RIDA®QUICK Rota/Adeno/Noro Combi

REF N1903

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1. Intended use

For *in vitro* diagnostic use. RIDA®QUICK Rota/Adeno/Noro Combi is a single step immunochromatographic lateral flow assay for the qualitative detection of rotaviruses, adenoviruses, and noroviruses from genogroups I and II in human stool specimens.

2. Summary and explanation of the test

Rotavirus is a double-stranded RNA virus of the family Reoviridae. These viruses have a low infectious dose. The virus is transmitted from person to person by direct contact through a fecal-oral route and less often through contaminated water and food. The rotavirus is one of the most important etiological pathogens of acute gastroenteritis throughout the world and is the primary cause of severe dehydration in children between six months and two years in developing countries, where mortality is high, and in industrialized countries. At the age of five years, the majority of children (> 95 %) have had at least one episode of gastroenteritis caused by rotavirus. Even though vaccines help reduce the incidence, only a few countries have integrated them into their national vaccination program. Rotavirus is divided into seven antigen serogroups (A to G). Only groups A, B, and C infect people. Group A is the triggering factor in almost all cases in industrialized as well as developing countries.

Adenovirus is the third most common cause of viral gastroenteritis in children (10 % to 15 %). It can cause respiratory diseases and, depending on serotype, diarrhea, conjunctivitis, cystitis, and other diseases. At least 51 adenovirus serotypes were identified, and the hexon antigen is present in all of them. Mainly serotypes 40 and 41 are associated with gastroenteritis. The primary clinical symptom of gastroenteritis caused by adenovirus is diarrhea lasting 9 to 12 days, accompanied by fever and vomiting.

Norovirus has single-stranded RNA with positive polarity and belongs to the Caliciviridae family. It is very contagious, and it is transmitted mainly through person-to-person contact and through contaminated food/water. The virus usually causes major epidemics in closed communities (hospitals, nursing homes, schools, preschools, restaurants, cruise ships, etc.) in which the infection spreads very quickly once the virus gets into the communities. Several studies have shown that norovirus is the main cause of viral gastroenteritis at all ages worldwide and is responsible for nearly 50 % of gastroenteritis outbreaks. Noroviruses are divided into five genogroups (GI to GV). The majority of clinical cases are due to strains of genogroups I and II. In general, GI infections are less common than GII infections.

The virus is divided into genotypes within each genogroup. As many as 19 different genotypes have been described in genogroup II. Of those, GII.4 is the most common, and it accounts for nearly 60 % to 80 % of cases worldwide. This genotype is followed by GII.6, GII.1, and GII.3.

3. Test principle

RIDA®QUICK Rota/Adeno/Noro Combi is a single step immunochromatographic procedure for the qualitative individual detection of antigens from rotavirus, adenovirus, and norovirus genogroup I (GI) and genogroup II (GII) in human stool specimens. A positive signal in a test line indicates to the physician that a rotavirus, adenovirus, and/or norovirus infection may be present. This is intended to help diagnose the patient. The assay is based on the immunological capture of stained microparticles as they flow along a membrane on which specific monoclonal antibodies to rotavirus, adenovirus, and norovirus GI and GII were immobilized in a double cassette on four separate lines on two strips.

The **Rota-Adeno strip** uses the following combination:

a. Blue latex particles that are conjugated to a specific antibody to the adenovirus hexon antigen that interacts with an adenovirus-specific antibody (T1 line) found on the membrane.
b. Red latex particles that are conjugated to a specific antibody to the VP6 antigen of rotaviruses of group A that interacts with a rotavirus-specific antibody (T2 line) found on the membrane.
c. Green latex particles that are conjugated to a hapten that is recognized by a specific antibody, bound to the membrane, for the said hapten, at which point the control line (C line) forms.

The **Norovirus strip** uses the following combination:

a. Red latex particles that are conjugated to a specific antibody to GGII and interact with specific antibodies for GII found on the membrane (GG2 line).
b. Red latex particles that are conjugated to a specific antibody to GGI and interact with specific antibodies for GGI found on the membrane (GG1 line).
c. Green latex particles that are conjugated to a hapten that is recognized by a specific antibody, bound to the membrane, for the said hapten, at which point the control line (C line) forms.

