SARS-CoV-2 variants

Viruses constantly change through mutation, and new variants of a virus are expected to occur over time. Sometimes new variants emerge and disappear. Other times, new variants emerge and persist. Many variants of the virus that cause COVID-19 have been detected globally during this pandemic. A variant may contain one or multiple mutations and these mutations can occur in locations such as the nucleocapsid protein or the spike protein region of the virus.

What is a "Variant of Concern" (VOC)?

A variant may be classified as "Of Concern" when there is evidence of an increase in transmissibility (including a growth rate potentially compatible with displacing the current dominant variant), increase in disease severity, significant reduction in neutralization by antibodies, reduced effectiveness of treatments or diagnostic detection failures. [6, 10]

The LumiraDx SARS-CoV-2 tests and variants

The LumiraDx SARS-CoV-2 Ag, LumiraDx, SARS-CoV-2 Ag Pool, LumiraDx SARS-CoV-2 Ag Ultra, LumiraDx SARS-CoV-2 Ag Ultra Pool, LumiraDx SARS-CoV-2 & Flu A/B and LumiraDx SARS-CoV-2 & RSV tests use antibodies (not nucleic acid based-primers like PCR) to capture SARS-CoV-2 nucleocapsid antigen (not the spike protein). Antibodies typically recognize 9-10 amino acid target sequences (equivalent to 27-30 nucleotide sequences). Thus, single nucleic acid point mutations are not likely to affect the performance of the LumiraDx tests. Furthermore, mutations outside of the nucleocapsid viral coding region (eg. Spike protein) are highly unlikely to have an effect on the performance of the test.

Testing status of SARS-CoV-2 variants with the LumiraDx tests

LumiraDx is actively monitoring for new mutations in the SARS-CoV-2 viral genome as they arise. The reactivity of the LumiraDx tests is assessed against all mutations prevalent in the population at a level of greater than 1.0% on the Regeneron COVID-19 Dashboard[1] which is one of the collaborations enabled by the data in the **gisaid.org** website. The LumiraDx SARS-CoV-2 Ag assay is used in the LumiraDx SARS-CoV-2 Ag test, LumiraDx SARS-CoV-2 Ag Pool test, LumiraDx SARS-CoV-2 & Flu A/B test, LumiraDx SARS-CoV-2 Ag Ultra test, LumiraDx SARS-CoV-2 Ag Ultra Pool test and LumiraDx SARS-CoV-2 & RSV test. Table 1 is a summary of the performance of this assay with Variants of Concern as designated by the WHO[6] at the time of writing this technical bulletin. Evaluation has been carried out using *in silico* analysis, direct testing using recombinant nucleocapsid protein containing the specific mutations, live viral culture testing and testing of positive live clinical samples.

Table 1: Summary of testing with the LumiraDx Ag test

WHO label[6]	Pango lineage[6]	Country in which first detected[6]	Nucleocapsid mutation[1]	LumiraDx Test Result
Alpha*	B.1.1.7	UK, Sep 2020	D3L, R203K, G204R, S235F	Positive
Beta*	B.1.351	South Africa, May 2020	T205I	Positive
Gamma*	P.1	Brazil, Nov 2020	P80R, R203K, G204R	Positive
Delta*	B.1.617.2	India, Oct 2020	D63G, R203M, G215C, D377Y	Positive
Omicron**	B.1.1.529	Multiple countries, Nov 2021	R203K, G204R, P13L, E31-, R32- and S33-	Positive

*No longer VOC

**Includes BA.1, BA.2, BA.3, BA.4, BA.5 and descendent lineages such as BQ.1 and BQ.1.1. It also includes recombinant forms such as XE and XBB.1.5. BA.1 has the same nucleocapsid mutations as B.1.1.529. Descendent Pango lineages of Omicron, BA.2, BA.3, BA.4, BA.5, BQ.1, BQ.1.1, XE and XBB.1.5, have the additional nucleocapsid mutation S413R. BA.4 also contains the nucleocapsid mutation P151S. BQ.1 and BQ.1.1 also contain the nucleocapsid mutation E136D. All nucleocapsid mutations were tested in-house using recombinant protein and tested positive at 50 pg/mL on the LumiraDx SARS-CoV-2 Antigen test.

