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Siemens Healthineers Molecular Diagnostic Response to COVID-19

16 September 2021

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MDX, Siemens Healthineers, MESA

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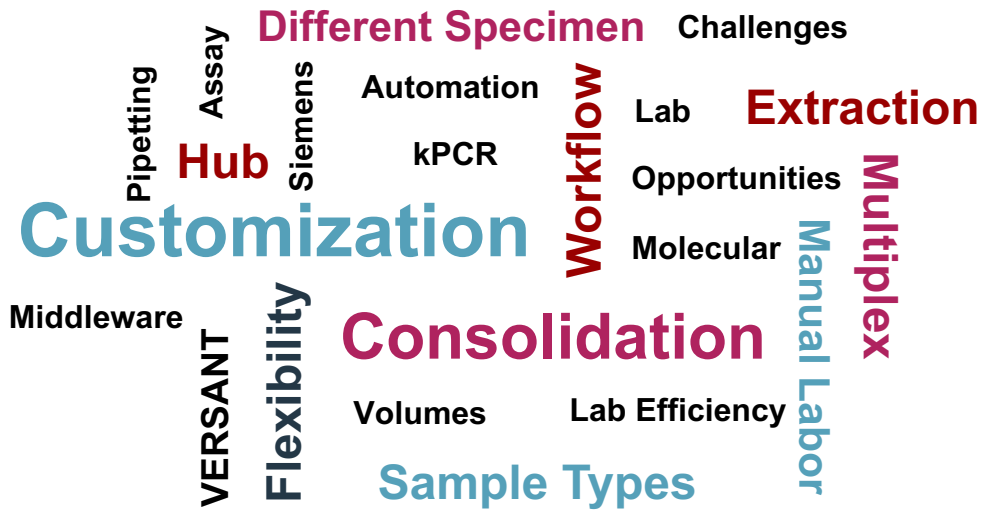
Siemens Healthineers Molecular Diagnostics Approach & Portfolio

Molecular Diagnostics Laboratories: Challenges and Needs



Siemens Healthineers Molecular Dx Approach

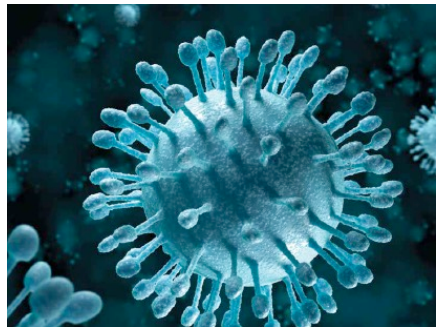
- Syndromic approach
- Large assay menu
- Multiplexing
- Same protocol for all kits
- Compatibility

Siemens Healthineers offers flexible and easy workflow solutions and innovations to help you overcome your laboratory challenges!

Siemens Healthineers Molecular Portfolio

Toward Precision Medicine

KPCR	LiPA	TPS	FTD	Future



Fast Track DIAGNOSTICS
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Extraction and PCR Set up	VERSANT® HCV Genotyping LiPA Market leader in HCV genotyping	Tissue Preparation System Fully-automated nucleic acid extraction from FFPE and fresh frozen tissues	Broad range of Multiplex Syndromic PCR assays

Product availability varies and is subject to country-specific regulatory requirements.

