SARS-CoV-2 Total and SARS-CoV-2 IgG Assays*

The importance of monitoring emerging SARS-CoV-2 variants to ensure antibody assay effectiveness

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*These tests have not been FDA cleared or approved. This test has been authorized by FDA under an EUA for use by authorized laboratories. This test has been authorized only for detecting he presence of antibodies against SARS-CoV-2, not for any other viruses or pathogens. This test is only authorized for the duration of the declaration that circumstances exist justifying the authorization of emergency use of in vitro diagnostics for detection and/or diagnosis of COVID-19 under Section 564(b)(1) of the Act, 21 U.S.C. § 360bbb-3(b)(1), unless the authorization is terminated or revoked sooner. Product availability may vary by country and is subject to varying regulatory requirements.

SIEMENS Healthineers

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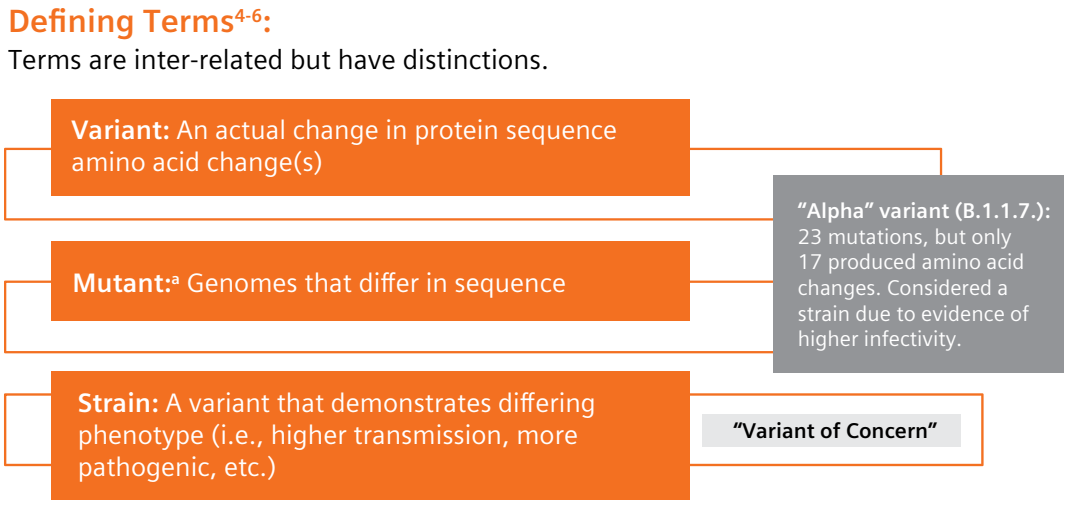
Introduction

SARS-CoV-2 is the RNA coronavirus responsible for the COVID-19 global pandemic. Just when newly approved vaccines (and many more in development) offered the prospect of a return to normalcy, the emergence of highly circulating variants has raised significant concerns about vaccine efficacy.[1-3] To better understand the potential impact of SARS-CoV-2 variants on testing and vaccines, it is important to know the differences between mutants, variants, and strains and understand how variants might compromise SARS-CoV-2 antibody testing. Siemens Healthineers has conducted testing to demonstrate that the Siemens Healthineers SARS-CoV-2 Total (COV2T) and SARS-CoV-2 IgG (sCOVG) assays* are capable of detecting the antibody response to common variants.

Difference between mutants, variants, and strains

The term "viral variant" can be confusing and is often (and incorrectly) used interchangeably with other terms, such as mutations, strains, and lineages.[1] Figure 1 includes formal definitions and distinctions. Mutations are normal, abundant, and expected, especially with an RNA virus. When a mutation or group of mutations confers an advantage, a new variant can emerge. If the altered phenotype allows it to outcompete existing virus (for example, if it is more infectious or more capable of evading immune pressure), it may become the dominant strain.

Figure 1. Definitions.



[a]Mutations have multiple mechanisms and can include changes, insertions and deletions. SARS-CoV-2: amino acid changes and deletions observed in variants of concern.

