WGene SARS-CoV-2

RT Detection

Method for the detection of RNA sequences of the SARS-CoV-2 virus by Real Time Polymerase Chain Reaction

SUMMARY

The coronavirus is a positive-sense single-stranded RNA virus that can cause a variety of acute and chronic diseases in domestic and pet animals and humans.

In late 2019, a new coronavirus was identified from viral pneumonia cases in Wuhan, China. This new virus was named by the International Committee on Taxonomy of Viruses (ICTV) as SARS-CoV-2. The disease caused by the SARS-CoV-2 is called COVID-19, which has mild forms with few or no symptoms until cases with pneumonia and death in more serious cases. The most common symptoms are fever, cough, pain in throat, loss of smell (anosmia) and taste (dysgeusia), difficulty breathing and dyspnea.

The RNA of the SARS-CoV-2 generally is detected in samples of the upper respiratory tract (nasopharyngeal or oropharyngeal swabs, saliva, etc.) during the acute phase of infection. Positive results are indicative of the presence of SARS-CoV-2 RNA. It is recommended to assess the clinical correlation with the patient history and other diagnostic parameters to help determine the infection status.

Positive results do not discard bacterial coinfection or coinfection with other viruses. Negative results do not exclude SARS-CoV-2 infection and should not be used as the sole basis for patient treatment decisions. Negative results should be combined with clinical observations, patient history and epidemiological information.

PRINCIPLE

WGene SARS-CoV-2 RT Detection is an "in vitro" test that includes the reverse transcription of viral RNA specific sequences, followed by one-step real-time PCR amplification (one step RT-qPCR). This qualitative detection test of viral genome sequences, is performed from respiratory biological samples (nasopharyngeal or oropharyngeal swabs) of individuals suspected of COVID-19.

The kit detects two of the viral genes of greater diagnostic relevance: RdRp (corresponding to the viral RNA polymerase RNA dependent) and N (corresponding to the nucleocapsid).

The complete procedure consists in the viral RNA purification of the biological sample, which is then used at the reverse transcription stage followed by real time PCR using TaqMan® type probes.

RNA of SARS-CoV-2 is transcribed to cDNA (DNA copy) by the reverse transcriptase enzyme, which is used as template for PCR amplification using a Hot Start DNA polymerase enzyme. During the PCR reaction, the enzyme exonuclease activity causes the TaqMan® type probe degradation, separating the fluorophore from the quencher. The increase in the fluorescence signal resulting from the accumulation of the tempered DNA is detected by the real-time PCR instrument: FAM channel for joint detection of RdRp and N genes, and YAK channel (Yakima Yellow, or VIC/JOE/HEX) for RNase P gene detection as endogenous internal control. This endogenous control ensures the presence of nucleic acids in the clinical sample and the absence of inhibitors in the amplification reaction.

Is necessary to include a reaction Negative Control (NC) to confirm the absence of reagent contamination. Thus, nuclease-free water (RNase / DNase-free H_2O reagent) is used as a sample. In case of a positive result, repeat the test searching for possible sources of contamination and discarding them.

PROVIDED REAGENTS

PC SARS-CoV-2/IC: Positive Control that consists in DNA sequences specific to SARS-CoV-2. It also includes DNA from an endogenous Internal Control (IC). Dry reagent in transparent tube x 0.5 ml with red cap.

RT Mix SARS-CoV-2 (40x): reaction mixture for viral RNA and IC reverse transcription. Contains: 100 mM DTT reaction buffer, 40 U/µl RNase inhibitors, Reverse Transcriptase, water treated with DEPC, stabilizers and preservatives. Liquid reagent in transparent tube x 0.5 ml with amber cap.

Master Mix SARS-CoV-2 (5x): reaction mixture for the amplification/detection of the cDNA resulting from reverse transcription. Contains: reaction buffer, 250 mM KCl, 1 mM dNTPs, Hot Start DNA polymerase, 15 mM $MgCl_2$, reducing agents, stabilizers and preservatives. Liquid reagent in transparent tube x 0.5 ml with blue cap.