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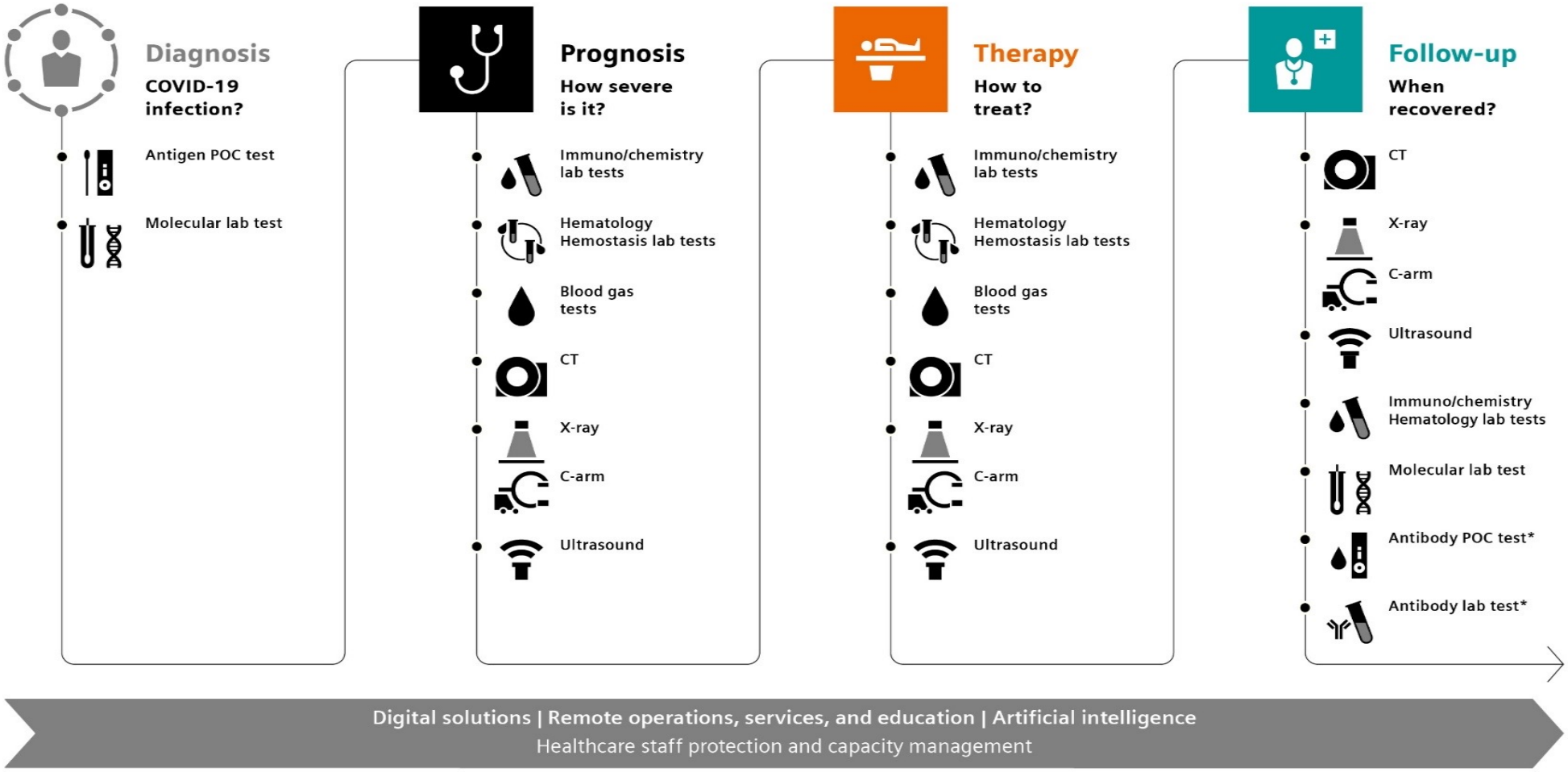
Siemens Healthineers DX COVID-19 Testing Solutions

COVID-19 patient pathway



* To help indicate an immune response

This pathway is for illustration purposes only. (Status Nov. 20. 2020)

The path to normalcy: COVID-19 testing options

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From the lab to the point of care, a full portfolio of COVID-19 testing solutions that consistently delivers sensitivity and performance—to get us to what's next

Satellite Testing

Near-patient testing can be used to identify and isolate infected people more quickly.

Point-of-care Rapid Antigen Testing

Rapid antigen testing can help communities **get ahead of the spread**.

CLINITEST® Rapid COVID-19 Antigen Test[1]

Anterior nasal swab

97.3% sensitivity

100.0% specificity

Nasopharyngeal swab

97.3% sensitivity

100.0% specificity

15 min to result[2]

Large-scale Testing and Diagnosis

Clinicians use diagnostic tests to determine if people have current COVID-19 infections, enabling patient management decisions.

High-throughput Lab Antigen Testing

Intended for **fast, safe and accurate, high-scale** community screening..

SARS-CoV-2 Antigen Assay[3]

Anterior nasal swab[4]

Nasopharyngeal swab

98.0% sensitivity[5]

100.0% specificity

26 min time to first result[2]

Up to 440 tests/hr[6]

Molecular PCR Testing

Gold standard for accurate and early detection of infection.[9]

FTD SARS-CoV-2 Assay[10]

Nasopharyngeal swab

Oropharyngeal swab[11]

100.0% sensitivity[11]

100.0% specificity[11]

<3 hr For 24 tests[12]

<7 hr For 96 tests[12]

Management and Monitoring

Management and monitoring are critical in determining the full scope of the disease, combating the pandemic, and rebuilding public confidence.

High-throughput Lab Antibody Testing

Highly accurate for detection and monitoring of immune response through infection and in vaccination.

SARS-CoV-2 Total Assay[10]

Blood draw

100.0% sensitivity[16]

99.8% specificity

10 min time to first result[2]

Up to 440 tests/hr[6]

SARS-CoV-2 IgG Assay[10]

Blood draw

Finger stick[15]

96.4% sensitivity[16]

99.9% specificity

24 min time to first result[2]

Up to 440 tests/hr[6]

Point-of-care Antibody Testing

OnSite COVID-19 IgG/IgM Rapid Test

Finger stick

97.8% sensitivity

97.1% specificity

15 min to result[2]

