SD BIOSENSOR

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Issue number: BA200-20221117-QA1

November 17th, 2022

Subject : Notification of internal test results for SARS-CoV-2 variants (Version 7.06)

Dear valued customers,

We, SD Biosensor, Inc., would like to inform you that STANDARD™ F products for SARS-CoV-2 diagnostic are not affected by **"Alpha(B.1.1.7), Beta(B.1.351), Gamma(P.1), Delta(B.1.617.2), Kappa(B.1.617.1) , Epsilon(B.1.429), Iota(B.1.526), Lambda(C.37), Zeta(P.2), Mu(B.1.621), Omicron(B.1.1.529, BA.1, BA.2, BA.3, BA.4.1, BA.5, BA.2.75, BF.7, BF.14, BJ.1, BQ.1.1, BA.4.6, BA.2.75.2, BA.2.12.1, BA.5.1, BA.5.2, BA.2.3.20, XBB, BA.2.10, BM.1.1.1, BS.1) SARS-CoV-2 variants"**. The list of applicable STANDARD™ F products is as follows.

No.	Product Name	Reference No.
1	STANDARD™ F COVID-19 Ag FIA	F-NCOV-01G
2	STANDARD™ F COVID/Flu Ag Combo FIA	F-CVFL-01C

We verified this through internal test, and detailed information about it is below.
Mutations commonly found in the Alpha (B.1.1.7), Beta(B.1.351), Gamma(P.1), Delta(B.1.617.2), Kappa(B.1.617.1), Epsilon(B.1.429), Iota(B.1.526), Lambda(C.37), Zeta(P.2), Omicron(BA.1, BA.2, BA.3, BA.4.1, BA.5) variants as well as the variants listed in part 1, analytical sensitivity, have been wet-lab tested using recombinant proteins, in the combinations indicated in the table in part 1 and no impact was observed in test performance. The mutations commonly found in the respective strains and in the Omicron(B.1.1.529, BA.2.75, BF.7, BF.14, BJ.1, BQ.1.1, BA.4.6, BA.2.75.2, BA.2.12.1, BA.5.1, BA.5.2, BA.2.3.20, XBB, BA.2.10, BM.1.1.1, BS.1) variant *(see the table in part 2, in-silico analysis)* have been analyzed in-silico, and no impact on performance is expected.

0. Monitoring information

0.1 Circulating mutations in nucleocapsid (N) protein

On a monthly basis, viral genomic sequences of the circulating strains will be gathered using GISAID. The most recent 2000 complete and high coverage entries will be analyzed at least monthly against the reference sequence (Wuhan-Hu-1/2019), and all non-synonymous mutations in the N protein will be identified. The percentage of single mutations and mutation combinations in the N protein will be analyzed. All mutations present in > 5% of the circulating isolates will be defined as "Relevant Mutations".

0.2 Variants of Concern/Interest globally

Additionally, Variants of Concern (VoCs) and Variants of Interest (VoIs) by the WHO and the European Centre for Disease Prevention and Control (ECDC), as well as Variants Being Monitored (VBMs), VOIs, VOCs and Variants of High Consequence (VOHCs) by the US CDC will be monitored regularly. Isolates from all variants listed above will be monitored on GISAID. The most recent 2000 complete and high coverage entries per variant will be analyzed against the reference sequence (Wuhan-Hu-1/2019), and all non-synonymous mutations in the N protein will be identified. The percentage of single mutations and mutation combinations in the N protein will be analyzed. All mutations present in > 5% of the variant will be defined as "Relevant Mutations" as well.

1. Analytical sensitivity

1.1 Purpose of test

The purpose of this test is to verify that the sensitivity of STANDARD™ F products is not affected by SARS-CoV-2 variants by using synthetic recombinant proteins.

1.2 Specimen of test

1) Specimen (Positive)

Since STANDARD™ F products target nucleocapsid protein (hereafter, N protein), recombinant N protein of 32 variants were synthesized and used as positive specimen.

#	Pango lineage	GISAID ACCESSION ID. EPI_ISL	WHO label
1-1	B	402125	N/A
1-2	B.1.1.7	835226	*Alpha
1-3	B.1.351	660190	*Beta
1-4	P.1	792680	*Gamma
1-5	B.1.617.1	1360306	N/A
1-6	B.1.617.1	1789542	N/A
1-7	B.1.617.1	1620161	N/A
1-8	B.1.617.1	1545312	N/A
1-9	B.1.617.1	1823120	N/A

