

CoDx - REGULATORY BULLETIN

Salt Lake City, December 7th, 2021

Re: Response to request for information on the impact of new SARS-CoV-2 variants of interest and variants of concern on the performance of SARS-CoV-2 molecular IVD test kits designed, developed, and manufactured by Co-Diagnostics, Inc. (Salt Lake City, USA)

The World Health Organization and other agencies around the world are currently tracking the predominant circulating and emerging SARS-CoV-2 variants to proactively anticipate their possible impact on public health.

On November 26, 2021, the WHO classified a new variant, B.1.1.529 (Omicron) first identified in South Africa and several other countries as a Variant of Concern (VOC).

According to the WHO, MHRA (UK), and CDC (US), there are currently five Variants of Concern (VOC) (Alpha, Beta, Gamma, Delta, and Omicron). An additional seven variants are currently listed by two or all three entities as Variants of Interest and/or Variants Under Investigation (VOI/VUI) (Eta, Zeta, Iota, Kappa, Lambda, Mu, and B.1.617.3).

Table 1 shows a current list of the VOC identified by WHO, MHRA, or CDC, as well as VOI/VUI listed by two or more entities.

Table 1 SARS-CoV-2 Genomic Variants Currently Classified as Variants of Concern or Interest

Variant of Concern / Interest Status by Agency	WHO Nomenclature	Pango Lineage	Nextstrain Clade	Designation	First detected, Date	BEI Reference Material Number
VOC [WHO, MHRA, CDC]	Alpha	B.1.1.7	20I (V1)	WHO: 18-Dec-20 MHRA: VOC-20DEC-01 CDC: Date not available	UK, Sep-2020	NR-54000
VOC [WHO, MHRA, CDC]	Beta	B.1.351	20H (V2)	WHO: 18-Dec-20 MHRA: VOC-20DEC-02 CDC: Date not available	South Africa, May-2020	NR-55282
VOC [WHO, MHRA, CDC]	Gamma	P.1	20J (V3)	WHO: 11-Jan-2021 MHRA: VOC-21JAN-02	Japan/Brazil, Nov-2020	NR-54982
VOC [WHO, MHRA, CDC]	Delta	B.1.617.2	21A	WHO: VOI-4-Apr-21/ VOC-11-May-21 MHRA: VOC-21APR-02 CDC: VOI-4-May-21 VOC-15-Jun-21	India, Oct-2020	NR-55611
VOC [WHO]	Omicron	B.1.1.529	21K	WHO: 26-Nov-2021	Multiple countries, Nov-2021	N/A
VOI [WHO, MHRA, CDC]	Eta	B.1.525	21D	WHO: VOI-17-Mar-2021 MHRA: VUI-21FEB-03	United Kingdom and Nigeria, Dec-2020	NR-55705
VUI [MHRA, CDC]	Zeta	P.2	20B	CDC: VBM-21-Sep-2021 MHRA: VUI-01-Jan-2021	Brazil, Apr-2020	NR-55439
VOI [WHO, CDC]	Iota	B.1.526	21F	WHO: VOI-24-Mar-21 CDC: VOI-21-Apr-21	United States (New York), Nov-2020	NR-55359
VOI [WHO, MHRA, CDC]	Kappa	B.1.617.1	21B	WHO: VOI-4-Apr-2021 MHRA: VUI-21APR-01 CDC: VOI-4-May-21	India, Oct-2020	NR-55486

Variant of Concern / Interest Status by Agency	WHO Nomenclature	Pango Lineage	Nextstrain Clade	Designation	First detected, Date	BEI Reference Material Number
VOI [MHRA, CDC]	None	B.1.617.3	20A	MHRA: VUI-21APR-03 CDC: VOI-4-May-21	India, Oct-2020	N/A
VOI [WHO, MHRA]	Lambda	C.37	21G	WHO: VOI-14-Jun-2021 MHRA: VUI-21JUN-01	Peru, Dec-2020	NR-55654
VOI [WHO, MHRA]	Mu	B.1.621	21H	WHO: VOI-30-Aug-2021 MHRA: VUI-21JUL-1	Colombia, Jan-2021	N/A

Note: VOC – Variant of Concern, VOI – Variant of Interest, VUI – Variant Under Investigation, VBM – Variant Being Monitored, WHO – World Health Organization, MHRA – Medicines and health Products Regulatory Agency (UK), CDC – Centers for Disease Control and Prevention (US)

The WHO has reported that PCR testing continues to effectively detect the B.1.1.529 (Omicron) variant, and that studies are currently underway to assess its impact on antigen-based rapid diagnostic tests. (WHO, 2021)

Since the initial design of CoPrimers targeting Gene RdRp and Gene E in Feb-2020, Co-Diagnostics has conducted monthly BLASTn queries of subsampled sequences in the Nextstrain database to monitor their homology against emerging strains. These in silico analyses confirm that none of the mutations related to the lineages B.1.1.529 (Omicron), B.1.1.7 (Alpha) (Public Health England, 2020) (Rambaut, et al., 2020), B.1.351 (Beta), P.1 (Gamma), B.1.525 (Eta), P.2 (Zeta), B.1.526 (Iota), B.1.617.1 (Kappa), B.1.617.3, C.37 (Lambda), or B.1.621 (Mu) occur in regions of RdRp or Gene E targeted by any COVID-19 tests designed and manufactured by Co-Diagnostics.

