GenVinSet

HLA B27v5

Instructions for use

Kit for allele detection in the HLA-B*27 group

For In Vitro Diagnostic Use

Product code GVS-B2705-48 (48 tests)
GVS-B2705-24 (24 tests)

Store from –18 to –30ºC

CE 2797

Rev03/08-04-2021

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Intended use

Genvinset® HLA B27v5 is a kit for HLA-B*27 group allele determination by Real Time PCR using Taqman® probes technology.

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Summary and explanation

The major histocompatibility complex (MHC) is the genetic region that contains the most polymorphic loci of the human genome involved in the mechanism of antigen presentation and, as such, defines the general immunological response.

Within the MHC, the allelic family HLA-B*27 is part of the HLA-B locus and is present in the 3-8% of the caucasian population. Despite this frequency the interest in this allelic family relies in its relation with different rheumatic diseases called spondyloarthropathies, among which it is worth highlighting the ankylosing spondylitis (AS).

Around 90% of the patients with AS are HLA-B*27 positive. Other related autoimmune diseases are juvenile rheumatoid arthritis (80% of patients), and the Reiter syndrome or reactive arthritis (50-80%).

The HLA-B*27 is also present in 50% of patients who suffer from spondylitis with inflammatory bowel disease or plaque psoriasis. The HLA-B*27 allele is not the root cause of these pathologies, but it shows a higher prevalence in affected patients.

In HLA-B*27 positive patients, the antigen (structural protein) is present in the membrane of all nucleated cells, including leukocytes.

If HLA-B*27 positive patients show symptoms like chronic pain, inflammation and/or degenerative bone changes (visible through radiology tests), it is very likely that they suffer from AS, Reiter syndrome or another autoimmune pathology associated with this antigen. Chances are higher in young male patients who start having symptoms before the age of 40.

The presence of the HLA-B*27 antigen can also be seen in other autoimmune pathologies like isolated acute anterior uveitis, idiopathic spondyloarthropaties and enteropathic synovitis.

The absence of the HLA-B*27 antigen does not rule out the autoimmune pathology, as 10% of the AS carriers and 40-50% of Reiter syndrome patients are HLA-B*27 negative.

Moreover, if a patient does not show any of the associated symptoms, the detection of the HLA-B*27 antigen per se does not allow to determine the presence of an autoimmune disease, it progression or prognosis.

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Procedure principles

The detection method used by Genvinset® is based on the Real Time PCR technology, monitored with Taqman® probes..

The Genvinset® HLA B27v5 kit allows for the detection of all the alelles belonging to the HLA-B*27 family(*) and a control gene (ß-Globin), used to verify the results of the assay.

Each pair of primers is complementary to two DNA sequences, located in cis, thus making of the current kit a high resolution technique with high sensitivity, specificity and reproducibility.

(*) See section 'Procedure limitations'.

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Kit contents

GVS-B2705-48 (48 tests)

- GVS-B27v5-PM: 2 vials x 220 µL Primer Mix (PM)
- GVS-B27v5-MM: 2 x 276 µL Master Mix (MM)
- GVS-B27v5-C+: 1 x 10 µL Positive Control (C+)
- GVS-RB: 1 x 100 µL Reaction Blank (RB)

GVS-B2705-24 (24 tests)

- GVS-B27v5-PM: 1 vial x 220 µL Primer Mix (PM)
- GVS-B27v5-MM: 1 vial x 276 µL Master Mix (MM)
- GVS-B27v5-C+: 1 vial x 10 µL Positive Control (C+)
- GVS-RB: 1 vial x 100 µL de Reaction Blank (RB)

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Kit storage

In order to ensure a proper performance, reagents should be stored from -18ºC to -30ºC until their expiration date, indicated on the label of the vial. Do not perform more than 3 freeze/thaw cycles to the Primer Mix (GVS-B27v5-PM) and Master Mix (GVS-B27v5-MM) vials, as this could decrease the sensitivity of the assay and impair results.

Due to the reagent's photosensitivity nature, avoid continuous exposure to light.

