Updated July 2021 – QIAGEN response to the SARS-CoV-2 variants with increased infectivity

It is well established that RNA viruses frequently mutate due to erroneous or ineffective replication of the viral genome (1). Coronaviruses, including SARS-CoV-2, sustain fewer mutations than most RNA viruses because they encode an enzyme that corrects some of the errors made during replication. In most cases, the fate of a new mutation in the viral genome is determined by natural selection. Those that confer a competitive advantage for viral replication, transmission, or escape from immunity will increase in frequency, and those that reduce viral fitness tend to be removed from the population of circulating viruses. However, mutations can also increase and decrease in frequency due to chance events. A variant is defined by one or more mutations that differentiate it from the reference **variant** and other variants in circulation. As expected, multiple variants of SARS-CoV-2 have been documented globally since the start of the COVID-19 pandemic.

SARS-CoV-2 variant classification

Although multiple viral variants have been detected throughout the pandemic, most appear to have little if any biological significance. However, since late 2020 a small number of variants have been classified as variants of interest (VOI) or variants of concern (VOC) by international health organizations like WHO (2), CDC (3) and ECDC (4).

Variants of concern (VOC) (2-5) are defined as **those for which evidence has been found** of an increase in transmissibility, more severe disease (increased hospitalizations or deaths), significant reduction in neutralization by antibodies generated during previous infection or vaccination, reduced effectiveness of treatments or vaccines, or diagnostic detection failures.

Variants of interest (VOI) (2-4) / **variant under investigation (VUI)** (5) are defined as those containing mutations that have been associated with changes to receptor binding, reduced neutralization by antibodies generated against previous infection or vaccination, reduced efficacy of treatments, potential diagnostic impact, or predicted increase in transmissibility or disease severity.

In silico assessment of the impact of mutations present in VOC and VOI/VUI

To address the possible impact of VOC and VOI/VUI mutations on assay performance, QIAGEN continuously assesses available sequences available from public databases (GISAID) by mapping primer designs of all available products against the mutated sequences of identified variants. This analysis allows for any potential impact on sensitivity to be immediately recognized for any of the QIAGEN assays currently used in the fight against COVID-19: the QIAstat-Dx® Respiratory SARS-CoV-2 Panel*, the NeuMoDx™ SARS-CoV-2 Assay*, the NeuMoDx Flu A-B/RSV/SARS-CoV-2 Vantage Assay*, and the *artus* SARS-CoV-2 Prep&Amp UM Kit*.

Upon the in silico analysis of available sequences of the VOC and VOI/VUI designated by the WHO (2), the CDC (3), the ECDC (4), and PHE (5) in their epidemiological updates (listed on the table below), we conclude that none of the recorded mutations present in the listed strains affects the sensitivity of the QIAGEN assays detecting SARS-CoV-2 to date (6).

Type of variant (VOC/VOI/VUI)									Impact on sensitivity of SARS-CoV-2 detection by			
CDC	ECDC	Public Health England	WHO	WHO label	Pango lineage	Name (Nextstrain clade)	Key Spike Mutations	First detected	QIAstat-Dx Respiratory SARS-CoV-2 Panel	NeuMoDx SARS-CoV-2 Assay	NeuMoDx Flu A-B/ RSV/SARS-CoV-2 Vantage Assay	*artus* SARS-CoV-2 Prep&Amp UM Kit
VOC	VOC	VOC-20DEC-01	VOC	Alpha	B.1.1.7	20I/501Y.V1 (also VOC 202012/01)	Δ69/70, Δ144, (E484K†), (S494P†), N501Y, A570D, D614G, P681H, T716I, S982A, D1118H (K1191N†)	United Kingdom (Sept. 2020)	No impact	No impact	No impact	No impact
VOC	VOC	VOC-20DEC-02	VOC	Beta	B.1.351	20H/501.V2 (also VOC 202012/02)	D80A, D215G, Δ241/242/243, K417N, E484K, N501Y, D614G, A701V	South Africa (May 2020)	No impact	No impact	No impact	No impact
VOC	VOC	VOC-21JAN-02	VOC	Gamma	B.1.1.28.1 (P.1)	20J/501Y.V3 (also VOC 202101/02)	L18F, T20N, P26S, D138Y, R190S, K417T, E484K, N501Y, D614G, H655Y, T1027I	Japan/Brazil (Nov. 2020)	No impact	No impact	No impact	No impact
VOC	VOI	n/a	VOI	Epsilon	B.1.427	20C/S:452R	L452R D614G	US-California (Mar. 2020)	No impact	No impact	No impact	No impact
VOC	VOI	n/a	VOI	Epsilon	B.1.429	20C/S:452R	S13I W152C L452R D614G	US-California (Mar. 2020)	No impact	No impact	No impact	No impact
VOI	VOI	VUI-21FEB-03	VOI	Eta	B.1.525	20A/S:484K	A67V, Δ69/70, Δ144, E484K, D614G, Q677H, F888L	United Kingdom and Nigeria (Dec. 2020)	No impact	No impact	No impact	No impact
VOI	Under monitoring	VUI-21JAN-01	VOI	Zeta	B.1.1.28.2 (alias P.2)	20J / 20B/S.484K	E484K, (F565L†), D614G, V1176F	Brazil (Apr. 2020)	No impact	No impact	No impact	No impact
n/a	VOI	VUI-21MAR-02	VOI	Theta	B.1.1.28.3 (alias P.3)	21E	141-143 deletion; E484K; N501Y; and P681H	Philippines and Japan (Jan. 2021)	No impact	No impact	No impact	No impact
VOI	Under monitoring	n/a	VOI	Iota	B.1.526	20C/S:484K	(L5F†), T95I, D253G, (S477N†), (E484K†), D614G, (A701V†)	USA - New York (Nov. 2020)	No impact	No impact	No impact	No impact