1. Distributed by Siemens Healthineers. CLINITEST Rapid COVID-19 Antigen Test: Not available for sale in the U.S. Product availability may vary by country.
2. Analytical time: time to generate a result on the cartridge or analytical device.
3. This test has not been reviewed by the FDA. In the U.S., use of this test is limited to laboratories that are certified under Clinical Laboratory Improvement Amendments of 1988 (CLIA) to perform high-complexity testing.
4. Anterior nasal swab only available in the U.S.
3. Product availability may vary by country and is subject to regulatory requirements.
5. Evaluated with PCR-positive results of symptomatic and asymptomatic individuals categorized by cycle threshold <29 (Ct) values 4. of a comparative PCR method. Tested with the Atellica® IM SARS-CoV2Ag Assay using the Atellica® IM Analyzer.
6. Depending on test mix and configuration using the Atellica® Solution. The Atellica IM SARS-CoV2Ag Assay5. has a throughput of 200 tests per hour.
7. Atellica IM assay LoD. ADVIA Centaur® CoV2Ag Assay LoD = 20.8 TCIDS0/mL
8. Installed base of ADVIA Centaur XP, ADVIA Centaur XPT, and Atellica Solution analyzers.
9. IFCC interim guidelines on molecular testing of SARS-CoV-2 infection.. https://doi.org/10.1515/cclm-2020-1412, September 18, 2020.
10. The SARS-CoV-2 molecular and antibody tests have not been FDA-cleared or approved. These tests have been authorized by FDA under an EUA for use by authorized laboratories. The molecular test has been authorized only for the detection of nucleic acid from SARS-CoV-2, not for any other viruses or pathogens. The antibody test has been authorized only for detecting the presence of antibodies against SARS-CoV-2, not for any other viruses or pathogens. These tests are 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 from country to country and is subject to varying regulatory requirements.
11. FTD SARS-CoV-2 Assay (CE-IVD) Instructions for Use 11416283_en Rev. B, 2020-12 and FTD SARS-CoV-2 Assay (EUA) Instructions for Use 11416299_en Rev. C, 2021-01.
12. Turnaround times are calculated based on theoretical analysis with one NUCLISENS EASYMAG and one Thermo Fisher ABI7500; not based on real workflow study. Using more instruments would decrease the total turnaround time.
13. https://www.fda.gov/medical-devices/coronavirus-covid-19-and-medical-devices/sars-cov-2-reference-panel-comparative-data. Accessed on March 2, 2021.
14. Data on file at Fast Track Diagnostics, A Siemens Healthineers Company, Luxembourg.
15. Some claims are not available in all countries. The SARS-CoV-2 IgG assays are for semiquantitative use in the U.S. The semiquantitation claim for the SARS-CoV-2 Total assays is not available.
16. The fingerstick claim is not available in the U.S. Claims for detection of neutralizing antibodies and correlation to PRNT are not available in the U.S. and are under development for the COV2T assays. Not available for sale in the U.S. Product availability may vary from country to country and is subject to varying regulatory requirements. For samples collected ≥21 days after positive PCR result, using the Atellica Solution.
17. Evaluation of sensitivity and specificity of four commercially available SARS-CoV-2 antibody immunoassays. Public Health England. 2020 Jul. GW-1386
18. Installed base of ADVIA Centaur XP, ADVIA Centaur XPT, ADVIA Centaur CP, Atellica Solution, Dimension Vista®, and Dimension® EXL™ analyzers.

HOOD0516203175384

FTD SARS-CoV-2 Assay

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Assay design

- Single-tube dual target assay covering highly conserved regions ORF1ab and N gene
- Same dye/channel for the two target regions
  - Increased signal
  - Lower chance for inconclusive results
  - Optimized detection of possible mutants

Target	Detection dye/channel
N	FAM/Green
ORF1ab	FAM/Green
IC (Equine Arteritis Virus)	Cy5/Red

Primer/probe regions

**CE-IVD labelled for diagnostic use in the EU. This test has 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 the detection of nucleic acid from 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.*

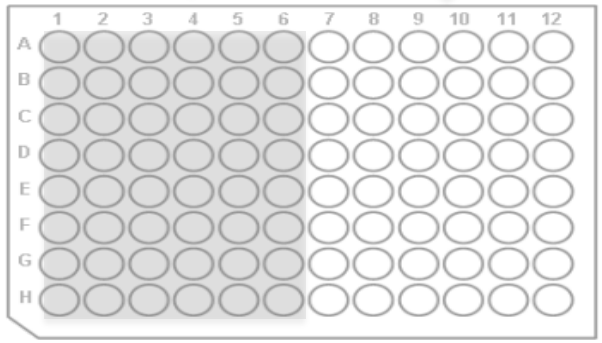
Different systems and laboratory space

Platform – agnostic workflow

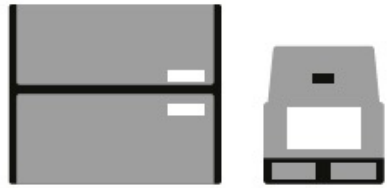
Extraction	PCR set up	Amplification detection	Analysis Interpretation

Different compatible extractors and manual methods*

SARS-CoV-2 FLU/HRSV



Same PCR cycling profile for all FTD assays



Different compatible thermocyclers*

* refer to compatibility list

VERSANT kPCR molecular system with FTD SARS CoV-2 assay: Siemens automation solution for sample-to-result

