MIKROGEN
DIAGNOSTIK

Instruction for Use

*alpha*Cube gastroplexVirus

For the qualitative *in-vitro* detection of RNA from Rotavirus, Norovirus (GI and GII), and DNA from Adenovirus in clinical specimens, environmental and food samples.

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1 Intended Use

The *alpha*Cube gastroplexVirus real time RT-PCR is an assay for the detection of the RNA of Rotavirus, Norovirus, and the DNA of Adenovirus in clinical specimens (e.g. stool samples, vomit), environmental and food samples using real time PCR microplate systems.

2 Pathogen Information

Acute gastroenteritis is a worldwide major cause of morbidity and mortality. Gastroenteritis or infectious diarrhea is an inflammation of the gastrointestinal tract. Both the stomach and the small intestine are involved. Typical symptoms are diarrhoea, vomiting, abdominal pain, and cramps, often followed by dehydration.
The causative agent can be viral or bacterial. Enteric viruses are the major pathogens for gastroenteritis especially in children. Noro-, Rota-, Adeno-, Sapo- and Astroviruses are the most important viral pathogens.

Noroviruses are small non-enveloped RNA viruses belonging to the family of Caliciviridae. They cause approximately 90 % of epidemic non-bacterial outbreaks of gastroenteritis around the world.
The viruses are transmitted by fecally contaminated food or water and by person-to-person contact. For this reason, outbreaks of norovirus infection often occur in closed or semi-closed communities, such as long-term care facilities, hospitals, prisons, dormitories, and cruise ships. Noroviruses are highly contagious and are stable at temperatures between -20°C to +60°C and in acidic environments up to pH 3. Norovirus infections occur throughout the year, however, in Europe, seasonal increases are observed between October and March.
The *alpha*Cube gastroplexVirus real time RT-PCR detects Norovirus strains of high genetic diversity, such as the following:
GI: Norwalk, Desert Shield, Winchester, Queensarms, Southhampton, Chiba
GII: Lordsdale, Bristol, Melksham, Toronto, Hawaii
Infections with **Rotavirus** are the most common cause of severe diarrhoea among children. Worldwide more than 450,000 children under 5 years of age die from rotavirus infections each year. Most of them in developing countries.
The double-stranded RNA virus of the family Reoviridae is transmitted faecal-orally and infects the enterocytes. It causes diarrhoea, vomiting, fever, and dehydration, seldomly abdominal pain. Sometimes infections of the upper respiratory tract occur in correlation with gastroenteritis. With each infection immunity develops, so subsequent infections are less severe. By the age of 5, nearly every child in the world has at least once gone through a rotavirus infection.
Rotaviruses are classified into the groups A-G, among which A-C are human pathogenic. More than 90 % of rotavirus infections are caused by group A viruses.
Adenoviruses mainly cause infections of the respiratory system. However, dependent on the serotype, numerous other diseases can be caused, such as gastroenteritis, keratoconjunctivitis epidemica, cystitis, rhinitis, pharyngitis, and diarrhoea. Respiratory symptoms range from mild flu to acute bronchitis and pneumonia. Immuno-suppressed patients are prone to severe complications, such as acute respiratory distress syndrome. Although the epidemiological characteristics of Adenoviruses vary from type to type, all types are transmitted by direct contact, feacal-orally, and rarely by water. Some types cause persistent, asymptomatic infections of the palatine and pharyngeal

tonsils, and the gastrointestinal tract. Spreading of the virus can occur over months or years.

3 Principle of the Test

The *alpha*Cube gastroplexVirus real time RT-PCR contains specific primers and hydrolysis probes for the detection of the nucleic acids of Rotavirus, Adenovirus, and Norovirus in clinical specimens (e.g. stool samples, vomit), environmental and food samples. The reverse transcription (RT) of viral RNA to cDNA and the subsequent amplification of virus specific fragments are performed in a one-step RT-PCR. The amplification can be detected when specific probes are hydrolysed by the Polymerase. The emitted fluorescence is measured in the FAM (*Norovirus*), ROX (*Rotavirus*) and Cy5 (*Adenovirus*) channel.