In April 2021, the WHO identified lineage B.1.167.2 (Delta) (PANGO lineages, 2021) as a Variant of Interest, and in June 2021 it was recategorized by the CDC as a Variant of Concern. This Delta lineage contains one point mutation in the region targeted by the RdRp Fwd (Forward) CoPrimer. As shown in **Table 2**, this CoPrimer is used in all COVID-19 tests designed and manufactured by Co-Diagnostics.

Table 2 COVID-19 Tests Designed and Manufactured by Co-Diagnostics, Inc.

Test Name	Product Code	Gene RdRp (CoPrimer RdRp Fwd / CoPrimer RdRp Rev)	Gene E (CoPrimer E Fwd / CoPrimer E Rev)
Logix Smart™ Coronavirus Disease 2019 (COVID-19)	COVID-K-001	Yes	No
Logix Smart SARS-CoV-2 (genes RdRp/E)	COVID-K-002	Yes	Yes
Logix Smart ABC (Influenza A/B, SARS-CoV-2)	ABC-K-001	Yes	Yes
	ABC-K-002	Yes	Yes
Logix Smart SARS-CoV-2 DS	COVDS-K-003	Yes	Yes
	COVDS-K-004	Yes	Yes

Since June 2021, Delta has expanded to represent a growing proportion of subsampled sequences in the Nextstrain database, as reflected in the monthly homology statistics for RdRp and E Gene Targets of Co-Diagnostics COVID-19 tests shown in **Table 3** and **Table 4**.

Table 3 In Silico Analysis Performed Over Time for RdRp Gene Target

Date of CoDx's Analysis for RdRp Marker	SARS-CoV-2 (number of sequences in analyzed subsample)	Sequences in the pool with 100% homology	Single nucleotide mutation events: Sequences with 1 mismatch on CoDx target (98% homology)	Double nucleotide mutation events: Sequences with 2+ mismatches on CoDx target (95% homology)	Multiple nucleotide mutation events: Sequences with 3+ mismatches on CoDx target <95% homology)
27-Jan-20	14	14 (100%)	0 (0%)	0 (0%)	0 (0%)
04-Feb-20	53	53 (100%)	0 (0%)	0 (0%)	0 (0%)
17-Mar-20	571	570 (99.8%)	1 (0.2%)	0 (0%)	0 (0%)
06-Apr-20	3639	3634 (99.86%)	5 (0.14%)	0 (0%)	0 (0%)
04-May-20	4468	4459 (99.80%)	9 (0.2%)	0 (0%)	0 (0%)
03-Jun-20	4558	4537 (99.54%)	21 (0.46%)	0 (0%)	0 (0%)
06-Jul-20	11361	11328 (99.71%)	33 (0.29%)	0 (0%)	0 (0%)
10-Aug-20	22054	22012 (99.81%)	42 (0.19%)	0 (0%)	0 (0%)
09-Sep-20	4417	4394 (99.48%)	23 (0.52%)	0 (0%)	0 (0%)
12-Oct-20	5139	5114 (99.51%)	25 (0.49%)	0 (0%)	0 (0%)
05-Nov-20	3494	3463 (99.11%)	31 (0.89%)	0 (0%)	0 (0%)
04-Dec-20	3407	3371 (98.94%)	36 (1.06%)	0 (0%)	0 (0%)
04-Jan-21	3540	3505 (99.01%)	35 (0.99%)	0 (0%)	0 (0%)
04-Feb-21	3962	3909 (98.66%)	53 (1.34%)	0 (0%)	0 (0%)
01-Mar-21	4024	3960 (98.41%)	64 (1.59%)	0 (0%)	0 (0%)
07-Apr-21	4025	3962 (98.43%)	63 (1.57%)	0 (0%)	0 (0%)
06-May-21	3923	3847 (98.06%)	76 (1.94%)	0 (0%)	0 (0%)
01-Jun-21	3883	3000 (97.86%)	83 (2.14%)	0 (0%)	0 (0%)
06-Jul-21	3883	3566 (91.84%)	317 (8.17%)	0 (0%)	0 (0%)
02-Aug-21	3782	3172 (83.87%)	610 (16.13%)	0 (0%)	0 (0%)
01-Sep-21	3534	2894 (81.89%)	637 (18.02%)	3 (0.08%)	0 (0%)
01-Oct-21	3559	2882 (80.98%)	672 (18.88%)	5 (0.14%)	0 (0%)
01-Nov-21	3572	1648 (46.14%)	1919 (53.72%)	5 (0.14%)	0 (0%)
06-Dec-21	3386	1239 (36.59%)	2140 (63.20%)	7 (0.21%)	0 (0%)