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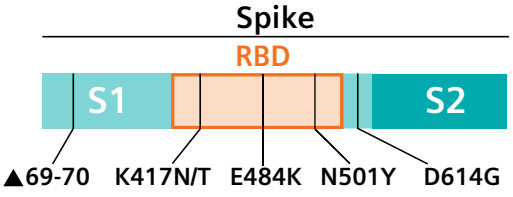
Variants have been with us since the beginning

As confirmed by the recent joint investigation by the World Health Organization (WHO) and Chinese scientific teams, variants have been with us since the dawn of the pandemic.[7] The identification of "variants of concern" (VOC) and/or "variants of interest" (VOI) in several parts of the world (including those first identified in the United Kingdom [B.1.1.7; Alpha], South Africa [B.1.351: Beta, B.1.1.529: Omicron], India (B.1.617; Delta, Kappa), Brazil [P.1; Gamma], and the United States [B.1.427, B.1.429: Epsilon], now detected in multiple countries) has elevated recognition and prompted investigation.[1-3] Currently the Omicron variant has become the dominant strain globally, found in more than 130 countries. A study conducted in France suggested that Omicron may be 105% more transmissible than Delta.[8] More variants continue to be identified globally, as countries initiate enhanced sequence surveillance programs, with the greatest focus on mutations in the spike protein. Concerns include impairment of some diagnostic tests, including a small subset of molecular tests in which the mutation affects primer annealing, and the possibility of changes that enhance athogenesis or transmission.

Figure 2. SARS-CoV-2 variants of concern (as of January 2022).[9]



Name: Alpha (B.1.1.7)	**Name:** Beta (B.1.351)	**Name:** Delta (B.1.617.2)	**Name:** Gamma (P.1)	**Name:** Omicron (B.1.1.529)
First detected: Sept. 2020	**First detected:** Oct. 2020	**First detected:** Oct. 2020	**First detected:** Dec. 2020	**First detected:** Nov. 2021
Country of first detection: United Kingdom	**Country of first detection:** South Africa	**Country of first detection:** India	**Country of first detection:** Brazil	**Country of first detection:** South Africa
Concerns: Increased transmissibility, increased disease severity, reduced response to neutralizing antibodies	**Concerns:** Increased transmissibility, reduced response to neutralizing antibodies	**Concerns:** Increased transmissibility, reduced response to neutralizing antibodies	**Concerns:** Reduced response to neutralizing antibodies	**Concerns:** Increased transmissibility, reduced response to neutralizing antibodies

Figures adapted from:
Xie X. et al. doi: https://doi.org/10.1101/2021.01.27.427998
https://www.astrazeneca.com/what-science-can-do/topics/disease-understanding/the-natural-evolution-of-sars-cov-2.html. Accessed Feb. 15, 2021.
Other sources: https://www.who.int/en/activities/tracking-SARS-CoV-2-variants

What is somewhat surprising in SARS-CoV-2 is how quickly it appears to have compiled multiple mutations within a single variant. One example is the likely more-infectious strain B.1.1.7, first identified in the UK and spread to over 180 countries, including the U.S.[10] The variant shares a mutation with the variants first noted in Brazil and South Africa at position 501 (N501Y) that may increase transmission. Of significant concern with any spike/RBD mutant is the potential for resistance to, or escape from, neutralizing antibodies from recovered infection or, more relevantly, vaccination.

Neutralizing antibodies and variants

All currently approved vaccines (and most in development) target the viral spike protein, which contains the receptor-binding domain (RBD) that recognizes and binds the virus to the ACE2 receptor on the host cell.[11] Therefore, a spike- or RBD-based assay must be used when assessing a vaccine antibody response if the nucleoprotein is not a part of the construct. Abundant data show the RBD is the primary target of neutralizing antibodies.[12-14] Since neutralizing antibodies can interfere with viral binding and so limit infection, they are especially appealing as a mechanism of inducing protection.

Vaccine study data using whole spike show highly correlated detection of binding and neutralizing antibodies using either spike- or RBD-based assays† (unsurprising, as the RBD is contained in the spike).[15-17] Neutralizing antibodies are defined by their ability to inhibit infection in vitro, which often translates to protection in vivo. Vaccine-related data generated with animal models have established the importance of spike/RBD antibodies for protection from SARS-CoV-2 challenge.[18,19] Thus, changes in the RBD are of particular concern, though mutations in the S1-NTD and S2 may also present a potential immune escape adaptation.