Oligo Mix SARS-CoV-2: mixture of oligonucleotides and probes for the specific amplification of SARS-CoV-2 and IC sequences. Dry reagent in conical base tube x 1.5 ml.

RNase/DNase-free H_2O: nuclease-free water. Liquid reagent in transparent tube x 2 ml with transparent cap.

NON-PROVIDED REAGENTS AND EQUIPMENT

- Commercial RNA purification system (using silica columns or magnetic particles).
  Note: While the **WGene SARS-CoV-2 RT Detection** was validated with the products listed below, similar commercial systems may be used.
  • MagnaPure Compact Nucleid Acid Isolation Kit (Roche, Cat. 03 730 964 001)
  • High Pure Viral Nucleid Acid Kit (Roche, Cat. 11 858 874 001)
  • EasyPure Viral DNA / RNA kit (TransGen Biotech, Cat. TGB-ER20102)
- Variable volume micropipettes
- Nuclease-free filter tips
- Nuclease-free microcentrifuge tubes (x 1.5 or 2 ml)
- Rack for 1.5 ml or 2 ml tubes
- Disposable latex, vinyl, or nitrile gloves without powder
- Reaction support according to the real-time PCR instrument used (e.g. microplates with optical films, qPCR tubes, etc.)
- Thermocycler or real-time PCR instrument: different commercial brands may be used, provided they have fluorescence detection channel for FAM and YAK/JOE/VIC.
  Note: this product has been validated in the following thermal cyclers:
  • QuantStudio® 3 (Applied Biosystems)
  • StepOne Plus® (Applied Biosystems)
  • Applied Biosystems 7500® (Applied Biosystems)
  • CFX96® (Biorad)
  • Gene Q® rotor (Qiagen)
  • Light Cycler 480® (Roche)
  • Mic® qPCR Thermal Cycler - 4 (Biomolecular Systems)
  • Mastercycler® RealPlex (Eppendorf)
- Vortex shaker
- Tabletop microcentrifuge with rotor for 1.5 to 2 ml tubes
- Container for the disposal of biological material
- Personal protective equipment

WARNING

- The reagents are for "in vitro" diagnostic use.
- All patient samples should be handled as if they were capable of transmitting infection.
- All components must be completely thawed (once reconstituted), homogenized and briefly centrifuged before starting the assay. It is recommended to keep them refrigerated, especially the DNA amplification mix. The latter must be smoothly homogenized, avoiding foam formation.
- Do not use the reagents after the expiration date.
- Do not interchange reagents from different lots or modify the test procedures.
- Do not use reagents of different origin than indicated.
- All reagents and samples must be discarded according to current local regulations.
- Prevent the components from undergoing microbial or nuclease contamination, when adding different elements.
- If the RNA purification system to be used contains washing solutions with ethanol, ensure the elimination of possible traces before eluting the RNA since it inhibits the qPCR reaction.
- It is essential for the use of this product to have the basic knowledge in the management of molecular diagnostic techniques. Due to the high sensitivity of amplification technology, it is necessary to respect the indicated work rules for this type of analysis (sample processing areas, pre and post amplification, workflow, use of appropriate material, etc.).

STABILITY AND STORAGE INSTRUCTIONS

The kit can be transported refrigerated (2-10ºC). Once received, store the kit at -20ºC until the expiration date indicated on the box.
Once lyophilized reagents are resuspended, store them at -20ºC.
Avoid repeated freeze/thaw cycles of reagents (no more than three cycles) as they may cause reactivity loss.
In case of not using the reagents regularly, it is advisable to divide them into aliquots and store at -20ºC, noting the use of nuclease-free material and that the Oligo Mix SARS-CoV-2 reagent contains probes that require to be protected from light.

