EDIT-B® notice

RNA blood test for differential diagnosis of bipolar disorder and unipolar depression

This document details the protocol to use the EDIT-B® test and is available on the EDIT-B® platform.

EDIT-B® is not a self-diagnostic test.

EDIT-B® is not a companion diagnostic test.

EDIT-B® should be used exclusively by qualified professionals.

Identification of the IVD device	Manufacturer
Product name: **EDIT-B®** Product reference: **0100**	ALCEDIAG Cap Gamma 1682 rue de la Valsiere 34790 GRABELS FRANCE Email: support.edit-b@alcediag-alcen.com Website: https://www.alcediag-alcen.com

EDIT-B® is a CE-marked in vitro diagnostic medical device according to European directive 98/79/EC.

IVD

CE

The IFU is available in three languages (FR, EN and ITA) in electronic format.

This version is compatible with the following software versions:

- ✓ **EDIT-B®** platform: 1.5.3
- ✓ **EDIT-B®** algorithm: 1.6.12

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1. Test description

Intended use

EDIT-B® is a qualitative in vitro medical device (IVD) intended to differentiate bipolar disorder from major depressive disorder to assist in diagnosis.

EDIT-B® combines RNA sequencing technology to measure RNA editing targets (from a panel of biomarkers using whole blood) and patient individual data (age, sex, treatment(s), substance use or addictions [tobacco, alcohol]) [1].

Prescription of EDIT-B® is exclusively intended for physicians authorized to establish a diagnosis of psychiatric illnesses.

EDIT-B® is part of the diagnostic process for mood disorders, complementing the usual diagnostic methods, such as the DSM-5 and ICD-11 criteria and clinical scales (MADRS, HDRS, BDI, etc.) [2, 3]. The test results should complement the clinical and behavioural arguments generally used by the physician to make a final diagnosis.

EDIT-B® is intended to be used on patients aged 18 years and older, male or female, with a current major depressive episode (moderate or severe) and being treated* for that depression at the time of testing.

**According to ATC classification, five treatment classes are considered: antiepileptics, antipsychotics, anxiolytics, hypnotics/sedatives and antidepressants.*

Test description

The device consists of two parts:

- A biological protocol for in vitro treatment of the blood sample
- Software for bioinformatics processing of the sequencing data obtained (consisting of a platform and an algorithm)

The steps for using the EDIT-B® product are presented below:

1. Clinician

EDIT-B® can only be supplied with a prescription, which can only be issued by physicians qualified to diagnose psychiatric disorders.

2. Blood sample

The blood sample is collected from the patient in an accredited clinical laboratory (Alcediag accreditation).

3. Central laboratory

The clinical laboratory processes the blood sample according to the EDIT-B® protocol. Next, the user uploads the sequencing data and the patient metadata from EDIT-B® to the EDIT-B® platform.

4. Analysis of Alcediag data

The EDIT-B® algorithm processes previously downloaded data. Alcediag checks the results before making them available on the EDIT-B® platform.

5. Transmission of results to the user by Alcediag

Once the results report has been validated by Alcediag, it is released and made accessible to the user, who can download it from the EDIT-B® platform.

6. Transmission of results to the clinician by the user

The central laboratory prepares its own results report on the basis of the report released in the EDIT-B® platform. The central laboratory sends this newly generated report to the clinician.

7. Diagnosis communicated to the patient

The patient is informed of the test results by the clinician.