First, the specimen will be treated with the sample dilution buffer (provided in the kit) for extraction of the viruses from the stool matrix. After the extraction, all the technician needs to do is add a certain volume of supernatant to the two reactive strips and wait 15 minutes. When the extracted specimen flows through the test membrane of the two strips, the stained particles migrate. In a positive sample, the specific antibodies present in the respective membrane will capture the colored particles. Different colored lines are visible depending on the virus the sample contains. The result will be interpreted based on these lines after an incubation period of 15 minutes at room temperature.

4. Reagents provided

The reagents in the kit are sufficient for 20 determinations.

Table 1: Reagents provided

Kit components	Amount	Description
Cassette	20 assays	20 individually packed test cassettes
Tube	20 x 1.5 mL	20 vials with sample buffer; ready to use
Pipet	20 pc.	Bag with 20 disposable pipettes

5. Storage instructions

The package can be stored at 2 - 30 °C and can be used until the printed expiration date. After the expiration date, the quality guarantee is no longer valid. Likewise, the usability of the cassettes cannot be guaranteed if the external packaging of the individual cassette is damaged.

6. Reagents required but not provided

6.1 Necessary reagents

The RIDA®QUICK Rota/Adeno/Noro Combi kit contains all necessary reagents.

6.2 Necessary laboratory equipment

The following equipment is required for carrying out the RIDA®QUICK Rota/Adeno/Noro Combi assay:

Equipment
Vortex mixer (optional)
Stopwatch/timer
Waste container containing 0.5 % hypochlorite solution

7. Warnings and precautions for the users

For *in vitro* diagnostic use only. This test must be carried out only by trained laboratory personnel. The guidelines for working in medical laboratories must be followed. Always adhere strictly to the operating manual when carrying out this test.

The sample dilution buffer contains sodium azide as a preservative. Avoid contact with skin or mucous membranes. Do not use buffers if signs of contamination or precipitation are present.

Specimens or reagents must not be pipetted by mouth, and contact with injured skin or mucous membranes must be prevented. Wear personal protective equipment (appropriate gloves, lab coat, safety glasses) when handling reagents and specimens, and wash hands after completing the test. Do not smoke, eat, or drink in areas where specimens or test reagents are being used.

All reagents and materials coming into contact with potentially infectious samples must be treated exactly like the specimens themselves with suitable disinfectants (e.g., sodium hypochlorite) or autoclaved at 121°C for at least one hour.

Users are responsible for the proper disposal of all reagents and materials after use. For disposal, please adhere to national regulations.

Hazardous materials are indicated according to labeling obligations.

Further details on the Safety Data Sheet (SDS) can be found under the item number at https://clinical.r-biopharm.com/search/.

The patient specimens must be treated as potentially infectious in compliance with the national safety guidelines. Ensure that all reagents and materials are disposed of properly and responsibly after use. Comply with the applicable national disposal regulations.

Do not exchange components of kits that have different lot numbers.

Do not use the kit components after the expiration date.

If the package is damaged, the product can still be used if none of the components are damaged.

Do not use this product if a colored line is shown in the strip’s result area prior to the test.

Collecting the right amount of specimen is very important (see Section 9.1 of Test procedure).

8. Collection and storage of samples

The stool specimen should be collected as soon as the symptoms occur (particularly diarrhea and vomiting) since fecal excretion of the virus is highest during the first three days after infection.

Do not use specimens that were collected in transport media or to which preservatives (such as formalin, SAF, PVA, etc.) or enrichment media were added since the presence of such substances could prevent the test from being carried out correctly.

The best results are achieved using fresh, untreated specimens. If specimens have to be stored for a certain amount of time, they can be stored in the refrigerator (+ 2 °C to + 8 °C) for one or two days (Table 2). For longer periods, they should be frozen at -20 °C, but it should be noted that some specimens can lose their immunoreactivity after freezing.

If specimens are frozen, ensure that they have fully thawed to room temperature before they are analyzed.

Avoid repeated freezing/thawing of the stool specimens as this can change the immunological recognition of the virus.

Table 2: Sample storage

Undiluted stool specimen	
2 - 8°C	≤ -20 °C
≤ 2 days	> 2 days

9. Test procedure

9.1 General information

The specimens, tubes containing sample dilution buffer, and the test cassettes must be brought to room temperature (20 - 30 °C) before use. Do not remove the test cassettes from the outer package until shortly before use. Once used, the cassettes must not be re-used. Do not perform the test in direct sunlight.