Furthermore, the *alpha*Cube gastroplexVirus real time RT-PCR contains a Control RNA, which is detected in a second amplification system. Added during RNA extraction, the Control RNA allows not only for the detection of RT-PCR inhibition but also detects possible mistakes during RNA extraction. This greatly reduces the risk of false-negative results. The Control RNA can also be used solely as Internal Control by adding it directly to the Mastermix. The fluorescence of the Control RNA is measured in the VIC®/HEX/JOE™/TET channel.

4 Package Contents

The reagents supplied are sufficient for 32 or 96 reactions respectively.

Table 1: Components of *alpha*Cube gastroplexVirus real time RT-PCR kit.

Label	Lid Colour	Content 32	96
Reaction Mix	yellow	1 x 506 µl	2 x 759 µl
Enzyme	blue	1 x 6.4 µl	1 x 19.2 µl
Positive Control	red	1 x 50 µl	1 x 100 µl
Negative Control	green	1 x 50 µl	1 x 100 µl
Control RNA	colourless	1 x 160 µl	2 x 240 µl

5 Equipment and Reagents to be Supplied by User

- RNA isolation kit (e.g. *alpha*Clean Pure RNA/DNA) or *alpha*Clean Mag RNA/DNA
- PCR grade Water
- Sterile microtubes
- Pipets (adjustable volume)
- Sterile pipet tips with filter
- Table centrifuge
- Vortexer
- Real time PCR instrument
- Optical PCR reaction tubes with lid
- Optional: Liquid handling system for automation
- Optional: VLP-RNA (please look at page 6 for details)

6 Transport, Storage and Stability

*alpha*Cube gastroplexVirus real time RT-PCR is shipped on dry ice or cool packs. All components must be stored at maximum -18°C in the dark immediately after receipt. Do not use reagents after the date of expiry printed on the package.
Up to 20 freeze and thaw cycles are possible.
For convenience, opened reagents can be stored at +2-8°C for up to 6 months.
Protect kit components from direct sunlight during the complete test run.

7 Important Notes

- *alpha*Cube gastroplexVirus real time RT-PCR must be performed by qualified personnel only.
- Good Laboratory Practice (GLP) has to be applied.
- Clinical samples must always be regarded as potentially infectious material and all equipment used has to be treated as potentially contaminated.

8 General Precautions

- Stick to the protocol described in the Instruction for use.
- Set up different laboratory areas for the preparation of samples and for the set up of the RT-PCR in order to avoid contaminations.
- Pipettes, tubes and other materials must not circulate between those different laboratory areas.
- Always use filter tips.
- Regulary decontaminate equipment and benches with ethanol-free decontaminant.
- Do not combine *alpha*Cube gastroplexVirus real time RT-PCR components of different lot numbers.

9 Sample Material

Starting material for the *alpha*Cube gastroplexVirus real time RT-PCR is the nucleic acid isolated from clinical specimens (e.g. stool samples, vomit), environmental or food samples.

10 Sample Preparation

The *alpha*Cube gastroplexVirus real time RT-PCR is suitable for the detection of *Rotavirus, Adenovirus, and Norovirus* in clinical specimens (e.g. stool samples, vomit), environmental and food samples isolated with suitable isolation methods.

Commercial kits for RNA isolation such as the following are recommended:

- *alpha*Clean Pure RNA/DNA
- *alpha*Clean Mag RNA/DNA

Important:
In addition to the samples always run a ‚water control' in your extraction. Treat this water control analogous to a sample.
Comparing the amplification of the Control RNA in the samples to the amplification of the internal control in the water control will give insights on possible inhibitions of the real time RT-PCR. Furthermore, possible contaminations during RNA extraction will be detectable.

Please note the chapter 11 ‚Control RNA'.

If the real time RT-PCR is not performed immediately, store extracted RNA and DNA according to the instructions given by the manufacturer.

