IMMUVIEW® COVID-19 Antigen Home Test Monitoring of SARS-CoV-2 Variants

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Summary

The ImmuView® COVID-19 Antigen Home Test is a lateral flow immunoassay for the qualitative detection of the SARS-CoV-2 virus in nasal swab specimens from symptomatic individuals suspected of COVID-19. The test detects the presence of antigens from the SARS- CoV-2 virus, namely the viral Nucleocapsid Protein (NP). The performance of the test has been extensively validated both internally and at multiple external clinical sites across the United States.

Multiple SARS-CoV-2 variants are now circulating globally. In this study, we analyzed the NP sequences from SARS-CoV-2 variants, B.1.1.7, B.1.351 and P.1, B.1.617+, B.1.525, B.1.526, B.1.617.1, C.37, B.1.427/B.1.429, P2, B.1.620, B.1.1.529.1, B.1.1.529.1.1, B.1.1.529.2, B.1.1.529.4, B.1.1.529.5, and B.1.1.529.2.75, and compared them to the original SARS-CoV-2. None of the analyzed variants have mutations within the epitopes recognized by the antibodies used in the ImmuView® COVID-19 Antigen Home Test. Therefore, the performance of the ImmuView® COVID-19 Antigen Home Test to detect these new variants should not be impacted.

1. Background

SARS-CoV-2, the virus that causes COVID-19, has changed over time since the beginning of the pandemic. Most changes have little to no impact on the virus' properties. However, some changes may affect the virus's properties, such as how easily it spreads, the associated disease severity, or the performance of vaccines, therapeutic medicines, diagnostic tools, or other public health and social measures.

The World Health Organization (WHO) has been monitoring and assessing the evolution of SARS-CoV-2 since January 2020. In late 2020, the emergence of variants that posed an increased risk to global public health prompted the characterization of specific Variants of Interest (VOIs) and Variants of Concern (VOCs), in order to prioritize global monitoring and research, and ultimately inform the ongoing response to the COVID-19 pandemic[1]. VOCs have one or more of the following changes: 1) Increase in transmissibility or detrimental change in COVID-19 epidemiology; 2) Increase in virulence or change in clinical disease presentation; 3) Decrease in the effectiveness of public health and social measures or available diagnostics, vaccines, therapeutics. The current SARS-CoV-2 VOCs are Delta and Omicron. Previous VOCs include B.1.1.7, B.1.351, and P.1. VOIs have one or more of the following changes: 1) have been identified to cause community transmission/multiple COVID- 19 cases/clusters, or have been detected in multiple countries; 2) are otherwise assessed to be a VOI by the WHO in consultation with the WHO SARS-CoV-2 Virus Evolution Working Group. Previous VOIs include B.1.427/B.1.429, P.2, B.1.525, P.3, B.1.526, B.1.617.1, C.37 and B.1.621.

The ImmuView® COVID-19 Antigen Home Test detects the presence of antigens from the SARS-CoV-2 virus in nasal swabs, within the first seven days of the onset of symptoms. Test results can be interpreted at 15-30 minutes, by minimally skilled personnel, without the use of cumbersome laboratory equipment. With the emergence of multiple SARS-CoV-2 variants, in this study, we evaluated the possible impact of the mutations identified from SARS- CoV-2 variants on the performance of the test. In this study, we analyzed the NP sequences from SARS-CoV-2 variants, B.1.1.7, B.1.351, P.1, B.1.617+, B.1.525, B.1.526, B.1.617.1, C.37, B.1.427/B.1.429, P2, B.1.620, B.1.1.529.1, B.1.1.529.1.1, B.1.1.529.2, B.1.1.529.4, B.1.1.529.5, and B.1.1.529.2.75 to see if they have any mutations within the epitopes of the antibodies used in the ImmuView® COVID-19 Antigen Home Test.

2. Assay description

The ImmuView® COVID-19 Antigen Home Test is a lateral flow chromatographic immunoassay. The test cassette consists of: 1) a colored conjugate pad containing anti-SARS- CoV-2 antibodies conjugated with colloidal gold (antibody conjugates) and 2) a nitrocellulose membrane strip containing a test line (Ag line) and a control line (C line). The test line is pre-coated with anti-SARS-CoV-2 antibody and the C line is pre-coated with control antibodies.