Collecting the right amount of specimen is very important: about 110 mg for solid specimens (a sample having a diameter of about 5 mm) or 110 µL for liquids (4 drops using the non-graduated disposable pipettes), or, if semi-liquid specimens are used (which cannot be collected with a pipette), a sample that can be collected using the grooves of the wand attached to the lid of the tube. Carefully transfer the sample into the provided tubes containing 1.5 mL of the sample dilution buffer.

It is very important that you drop the right volume of a specimen extracted in the sample diluent into the two specimen application windows of the cassette. If less volume is used than stated, chromatography may not work since sometimes a sufficient amount of specimen will not reach the reaction areas. On the other hand, too much specimen in relation to the 1.5 mL of buffer can prevent chromatography from working correctly. This is especially important with solid specimens since they are not always easy to divide into portions once they are removed from the primary stool specimen.

When analyzing hemorrhagic specimens, take special note that these specimens can result in non-specific reactions if they have a high blood concentration. It may be possible to detect an indication of the instability of the test caused by this in a change of the otherwise specific colors of the lines that are to be expected, especially the control line (instead of green, it can have a violet or navy blue color).
Avoid repeated freezing and thawing of stool specimens since such can change the specific immunological recognition of the virus.

9.2 Preparing the specimens

Carefully unscrew the cap of the dilution buffer tube.

If stool is solid or semi-solid, use the applicator in the lid to take a specimen of about 110 mg (a small ball with a diameter of about 5 mm) from at least three different places to get as representative of a specimen as possible. Place the applicator with the specimen in the tube. Tighten the cap securely, and shake the tube thoroughly to create a homogeneous mixture.

If stool is liquid or semi-liquid, collect at least 110 µL specimen using a non-graduated disposable pipette included in the kit, and add 4 drops to the tube containing the dilution buffer. Tighten the cap securely, and shake the tube thoroughly to create a homogeneous mixture.

9.3 Sample testing

Remove the test cassette from the aluminum bag and place it on a level surface. Dispose of the empty bag along with the desiccant bag.

Break off the nipple of the cap of the dilution buffer tube.

Place **4 drops** each in the two specimen application areas of the cassette (windows marked with an arrow). Ensure that the liquid flows through the membrane unhindered. Any dispensed particles can cause obstructions and have to be removed from the specimen application field in advance.

Wait 15 minutes before reading and interpreting the results.

10. Quality control - Indication of instability or expiration of reagents

The test should be evaluated only if the test cassette is intact prior to the pipetting of the sample suspension and there are no color changes or lines visible on the membranes. Also at least the green control line (Rota/Adeno strip) and the green control line (Noro strip) must be visible after the test incubation period. If one of these lines is missing, check the following before repeating the test:

- Shelf life of the test cassettes and of the extraction buffer tubes used
- Correct test procedure
- Contamination of the extraction buffer

If the control lines are still not visible after the test is repeated with another test cassette, please contact the manufacturer or your local R-Biopharm sales partner.