11 Control RNA

A Control RNA is supplied and can be used as extraction control or only as inhibition control. This allows the user to control the RNA isolation procedure and to check for possible real time RT-PCR inhibition.
The Virus-Like Particles (VLP-RNA) are not supplied, but must be added to the clinical or environmental samples directly. VLP-RNA can be used as patient-side extraction control and in automated extraction systems, when pipetting of the Control RNA to the first buffer of (e.g. binding buffer) of the respective extraction kit is not possible due to extraction instrument specifications.

RNA isolation from clinical specimens (e.g. stool samples, vomit), environmental and food samples

a) Control RNA or VLP-RNA used as Extraction Control:
*alpha*Cube gastroplexVirus real time RT-PCR Control RNA or VLP-RNA is added to the RNA extraction.
Add 5 µl Control RNA or VLP-RNA per extraction (5 µl x (N+1)). Mix well. Perform the RNA isolation according to the manufacturer's instructions. Please follow protocol A.

The Control RNA must be added to the Lysis Buffer of the extraction kit.

b) Control RNA used as Internal Control of the real time PCR:
If only inhibition will be checked please follow protocol B.

12 Real time RT-PCR

12.1 Important Points Before Starting:

- Please pay attention to the chapter 7 ‚Important Notes'.
- Before setting up the real time RT-PCR familiarise yourself with the real time PCR instrument and read the user manual supplied with the instrument.
- The programming of the thermal profile should take place before the RT-PCR set up.
- In every RT-PCR run one Positive Control and one Negative Control should be included.
- Before each use, all reagents - except the Enzyme - should be thawed completely at room temperature, thoroughly mixed (do NOT vortex the Reaction Mix but mix by pipetting up and down repeatedly), and centrifuged very briefly.

12.2 Procedure

If the Control RNA or VLP-RNA is used to control both, the real time RT-PCR and the RNA isolation procedure, please follow protocol A. If the Control RNA is solely used to detect possible inhibition of the real time RT-PCR, please follow protocol B.

Protocol A

The Control RNA or VLP-RNA was added during RNA extraction (see chapter 11 ‚Control RNA'). In this case, prepare the Master Mix according to Table 2.
The Master Mix contains all of the components needed for RT-PCR except the sample. Prepare a volume of Master Mix for at least one sample more than required, in order to compensate for pipetting inaccuracy.

Table 2: Preparation of the Master Mix (Control RNA or VLP-RNA was added during RNA extraction)

Volume per Reaction	Volume Master Mix
15.8 µl Reaction Mix	15.8 µl x (N+1)
0.2 µl Enzyme	0.2 µl x (N+1)

Protocol B

The Control RNA is used for the control of the real time RT-PCR only (see chapter 11 ‚Control RNA'). In this case, prepare the Master Mix according to Table 3.

The Master Mix contains all of the components needed for real RT-PCR except the sample. Prepare a volume of Master Mix for at least one sample more than required, in order to compensate for pipetting inaccuracy.

Important: Dilute the Control RNA **1:10** in PCR grade Water (e.g. 1 µl Control RNA + 9 µl PCR grade Water) before adding it to the Master Mix.

Table 3: Preparation of the Master Mix (Control RNA is added directly to the Master Mix)

Volume per Reaction	Volume Master Mix
15.8 µl Reaction Mix	15.8 µl x (N+1)
0.2 µl Enzyme	0.2 µl x (N+1)
0.2 µl Control RNA* (diluted 1:10)	0.2 µl x (N+1)*

*The increase in volume caused by adding the Control RNA is not taken into account when preparing the PCR assay.

Protocol A and B: real time RT-PCR set up

- Place the number of optical PCR reaction tubes needed into the respective tray of the real time PCR instrument.
- Pipet **16 µl** of the Master Mix into each optical PCR reaction tube.
- Add **4 µl** of the eluates from the RNA isolation (including the eluate of the water control), the Positive Control and the Negative Control to the corresponding optical PCR reaction tube (Table 4).
- Close the optical PCR reaction tubes immediately after filling in order to reduce the risk of contamination.