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Materials required but not supplied

General

- Gloves
- Lab coat

Consumables

- Filter tips (P200, P100 and P10)
- 1,5 mL Autoclaved Tubes
- q-PCR instrument specific reagents (in the case of using RotorGene® Q, only 0.1 mL tubes are allowed).

Equipment

- q-PCR instrument, with FAM and HEX/VIC detection channels. The following devices have been validated:
  - Rotor-Gene® Q, Qiagen®
  - DTlite, DNA Technologies
  - QTower, Analytic Jena
  - 7500 Real-Time PCR System, Applied Biosystems™
  - QuantStudio 6, Applied Biosystems™
- Vortex mixer
- Pipettes (P200, P100 and P10)

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Sample collection and preparation

This test should only be performed with complete blood samples treated with EDTA anti coagulation agents or citrate. Heparin can interfere with the PCR process and should not be used in this procedure.

The technique is compatible with several DNA extraction methods. Before delivering results with a diagnostic purpose, a validation assay with such extraction method should be done.

Caution

All biological and blood samples should be treated as potencially infectious. All the corresponding basic (universal) precautions should be taken. Samples should always be handled wearing the appropriate personal protection equipment.

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Procedure

A) PCR setup

Precautions

- Thaw all components of the kit before starting the assay, mix and centrifuge them.
- Work on ice or over a cool block.
- The PCR should be set up in the Pre-PCR area.
- Use only filtered tips and autoclaved tubes 1,5 mL.
- Use gloves and lab coat at all times.
- In each session it is recommended to test the contamination control (Reaction Blank) and the Positive Control (B*27+) included in the kit, as well as a B*27 negative sample.

1. Thaw the samples. Vortex (or gently mix with the fingers).
2. Prepare the following mix for n+1 samples:

	Vol. per sample (µL)
Master Mix	10
Primer Mix	8

3. Pipette 18 µL of the mix in each well. Then add 2 µL of DNA, Positive Control or Reaction Blank in the corresponding well.

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4. Seal the plate or the tubes. Perform a brief spin to ensure that all the volume settles to the bottom of the tube.

5. Place the plate in the thermal cycler and start the following program.

B) Thermal cycler configuration

1. Set up the following amplification program:

	Cycle Number	Temperature (ºC)	Time (mm:ss)	Ramp (%)	Analysis
Denaturation	1	95	05:00	100	X
Cycles	40	95	00:15	100	X
		64	01:00	100	Single
Cooling	1	15	∞	100	X

2. Set up the reading channels as indicated below:

The emitted fluorescence must be read in the FAM (495-520 nm) and HEX (535-554 nm) channels. Both fluorescences should be detected in every well (biplex reaction).

NOTE – Set the following configuration in the Rotor-Gene® Q software:

a. Open the Rotor-Gene® Q – Pure Detection software. Select the tab "Advanced" within the "New Run" window, and click on "New".

b. Choose the "72-Well Rotor" format and check the box "Locking Ring Attached". Then, click on "Next".

c. Set the "Reaction Volume" as 20 µL, and identify the operator and the samples.

d. Click on "Edit Profile" and set up the amplification program. Set the 60 sec step at 64 ºC, and click on "Acquiring to Cycling A". Set "Green" and "Yellow" as the fluorescence acquisition channels. Click on "OK" to accept and close the "Edit Profile" window.

e. Click on "Gain Optimisation" in the "Run New Wizard" dialog box to open the "Auto-Gain Optimization Setup" window. Scroll down the "Channel Settings" menu and select "Acquiring Channels". Then click on "Add". In the window "Auto-Gain

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Optimisation Channel Settings", set the following parameters for each channel ("Green" and "Yellow"):

- Tube position = 1
- Target Sample Range: 5 FI up to 10 FI
- Acceptable Gain Range: -10 to 10

f. Check the box "Perform Optimisation Before 1st Acquisition", and click on "Close".

g. Click on "Next" and then on "Start Run" in the "New Run Wizard" window.