Table 4 In Silico Analysis Performed Over Time for Gene E Target

Date of CoDx's Analysis for Gene E Marker	SARS-CoV-2 (number of sequences in analyzed subsample)	Sequences in the pool with 100% homology	Single nucleotide mutation events: Sequences with 1 mismatch on CoDx target (98% homology)	Double nucleotide mutation events: Sequences with 2+ mismatches on CoDx target (95% homology)	Multiple nucleotide mutation events: Sequences with 3+ mismatches on CoDx target <95% homology)
27-Jan-20	14	14 (100%)	0 (0%)	0 (0%)	0 (0%)
04-Feb-20	53	53 (100%)	0 (0%)	0 (0%)	0 (0%)
09-Sep-20	4417	4400 (99.62%)	14 (0.32%)	2 (0.05%)	1 (0.02%)
12-Oct-20	5139	5126 (99.96%)	11 (0.21%)	0 (0%)	2 (0.04%)
05-Nov-20	3494	3478 (99.54%)	16 (0.46%)	0 (0%)	0 (0%)
04-Dec-20	3407	3397 (99.71%)	10 (0.29%)	0 (0%)	0 (0%)
04-Jan-21	3540	3530 (99.72%)	10 (0.28%)	0 (0%)	0 (0%)
04-Feb-21	3962	3944 (99.55%)	18 (0.45%)	0 (0%)	0 (0%)
01-Mar-21	4024	3999 (99.38%)	25 (0.62%)	0 (0%)	0 (0%)
07-Apr-21	4025	3991 (99.16%)	34 (0.84%)	0 (0%)	0 (0%)
06-May-21	3923	3870 (98.65%)	53 (1.35%)	0 (0%)	0 (0%)
01-Jun-21	3883	3820 (98.38%)	63 (1.62%)	0 (0%)	0 (0%)
06-Jul-21	3883	3823 (98.45%)	59 (1.52%)	0 (0%)	1 (0.03%)
02-Aug-21	3782	3723 (98.44%)	58 (1.53%)	0 (0%)	1 (0.03%)
01-Sep-21	3534	3476 (98.36%)	56 (1.58%)	2 (0.06%)	0 (0%)
01-Oct-21	3559	2882 (98.76%)	44 (1.24%)	0 (0%)	0 (0%)
01-Nov-21	3572	3527 (98.74%)	44 (1.23%)	1 (0.03%)	0 (0%)
06-Dec-21	3386	3527 (99.03%)	33 (0.97%)	0 (0%)	0 (0%)

As in any other primer used in qPCR techniques, the single mismatch caused by the Delta point mutation is not expected to prevent primer binding or functionality toward the SARS-CoV-2 genome. In theory, a single CoPrimer with 2 mismatches is expected to retain sensitivity with marked Ct delay and with 3+ mismatches, a CoPrimer is expected to have serious impairment (U.S. FDA, 2021) (FDA, 2021).

In addition, the qualitative detection of SARS-CoV-2 by more than 1 redundant marker minimizes the expected impact of a point mutation in any single CoPrimer or assay. As demonstrated by

Table 2, only COVID-K-001 has a single marker, all the other products, COVID-K-002, ABC-K-001, and COVDS-K-003 / COVDS-K-004 target at least 2 markers.

As discussed previously, although the Co-Diagnostics risk analysis did not indicate that loss of sensitivity was likely with any of the products listed in **Table 2**. The impact of the single point mutation in lineage Delta was analyzed for Tm impact on COVID-K-001. The impact on Tm was determined to be modest, and the affected portion of the CoPrimer retained a predicted annealing temperature above that used in the validated thermocycling protocols. Therefore, the predicted Tm impact analysis corroborated the previous risk determination that sensitivity toward Delta was unlikely to be affected. As a final analysis, synthetic RNAs were obtained with the Wild Type sequence and with the single point mutation present in the Delta lineage. The wet testing analysis confirmed that both RNAs exhibited estimated and confirmed Limits of Detection (LoD) within the 3-fold limit set as the acceptance criterion.

Based on these evaluations, Co-Diagnostics remains confident that all Logix Smart SARS-CoV-2 assays, namely COVID-K-001, COVID-K-002, ABC-K-001, and COVDS-K-003/COVDS-K-004, retain full sensitivity for lineages classified as Variants of Concern (VOC) or Variants of Interest (VOI) at this time, including the recently identified Omicron, Alpha, Beta, Gamma, Delta, Eta, Zeta, Iota, Kappa, B.1.617.3, Lambda, and Mu, as well as other emerging variant sequences present in monthly analyses of the Nextstrain database thus far.

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