Table 4: Preparation of the real time PCR

Component	Volume
Master Mix	16.0 µl
Sample	4.0 µl
Total Volume	20.0 µl

12.3 Instrument Settings

For the real time RT-PCR use the thermal profile shown in table 5.

Table 5: real time RT-PCR thermal profile

Description	Time	Temperature	Number of Cycles
Reverse Transcription	10 min	45°C	1
Initial Denaturation	5 min	95°C	1
Amplification of cDNA			45
Denaturation	10 sec	95°C	
Annealing and Extension	40 sec Aquisition at the end of this step	60°C	

Dependent on the real time instrument used, further instrument settings have to be adjusted according to table 6.

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Table 6: Overview of the instrument settings required for *alpha*Cube gastroplexVirus real time RT-PCR.

Reaction Mix

Real time PCR Instrument	Parameter	Detection Channel	Notes		
LightCycler 480I	Norovirus	483-533	*alpha*Cube LC480 Colour Compensation required		
	Rotavirus	558-610			
	Control RNA	523-568			
	Adenovirus	615-670			
LightCycler 480II			*alpha*Cube LC480 Colour Compensation required		
			Melt Factor	Quant Factor	Max Integration Time (sec)
	Norovirus	465-510	1	10	1
	Rotavirus	533-610	1	10	2
	Control RNA	533-580	1	10	2
	Adenovirus	618-660	1	10	3
Stratagene Mx3000P / Mx3005P	Norovirus	FAM	Gain 8		Reference Dye: None
	Rotavirus	ROX	Gain 1		
	Control RNA	HEX	Gain 1		
	Adenovirus	Cy5	Gain 4		
ABI 7500	Norovirus	FAM	Option Reference Dye ROX: NO		
	Rotavirus	ROX			
	Control RNA	JOE			
	Adenovirus	Cy5			
Rotor-Gene Q, Rotor-Gene 3000 Rotor-Gene 6000	Norovirus	Green	Gain 5		
	Rotavirus	Orange	Gain 5		
	Control RNA	Yellow	Gain 5		
	Adenovirus	Red	Gain 5		

13 Data Analysis

The virus specific amplifications are measured in the FAM, ROX, Cy5 channels. The amplification of the Control RNA is measured in the VIC®/HEX/JOE/TET channel. The Positive Control contains in vitro transcripts of the respective nucleic acid sequences of Rotavirus, Norovirus and Adenovirus. For the Positive Control signals in the FAM, ROX, Cy5 channels must be detected.

Following results can occur:

- **A signal in the FAM, ROX, Cy5 channels is detected:**
  The result is positive, the sample contains viral RNA.
  In this case, detection of a signal of the Control RNA in the VIC®/HEX/JOE/TET channel is inessential, as high concentrations of cDNA may reduce or completely inhibit amplification of the Control RNA.

- **No signal in the FAM, ROX, Cy5 channels, but a signal in the VIC®/HEX/JOE/TET channel is detected:**
  The result is negative, the sample does not contain viral RNA.
  The signal of the Control RNA excludes the possibilities of RNA isolation failure (in case the Control RNA is being used as an Extraction Control) and/or real time RT-PCR inhibition. If the C_T value of a sample differs significantly from the C_T value of the water control, a partial inhibition occured, which can lead to negative results in weak positive samples (see 'Troubleshooting').

- **Neither in the FAM, ROX, Cy5 channels nor in the VIC®/HEX/JOE/TET channel a signal is detected:**
  A diagnostic statement cannot be made.
  The RNA isolation was not successful or an inhibition of the RT-PCR has occurred. In case the Control RNA was added during RNA isolation and not directly to the PCR Master Mix, the Negative Control is negative in both channels.

Figure 1 and **Figure 2** show examples for positive and negative real time RT-PCR results.

