I. GENERAL INFORMATION FOR PATIENTS

Information on hereditary disorders and the test

Broadly speaking, diseases in humans can be classified as either acquired (due to external factors) or genetic. Genetic disorders are caused by changes or alterations in our genes. Genes are small instructions found in our cells that determine how our body develops and functions. These instructions are written in a molecule called DNA. There are different types of genetic diseases; some can occur due to spontaneous changes in genes, without being inherited. These spontaneous genetic changes are known as *"de novo"* mutations or variants. Other genetic diseases are inherited, meaning they are passed down through the genes from parent (or donor) to child. Currently, more than 7,000 inherited disorders have been described. Inherited genetic diseases can be autosomal when they are caused by changes in genes found on non-sex chromosomes (the chromosomes common between males and females), or they can be X-linked when the altered genes are found on the X chromosome, one of the two sex chromosomes (males have one X and one Y chromosome, while females have two X chromosomes). In turn, genetic diseases can be classified as dominant and recessive. In dominant disorders, the presence of a single altered copy of the gene is sufficient to develop the disease. Recessive diseases, on the other hand, require two altered copies of a gene to develop the disease. In this type of disease, people with only one altered copy of the gene are considered to be carriers of the disease. Carriers of autosomal recessive diseases are generally not expected to develop symptoms associated with the disease. However, if their reproductive partner is a carrier of the same disorder, their offspring would have a 25% risk of inheriting 2 altered copies of the gene and therefore would be affected by the disease.

It is important to note that variants affecting genes on the X chromosome are usually recessive in females, i.e. female carriers do not usually develop disease symptoms of the variants they carry (because females have two copies of the X chromosome). If a woman is a carrier of a disease-causing variant on the X chromosome, her sons have a 50% chance to be affected with the disorder. Males, however, have only one copy of the X chromosome and, consequently, if they inherit a defective gene on this chromosome, they will not have any properly functioning copies of the gene and may therefore develop symptoms of an inherited disorder.

The JunoSeq CARRIER™ test allows the analysis of variants responsible for a large number of severe autosomal recessive hereditary disorders and, for females only, also includes the analysis of variants in certain X-linked genes. The number of diseases tested depends on the specific panel ordered. The CARRIER™ test identifies which genetic diseases a person is a carrier of. It is not uncommon to discover that we are carriers of a mutated gene, even when there is no family history of genetic disease. In fact, the most recent scientific studies estimate that, on average, most people are healthy carriers of two or three diseases.

When the CARRIER™ test is performed preconceptionally, whether in couples who wish to conceive using their own gametes or in patients who plan to use donor gametes, the results can be used to assess reproductive risk through genetic pairing analysis ("matching"), in order to avoid the co-occurrence of pathogenic variants in the same genes.

If the study indicates an increased probability of transmitting a hereditary disorder, measures to mitigate this risk may be considered. These measures include, among others, preimplantation genetic testing for monogenic diseases (PGT-M), prenatal genetic diagnosis, the use of donor gametes, or other strategies.

II. LIST OF GENES ANALYSED

The JunoSeq CARRIER™ test does not include all genes in the human genome.

The number of genes analysed will vary depending on the panel chosen. The type of panel chosen will depend on the decision of the healthcare personnel and the policy of the requesting centre. A breakdown of the genes tested in the different JunoSeq CARRIER™ panels can be found on the website below:

https://junogenetics.eu/junoseq/carrier/

The X-linked genes listed here are only analysed in females.

The list of genes, their variants, as well as their impact on health may be altered in the future based on a better understanding of these genes by the scientific community. The results shown in the reports issued show the best possible result, based on the best information available at the time of the test.

III. FOR WHOM AND IN WHICH CASES IS THE TEST INDICATED?

The test may be considered by patients and couples with reproductive intentions, prior to conception, to identify whether there is a risk of transmitting certain genetic disorders to their future offspring.