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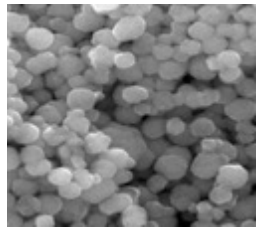
VERSANT® kPCR Molecular System

Nucleic Acid Extraction + PCR Set up + PCR run + Analysis

Sample Collection

VERSANT® kPCR SP Module



VERSANT Sample Preparation 1.0 Reagent kit

+

VERSANT kPCR AD Module (QS5 DX MiPLX SWv2.0)

FTD SARS-CoV-2 Kit

Result Analysis and Interpretation

Proficiency study for sensitivity with FDA Reference Panel

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- FDA provided protocol and reference SARS-CoV-2 sample panel to document and publish comparable analytical sensitivity or limit of detection (LOD) performance among all EUA manufacturers.
- **FTD SARS-CoV-2 Assay on the VERSANT kPCR Molecular System** is ranked as one of the **TOP FIVE most-sensitive tests out of 117 manufacturers** listed on the FDA website.
- Limit of detection of **540 NDU/mL*** provides better sensitivity than most other kit manufacturers

*

Product LoD (NDU/mL)	Developer	Test
180	PerkinElmer, Inc.	PerkinElmer New Coronavirus Nucleic Acid Detection Kit
180	Viracor Eurofins Clinical Diagnostics	Viracor SARS-CoV-2 assay
450	Zymo Research Corporation[1]	Quick SARS-CoV-2rRT-PCR Kit
540	ScienCell Research Laboratories	ScienCell SARS-CoV-2 Coronavirus Real-time RT-PCR (RT-qPCR) Detection Kit
540	Fast Track Diagnostics Luxembourg S.á.r.l. (a Siemens Healthineers Company)	FTD SARS-COV-2

https://www.fda.gov/medical-devices/coronavirus-covid-19-and-medical-devices/sars-cov-2-reference-panel-comparative-data?utm_medium=email&utm_source=govdelivery

*NAAT detectable units/mL (NDU/mL): calibration unit of FDA reference sample delivered by FDA to all manufacturers for LoD determination.

Emergence of variants: A fast response from FTD…

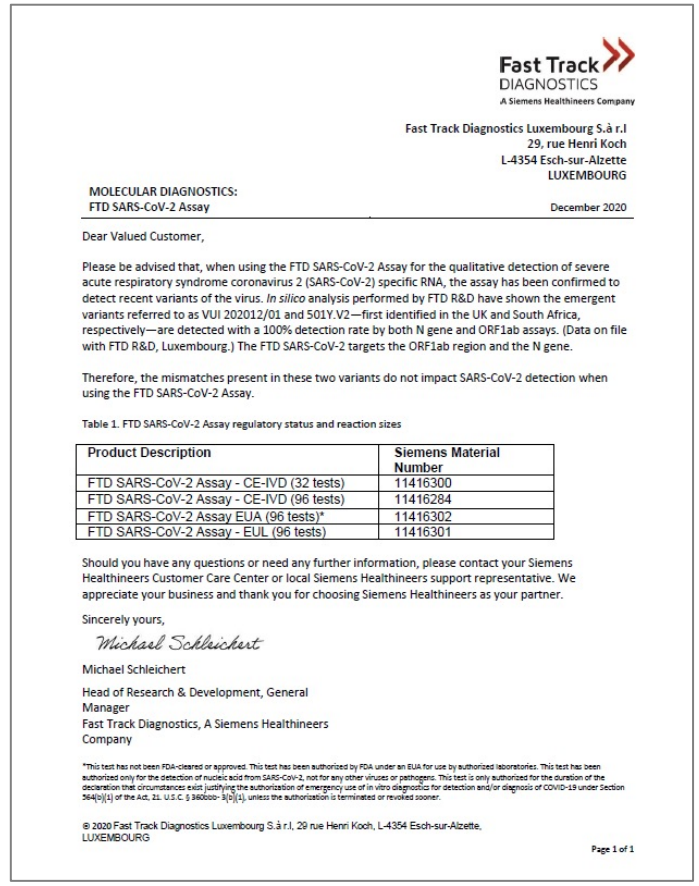
- *In silico* analysis on a large number of sequences was performed to investigate any possible change in detection of these 2 emerging variants with the FTD SARS-CoV-2 Assay

- The *in silico* analysis has shown that the emergent variants are detected with a **100% detection rate** by both N gene and ORF1ab assays*

- **Customer letter** issued on December 28, 2020

- *In silico* analysis is an ongoing process by FTD to determine assay performance on new variants as they emerge. So far, over 1.2 million complete sequences of SARS-CoV-2 have been tested giving similar (100%) detection rate

- Another **customer letter**: June 2021



Fast Track DIAGNOSTICS
A Siemens Healthineers Company

Fast Track Diagnostics Luxembourg S.à r.l
29, rue Henri Koch
L-4354 Esch-sur-Alzette
LUXEMBOURG

MOLECULAR DIAGNOSTICS:
FTD SARS-CoV-2 Assay — December 2020

Dear Valued Customer,

Please be advised that, when using the FTD SARS-CoV-2 Assay for the qualitative detection of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) specific RNA, the assay has been confirmed to detect recent variants of the virus. *In silico* analysis performed by FTD R&D have shown the emergent variants referred to as VUI 202012/01 and 501Y.V2—first identified in the UK and South Africa, respectively—are detected with a 100% detection rate by both N gene and ORF1ab assays. (Data on file with FTD R&D, Luxembourg.) The FTD SARS-CoV-2 targets the ORF1ab region and the N gene.