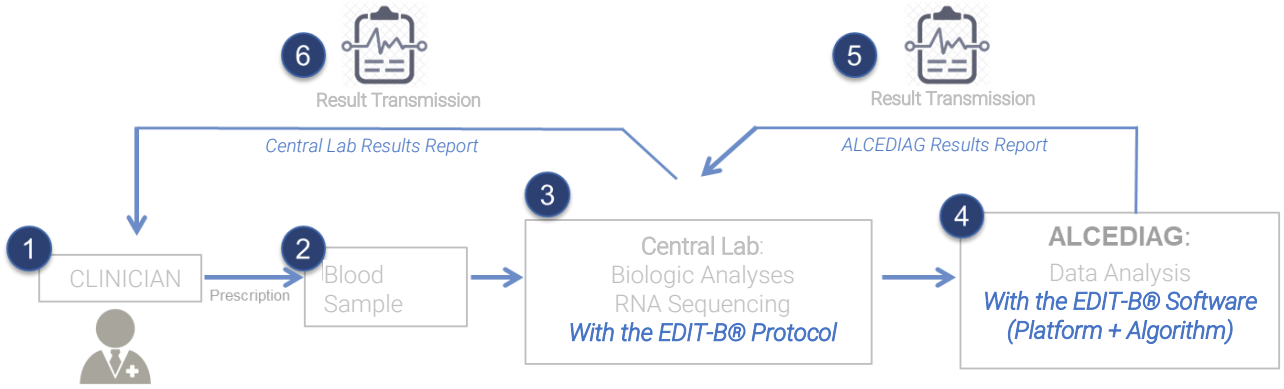

*Figure 1 - Overall process for using **EDIT-B®***

Description of the biological protocol

Alcediag has developed a biological protocol carried out by a medical laboratory accredited by Alcediag.

Total RNA is extracted from a blood sample collected in a PAXgene® tube and analysed.

Several quality controls are carried out to check the concentration and integrity of the RNA by measuring the RNA Integrity Number (RIN).

The RNA is then reverse-transcribed into complementary DNA.

For each target, a PCR step using specific primers is performed separately.

The various PCR products are diluted and pooled per patient to carry out an indexing PCR, enabling the preparation of the sequencing library.

The final step of this biological protocol is next-generation sequencing on the Illumina NextSeq 500/550. The extraction step and the final library step are interspersed with quality controls to ensure that the experiment runs smoothly (RNA concentration after extraction/Profile, purity and concentration of the library).

The raw sequencing data are then transferred to ALCEDIAG by the medical laboratory in a suitable format (*.fastq.gz) through a secure web portal for processing and bioinformatics analysis using the EDIT-B® software.

Description of the software

The EDIT-B® software system consists of an algorithm and a web platform. The following figure describes the overall software architecture:

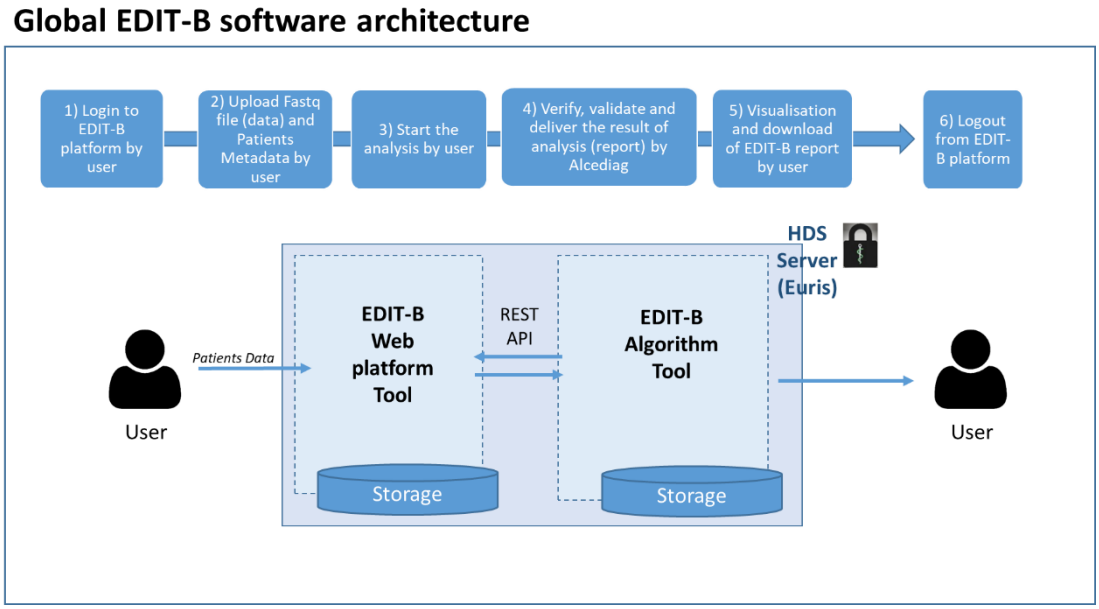

Figure 2 – Overall EDIT-B® software architecture

Once the biological protocol has been completed, and the data have been transferred to the platform (NGS sequencing data and metadata), the RNA sequences are cleaned and checked for quality. The sequences are then aligned with the reference genome, and the RNA A-to-I editing level is measured for each target marker. Using calculated RNA editing levels combined with patient metadata, ALCEDIAG's EDIT-B® algorithm can determine a qualitative diagnosis for each evaluated sample.

A report is then generated with all the relevant data for the biologist who analysed the sample: qualitative diagnosis, sequencing depth and quality, quality of sequence alignment control, etc.

The resulting report is made available via the secure EDIT-B® web portal for the clinical laboratory to download, sign and send to the prescribing physician.

Overview of the test

From a blood sample collected in a PAXgene® Blood RNA tube at usual collection points, the biological analyses are carried out by medical biology laboratories accredited for RNA sequencing and approved by the ALCEDIAG.

Then a score is calculated by software developed by ALCEDIAG, which contains modules for quality control and an algorithm to determine the patient's result. The score calculation algorithm is hosted on a SaaS (Software as a Service) platform, accessible via the website http://edit-b.alcediag-alcen.com/. The platform offers dedicated access to medical biology laboratories (access authorization administered by the company ALCEDIAG). It complies with European security, GDPR (General Data Protection Regulation) and health data management standards. The analysis and algorithm calculation processes are patented.

2. Scientific and technical principles of the test

The biological component of the EDIT-B® test falls under a specific sub-category of molecular biology called epigenetics. While genetics is the study of genes and heredity, epigenetics focuses on a complementary aspect, in particular how environmental factors turn on/off or regulate genes and affect gene expression [4, 5]. Epigenetic processes are reversible and dynamic, as they evolve over time. They are affected by environmental factors in the broad sense (pathologies, nutrition, physical activity, stress, medication, etc.) [6, 7]. Thus, epigenetic biomarkers allow a dynamic approach to diagnosis [8], taking into account the condition of the patient, the potential progression of the disease as well as the impact of treatment [9, 10].

RNA editing is one of the epigenetics phenomena. This is a physiological mechanism that occurs in any individual and influenced by – among other factors – the pathology and/or the medication [11-13]. It consists of substituting in specific places on the RNA an adenosine with an inosine under the specific action of enzymes [11, 14]. Several studies have shown that RNA editing is involved in many physiological functions and can affect proteins and regulation mechanisms [4].

One of the most studied processes occurring at the RNA level is the Adenosine to Inosine (A-to-I) deamination, that has been shown to be modified in several neuropsychiatric disorders. In particular, RNA editing regulates some synaptic functions via an alteration of the functioning of key receptors, leading to a direct impact on synaptic transmission [15]. RNA editing is a mechanism linking inflammation and neuropsychiatry [11, 16-19], changes in RNA editing being associated with some mental illnesses (such as depression, suicidal tendencies, etc.), but also with some inflammatory diseases[20] and certain cancers [21]. ALCEDIAG used targeted RNA sequencing on 8 genes selected through several scientific and clinical studies combined with artificial intelligence[46-50] to objectify and quantify the RNA editing mechanism and to develop a tool for the differential diagnosis of unipolar depression and bipolar disorder [47].