The specimen is collected with a nasal swab and the SARS-CoV-2 antigen is extracted from the swab with an extraction buffer. When applied to the sample well, the extracted specimen migrates across the test strip by capillary action. SARS-CoV-2 antigen, if present in the extract, binds to the antibody conjugates, and the immunocomplex is then captured on the membrane by the pre-coated anti-SARS-CoV-2 antibody, forming a colored Ag line that indicates a COVID- 19 positive test result.

The test contains an internal control (C line), which should exhibit a colored line regardless of color development on the Ag line. If the C line does not develop, the test result is invalid and the specimen must be retested with a new device.

3. Methods

3.1 GISAID Initiative EpiCoV database

The GISAID Initiative (www.epicov.org) helps monitor emerging hCoV-19 variants that could become relevant due to signs of increased spread (estimated by change in the number of locations) combined with potential effects on receptor or antibody binding as annotated in CoVsurver. Currently, 147 amino acid changes and deletions in the Spike protein that occur in at least 10 different geographical locations and were identified in studies to cause antibody escape, increase ACE2 binding, or increase Spike protein expression and stability are considered as part of combinations or constellations forming potential variants to be monitored.

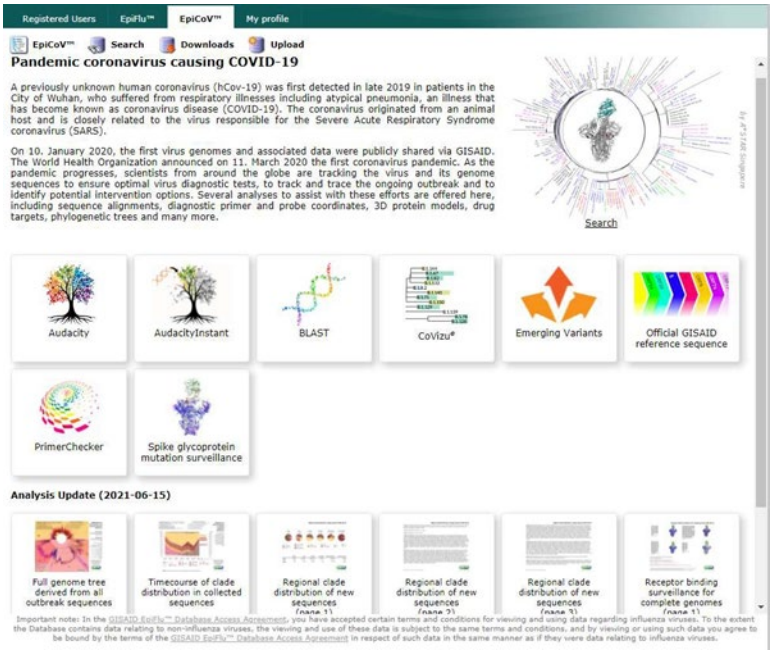

Figure 1. GISAID Initiative EpiCoV database.

The variants for each month (by collection date) are ranked by SxC (S**: Δ#Loc, C: #aachanges**) (Figure 2), which is the product of the change in the number of locations (compared to previous months; akin towards the spread S) and the number of relevant amino acid changes with potential effect contributing to a constellation (C). The variants also are ranked by #Locations.