This type of testing may be recommended to:

- Couples who are going to undergo reproductive treatment in an IVF clinic with their own gametes, in order to identify if there is a genetic risk for their offspring.
- Patients or couples who are going to undergo reproductive treatment in an IVF clinic with donated gametes, with the aim of reducing the risk of affected offspring.
- Couples at high risk for Mendelian recessive disorders, such as in certain ethnicities with high prevalence for certain recessive disorders, or in people from communities with high levels of consanguinity, or consanguineous couples.

- Couples with a family history of diseases of genetic origin, so they seek to minimise the risk of transmitting certain diseases associated with serious disorders to their children.
- Couples seeking a spontaneous pregnancy but who wish to assess the genetic risk for recessive and X-linked diseases for their future offspring.

IV. THE PROCEDURE

For the JunoSeq CARRIER™ test analysis, a blood sample will be obtained using standard techniques, which pose little or no risk to health. Only in previously agreed cases, the sample may be obtained by saliva or buccal swab.

Once the genetic test has been performed, the samples will be kept for further analysis and verification of the results if necessary.

The CARRIER™ test is performed as follows:

1. Collection of a blood sample using standard techniques, which pose a minimal risk to health. In exceptional cases and previously agreed with JUNO GENETICS, the sample may be obtained by saliva or buccal swab.
2. DNA is extracted from the cells of the sample received.
3. The exome (the part of the genome that contains the protein-coding regions, and where disease-causing genetic variants are most commonly identified) is sequenced using a technology known as "next-generation sequencing" (NGS). This technique analyses specific regions of genes, making it possible to detect disease-causing variants. However, some genes present technical difficulties to be detected by NGS and require additional complementary genetic tests depending on the selected test (e.g. for *CYP21A2, HBA1/2, SMN1, DMD, F8* and *FMR1* genes). An updated gene list can be found on the JUNO GENETICS website (see section II of this document for more information).
4. The data obtained by NGS are processed through secondary analysis and evaluated with specialised software by JUNO GENETICS staff. The data is compared with reference values from our databases to help us distinguish between normal variations in the DNA sequence and variants responsible for hereditary disorders. Additionally, other complementary tests may be performed. If necessary, a new sample will be requested for analysis
5. The results are provided in a report that includes the variants detected in the genes studied according to the test requested.

V. RESULTS

The results of genetic testing and analysis must be interpreted in the context of additional laboratory tests, family history and other clinical findings. We recommend genetic counselling to assess the implications of test results.

JunoSeq CARRIER™ test results may include the following types of results:

PATHOGENIC/ LIKELY PATHOGENIC VARIANTS NOT DETECTED:

No pathogenic or likely pathogenic variants associated with a hereditary condition were identified in the genes analysed. This significantly reduces the likelihood that a future child will have a disorder associated with the genes examined. However, the test is unable to detect all possible clinically significant variants, and therefore, the risk is not zero (see Test Limitations below).

VARIANTS DETECTED (for autosomal recessive conditions):

A DNA sequence variant has been identified in one or more of the genes tested. In most cases, this result will have no direct clinical consequences for the carrier him/herself. However, there is a 50% chance that the variant will be passed on to offspring. If the other parent also has a pathogenic or probably pathogenic variant in the same gene, there is a high risk that the couple's offspring will be affected by a genetic disorder (approximately 25% risk for each gene when both parents carry a variant with clinical implications). It is recommended that the results of this test be evaluated with a genetic counsellor, or other qualified health professional to fully understand the implications of any variants detected.

VARIANTS DETECTED (for X-linked conditions when the patient is female):

A DNA sequence variant has been detected in one or more of the genes tested. In most cases, this finding has no direct clinical consequences for the carrier patient. However, there is a 50 % chance that the detected variant will be passed on to offspring. All males who inherit the pathogenic or probably pathogenic variant will develop the disease and in some cases, female carriers may show symptoms. It is recommended that the results of this test be evaluated with a genetic counsellor, or other qualified health professional to fully understand the implications of any variant detected.

No result (NO Call):

List of genomic positions for which it has not been possible to obtain a result due to insufficient or poor-quality DNA sequencing.