Therefore, the mismatches present in these two variants do not impact SARS-CoV-2 detection when using the FTD SARS-CoV-2 Assay.

Table 1. FTD SARS-CoV-2 Assay regulatory status and reaction sizes

Product Description	Siemens Material Number
FTD SARS-CoV-2 Assay - CE-IVD (32 tests)	11416300
FTD SARS-CoV-2 Assay - CE-IVD (96 tests)	11416284
FTD SARS-CoV-2 Assay EUA (96 tests)*	11416302
FTD SARS-CoV-2 Assay - EUL (96 tests)	11416301

Should you have any questions or need any further information, please contact your Siemens Healthineers Customer Care Center or local Siemens Healthineers support representative. We appreciate your business and thank you for choosing Siemens Healthineers as your partner.

Sincerely yours,

Michael Schleichert

Michael Schleichert

Head of Research & Development, General Manager
Fast Track Diagnostics, A Siemens Healthineers Company

*This test has 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 the detection of nucleic acid from 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.

* Data on file

FTD SARS-CoV-2 assay

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CE IVD
April 27

EUA
May 5

WHO Listing
May 21

WHO listed assays	Supplier	CE	FDA	WHO
FTD-114 SARS-CoV-2	**Siemens/FTD**	✓	✓	✓
Cobas SARS-CoV-2 Qualitative	**Roche**	✓	✓	✓
Primerdesign Ltd COVID-19 genesig Real-Time PCR	**Primerdesign**	✓	✓	✓
Abbott Realtime SARS-CoV-2	**Abbott**	✓	✓	✓
PerkinElmer® SARS-CoV-2 Real-time RT-PCR	**Perkin Elmer**	✓	✓	✓
Real-time fluorescent RT-PCR kit for detecting 2019-nCoV	**BGI**	✓	✓	✓
Detection Kit for 2019-nCoV RNA	**Da An Gene Co**	✓		✓
Multiple Real-Time PCR Kit for Detection of 2019-nCoV	**Beijing ABT Co**	✓		✓
Novel Coronavirus (SARS-CoV-2) Multiplex RT-PCR Kit	**Liferiver**	✓		✓

WHO Emergency Use Listing (EUL) - Product eligible for listing

Product name: FTD SARS-CoV-2 (FTD-114-32)
Application number: EUL 0502-193-00
Product codes: 11416300
Regulatory version: CE marked version

World Health Organization

21 May 2020

Dear Dr Schleichert,

Subject: **WHO Emergency Use Listing (EUL) - Product eligible for listing**

Product name: FTD SARS-CoV-2 (FTD-114-32)
Application number: EUL 0502-193-00
Product codes: 11416300
Regulatory version: CE marked version

We are pleased to inform you that the above-referenced product was listed as eligible for WHO procurement on **21 May 2020.** The EUL listing can be leveraged by other international, regional and national procurement agencies. The product will be eligible for procurement for 1 year, unless circumstances dictate otherwise.

Please be advised that the on-going eligibility status of the above-referenced product depends on fulfilling the commitments to EUL listing identified in the "Dossier review complete" letter sent **21 May 2020.**

The following activities are required to maintain the eligibility status:

1. Notification to WHO of any planned changes to the above-referenced product, in accordance with "*WHO procedure for changes to a WHO prequalified in vitro diagnostic*" (document number PQDx_121); and
2. Post-market surveillance activities, in accordance with "*WHO guidance on post-market surveillance of in vitro diagnostics*" (ISBN 978 92 4 150921 3).

Failure to comply with any of the above-mentioned requirements may lead to remedial action by WHO, including but not limited to, de-listing from the WHO EUL procedure list of eligible in vitro diagnostics products.

