Blank space reserved for IGENOMIX use only

Igenomix® PART OF VITROLIFE GROUP®

Products of Conception (POC) Test Requisition Form - POC by NGS and niPOC

The fields marked with (*) are mandatory to carry out the test

Non-invasive analysis performed on a maternal blood sample. Only valid for singleton pregnancies BEFORE the uterine evacuation.	Direct analysis performed on tissue (medical or surgical evacuation). Valid for singleton and multiple pregnancies.
☐ **niPOC** • A single STRECK blood tube required. • Aneuploidy for all 24 chromosomes. • Deletions and duplications greater than 7Mb • Triploidies are not studied.	☐ **POC by NGS** • Foetal tissue required, as well as a maternal sample (single blood tube). • Aneuploidy for all 24 chromosomes. • Deletions and duplications greater than 10Mb. • Triploidies and maternal cell contamination studied by complementary STR analysis.

Clinician Information

*Clinic

*Referring Clinician:

* E-mail: Telephone:

*Address:

Patient Information

*MRN/Unique patient ID: If not available, please state NOT APPLICABLE

*Patient's full name: *Date of Birth

Partner's full name: Date of Birth

Test indication

☐ Advanced maternal age
☐ Family or personal history of aneuploidy or genetic disease
_____
☐ Abnormal patient/partner karyotype. Specify: _____
☐ Other _____

☐ Abnormal ultrasound
☐ High-risk combined screening
Specify value: _____

Clinical Information

***Gestational age (weeks)**: _ _ _ _ / _ _ _ _

***Date of miscarriage:** _____/_____

***Pregnancy**

☐ Singleton ☐ Twin (☐ Monochorionic ☐ Dichorionic) ☐ Multiple Nº____

Previous miscarriages ☐ YES Nº___ ☐ NO

Patient height _____ cm **Patient weight**_____ kg

Type of pregnancy

☐ Natural
☐ Artificial Reproductive Treatment

☐ HAI
☐ DAI
☐ FIV
☐ ICSI
☐ PGT-A (PGS)
☐ EMBRACE
☐ PGT-SR (PGD)
☐ PGT-M (PGD)

Transferred embryos:
☐ 1 ☐ 2 ☐ >2

Oocyte origin:
☐ Own
☐ Donated

☐ **Organ transplant** ☐ **Neoplastic history** ☐ **Blood transfusion** (<60 days) ☐ **Congenital or acquired chimerism**

Observations_____

Sample Information

***Type of sample** ☐ Blood ☐ Guided biopsy ☐ Conventional curettage ☐ Spontaneous miscarriage ☐ Other _____

***Date of blood(s) sample collection** _____/_____/_____ **Sampling performed by (complete name)** _____

***Date of foetal sample collection** _____/_____/_____ (if relevant) **Sampling performed by (complete name)** _____

Clinician authorisation

I certify that the information on this requisition form is correct to the best of my knowledge and that I have requested the above test based on my professional judgement. I have explained the limitations of this test and I have answered any questions based on medical judgement. I understand that Igenomix may need additional information and I agree to provide this information if necessary.

***Clinician´s signature** _____ ***Date**_____

Patient consent

By signing this requisition form, I voluntarily request Igenomix to carry out the test indicated above. I have read and received a copy of the informed consent included in the following pages. The risks, benefits and limitations of this test have been explained to me.

***Patient´s signature** _____ ***Date**_____

I would like to receive information regarding incidental findings ☐ **YES** ☐ **NO**

INFORMED CONSENT FOR ANALYSIS OF FOETAL REMAINS OR PRODUCTS OF CONCEPTION (POC)

Screening for aneuploidy of all 24 chromosomes

DESCRIPTION, PURPOSE AND BENEFITS OF THE ANALYSIS

Chromosomal abnormalities can lead to foetuses with deformities, miscarriages or even neonatal deaths. Estimates of the frequency of chromosomal abnormalities in miscarriages range from 15% to 60%.

In the case of early termination of pregnancy or miscarriage, the diagnosis of a chromosomal abnormality may be important for planning future pregnancies.

Chromosomal tests on foetal DNA can provide useful information and help patients and doctors to determine the causes of miscarriages, the risk of recurrent miscarriages and the subsequent risk of having children with chromosomal abnormalities.

Products of Conception or POC tests provide comprehensive information faster than traditional cytogenetic karyotyping. With NGS (Next Generation Sequencing) or with a combination of NGS and STR (Short Tandem Repeat) techniques, the presence of extra or missing chromosomes is detected, as well as any partial chromosome losses or duplications. The presence of maternal cell contamination (MCC) is either ruled out or detected in the POC by NGS test that performs genetic analysis directly on the evacuated foetal remains.