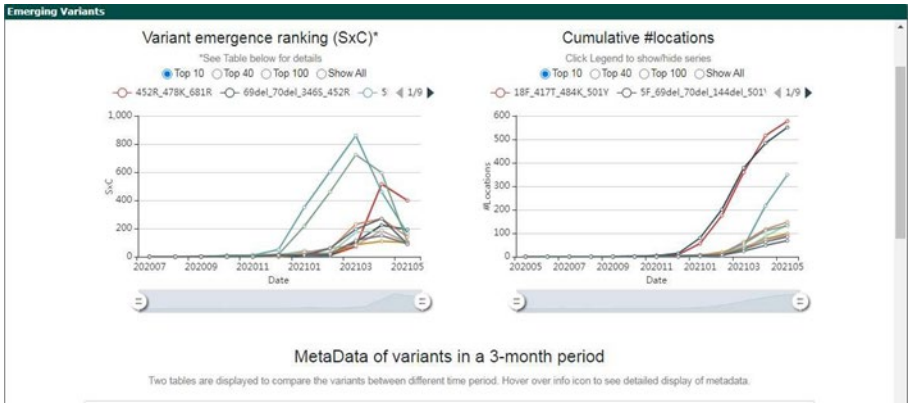

Figure 2. SARS-CoV-2 emerging variants. The variant emergence ranking (SxC) and variant cumulative #locations are shown on the left and right, respectively.

The details of variants in April 2021 are shown in Figure 3. The top 3 variants were **B.1.1.7** 69del_70del_144del_501Y, **P.1** 18F_417T_484K_501Y and **B.1.617.2** 452R_478K_681R. The variants were ranked by SxC value.

Emerging Variants

Variant	Literature Ref	#Genomes	#Top Location	#Top Clade	#Top Lineage	Co-occurring Changes	occurring Changes	Δ#Loc
69del_70del_144del_501Y		527510	114736 England	521133 GRY	526928 B.1.1.7	Spike_A570D, Spike_Y145del, Spike_P681H	21	197
18F_417T_484K_501Y		20801	2727 Sao Paulo	19374 GR	18109 P.1	Spike_D138Y, Spike_R190S, Spike_T20N	20	152
452R_478K_681R		5149	1082 England	5138 G	5022 B.1.617.2	Spike_T19R, Spike_D950N, Spike_D614G	13	172
5F_69del_70del_144del_501Y		16475	2641 England	16375 GRY	16455 B.1.1.7	Spike_A570D, Spike_Y145del, Spike_P681H	20	99
69del_70del_144del_490L_501Y		892	284 England	867 GRY	891 B.1.1.7	Spike_A570D, Spike_F490S, Spike_Y145del	22	57
69del_70del_144del_484K_501Y		974	216 Tyrol	965 GRY	965 B.1.1.7	Spike_A570D, Spike_Y145del, Spike_P681H	20	56
69del_70del_144del_501Y_1237I		741	186 Germany	735 GRY	740 B.1.1.7	Spike_A570D, Spike_Y145del, Spike_P681H	21	55
69del_70del_144del_242del_243del_244del_477N_484K		282	46 South Korea	281 G	280 B.1.620	Spike_H245Y, Spike_P681H, Spike_D1118H	16	34
18F_69del_70del_144del_501Y		3455	2170 England	3435 GRY	3442 B.1.1.7	Spike_A570D, Spike_Y145del, Spike_P681H	21	51
452R_484Q_681R		2810	1096 Maharashtra	2804 G	2649 B.1.617.1	Spike_Q1071H, Spike_D614G, NS3_S26L	11	76

Figure 3. Top ten emerging variants in April 2021.

3.2 SARS-CoV-2 variants NP sequence analysis

The criterion for selection of SARS-CoV-2 variants sequences included the following information: select variant, with host information, with complete and high coverage, patient status, and with collection date (Figure 4). Table 1 shows the SARS-CoV-2 variants analyzed in this study.