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1-10	B.1.617.1	1904467	N/A
1-11	B.1.617.1	1660436	N/A
1-12	B.1.617.1	1913208	N/A
1-13	B.1.617.1	1969991	N/A
1-14	B.1.617.2	1970310	*Delta
1-15	B.1.617.2	1660458	*Delta
1-16	B.1.617.2	1807318	*Delta
1-17	B.1.617.2	1913205	*Delta
1-18	A.23.1	925892	N/A
1-19	B.1.429	1771435	Epsilon
1-20	B.1.526.2	1080752	N/A
1-21	B.1.526	1227165	Iota
1-22	B.1.617.3	1704494	N/A
1-23	C.36	1936140	N/A
1-24	C.37	1111296	Lambda
1-25	P.2	1182578	Zeta
1-26	B.1.616	1239370	N/A
1-27	C.1.2	3164100	N/A
1-28	BA.1	6640917	Omicron
1-29	BA.2[1)]	7190366	Omicron
1-30	BA.4.1[2)]	12043292	Omicron
1-31	BA.5	11903045	Omicron
1-32	BA.5	12307612[a)]	Omicron

1) In the case of BA.3 variant, wet-testing is omitted since the mutation sites of N protein are same as BA.2.
2) BA.4.1 (hCoV-19/South Africa/NCV1112/2022) was first designated as BA.4 on April 14, 2022, and re-designated on May 22, 2022 (from pango-designation issue #548).
a) Accession number of 12307612 is BA.5 sub-lineage with very small portion (7.93% by GISAID, 2022.07.29)
** Previously circulating Variants of Concerns*
*** Previously circulating Variants of Interest*
**** Formerly Monitored Variants*

2) Specimen (Negative)

ID	PCR result
*Negative human swab	Negative

** Negative human swabs were collected from healthy donors and were confirmed to be negative by PCR (US FDA EUA approved, STANDARD M nCoV Real-Time Detection kit, CFX96).*

3) Test strip
3 LOTs of test strips were used for the test.

1.3 Method of test

1) Each of the recombinant N proteins was diluted in successive concentrations.
2) The dilutions were spiked with a swab.
3) The spiked swab was tested in the same method as the IFU.
4) Dilutions of the recombinant N proteins were tested repeatedly 20 times for each LOT of test strips.

1.4 Result of test

The recombinant N protein of 32 variants showed a similar limit of detection to the Wuhan-Hu-1 recombinant N protein (#1-1) used as a positive control. Therefore, it was confirmed that the sensitivity of the STANDARD™ Q product was not affected by the 32 variants.

2. In-silico analysis

2.1 Purpose of test

The purpose of this test is to theoretically verify that STANDARD™ F products are not affected by SARS-CoV-2 variants.

2.2 Method of test

1) Compare the region where the variant was mutated (hereinafter, mutation site) with the region that STANDARD™ F targets to detect SARS-CoV-2 (hereinafter, epitope region).
2) If the mutation site corresponds to the epitope region, it is predicted that there is a possibility of affecting the STANDARD™ F product, and the evaluation result is marked with 'P'.
3) If the mutation site does not correspond to the epitope region, it is predicted that there is no possibility of affecting the STANDARD™ F product, and the evaluation result is marked with 'N'.

2.3 Result of test

As a result of in-silico analysis of 73 variants, the mutation sites of 3 variants (#2-14: 1239370, #2-31: 1969991, #2-62: 14167044) corresponded to the epitope region. However, it was confirmed that #2-14 and #2-31 did

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not affect the sensitivity of STANDARD™ F products through the test for analytical sensitivity (#1-26 and #1-13).