PROCEDURE, RISKS AND LIMITATIONS

In order to process the sample, it will be necessary that the test request document is correctly completed. Otherwise, the analysis may be stopped until the required information is provided to the laboratory.

POC by NGS

For cases in which a genetic analysis is requested to be performed directly on the evacuated foetal remains, the samples must be collected (either by the patient if it is a spontaneous abortion or by curettage by the gynaecologist if the abortion is missed or incomplete) and sent using the sample collection kit provided by Igenomix. To rule out or detect contamination with maternal cells, it is necessary to obtain a biological sample from the patient (blood in EDTA tube, preferably using the one sent in the kit), which should be sent together with the POC sample. Whenever possible, it is recommended to obtain the blood sample prior to the curettage procedure or pharmacological treatment. The risks derived from these procedures should be explained by the professionals in charge of performing them.
Once in the laboratory, whenever possible, foetal versus maternal tissue is identified in the POC sample received. The sample is cleaned, dissected, DNA is extracted and analysed using 24-chromosome bulk sequencing (NGS). The STR protocol is used to detect or rule out maternal cell contamination as well as some types of polyploidy.

niPOC

For cases in which niPOC is requested, only the blood of the pregnant female is used as the biological sample for the genetic analysis. The biological sample - blood in a "STRECK" tube - should be obtained using standard techniques. To perform the niPOC test, the blood sample must be obtained prior to the curettage procedure or pharmacological treatment; niPOC is not appropriate for cases in which uterine evacuation has already occurred (by surgical, medical treatment or spontaneous evacuation). Once in the laboratory, circulating free DNA is extracted and analysed using 24-chromosome sequencing (NGS).

Possible Results

Before performing the genetic study, you should consider the implication of the possible results. There are four possible results:
a) Positive results: One or more alterations are detected that could be the cause of the gestational loss.
b) Negative results: No genetic alterations are detected within the resolution of the platform used. A negative result does not necessarily indicate the absence of a genetic cause, depending on the extent of the study requested according to the diagnostic suspicion and the limitations of the technique used.
c) Non-informative results: Exceptionally, contamination of the sample, poor quality or low quantity of the sample may result in no results being obtained.
d) Incidental/secondary results: On rare occasions, the test may reveal an important genetic change that is not directly related to the indication for the study. For example, this test may provide information about a person's risk for other genetic conditions. This information could have implications for the individual's medical care and will only be reported based on informed consent provided by the patient.

Risks and Limitations

Due to the complexity of genetic testing and the important implications of the test results, the results obtained must be interpreted together with other clinical data, within the general context of a medical consultation to be conducted by healthcare professionals. Reports of the results will be kept strictly confidential. The test result will be available within 7 working days for the "niPOC" service and 12 working days for the "POC by NGS" service, following receipt of the sample(s). A small percentage of samples may experience a variable delay due to unforeseen causes. Should this occur, the relevant clinical manager will be informed of the delay and Igenomix will not be responsible, under any circumstances, for any delay beyond the aforementioned period.

The main limitations of the POC tests, common to both services (POC by NGS and niPOC) consist of:

1. POC tests detect the most frequent genetic conditions associated with gestational losses, but do not detect all genetic conditions and/or all possible chromosomal abnormalities. The following conditions may not be detected:

- Balanced chromosomal rearrangements.

- Complete trisomies of acrocentric chromosomes will not be distinguishable from trisomies caused by a Robertsonian translocation (affecting chromosomes 13, 14, 15, 21, or 22) or an isochromosome in one of the parents.

- Detection of uniparental disomy (a condition in which both copies of a chromosome come from the same parent).

- Conditions caused by variants in single genes, such as sickle cell disease, cystic fibrosis, or Tay-Sachs disease.

- Other causes of miscarriage not yet identified.

2. Risk of misdiagnosis due to incorrect sample identification, inaccurate parentage information, mosaicism or other unidentified genetic abnormalities. Diagnostic errors due to test failure account for <1%.

3. There is the possibility of unpredictable and uncontrollable problems with transportation, such as those related to weather and air transport, or other circumstances beyond control, which would not allow timely results. There is also the possibility that the sample received at the laboratory is unacceptable for analysis, and therefore, results cannot be obtained from the sample provided.

In addition, there are specific limitations for each type of service:

1. Detection of ploidy (loss or gain of a complete set or sets of chromosomes):

- The POC by NGS test detects most polyploidies, such as triploidy 69,XXY, 69,XXX, and tetraploidy 92,XXXY and 92,XYYY. However, it cannot detect some tetraploidies, such as 92,XXXX or 92,XXYY.