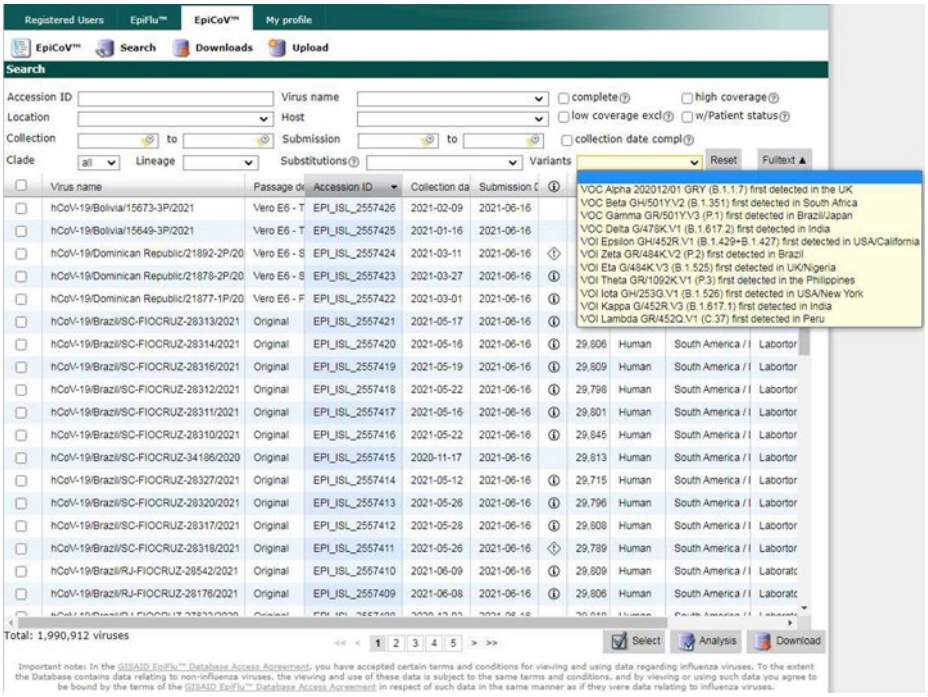

Figure 4. SARS-CoV-2 variants sequences in EpiCoV database.

Variants	Other names	Sequence No.
B.1.1.7	Alpha/UK variant	5492
B.1.351	Beta/South Africa variant	273
P.1	Gamma/Brazil variant	101
B.1.617+	Delta/India variant	541
B.1.525	Eta/Nigeria variant	105
B.1.526	Iota/USA	250
B.1.617.1	Kappa/India	246
C.37	Lambda/Peru	500
B.1.429 + B.1.427	California variant	586
P.2	Brazil	500
B.1.620	None	500
B.1.1.529.1	Omicron BA.1	107
B.1.1.529.1.1	Omicron BA.1.1	94
B.1.1.529.2	Omicron BA.2	85
B.1.1.529.4	Omicron BA.4	162
B.1.1.529.5	Omicron BA.5	132
B.1.1.529.2.75	Omicron BA.2.75	159

Table 1. SARS-CoV-2 variants sequence number.

The sequences were aligned with Clustal Omega online tools (Figure 5) at EMBL-EBI

(https://www.ebi.ac.uk/Tools/msa/clustalo/). The full-length NP genes (NP Position 28274 to 29533) from aligned sequences were translated to amino acid sequences and a consensus sequence was generated using BioEdit software. All the NP consensus sequences from variants were aligned with official reference NP sequence from hCoV-19/Wuhan/WIV04/2019 (WIV04, EPI_ISL_402124).

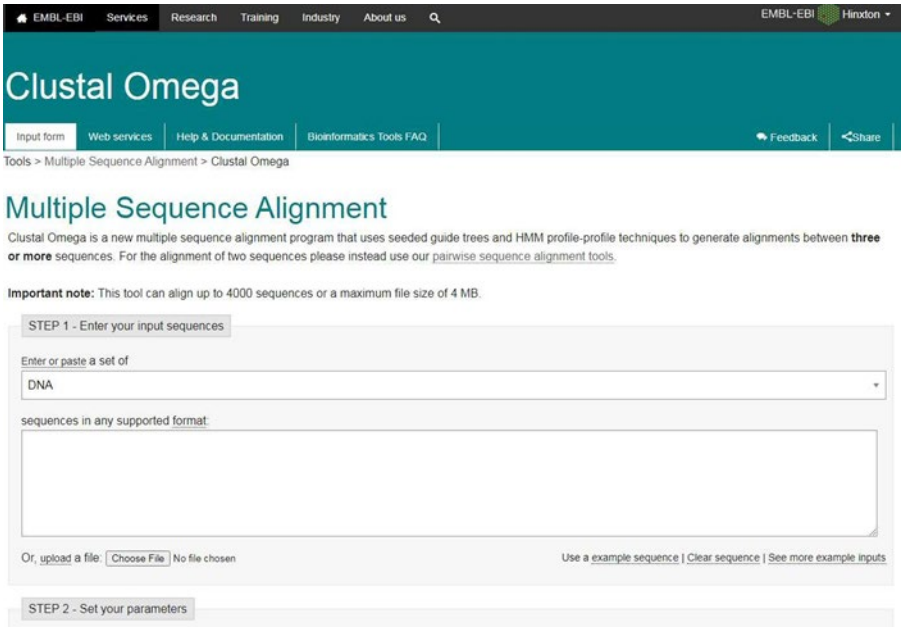

Figure 5. Multiple Sequence Alignment at EMBL-EBI.

