

In-silico Analysis for the impact of SARS-CoV-2 Variants on the STANDARD™ Q COVID-19 Ag Test

Revision History

Revision	Date	Description of changes
00	2021. 06. 24	Established In-silico Analysis for the SARS-CoV-2 Variants on STANDARD™ Q COVID-19 Ag Test
01	2021. 07. 08	Updated the in-silico Analysis for the B.1.617.1 and B.1.617.2
02	2021. 08. 18	Updated the in-silico Analysis for the Delta virus designated by WHO
03	2021. 09. 10	Updated the in-silico Analysis for the Mu (SARS-CoV-2) designated by WHO and C.1.2
04	2021. 11. 12	Updated the product category and WHO label. Revised some descriptions.
05	2021. 11. 24	Corrected typos.
06	2021. 11. 29	Updated the in-silico Analysis for the Omicron (B.1.1.529) designated by WHO
07	2021. 12. 08	Updated the in-silico Analysis for the Stealth Omicron (B.1.1.529.2)
08	2021. 12. 23	Updated the changed labelling for B.1.1.529 Sub-lineages (BA.1, BA.2 and BA3) from B.1.1.529
09	2022. 01. 06	Updated the B.1.640.1 and B.1.640.2
10	2022. 04. 19	Updated the XD, XE, XF

Authorization

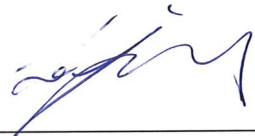
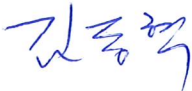
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1. PURPOSE AND SCOPE

1) Purpose

This document describes the in-silico analysis for the impact of SARS-CoV-2 variants on the STANDARD™ COVID-19 Ag Test

2) Goal

This in-silico analysis aims to assess if a mutation in the nucleocapsid protein sequence of SARS-CoV-2 variants could theoretically affect performance of the STANDARD™ COVID-19 Ag Test. For this purpose, potential changes in reactivity of the antibodies to the antigen were predicted by comparing the mutation site in the nucleocapsid (N) protein of each SARS-CoV-2 variant with the epitope region of the antibodies used in the products.

Product Name	Used antibodies
• STANDARD™ Q COVID-19 Ag Test (REF: Q-NCOV-01G)	Monoclonal antibody A Monoclonal antibody B

3) Reference documents

- Q COVID-19 Ag_Epitope mapping analysis for the antibodies_Rev.03
- Q COVID-19 Ag_Wet-testing report_Rev.03

4) Scope

STANDARD™ Q COVID-19 Ag Test

2. OVERVIEW

1) Testing Condition

Investigating Date	2021. 06. 21 ~ 2022. 04. 18 (Regulately)
Revised Date	2022. 01. 06
Site	Department of R&D, BioNote, INC.
Testing Representative	Preparer: Dong-Hyuk Kim, Bionote R&D Operator: Jin-Soo Kim, Bionote R&D Operator: Se-Jung Lee, Bionote R&D Reviewer: Jung-Ho Kim, Bionote R&D
In-silico analyzer	1. Program: NCBI blastp (Needleman-Wunsch) Onsite link: https://blast.ncbi.nlm.nih.gov/Blast.cgi

2) SARS-CoV-2 Variants

A total of 47 variants were analyzed and are listed in the table below.

For the N protein, the target protein of all SARS-CoV-2 antigen diagnostic products, the mutation sites found in variants with a frequency of >29% from 105-9475 sequences the public resource GISAID for the respective variants were investigated. The number of sequences at the time of analysis was limited for some variants since not more sequences that are valid were available.

In Rev.06, New VOC (B.1.1.529) designated by WHO is added.

In Rev.07, Stealth Omicron (B.1.1.529.2= BA.2) is added.

In Rev.08, sub-lineages (BA.1, BA.2, BA.3) from B.1.1.529 were added, previous described B.1.1.529 in rev.06 is sorted to BA.1. other B.1.1.529 is added. previous described B.1.1.529.2 in rev.07 is revised to BA.2. B.1.1.529.2 and BA.2 are the synonym, but BA.2 has being usually used.