3. Conditions of use

EDIT-B® must be prescribed by a physician authorized to characterize a depressive episode. The medical prescription must include the patient's general information, the therapeutic classes of the treatment taken by the patient related to the EDIT-B® test and any substance use or addictions (tobacco/alcohol).

The necessary details to be provided in the prescription are described in the EDIT-B® user manual.

The test must be carried out during the patient's depressive episode as part of a medical consultation.

As a diagnostic aid, the EDIT-B® test result provides supplementary data on the patient for the physician.

The EDIT-B® test is carried out according to a standardized method requiring strict compliance with pre-analytical, analytical and post-analytical procedures, as described in the EDIT-B® protocol provided to the laboratory by ALCEDIAG. To perform the test, the laboratories need to be approved by ALCEDIAG.

4. Precautions for use

EDIT-B® pre-analytical precautions:

- The blood sample should be taken soon after the prescription (in the days that follow) to ensure that the patient is still in the same state of depression.
- The laboratory should respect the pre-analytical and analytical recommendations provided in the EDIT-B® protocol.

Precautions for interpreting EDIT-B® results for healthcare professionals:

- A result indicating a unipolar depression profile does not necessarily exclude the presence of bipolar disorder. It is mandatory to establish the diagnosis taking into account all the clinical and biological factors related to the patient, and to maintain regular patient monitoring.
- A result indicating a bipolar disorder profile does not formally mean that the patient is affected with bipolar disorder. It is mandatory to establish the diagnosis taking into account all the clinical and biological factors related to the patient, and to maintain regular patient monitoring.
- In the event of a discrepancy between the EDIT-B® result and other diagnostic tools (DSM-5, ICD-11, MADRS, HDRS, BDI, etc.), it is imperative to refer to the prescribing physician's conclusions.
- EDIT-B® cannot replace the prescribing physician's clinical diagnosis. The causes of these discrepancies may be of pre-analytical, analytical or post-analytical origin, due to non-compliance with the conditions of use of the diagnostic test and/or non-compliance

to the protocol and/or associated with the percentages of false positives and false negatives.

5. Use limitations and technical recommendations

Use limitation

EDIT-B® is not intended for the following cases:

- Patient under the age of 18;
- Patient with manic symptoms;
- For self-diagnostic testing

EDIT-B® has not been tested for the following types of patients:

- Pregnant women.

Technical recommendations

Protocol

EDIT-B® should be used:

- For a minimum of 8 samples (1 NTC + 7 patient samples) and a maximum of 96 samples (1 NTC + 95 patient samples)
- With the reagents, materials and primers indicated in the EDIT-B® user manual.
- With a No Template Control (NTC), i.e. water in a quality control process.

Blood collection in PAXgene® tubes should follow the manufacturer's recommendations (PreAnalytix reference 762165).

All reagents and samples should be handled with the usual precautions. Waste disposal should comply with local regulations.

Software and IT

The use of EDIT-B® is subject to the following technical conditions:

- Sequencing Analysis Viewer (SAV): version 2.4 and higher
- Illumina IEM Experiment Manager: version 1.19 or higher
- Illumina BaseSpace Hub or Illumina BCL convert
- Computer with an internet connection
- Web browser (including Mozilla Firefox (version 133.0 or higher), Google Chrome (version 131.0.6778 or higher), Apple Safari (version 14 or higher), Microsoft Edge (version 130.0.2849 or higher) and Opera Browser (version 115.0.5322.68 or higher)).

6. Cybersecurity measures associated with EDIT-B®

The following IT security measures have been implemented by ALCEDIAG:

- HDS server
- Security by design (3-level software architecture)
- Data encryption
- Access control (multi-factor authentication, CAPTCHA mechanism)
- Network segmentation and monitoring
- Periodic intrusion testing
- Data backup and off-site storage (redundant storage)

7. Collection and storage of samples

EDIT-B® is performed from a whole blood sample taken in a 2.5 ml PAXgene® Blood RNA tube (CE-marked device). Collection of blood samples can be performed at any time of the day. The sample should be shaken and stored according to the instructions for use of PAXgene® tubes.