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Results

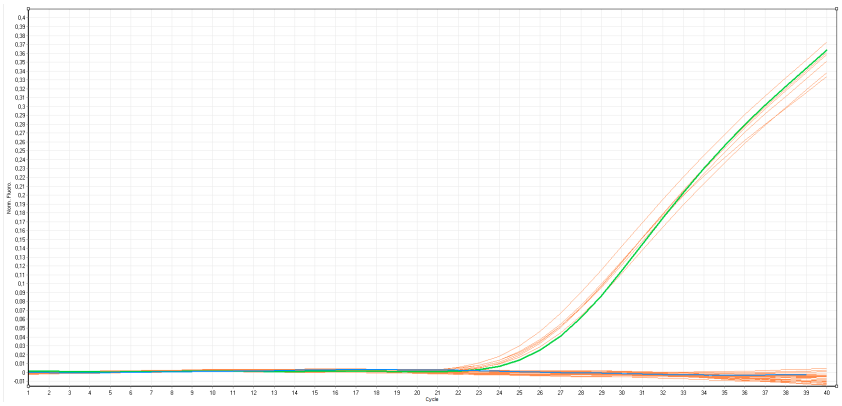
The Genvinset® HLA B27v5 constitutes a qualitative technique to determine the presence or absence of the HLA-B*27 family of alleles.

It is not necessary to select any passive reference.

The interpretation of results should be done as follows:

B*27 results

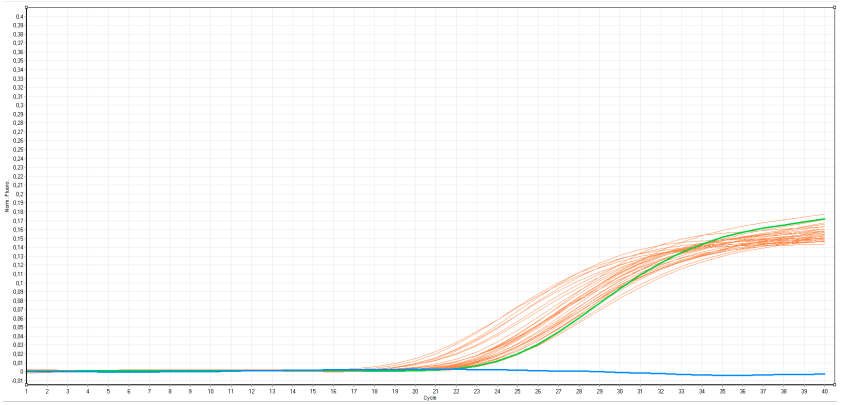
Selecting the "Green" channel (FAM) in the Amplification Plot, a graphic similar to the following one can be displayed:



Samples generating an amplification curve are to be considered as B*27 positive and can be identified by a numeric value called Crossing Point (Cp), which corresponds to the cycle in which fluorescence can be detected.

ß-globin results

Selecting the "Yellow" channel (HEX/VIC) in the Amplification Plot, a graphic similar to the following one can be displayed:



Samples generating an amplification curve are positive for the internal control (ß-globin).

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Quality control

Due to the qualitative nature of this test, it will not be necessary to perform a calibration.

It is recommended to perform a contamination control (Reaction Blank) by replacing the DNA for the negative control supplied with the kit and a positive control (HLA-B*27 positive sample).

The following criteria have to be taken into account in order to validate an assay:

- The Reaction Blank should report negative results in both "Green" and "Yelow" channels. An amplification curve with a Cp>35 value should be considered as negative. A Cp<35 value is associated with a contamination in the Reaction Blank and, therefore, all results from the experiment should be discarded.
- A positive control sample must render positive results for both B*27 and for ß-globin.
- DNA samples should always be positive for ß-globin (Cp<35).
- DNA samples generating results with Cp>35 for ß-globin and/or B*27 genes must be considered as doubtful and should be re-tested performing a new DNA extraction.

The assay must be performed according to the kit recommendations, as well as other quality control procedures that comply with local, federal and/or certifying agencies specifications.

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Specific operation data

1. Analytical specificity

The alignment of primers and probes in the most common HLA database regions (IMGT-HLA) has revealed the absence of non-specific bindings. No cross-reaction phenomena with genomic DNA have been reported.

