I. BACKGROUND INFORMATION FOR PATIENTS

The main purpose of this procedure is to examine tissue from products of conception (POC), or fetal remains analysis and determine the presence/absence of chromosome abnormalities. In some cases, this test can provide a useful insight into the underlying cause of miscarriage, assisting in the management of a patient's future expectations and the consideration of different treatment options.

More than half of these losses are due to chromosome abnormalities in the cells of the embryo or fetus. In fact, in the vast majority of cases chromosomally abnormal embryos will not be capable of normal development and will eventually miscarry. Rarely, embryos with aneuploid cells can survive to term, but the children born usually have significant health problems, congenital abnormalities and/or mental retardation (for example Down syndrome).

Pregnancy losses can be tested using cells obtained from tissue expelled during the miscarriage or collected surgically by a doctor. Such tissue samples are known as products of conception (POC). POC samples are traditionally tested using a method called karyotyping where cells from the embryo/fetus are grown (cultured) in an incubator. The karyotyping procedure for testing a POC sample typically requires more than seven days and a considerable proportion of the samples collected fail to grow, meaning that no insight into the cause of the miscarriage can be gained. Moreover, cells from the mother can contaminate the sample and tend to grow faster in culture than those from the embryo/fetus, which potentially confuses the analysis.

The method used at Juno Genetics avoids the need to culture the POC sample and thereby minimises the risk of contamination, and dramatically reduces the time required to report the results (only approximately one week is required from sample receipt). Moreover, it includes a comparison of variations in the DNA from the mother and the embryo/fetus, which reveals if maternal cell contamination has occurred.

II. WHEN IS THE POC TEST INDICATED

POC test is indicated for investigating potential genetic causes of a pregnancy loss. This test is highly recommended for women with recurrent pregnancy losses (two or more failed pregnancies).

III. PROCEDURE

The POC sample should be collected by a medical doctor and should be placed in the container provided in the sample collection kit and sent to Juno Genetics immediately, without any delay. The kit contains a sterile plastic container and a blood collection tube used for maternal peripheral blood collection. Alternatively any sterile plastic container may be used for POC if Juno's kit is not available.

Briefly, the sample is cleaned, dissected and the DNA is extracted. The DNA from the embryo/fetus is subsequently subjected to NGS. The software used to analyse the NGS data generates a graph representing the genetic information in terms of the number of copies of each chromosome in the sample. Additionally, polymorphic markers scattered across the genome, known as single nucleotide polymorphisms (SNPs), are analysed too. These variations in the DNA sequence aid in the determination of chromosome copy number, as well as assisting in the detection of contamination, including that derived of maternal cells, and also permit the detection of loss or duplication of the entire set of chromosomes [haploidy (the presence of only one set of chromosomes) and triploidy (the presence of three sets of chromosomes)]. . A sample is interpreted as normal when there are no deviations from the baseline for any of the 24 chromosomes. A sample is interpreted as abnormal when the graph produced by the software shows deflection for one or more chromosomes. The direction of the deviation from the baseline indicates whether the aneuploidy in question involves a gain or a loss of chromosomal material.

IV. RESULTS

The results of genetic trials and tests should be interpreted in the context of additional laboratory test results, family history, and other clinical findings. Genetic counseling is recommended to discuss the implications of the results of these tests.

Possible outcomes in cases of POC test cases would include:

- **NORMAL MALE:** The result obtained from the analysed POC sample indicates a 46,XY (euploid male) chromosomal constitution.
- **NORMAL FEMALE:** The result obtained from the analysed POC sample indicates a 46,XX (euploid female) chromosomal constitution.
- **ABNORMAL:** The result obtained from the analysed POC sample indicates an abnormal number of chromosomes.
- **NO RESULT:** It was not possible to obtain results for the POC sample. There are several possible reasons why a test may fail to produce results, including the presence of contamination, lack of fetal material in the sample, DNA amplification failure or suboptimal DNA quality in the sample leading to poor quality results that cannot be reliably interpreted. Therefore, the chromosomal status of this sample remains unknown.

V. LIMITATIONS OF POC TEST

With this technology it is not possible to identify segmental aneuploidies below 3Mb, however, the limits of detection of segmental aneuploidies vary depending on the chromosome and the sample quality. The test cannot detect either balanced structural anomalies, mosaic aneuploidies, and some defects that affect the complete set of chromosomes, such as tetraploidy (e.g., 92,XXXX or 92,XXXY).

The cause of the pregnancy loss may be established if a chromosome abnormality is found using the NGS method employed by Juno

Genetics. However, even if a chromosome abnormality is present, it is not possible to entirely rule out the possibility that other factors have contributed to the miscarriage.

There is a possibility that you may not be able to get a result from a POC sample. This could happen if the sampled cells extracted contain degraded DNA, as well as for other reasons.

