Genvinset®

HLA DQA1*05

INSTRUCTIONS FOR USE

*Kit for detection of the HLA-DQA1*05 alleles*

For In Vitro diagnostic use

Rev. 01 / 2022-10-20

Camino del Pilón 86, Casa 7, Local
50011 – Zaragoza (Spain)

www.bdrdiagnostics.com

CE

Reference No.	UDI-DI:	Store
GVS-DQA5-24 (24 tests)	8437016942918	from -30°C to -18°C
GVS- DQA5-48 (48 tests)	8437016942925	

Genvinset®

HLA DQA1*05

Index

1- Information for safety

Please, read completely these instructions for use and follow them during the use of the current IVD kit.

The IVD kit shall be used by experts with strong experience in DNA analysis and interpretation of genetic results.

Consult the manufacturer if there are doubts involving the description of the assay method. Contact by phone at +34 976 094 603 or email address *customersupport@bdrdiagnostics.com*.

The IVD kit has a limited shelf life. Make sure that the shelf life is not expired before using the kit. Reagents from a kit beyond its expiry date might be degraded, which could impair results. Discard the expired reagents following applicable regulations.

The contamination of the sample or the reagent can render incorrect results. Be careful during the DNA extraction and sample and reagents manipulation.

This kit can be damaged during transport or storage. Do not use the kit in case of suspected damage during transport. Follow carefully the storage conditions described in the label and the IFU.

Ensure that the waste is managed according to local regulations. Incorrect waste management can result in environmental contamination.

The toxicological properties of the kit have not been studied in-depth, so it is recommended to avoid contact with skin and mucous membranes. Do not ingest. Manual Safety Data Sheets (MSDS) are available for the customer by request.

Ensure that this kit is adequate for the requested analysis by the clinician.

2- Intended Use

Genvinset® HLA DQA1*05 is a semi-automated *in vitro* diagnostic kit for the qualitative detection of the HLA-DQA1*05 allele in genomic DNA extracted from whole blood, associated with the immunogenicity of anti-TNF drugs, by Real-Time PCR using TaqMan® probes technology.

Patients who can benefit from this determination are those referred by a specialist. The results of this test should not be the only ones on which the therapeutic decision is based and should be used in conjunction with clinical data and results of other tests performed on the patient.

The intended user of the kit is technical personnel trained to carry out the protocol and the interpretation of results described in this document

3- Summary and explanation

Biological therapies, commonly known as biologics, are typically large and complex proteins manufactured in or derived from living sources. Biologics have transformed the management of immune-mediated diseases in recent years[1].

Several studies suggested the role of tumor necrosis factor alpha (TNF) in chronic immune-mediated diseases, such as Crohn's disease, inflammatory bowel disease (IBD), psoriasis and rheumatoid arthritis[2]. Therefore, anti-TNF therapies were developed and are now the most

widely used biological therapies for treating immune-mediated diseases. The most prescribed anti-TNF antibodies are infliximab and adalimumab[3].

Prolonged use of these anti-TNF antibodies may lead to the formation of anti-drug antibodies (ADA), which can decrease the efficacy of these biologics and promote adverse reactions and treatment failure. The risk of developing anti-drug antibodies, referred to as immunogenicity, is seen to be higher for patients treated with infliximab than adalimumab[1].

However, recent breakthroughs revealed that combined biologic and immunomodulatory therapy reduces the immunogenicity of both adalimumab and infliximab and even improves treatment outcomes in the last case[5),5]. Yet, despite these benefits, many patients are still treated with anti-TNF monotherapy because of concerns about an increased risk of adverse drug reactions, opportunistic infections and malignancies associated with combination therapy[6-9].

The biological mechanisms underlying antibody formation are unknown but the ability to identify subjects at higher risk would have significant clinical benefits[9]. In a retrospective study, HLA-DQA1*05 alleles were independently associated with a high risk of infliximab antibody formation in addition to the loss of response and treatment discontinuation[10]. In an observational study, a genome-wide significant association between HLA-DQA1*05 and the development of antibodies against anti-TNF agents was found[11]. Therefore, the screening of the HLA-DQA1*05 allele may be a useful clinical tool that could predict ADA risk and guide the clinical approach of anti-TNF therapies[10-12].