2. Analytical sensitivity

A serial dilution assay was performed using two DNA samples (one B*27 positive and one B*27 negative), at a concentration of 35,7 and 13,7 ng/µL, respectively. Both were obtained with a conventional DNA extraction system. The following results for the analytical sensitivity of the test were obtained:

- DNA sample obtained by conventional extraction system:
  Detection Limit = 0,14 ng/µL (*)

  (*) Cp < 35

3. Diagnostic sensitivity and specificity

In three studies of human genomic DNA, one performed in an internal laboratory and the other two in external laboratories, a total of 159 samples were analysed. These samples had been previously typed by SSO (Sequence Specific Oligonucleotides) technology.

All the 159 tested samples were validated (positive amplification of the ß-Globin control gene). Among those, 26 were found to be B*27 positive.

	Genvinset® HLA B27v5		
	Samples	B*27+	B*27-
SSO	B*27 +	26	0
	B*27 -	0	133

There is a 100% match in the results obtained with the Genvinset® HLA B27v5 kit and the previously obtained genotype by SSO technology.

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HLA-B*27 (IMGT-HLA 3.43.0) family alleles detected by Genvinset® HLA B27v5 kit

B*27:01	B*27:05:02:09	B*27:05:16	B*27:05:43
B*27:02:01:01	B*27:05:02:10	B*27:05:17	B*27:05:44
B*27:02:01:02	B*27:05:02:11	B*27:05:18:01	B*27:05:45
B*27:02:01:03	B*27:05:02:12	B*27:05:18:02	B*27:05:46
B*27:02:01:04	B*27:05:02:13	B*27:05:19	B*27:05:47
B*27:02:01:05	B*27:05:02:14	B*27:05:20	B*27:05:48
B*27:02:01:06	B*27:05:02:15	B*27:05:21	B*27:05:49
B*27:02:02	B*27:05:02:16	B*27:05:22	B*27:05:50
B*27:02:03	B*27:05:02:17	B*27:05:24	B*27:05:51
B*27:02:04	B*27:05:02:18	B*27:05:25	B*27:05:52
B*27:02:05	B*27:05:02:19	B*27:05:26	B*27:05:53
B*27:02:06	B*27:05:02:20	B*27:05:27	***B*27:06:01:01***
B*27:03	B*27:05:02:21	B*27:05:28	B*27:06:01:02
B*27:04:01	B*27:05:02:22	B*27:05:29	***B*27:07:01***
B*27:04:02	B*27:05:03	B*27:05:30	B*27:07:02
B*27:04:03	B*27:05:04	B*27:05:31	B*27:07:03
B*27:04:04	B*27:05:05	B*27:05:32	B*27:07:04
B*27:04:05	B*27:05:06	B*27:05:33	B*27:07:05
B*27:04:06	B*27:05:07	B*27:05:34	B*27:07:06
B***27:05:02:01***	B*27:05:08	B*27:05:35	***B*27:08***
B*27:05:02:02	B*27:05:09	B*27:05:36	B*27:09
B*27:05:02:03	B*27:05:10	B*27:05:37	B*27:10
B*27:05:02:04Q	B*27:05:11	B*27:05:38	B*27:11
B*27:05:02:05	B*27:05:12	B*27:05:39	B*27:12:01:01
B*27:05:02:06	B*27:05:13	B*27:05:40	B*27:12:01:02
B*27:05:02:07	B*27:05:14	B*27:05:41	B*27:12:01:03
B*27:05:02:08	B*27:05:15	B*27:05:42	B*27:13:01

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- Detected Allele
- Non tested Allele. Possible weak amplification
- *CWD alleles marked in bold and italics*