VI. INCIDENTAL FINDINGS RELATED TO CARRIER™ TEST

CARRIER™ test has been designed and validated by experts with the specific objective of evaluating recessive genetic variants for reproductive screening purposes. Therefore, in most cases, the results will not have clinical implications for the carrier individual. However, due to the inherent complexity of human genetics, there are some exceptions that may have medical relevance for the evaluated individual. These types of results are known as incidental findings and are estimated to be present in

1% of the analysed samples.

Incidental findings may involve:

- The detection of variants in X-linked genes, which in some cases may have clinical implications for female carriers.
- The finding of variants in apparent homozygosity or compound heterozygosity, which could be indicative of a genetic diagnosis in the individual.
- The identification of variants in genes that, in addition to their role in recessive diseases, are also associated with conditions of dominant inheritance, such as cancer predisposition, cardiovascular diseases, or neurological disorders.
- The detection of deletions or duplications that, due to their genomic extent, may involve genes not included in the panel, which in some cases may have clinical implications for the patient.

In cases in which an incidental finding is identified, genetic counselling by qualified healthcare professionals will be recommended in order to properly interpret the results together with the patient's personal and family medical history.

VII. LIMITATIONS OF THE TEST AND IMPORTANT POINTS TO NOTE

The JunoSeq CARRIER™ test is highly useful in the reproductive context. However, there are several limitations:

1. The test only reports pathogenic or likely pathogenic variants for autosomal recessive diseases and X-linked diseases. Mitochondrial diseases, disorders with a dominant, multifactorial or polygenic inheritance pattern, or diseases due to genetic imprinting defects are outside the scope of the test. Similarly, the test would not be able to identify risk for "de novo" variants, as they are not considered to be inherited phenomena.
2. Not all currently described autosomal recessive and X-linked diseases are analysed, but each panel of the test analyses a selection of diseases based on their prevalence in the general population, severity and clinical utility.
3. Even for those genes included in the requested panel list, there are certain technical limitations that may lead to the variant not being detected:
    a. The NGS technology used does not allow the identification of all possible variants. For example, large gene rearrangements (deletions, insertions or significant inversions) cannot be identified, nor can triplet expansions of nucleotides or variants in gene regions that are not being studied (e.g. deep intronic variants).
    b. Duplications will only be analysed in X-linked genes. Deletions and duplications involving fewer than two coding exons may be below the detection limit depending on the size of the region. Copy number variants (CNV) in genes with insufficient evidence in the literature may be not reported.
    c. Occasionally, there are genetic variants for which it is not possible to obtain a result due to insufficient or poor-quality DNA sequencing ("No call" result). These variants will be described in the test report.
    d. Variants that are found only in some but not all cells in the body (known as "mosaicism") may not be detected by the test. If germline cells (sperm or egg cells) are affected by mosaicism, there is a risk of transmission to offspring.
    e. The presence of low-frequency polymorphisms (rare variations in the DNA sequence) can sometimes prevent the analysis of one copy of a gene, meaning that we can only obtain results from the other copy. Similarly, the presence of pseudogenes (areas in the DNA sequence that are very similar to another gene) can also confound the analysis. Both circumstances can lead to false negatives or false positives.
4. Interpretation of the identified genetic variants is done based on the medico-scientific evidence available at the time of analysis, as well as the prediction of pathogenicity by some bioinformatics tools.
    a. Once CARRIER™ test results are issued, the variants identified will not be reanalysed by JUNO GENETICS at any future time. Although variant interpretation in general is a dynamic process that may result in variants being "reclassified" to a different pathogenicity category (for example, from "likely pathogenic" to "likely benign") as more clinical evidence becomes available, the pathogenicity of any variants discovered in testing (both those reported as well as those not reported) will not be routinely reevaluated.
    b. Certain variants are classified as "variants of unknown significance" (VUS), where the association with disease risk is unclear at the time of analysis. CARRIER™ test only reports pathogenic and likely pathogenic variants, not VUS, as classified by the scientific societies at the time of testing.
5. Every laboratory analysis carries a margin of error, which may arise from factors such as human error during sample collection or processing, issues with laboratory equipment or materials, contamination by other cells or external genetic material, or failure to follow pre-analytical conditions necessary to ensure the validity of the results.