Recommendations from the manufacturer of PAXgene®

PAXgene® Blood RNA tubes contain a proprietary reagent composition based on patented RNA stabilisation technology (US patents 6,602,718 and 6,617,170). This reagent helps protect RNA molecules from degradation by RNases and minimises ex vivo changes in gene expression.

PAXgene Blood RNA tubes are designed for the collection of whole blood and the stabilisation of intracellular RNA. Immediately after blood collection, the PAXgene Blood RNA tubes should be gently inverted 8 to 10 times. The tubes should then be left standing at room temperature (18–25°C) for at least 2 hours and a maximum of 72 hours before being processed or transferred to a refrigerator (2–8°C) or freezer (–20°C). If storage at –70°C or –80°C is required, the tubes should first be frozen at –20°C for 24 hours, then transferred to –70°C or –80°C.

RNA stability in PAXgene tubes is:

- Up to 3 days at room temperature (18–25°C)
- Up to 5 days at 2–8°C
- 11 years at –20°C or –70°C.

Given the instructions above, ALCEDIAG takes into account the PreAnalytiX sample stability specifications. In conclusion, Alcediag considers that there is no need for further testing.

8. Sample analysis method

The EDIT-B® library preparation protocol is provided to laboratories accredited by ALCEDIAG to perform the EDIT-B® test.

The Instructions for Use (IFU) of EDIT-B® are intended for the professionals who will perform the test.

EDIT-B® is intended to be used with a PAXgene® automated RNA extraction device, followed by a manual process until the sequencing step.

Reagent

EDIT-B® must be used with certain reagents listed in the table below according to the following criteria:

- **Critical reference:** the reference is mandatory in the EDIT-B® protocol.
- **Non-critical reference:** the reference is not mandatory in the EDIT-B® protocol. You can use another reference from another manufacturer.

*Table 1 - List of reagents to be used for **EDIT-B®***

Function		Product name	Reference	CE/RUO	Manufacturer
Sample Extraction	Blood collection	Tubes PAXgene Blood ARN-2,5ml-16x100mm-CE/IVD-100	762165	CE	PreAnalytiX
	Tube preparation	DPBS	Non critical reference	RUO	Non critical Manufacturer
	Automated RNA PAXgene extraction Kit	RNA PAXgene extraction kit of QIAsymphony SP instrument / QIAsymphony® PAXgene Blood RNA kit	762635	RUO	QIAGEN
		RNA PAXgene extraction kit of MagNA Pure 96 Instrument / MagNA Pure 96 Cellular RNA Large Volume Kit	05467535001	RUO	ROCHE
	QC RNA	RNA Reagent Kit corresponding to the Automated eclectrophresis (5 ng/µl sensitivity)	Non critical reference	RUO	Non critical Manufacturer
Library preparation process	Reverse transcription	Prime Script Reagent kit 200rxns Tak	RR037A	RUO	Takara
	Amplification Target (PCR1)	Q5® Hot Start High-Fidelity 2X	M0494S	RUO	NEB
	Purification of PCR1 pool	magnetic beads - CleanPCR - 50ML	CPCR0050	RUO	Cleanna
		Ethanol absolut	Non critical reference	RUO	Non critical Manufacturer
	Index samples (PCR2)	Q5® Hot Start High-Fidelity 2X	M0494S	RUO	NEB
		Nextera XT Index Kit v2 Set A (96 indexes, 384 samples)	FC-131-2001 / 15052163	RUO	ILLUMINA
	Purification of library	magnetic beads - CleanPCR - 50ML	CPCR0050	RUO	Cleanna
		Ethanol absolu	Non critical reference	RUO	Non critical Manufacturer
	QC library	Qubit® dsDNA BR Assay kit	Q32853	RUO	Thermo Fisher
		DNA Reagent Kit corresponding to the Automated eclectrophresis (analysis under DNA 1000 pb)	Non critical reference	RUO	Non critical Manufacturer
	Library preparation	NaOH 10N	Non critical reference	RUO	Non critical Manufacturer
		Nextseq Phix control Kit	15041963 / FC-110-3002	RUO	ILLUMINA
		Tris HCl pH=7,0	Non critical reference	RUO	Non critical Manufacturer
	Sequencing Nextseq	Cartridge NGS NextSeq® 500/550 Mid Output Kit v2 (300 cycles)	15057939	RUO	ILLUMINA
		Buffer v2 Nextseq 500/550	15057941	RUO	ILLUMINA
		Nextseq Accessory Box V2	15058251	RUO	ILLUMINA
		Nextseq 500/550 Mid output flowcell cartridge V2.5	20022409	RUO	ILLUMINA
		Tween 20	Non critical reference	RUO	Non critical Manufacturer
Optional quality control		DNA Reagent Kit corresponding to the Automated eclectrophresis (analysis under DNA 1000 pb)	Non critical reference	RUO	Non critical Manufacturer

