ALCEDIAG

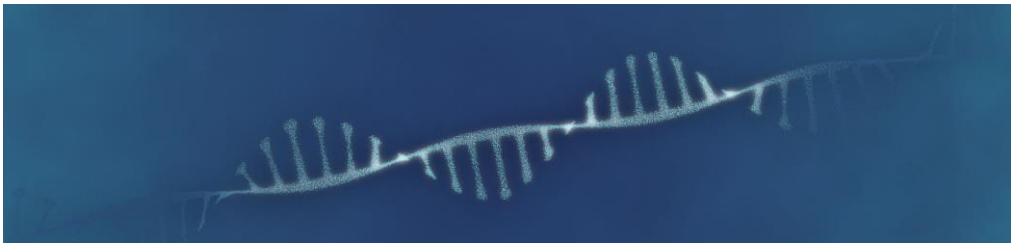
FOR HEALTH

Frequently Asked Questions

Patients & Relatives

EDIT-B Test

April 2025



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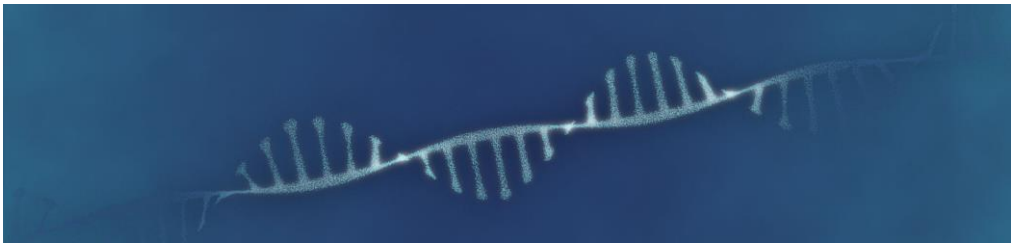

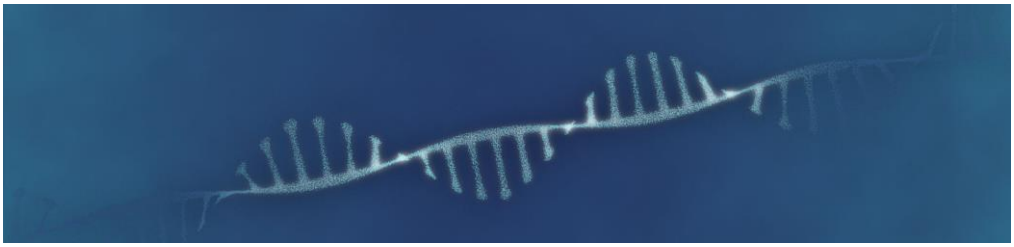

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Introduction

The EDIT-B test, developed by ALCEDIAG, is a clinically validated blood test with sensitivity and specificity above 80%, designed to support the differential diagnosis of bipolar disorder (BD) and major depressive disorder (MDD) in adults (18+) treated for moderate to severe depressive symptoms. It serves as a decision-support tool for physicians, particularly psychiatrists.

This FAQ is designed to answer any questions you may have about the EDIT-B test.

DEPRESSION AND BIPOLAR DISORDERS

What are bipolar disorders and what are their symptoms?

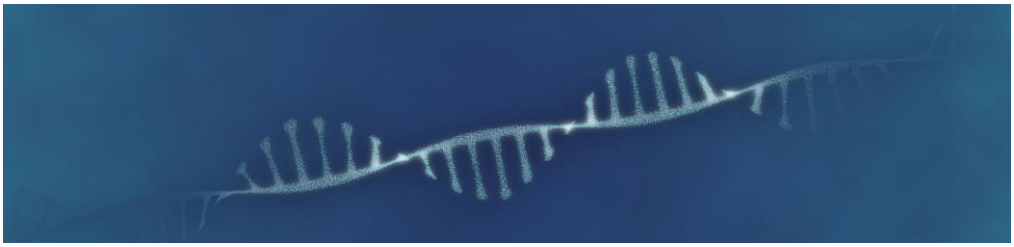
According to the American Psychiatric Association, bipolar disorders are "mental health conditions characterized by periodic, intense emotional states affecting a person's mood, energy, and ability to function. These periods, lasting from days to weeks, are called mood episodes. Mood episodes are categorized as manic/hypomanic episodes when the predominant mood is intensely happy or irritable, or depressive episodes when there is an intensely sad mood or the ability to experience joy or pleasure disappears. People with bipolar disorder generally have periods of neutral mood as well. When treated, people with bipolar disorder can lead full and productive lives."