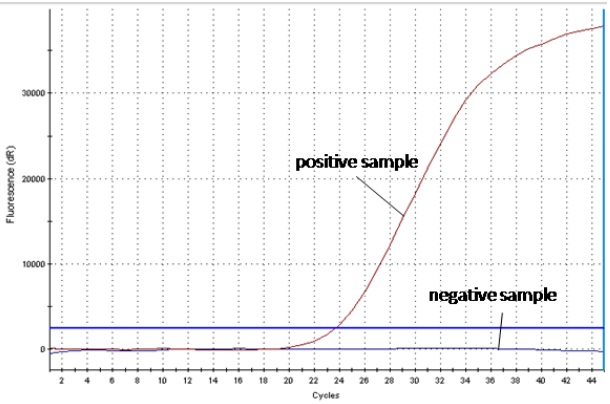

Figure 1: The positive sample shows virus-specific amplification in the FAM channel, whereas no fluorescence signal is detected in the negative sample.

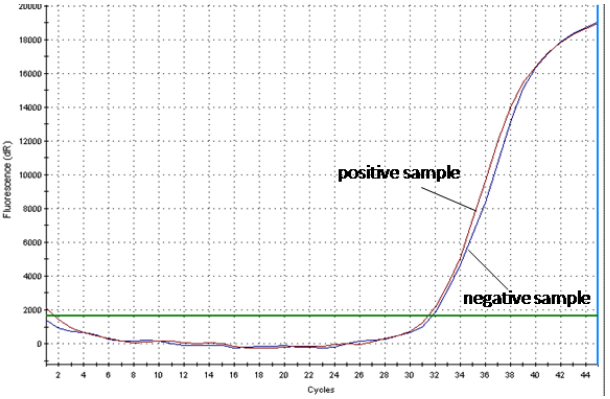

Figure 2: The positive sample as well as the negative sample show a signal in the Control RNA specific VIC®/HEX/JOE/TET channel. The amplification signal of the Control RNA in the negative sample shows, that the missing signal in the virus specific FAM channel is not due to RT-PCR inhibition or failure of RNA isolation, but that the sample is a true negative.

14 Assay Validation

Set a threshold as follows:

Negative Controls

All negative controls should be below the threshold. If there is a potential contamination (appearance of a curve in the negative control or a cluster of curves in specimens at high C_T – for example above 36), results obtained are not interpretable and the whole run (including extraction) has to be repeated.

Positive Controls

All the positive controls must show a positive (i.e. exponential) amplification curve. The positive controls must fall below a C_T of 30.

Internal Controls

All internal controls must show a positive (i.e. exponential) amplification curve. The internal control must fall below a C_T of 33. If the internal control is above C_T 34, this points to a purification problem or a strong positive sample that can inhibit the IC. In the latter case, the assay is valid. If a water control run is performed, the IC must fall below a C_T of 33.

15 Limitations of the method

The results must always be considered in relation to the clinical symptoms. Therapeutical consequences should be made in consideration of clinical data.
A negative test result does not exclude a gastroenteric virus infection.

16 Troubleshooting

The following troubleshooting guide is included to help you with possible problems that may arise when performing a real time RT-PCR.

No fluorescence signal in the FAM, ROX, Cy 5 channel of the Positive Controls	
The selected channel for analysis does not comply with the protocol	Select the FAM channel for analysis of the Norovirus specific amplification, the ROX channel for analysis of the Rotavirus specific amplification and the Cy5 channel for analysis of the Adenovirus specific amplification (Reaction Mix). Select the VIC®/HEX/JOE™/TET channel for the amplification of the Control RNA. Due to amplification in the specific channels, amplification of the Internal Control can be inhibited in the Positive Control.
Incorrect configuration of the real time RT-PCR	Check your work steps and compare with ‚Procedure' on page 7.
The programming of the thermal profile is incorrect	Compare the thermal profile with the protocol (Table 5, page 9).

