aware that two positive targets and one negative target showing the S-gene drop out (reduced sensitivity with the S-gene target) when using the TaqPath COVID-19 Combo Kit is consistent with certain mutations, including those in the B.1.1.7 variant. If local or state clinical laboratories have access to quick turnaround whole genome sequencing services, such as those using the EUA-authorized Illumina COVIDSeq Test (/media/138778/download), these labs should consider further characterizing the specimen with genetic sequencing when this pattern is identified. If such services are not readily available, local or state clinical laboratories should consider reaching out to the Centers for Disease Control and Prevention at EOCenter177@cdc.gov (mailto:EOCenter177@cdc.gov) for additional information.

Xpert Xpress SARS-CoV-2, Xpert Xpress SARS-CoV-2 DoD, Xpert Omni SARS-CoV-2

- **Test Name (Link to EUA):** Xpert Xpress SARS-CoV-2 (/media/136316/download); Xpert Xpress SARS-CoV-2 DoD (/media/144790/download); Xpert Omni SARS-CoV-2 (/media/144029/download)
- **Manufacturer:** Cepheid
- **The FDA's Analysis:** While it is generally unexpected that a single point mutation will impact test performance for most SARS-CoV-2 molecular tests, the FDA's analysis indicates that the Cepheid tests are impacted by a single point mutation in the target area of the test. There are reports noting that two independent single point mutations reduce the test's sensitivity for detecting the N2 target. The E target is still detected when enough virus is present leading to a "presumptive positive" result in the Xpert Xpress SARS-CoV-2 and Xpert Xpress SARS-CoV-2 DoD tests. Detection of the E target without detecting the N2 target will be reported as "positive" in the Xpert Omni SARS-CoV-2 (/media/144029/download)
- **Potential Impact:** Since this test is designed to detect multiple genetic targets, and these mutations do not lead to a false negative patient result (instead reporting as "presumptive

positive" or "positive" based on detection of the conserved E gene target), the impact on test performance does not appear to be significant. However, the FDA is providing this information out of an abundance of caution. The FDA's analysis suggests that the impact of a single point mutation on the test performance is associated with the unique chemistry of the Cepheid tests.

- **Notes:** The FDA continues to gather additional information and work with the manufacturer to address this issue.

Recommendations for Clinical Laboratory Staff and Health Care Providers Using This Test

Be aware of the current instructions for use for each test, especially the "Possible Results" and "Results and Interpretation" tables, which describe when a result is positive, presumptive positive, negative, and invalid, and how to interpret each result. Specifically, "SARS-CoV-2 Presumptive Positive" results may indicate the presence of SARS-CoV-2 nucleic acids, and repeat testing may be indicated; refer to the authorized instructions for use. Clinical laboratory staff and health care providers should contact Cepheid if they have any questions or concerns or suspect an issue with their Cepheid test.