4- Procedure principles

The test is based on real-time PCR technology with TaqMan® probes. Each sample is analysed with:

- A pair of primers for the amplification of HLA-DQA1*05 alleles and a pair of primers for β-globin (*HBB*) gene amplification that serves as internal positive control (IPC).
- A hydrolysis probe specific for the HLA-DQA1*05 alleles labelled at the 5` end with FAM fluorophore and a hydrolysis probe specific for the IPC (β-globin; *HBB* gene) labelled at the 5' end with HEX fluorophore. Both probes are labelled at the 3` end with a quencher that inhibits fluorescence emission when the probe is intact

As the PCR reaction proceeds, the 5'→3'exonuclease activity of Taq polymerase cleaves the probes hybridized to their complementary sequence, separating fluorophore from the quencher and producing a fluorescent signal (in real-time), which is proportional to the amount of PCR product generated and monitored in a real-time PCR instrument. Thus:

- In the case of samples with one or two copies of the HLA-DQA1*05 alleles (HLA-DQA1*05 positive), the FAM-labelled probe binds to its complementary DNA sequence, the HEX-labelled probe binds to its complementary DNA sequence in the IPC and the following is observed:
    - Fluorescent signal in the FAM channel (λmax 518 nm) and
    - Fluorescent signal in the HEX channel (λmax 556 nm).
- In the case of samples with no copies of HLA-DQA1*05 alleles (HLA-DQA1*05 negative), the HEX-labelled probe binds to its complementary DNA sequence in the IPC and the following is observed:
    - No signal or weak signal in the FAM channel and
    - Fluorescent signal in the HEX channel.

5- Kit contents

➔ **GVS-DQA5-24 (24 tests)**

- GVS-DQA5-PM: 1 vial x 192 µL Primer Mix (PM) - Blue cap
- GVS-DQA5-MM: 1 vial x 240 µL Master Mix (MM) - Red cap
- GVS-DQA5-C+: 1 vial x 15 µL Positive Control (C+) - Green cap
- GVS-RB: 1 vial x 100 µL Reaction Blank (RB) - Natural cap

➔ **GVS- DQA5-48 (48 tests)** (*)

- GVS- DQA5-PM: 2 vials x 192 µL Primer Mix (PM) - Blue cap
- GVS- DQA5-MM: 2 vials x 240 µL Master Mix (MM) - Red cap
- GVS- DQA5-C+: 1 vial x 15 µL Positive Control (C+) - Green cap
- GVS-RB: 1 vial x 100 µL Reaction Blank (RB) - Natural cap

(*) Kit's format available under request.

6- Kit storage

All the components of the kit must be stored between -30°C and -18°C upon reception. Under these conditions, they are stable up to their expiry date indicated on the label.

Do not perform more than 3 freeze/thaw cycles to the kit vials as this may reduce the sensitivity of the assay and affect the results. If assays are to be performed with few samples, it is recommended to use aliquots of the reagents to avoid exceeding the recommended number of freeze/thaw cycles.

Due to the photosensitive nature of the Primer Mix, avoid continuous exposure to light.

7- Materials required but not supplied

General

- Disposable gloves
- Lab coat

Consumables

- Filter tips (P200, P20 and P10)
- 1.5 mL autoclaved tubes
- Compatible consumables for each real-time PCR instrument

Equipment

- Vortex mixer
- Centrifuge
- Micropipettes (P200, P20 and P10)
- Real-time PCR instrument, with FAM and HEX/VIC detection channels. The following devices have been validated:
  - 7500, QuantStudio™ 5 Dx and QuantStudio™ 6 Real-Time PCR Systems, Applied Biosystems™.
  - LightCycler® 96 and LightCycler® 480 systems, Roche.
  - Rotor-Gene® Q, Qiagen®.