- **Alpha Variant[2], Beta Variant[3] and Gamma Variant[3] –** Detection was demonstrated in patient samples by UK Department of Health and Social Care, COVID-19 Technologies Validation Group.
- **Beta Variant[4] –** Detection was demonstrated in patient samples by the South African National Health Laboratory Service.
- **Delta Variant[5] –** Detection was demonstrated in patient samples as discussed by the UK Department of Health and Social Care, COVID-19 Technologies Validation Group.
- **Omicron Variant –** Testing with patient live samples was completed by LumiraDx.[8] In addition, a prospective clinical study was carried out by Medical Research Network Diagnostics.[9] Both studies showed that Omicron is detected by the LumiraDx SARS-CoV-2 Ag test with comparable sensitivity to the Delta variant.

In addition, the LumiraDx SARS-CoV-2 Ag test has been evaluated as part of the Foundation for Innovative New Diagnostics (FIND) process (www.finddx.org). For the COVID-19 response, FIND has commissioned independent evaluations of in vitro diagnostics following an Expression of Interest (EOI) process available on FIND's website by which all test submissions were scored according to their regulatory status and time to market, the manufacturing and distribution capacity of the supplier and the supplier-reported clinical and analytical performance.

As part of this evaluation, the Analytical sensitivity, i.e., Limit of detection (LoD), was performed at the Liverpool School of Tropical Medicine, U.K in which standardized serial dilutions of cultured viral isolate were prepared. Viral dilution was applied directly to the LumiraDx SARS-CoV-2 Ag test strip. Dilutions were tested in triplicate and the LoD was defined as the last dilution where all repeats were interpreted as positive. The data (Table 2) demonstrate that the LumiraDx SARS-CoV-2 Ag test can detect the U.K Wild Type (B.1), Alpha (B.1.1.7), Gamma (P.1), Delta (B.1.617.2) and Omicron (B.1.1.529 and B.1.1.529 sub lineage BA.2) variants.

Table 2: Estimation of analytical performance carried out by the Liverpool School of Tropical Medicine, demonstrating comparable LoD across all variants tested.

Variant strain	Verified LoD concentration
UK Wild type (B.1)[7]	1.0 x 10^2 pfu/mL
Alpha (B.1.1.7)[7]	5.0 x 10^2 pfu/mL
Gamma (P.1)[7]	1.0 x 10^2 pfu/mL
Delta (B.1.617.2)[7]	2.5 x 10^1 pfu/mL
Omicron (B.1.1.529)[11]	1.0 x 10^3 pfu/mL
Omicron (B.1.1.529) sub lineage BA.2[12]	1.0 x 10^2 pfu/mL

Conclusion

All testing to date has demonstrated that the LumiraDx SARS-CoV-2 Ag test can detect all the SARS-CoV-2 variants of concern with comparable sensitivity.

Definitions

Ag	Antigen
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
VOC	Variant of concern
WHO	World Health Organisation
PCR	Polymerase Chain Reaction
LoD	Limit of Detection
FIND	Foundation for Innovative New Diagnostics
pg	Picogram
pfu	Plaque Forming Unit

1. GISAID Regeneron Database (Regeneron COVID-19 Dashboard) accessed December 2022
2. UK Department of Health and Social Care (UK DHSC), COVID-19 Technologies Validation Group (TVG) report on LumiraDx SARS-CoV-2 Antigen test Report (January 2021)
3. UK DHSC COVID-19 TVG: Personal Communication by email (March 2021) Data on File
4. South African National Health Laboratory Service: Laboratory Evaluation Report (April 2021) Data on File
5. UK DHSC COVID-19 TVG: Personal Communication (Data on File May 2021)
6. World Health Organisation (https://www.who.int/en/activities/tracking-SARS-CoV-2-variants/) Accessed December 2022
7. FIND Report on the LumiraDx SARS-CoV-2 Ag test https://www.finddx.org/wp-content/uploads/2021/10/Lumira_Ag-Public-Report_v2_20211008.pdf
8. Data on File (Jan 2022)
9. Data on File (Feb 2022)
10. https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/1063424/Tech-Briefing-39-25March2022_FINAL.pdf
11. Data on File (Feb 2022)
12. Data on File (May 2022)

Not all products are available in all countries and regions. Please check with your local LumiraDx sales representative or distributor for availability in specific markets.

The LumiraDx, SARS-CoV-2 Ag Pool, LumiraDx SARS-CoV-2 Ag Ultra, LumiraDx SARS-CoV-2 Ag Ultra Pool, LumiraDx SARS-CoV-2 & Flu A/B and LumiraDx SARS-CoV-2 & RSV tests are not available in the US.