There are three main types of bipolar disorder:

- **Bipolar I Disorder**: Characterized by manic episodes lasting at least 7 days or requiring hospitalization, often followed by depressive episodes.
- **Bipolar II Disorder**: Characterized by a pattern of depressive episodes and hypomanic episodes, without full manic episodes.
- **Cyclothymic Disorder (Cyclothymia):** Involves numerous periods of hypomanic symptoms and mild depressive symptoms lasting at least 2 years.
- **Other Specified and Unspecified Bipolar and Related Disorders**: A category for cases that do not fit the criteria of the three main types but still involve episodes of elevated mood.

Furthermore, it is important to note that many cases of treatment-resistant or hard-to-treat depression, in the context of personality disorders, hyperthymic temperament, high intellectual potential, addictive behaviors, simple or complex psychological trauma, or social vulnerability, may fall within the bipolar spectrum under some definitions.

Bipolar disorder may present without manic or hypomanic episodes, manifesting only in depressive or even misleading psychotic forms.



Symptoms of bipolar disorder can vary significantly from one individual to another.

The first symptoms generally appear in late adolescence or early adulthood, but they can also emerge at any age, even without prior clinical history (such as a first depressive episode, family history, postpartum depression, etc.).

For more information, please consult the following website: Bipolar Disorder - National Institute of Mental Health (NIMH)

What is unipolar depression?

Unipolar depression is another name for Major Depressive Disorder (MDD). Both terms are used interchangeably in this document.

How do you differentiate depressive symptoms, unipolar depression, and Major Depressive Disorder?

Depressive symptoms refer to the symptoms themselves, while unipolar depression or Major Depressive Disorder refers to the actual disease.

Depressive symptoms can be present in illnesses other than unipolar depression/MDD, such as bipolar disorders.

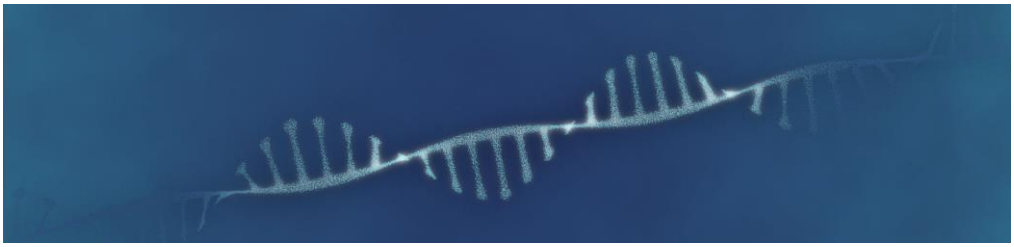
What is the average time to diagnose bipolar disorders?

On average, there is an 8-year delay in receiving a correct bipolar diagnosis (McIntyre et al., 2020).

How do scientific publications and experts explain the delay in diagnosing bipolar disorders and the associated challenges?

Bipolar disorder is one of the most complex psychiatric conditions to diagnose today, even though it ranks among the most disabling mental health conditions (5th most disabling mental disorder according to IHME).

As highlighted in the Lancet publication by Prof. Phillips and Prof. Kupfer (Lancet. 2013 May 11;381(9878):1663–1671. doi: 10.1016/S0140-6736(13)60989-7), one of the main reasons for this delay is the difficulty in distinguishing the depressive phase of bipolar disorder from unipolar depression. The publication particularly notes:



- A much higher prevalence of depressive symptoms compared to manic/hypomanic symptoms
- A large number of patients without a clear history of mania/hypomania
- A lack of recognition of manic/hypomanic symptoms by patients and a lack of detection by physicians and families
- Difficulty in identifying mania/hypomania in mixed episodes
- Etc.

For example, 69% of individuals with bipolar disorder initially received an incorrect diagnosis (Singh et al., 2006), and up to 40% of patients diagnosed with depression could potentially be bipolar (Angst et al., 2011).

Why is a precise, reliable, and early diagnosis of bipolar disorder essential?