In Rev.09, two sub-lineages (B.1.640.1 and B.1.640.2) from B.1.640 were added. B.1.640 is designed "Variant Under Monitoring, VUM" from WHO. (06 January, 2022)

In Rev.10, three recombined variants (XD, XE and XF) from Omicron and Delta were added. XD, XE and XF were given named by cov-lineages (the earliest date XD 03 January, 2022, XE 19 January, 2022 and XF 07 January, 2022, reference on site: <https://github.com/cov-lineages>).

No.	Virus sort	WHO label	PANGO Lineage	GISAID ACCESSION ID. EPI_ISL	Outbreak country
1	SARS-CoV-2	N/A	B	402125	China
2	SARS-CoV-2	N/A	A.23.1	925892	United kingdom
3	SARS-CoV-2	N/A	AT.1	2385327	Russia
4	SARS-CoV-2	N/A	AT.1	1259283	Russia
5	SARS-CoV-2	Alpha	B.1.1.7	835226	United kingdom
6	SARS-CoV-2	Beta	B.1.351	660190	South Africa
7	SARS-CoV-2	Epsilon	B.1.427	1060793	USA
8	SARS-CoV-2	Epsilon	B.1.429	1771435	USA
9	SARS-CoV-2	Epsilon	B.1.429	1194304	USA
10	SARS-CoV-2	Eta	B.1.525	2432518	Nigeria
11	SARS-CoV-2	N/A	B.1.526.1	2204920	USA
12	SARS-CoV-2	N/A	B.1.526.2	1080752	USA
13	SARS-CoV-2	B.1.526	B.1.526	1227165	USA
14	SARS-CoV-2	N/A	B.1.616	1239370	France
15	SARS-CoV-2	Kappa	B.1.617.1	1360306	India
16	SARS-CoV-2	Delta	B.1.617.2	1508996	India
17	SARS-CoV-2	N/A	B.1.617.3	1704494	India
18	SARS-CoV-2	Mu	B.1.621	1582980	Colombia
19	SARS-CoV-2	N/A	C.36	1936140	Egypt
20	SARS-CoV-2	Lambda	C.37	1111296	Peru
21	SARS-CoV-2	Gamma	P.1	792680	Japan/Brazil

22	SARS-CoV-2	Lambda	P.2	1182578	Brazil
23	SARS-CoV-2	Gamma	P.3	1213573	Philippines
24	SARS-CoV-2	Zeta	B.1.617.1	1789542	India
25	SARS-CoV-2	Theta	B.1.617.1	1620161	India
26	SARS-CoV-2	Kappa	B.1.617.1	1545312	Angola / Luanda
27	SARS-CoV-2	Kappa	B.1.617.1	1823120	Jordan / Amman
28	SARS-CoV-2	Kappa	B.1.617.1	1904467	Australia / New South Wales
29	SARS-CoV-2	Kappa	B.1.617.1	1660436	Bahrain
30	SARS-CoV-2	Kappa	B.1.617.1	1913208	Canada / Victoria
31	SARS-CoV-2	Kappa	B.1.617.1	1969991	Pakistan
32	SARS-CoV-2	Delta	B.1.617.2	1970310	India / Delhi
33	SARS-CoV-2	Delta	B.1.617.2	1660458	Bahrain
34	SARS-CoV-2	Delta	B.1.617.2	1807318	Australia / Capital Territory
35	SARS-CoV-2	Delta	B.1.617.2	1913205	Canada / Victoria
36	SARS-CoV-2	Delta	AY.1	3244751	India
37	SARS-CoV-2	Delta	AY.2	3123565	Albania
38	SARS-CoV-2	Delta	AY.3	3352221	USA
39	SARS-CoV-2	Delta	AY.3.1	2920875	USA
40	SARS-CoV-2	Mu	B.1.621	3477571	South America / Colombia
41	SARS-CoV-2	N/A	C.1.2	2695610	South Africa
42	SARS-CoV-2	Omicron	B.1.1.529	6647959	South Africa / Gauteng
43	SARS-CoV-2	Omicron	BA.1	6640917	Africa/ Botswana
44	SARS-CoV-2	Omicron	BA.2	7190366	Oceania / Australia
45	SARS-CoV-2	Omicron	BA.3	7526186	United Kingdom / England
46	SARS-CoV-2	N/A	B.1.640.1	6700813	Republic of the Congo
47	SARS-CoV-2	N/A	B.1.640.2	7181977	Europe / United Kingdom
48	SARS-CoV-2	N/A	XD (Delta and BA.1)	9879437	France
49	SARS-CoV-2	Omicron*	XE (BA.1 and BA.2)	9177743	United Kingdom
50	SARS-CoV-2	N/A	XF (Delta and BA.1)	8894978	United Kingdom

* Omicron Includes BA.1/BA.2 circulating recombinant forms such as XE.