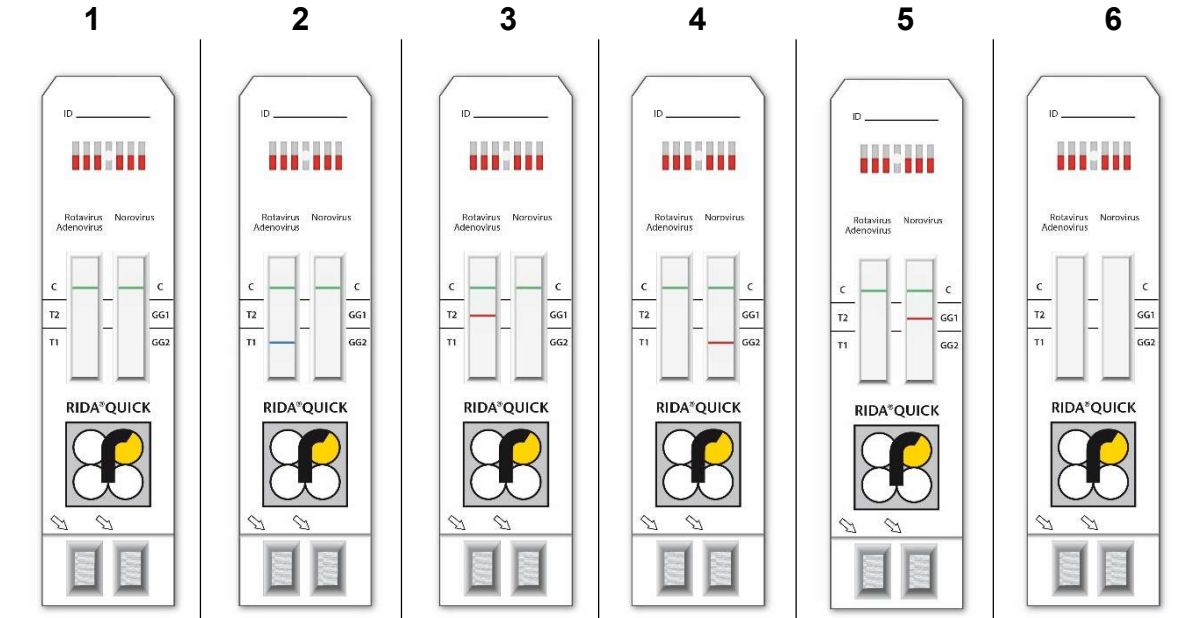
11. Evaluation and interpretation

The six images in Fig. 1 illustrate some of the different results that can be achieved using the double cassette test.

Different colored lines can appear within the three areas that are marked by the black lines on the cassette in each of the two test strips. The green control lines in the two strips should appear always. The additional presence of other lines indicates the presence of adenovirus (blue line) and/or rotavirus (red line) and/or norovirus (red lines).

Negative results (cassette 1)

In the two strips there is only one horizontal green line present at the level of the letter “C” marked on both sides of the cassette. These are the control lines and they should always appear as an indication that chromatography was successful in the two strips.



1	2	3	4	5	6
Adeno - **Rota -** **Noro -**	**Adeno +** **Rota -** **Noro -**	**Adeno -** **Rota +** **Noro -**	**Adeno-** **Rota -** **Noro GG2+**	**Adeno -** **Rota -** **Noro GG1+**	**Invalid**

Fig. 1: Pattern of possible results

Positive results (cassettes 2 - 5)

Rota-Adeno strip:

- Lower blue line (T1): Adenovirus is present in the specimen.
- Upper red line (T2): Rotavirus is present in the specimen.
- Green line (C): This control line indicates that the test worked correctly.

Norovirus strip:

- Lower red line (GG2): Norovirus genogroup II is present in the specimen.
- Upper red line (GG1): Norovirus genogroup I is present in the specimen.
- Green line (C): This control line indicates that the test worked correctly.

Invalid results (cassette 6)

The following test results are invalid:

1. The control line does not appear, or the color of the line is not green and is completely different from the expected green line.
2. Test lines do not appear as the expected red or blue line; instead they are a completely different color than the expected line.
3. Likewise, changes in the color of the line that do not occur until after the reading period of 15 minutes should be regarded as having no diagnostic relevance and may not be used for evaluation.

Possible reasons for invalid results:

- One or more of the reagents are spoiled or expired.

- The specimen was not prepared according to the instructions for use.

- The specimen has a high blood concentration.

If a result is invalid, it is recommended to repeat the test using a new cassette and to adhere strictly to the instructions for use. For specimens that have a high blood concentration, it is recommended to use an alternative technique since any instability that may have resulted is usually due to the complexity of the specimen matrix and not to the test strip.

12. Limitations of the method

The RIDA®QUICK Rota/Adeno/Noro Combi assay is used for the differential identification of rotavirus, adenovirus, and norovirus GI and GII. The presence of a virus in the prepared stool specimen will be detected if the viral load is equal to or higher than the detection limit of the product for each analyte. This product is qualitative, not quantitative, even though the intensity of the positive lines is related to the amount of virus detectable in the stool specimen.

It is not possible to associate the intensity of the visible specific test line with the occurrence or severity of clinical symptoms. The results obtained must always be interpreted in combination with the complete clinical symptoms.

A positive result does not rule out the presence of other infectious pathogens. In any case, co-infections can be clarified only through differential diagnostic testing.

A negative result does not necessarily rule out a rotavirus, adenovirus, or norovirus infection. It can be caused by intermittent excretion of the pathogen, by too few

antigens in the specimen (collection of the specimen in an inappropriate stage of the disease when only very little virus is eliminated in the stool), by incorrect storage of the specimen, and by inadequate specimen transport. If the patient has a suspected infection with the examined pathogens, another stool specimen should be tested.