#	Pango lineage	GISAID ACCESSION ID. EPI_ISL	Dominant Mutation site (amio acid number)	Result (P or N)
2-1	B	402125	N/A (as standard)	N/A
2-2	A.23.1	925892	202	N
2-3	AT.1	2385327	67, 203, 204	N
2-4	AT.1	1259283	203, 204	N
2-5	B.1.1.7	835226	3, 203, 204, 235	N
2-6*	B.1.351	660190	205	N
2-7*	B.1.427	1060793	205	N
2-8	B.1.429	1771435	205, 234	N
2-9*	B.1.429	1194304	205	N
2-10	B.1.525	2432518	2, 12, 205	N
2-11	B.1.526.1	2204920	205, 234	N
2-12	B.1.526.2	1080752	13, 202	N
2-13	B.1.526	1227165	199, 234	N
2-14	B.1.616	1239370	325	P
2-15	B.1.617.1	1360306	203, 377	N
2-16	B.1.617.2	1508996	63, 203, 215, 377	N
2-17	B.1.617.3	1704494	67, 203, 377	N
2-18	B.1.621*	1582980	205	N
2-19	C.36	1936140	203, 204, 212	N
2-20	C.37	1111296	13, 203, 204, 214, 366	N
2-21	P.1	792680	80, 203, 204	N
2-22	P.2	1182578	119, 203, 204, 234	N
2-23	P.3	1213573	203, 204	N
2-24	B.1.617.1	1789542	203, 377, 385	N
2-25	B.1.617.1	1620161	3, 203, 377	N
2-26	B.1.617.1	1545312	203, 204	N
2-27	B.1.617.1	1823120	203, 236, 377	N
2-28	B.1.617.1	1904467	3, 13, 203, 243, 377	N
2-29	B.1.617.1	1660436	3, 63, 203, 377	N
2-30	B.1.617.1	1913208	30, 203, 377	N
2-31	B.1.617.1	1969991	203, 310, 377	P
2-32	B.1.617.2	1970310	63, 203, 377. 385	N
2-33	B.1.617.2	1660458	63, 203, 377	N
2-34	B.1.617.2	1807318	63, 203, 204, 205, 206, 207, 208, 377, 385	N
2-35	B.1.617.2	1913205	63, 203, 215, 377	N
2-36	AY.1	3244751	63, 203, 215, 377	N
2-37	AY.2	3123565	63,203,377	N
2-38	AY.3	3352221	63, 203, 215, 377	N
2-39	AY.3.1	2920875	63, 203, 215, 377	N
2-40	B.1.621*	3477571	205	N
2-41	C.1.2	2695610	13, 204, 384, 203	N
2-42	B.1.1.529	6647959	13, 31(deletion), 32(deletion), 33(deletion), 203, 204	N
2-43	BA.1 (B.1.1.529.1)	6640917	13, 31(deletion), 32(deletion), 33(deletion), 203, 204	N
2-44	BA.2 (B.1.1.529.2)	7190366	13, 31(deletion), 32(deletion), 33(deletion), 203, 204, 413	N
2-45	BA.3 (B.1.1.529.3)	7526186	13, 31(deletion), 32(deletion), 33(deletion), 203, 204, 413	N
2-46	B.1.640.1	6700813	63, 205, 378	N
2-47	B.1.640.2	7181977	22, 205	N
2-48	XD** (Delta and BA.1)	9879437	63, 203, 215, 377	N
2-49	XE** (BA.1 and BA.2)	9177743	13, 31(deletion), 32(deletion), 33(deletion), 203, 204 204, 413	N
2-50	XF** (Delta and BA.1)	8894978	13, 31(deletion), 32(deletion), 33(deletion), 203, 204	N
2-51	BA.1.1	9754508	P13L, E31(deletion), R32(deletion), S33(deletion), R203K,	N

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			G204R	
2-52	BA.2.2	12417574	P13L, E31(deletion), R32(deletion), S33(deletion), R203K, G204R, S413R	N
2-53	BA.2.12	10842022	P13L, E31(deletion), R32(deletion), S33(deletion), R203K, G204R, S413R	N
2-54	BA.2.12.1	11490263	P13L, E31(deletion), R32(deletion), S33(deletion), R203K, G204R, S413R	N
2-55	BA.4.1[a)]	12043292	P13L, E31(deletion), R32(deletion), S33(deletion), P151S, R203K, G204R, S413R	N
2-56	BA.5	11903045	P13L, E31(deletion), R32(deletion), S33(deletion), R203K, G204R, S413R	N
2-57	BA.5	12307612 **	P13L, E31(deletion), R32(deletion), S33(deletion), E136D, R203K, G204R, S413R	N
2-58	BA.2.75	13826295***	P13L E31(deletion), R32(deletion), S33(deletion), R203K, G204R, S413R]	N
2-59	BA.2.75	13711333***	[P13L, G204R, R203K, S413R]	N
2-60	BF.7	12810243	P13L, G30(deletion), E31(deletion), R32(deletion), S33F, R203K, G204R, S413R	N
2-61	BF.14	13490388	P13L, E31(deletion), R32(deletion), S33(deletion), R203K, G204R S413R	N
2-62	BJ.1	14167044	P13L, E31(deletion), R32(deletion), S33(deletion), R203K, G204R, T282I, S413R	P
2-63	BQ.1.1[b)]	15155651	P13L, E31(deletion), R32(deletion), S33(deletion), E136D, R203K, G204R, S413R	N
2-64	BA.4.6	12475182	P13L, E31(deletion), R32(deletion), S33(deletion), P151S, R203K, G204R, S413R	N
2-65	BA.2.75.2	14290506	P13L, E31(deletion), R32(deletion), S33(deletion), R203K, G204R, S413R	N
2-66	BA.2.12.1	9801346	P13L, E31(deletion), R32(deletion), S33(deletion), R203K, G204R, S413R	N
2-67	BA.5.1	11941796	P13L, E31(deletion), R32(deletion), S33(deletion), R203K, G204R, S413R	N
2-68	BA.5.2	11763535	P13L, E31(deletion), R32(deletion), S33(deletion), R203K, G204R, S413R	N
2-69	BA.2.3.20	15031190	P13L, E31(deletion), R32(deletion), S33(deletion), R203K, G204R, S413R	N
2-70	XBB	14891630	P13L, E31(deletion), R32(deletion), S33(deletion), R203K, G204R , S413R	N
2-71	BA.2.10	8092783.2	P13L, E31(deletion), R32(deletion), S33(deletion), R203K, G204R S413R	N
2-72	BM.1.1.1	13949278	P13L, E31(deletion), R32(deletion), S33(deletion), R203K, G204R S413R	N
2-73	BS.1[C)]	14853841	P13L, E31(deletion), R32(deletion), S33(deletion), T135I, R203K, G204R	N