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HLA B27v5

HLA-B*27 (IMGT-HLA 3.43.0) family alleles detected by Genvinset® HLA B27v5 kit

B*27:13:02	B*27:40	B*27:66N	B*27:91
B*27:14	B*27:41	B*27:67	B*27:93
B*27:15	B*27:42	B*27:68	B*27:94N
B*27:16	B*27:43	B*27:69	B*27:95
B*27:17	B*27:44	B*27:70	B*27:96:01
B*27:18	B*27:45	B*27:71	B*27:96:02
B*27:19:01:01	B*27:46	B*27:72	B*27:97
B*27:19:01:02	B*27:47	B*27:73	B*27:98
B*27:20	B*27:48	B*27:74	B*27:99
B*27:21:01	B*27:49	B*27:76	B*27:100
B*27:21:02	B*27:50:01	B*27:77	B*27:101
B*27:24	B*27:50:02	B*27:78	B*27:102
B*27:25	B*27:51	B*27:79	B*27:103
B*27:26	B*27:52	B*27:80	B*27:104
B*27:27	B*27:53	B*27:81	B*27:105
B*27:28	B*27:54	B*27:82	B*27:106
B*27:29	B*27:55	B*27:83	B*27:107
B*27:30	B*27:56	B*27:84	B*27:108
B*27:31	B*27:57	B*27:85	B*27:109
B*27:32	B*27:58	B*27:86	B*27:110
B*27:33	B*27:59N	B*27:87	B*27:111
B*27:34	B*27:60	B*27:88	B*27:112
B*27:35	B*27:61	B*27:89	B*27:113
B*27:36	B*27:62	B*27:90:01	B*27:114
B*27:37	B*27:63	B*27:90:02	B*27:115
B*27:38	B*27:64N	B*27:90:03	B*27:116
B*27:39	B*27:65N	B*27:90:04	B*27:117

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- Detected Allele
- Non tested Allele. Possible weak amplification
- *CWD alleles marked in bold and italics*

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HLA-B*27 (IMGT-HLA 3.43.0) family alleles detected by Genvinset® HLA B27v5 kit

B*27:118	B*27:144:02	B*27:172	B*27:200
B*27:119	B*27:145	B*27:173	B*27:201
B*27:120	B*27:146	B*27:174	B*27:202
B*27:121	B*27:147	B*27:175	B*27:203
B*27:122	B*27:148	B*27:176N	B*27:204
B*27:123	B*27:149	B*27:177	B*27:205
B*27:124	B*27:150	B*27:178	B*27:206
B*27:125	B*27:151	B*27:179	B*27:207
B*27:126	B*27:152	B*27:180	B*27:208
B*27:127	B*27:153	B*27:181	B*27:209
B*27:128	B*27:154	B*27:182	B*27:210
B*27:129	B*27:155	B*27:183	B*27:211
B*27:130	B*27:156	B*27:184	B*27:212N
B*27:131	B*27:158	B*27:185Q	B*27:213
B*27:132	B*27:159	B*27:186	B*27:214
B*27:133	B*27:160	B*27:187	B*27:216
B*27:134	B*27:161	B*27:188	B*27:217
B*27:135	B*27:162	B*27:190	B*27:218
B*27:136	B*27:163	B*27:191	B*27:219
B*27:137	B*27:164	B*27:192	B*27:220
B*27:138	B*27:165	B*27:193	B*27:221
B*27:139	B*27:166	B*27:194	B*27:222
B*27:140	B*27:167	B*27:195	B*27:223N
B*27:141	B*27:168	B*27:196	B*27:224
B*27:142	B*27:169	B*27:197	B*27:225N
B*27:143	B*27:170	B*27:198	B*27:226
B*27:144:01	B*27:171	B*27:199	B*27:227

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- Detected Allele
- Non tested Allele. Possible weak amplification
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GenViNSeT

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HLA-B*27 (IMGT-HLA 3.43.0) family alleles detected by Genvinset® HLA B27v5 kit

B*27:228

B*27:229

B*27:230

B*27:231

B*27:232

B*27:233

B*27:234

B*27:235

B*27:236

B*27:237

B*27:238

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- Detected Allele
- Non tested Allele. Possible weak amplification
- *CWD alleles marked in bold and italics*