SAMPLE

RNA purified from nasopharyngeal or oropharyngeal swab

a) Collection and transport of the respiratory sample:

The samples must be collected and transported in accordance with the recommendations of the local health authorities.

b) RNA purification:
The RNA was purified according to the requirements and instructions of the manufacturer of the RNA extraction kit used, which must be compatible with the qPCR methodology, ensuring high quality purified RNA.
The procedure was performed in safety conditions suitable for handling of infectious materials (according to M29-Protection of Laboratory Workers from Occupationally Acquired Infections document of the NCCLS).
c) RNA stability and storage instructions:
Molecular assays are particularly sensitive to suboptimal preanalytical conditions, so the quality of the sample to be used is essential.
The purified RNA should be kept in an ice bath and/or cold block until use. If it is necessary to store it for a longer period, it should be stored at ≤ -70ºC. If necessary, to avoid more than one freeze/thaw cycle, it is recommended to aliquot.

COMPLETE TEST PROCEDURE

1- RNA extraction (see SAMPLE)

2- Reconstitution of lyophilized reagents
Perform a brief centrifugation to avoid losses when opening the tubes.
In the pre-amplification area:
Reconstitute the Oligo Mix SARS-CoV-2 reagent using 110 µl RNase / DNase-free H_2O reagent. Mix by vortexing for 30 seconds leaving for 5 minutes at room temperature, homogenize again and centrifuge briefly before use. Keep reconstituted reagent refrigerated (on ice or cold block) during use.
Store reconstituted reagent at -20ºC after use.
In the amplification area:
Reconstitute the PC SARS-CoV-2/IC reagent using 500 µl RNase / DNase-free H_2O reagent. Mix by vortexing for 30 seconds leaving for 5 minutes at room temperature, homogenize again and centrifuge briefly before use.
Store reconstituted reagent at -20ºC after use.

3- Preparation of the reaction mixture
In the pre-amplification area:
Thaw reagents completely and mix.
RT Mix SARS-CoV-2 (40x) and Master Mix SARS-CoV-2 (5x) reagents should be mixed gently avoiding foaming and placed immediately in ice or cold block once thawed.
Perform a brief centrifugation to avoid losses when opening the tubes.
Prepare the reaction mixture following the proportions indicated in the table, considering the number of reactions to perform in the test.

Reagent	Volume per reaction (µl)	Volume per n reactions (µl)
RT Mix SARS-CoV-2 (40x)	0.5	
Master Mix SARS-CoV-2 (5x)	4	
Oligo Mix SARS-CoV-2	1	
RNase / DNase-free H_2O	9.5	

n = Nº of clinical samples to test + PC SARS-CoV-2/IC (duplicate) + NC (Negative Control) + 10%

Dispense 15 µl of the reaction mixture in each tube/reaction well.
Add 5 µl of the clinical sample or controls to the corresponding wells/reaction tubes, as follows:
- Samples to test: 5 µl of purified RNA corresponding to each sample
- NC: 5 µl RNase/DNase-free H_2O reagent
- PC: 5 µl PC SARS-CoV-2/IC reagent

The final reaction volume is 20 µl.
It is always recommended to handle the samples in the area designated for this purpose and the PC in the amplification area, to avoid contaminating the other reagents.
Close the reaction tubes/wells and start the reaction in the thermal cycler.

4- Programming the thermal cycler
It is necessary to have basic information regarding the handling and programming of the thermal cycler to be used, therefore it is recommended to refer to the corresponding User Manual.
The general conditions to perform the qPCR reaction are the following:

General conditions	
Program	Absolute quantification
Reaction volume	20 µl
Passive reference dye*	Not provided
Enzyme type (Taq)	Standard
Chemistry type	Hydrolysis probe

*Only in equipment using passive dyes (Applied Biosystems® 7500, StepOne™, StepOnePlus™, QuantStudio™, etc.)

Fluorescence detectors	
Detection	**Fluorophore** (absorption/emission)
SARS-CoV-2	FAM (492 nm / 516 nm)
IC	YAK* (530 nm / 550 nm)

*The absorption / emission spectrum is like JOE/VIC

Amplification and detection program				
Stage	**Temperature**	**Time (min:sec)**	**Cycles**	**Acquisition**
Reverse transcription	50ºC	10:00	1	
Denaturation/ Taq Activation	95ºC	10:00	1	-
Amplification	95ºC	0:15	45	Yes*
	58ºC	0:30		

*Fluorescence data should be recorded during the extension step (58ºC).