** The identical mutation as found as the dominant mutation in this variant was already tested for #2-6*

*** XD, XE, XF are characterized by combining with the other two lineages (Delta + Omicron) by considering all mutation site including both spike protein and nucleocapsid protein. However, if only the sequence of nucleocapsid protein is considered, a single lineage can be characterized.*

※ Accession number of 12307612 is BA.5 sub lineage with very small portion (7.86 by GISAID, 2022.06.16.)

**** E31, R32 and S33 amino acid deletions of BA.2.75 occur in 74.15%, 74.15% and 72.79% respectively (Cov-spectrum.org, 2022.07.22).*

a) BA.4.1 (hCoV-19/South Africa/NCV1112/2022) was first designated as BA.4 on April 14, 2022, and re-designated on May 22, 2022 (from pango-designation issue #548).

b) BQ.1 was included to BQ.1.1 (cov-lineages/ pango-designation on GitHub)

c) The prevalence of BS.1 was 0.00% (Cov-spectrum.org, 2022.10.21), there were only 106 sequences in the database.

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3. Final conclusion of the test

As a result of analytical sensitivity and In-silico analysis, it is verified that STANDARD™ F products are not affected by "Alpha(B.1.1.7), Beta(B.1.351), Gamma(P.1), Delta(B.1.617.2), Kappa(B.1.617.1), Epsilon(B.1.429), Iota(B.1.526), Lambda(C.37), Zeta(P.2), Omicron(BA.1, BA.2, BA.3, BA.4.1, BA.5) SARS-CoV-2 variants". In addition, as a result of In-silico analysis, it is verified that STANDARD™ F products are not affected by "Mu(B.1.621), Omicron(B.1.1.529, BA.2.75, BF.7, BF.14, BJ.1, BQ.1.1, BA.4.6, BA.2.75.2, BA.2.12.1, BA.5.1, BA.5.2, BA.2.3.20, XBB, BA.2.10, BM.1.1.1, BS.1) SARS-CoV-2 variants".

As a result of the investigation of emerging Omicron sub-variants, it was identified that the mutation site of specified variant (BJ.1) is located in the epitope region. Although it may affect the performance of the test, BJ.1 has low risk due to the very low prevalence (0.01% in last 6 months). Even though, wet testing using recombinant protein will be performed. In addition, the mutation sites in the N protein of other 9 sub-variants of Omicron are not located in the epitope region, with their N protein aa sequences showing from 99% to 100% of homology with BA.2 or BA.4 or BA.5, previously evaluated. It is expected that BF.7, BF.14, BQ.1.1, BA.4.6, BA.2.75.2, BA.2.12.1, BA.5.1, BA.5.2 and BA.2.3.20 will not have affect the performance of the test.

XBB, BA.2.10 and BM.1.1.1 have same mutation sites in the N protein as BA.2. We have previously wet tested BA.2 and no impact on the performance of the test was detected. Therefore, XBB, BA.2.10 and BM.1.1.1 are expected to not have impact on the performance of the test. BS.1 showed additional mutation site at 135 a.a, it is not located in the epitope region. The current prevalence is very low (106 cases in total). If the prevalence increases in future, wet-testing will be performed for BS.1.

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4. Interpretation of test result

A negative result may occur if the concentration of antigen in a specimen is below the limit of detection of the test or if the specimen was collected or transported improperly, therefore a negative test result does not eliminate the possibility of SARS-CoV-2 infection, and should be confirmed by molecular assay.

Result	COI(Cutoff index) value	SARS-COV-2 Ag
Positive	COI ≥ 1.0	Positive for SARS-COV-2 Ag
Negative	COI < 1.0	Negative for SARS-COV-2 Ag
Invalid	COI value is not displayed	Retest should be performed with a new test device and a new patient's specimen.

We will continue our efforts to comply with high quality management standards and to maintain a consistent high quality management system to ensure customer's satisfaction and product safety. If you have any questions, please contact our sales representative.

Sincerely,
Jongkwan Ko
QMR
SD BIOSENSOR, Inc.