Unipolar and bipolar depression share clinical similarities, yet their treatment (pharmacological and otherwise) differs significantly.

As highlighted in many publications (notably McIntyre et al., 2022), delays in diagnosing bipolar disorder negatively impact patients' lives, may lead to numerous comorbidities (e.g., addictions, cardiovascular diseases), and increase the risk of premature death (especially through suicide attempts and completion).

Professor McIntyre emphasizes that early and reliable diagnosis is a critical need for patients (McIntyre et al., The Lancet, 2020). As stated in Vidal, with appropriate care following an accurate diagnosis, bipolar patients can return to normal life. It even notes that after several months of treatment, "manic-depressive cycles (former term for bipolar disorder) may become less frequent or even disappear entirely."

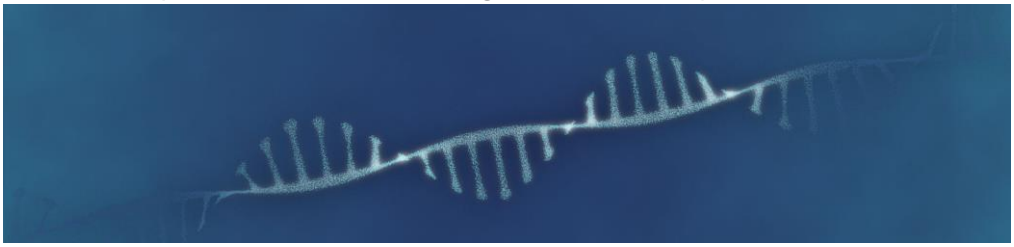
What is the prevalence of bipolar disorder and unipolar depression?

According to the World Health Organization, in 2019, 280 million people were living with depression and 40 million with bipolar disorder. Bipolar disorder may be significantly underdiagnosed due to the challenges in identifying the condition.

SCIENTIFIC BACKGROUND

What is epigenetics?

Epigenetics studies the mechanisms that modify the activity and expression of genes without altering the DNA sequence itself. These changes, influenced by environmental factors such as



nutrition, stress, or medication, act like switches on genes, turning them on, off, or adjusting their expression. Unlike genetic changes, epigenetic modifications are reversible. Epigenetics encompasses several processes, including DNA methylation, histone modifications, and RNA editing.

For example, identical twins share the same DNA, yet they can develop differences over time due to epigenetics. Their unique environments, such as stress, diet, or life experiences, can modify gene expression without altering their genetic code. These changes help explain why identical twins can age differently or develop different susceptibilities to certain diseases.

What is RNA editing, the epigenetic mechanism behind the EDIT-B test?

RNA is a temporary copy of DNA that, unlike DNA, can exit the cell nucleus to help produce proteins, which are essential for cell function.

A-to-I RNA editing is a process in which one of RNA's building blocks, a nucleotide called adenosine, is converted into inosine. This process is an early regulatory system for gene expression and contributes to the diversity of proteins in the body. Proteins are key components of our cells and essential for the functioning of our body.

This mechanism is particularly important in the brain, as it helps regulate specific neurotransmitter networks. Disruption in A-to-I RNA editing can lead to imbalances in neurotransmission processes in the brain.

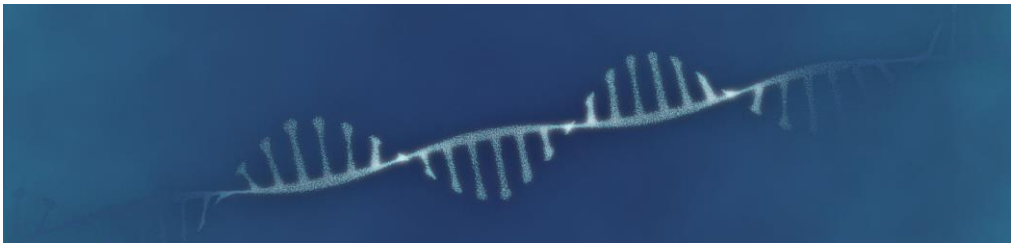
What is a biomarker?

Biomarkers are measurable indicators such as genetic characteristics, proteins, metabolites, and digital biomarkers. They are used to characterize physiological or pathological states, track disease progression, or evaluate treatment responses.

What is next-generation sequencing (NGS), and why is this technique specifically used in the analysis of EDIT-B blood tubes?