Incorrect storage conditions for one or more kit components or kit expired	Check the storage conditions and the date of expiry printed on the kit label. If necessary, use a new kit and make sure kit components are stored as described in ‚Transport, Storage and Stability', page 5.
Weak or no signal of the Control RNA and simultaneous absence of a signal in the virus specific FAM channel, ROX channel or Cy5 channel.	
real time RT-PCR conditions do not comply with the protocol	Check the real time RT-PCR conditions (page 7).
real time RT-PCR inhibited	Make sure that you use an appropriate isolation method (see ‚Sample Preparation', page 6) and follow the manufacturer's instructions. Make sure that the ethanol-containing washing buffer of the isolation kit has been completely removed. An additional centrifugation step at high speed is recommended before elution of the RNA.
RNA loss during isolation process	In case the Control RNA was added before extraction, the lack of an amplification signal can indicate that the RNA isolation was not successful. Make sure that you use an appropriate isolation method (commercial kits are recommended) and stick to the manufacturer's protocol.
Incorrect storage conditions for one or more components or kit expired	Check the storage conditions and the date of expiry printed on the kit label. If necessary, use a new kit and make sure kit components are stored as described in ‚Transport, Storage and Stability', page 5.
Detection of a fluorescence signal in the FAM channel, ROX channel or Cy5 channel of the Negative Control.	
Contamination during preparation of the RT-PCR	Repeat the real time RT-PCR in replicates. If the result is negative in the repetition, the contamination occured when the samples were pipetted into the optical PCR reaction tubes. Make sure to pipet the Positive Control last and close the optical PCR reaction tube immediately after adding the sample. If the same result occurs, one or more of the kit components might be contaminated. Make sure that work space and instruments are decontaminated regularly. Use a new kit and repeat the real time RT-PCR.

17 Kit Performance

17.1 Diagnostic Sensitivity and Specificity

During the validation study of the *alpha*Cube gastroplexVirus real time RT-PCR 163 positive and 89 samples, negative for enteric pathogens were tested. The positive samples were also tested for the other pathogens to exclude unspecific reactions. The diagnostic sensitivity was found to be 100 % and the diagnostic specificity 100 %.
The positive predictive value was found to be 100 %, the negative predictive value showed to be 100 %.

Table 7: Overview of the amount of samples tested and the resulting sensitivity and specificity.

	*alpha*Cube gastroplexVirus **positive**	*alpha*Cube gastroplexVirus **negative**
Norovirus positive	45	0
Norovirus negative	0	207
Rotavirus positive	39	0
Rotavirus negative	0	213
Adenovirus positive	35	0
Adenovirus negative	0	217
Sensitivity	100 %	
Specificity	100 %	

17.2 Analytical Sensitivity

The limit of detection (LoD) of *alpha*Cube gastroplexVirus **r**eal time RT-PCR was determined using serial dilutions of in vitro transcripts (RNA Viruses) and cloned DNA (Adenovirus) in nucleic acid stabilization buffer in a Stratagene Mx3000 real time PCR instrument. Total nucleic acids were extracted using *alpha*Clean Pure RNA/DNA according to the manufacturer´s instructions. Each sample (200 µl of diluted nucleic acid) was supplemented with 5 µl Control-RNA prior to extraction. Total nucleic acids were eluted with 50 µl and 4 µl of the eluates were applied to the subsequent real time RT-PCR.
The LoD of *alpha*Cube gastroplexVirus real time RT-PCR for *Norovirus, Rotavirus, and Adenovirus* is $\geq$10 copies per reaction each.

Table 8: Samples tested for the validation of the sensitivity of *alpha*Cube gastroplexVirus.