- DT Lite Real-Time PCR System, DNA-Technology.
- qTOWER³G, Analytik Jena.
- CFX96 Real-Time PCR, BioRad.
- Mic qPCR, Molecular Systems.

8- Sample collection and preparation

Samples must be collected in line with the instructions for use of the collection device (not included with the kit) and under national and international guidelines.

The present test should only be performed with DNA extracted from whole blood samples preserved with anticoagulant agents such as EDTA or citrate. Heparin can interfere with the PCR process and should be avoided.

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 potentially infectious. When manipulating them, take the corresponding basic and universal precautions.

9- Usage procedures

➔ PCR setup

CAUTION!

- Define pre- and post-PCR work areas that should be kept separated to reduce the risk of contamination. Prepare the PCR in the pre-PCR area. Use lab coat and disposable gloves.
- Work on ice or over a cool block. Minimize the time between plate preparation and the start of the assay.
- For each session, it is recommended to include the contamination control (Reaction Blank) and the Positive Control (C+) provided with the kit.

1. Thaw all the kit components before starting the assay. Vortex the Primer Mix vial and carefully mix the Master Mix vial. Centrifuge briefly to collect the volume at the bottom of the tubes.
2. Prepare the reaction mix for n+1 samples, using the quantities indicated in the following table:

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

   Gently mix and centrifuge to ensure that all volume settles to the bottom of the tube.
3. Pipette 18 µL of this mix into the PCR plate/tubes.
4. Add into each well 2 µL of DNA (recommended concentration between 10 and 200 ng/µL), Reaction Blank, or Positive Control (C+).

5. Seal the plate/tubes using the appropriate sealer and centrifuge briefly to ensure that all the volume settles to the bottom of the well. If possible, make sure there are no bubbles in the wells.
6. Place the plate/tubes in the thermal cycler and set up the thermal cycler amplification program as described in the following section.

➔ Thermal cycler configuration

1. Set up the following readout channels:
   - FAM channel for FAM-labelled probe detection.
   - HEX/VIC channel for HEX-labelled probe detection.
2. Set up the appropriate amplification profile (*), and start the run:

	Cycles	Temperature (°C)	Time (mm:ss)	Analysis
Denaturation	1	95	05:00	X
Cycles	40	95	00:10	X
		64	**00:30**(*)	Single
Cooling	1	15	∞	X

(*) For both Rotor-Gene® Q (Qiagen) and DT Lite (DNA-Technology) real-time PCR thermal cyclers, please set up the following amplification program:

	Cycles	Temperature (°C)	Time (mm:ss)	Analysis
Denaturation	1	95	05:00	X
Cycles	40	95	00:10	X
		64	**00:25**	Single
Cooling	1	15	∞	X

➔ Disposal

Waste products shall be managed according to local regulations.

10- Results

➔ Results visualization

The analysis of the results is performed with the specific software of the real-time PCR instrument being used, and according to the manufacturer's instructions for use.

Once the run is finished, select the linear scale to visualize the amplification curves. It is recommended to check the correct behaviour of the obtained amplification curves:

- An amplification signal is considered positive if a quick and regular increase of fluorescence values (exponential) is observed (sigmoidal amplification) with Ct<35.
- A weak fluorescent, background lineal or exponential signal with Ct>35 should not be considered a positive amplification. This assay allows the detection of some of the alleles included in the group of highly polymorphic HLA alleles, among which little differences in their sequences have been described. Therefore, weak non-specific

signals from other similar in sequence but not-detected HLA alleles can be observed in the FAM channel. The appearance of these signals does not invalidate the assay.

A sample is considered positive if it produces an exponential amplification with Ct<35. A sample is considered negative if it produces a non-exponential amplification with low intensity or an exponential amplification with a Ct value >35.

CAUTION!