4. Results

4.1 Mapping the binding regions for the antibodies used in the ImmuView® COVID-19 Antigen Home Test

The ImmuView® COVID-19 Antigen Home Test uses one capture antibody and two conjugate antibodies for the SARS-CoV-2 Ag target. In this study, we mapped the antibodies' binding regions by using peptide scanning. The capture antibody detects NP epitopes within aa100- aa114 and the binding epitopes of the two conjugate antibodies are within aa105-aa122 and aa47-aa175, respectively.

Since there are more and more emerging variants, we developed a strategy to monitor if SARS-CoV-2 variants have mutations within conjugate and capture antibodies' epitopes, and if the ImmuView® COVID-19 Antigen Home Test is still able to detect these new variants. In this study, we analyzed the NP sequences from variants B.1.1.7, B.1.351, P.1, B.1.617+, B.1.525, B.1.526, B.1.617.1, C.37, B.1.427/B.1.429, P2, B.1.620, B.1.1.529.1, B.1.1.529.1.1, B.1.1.529.2, B.1.1.529.4, B.1.1.529.5, and B.1.1.529.2.75. The NP consensus sequences from each variant were aligned to reference sequence WIV04 and the mutations are shown in Figure 6 and Table 2.

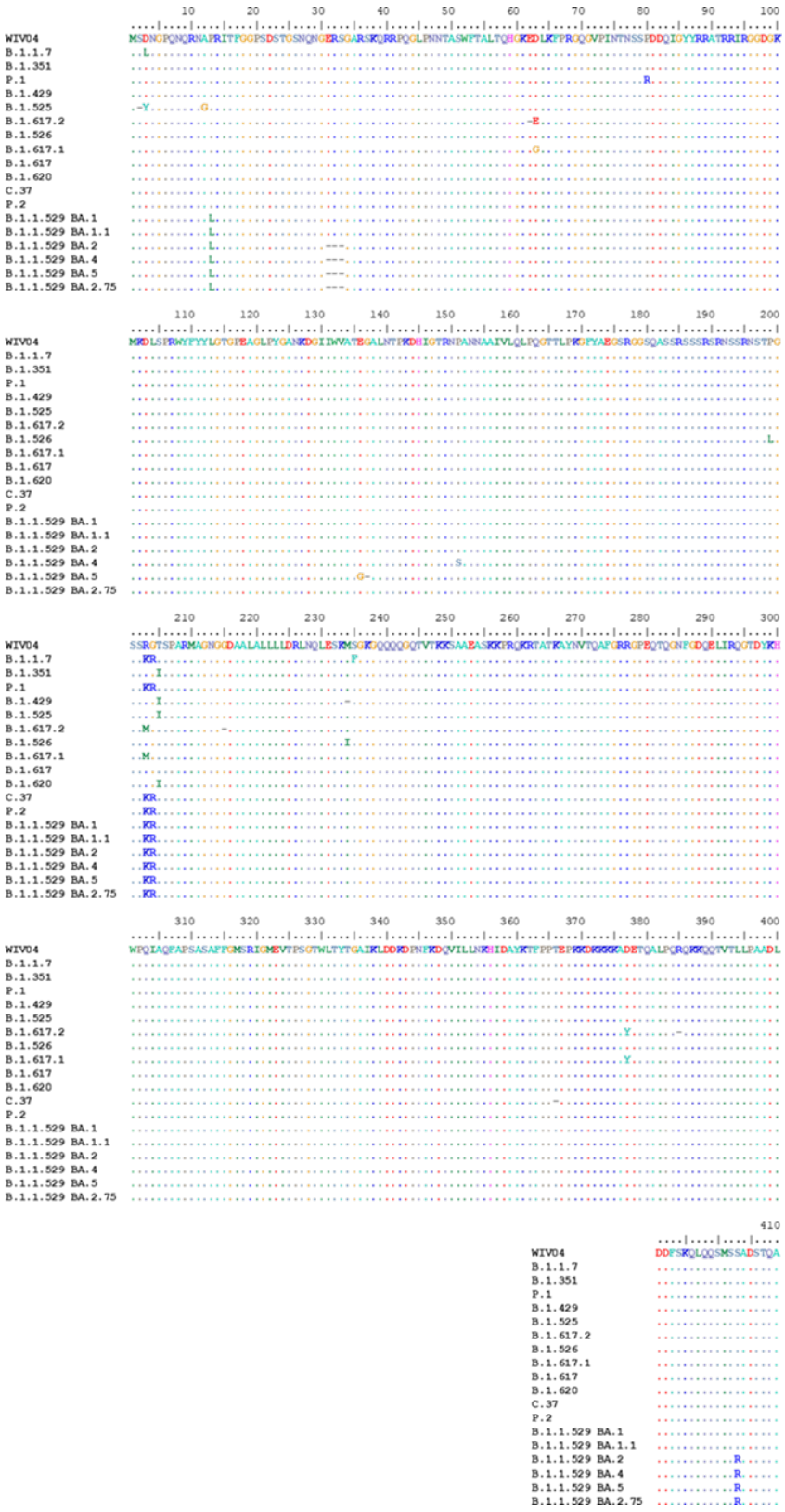

Figure 6. SARS-CoV-2 variants NP sequence alignment.