Norovirus	**Copies per Reaction**	**Expected Result**	**CT-value *alpha*Cube gastroplexVirus**	**Mean CT**
Noro 10-2	1.000.000	positive	20.20/ 20.52	20.36
Noro 10-3	100.000	positive	23.65/ 23.12	23.39
Noro 10-4	10.000	positive	26.44/ 26.69	26.57
Noro 10-5	1.000	positive	30.16/ 29.81	29.98
Noro 10-6	100	positive	32.4/ 33.36	32.88
Noro 10-7	10	positive	36.27/ 35.82	36.05
Noro 10-8	1	positive	39.73/ no Ct	39.73

Rotavirus	**Copies per Reaction**	**Expected Result**	**CT-value *alpha*Cube gastroplexVirus**	**Mean CT**
Rota 10-2	1.000.000	positive	20.43/ 20.74	20.59
Rota 10-3	100.000	positive	23.27/ 23.19	23.23
Rota 10-4	10.000	positive	26.89/ 27.22	27.10
Rota 10-5	1.000	positive	31.56/ 31.71	31.64
Rota 10-6	100	positive	34.84/ 35.18	35.01
Rota 10-7	10	positive	38.41/ 38.62	38.52
Rota 10-8	1	positive	no Ct/ no Ct	-

Adenovirus	**Copies per Reaction**	**Expected Result**	**CT-value *alpha*Cube gastroplexVirus**	**Mean CT**
Adeno 10-2	1.000.000	positive	20.49/ 20.05	20.27
Adeno 10-3	100.000	positive	23.58/ 23.29	23.44
Adeno 10-4	10.000	positive	26.95/ 27.42	27.19
Adeno 10-5	1.000	positive	31.12/ 31.5	31.31
Adeno 10-6	100	positive	34.34/ 34.59	34.47
Adeno 10-7	10	positive	37.79/ 36.88	37.34
Adeno 10-8	1	positive	39.86/ 40.42	40.14

17.3 Analytical Specificity

The specificity of *alpha*Cube gastroplexVirus real time RT-PCR was evaluated by in silico analysis and additionally by amplification of RNA and DNA of other relevant viruses and bacteria found in clinical samples.

Results:

The *alpha*Cube gastroplexVirus real time RT-PCR showed a positive result for the samples containing *Noroviruses, Rotavirus, and Adenovirus,* whereas samples containing other pathogens were reliably tested negative. The results are shown in Table 9.

Table 9: Bacterial and viral pathogens tested for the determination of the analytical specificity of *alpha*Cube gastroplexVirus real time RT-PCR.

Strain	Expected Result	Result
Enterovirus 68	negative	negative
Coxsackievirus B3	negative	negative
Coxsackievirus A16	negative	negative
Coxsackievirus B5	negative	negative
Salmonella	negative	negative
Listeria monocytogenes	negative	negative
Escherichia coli	negative	negative
Campylobacter	negative	negative
Shigella	negative	negative
Yersinia	negative	negative
Sapovirus	negative	negative
Astrovirus	negative	negative
Norovirus GI	positive	positive
Norovirus GII	positive	positive
Rotavirus	positive	positive
Adenovirus	positive	positive

18 Abbreviations and Symbols

cDNA	complementary Deoxyribonucleid Acid
RNA	Ribonucleid Acid
PCR	Polymerase Chain Reaction
RT	Reverse Transcription
REACTION MIX	Reaction Mix
ENZYME	Enzyme
CONTROL +	Positive Control
CONTROL −	Negative Control
CONTROL RNA IC	Control RNA

REF	Catalog number
Σ	Contains sufficient for <n> test
- 18°C	Upper limit of temperature
	Manufacturer
	Use by YYYY-MM
LOT	Batch code
CONT	Content
	Consult instructions for use
IVD	*In vitro* diagnostic medical device

gerbion gmbH & Co. KG
Remsstr. 1
70806 Kornwestheim
Germany
phone: +49 7154 806 20 0
fax: +49 7154 806 20 29
e-mail: info@gerbion.com
www.gerbion.com

Distributor
Mikrogen GmbH
Floriansbogen 2-4
D-82061 Neuried
Germany
phone: +49 (0) 89-54801-0
fax: +49 (0) 89-54801-100
e-mail: mikrogen@mikrogen.de
www.mikrogen.de

19 Literature

[1] Lothar Thomas, Labor und Diagnose: Indikation und Bewertung von Laborbefunden für die medizinische Diagnostik, 8. Auflage, 2012, TH-Books, ISBN-10: 3980521583