- The niPOC test cannot detect any type of polyploidy (triploidy or tetraploidy).

2. Mosaicism (presence of more than one distinct cell line in the sample)

- POC by NGS and niPOC do not detect low levels of mosaicism, less than 30%.

- niPOC does not report mosaicism, only the presence or absence of the anomalies studied.

3. Detection limit: deletions or duplications of chromosomal material below a certain threshold, specific to the service requested, cannot be detected:

- In the case of the POC by NGS test, deletions and duplications below 10Mb cannot be detected.

- In the case of the niPOC test, deletions and duplications below 7Mb cannot be detected.

4. There is a possibility that the results may not be conclusive. The reasons may be:

- In the POC by NGS test, because of the possibility of contamination with maternal cells.

- In the niPOC test, due to low foetal fraction (below 2%).

5. In the niPOC service, there is a small chance that the test results may not reflect the chromosomal status of the products of conception (false positives) but reflect constitutional or acquired genetic abnormalities in the mother, or due to allogeneic blood transfusion, transplantation or stem cell therapy. In addition, test results may not reflect the chromosomal status of the products of conception if the blood was drawn after evacuation of the uterus. Chronic treatments with low molecular weight heparin may interfere with the analysis.

DATA PRIVACY, STORAGE AND RESEARCH USE OF THE SAMPLES

Your privacy is a priority for the Igenomix Group ("Igenomix"). Your identity and all data concerning your personal information will be kept confidential, and access will only be permitted to Igenomix personnel and appropriate authorities where required by the laws of the applicable jurisdiction. You will find further details of Igenomix's Privacy Policy and your rights at www.igenomix.com or will be provided to you upon request at privacy@igenomix.com.

We would like to inform you that your personal data will only be processed for the following purposes: (1) To fulfill the obligations arising from the provision of the services contracted by you; (2) To review and ensure the quality of the services provided (internal audits, quality controls, laboratory validation studies); (3) For educational purposes, provided that you remain anonymous during the same and are not identified during the analysis of the data, which will be removed from any publication; (4) For research purposes, scientific publications and presentations, provided that you remain anonymous during the same and are not identified during the analysis of the data, which will be removed from any publication; (5) To address any questions or concerns raised by you during the process and to monitor the correct execution and resolution of the test, including the indefinite conservation of your data, unless the local laws of the applicable jurisdiction establish otherwise; and (6) To contact you in the future to request your assessment of the services received, to carry out commercial communications (including 'cross-selling' and 'up-selling') of associated companies, as well as for the participation in market studies and development of new products.

You also declare that you understand and agree that you will not now or in the future derive any financial benefit from any research conducted, nor receive compensation for products developed from any research.

The sample analysis will be performed by Igenomix or an associated group selected by Igenomix on an international level. Igenomix reserves the right to perform part or all the analyses that make up the test through Third Party Laboratories accredited to recognised international quality standards, or otherwise periodically evaluated by Igenomix. The results obtained in this way will be reviewed by Igenomix and such circumstances will be indicated in the final report issued.

In accordance with the Personal Data Protection laws[1], the requesting party must have the patient's consent to carry out the requested diagnostic tests and to process the patient's data. You may at any time exercise your rights of access, rectification, opposition, suppression, automated decisions, limitation, portability, through the e-mail privacy@igenomix.com, providing documentation proving the identity of the applicant.

HAVING READ AND UNDERSTOOD THE ABOVE, I AM INFORMED OF:

The indication, procedure, probability of success, risks, and complications of the proposed treatment, as well as the economic cost of such test(s). My clinician has been willing to expand on any aspect of the information that is not sufficiently clear.

The explanations have been provided to me in clear and simple language, and my clinician has allowed me to ask questions and has addressed any concerns I have raised. They have also informed me that I can freely renounce this consent at any time.

I am satisfied with the information received and freely give my consent for the collected foetal remains (if relevant) to be sent to Igenomix's facilities in order for the requested POC test to be performed.

I also accept that the test results may be communicated to my clinician so that they may advise me appropriately in the planning of future pregnancies.

1 **For patients residing outside the U.S.:** Customers domiciled outside the United States in certain jurisdictions may have the option to request that their personal information be removed at any time from our active databases, subject to the applicable laws and regulations of that jurisdiction. Although we may remove your personal information from our active databases, some or all of your personal information will remain archived in backup copies to comply with legal, regulatory and other requirements. Information that has already been encrypted and/or anonymized may not be retrievable or traceable for destruction, deletion or modification. If you choose to have your personal information removed from our active databases, please contact us at privacy@igenomix.com.