B.1.1.7 has 4 mutations (D3L, R203K, G204R, and S235F), B.1.351 has one mutation (T205I), P.1 has 3 mutations (P80R, R203K, and G204R), B.1.617.2 has 3 mutations (D63E, R203M, and D377Y) and 3 deletions (ΔE62, Δ G214, and Δ R385). B.1.525 has 3 mutations (S2Y, A12G, and T205I) and 1 deletion (ΔD3), B.1.526 has 2 mutations (P199L and M234I), B.1.617.1 has 3 mutations (D63G, R203M, and D377Y), C.37 has 2 mutations (R203K, G204R) and 1 deletion (ΔT366), B.1.427 and B.1.429 variant has 1 mutation (T205I) and 1 deletion (ΔM249), P.2 has 2 mutations (R203K and G204R), B.1.620 has 1 mutation (T205I), B.1.1.529.1 has 3 mutations (P13L, R203K, G204R), B.1.1.529.1.1 has 3 mutations (P13L, R203K, G204R), B.1.1.529.2 has 4 mutations (P13L, R203K, G204R, and S413R) and 3 deletions (Δ31ERS33). B.1.1.529.4 has 5 mutations (P13L, P151S, R203K, G204R, and S413R) and 3 deletions (Δ31ERS33). B.1.1.529.5 has 4 mutations (P13L, R203K, G204R, and S413R) and 4 deletions (Δ31ERS33 and ΔE136). B.1.1.529.2.75 has 4 mutations (P13L, R203K, G204R, and S413R) and 3 deletions (Δ31ERS33). There are 3 variants that have mutations within one of two conjugate antibodies' binding regions, P.1 (P80R), B.1.617.1 (D63G), and B.1.617.2 (ΔE62, D63E). No mutations were found in the capture antibody's epitope and one conjugate antibody's binding epitope. Therefore, the ImmuView® COVID-19 Antigen Home Test can detect these variants.