منظمة الصحة العالمية • 世界卫生组织
Organisation mondiale de la Santé • Всемирная организация здравоохранения • Organización Mundial de la Salud

https://www.who.int/diagnostics_laboratory/eual/listing/en/

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Molecular Diagnostics: COVID-19 Variants Response

Variants of Concern (VOC) and Variants of Interest (VOI)*

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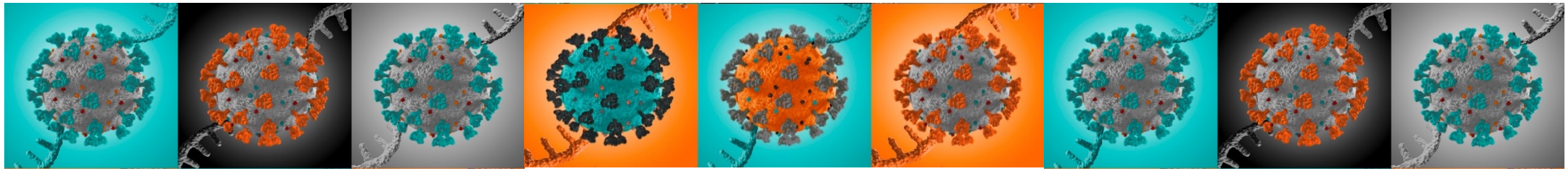
	VOC				VOI			
WHO label	Alpha	Beta	Gamma	Delta	Kappa	Iota	Eta	Lambda
Country first identified	UK	SA	BRA	India	India	USA (NY)	UK	Peru
Common name	VOC 202012-01	501Y.V2	P.1				VUI-202102/03	
Next strain	20I/501Y.V1	20H/501YV2	20J/501Y.V3	20A/S:478K	20A/S:154K	20C/S:484K	20A/S484K	20D
GISAID	GR/501Y.V1	GH/501Y.V2	GR/484K.V2				G/484K.V3	GR/452Q.V1
Lineage (Pango)	B1.1.7	B.1.351	P.1 /B.1.1.28.1	B.1.617.2	B.1.617.1	B.1.526	B.1.525	C.37



* https://www.who.int/en/activities/tracking-SARS-CoV-2-variants/

Current Testing Strategies and Algorithms for SARS-CoV-2 Mutations and Variants*

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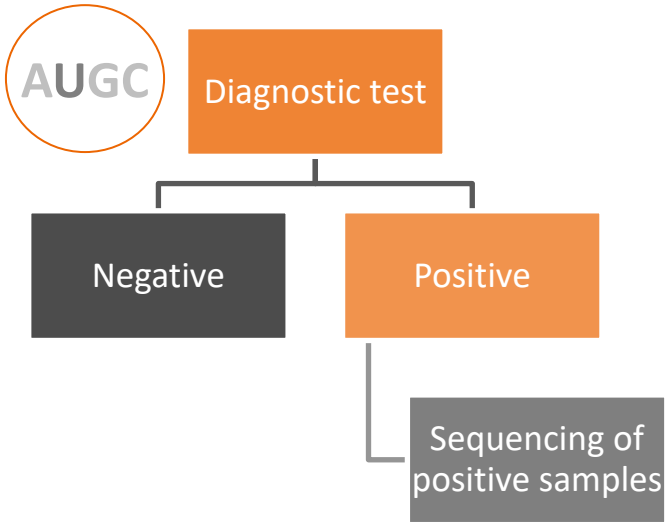
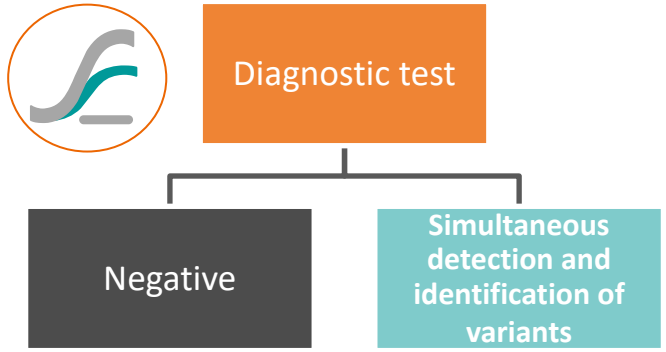


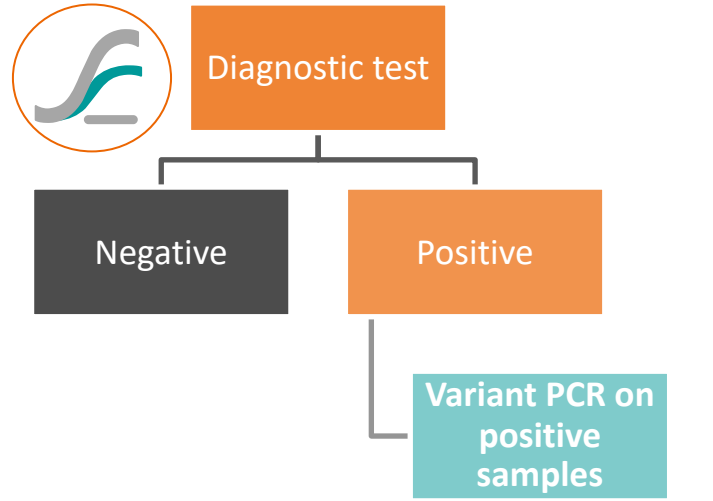
GOLD STANDARD

- **Comprehensive mutation information**
- **New mutations/variants discovery**
- Long TAT
- Potential sensitivity issue especially for samples with low viral load