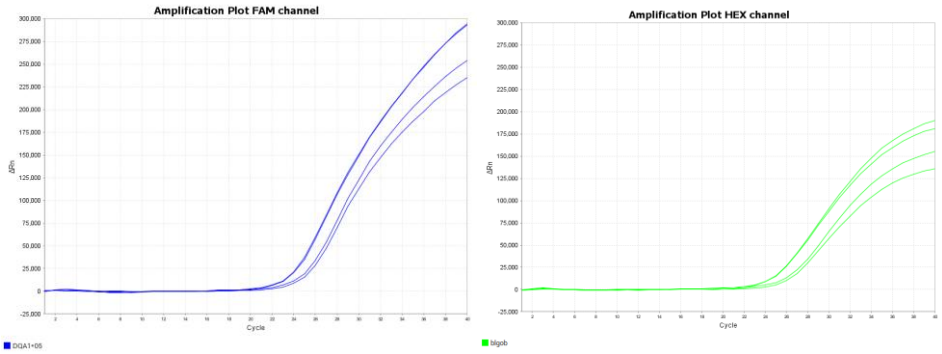
To determine the Ct value in each channel, adjust the threshold line as follows:

Select linear scale view and choose the region where the fluorescence signal is stable before exponential amplification. Place the threshold line above this background signal, so that it crosses close to the inflection point of the amplification curve. This line should slightly exceed the value of the highest fluorescence obtained with negative samples for the allele detected in this channel.

➔ Interpretation of results

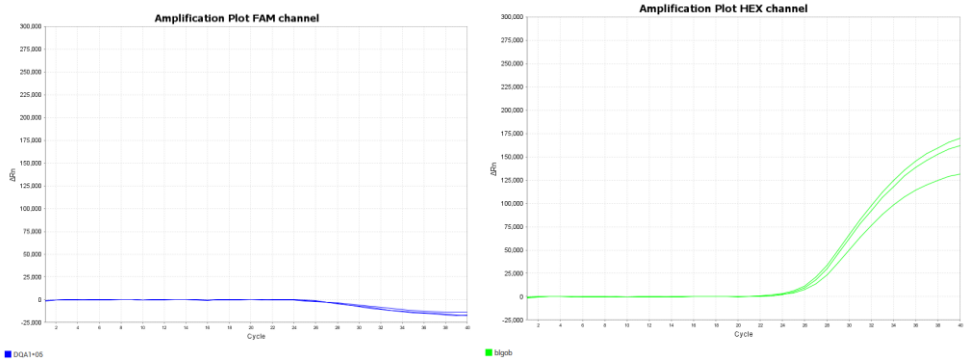
Results obtained with this kit must be interpreted by visualization of the amplification curves in both FAM and HEX channels. Select "linear scale" and determine the absence/presence of sigmoid amplification in each channel.

HLA-DQA1*05 positive samples



Exponential amplification curves with Ct<35 in both FAM and HEX channels.

HLA-DQA1*05 negative samples



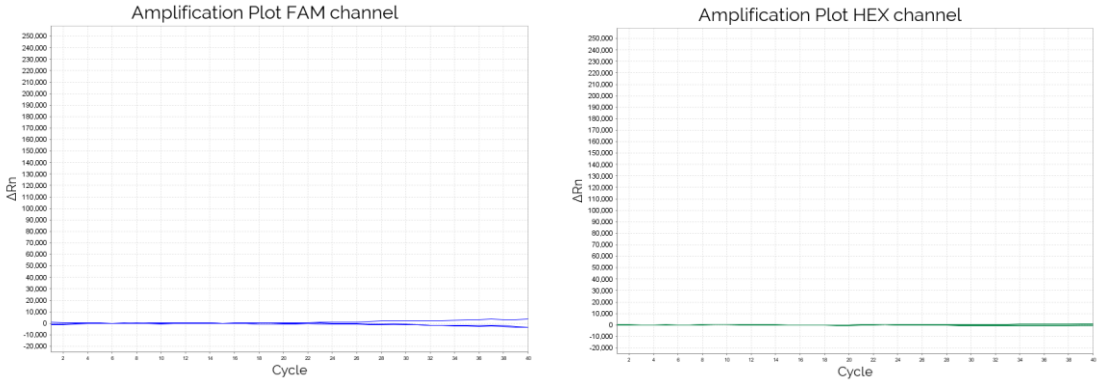
No signal or low intensity signal in FAM channel and exponential amplification in HEX channel (Ct<35)

11- Quality control

The kit includes a Reaction Blank and a Positive Control (C+) that must be included in each assay. An adequate behaviour of the control samples is a guarantee of the proper performance of the kit.