3) Epitope of antibodies

Studies investigating the epitopes of the antibodies in the materials used in all SARS-CoV-2 antigen diagnostic products were conducted previously. (Document: Q COVID-19 Ag_Epitope mapping analysis for the antibodies_Rev.03) The epitopes of paired antibodies used (A and B) are located in the CTD region spanning the amino acids (aa) 258-361 of the SARS-CoV-2 N protein.

3. CRITERIA

The most frequent mutation site(s) of each variant was (were) compared to the epitope region by in-silico analysis. If the mutation site is located within the epitope region, a possible impact on test performance was predicted. If the mutation site is not located within the epitope region, impact on test performance was predicted to be unlikely.

The criteria below were used for classification.

Result of in-silico analysis	Classification	Prediction
Mutation site is not located in the epitope region	N	A change in performance is unlikely
Mutation site is located in the epitope region	P	There is a possibility of a change in performance

If the in-silico result is decision “**P**”, **the variant should be tested** by wet testing.

4. RESULT

[Overall Variants list]

No.	Virus sort	WHO label	PANGO Lineage	Country of first outbreak	GISAID ACCESSION ID. EPI_ISL	Most frequent mutation sites (amio acid numbers)	Epitope region	Classification
1	SARS-CoV-2	N/A	B	China	402125	N/A (as standard)	258~361	N/A
2	SARS-CoV-2	N/A	A.23.1	United kingdom	925892	202		N
3	SARS-CoV-2	N/A	AT.1	Russia	2385327	67, 203, 204		N
4	SARS-CoV-2	N/A	AT.1	Russia	1259283	203, 204		N
5	SARS-CoV-2	Alpha	B.1.1.7	United kingdom	835226	3, 203, 204, 235		N
6	SARS-CoV-2	Beta	B.1.351	South Africa	660190	205		N
7	SARS-CoV-2	Epsilon	B.1.427	USA	1060793	205		N
8	SARS-CoV-2	Epsilon	B.1.429	USA	1771435	205, 234		N
9	SARS-CoV-2	Epsilon	B.1.429	USA	1194304	205		N
10	SARS-CoV-2	Eta	B.1.525	Nigeria	2432518	2, 12, 205		N
11	SARS-CoV-2	N/A	B.1.526.1	USA	2204920	205, 234		N
12	SARS-CoV-2	N/A	B.1.526.2	USA	1080752	13, 202		N
13	SARS-CoV-2	B.1.526	B.1.526	USA	1227165	199, 234		N
14	SARS-CoV-2	N/A	B.1.616	France	1239370	325		P
15	SARS-CoV-2	Kappa	B.1.617.1	India	1360306	203, 377		N
16	SARS-CoV-2	Delta	B.1.617.2	India	1508996	63, 203, 215, 377		N
17	SARS-CoV-2	N/A	B.1.617.3	India	1704494	67, 203, 377		N
18	SARS-CoV-2	Mu	B.1.621	Colombia	1582980	205		N
19	SARS-CoV-2	N/A	C.36	Egypt	1936140	203, 204, 212		N
20	SARS-CoV-2	Lambda	C.37	Peru	1111296	13, 203, 204, 214, 366		N
21	SARS-CoV-2	Gamma	P.1	Japan/Brazil	792680	80, 203, 204		N