Procedure limitations

- The current method allows for the detection of HLA-B*27 group of alleles, as specified in the previous section (IMGT-HLA 3.43.0).
- The presence of mutations or polymorphisms at the primer/probes annealing sites is possible and may result in the lack of allele definition. Alternative technologies could be necessary to resolve the typing.
- All the aforementioned conditions for the setup of the PCR should be carefully controlled. Any performances that do not meet such indications, can lead to poor results.
- All Genvinset® components manipulation must be done according to general lab best practices and be adjusted to local regulations, like the EFI standard (European Federation of Immunogenetics).
- The q-PCR thermal cycler must be calibrated and used according to the manufacturer's instructions.
- Do not mix components from other kits or lot numbers.
- Do not use the kit after its expiration date.
- Do not use the kit if there are any suspicions of possible loss of reactivity, contamination, external box deterioration or any other incidence that might affect the kits performance.
- Due to the complexity of HLA typing, data and result interpretation should be revised by qualified personnel.
- Discard expired reagents according to applicable regulations.

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Troubleshooting guide

Problem

- **Probable cause(s)**
  - Suggested corrective measure(s).

Reaction Blank (H_2O) is positive

- **Primer Mix/Master Mix/Reaction Blank contamination**
  - Repeat the experiment with new Primer Mix/Master Mix/ Reaction Blank aliquots.
  - Handle the kit components always according to accepted lab practices in order to avoid contamination.
  - Check the manipulation and storage conditions.
  - Discard any contaminated reagents.
- **Pre-PCR area is contaminated**
  - Confirm that all necessary precautions in the pre-PCR area have been followed.
  - Check for possible contamination problems in other PCR techniques.
  - Confirm suitability of the used reagents (1.5 mL tubes, pipette tips).
- **Pipetting error**
  - Check that the sample added in a certain position corresponds to the one indicated on the worksheet.

Low or no signal in all samples. Control samples are OK.

- **Samples with very low DNA concentration**
  - Check the DNA concentration and repeat the extraction if necessary.
- **DNA samples with high concentration**
  - Perform the assay using diluted samples.

Fluorescence intensity too low

- **Kit degradation (Primer Mix or Master Mix vials)**
  - Check that the storage of the kit is correct, reviewing both proper temperature conditions and light exposure (which should be avoided).
  - Avoid performing more than 3 freeze/thawing cycles to the reagents.

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- Aliquote the reagents if necessary.
- Repeat the test with new reagents.

Negative control sample is positive

- **Cross contamination**
  - Always handle the kit components following all necessary practices to avoid contamination.
- **Pipetting error**
  - Check that the sample added in a certain position corresponds to the one indicated on the worksheet.

Positive control sample is negative

- **Pipetting error**
  - Check that the sample added in a certain position corresponds to the one indicated on the worksheet.

Fluorescence intensity varies

- **The dirtiness on the outside of the tube walls interferes with the signal.**
  - Handle all consumables wearing gloves.
- **Volume is not settled to the bottom of the well or there are bubbles**
  - Perform a brief centrifugation to ensure that the volume settles to the bottom of the well and to remove all bubbles.
- **Pipetting error**
  - Check that the correct volume has been added.

There is no fluorescence signal

- **Incorrect reading channels selected**
  - Set the appropriate reading channels.
- **Pipetting error or reagent absence**
  - Control the pipetting and the reaction setup.
  - Repeat the PCR.
- **No reading channel was selected in the thermal cycler program.**
  - Check and modify the thermal cycler program.

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References

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2. "Optimization of Dnase I removal of contaminating DNA from RNA for use in quantitative RNA-PCR." Huang Z, Fasco MJ, Kaminsky LS. School of Public Health, State University of New York, New York 12201-0509, USA.

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Blackhills Diagnostic Resources

Cno. del Pilón 86, Casa 7 Local
50011- Zaragoza - Spain
www.bdrdiagnostics.com

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Changes to version 01

Version	Description of the modification
Rev. 01	First document version
Rev. 02	Updating of validated qPCR thermal-cyclers

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Explanation of symbols used on the labels

For in vitro diagnostic use

This product fulfills the requirements of Directive 98/79/EC on in vitro diagnostic medical device

Catalogue number

Lot number

Expiration date

Contents sufficient for <n> tests

Manufactured by

Store at

Keep away from sunlight

Positive control

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