5- Analysis of the results

It is important to have basic information regarding the data analysis procedure of the thermal cycler used in the qPCR reaction, so it is recommended to refer to the User Manual.

To analyze the amplification curves, it is necessary to get the following parameters: baseline and fluorescence threshold value. These parameters can be selected automatically by the program, according to the algorithm used, or manually.

Both parameters influence the determination of the Ct value (cycle that exceeds the fluorescence threshold value) for each sample.

• The baseline must include the PCR cycles in which the fluorescence signal is located below the detection limits of the instrument (normally a Ct value range from 3 to 15).

• The fluorescence threshold value should be set in the exponential phase of the amplification curves of the positive samples for the temperate being analyzed. Generally, it is fixed around 10% with respect to the maximum fluorescence of the overall plateau of the amplification curves.

ASSAY VALIDATION CRITERIA

Once the above parameters have been defined, the test is considered valid if the following terms are simultaneously met:

Control	**Detection in FAMTM** (Ct)	**Detection in YAKTM** (Ct)
PC	≤ 32	≤ 32
NC	> 40	> 35*

* Eventually nonspecific signals can be observed in the NC in the YAK channel, which do not have a sigmoid shape and usually appear at Ct > 35.

INTERPRETATION OF RESULTS FOR CLINICAL SAMPLES

- A detectable sample for SARS-CoV-2 is considered when, in the FAM fluorescence channel, an amplification curve is observed that crosses the threshold, giving rise to a value of Ct ≤ 40.
- A non-detectable sample for SARS-CoV-2 is considered when, in the FAM fluorescence channel, the fluorescence curve does not cross the threshold resulting in the absence of Ct or it intersects with a value greater than 40.
- The samples must also detect IC, presenting an amplification curve in the YAK channel that crosses the fluorescence threshold with Ct ≤ 35. However, for detectable samples for SARS-CoV-2 (FAM channel) IC amplification may be inhibited (not detectable in YAK channel), not invalidating the result (See note 1 in the table below).

In case a sample is of doubtful interpretation or invalid, it is recommended to repeat the test starting from a new RNA purification or to collect a new patient respiratory sample.

Sample	Detection in FAM	Detection in YAK	Result interpretation
A	Detectable (Ct ≤ 40)	Detectable (Ct ≤ 35) / Not Detectable (Ct > 35)[1]	Presence of SARS-Cov-2 RNA
B	Not Detectable (Ct > 40)	Detectable (Ct ≤ 35)	Absence of RNA from SARS-Cov-2
C	Not Detectable (Ct > 40)	Not Detectable (Ct > 35)	Invalid[2]

[1] IC detection in the YAK channel (detectable YAK) is not required for detectable results in the FAM channel.

[2] qPCR inhibition problem with RNA purification and/or clinical sample collection.

TEST LIMITATIONS

- Any diagnostic result obtained with this kit should be interpreted together with other clinical and/or laboratory findings.
- Negative results do not rule out SARS-CoV-2 infection and should not be the sole basis for patient treatment decision.
- A positive result indicates SARS-CoV-2 nucleic acid detection.
- False positive results may come up due to cross contamination by SARS-CoV-2, due to samples containing high viral RNA concentrations or contamination due to PCR products of previous reactions.
- False negative results may be due to: inadequate sample collection; viral RNA degradation during shipment/storage; presence of qPCR inhibitors, etc.

TEST SPECIFICATIONS

1- Analytical Sensitivity - Limit of Detection (LOD)

Analytical sensitivity was determined by testing samples of different SARS concentrations by octuplicate, repeating the scheme for 4 days (32 data for each concentration). Samples were prepared from a quantified SARS-CoV-2 complete viral RNA (AMPLIRUN® CORONAVIRUS SARS-CoV-2 RNA CONTROL, Vircell, Ref. MBC137-R) in a pool of SARS-CoV-2 negative oropharyngeal swab samples. A summary of the positive results obtained are as follows:

SARS-CoV-2 controls (copies / reaction)	No. of positives					% positive
	Day 1	Day 2	Day 3	Day 4	TOTAL	
50	8	8	8	8	32	100
25	8	8	8	8	32	100
10	8	8	8	8	32	100
5	4	2	6	5	17	53.13
2.5	3	1	0	2	6	18.75
1	0	0	0	0	0	0
0.5	0	0	0	0	0	0
0.25	0	0	0	0	0	0

With the above data, a Probit regression analysis was carried out. **WGene SARS-CoV-2 RT Detection** showed a LOD of 9.6 copies/reaction for a 95% CI.