22	SARS-CoV-2	Lambda	P.2	Brazil	1182578	119, 203, 204, 234		N
23	SARS-CoV-2	Gamma	P.3	Philippines	1213573	203, 204		N
24	SARS-CoV-2	Zeta	B.1.617.1	India	1789542	203, 377, 385		N
25	SARS-CoV-2	Theta	B.1.617.1	India	1620161	3, 203, 377		N
26	SARS-CoV-2	Kappa	B.1.617.1	Angola / Luanda	1545312	203, 204		N
27	SARS-CoV-2	Kappa	B.1.617.1	Jordan / Amman	1823120	203, 236, 377		N
28	SARS-CoV-2	Kappa	B.1.617.1	Australia / New South Wales	1904467	3, 13, 203, 243, 377		N
29	SARS-CoV-2	Kappa	B.1.617.1	Bahrain	1660436	3, 63, 203, 377		N
30	SARS-CoV-2	Kappa	B.1.617.1	Canada / Victoria	1913208	30, 203, 377		N
31	SARS-CoV-2	Kappa	B.1.617.1	Pakistan	1969991	203, 310, 377		P
32	SARS-CoV-2	Delta	B.1.617.2	India / Delhi	1970310	63, 203, 377, 385		N
33	SARS-CoV-2	Delta	B.1.617.2	Bahrain	1660458	63, 203, 377		N
34	SARS-CoV-2	Delta	B.1.617.2	Australia / Capital Territory	1807318	63, 203, 204, 205, 206, 207, 208, 377, 385		N
35	SARS-CoV-2	Delta	B.1.617.2	Canada / Victoria	1913205	63, 203, 215, 377		N
36	SARS-CoV-2	Delta	AY.1	India	3244751	63, 203, 215, 377		N
37	SARS-CoV-2	Delta	AY.2	Albania	3123565	63,203,377		N
38	SARS-CoV-2	Delta	AY.3	USA	3352221	63, 203, 215, 377		N
39	SARS-CoV-2	Delta	AY.3.1	USA	2920875	63, 203, 215, 377		N
40	SARS-CoV-2	Mu	B.1.621	South America / Colombia	3477571	205		N
41	SARS-CoV-2	N/A	C.1.2	South Africa	2695610	204, 13, 384, 203		N
42	SARS-CoV-2	Omicron	B.1.1.529	South Africa / Gauteng	6647959	13, 31del, 32del, 33del, 203, 204		N
43	SARS-CoV-2	Omicron	BA.1 (previously B.1.1.529)	Africa / Botswana	6640917	13, 31del, 32del, 33del, 203, 204		N

44	SARS-CoV-2	Omicron	BA.2	Oceania / Australia	7190366	13, 31del, 32del, 33del, 203, 204, 413	N
45	SARS-CoV-2	Omicron	BA.3	United Kingdom / England	7526186	13, 31del, 32del, 33del, 203, 204, 413	N
46	SARS-CoV-2	N/A	B.1.640.1	Republic of the Congo	6700813	63, 205, 378	N
47	SARS-CoV-2	N/A	B.1.640.2	Europe / United Kingdom	7181977	22, 205	N
48	SARS-CoV-2	N/A	XD (Delta and BA.1)	XD	9879437	63, 203, 215, 377	N
49	SARS-CoV-2	Omicron	XE (BA.1 and BA.2)	XE	9177743	13, 31del, 32del, 33del, 203, 204, 413	N
50	SARS-CoV-2	N/A	XF (Delta and BA.1)	XF	8894978	13, 31del, 32del, 33del, 203, 204	N

[Rev.10, XD, XE and XF nucleocapsid protein sequence analysis]

New investigating variant	Previous investigated variant	% of homology
XD	B.1.617.2 (Delta)	
Nucleocapsid Protein Sequence (accession no. GISAID ACCESSION ID. EPI_ISL_9879437)		
[D63G, R203M, G215C, D377Y] MSDNGPQNQRNAPRITFGGSDSTGSNQNGERSGARKORRQGLPNNTASWFTALTQHGKE LKFFPRGGVPINTNSSPDDQIGYYRRATRIRRGDGKMKDLSRWYFYLYLGTGPEAGLPYGANK DGIWVATEGALNTPKDHIGTRNPANNAIVLQLPQGTTLPGFYAEGSRGSGQASSRSSRSRNS SRNSTPGSSVGTSPARMAGNGCDAALALLLLDRLNLQLESKMSGKGQQGQQTIVTKKSAEASK KPRQKRTATKAYNVTQAFGRGPEQTQGNFGDQELIRQGTDYKHWPIAQFAPSASAFFGMSRI GMEVTPSGTWLTYYTGAIKLDDKDPNFKDQVILLNKHIDAYKTFPPTPEPKDKKKKAYETQALPQRQ KKQQTIVTLLPAADLDDFSKQLQQSMSSADSTQA	[D63G, R203M, G215C, D377Y] MSDNGPQNQRNAPRITFGGSDSTGSNQNGERSGARKORRQGLPNNTASWFTALTQHGKE GLKFFPRGGVPINTNSSPDDQIGYYRRATRIRRGDGKMKDLSRWYFYLYLGTGPEAGLPYGAN KDGIIWVATEGALNTPKDHIGTRNPANNAIVLQLPQGTTLPGFYAEGSRGSGQASSRSSRSR NSSRNSTPGSSVGTSPARMAGNGCDAALALLLLDRLNLQLESKMSGKGQQGQQTIVTKKSAAEA SKKPRQKRTATKAYNVTQAFGRGPEQTQGNFGDQELIRQGTDYKHWPIAQFAPSASAFFGMS RIGMEVTPSGTWLTYYTGAIKLDDKDPNFKDQVILLNKHIDAYKTFPPTPEPKDKKKKAYETQALPQR QKKQQTIVTLLPAADLDDFSKQLQQSMSSADSTQA	100%