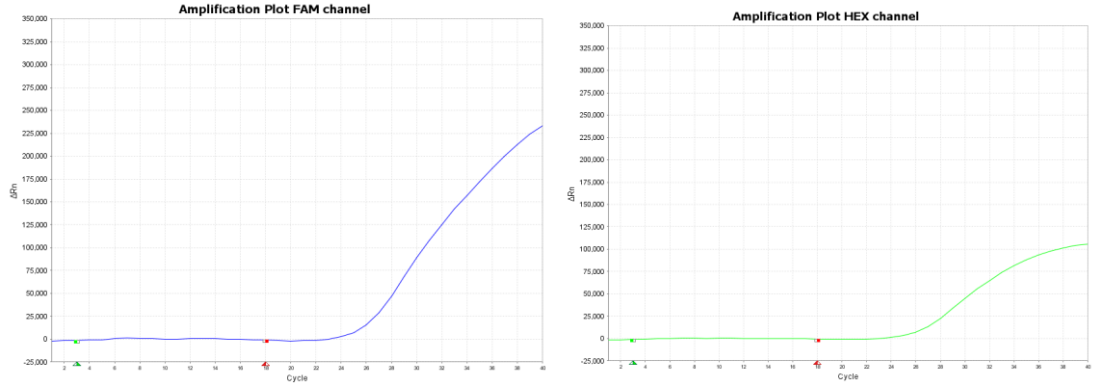
The assay is considered valid if the following amplification pattern is obtained in the controls:

Reaction Blank



No signal in both FAM and HEX channels or amplification with Ct>35

Positive Control (C+)



Exponential amplification with a Ct<35 value in both FAM and HEX channels.

The IPC is detected in the HEX channel and used as an internal positive control for each analysed sample. Therefore, the result of a sample is considered valid if there is, at least, sigmoidal amplification with Ct<35 in the HEX channel.

The result is to be considered invalid and should be repeated if:

- An amplification curve with Ct<35 is observed in FAM and/or HEX channels in the Reaction Blank.
- Non-exponential amplification signal is observed or an amplification signal with Ct>35 appears in the Positive Control.
- DNA samples with amplification curves with Ct>35 in FAM and/or HEX channels must be considered doubtful and should be retested performing a new DNA extraction.

If adequate behaviour is observed in the above-mentioned controls, proceed with the interpretation of the samples as indicated in the previous section.

12- Specific operation data

➔ Analytical specificity

Cross-reactivity has been assessed in different independent Genvinset® HLA DQA1*05 kit validation studies, as stated in the "Diagnostic sensitivity and specificity" section.

Due to the highly polymorphic nature of the HLA system, the *in-silico* alignment of primers and probes in the most common HLA database (IMGT-HLA) gave a list of detected, no detected and no tested with possible low-intensity signal alleles that can be found at *www.bdrdiagnostics.com*. It would be possible that intronic regions of some non-frequent alleles have not yet been sequenced, so the *in silico* alignment of the kit primers and probes in those areas is unknown. No cross-reaction phenomena with other DNA regions have been reported.

Interference has been studied by means of a bibliographic search. Heparin can inhibit Taq polymerase activity and compete with target nucleic acid, so the collected blood must be treated with other anticoagulants, as stated in the "Sample collection and preparation" section. Some substances found in blood are known as PCR inhibitors: haemoglobin, hemin, bilirubin, bile salts, lactoferrin, and immunoglobulin G. The polymerase included in Genvinset® HLA DQA1*05 has demonstrated high resistance to inhibition, and Master Mix composition is designed to deal with interference substances. Nevertheless, the presence of potentially inhibitory substances must be eliminated during DNA extraction and purification protocols. Before delivering results with a diagnostic purpose, a validation assay with such extraction method should be done.