2- Analytical Specificity

***In silico* Analysis**

The *in silico* analysis is performed by comparing the sequences of the oligonucleotides/probes used in **WGene SARS-CoV-2 RT Detection** with the nucleic acid sequences phylogenetically related microorganisms and/or that may be present in the clinical sample. It is defined as cross reactivity the presence of nucleotide identity above 80% between the oligonucleotides and any sequence present in the target microorganism. After this analysis, no cross-reactivity was found with species other than SARS-CoV-2, except with the sequence of the SARS-CoV-2 virus. It was identified that the oligonucleotides of the RdRp gene yielded an identity greater than 80%, having the probe an identity of 88%. Based on this analysis, it cannot be ruled out that this virus is amplified and detected by **WGene SARS-CoV-2 RT Detection**. However, SARS-CoV virus has not been detected in human population since 2004 (*https://www.cdc.gov/sars/index.html*).

The following table lists the pathogens included in the *in silico* analytical specificity analysis.

Microorganism	GenBank access number
Human coronavirus 229E	NC_002645.1
Human coronavirus HKU1	NC_006577.2
Human Coronavirus NL63	NC_005831.2
Human coronavirus OC43 strain ATCC VR-759	NC_006213.1
Middle East respiratory syndrome coronavirus	NC_019843.3
SARS coronavirus	NC_004718.3
Bat coronavirus BM48-31/BGR/2008	NC_014470.1
Human adenovirus type 1	AC_000017.1
Human parainfluenza virus 1 isolate NM001	KX639498.1
Human parainfluenza virus 2 isolate VIROAF10	KM190939.1
Human parainfluenza virus 3 strain HPIV3/AUS/3/2007	KF530243.1
Respiratory syncytial virus strain B/WI/629-Q0190/10	JN032120.1
Human enterovirus D	NC_001430.1
Human rhinovirus 14	NC_001490.1
Human metapneumovirus strain HMPV/Homo sapi-ens/PER/FPP00726/2011/A	KJ627437.1
Influenza A virus (A/New York/PV305/2017(H1N1))	MH798556.1
Influenza B virus (B/Nicaragua/8689_13/2017)	MK969560.1
Bordetella pertussis strain B3921	CP011448.1
Candida albicans strain L757 mitochondrion	NC_018046.1
Haemophilus influenzae PittGG	CP000672.1
Legionella pneumophila strain Philadelphia_1_CDC chromo-some	CP015928.1
Mycobacterium tuberculosis DNA strain: HN-506	AP018036.1
Mycoplasma pneumoniae strain 14-637 chromosome	CP039772.1
Pneumocystis jirovecii isolate SW7_full mitochondrion	MH010446.1
Pseudomonas aeruginosa UCBPP-PA14	CP000438.1
Staphylococcus aureus subsp. aureus NCTC 8325 chromosome	NC_007795.1
Staphylococcus epidermidis ATCC 12228	NC_004461.1
Staphylococcus epidermidis ATCC 12228 plasmid pSE-12228-01	NC_005008.1
Staphylococcus epidermidis ATCC 12228 plasmid pSE-12228-02	NC_005007.1
Staphylococcus epidermidis ATCC 12228 plasmid pSE-12228-03	NC_005006.1
Staphylococcus epidermidis ATCC 12228 plasmid pSE-12228-04	NC_005005.1
Staphylococcus epidermidis ATCC 12228 plasmid pSE-12228-05	NC_005004.1
Staphylococcus epidermidis ATCC 12228 plasmid pSE-12228-06	NC_005003.1
Streptococcus pneumoniae strain D39V chromosome	CP027540.1
Streptococcus pyogenes MGAS8232	AE009949.1
Streptococcus salivarius strain FDAARGOS_259 chromosome	CP020451.2

***In vitro* Assay**

Nucleic acid samples from other respiratory pathogens that may be cross-reactive and generate false positive results with the **WGene SARS-CoV-2 RT Detection** Kit were tested.