XE	BA.2 (Omicron)	
	Nucleocapsid Protein Sequence (accession no. GISAID ACCESSION ID. EPI_ISL_9177743)	
[P13L, E31(Del*), R32(Del*), S33(Del*), R203K, G204R, S413R]	[P13L, E31(Del*), R32(Del*), S33(Del*), R203K, G204R, S413R]	
MSDNGPQNQRNALRITFGGSPDSTGSNQNGERSGARSQRRPQGLPNNNTASWFTALTQHGKED	MSDNGPQNQRNALRITFGGSPDSTGSNQNGERSGARSQRRPQGLPNNNTASWFTALTQHGKED	
LKFRPGQGVPIINTNSSPDDQIGYYRRATRIRGGDGKMKDLSRWYFYLYGTGPEAGLPYGANK	LKFRPGQGVPIINTNSSPDDQIGYYRRATRIRGGDGKMKDLSRWYFYLYGTGPEAGLPYGANK	
DGIWVATEGALNTPKDHIGTRNPANNAIVLQLPQGTTLPKGFYAEGSRGGSQASSRSSRSRNS	DGIWVATEGALNTPKDHIGTRNPANNAIVLQLPQGTTLPKGFYAEGSRGGSQASSRSSRSRNS	
SRNSTPGSSKRTSPARMAGNGGDAALALLLDRLNQLESKMSGKGQQQQGQTVTKKSAAEASK	SRNSTPGSSKRTSPARMAGNGGDAALALLLDRLNQLESKMSGKGQQQQGQTVTKKSAAEASK	
KPRQKRTATKAYNVYTAQFGRRGPEQTQGNFGDQELIRQGTDYKHWPIAQFAPSASAFFGMSRI	KPRQKRTATKAYNVYTAQFGRRGPEQTQGNFGDQELIRQGTDYKHWPIAQFAPSASAFFGMSRI	
GMEVTPSGTWLTYTGAIKLDDKDPNFKDQVILLNKHIDAYKTFPPTPEPKDKKKKADETOALPQRQ	GMEVTPSGTWLTYTGAIKLDDKDPNFKDQVILLNKHIDAYKTFPPTPEPKDKKKKADETOALPQRQ	
KKQQTVTLLPAADLDDFSKQLQQSMSRADSTQA	KKQQTVTLLPAADLDDFSKQLQQSMSRADSTQA	
XF	BA.1 (Omicron)	
	Nucleocapsid Protein Sequence (accession no. GISAID ACCESSION ID. EPI_ISL_8894978)	
[P13L, E31(Del*), R32(Del*), S33(Del*), R203K, G204R]	[P13L, E31(Del*), R32(Del*), S33(Del*), R203K, G204R]	
MSDNGPQNQRNALRITFGGSPDSTGSNQNGERSGARSQRRPQGLPNNNTASWFTALTQHGKED	MSDNGPQNQRNALRITFGGSPDSTGSNQNGERSGARSQRRPQGLPNNNTASWFTALTQHGKED	
LKFRPGQGVPIINTNSSPDDQIGYYRRATRIRGGDGKMKDLSRWYFYLYGTGPEAGLPYGANK	LKFRPGQGVPIINTNSSPDDQIGYYRRATRIRGGDGKMKDLSRWYFYLYGTGPEAGLPYGANK	
DGIWVATEGALNTPKDHIGTRNPANNAIVLQLPQGTTLPKGFYAEGSRGGSQASSRSSRSRNS	DGIWVATEGALNTPKDHIGTRNPANNAIVLQLPQGTTLPKGFYAEGSRGGSQASSRSSRSRNS	
SRNSTPGSSKRTSPARMAGNGGDAALALLLDRLNQLESKMSGKGQQQQGQTVTKKSAAEASK	SRNSTPGSSKRTSPARMAGNGGDAALALLLDRLNQLESKMSGKGQQQQGQTVTKKSAAEASK	
KPRQKRTATKAYNVYTAQFGRRGPEQTQGNFGDQELIRQGTDYKHWPIAQFAPSASAFFGMSRI	KPRQKRTATKAYNVYTAQFGRRGPEQTQGNFGDQELIRQGTDYKHWPIAQFAPSASAFFGMSRI	
GMEVTPSGTWLTYTGAIKLDDKDPNFKDQVILLNKHIDAYKTFPPTPEPKDKKKKADETOALPQRQ	GMEVTPSGTWLTYTGAIKLDDKDPNFKDQVILLNKHIDAYKTFPPTPEPKDKKKKADETOALPQRQ	
KKQQTVTLLPAADLDDFSKQLQQSMSRADSTQA	KKQQTVTLLPAADLDDFSKQLQQSMSRADSTQA	