➔ Analytical sensitivity

LoD: A dilution assay was performed using two DNA samples (HLA-DQA1*05 positive and HLA-DQA1*05 negative). Input DNA levels tested ranged from 40 ng to 0.016 ng (**) in a three-fold dilution series. Each level was tested in triplicate. The following data was obtained:

- Detection Limit: 0.49 ng (Ct<35)

Upper limit: 2 samples with different genotypes (HLA-DQA1*05 positive and negative) were assayed in a two-fold dilution series ranging from 400 ng to 3.125 ng. Assay performance remained acceptable at all input levels: suitable sigmoidal amplification curves and genotyping calls were accurately made at all levels (with Ct values<35).

(**) DNA concentration was measured using Nanodrop 1000 Spectrophotometer (Thermo Scientific).

➔ Diagnostic sensitivity and specificity

180 DNA samples were analysed in different studies at different laboratories. These samples were previously typed using a genotyping methodology different from Genvinset® HLA DQA1*05. The following results were obtained:

	Genvinset® HLA DQA1*05	
Previous method	**HLA-DQA1*05 Positive**	**HLA-DQA1*05 Negative**
HLA-DQA1*05 Positive	78	0
HLA-DQA1*05 Negative	0	102

There is a 100% match in the results obtained with the Genvinset® HLA DQA1*05 kit and the genotypes previously obtained by a different typing method.

➔ Accuracy

Repeatability studies consist in the measurement of within-run variability, through the analysis of replicas of every kind of sample that can be determined with the kit (HLA-DQA1*05 positive and HLA-DQA1*05 negative samples). Each sample was analysed in duplicate.

Genvinset® HLA DQA1*05 showed 100% repeatability.

A study to determine the reproducibility of the reagent was performed. It allows to estimate the variability between runs, lots and operators. Samples used represent the full range of expected analyte that can be measured with Genvinset® HLA DQA1*05, that is, HLA-DQA1*05 positive and negative samples. Three different lots in three different real-time PCR thermal cyclers were assayed by different operators.

Genvinset® HLA DQA1*05 showed 100% reproducibility.

➔ Trueness

The trueness of the analytical procedure of Genvinset® HLA DQA1*05 is assessed by comparison with a reference method. The study was developed as an internal validation of the reagent, in which trueness has been demonstrated with a 100% value. See the "Diagnostic Sensitivity and Specificity" section.

13- Procedure limitations

- The kit detects the HLA-DQA1*05 alleles included in the "HLA alleles detected_GVS-DQA5" document uploaded at *www.bdrdiagnostics.com*. Due to the highly polymorphic nature of the HLA alleles, weak signals from other alleles similar in sequence could appear.
- Mutations or polymorphisms at annealing primer/probe sites are possible and may result in the lack of allele definition. Other technologies could be necessary to resolve the typing.
- All the recommendations mentioned in this document should be carefully followed. Any performances that do not meet such indications, can lead to poor results.
- 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 kit's performance.
- All Genvinset® reagent manipulations must be done according to good laboratory practice, being adapted to local regulations.
- Do not mix components from other kits or lot numbers.
- Do not use the kit after its expiration date. Discard expired reagents according to applicable regulations.
- The real-time PCR thermal cycler must be calibrated according to the manufacturer´s recommendations and should be used accordingly to the manufacturer's instructions.
- Due to the complexity of HLA typing, data and result interpretation must be revised by qualified personnel.
- This product is an auxiliary tool for the clinical approach of biological therapies with an associated influence of the HLA-DQA1*05 allele. Use these results in conjunction with clinical data and results of other tests performed on the patient.