Type of variant (VOC/VOI/VUI)									Impact on sensitivity of SARS-CoV-2 detection by			
CDC	ECDC	Public Health England	WHO	WHO label	Pango lineage	Name (Nextstrain clade)	Key Spike Mutations	First detected	QIAstat-Dx Respiratory SARS-CoV-2 Panel	NeuMoDx SARS-CoV-2 Assay	NeuMoDx Flu A-B/ RSV/SARS-CoV-2 Vantage Assay	*artus* SARS-CoV-2 Prep&Amp UM Kit
n/a	VOI	n/a	n/a	-	B.1.616	20C	G142 deletion; D66H; Y144V; D215G; V483A; D614G; H655Y; G669S; Q949R; and N1187D	France (Feb. 2021)	No impact	No impact	No impact	No impact
n/a	Under monitoring	VUI-21FEB-01	n/a	-	A.23.1 with E484K	-	F157L, V367F, Q613H, P681R, R102I	England, UK	No impact	No impact	No impact	No impact
n/a	VOC	VOC-21FEB-02	n/a	-	B.1.1.7 with E484K	-	Δ69/70, Δ144, E484K, (S494P†), N501Y, A570D, D614G, P681H, T716I, S982A, D1118H (K1191N†)	England, UK (Sept. 2020)	No impact	No impact	No impact	No impact
n/a	Under monitoring	VUI-21FEB-04	n/a	-	B.1.1.318	-	T95I, Δ144, E484K, P681H, D796H	UK	No impact	No impact	No impact	No impact
VOI	n/a	VUI-21APR-01	n/a	-	B.1.617	20A	L452R, E484Q, D614G	India (Feb. 2021)	No impact	No impact	No impact	No impact
VOI	VOI	n/a	VOI	Kappa	B.1.617.1	20A/S:154K	(T95I), G142D, E154K, L452R, E484Q, D614G, P681R, Q1071H	India (Dec. 2020)	No impact	No impact	No impact	No impact
VOI	VOC	VOC-21APR-02	VOC	Delta	B.1.617.2 AY.1 AY2	20A/S:478K 21A	T19R, (G142D), 156del, 157del, R158G, L452R, T478K, D614G, P681R, D950N	India (Dec. 2020)	No impact	No impact	No impact	No impact
VOI	VOI	VUI-21APR-03	n/a	-	B.1.617.3	20A	T19R, G142D, L452R, E484Q, D614G, P681R, D950N	India (Oct. 2020)	No impact	No impact	No impact	No impact
n/a	Under monitoring	VUI-21MAY-01	n/a	-	AV.1	-	D80G, T95I, G142D, 144del, N439K, E484K, D614G, P681H, I1130V, D1139H	UK (Mar 2021)	No impact	No impact	No impact	No impact