There are certain medical reasons why CARRIER™ test may not be suitable for some patients, and healthcare personnel should consider these before recommending/requesting the test. One example is chimeras, which arise when cells from two genetically different individuals are found within the body of the person being tested. This condition may be congenital (usually as a result of a rare fusion of twin embryos at a very early stage of development), or it may develop temporarily (e.g. through a blood transfusion) or permanently (e.g. as a result of a bone marrow transplant). It is important to note that these circumstances are

likely to produce unreliable results. The use of a saliva sample instead of blood may help to obtain more accurate results in certain situations, but is not recommended for all cases. JUNO GENETICS can provide more information upon request.

The CARRIER™ test can significantly reduce the risk of affected offspring (either in couples with their own gametes or with a gamete donor). However, due to the limitations described in this consent, the risk of affected offspring is not zero. The test results should be interpreted by a healthcare professional in combination with a detailed assessment of personal and family history and proper genetic counselling.

VIII. ACCESS TO TEST RESULTS

Regarding my JunoSeq CARRIER™ test results, my preference is as follows (choose one of the following options):

☐ I DO want to receive the final results: I want the clinic from which I have requested the CARRIER™ test to inform me of its findings, knowing that these results may reveal information about my risk of having one or more of the serious disorders tested and/or my risk of passing on genetic abnormalities to my children, even if I do not currently have any symptoms of these disorders. The results of the CARRIER™ test will be available and delivered within approximately 20 working days.

☐ I do NOT wish to receive any information: I do not wish to have access to my results, nor do I wish to receive information about them. However, I understand that, if the information is necessary to prevent serious harm to my health, I or a legally authorised representative may be informed under the terms of article 49.2 of Law 14/2007. In any case, the communication will be limited exclusively to the information necessary for this purpose. Please provide the contact details of the authorised person or representative to be contacted for the above purposes.

In any case, I declare that I have received appropriate genetic counselling from qualified staff at the clinic I have visited. I have been provided with information about the significance of the test, including the possible options that could be offered depending on the results obtained, and I understand that they are available to answer any questions I may have and to offer any additional genetic counselling I may need once the results of my CARRIER™ test are available.

Taking into account my medical history and that of my close family members, if I suspect that I or any of my close family members may have an inherited disorder, or if I become aware of any diagnosis or test result that may indicate an increased risk, I agree to immediately notify the healthcare personnel. This is important, as the CARRIER™ test may not look for the specific variant potentially present in my family, which could result in a false negative.

IX. FINANCIAL INFORMATION

The prices and conditions applied by the centre for the performance of these tests, if any, will be explained at the centre indicated by the JunoSeq CARRIER™ test.

X. GENERAL LEGAL ASPECTS OF ASSISTED REPRODUCTION AND SPECIFIC INFORMATION

The biological sample submitted, together with the personal data necessary for the provision of the service, will be sent for analysis to the facilities of JUNO GENETICS ESPAÑA, S. L. in the Technological Park of Paterna (46980), Valencia, Spain, Ronda de Guglielmo Marconi, 11, building A, first floor, premises A-1-2 and A-2-2. The sample will be genetically analysed in accordance with the applicable Spanish legislation, mainly Law 14/2006, on Assisted Human Reproduction Techniques, and Law 14/2007, on Biomedical Research.

In the event that part or all of the test cannot be performed in the laboratory indicated above, JUNO GENETICS reserves the right to carry out the analysis through a reference laboratory, anonymising personal data and samples if the reference laboratory is not located in the EU or another country with an equivalent level of data protection security. This circumstance shall be indicated in the final report issued.

In all cases, the 1997 Oviedo Convention on Human Rights and Biomedicine will apply, which stipulates that research and medical diagnosis of genetic conditions may only be carried out if the subject also receives appropriate genetic counselling.