14- Troubleshooting guide

➔ No amplification signal is detected in any sample (neither in positive controls) or the intensity is very low

- The real-time PCR instrument is not correctly programmed. The thermal profile is not correct/the reading channels are not correctly configured/the selected fluorophores are not suitable.
    - Check that the instrument has been programmed correctly.
- The positions of the samples and controls indicated during the preparation of the assay do not match the positions in which they have been placed in the device.
    - Correctly assign the position of the samples.
- The reagent does not work properly.
    - Ensure that the kit is stored at an appropriate temperature (between -30°C and -18°C) and protected from light. Avoid unnecessary freeze/thaw cycles. Do not use it beyond the expiry date.
- The indicated amounts of each of the reagents have not been added to the reaction mix.
    - Check the volume of each component added to the mix.
- The consumables used are not compatible with the equipment being used.
    - Make sure that the right consumables have been used (compatible with the PCR instrument used).

➔ No signal is detected in clinical samples (signal appears in positive control)

- Poor quality of the DNA used.
    - Check the Absorbance ratio 260/280 and discard poor-quality samples. Avoid the presence of inhibitors (heparin, haemoglobin, hemin, bilirubin, bile salts, lactoferrin, immunoglobulin G). Repeat sampling and DNA extraction.
- Inadequate DNA concentration.
    - Adjust the DNA concentration to the recommended concentration range.
    - Check that the DNA concentration is above the limit of detection.
- Inhibition of amplification.
    - Collect whole blood in EDTA or citrate tubes.
- No sample was added.
    - Repeat assay making sure that samples have been added.

➔ Signal detected in the negative control

- Pipetting error
    - Change the pipette tip each time DNA is added to a well. Check that the sample added to the well corresponds to what is written on the worksheet.
- Contamination of the Primer Mix/Master Mix/Reaction Blank vial.
    - Repeat the assay with fresh aliquots.
- The PCR preparation area is contaminated.
    - Clean surfaces, instruments, lab coats, and change consumables and reagents. Repeat the assay.

➔ Fluorescence intensity varies between samples or abnormal amplification curves

- Dirtiness outside the reaction tube interferes with the detection of fluorescence.
    - Clean the equipment thoroughly. Check that the outside of the tubes/plate is clean. Handle the plate/tube with gloves.
- The volume is not at the bottom of the well or there are bubbles.
    - Centrifuge the tubes/plate before placing them in the thermal cycler.
    - Check if there are any bubbles. If so, perform a brief spin to remove them.
- The plate/tubes have not been closed properly.
    - Repeat the assay checking that the tubes/plates have been sealed correctly.
- DNAs with different concentrations have been used or the sample used contains a reaction inhibitor.
    - Repeat the sampling and DNA extraction.
- Presence of polymorphisms or mutations at the probe/primer binding sites.
    - Contact our Technical Support department at *customersupport@bdrdiagnostics.com.*