Type of variant (VOC/VOI/VUI)									Impact on sensitivity of SARS-CoV-2 detection by			
CDC	ECDC	Public Health England	WHO	WHO label	Pango lineage	Name (Nextstrain clade)	Key Spike Mutations	First detected	QIAstat-Dx Respiratory SARS-CoV-2 Panel	NeuMoDx SARS-CoV-2 Assay	NeuMoDx Flu A-B/ RSV/SARS-CoV-2 Vantage Assay	*artus* SARS-CoV-2 Prep&Amp UM Kit
n/a	VOI	n/a	n/a	-	B.1.620	-	S477N, E484K, D614G, P681H	Unclear (Feb 2021)	No impact	No impact	No impact	No impact
n/a	VOI	n/a	n/a	-	B.1.621	-	R346K, E484K, N501Y, D614G, P681H	Colombia (Jan. 2021)	No impact	No impact	No impact	No impact
n/a	Under monitoring	VUI-21JUN-01	VOI	Lamda	C.37	20D	L452Q, F490S, D614G	Peru (Dec 2020)	No impact	No impact	No impact	Potential impact in vitro tests ongoing
n/a	Under monitoring	VUI-21MAY-02	n/a	-	C.36+L4 52R	-	L452R, D614G, Q677H	Egypt (2020)	No impact	No impact	No impact	No impact

† Detected in some sequences but not all.

The majority of the listed variants above concentrate the highest incidence of genetic variability in the S-gene that encodes for the Spike protein. None of the assays included in the QIAGEN products target the S-gene to detect SARS-CoV-2. Most of the few mutations that occur within the nucleocapsid and other ORF regions are not predicted to alter the annealing efficiency of the oligonucleotides used in the assays. One mutation, however, characteristic to Lambda variant (C.37 lineage), can potentially impact detection of N1 target of *artus* SARS-CoV-2 Prep&Amp UM Kit.

	QIAstat-Dx Respiratory SARS-CoV-2 Panel	NeuMoDx SARS-CoV-2 Assay	NeuMoDx Flu A-B RSV/ SARS-CoV-2 Vantage Assay	*artus* SARS-CoV-2 Prep&Amp UM Kit
Genomic regions targeted by the QIAGEN products	E-gene & Orf1ab gene	N- gene & Nsp2 gene	Nsp2 gene	N1 and N2 gene
Relevant mutations identified in current variants	Eta variant (B.1.525 lineage) contains one identified mismatch in gene E assay binding region. This mutation located in a non-critical position and no impact on annealing efficiency or assay performance is predicted.	Alpha variant (B.1.1.7 lineage) contains one identified mismatch in gene Nsp2 assay binding region. This mutation located in a non-critical position and no impact on annealing efficiency or assay performance is predicted. B.1.616 lineage contains one identified mismatch in gene N assay binding region. This mutation is located on a non-critical position and no impact on annealing efficiency or assay performance is predicted.		B.1.616 lineage contains one identified mismatch in gene N1 assay binding region. This mutation is located on a non-critical position and no impact on annealing efficiency or assay performance is predicted. B.1.620 lineage contains one identified mismatch in gene N1 assay binding region. This mutation is located in a non-critical position and no impact on annealing efficiency or assay performance is predicted. Lambda variant (C.37 lineage) contains one identified mismatch in gene N1 assay binding region. This mutation is located in a critical position and its impact on assay's performance is going to be checked experimentally.

Genetic variability alignment and impact assessment using all sequences available on public databases

In addition to this assessment of publicly identified VOCs and VOIs/VUIs of SARS-CoV-2, QIAGEN also performs a thorough surveillance activity. This includes the analysis of all sequences of SARS-CoV-2 available from public databases (GISAID) to ensure designs utilized on available products remain unaffected by mutations found with any significant frequency. Regulatory Authorities/Agencies recommendations are strictly followed to perform both *in-silico* and in vitro testing when required.

After performing the analysis following our published methodology (6,7) for all QIAGEN assays currently used in the fight against COVID-19: the QIAstat-Dx Respiratory SARS-CoV-2 Panel, the NeuMoDx SARS-CoV-2 Assay, the NeuMoDx Flu A-B/RSV/SARS-CoV-2 Vantage Assay, and the *artus* SARS-CoV-2 Prep&Amp UM Kit, it was concluded that over 98.5% of the genomes analyzed and so far contained either no mismatches or no mismatches located in critical positions of the oligonucleotide binding sites.

The small number of sequences that contained any mutations in critical positions of the binding sites of the oligonucleotides have been assessed based on their prevalence and increased frequency. The few mutations for which some level of criticality has been encountered will be tested in vitro to ensure the sensitivity of the QIAGEN assays is kept as specified.

From the onset of the novel coronavirus outbreak, QIAGEN's dedicated global teams have been working around the clock to support the worldwide fight against COVID-19. We will continue with our genetic variation surveillance on a regular basis. Please do not hesitate to reach out to your local QIAstat-Dx, NeuMoDx, or *artus* specialist with questions.

References:

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