100%

100%

5. CONCLUSION

The mutation sites of the most frequent mutations determined for 47 variants using the GISAID database in the SARS-CoV-2 nucleocapsid protein compared to the Wuhan-Hu-1 sequence were compared to the epitope region of the paired antibodies used in the STANDARD™ COVID-19 Ag (aa 258-361). Two variants (B.1.616, listed as no.14 and B.1.617.1, listed as no.31) show a mutation within the epitope region (no.14 is at aa 325, no.31 is at aa 310). B.1.616 variant was detected in France in the spring of 2021 and remained very locally restricted. Per 18 November 2021, it is not currently classified as a VoC or Variants of Interest (Vol) by the WHO, nor is it classified as a Variant Being Monitored (VBM), a VOI, a VOC or a Variant of High Consequence (VOHC) by the US CDC.

All other 45 variants showed mutations outside of the epitope region and would not affect assay performance.

Nonetheless, B.1.616 and B.1.617.1 (GISAID Accession ID EPI_ISL 1969991) should be wet-tested for potential changes in assay performance.

The B.1.1.529 variant was designated by WHO at 2021.11.26 as the VoC.

New emerged variant B.1.1.529 (no.42, Omicron) and its sub-lineages (no.43-45, BA.1, BA.2, BA.3) have especially feature that the deleted sites (31del, 32del, 33del) of N protein. all mutation sites of B.1.1.529 and sub-lineages are not located in epitope region.

Nonetheless, wet-testing of the new emerged variants can help with confidence of performance along with the in-silico analysis.

New emerging variants B.1.640.1 and B.1.640.2 are sub-lineage from B.1.640.

B.1.640.1 and B.1.640.2 would not affect assay performance, since the mutation sites on N protein of both B.1.640.1 and B.1.640.2 are not located in epitope region.

New recombined variant (XD, XE and XF) were from Delta and Omicron. Nucleocapsid protein of XD is same to the delta (B.1.617.2) variant, XE is same the omicron (BA.2) variant and XF is same to the omicron (BA.1) We previously investigated the B.1.617.2, BA.2 and BA.2, all do not affect the performance of STANDARD™ COVID-19 Ag Test.

To be conclusion, XD, XE and XF also do not affect the performance of STANDARD™ COVID-19 Ag and they are unnecessary to study with wet-testing.

6. REFERENCES

- (1) GISAID: <https://www.epicov.org>
- (2) Nextstrain: <https://nextstrain.org>
- (3) PANGO lineages: <https://cov-lineages.org>
- (4) European Centre for Disease Prevention and Control: <https://www.ecdc.europa.eu/en/covid-19/variants-concern>
- (5) CDC: https://www.cdc.gov/coronavirus/2019-ncov/variants/variant-info.html#anchor_163215888516C
- (6) WHO tracking of variants: <https://www.who.int/en/activities/tracking-SARS-CoV-2-variants/>