Material

*Table 2 - List of materials to use for **EDIT-B®***

Device & Function	Name	Reference	Supplier
Paxgene centrifuge & Plate centrifuge	Non critical material	Non critical reference	Non critical supplier
Automated RNA PAXgene device (RNA Extraction)	MagNA Pure 96 Instrument	06541089001	ROCHE
	QIAsymphony SP instrument	9001297	QIAGEN
Automated Electrophoresis device (RNA & DNA QC)	Non critical material *(e.g. Agilent 2100 bioanalyzer / Agilent TapeStation / Revvity Labchip)*	Non critical reference	Non critical supplier
Sequencing device	ILLUMINA NEXTSEQ 500/550	ILLUMINA	ILLUMINA
Thermocycler (PCR) / *the same reference material needs to be used for all PCR*	Non critical material	Non critical reference	Non critical supplier
DNA Quantification device	QUBIT INVITROGEN	2286613612	Invitrogen
Purification device	Magnetic plate	MYMAG-96	MAGBIOGENOMICS

The EDIT-B® protocol is described in the EDIT-B® user manual available on the EDIT-B® platform (http://edit-b.alcediag-alcen.com/).

9. EDIT-B® platform:

Access to the EDIT-B® platform is provided to laboratories accredited by ALCEDIAG to use EDIT-B®.

10. EDIT-B® test results

At the end of the EDIT-B® analysis, a medical report consisting of the results provided by the software is provided to the medical biology laboratory via the EDIT-B® platform. The latter will validate this report and then send it to the physician who issued the prescription.

Decision rules for EDIT-B® test results

The EDIT-B® test algorithm returns a probability of having a bipolar profile between 0 and 1. The classification threshold, also called the decision threshold in the EDIT-B® algorithm, allows us to match the output of the EDIT-B® algorithm with a qualitative category (Unipolar/Bipolar). This decision threshold was selected to have a sensitivity, specificity and precision greater than 80%. Using these criteria, the decision threshold of the EDIT-B® algorithm has been set to 0.5 to define the EDIT-B® algorithm as qualitative (a patient has a bipolar profile when the EDIT-B® score is ≥ 0.5 and a unipolar profile when it is < 0.5).

Thus, the results are presented in qualitative form (Bipolar / Unipolar).

Table 3 - Presentation of EDIT-B® results

Outcomes	Algorithm score	Description
Bipolar	≥ 0,5	The RNA editing profile measured by EDIT-B® corresponds to a bipolar patient profile.
Unipolar	< 0.5	The RNA editing profile measured by EDIT-B® corresponds to a unipolar patient profile.
No result	Uninterpretable	Requirements to run the EDIT-B® test are not fulfilled.