VARIANTS	OTHER NAMES	MUTATIONS
B.1.1.7	Alpha/ UK variant	D3L R203K G204R S235F
B.1.351	Beta/ South Africa variant	T205I
P.1	Gamma/ Brazil variant	P80R R203K G204R
B.1.617.2	Delta/ India variant	ΔE62 D63E R203M ΔG214 D377Y ΔR385
B.1.525	Eta/ Nigeria variant	S2Y ΔD3 A12G T205I
B.1.526	Iota/ USA	P199L M234I
B.1.617.1	Kappa/ India	D63G R203M D377Y
C.37	Lambda/ Peru	R203K G204R ΔT366
B.1.429 + B.1.427	California variant	T205I ΔM249
P.2	Zeta/ Brazil	R203K G204R
B.1.620	Lithuanian strain	T205I
B.1.1.529.1	Omicron BA.1	P13L R203K G204R
B.1.1.529.1.1	Omicron BA.1.1	P13L R203K G204R
B.1.1.529.2	Omicron BA.2	P13L Δ31ERS33 R203K G204R S413R
B.1.1.529.4	Omicron BA.4	P13L Δ31ERS33 P151S R203K G204R S413R
B.1.1.529.5	Omicron BA.5	P13L Δ31ERS33 ΔE136 R203K G204R S413R
B.1.1.529.2.75	OMICRON BA.2.75	P13L Δ31ERS33 R203K G204R S413R

Table 2. SARS-CoV-2 variants NP mutations.

5. Discussions and Conclusion

The SARS-CoV-2 UK variant is estimated to have first emerged in the UK in September 2020[2]. Since December 2020, several countries have reported cases of the B.1.1.7 lineage, including the United States. This variant is associated with increased transmissibility (i.e., 40% to 80% more transmissible)[3-5]. In January 2021, scientists from the UK reported evidence that suggests the B.1.1.7 variant may be associated with an increased risk of death compared with the original strain[6].

The South Africa variant (B.1.351) was first identified in Nelson Mandela Bay, South Africa, in samples dating back to the beginning of October 2020[7], and cases have since been detected outside of South Africa, including the United States. The variant also was identified in Zambia in late December 2020, at which time

it appeared to be the predominant variant in the country[8].

The Brazil variant was identified in Manaus and was named as P.1 lineage. The new variant's detection frequency was increased from 0% in November 2020 to 42% in December 2020[9]. There is evidence to suggest that some of the mutations in the P.1 variant may affect its transmissibility and antigenic profile, which may affect the ability of antibodies generated through previous natural infection or through vaccination to recognize and neutralize the virus. This variant was identified in the United States at the end of January 2021.

The B.1.617.2, also known as Delta variant, was first discovered in India. Descendant of lineage B.1.617, which also includes B.1.617.1, it was first discovered in October 2020 and has since spread internationally[10-12]. On 6 May 2021, British scientists declared B.1.617.2 as a "variant of concern", labeling it VOC-21APR-02 after they flagged evidence that it spreads more quickly than the original version of the virus and could spread as quickly as Alpha (B.1.1.7)[13-14]. On 3 June 2021, Public Health England reported that twelve of the 42 deaths from the B.1.617.2 variant in England were among the fully vaccinated and that it was spreading almost twice as fast as the B.1.1.7 variant[15]. Also on 11 June, Foothills Medical Centre in Calgary, Canada reported that half of their 22 cases of the B.1.617.2 variant occurred among the fully vaccinated[16]. On 14 June 2021, India detected a mutated variant of B.1.617.2 or Delta variant which is known as A.Y or 'Delta Plus' variant[17].

The lineage B.1.525 or Eta variant, does not carry the same N501Y mutation found in B.1.1.7, B.1.351, and P.1, but carries the same E484K-mutation as found in P.1, P.2, and B.1.351 variants, and also carries the same ΔH69/ΔV70 deletion (a deletion of the amino acids histidine and valine in positions 69 and 70) as found in B.1.1.718. B.1.525 differs from all other variants by having both the E484K-mutation and a new F888L mutation. As of March 5, it had been detected in 23 countries, including the UK, Denmark, Finland, Norway, Netherlands, Belgium, France, Spain, Nigeria, Ghana, Jordan, Japan, Singapore, Australia, Canada, Germany, Italy, Slovenia, Austria, Malaysia, Switzerland, the Republic of Ireland and the [US15-18].

The variant B.1.526 was first discovered in November 2020, in New York City[19]. As of 11 April 2021, the variant has been detected in at least 48 U.S. states and 18 countries. In a pattern mirroring Epsilon, Iota was initially able to reach relatively high levels in some states, but by May 2021 it was outcompeted by the more transmissible Delta and Alpha[20].