15- References

1) Vermeire S, Gils A, Accossato P, Lula S, Marren A. Immunogenicity of biologics in inflammatory bowel disease. Therap Adv Gastroenterol 2018; 11: 1756283X17750355.
2) Shealy, D. J. & Visvanathan, S. Anti-TNF antibodies: lessons from the past, roadmap for the future. *Handb Exp Pharmacol* 2008, 181, 101–129.
3) Mogilevski T, Sparrow MP. Infliximab Versus Adalimumab in Patients with Biologic-Naïve Crohn's Disease: Is the Difference Real? Dig Dis Sci 2018; 63: 1094–6.
4) Colombel JF, Sandborn WJ, Reinisch W, et al. Infliximab, azathioprine, or combination therapy for Crohn's disease. N Engl J Med 2010; 362: 1383–95.
5) Panaccione R, Ghosh S, Middleton S, et al. Combination therapy with infliximab and azathioprine is superior to monotherapy with either agent in ulcerative colitis. Gastroenterology 2014; 146: 392–400.e3.
6) D'Haens G, Reinisch W, Panaccione R, et al. Lymphoma Risk and Overall Safety Profile of Adalimumab in Patients With Crohn's Disease With up to 6 Years of Follow-Up in the Pyramid Registry. Am J Gastroenterol 2018; 113: 872–82.
7) Lichtenstein GR, Feagan BG, Cohen RD, et al. Drug therapies and the risk of malignancy in Crohn's disease: results from the TREATTM Registry. Am J Gastroenterol 2014; 109: 212–23.
8) Osterman MT, Sandborn WJ, Colombel J-F, et al. Increased risk of malignancy with adalimumab combination therapy, compared with monotherapy, for Crohn's disease. Gastroenterology 2014; 146: 941–9.
9) Lichtenstein GR, Rutgeerts P, Sandborn WJ, et al. A pooled analysis of infections, malignancy, and mortality in infliximab- and immunomodulator-treated adult patients with inflammatory bowel disease. Am J Gastroenterol 2012; 107: 1051–63.
10) Wilson A, Peel C, Wang Q, et al. HLADQA1*05 genotype predicts anti-drug antibody formation and loss of response during infliximab therapy for inflammatory bowel disease. Aliment Pharmacol Ther. 2020 Feb;51(3):356-363. Erratum in: Aliment Pharmacol Ther. 2021 Nov;54(9):1220.
11) Sazonovs A, Kennedy NA, Moutsianas L, et al.; PANTS Consortium. HLA-DQA1*05 Carriage Associated With Development of Anti-Drug Antibodies to Infliximab and Adalimumab in Patients With Crohn's Disease. Gastroenterology. 2020 Jan;158(1):189-199.
12) Gonzalez, H. *et al.* HMO-5 Association of anti-infliximab antibodies and HLA-DQA1*05 variant in ulcerative colitis: A retrospective single centre study. 2021; *Gut* 70, A32–A33.

16- Notice to purchaser

- This product has been developed for *in vitro* diagnostic purposes.
- When the kit is used within the territory of any Member State of the European Union, should there be any serious incident regarding the use of the kit, the user must report it to the manufacturer and the Competent Authority of their country and/or the patient´s country. Serious incident reporting for all other countries must be conducted according to local requirements for each country.

- The Summary of Safety and Performance (SSP) is uploaded into EUDAMED database and it is accessible to the users of the kit (https://ed.europa.eu/tools/eudamed/#/screen/home).
- Blackhills Diagnostic Resources, S.L.U. products should not be resold, modified for reselling or used to manufacture other commercial products without the written consent of Blackhills Diagnostic Resources, S.L.U.
- All information contained in this document can suffer modifications without prior notice. Blackhills Diagnostic Resources, S.L.U. does not assume any responsibility for possible errors in the document. This document is considered complete and accurate at the time of its publication. In no case will Blackhills Diagnostic Resources, S.L.U. be responsible for accidental, special, multiple or derived damages from the use of this document.
- The purchase of this product grants rights to the purchaser under certain Roche patents only used to provide *in vitro* diagnostic services. It does not grant any generic patent or any other patents aimed at any other usage apart from the one specified.
- FAM™ and HEX™ are trademarks of Life Technologies Corporation.
- FAM™ and HEX™ may be covered by one or more patents owned by Applied Biosystems, LLC. The purchase price of this product includes limited, non-transferable rights.
- TaqMan® is a registered trademark of Roche Molecular Systems, Inc.
- Genvinset® is a trademark of Blackhills Diagnostic Resources, S.L.U.

17- Changes control

Version	Description of the modification
00	First version of the document
01	Changes in Control Positive (C+) volume. Change in the list of validated real time PCR cyclers. Update of the number of samples analyzed in kit validation. Insertion of UDI-DI codes. Inclusion of the fact that the SSP is uploaded into EUDAMED and it is accessible to the users. Correction of typos and translation mistakes. CE logo is added.

18- Explanation of symbols used on the labels

IVD	*In vitro diagnostic* medical device		Expiration date
REF	Catalogue number	Σ	Contents sufficient for <n> tests
LOT	Lot number		Manufacturer

	Temperature limit		Keep away from sunlight
	Positive control		Consult electronic Instructions For Use document
	This product fulfills the requirements of Directive 98/79/EC on *in vitro* diagnostic medical device		