FIRST LINE ASSAY

- **Replaces the routine diagnostics assay**
- **Faster TAT**
- **Limited number of mutations**
- Detects known mutations
- Complex development



REFLEX ASSAY

- **High sensitivity for diagnosis**
- **Easy to implement**
- Flexible approach with evolution of new mutations/variants
- Detects known mutations

https://www.ecdc.europa.eu/sites/default/files/documents/Methods-for-the-detection-and-identification-of-SARS-CoV-2-variants-WHO-ECDC.pdf

Siemens Healthineers Strategy for SARS-CoV-2 Mutation Detection and Variant Identification

The Siemens Healthineers approach provides molecular laboratories an **add-on, flexible workflow solution** for the surveillance of critical SARS-CoV-2 mutations and the identification of variants without affecting routine testing for SARS-CoV2 diagnosis.

Reflex testing approach

Cost effective Fast and easy to implement

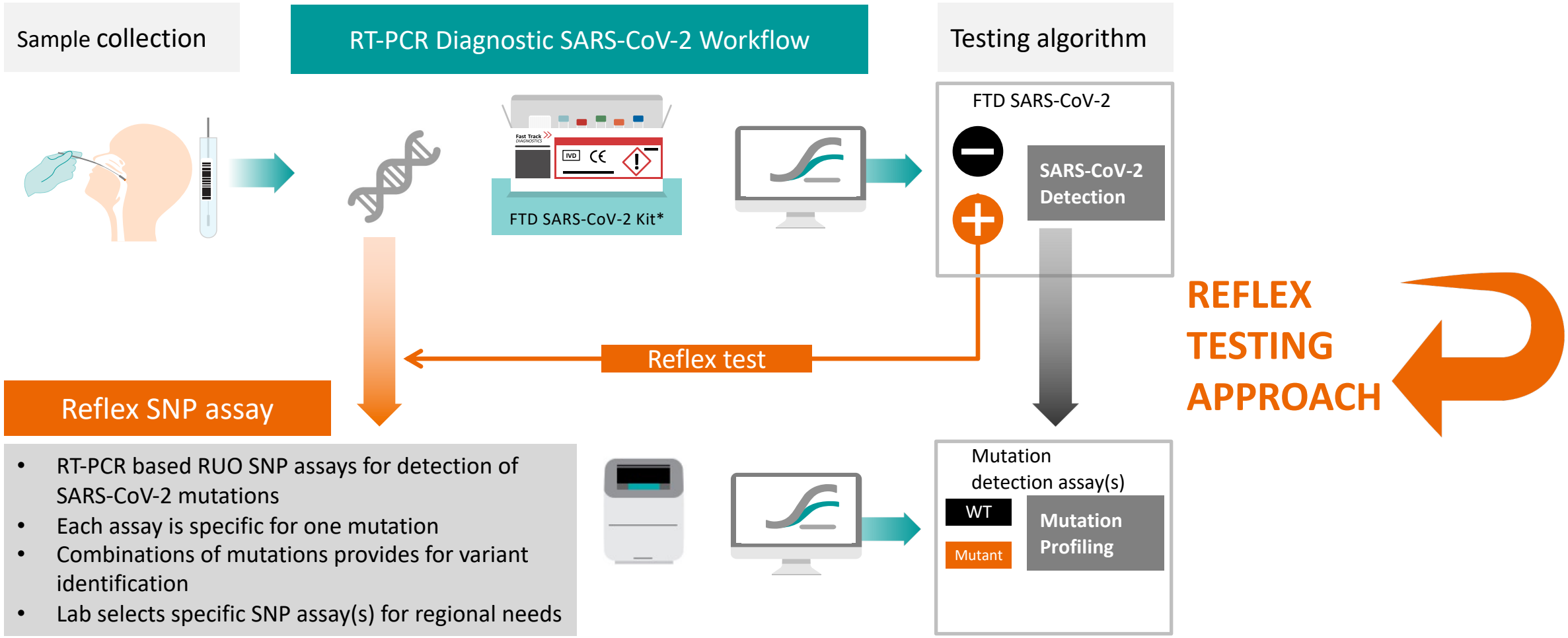
SNPs assays for mutation profiling

Detection of **critical mutations** that might appear due to convergent evolution

Flexible and **regionalized** solution to detect variants

High sensitivity and broad testing infrastructure vs. sequencing approach

Reflex Testing Approach for Detection of SARS-CoV-2 Mutations/Variants



- RT-PCR based RUO SNP assays for detection of SARS-CoV-2 mutations
- Each assay is specific for one mutation
- Combinations of mutations provides for variant identification
- Lab selects specific SNP assay(s) for regional needs

*CE-IVD–labeled for diagnostic use in the EU. This test has 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 the detection of nucleic acid from 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.