Breakthrough infection despite vaccination

Vaccine trial data indicates variants may be more likely to infect despite vaccination, but average disease severity appears lessened. While average antibody levels following vaccination tend to exceed those seen in natural infection, significant variation in levels exists.[20-23]

Quantitative testing, which is technically semiquantitative in the U.S. as no accepted international standard exists, using spike-based assays such as RBD could reveal if the level of antibody matters for protection, as is indicated in in vitro testing. Vaccine manufacturers utilized neutralizing antibody titers as a surrogate of vaccine efficacy in their clinical trials. That is why most current vaccines have a two-dose regimen and vaccine manufacturers such as Pfizer have announced that a booster may be needed, as each boost can stimulate increased neutralizing antibody. Further studies using quantitative neutralizing antibody testing post-vaccination should elucidate this.[24-28] Recently evaluation of data from seven vaccine trials and convalescent plasma further supported a role for the level of neutralizing antibodies in vaccine-induced protection.[29]

Variant testing†

Siemens Healthineers is committed to the continuous monitoring of emerging variants and conducting evaluations to ensure that its assays remain effective at detecting them. Siemens Healthineers Global Assay Development, Tarrytown, NY, USA, recently tested patient samples infected with variants using the Atellica® IM SARS-CoV-2 Total (COV2T)* and SARS-CoV-2 IgG (sCOVG) Assays.*

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†Claims for detection of SARS-CoV-2 variants and detection of neutralizing antibodies have not been reviewed by the FDA and are not available in U.S. Availability of these claims varies from country to country and is subject to varying regulatory requirements.

Gamma (P.1) variant study†

Fourteen specimens identified as Gamma variant-positive through genomic sequencing were evaluated with the Atellica IM COV2T and sCOVG Assays as well as the Genscript C-Pass neutralization antibody test (NAb). The samples were collected from unvaccinated individuals. The S1 RBD amino acid substitutions found in these samples were K417T, E484K and N501Y. The samples were collected between 19 and 31 days after diagnosis by RT-PCR.

Result interpretation†

The COV2T and sCOVG assays cutoff is 1.0 Index (U/mL). Results ≥1.0 Index (U/mL) are reactive, and results <1.0 Index (U/mL) are nonreactive. The C-Pass NAb assay results are interpreted as follows: ≥20% is reactive, <20% is nonreactive.

The COV2T and sCOVG assays of the P.1 variant samples. Based on the limited number of samples analyzed, the study results indicate that the Gamma variant can be detected by both assays. Although the study was conducted on the Atellica IM Analyzer the results also apply to the ADVIA Centaur COV2T and sCOVG assays.

Table 1. Atellica IM SARS-CoV-2 Total and SARS-CoV-2 IgG Assays results demonstrated reactivity in samples with known Gamma variant confirmed by genomic sequencing.†

Sample #	Days after Diagnosis by RT-PCR	sCOVG (Index [U/mL])	COV2T (Index [U/mL])	C-Pass NAb (%)
1	22	6.46	4.38	45%
2	21	13.52	6.59	64%
3	21	11.13	13.48	67%
4	21	27.36	>75	53%
5	31	7.06	9.14	52%
6	26	64.49	45.33	72%
7	21	77.16	36.94	74%
8	21	18.64	31.09	80%
9	30	>150	>75	93%
10	21	104.07	>75	90%
11	21	16.32	30.39	58%
12	19	>150	>75	77%
13	24	38.41	>75	67%
14	21	131.54	71.04	48%

†Claims for detection of SARS-CoV-2 variants and detection of neutralizing antibodies have not been reviewed by the FDA and are not available in U.S. Availability of these claims varies from country to country and is subject to varying regulatory requirements.

Alpha (B.1.1.7) variant study†

Nine specimens identified as Alpha variant positive through PCR testing were evaluated with the Atellica IM COV2T and sCOVG Assays. The samples were collected between 39 and 76 days after diagnosis by RT-PCR. The individuals were unvaccinated.

Result interpretation†

The COV2T and sCOVG assays cutoff is 1.0 Index (U/mL). Results ≥1.0 are reactive, and results <1.0 are nonreactive. The COV2T and sCOVG assays detected 9/9 and 8/9, respectively, of the Alpha variant samples. Based on the limited number of samples analyzed, the study results indicate that the Alpha variant can be detected by both assays. Although the study was conducted on the Atellica IM Analyzer the results also apply to the ADVIA Centaur COV2T and sCOVG assays.