Next-generation sequencing (NGS), also known as high-throughput sequencing, is an advanced technology that allows for the rapid and parallel sequencing of millions to billions of DNA or RNA strands. Sequencing involves determining or "reading" the order of the building blocks, called nucleotides, that make up DNA or RNA. Unlike traditional sequencing methods, NGS enables massive parallel processing of multiple sequences at once, significantly increasing the speed and efficiency of DNA or RNA analysis.

This technology has revolutionized genomics, transcriptomics, and many areas of biological research, making it possible to decode entire genomes and provide detailed insights into genetic variations, gene expression, and more. For EDIT-B, next-generation sequencing (NGS) offers a



unique opportunity to investigate RNA editing events across multiple regions of the RNA simultaneously.

EDIT-B Test Technology

How was the EDIT-B test developed? What are the biomarkers used in the EDIT-B test?

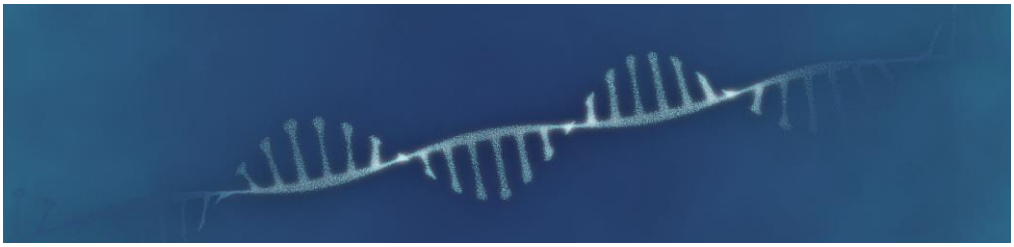
The EDIT-B test is the result of over a decade of research in the fields of epigenetics (specifically RNA editing) [see definitions in the science section of the FAQ], artificial intelligence, and neuroscience.

The biomarkers of the EDIT-B test target specific RNA sequences extracted from blood samples, which show notable differences between patients with bipolar disorder and those with depression. Specifically, the analysis of these RNA sequences focuses on particular changes in blocks of RNA called nucleotides. These specific nucleotide changes are known as A-to-I RNA editing events, an epigenetic modification (see explanation of epigenetics in the science section) caused by enzymes called ADARs. This mechanism involves the substitution of the nucleotide adenosine (A) with inosine (I) within RNA sequences.

The selection of specific nucleotide sequences used in the EDIT-B test is based on studies demonstrating their relevance, especially for the central nervous system and mood disorders (through RNA analysis and biological network analysis related to these conditions, combined with the establishment of rigorous analytical and technical criteria) (Salvetat et al. 2022, Hayashi et al. 2023). In addition to these RNA sequences, the EDIT-B test takes into account the patient's age, sex, addictions, and current treatments. All these data are used as inputs for the EDIT-B algorithm, which was developed using machine learning techniques.

Alcediag's work to develop the EDIT-B test includes two clinical studies where the test showed performance levels above 80% (Salvetat et al. 2024).

- **Study 1**: A monocentric clinical study conducted at the Montpellier University Hospital including healthy controls (non-depressed individuals), unipolar depressive patients, and bipolar depressive patients. The final dataset included 245 depressive patients. Recruitment ended in 2018.
- **Study 2**: A multicentric clinical study conducted with the psychiatric clinic group Les Toises, with recruitment completed at the end of 2022.



What are the technical steps involved in performing the EDIT-B test?

The EDIT-B test involves two main phases:

- **Phase 1 = Biological analysis**
- **Phase 2 = Algorithmic analysis**

Phase 1 – Biological analysis
The first phase of the EDIT-B test is conducted in a medical biology laboratory and involves a patient's blood sample. Initially, RNA is extracted and purified from the blood sample. Then, specific RNA sequences, namely the biomarkers of the EDIT-B test (for more details on the biomarkers, see the previous question), are amplified and subsequently sequenced using NGS (next-generation sequencing) technology (refer to the scientific background section for more on NGS).