DIAGNOVITAL SARS-CoV-2 Mutation Detection Assays

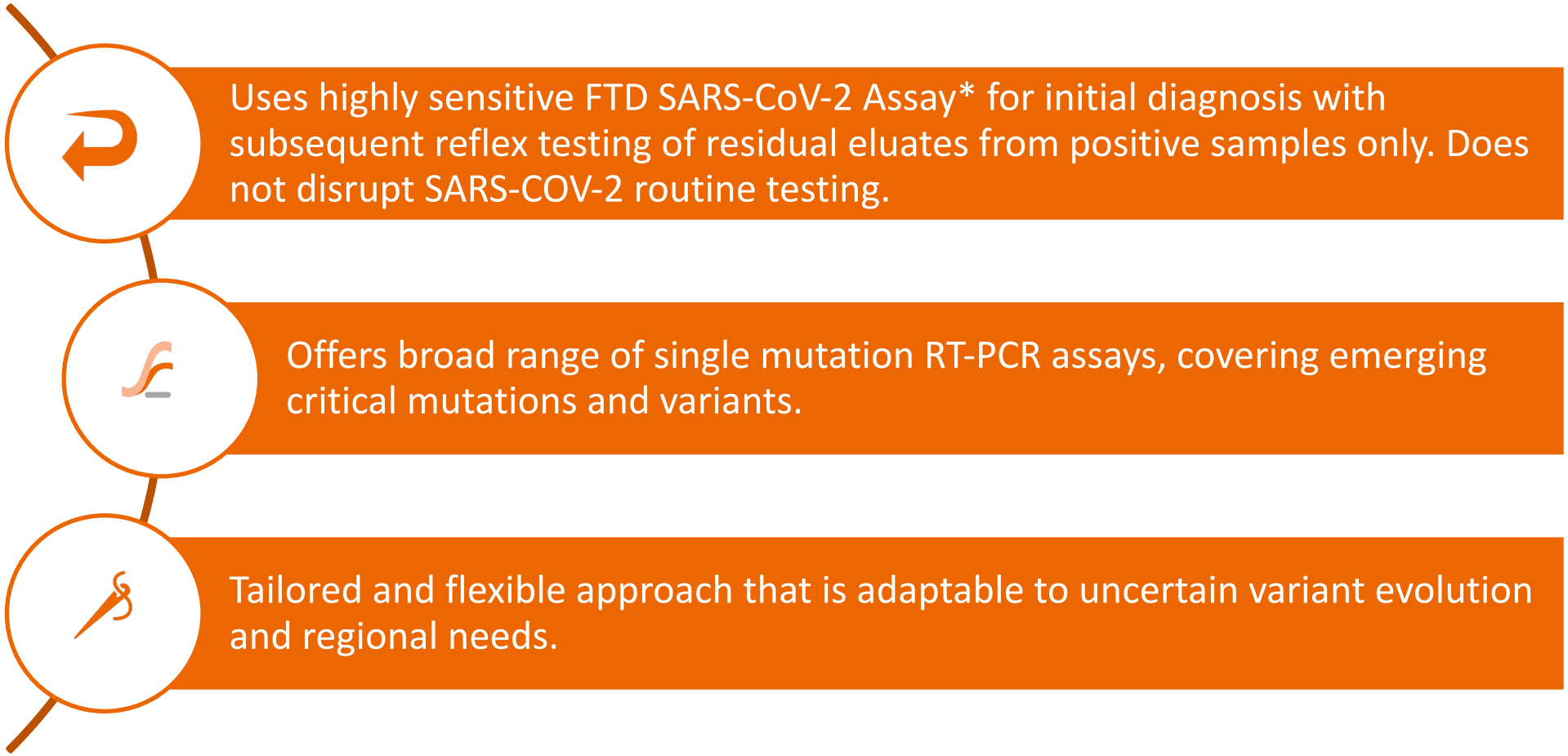
A1 LIFE SCIENCE

	VOC				VOI (WHO)			
WHO label	Alpha	Beta	Gamma	Delta	Kappa	Iota	Eta	Diagnovital kits
Pango lineage	B1.1.7	B.1.351	P1	B.1.617.2	B.1.617.1	B.1.526	B.1.525	
69/70 del	x						x	Diagnovital SARS-CoV-2 del HV69/70 Mutation Detection Kit (RUO*)
K417N		x						Diagnovital SARS-CoV-2 K417N Mutation Detection Kit (RUO*)
L452R				x	x			Diagnovital SARS-CoV-2 L452R Mutation Detection Kit (RUO*)
E484K		x	x			x	x	Diagnovital SARS-CoV-2 E484K Mutation Detection Kit (RUO*)
E484Q					x			Diagnovital SARS-CoV-2 E484Q Mutation Detection Kit (RUO*)
N501Y	x	x	x					Diagnovital SARS-CoV-2 N501Y Mutation Detection Kit (RUO*)

- Six single mutation reflex RT-PCR assays selected for the detection of critical mutations and the identification of Variants of concern (VOC) and major variants of interest (VOI)

*For Research Use Only.

Siemens Healthineers Total Solution for SARS-CoV-2 Diagnosis, Mutation Detection, and Variant Identification



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Thank you for your enthusiasm!

Said Al Dhahiry (Dr.)

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