Table 2. Atellica IM SARS-CoV-2 Total and SARS-CoV-2 IgG Assays results in samples with known Alpha variant confirmed through PCR testing.†

Sample #	Days after Diagnosis by RT-PCR	COV2T (Index [U/mL])	sCOVG (Index [U/mL])
1	39	3.51	0.22
2	42	2.54	2.78
3	50	28.71	12.62
4	54	36.04	41.64
5	67	10.56	1.71
6	70	>75	53.11
7	66	49.53	20.82
8	70	10.84	6.31
9	76	31.56	16.38

Delta (B.1.617.2) variant studies†

Atellica IM COV2T and sCOVG Assays Study
Ten specimens identified as Delta variant positive through genomic sequencing were evaluated with the Atellica IM COV2T and sCOVG Assays. The samples were collected between 24 and 45 days after diagnosis by RT-PCR. The individuals were unvaccinated.

Result interpretation†

The COV2T and sCOVG assays cutoff is 1.0 Index (U/mL). Results ≥1.0 are reactive, and results <1.0 are nonreactive. The COV2T and sCOVG assays detected 10/10 of the Delta variant samples. Based on the limited number of samples analyzed, the study results indicate that the Delta variant can be detected by both assays. Although the study was conducted on the Atellica IM Analyzer the results also apply to the ADVIA Centaur COV2T and sCOVG assays.

†Claims for detection of SARS-CoV-2 variants and detection of neutralizing antibodies have not been reviewed by the FDA and are not available in U.S. Availability of these claims varies from country to country and is subject to varying regulatory requirements.

Table 3. Atellica IM SARS-CoV-2 Total and SARS-CoV-2 IgG Assays results in samples with known Delta variant confirmed through PCR testing.†

Sample #	Days after Diagnosis by RT-PCR	COV2T (Index [U/mL])	sCOVG (Index [U/mL])
1	32	>75	100.81
2	24	8.48	32.39
3	26	>75	69.19
4	28	53.85	47.99
5	34	33.69	35.33
6	41	>75	24.18
7	37	>75	16.64
8	33	>75	21.92
9	45	>75	19.51
10	31	>75	114.00

Dimension EXL CV2T and CV2G Assays Study*†

Ten specimens identified as Delta variant positive through PCR testing were evaluated with the Dimension EXL CV2T and CV2G assays. The samples were collected between 24 and 45 days after diagnosis by RT-PCR. The individuals were unvaccinated.

Result interpretation†

The CV2T and CV2G assays cutoffs are 1000 QUAL (CV2T) and 1000 Ind (CV2G) units. Results ≥1000 QUAL or Ind are positive, and results <1000 QUAL or Ind are negative. The CV2T and CV2G assays detected 10/10 of the Delta variant samples. Based on the limited number of samples analyzed, the study results indicate that the Delta variant can be detected by both assays. Although the study was conducted on the Dimension EXL system the results also apply to the Dimension Vista COV2T and COV2G assays.*

Table 4. Dimension EXL SARS-CoV-2 Total and SARS-CoV-2 IgG Assays results in sames with known Delta variant confirmed through PCR testing.†

Sample #	Days after Diagnosis by RT-PCR	CV2T (QUAL)	CV2G (Ind)
1	32	96731	90305
2	24	9178	3950
3	26	46320	40599
4	28	27695	23641
5	34	12414	9531
6	41	22339	13470
7	37	13217	8931
8	33	25792	14764
9	45	18758	8025
10	31	93228	73425

*These tests have not been FDA cleared or approved. This test has been authorized by FDA under an EUA for use by authorized laboratories. This test has been authorized only for detecting he presence of antibodies against SARS-CoV-2, not for any other viruses or pathogens. This test is only authorized for the duration of the declaration that circumstances exist justifying the authorization of emergency use of in vitro diagnostics for detection and/or diagnosis of COVID-19 under Section 564(b)(1) of the Act, 21 U.S.C. § 360bbb-3(b)(1), unless the authorization is terminated or revoked sooner. Product availability may vary by country and is subject to varying regulatory requirements.

†Claims for detection of SARS-CoV-2 variants and detection of neutralizing antibodies have not been reviewed by the FDA and are not available in U.S. Availability of these claims varies from country to country and is subject to varying regulatory requirements.

Omicron (B.1.1.529) variant studies†

Atellica IM COV2T and sCOVG Assays Study
Ten specimens identified as Omicron variant positive through genomic sequencing were evaluated with the Atellica IM COV2T and sCOVG Assays. The samples were collected between 18 and 32 days after diagnosis by RT-PCR. The samples were obtained from unvaccinated individuals with no reported history of previous SARS-CoV-2 infection.