Like any other laboratory technique, POC test can be affected by errors that can compromise the result obtained. The usual sources of these errors are associated with: human errors during the collection and processing of samples, errors in laboratory equipment and materials, contamination of samples by other cells or external genetic material and/or, non-compliance with pre-analytical conditions established to ensure the validity of the results obtained.

VI. ECONOMIC INFORMATION

The prices and conditions that apply in the centre for these tests, if applicable, will be detailed in the centre where you are being treated.

The JUNO laboratory does not handle POC cases directly for patients and therefore cannot, under any circumstances, provide you with an estimate or approximate cost for this service.

VII. GENERAL AND PARTICULAR LEGAL ASPECTS RELATED TO THE POC TEST

The biological sample submitted, along with the necessary personal data for the provision of the service, will be sent for analysis to the facilities of Juno Genetics Spain, S.L., at Parque Tecnológico de Paterna (46980), Valencia, Spain, Ronda de Guglielmo Marconi, 11, Building A, second floor, premises A-1-2 and A-2-2. The genetic analysis of the sample will be carried out in accordance with the applicable Spanish regulations, primarily Law 14/2006 on Assisted Human Reproduction Techniques and Law 14/2007 on Biomedical Research.

However, please be informed that in the event of any temporary impediment or incident occurring in this Laboratory that could delay the result of your test (e.g., equipment breakdown in genetic analysis, technical maintenance shutdowns, interruptions in the supply of resources, etc.), in order to provide the committed service and obtain the analysis result in the shortest possible time, your sample and necessary personal data for the provision of the service will be sent to Juno Genetics Ltd., Hayakawa Building, Edmund Halley Road, Oxford Science Park, Oxford OX4 4GB, United Kingdom, at no additional cost. If this is the case, it will be noted in the report that will be provided to you regarding the analysis result of your sample issued by this Laboratory, which will have conducted the test in accordance with the provisions of the *Human Tissue Act* of 2004.

In the event that part or all of the tests cannot be performed in any of the aforementioned laboratories, Juno Genetics reserves the right to carry out the analyses through a reference laboratory. This circumstance will be indicated in the final report that is issued.

In any case, the provisions of the Convention on Human Rights and Biomedicine (Oviedo Convention) of 1997 shall apply, as it restricts the genetic diagnosis and research of genetic conditions only when the subject receives appropriate genetic counselling.

If 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 is in accordance with the stipulations of its national or regional regulations, as well as for informing the subject of the test of any particularly relevant issue that such legislation contemplates.

VIII. DATA PRIVACY, STORAGE AND USE FOR THE STUDY OF SAMPLES

Patient and donor privacy is a top priority at Juno Genetics. All personal information and genetic results are strictly confidential. The only individuals who can access this information are the personnel at the reproductive clinic, the Juno Genetics Laboratory analyzing the sample, and the relevant authorities if required by the laws of the applicable jurisdiction.

In accordance with the current data protection regulations, such as the EU General Data Protection Regulation (EU2016/679) and national data protection laws including the Spanish Organic Law 3/2018 on the Protection of Personal Data and Guarantee of Digital Rights, and, where applicable, the UK *Data Protection Act* 2018, you have the right to exercise your rights, if desired, including the right to access, rectify, erase, and revoke your consent, as well as the right to restrict processing, data portability, and to not be subject to automated decision-making based solely on your data. These rights can be exercised by contacting the following postal 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 analysis is carried out at this laboratory).
- Juno Genetics Ltd., Hayakawa Building, Edmund Halley Road, Oxford Science Park, Oxford OX4 4GB, United Kingdom (in exceptional circumstances as stated in this document, if your analysis is carried out at this laboratory).
- In both cases, you can also contact the Juno Genetics DPO (Data Protection Officer) at: Juno.DPO@junogenetics.com

Personal data will only be processed for the following purposes: (1) fulfilling obligations arising from the requested services (legitimate basis under Art. 6(1)(b) and 9(2)(h) of the GDPR); (2) reviewing and ensuring the quality of the provided services (internal audits, quality controls, laboratory validation studies based on Art. 6(1)(f) of the GDPR); (3) educational/training purposes, always subject to anonymization prior to use to prevent identification of the patient in question; (4) research purposes, scientific publications, and presentations, always subject to prior anonymization to ensure non-identifiability of individuals. Research will be conducted in compliance with the General Data Protection Regulation and national data protection laws. (5) providing personalized responses to inquiries or

suggestions from patients requesting the test and ensuring that the test has been carried out correctly and addressing any concerns (legitimate basis under Art. 6(1)(b) of the GDPR); and (6) monitoring patients in the future to obtain feedback on the service received (legitimate basis under Art. 6(1)(f) of the GDPR). Data will be stored for a minimum of five years unless local laws in the applicable jurisdiction state otherwise. Finally, if you believe that your data protection rights have been violated, you have the right to lodge a complaint with the competent Data Protection Authority.