No Template Control (NTC)

EDIT-B® must be used with a No Template Control (NTC), i.e. water in a quality control process. Quality control with water allows the detection of possible contamination or non-specific amplification in the analyzed plate. If the number of readings is abnormally high, contact ALCEDIAG technical support.

EDIT-B® test specifications

In order to successfully deliver a diagnostic aid report, the EDIT-B® test must meet several quality criteria and specifications. These criteria are described in the table below:

Quality Control	Description	Minimal Requirement
Sequencing depth	The coverage per biomarker after filtering and mapping must be greater than the minimal requirement.	10,000 reads
Sequencing quality control	The mean quality of biomarkers should be greater than the minimal requirement.	Phred score=30
Alignment quality	The mean alignment quality of biomarkers should be greater than the minimal requirement.	MAPQ=30

11. EDIT-B® test performance

Clinical performance

The clinical performance results of the **EDIT-B®** test conducted on an independent multicentre study are presented in the table below.

Sample type: Whole blood collected with PAXgene® Blood RNA tubes

Clinical performance	Outcomes*
Total population size Including: • 38.3% Male / 61.7% Female • 70.2% Unipolar / 29.8% Bipolar	94
Sensibility (%)	85.7
Specificity (%)	81.8
False Positive Rate (%)	18.2
False Negative Rate (%)	14.3
Positive Predictive Value (%)	66.7
Negative Predictive Value (%)	93.1
Clinical precision (%)	83.0

**Results of the clinical replication/validation study conducted at the Les Toises psychiatric center in Switzerland*

Analytical performance

Studies have been conducted to determine the analytical performance of the **EDIT-B®** test.

Sample type: Whole blood collected with PAXgene® Blood RNA tubes, IQC (Internal Quality Control)

Analytical performance	Outcomes
Precision - Intra-run repeatability for n= 3 runs, CV% (SD) on the score generated by the EDIT-B® algorithm	16.5% CV (or 0.07 SD)
Precision - Inter-run reproducibility for n= 3 runs, CV% (SD) on the score generated by the EDIT-B® algorithm	10.3% CV (ou 0.05 SD)
Accuracy (bias) (editing in % (±SD))	14.9% (±4.8) mean bias
Limit of Blank (LoB) (editing in %)	0.06%
Limit of Detection (LoD) (editing in %)	0.09%
Cross-contamination (% of contaminated wells)	4.4%
EDIT-B® primer reactivity (% specificity)	100%
Known endogenous and exogenous interferences, cross-reactions	No statistically significant difference was observed between the test conditions and reference conditions for the tested substances (Bilirubin, Hemoglobin, Triglycerides, and Proteinase K)

12. Contact

For technical assistance, contact ALCEDIAG Technical Support via:

- Website: https://www.alcediag-alcen.com/contact/
- E-mail: editb-support@alcediag-alcen.com

13. Symbols

Manufacturer: ALCEDIAG, 1682 RUE DE LA VALSIERE, 34790 GRABELS, FRANCE	
Complies with the demands of directive 98/79/CE	
IVD Diagnostic Medical Device	
Catalogue Reference: 0100	
Consult instructions for use	

14. Abbreviation

ATC: Anatomical Therapeutic Chemical classification system
BDI: Beck Depression Inventory
DSM-V: Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition
EN: English
FASTQ: text-based format for storing both a biological sequence and its quality scores
GDPR: General Data Protection Regulation
HDRS: Hamilton Depression Rating Scale
ICD-11: International Classification of Diseases, eleventh revision
IFU: Instructions for Use
ITA: Italian
IVD: In Vitro Diagnostic device
MADRS: Montgomery–Åsberg Depression Rating Scale
MAPQ: MAPping Quality
NTC: No Template Control (water quality control)
Phred: Quality score to measure the quality of the identification of the sequenced nucleobases
RNA: RiboNucleic Acid

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