An excess of stool specimen can cause brownish strips to appear instead of the specifically colored strips. These brownish lines do not have any diagnostic value. If this happens, the test needs to be repeated using a smaller amount of stool, or the previously prepared suspension needs to be further diluted to clarify whether the examined viruses are present in the specimen and were masked by too much stool matrix.

An incorrectly stored sample can cause weak positive to false negative results.

The RIDA®QUICK Rota/Adeno/Noro Combi assay was not validated using all norovirus genotypes. Because of the extreme antigen diversity of the currently known norovirus strains, it may happen that a strain is not detected.

It has been observed that stool specimens having a high blood concentration have a negative effect on the assay, since non-specific reactions to specimens that are negative for rotavirus, adenovirus, and norovirus may occur. This instability of the assay is usually accompanied by a change in the color of the control lines.

The RIDA®QUICK Rota/Adeno/Noro Combi test has a good correlation with other techniques (RT-PCR, ELISA and rapid tests). It cannot be ruled out that other stool samples can potentially interfere with the test process.

Make sure the correct incubation period is used. If the reaction period is not long enough, positive samples containing high concentrations of antigen may still be easily detected as positive. Positive samples that have only a low concentration of antigen close to the limit of detection may no longer be detected as positive. If the incubation period is too long, the rapid test's performance data will change and erroneous results could be interpreted (e.g., false-positive results).

The assay can yield positive [rotavirus] results in the patient's stool up to 15 days after the administration of a live oral vaccine (e.g., RotaTeq vaccine).

13. Performance characteristics

13.1 Clinical performance characteristics

The RIDA®QUICK Rota/Adeno/Noro Combi rapid test was assessed based on the following samples:

- 52 negative specimens for rotavirus
- 58 negative specimens for adenovirus
- 71 negative specimens for norovirus GI and GII
- 30 positive specimens for rotavirus
- 16 positive specimens for adenovirus
- 8 positive specimens for norovirus GI

- 68 positive specimens for norovirus GII

Reference techniques used follow:

- an enzyme immunoassay for rotavirus-negative specimens
- an RT-PCR (Eurorotanet method of 2009: “European Rotavirus detection and typing methods”) for rotavirus-positive specimens
- an RT-PCR (methods from Vinjé et al., Kageyama, et al., Sabrià et al.) for Norovirus G1 and G2 specimens
- a rapid test for adenovirus-positive and -negative specimens

The results of that study are listed in Table 3.

Table 3: Relative sensitivity and specificity of RIDA®QUICK Rota/Adeno/Noro Combi

	Relative sensitivity	Relative specificity
Rotavirus	> 99.9 %	> 99.9 %
Adenovirus	> 99.9 %	> 99.9 %
Norovirus GI	75 %	97.2 %
Norovirus GII	92.6 %	97.2 %

A clinical study of the RIDA®QUICK Rota/Adeno/Noro Combi rapid test examined 173 stool samples compared with one commercial RT-PCR for rotavirus, adenovirus, and norovirus.

The sample set consisted of RT-PCR-characterized specimens:

- 113 negative specimens for rotavirus
- 119 negative specimens for adenovirus
- 118 negative specimens for norovirus GI and GII
- 60 positive specimens for rotavirus (Ct 10-33.6)
- 54 positive specimens for adenovirus (Ct 7.8-27.7)
- 55 positive specimens for norovirus (Ct 17.2-33.5)

50 of the 55 specimens positive for norovirus were genotyped (method per Cannon et al.). 36 were positive for norovirus GII and 15 positive for norovirus GI. One specimen contained norovirus GI and GII.

The results of the study are summarized in Table 4.

Table 4: Relative sensitivity and specificity of RIDA®QUICK Rota/Adeno/Noro Combi

	Relative sensitivity	Relative specificity
Rotavirus	71.7 %	> 99.9 %
Adenovirus	75.9 %	99.2 %
Norovirus GI+GII	87.3 %	> 99.9 %
Norovirus GI	66.7 %	> 99.9 %
Norovirus GII	94.4 %	> 99.9 %

The tests resulted in 17 false negative specimens for rotavirus, which in another immunochromatographic rapid test were likewise found to be false negative for rotavirus compared to RT-PCR. The discrepancy arises from the sensitivity difference of the two techniques.