In addition to the above, Juno Genetics will only distribute test results to your physician unless otherwise specified in writing by you (or a person legally authorized to act on your behalf) or required by a court of law.

Recipients of the data

In In order to improve research and development in assisted reproduction techniques, other centres or entities within the group may have access to personal and genetic data in cases where information derived from the tests performed may be used in clinical studies by any of these entities, in accordance with the General Data Protection Regulation and national data protection laws. It is important to note that any data that may reveal your personal identity and/or that of your family will be anonymized, treated with absolute confidentiality, and used only for research and development purposes related to the services provided by the group. Necessary security measures will be implemented to ensure the security and confidentiality of your data.

Regarding the communication of data for research and development purposes:

☐ YES, I wish for Juno Genetics to share my information for research and development purposes

☐ NO, I do not wish for Juno Genetics to share my information for research and development purposes

IX. AUTHORISATION TO USE LEFTOVER OR DISCARDED SAMPLES FOR OPTIMISATION AND VALIDATION OF NEW TESTS

It is important for Juno Genetics to be able to use surplus or discarded samples for the optimization and validation of new tests and the development of new analysis methodologies, including new technologies based on the development of Artificial Intelligence applications, so that these advancements and improvements can benefit future couples, including your case. The surplus samples used for this purpose would be anonymized and processed blindly, ensuring that no findings can be reported to you. This would only take place in Juno Genetics' laboratory.

Clinical results, information, and raw data may be reviewed and/or reanalysed for future publications and scientific presentations. At all times, these data will be subject to prior anonymization, ensuring that personal identification is not possible under any circumstances. All treatments and processes will be carried out in accordance with the General Data Protection Regulation and national data protection laws.

I also understand that Juno Genetics may use the resulting information for scientific publications of results and their presentation after anonymizing any personal information.

I understand and accept that, since all information will have been previously anonymized, I will not be able to access new results or findings in the present or future, nor will I receive any financial benefits from publications and presentations, nor will I be compensated for products developed as a result of these activities.

X. HAVING READ AND UNDERSTOOD THE FOREGOING WE ARE INFORMED OF:

- I have been informed that I am not obligated to undergo this genetic analysis, and I freely and voluntarily consent to its performance.
- The indication, procedure, success probabilities, limitations, risks, and complications of the proposed testing programme.
- My test results may have implications for other members of my family. I acknowledge that my results may sometimes be used to provide appropriate medical care for others. This could be done by discussing it with me or in such a way that I am not personally identified in this process.
- Procedures may be cancelled at any time during their implementation, either for medical reasons or at the request of the interested party, provided that it does not cause harm to patients.
- It is common practice in genetic analysis laboratories to store the DNA extracted from received samples, even after the current test is completed.
- My sample could be used as a "quality control" for other tests, such as those for family members. The DNA extraction methodology or the "raw data" generated may render it unfeasible for use by third-party laboratories.
- Both my test results and the test report will be part of my patient record.
- I am informed of the availability of the healthcare staff at this facility to further clarify any aspect of the information that has not been sufficiently clarified.

We have understood the explanations provided to us in clear and simple language. In the event that the test has been conducted in the context of assisted reproductive treatment, the healthcare professional who has attended to us at the clinic where we are patients has allowed us to make all observations, clarified all doubts we have raised, and explained the implications of potential test results.

We also understand that at any time and without the need to provide any explanation, we can revoke the consent we are now giving. However, please note that, depending on when the test is revoked, you may have to pay for any costs associated with the test that have already been incurred prior to the revocation. Mainly the materials and reagents associated with the test, as well as the costs of transporting the samples.

Therefore, we declare that we are satisfied with the information received and that we understand the scope and risks of the treatment.

XI. PATIENT AND AUTHORISED HEALTHCARE PROFESSIONAL INFORMATION

PATIENT 1	PATIENT 2 (except for single woman)
Name PATIENT 1	Name PATIENT 2
Date of birth PATIENT 1	Date of birth PATIENT 2
Address PATIENT 1	Address PATIENT 2 (☐ Same address as PATIENT 1)
ID patient number PATIENT 1	ID patient number PATIENT 2

Authorisation:

After reading the COMPLETE document consisting of a total of 5 pages and 11 (XI) sections, we authorize the personnel of the Reproductive Unit to carry out the proposed testing programme with our sample.

Signature PATIENT 1	Signature PATIENT 2

Name of the AUTHORIZED HEALTHCARE PERSONNEL	Professional Registration Number	Date and signature
I declare that:		
I have explained the content of these tests and their risks, and clarified any doubts and questions raised by the individual. Furthermore, I commit to providing the necessary genetic counselling based on the test results.		