Phase 2 – Algorithmic analysis
The next step takes place on a bioinformatics platform developed by ALCEDIAG to measure RNA editing. Its purpose is to interpret the RNA editing events of the EDIT-B biomarkers. After this, ALCEDIAG uses a proprietary algorithm, which takes as input both biomarker-related data and the patient's clinical data (age, sex, addiction, and treatment). This model interprets the combination and relationships between this information and produces several numerical decision values to determine whether a sample corresponds to a bipolar or unipolar profile. The algorithm was built with the help of artificial intelligence, meaning that it was previously trained using a robust, reproducible, and repeatable mathematical model based on RNA editing targets and clinical data.

Can this test identify other medical conditions?

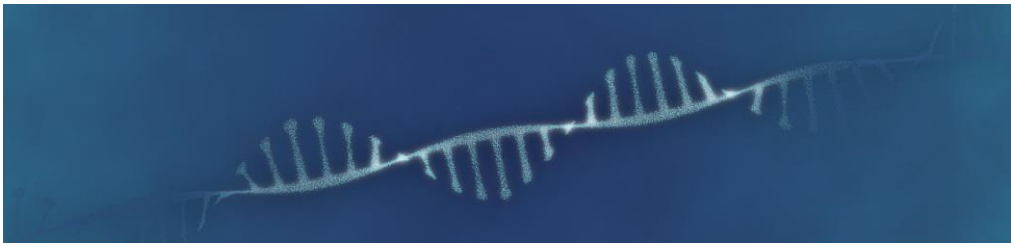
This test cannot detect other pathologies. EDIT-B focuses specifically on identifying RNA editing modifications and interprets this information exclusively to classify bipolar versus unipolar depression. It does not account for other conditions or diseases.

What genetic data can ALCEDIAG obtain from this blood sample analysis?

No genetic data is collected via EDIT-B. The EDIT-B test is based on pre-mRNA and focuses exclusively on A-to-I RNA editing. Any other data is filtered out by biological and bioinformatics protocols.

Are there any potential risks associated with taking this test?

The only risk associated with the test is the blood draw procedure, which is similar to standard blood tests currently used in clinical practice.



Can the EDIT-B test be used to monitor a patient's response to treatment?

EDIT-B is intended to differentiate bipolar disorder from major depression in adults with depressive symptoms who are receiving treatment for those symptoms. It is not indicated for any other purpose.

Can the EDIT-B test assess the severity of my condition (depression or bipolar disorder)?

The EDIT-B test does not assess the severity of the depression or bipolar disorder the patient may be experiencing. It provides a diagnostic profile, indicating whether the patient is more likely to be bipolar or unipolar.

EDIT-B test in clinical routine

For which type of patient is the EDIT-B test indicated?

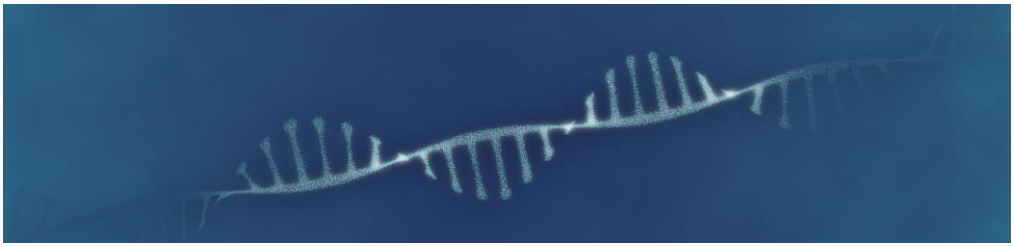
EDIT-B is an in-vitro blood diagnostic test intended to differentiate bipolar disorder from major depressive disorder in the adult population, as a diagnostic aid. EDIT-B is indicated for patients over 18 years old who are experiencing moderate to severe depressive symptoms and are receiving treatment for these symptoms.

Can the EDIT-B test be prescribed as a preventive measure for possible bipolar disorder?

No. The EDIT-B test, which requires a medical prescription, is indicated for patients over 18 years old who are experiencing depressive symptoms and are being treated for these symptoms.

What does "diagnostic aid" mean in the context of the EDIT-B test?

EDIT-B is a diagnostic aid, which means it provides information intended to help the clinician make a diagnosis. EDIT-B was designed to offer additional information to the physician and to complement the usual diagnostic tools, such as ICD-11 criteria, the patient's medical history, and clinical rating scales (e.g., MADRS, HDRS, and BDI).
The diagnosis must always be made by the physician themselves, using all available data and information (EDIT-B and others).