The following table lists the pathogens tested:

Identified pathogen	SARS-CoV-2 result	IC result
Adenovirus humano TIPO A/B/C/D/E	Negative	Positive
Rhinovirus TIPO A/B/C	Negative	Positive
Moraxella catarrhalis	Negative	Positive
Haemophilus influenzae	Negative	Positive
Influenza A	Negative	Positive
Rhinovirus TIPO A/B/C	Negative	Positive
Streptococcus pneumoniae	Negative	Positive
Coronavirus 229E/NL63	Negative	Positive

The product did not show cross-reactivity with any of the pathogens tested in the assay.

3- Inclusivity Study

The in silico analysis was performed using the 16.378 SARS-CoV-2 virus sequences available worldwide in the GISAID database (Global Initiative on Sharing All Influenza Data, *https://www.gisaid.org*), access 13 of May 2020. Considering the identities presented by the oligonucleotides designed in the RdRp and N genes, 16.347 (99.8%), the sequences presented 100% identity with at least one of the genes. The remaining 31 sequences presented 1 unpaired base (mismatch) in some of the oligonucleotides involved.

4- Precision Study

The precision was determined through the evaluation of a clinical sample diluted in negative matrix (MC-1), the positive control (PC) and a SARS RNA sample of 50 copies/reaction, in 3 different instruments (QuantStudio® 3 (Applied Biosystems), Mic qPCR Thermal Cycler - 4 (Biomolecular Systems) and Mastercycler® RealPlex (Eppendorf)) repeating the scheme for 5 days. A summary of the parameters obtained is as follows:

Sample	Ct SARS-CoV-2 average	SD repeatability	CV repeatability	Intra instrument SD	Intra instrument CV	Reproducibility SD	Reproducibility CV
CP kit	28.78	0.16	0.6%	0.22	0.8%	0.45	1.6%
MC-1	29.50	0.11	0.4%	0.21	0.7%	0.35	1.2%
SARS-CoV-2	32.40	0.26	0.8%	0.34	1.1%	0.49	1.5%

The **WGene SARS-CoV-2 RT Detection** kit yields a coefficient of variation (CV) for all tested samples <2% in the intra and inter instrument determinations, confirming the robustness of the product.

5- Clinical Validation

The clinical validation of the **WGene SARS-CoV-2 RT Detection** was performed by the analysis of 185 clinical samples previously tested with a reference method which is commonly used for the diagnosis of infection by SARS-CoV-2 virus, 113 negative and 72 positive samples were tested for SARS-CoV-2. The table shows the summary of the results obtained:

		Reference method		
		Positive	Negative	TOTAL
WGene SARS-CoV-2 RT Detection	Positive	72	0	72
	Negative	0	113	113
	TOTAL	72	113	185

% concordance +	100%
% concordance -	100%

The **WGene SARS-CoV-2 RT Detection** kit showed 100% agreement with the reference method in the samples tested.

WIENER LAB. PROVIDES

- Kit for 100 tests (Cat. Nº 1060080)

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Symbols

The following symbols are used in the packaging for Wiener lab. diagnostic reagent kits.

This product fulfills the requirements of the European Directive 98/79 EC for "in vitro" diagnostic medical devices

Authorized representative in the European Community

"In vitro" diagnostic medical device

Contains sufficient for <n> tests

Use by

Temperature limitation (store at)

Do not freeze

Biological risks

Volume after reconstitution

Contents

Batch code

Manufactured by:

Harmful

Corrosive / Caustic

Irritant

Consult instructions for use

Calibrator

Control

Positive Control

Negative Control

Catalog number

Product authorized in the context of the health emergency due to COVID-19

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