In the event that the performance of this test has been indicated from a country other than Spain, the professional or clinic requesting the test will be responsible for ensuring that both the test itself and its application in the specific case are in accordance with the stipulations of their national or regional regulations, as well as for informing the test subject of any particularly relevant issue that said legislation contemplates.

XI. PRIVACY, STORAGE AND USE OF DATA FOR TEST SAMPLES

Patient and donor privacy is a priority for JUNO GENETICS. All personal information and genetic results are strictly confidential. The only persons who may have access to this information are the employees of the reproduction clinic, the JUNO GENETICS Laboratory analysing the sample and the relevant authorities, if required by the laws of the applicable jurisdiction.

In accordance with the current data protection regulations stipulated by Regulation (EU) 2016/679 of the European Parliament and of the Council of 27 April 2016 on the protection of natural persons with regard to the processing of personal data and on the free movement of such data, in addition to Spanish data protection laws, such as Organic Law 3/2018, of 5 December, on the Protection of Personal Data and guarantee of digital rights applicable in Spain, you have the right to access, rectify or delete

your data, revoke the consent given and limit the processing of your data, as well as the right to data portability and not to be subject to decisions based solely on the automated processing of your data. You may exercise these rights by writing to the following address:

- JUNO GENETICS ESPAÑA, S. L., Parque tecnológico de Paterna (46980), Valencia, Spain, Ronda de Guglielmo Marconi, 11, edificio A, segunda planta, locales A-1-2 y A-2-2 (if your test is performed in this laboratory).
- Alternatively, you can contact the JUNO GENETICS DPO at Juno.DPO@junogenetics.com.

Personal data will only be processed for the following purposes: (1) to fulfil the obligations arising from the provision of the requested services (lawfulness based on Art. 6.1.b and 9.2.h of the GDPR); (2) to review and ensure the quality of the services provided (internal audits, quality controls, laboratory validation studies, whose lawfulness is based on Art. 6.1.f of the GDPR); (3) educational/training purposes, where the data are made anonymous at all times prior to use, so that it is impossible to identify the patient concerned; (4) research purposes or scientific publications and presentations, where the data have always been made anonymous beforehand, to ensure that the subjects of such data cannot be identified. The research will be carried out in accordance with the provisions of the General Data Protection Regulation and Spanish data protection legislation; (5) to provide personalised answers to queries or suggestions from the patient requesting the test, and to ensure that the test has been carried out correctly and all doubts have been resolved (lawfulness based on art. 6.1.b of the GDPR); and (6) to follow up patients in the future to obtain information about the service provided (lawfulness based on art. 6.1.f of the GDPR). The data will be retained for a minimum of five years, unless otherwise stipulated by the local law of the applicable jurisdiction. Finally, please note that if you feel that your data protection rights have not been respected, you may lodge a complaint with the competent Data Protection Authority.

In addition to the above, JUNO GENETICS will provide your test results only to your healthcare personnel, unless you (or a person legally authorized to act on your behalf) so specify in writing or if required by law.

Authorisation for the use of data

In order to improve the research and development of assisted reproduction techniques, other centres or entities of the group may access personal and genetic data in those cases in which the information resulting from the tests carried out may potentially be used in clinical studies by any of these entities, in accordance with the General Data Protection Regulation and Spanish data protection legislation. To this effect, we inform you that the data that may reveal your personal identity and/or that of your family will be dissociated and treated with absolute confidentiality and only for the purposes of research and development related to the services provided by the group, with the necessary security measures implemented to guarantee the security and confidentiality of your data.

In connection with the communication of data for research and development purposes:

☐ YES, I agree to JUNO GENETICS sharing my information for research and development purposes, with the possibility of further contact if additional medical history or clinical information is required.

☐ NO, I do not agree to JUNO GENETICS sharing my information for research and development purposes.