If I am seeing a psychiatrist, how does this test fit into my current care?

If you are seeing a psychiatrist, you can discuss the EDIT-B test with him. He may prescribe the test if you meet the relevant criteria. In some countries, your general practitioner can also prescribe the EDIT-B test.

What clinical evidence is included in the CE regulatory dossier of the EDIT-B test?

EDIT-B is the result of more than a decade of research in the fields of epigenetics (specifically RNA editing) and neuroscience, as detailed in the technology section of this document. Following this initial research phase, two clinical studies were conducted to validate the performance of the EDIT-B test and obtain CE marking. In addition, other studies are ongoing or in preparation to enrich our clinical data set, meet further regulatory requirements, collect real-world data to support utility, and obtain reimbursement. To date, ALCEDIAG has included more than 800 patients in its clinical development.

The first study conducted by ALCEDIAG was carried out in collaboration with the Department of Psychiatry at Montpellier University Hospital in France, as a monocentric trial including 255 patients. The second study (replication study) was conducted in collaboration with Les Toises psychiatric clinics in Switzerland, as a multicentric trial, entirely independent from the first clinical trial.

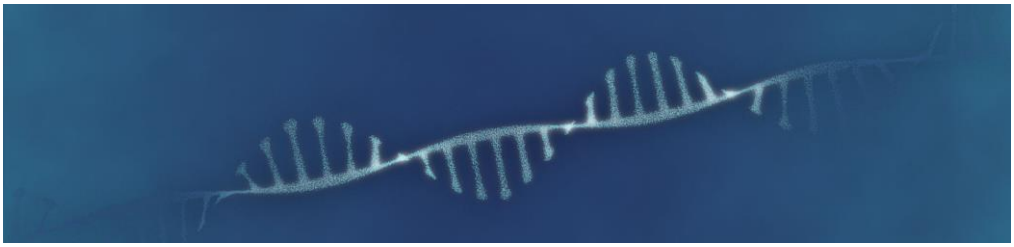
The research protocols of both studies were approved by the French local ethics committee (CPP Sud-Méditerranée IV in Montpellier, CPP no. A01978-41) and the Ethics Committee of the Canton of Vaud (CER-VD), with written informed consent obtained from all subjects.

The training and testing of the algorithm were performed on the Montpellier cohort, and external validation was conducted on the independent Swiss cohort. Based on these successful initial trials, EDIT-B is currently CE-marked under Directive 98/79/EC for in vitro diagnostic medical devices.

Clinical Performance

The clinical performance results of the EDIT-B® test from an independent multicentric study are presented in the table below.
Sample type: Whole blood collected in PAXgene® Blood RNA tubes.

Clinical Performances	Results*
Total population size Including: • 38,3% Male / 61,7% Female • 70,2% Unipolar / 29,8% Bipolar	94



Sensitivity (%)	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 Les Toises psychiatric center in Switzerland*

Who is authorized to prescribe the EDIT-B test?

EDIT-B requires a medical prescription and is performed through a simple blood draw. It can be prescribed by the psychiatrist or in some countries by a general practitioner who is treating the patient for a major depressive episode. Integrated into the clinical process, EDIT-B complements the usual diagnostic tools such as DSM-V and ICD-11 diagnostic criteria, the patient's medical history, and clinical assessment scales (e.g., MADRS, HDRS, and BDI).

What documents must the patient bring to the lab to have the blood draw for the EDIT-B test?

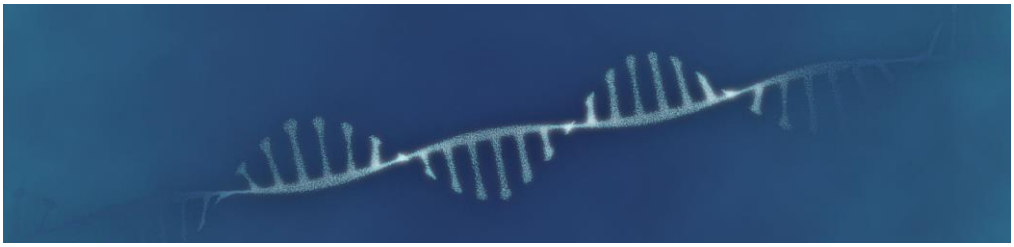
Please refer to the product page: *EDIT-B, a blood test to differentiate depression from bipolar disorder | ALCEDIAG*. You will find all the relevant information under the section “How to perform the EDIT-B test?”