The Kappa variant B.1.617.11 is one of the three sub-lineages of lineage B.1.617. It is also known as lineage B.1.617.1, 21B,[21] or 21A/S:154K[22,] and was first detected in India in December 2020[23]. By the end of March 2021, Kappa accounted for more than half of the sequences being submitted from India[30]. On 1st April 2021, it was designated a variant under investigation (VUI-21APR-01) by Public Health England[15]. It has notable mutations L452R, E484Q, and P681R[31].

The Lambda variant, also known as lineage C.37, was first detected in Peru in August 2020 and was designated by the WHO as a variant of interest on 14 June 2021[1]. It spread to at least 30 countries[32] around the world and, as of July 2021, it is unknown whether it is more infectious and resistant to vaccines than another strains[33-34].

The lineage B.1.429 or Epsilon variant, was of particular concern[18-19]. B.1.429 is possibly more transmissible, but further study is necessary to confirm this[19]. CDC has listed
B.1.429 and the related B.1.427 as "variants of concern," and cites a preprint for saying that they exhibit a ~20% increase in viral transmissibility, have a "Significant impact on neutralization by some, but not all," therapeutics that have been given Emergency Use Authorization (EUA) by FDA for treatment or prevention of COVID-19, and moderately reduce neutralization by plasma collected by people who have previously infected by the virus or who have received a vaccine against the virus[20-21]. According to WHO, it has been labeled as the Epsilon variant.

The Zeta variant or lineage P.2, a sub-lineage of B.1.1.28 like Gamma (P.1), was first detected in circulation in the state of Rio de Janeiro; it harbors the E484K mutation, but not the N501Y and K417T mutations[35]. It evolved independently in Rio de Janeiro without being directly related to the Gamma variant from Manaus36. Though previously Zeta was labeled a variant of interest, as of July 2021, it is no longer considered as such by the WHO[1].

In March 2021, Linage B.1.620 was discovered in Lithuania. It was named lineage B.1.620[37], also known as the 'Lithuanian strain'. It is found in Central Africa as well as North America[38]. Apart from Lithuania, other European countries including France and Belgium have also found presence of this variant[36]. This lineage

has 23 mutations and deletions compared to the reference strain, some of which are unique mutations. The lineage contains an E484K mutation[37-38]. D614G, a mutation present in the most circulating strain, is also found in this variant[39]. Other notable mutations include P681H and S477N[40].

The SARS-CoV-2 Omicron variant (B.1.1.529) is a variant of SARS-CoV-2. The variant was first reported to the World Health Organization (WHO) from South Africa on 24 November 2021[41]. On 26 November 2021, the WHO designated it as a variant of concern and named it Omicron. The variant contains an unusually large number of mutations, several of which are novel (also known as autapomorphy), and several of which affect the spike protein used for most available vaccines. This level of variation has led to concerns regarding transmissibility, immune system evasion, and vaccine resistance. As a result, the variant was rapidly designated as being "of concern", and travel restrictions were introduced by several countries to limit or slow its international spread. The Omicron variant is comprised of a number of lineages and sub-lineages. The three most common lineages of Omicron currently are B.1.1.529.1, B.1.1.529.1.1, B.1.1.529.2, B.1.1.529.4, B.1.1.529.5, and B.1.1.529.2.75.

Here we have analyzed NP sequences from 17 SARS-CoV-2 variants, B.1.1.7, B.1.351, P.1, B.1.617.2, B.1.525, B.1.526, B.1.617.1, C.37, B.1.427/B.1.429, P2, B.1.620, B.1.1.529.1, B.1.1.529.1.1, B.1.1.529.2, B.1.1.529.4, B.1.1.529.5, and B.1.1.529.2.75. There are 3 variants that have mutations within one of two conjugate antibodies' binding region, P.1 (P80R), B.1.617.1 (D63G), and B.1.617.2 (ΔE62, D63E). No mutations were found in the capture antibody's binding region and conjugate antibody's binding regions. Therefore, the ImmuView® COVID-19 Antigen Home Test should detect these variants without any impact on its performance.

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