XII. AUTHORISATION TO USE LEFTOVER OR DISCARDED SAMPLES TO OPTIMISE AND VALIDATE NEW TESTS

It is important that JUNO GENETICS can use leftover or discarded samples to optimise or validate new tests and develop new analysis methodologies, including new technologies based on the development of artificial intelligence applications, so that these developments and improvements can help future patients as you yourselves have been helped. We will only use these samples for this purpose if you authorise us to do so, and they will always be used anonymously and blindly, so it will not be possible to inform you of any findings. This will only be carried out in the JUNO GENETICS laboratory.

Clinical results, information and unprocessed data may be reviewed and/or reanalysed for future scientific publications and presentations. These data will always be previously anonymised, to ensure that in no case can the subject be identified. All processing and procedures will be carried out in accordance with the General Data Protection Regulation and Spanish data protection legislation.

I also understand that JUNO GENETICS may use the resulting information for scientific publication or presentation of results, once all personal information has been anonymised.

I understand and agree that since all information will have been anonymised in advance, I will never be able to access new results or findings, now or in the future, nor will I be able to derive any financial benefit from publications or presentations, and I will not be compensated for any resulting products developed.

XIII. HAVING READ AND UNDERSTOOD THE ABOVE INFORMATION, I HAVE BEEN INFORMED OF THE FOLLOWING:

- I have been informed that I am under no obligation to undergo this genetic analysis, and I therefore give my free and voluntary consent.
- The suitability, procedure, purpose, limitations, risks and complications of the proposed genetic screening test.
- My test results may reveal a genetic variant of uncertain significance (VUS). My information may be shared to determine if this variant is significant, including comparisons with the same variant in other patients, both in Spain and in other countries. Any data shared will be anonymised so that it cannot be linked to any patient. I acknowledge that the interpretation of my results may evolve over time as more evidence is obtained from other cases.
- The results of this test may be analysed by the IVF clinic or donor bank in order to compare the genetic profiles of the patients or donors in order to confirm that no variants in the same genes are identified.
- Procedures may be cancelled at any stage, either for medical reasons or at the request of the test subject.
- It is common practice in genetic testing laboratories to store DNA extracted from samples, even after the current test has been completed. My sample once validated can be used as "quality control" in other genetic tests. The methodology of DNA extraction or the "raw data" generated by the laboratory equipment may make it unfeasible for third party laboratories to use it.
- My test results and test report will be included in my patient file.
- That the health professionals who have attended you are at your disposal to provide any additional information that may not have been entirely clear.

I understood the information explained to me in clear and simple language. The healthcare personnel allowed me to ask all the questions I needed, clarified any doubts I had and explained the implications of the possible results of the test. I also understand that at any time and without explanation, I may revoke the consent I now give. However, you are informed that, depending on the time of revocation, you may be required to pay for any costs associated with the test that have already been incurred prior to revocation. Primarily the materials and reagents associated with the test, as well as the costs of transporting the samples.

I also understand that at any time and without explanation, I may revoke the consent I now give. However, you are informed that, depending on the time of revocation, you may be required to pay for any costs associated with the test that have already been incurred prior to revocation. Primarily the materials and reagents associated with the test, as well as the costs of transporting the samples.

JUNO GENETICS ESPAÑA, S.L.
Ronda de Guglielmo Marconi, 11-A, 2º, A1-2, A2-2.
46980 Paterna Valencia.
supportspain@junogenetics.com

PATIENT SIGNATURE

CARRIER by JunoSeq

XIV. PATIENT AND AUTHORISED HEALTHCARE PERSONNEL INFORMATION

Name	Identification number	Date of birth

Address

AUTHORISATION:

After reading the ENTIRE document, I authorise the staff of JUNO GENETICS ESPAÑA S.L. to submit my sample to the proposed carrier test for the chosen gene panel.

Signature and date

Name of the AUTHORISED HEALTHCARE PERSONNEL	Member no.	Date and Signature

I declare that:

I have explained the content of these tests and their risks and clarified the doubts and questions raised by the interested party. Furthermore, I undertake to provide the necessary subsequent genetic counselling depending on the results of the test.