The tests resulted in 13 false negative specimens for adenovirus, 11 of which in another immunochromatographic rapid test were likewise found to be false negative for adenovirus compared to RT-PCR.
The tests resulted in one false positive specimen for adenovirus, which in another immunochromatographic rapid test was likewise found to be false positive for adenovirus compared to RT-PCR. This indicates that either the specimen was actually positive or that this specimen is not suitable for analysis using this method.

The tests resulted in 7 false negative specimens for norovirus GI and GII, which in another immunochromatographic rapid test were likewise found to be false negative for norovirus GI and GII compared to RT-PCR.

13.2 Analytical performance characteristics

13.2.1 Detection limit

Rota-Adeno strip:

For adenovirus, an average sensitivity of 16 ng adenovirus antigen/mL was determined, although lower concentrations of up to 8 ng/mL are often detected for this virus. For rotavirus, an average sensitivity of 2 ng adenovirus antigen/mL was determined, although lower concentrations of up to 1 ng/mL are often detected for this virus.

Norovirus strip:

Recombinant viral-like particles (VLPs) were used to determine analytical sensitivity. For norovirus GI, an average sensitivity of 3.25 ng/mL was determined and for norovirus GII 0.625 ng/mL, although lower concentrations of up to 1.6 ng/mL and 0.31 ng/mL are detected for norovirus GI and GII, respectively.

13.2.2 Analytical specificity

Interfering substances

The substances listed did not affect the test results when they were added to stool specimens (positive and negative).

Table 5: Potentially interfering substances

Potentially interfering substance	Concentration
Racecadotril	0.135 mg/mL
Vancomycin	0.9 mg/mL
Loperamide	4.5 µg/mL
Metronidazole	0.255 mg/mL
Omeprazole	27 µg/mL
Atropine sulfate	0.315 µg/mL
Sodium carbonate	3.78 mg/mL
Amoxicillin	0.9 mg/mL
Ibuprofen	1.080 mg/mL
Acetylsalicylic acid	0.9 mg/mL
Sucrose	1.5 mg/mL
Palmitic acid	20 %
Paracetamol	1.125 mg/mL
Mucin	2.5 %
Ciprofloxacin	0.225 mg/mL
Whole blood	0.16 %

Cross-reactivity

The following microorganisms did not affect the results:

Escherichia coli, *Escherichia coli* O157, *Salmonella* spp., *Campylobacter coli*, *Campylobacter jejuni*, *Yersinia enterocolitica*, *Entamoeba histolytica*, *Giardia lamblia*, *Cryptosporidium parvum*, *Helicobacter pylori*, *Clostridium difficile*, Adenovirus, Rotavirus, Norovirus GI /GII and Astrovirus.

13.2.3 Precision

The intra-assay precision of RIDA®QUICK Rota/Adeno/Noro Combi was measured in 5 replicates of a 1:2 dilution series with internal standards together with actual samples that were identified as PC (positive control), LPC (low positive control), and NC (negative control) for each analyte. It was measured on the same day by the same operator. High reproducibility was determined. The observed differences in the stands were fewer or corresponded to a 1:2 dilution level; the results of the actual samples were identical.

The inter-day precision of RIDA®QUICK Rota/Adeno/Noro Combi was determined using a single batch, in which the sensitivity curve of each of the analytes was measured in duplicate over a period of five days. The results for rotavirus, adenovirus, norovirus GII were 100 % reproducible. For norovirus GI, the difference across the
2-day period was only one half a 1:2 dilution level.

The inter-operator precision of RIDA®QUICK Rota/Adeno/Noro Combi was determined by assessing the sensitivity curve for each analyte in triplicate. In no case did sensitivity differences observed exceed a 1:2 dilution level.

The inter-lot precision of RIDA®QUICK Rota/Adeno/Noro Combi was determined by assessing the sensitivity curves of 3 lots. The analysis was performed by the same operator on the same day. The maximum differences observed were fewer than one 1:2 dilution level or corresponded to a 1:2 dilution level, which indicates a high inter-lot precision of the test.

14. Version history

Version number	Section and designation
2019-09-16	Previous version
2022-03-03	7. Warnings and precautions for the users 12. Limitations of the method 13. Performance characteristics

15. Explanation of symbols

General symbols

IVD	For *in vitro* diagnostic use
	Observe operating manual
LOT	Batch number
	Use before
	Storage temperature
REF	Item number
	Number of tests
	Date of manufacture
	Manufacturer

Test-specific symbols

Cassette	Test cassette
Tube	Dilution buffer tube
Pipet	Pipette

16. References

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