Is EDIT-B indicated for diverse populations?

The test has been validated in the EU and is CE-marked under Directive 98/79/EC (IVDD). No statistical analyses were performed on different ethnic groups during the clinical trials.

Are there any specific requirements for blood drawing for this test?

No, from the patient’s perspective, it is a standard blood draw (in terms of blood volume). There are no requirements regarding fasting or the time of day. Additionally, as previously stated, the blood draw can only be performed if the patient has a medical prescription for the EDIT-B test.



Can the test be performed on sample types other than blood, such as serum?

Currently, the test can only be performed using one type of sample: whole blood. Furthermore, the blood must be collected in specific tubes that preserve RNA, called PAXgene tubes.

Will patients have access to the report sent by the medical laboratory?

The test results will be sent exclusively to the prescribing physician. They will decide how to use the test results in the diagnostic process and how to communicate them to the patient.

How much time passes between the blood draw and the test results?

While turnaround times may vary depending on location, the goal is to deliver the results to the prescriber within four weeks of the blood draw.

What happens to the patient's data?

In accordance with the General Data Protection Regulation (GDPR) of April 27, 2016, ALCEDIAG protects personal data, including patient data. The data is stored on an HDS (Health Data Hosting) certified server for as long as necessary for processing by the relevant services, and for a maximum of five years, unless the patient objects by sending an email to ALCEDIAG at: contact@alcediag-alcen.com.

I am a patient, who can I contact about the EDIT-B test?

You can contact ALCEDIAG through the following contact form: *Contact | ALCEDIAG*

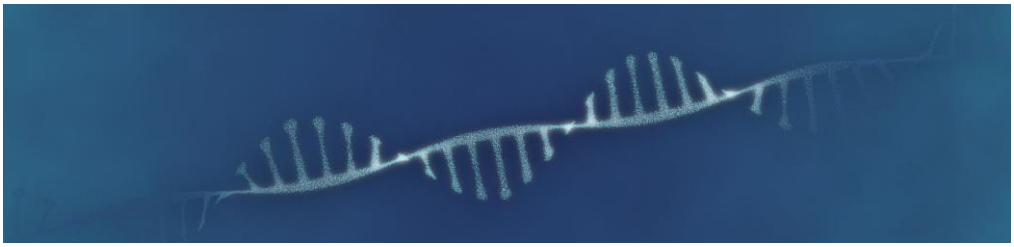
How much does the EDIT-B test cost?

For more information on this topic, please contact the laboratory performing the test in your country (link available via the EDIT-B page on the website).

Is EDIT-B covered by public health insurance?

For more information on this topic, please contact the laboratory performing the test in your country (link available via the EDIT-B page on the website).

REGULATORY ASPECT



Does this test have regulatory approval? What does this mean in practice?

EDIT-B has been CE marked since May 2022, in accordance with Directive 98/79/EC and is compliant with the Swiss In Vitro Diagnostic Medical Devices Ordinance (IvDO). CE marking means that the test can be marketed within the European Economic Area (EEA) and meets all safety, health, and environmental protection requirements.
Directive 98/79/EC for in vitro diagnostic devices is currently being replaced by a new European regulation (EU) IVDR 2017/746. EDIT-B is currently undergoing compliance with this new regulation.

What type of device is EDIT-B?

According to the definition in Directive 98/79/EC, EDIT-B is a system composed of a biological protocol and software, intended by ALCEDIAG to be used in vitro for the examination of RNA editing extracted from blood samples, with the aim of providing information on a pathological process. In this context, EDIT-B qualifies as an in vitro diagnostic medical device.

About ALCEDIAG

What is ALCEDIAG? Why is ALCEDIAG behind this test?

ALCEDIAG is the company that developed EDIT-B and is the legal manufacturer of the test. ALCEDIAG has been conducting research and development in the field of neuroscience and psychiatry for over 10 years.

ALCEDIAG's ambition is to develop blood tests for mental health, with the goal of advancing biology and personalized medicine to make a positive impact on patients' lives.

How can I contact ALCEDIAG?

You can contact ALCEDIAG through the website or by sending an email to: contact@alcediag-alcen.com.