Result interpretation†

The COV2T and sCOVG assays cutoff is 1.0 Index (U/mL). Results ≥1.0 are reactive, and results <1.0 are nonreactive. The COV2T and sCOVG assays detected 10/10 of the Omicron variant samples. Based on the limited number of samples analyzed, the study results indicate that the Omicron variant can be detected by both assays. Although the study was conducted on the Atellica IM Analyzer the results also apply to the ADVIA Centaur COV2T and sCOVG assays.

Table 5. Atellica IM SARS-CoV-2 Total and SARS-CoV-2 IgG Assays results in samples with known Omicron variant confirmed through PCR testing.†

Sample #	Days after Diagnosis by RT-PCR	COV2T (Index [U/mL])	sCOVG (Index [U/mL])
1	27	>75.00	4.48
2	26	>75.00	11.75
3	23	7.13	3.02
4	23	85.70	4.07
5	20	120.12	>150
6	21	52.27	15.58
7	23	>75.00	4.98
8	32	>75.00	4.9
9	32	141.99	2.02
10	18	>75.00	37.38

†Claims for detection of SARS-CoV-2 variants and detection of neutralizing antibodies have not been reviewed by the FDA and are not available in U.S. Availability of these claims varies from country to country and is subject to varying regulatory requirements.

Dimension EXL CV2T and CV2G Assays and Dimension Vista COV2T and COV2G Assays Study

Ten specimens identified as Omicron variant positive through genomic sequencing were evaluated with the Dimension EXL and Dimension Vista SARS-CoV-2 Total and SARS-CoV-2 IgG assays. These were the same samples used in the Atellica IM Omicron evaluation.

Result interpretation†

The SARS-CoV-2 Total and SARS-CoV-2 IgG assays cutoff on both the Dimension EXL and Dimension Vista is 1000 Index/QUAL. Results ≥1000 are reactive, and results <1000 are nonreactive. All assays tested detected 10/10 of the Omicron variant samples. Based on the limited number of samples analyzed, the study results indicate that the Omicron variant can be detected by both assays.

Table 6. Dimension EXL CV2T and CV2G Assays results in samples with known Omicron variant confirmed through PCR testing.†

Sample #	Days after Diagnosis by RT-PCR	CV2T (QUAL)	CV2G (Index)
1	27	9943	9397
2	26	16011	16216
3	23	1620	2503
4	23	6827	5953
5	20	58468	143459
6	21	11089	29068
7	23	11957	8367
8	32	12251	5060
9	32	5563	4341
10	18	48750	57689

Table 7. Dimension Vista COV2T and COV2G Assays results in samples with known Omicron variant confirmed through PCR testing.†

Sample #	Days after Diagnosis by RT-PCR	COV2T (QUAL)	COV2G (Index)
1	27	11060	12882
2	26	18323	20899
3	23	1708	3347
4	23	6833	8343
5	20	62743	128027
6	21	13072	32849
7	23	12921	11280
8	32	12660	7082
9	32	5803	5835
10	18	58737	57896

†Claims for detection of SARS-CoV-2 variants and detection of neutralizing antibodies have not been reviewed by the FDA and are not available in U.S. Availability of these claims varies from country to country and is subject to varying regulatory requirements.

Conclusion

Variants of concern will continue to emerge, and enhanced surveillance will support earlier identification. Currently, data indicate that, at least with most available vaccines, protection is maintained, albeit at a reduced level for some. It is unknown if new viable variants with additional spike mutations will emerge, or what further impact they might have on vaccination effectiveness. Spike/RBD-based quantitative antibody tests could prove highly useful, especially if levels of antibody post-vaccination are confirmed as a relevant correlate of protection from circulating virus, including variants.

- Mutations are normal and expected. When a variant exhibits altered behavior, such as being more infectious, it may become a dominant strain.
- Several variants of concern with RBD mutations have been identified and can at least partially evade some neutralizing antibody.
- Detection of the antibody response to the Alpha, Delta, Gamma, and Omicron variants appears to be mostly maintained with the Siemens Healthineers COV2T and sCOVG assays. Quantitative testing may shed insight on the level of antibody required to reduce likelihood of infection.

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