NIMGenetics
New Integrated Medical Genetics

COD.

To be filled by the laboratory

INFORMED CONSENT

TrisoNIM® Advance 24 ☐	TrisoNIM® Premium 24 ☐	TrisoNIM® Excellence ☐	TrisoNIM® NeoSeq ☐	TrisoNIM® Twin ☐

PATIENT AND SAMPLE DATA

Identification code:		
Date of sample extraction:		
Name and Surname:		
Date of Birth:	Weight: kg	Height: m
ID:	Telephone Number:	
E-mail address:		
Address:		
Post code:	City:	

CLINICAL DATA

Nº of foetuses:	☐ Vanishing twin
Weeks of pregnancy:	

Reason for consultation:

- ☐ No relevant observations:
- ☐ Increase in Nuchal Translucency
  Specify: _____
- ☐ Ultrasound markers
  Specify: _____
- ☐ Risk in combined screening
  Specify: _____
- ☐ Others (family history, affected children, etc.)
  Specify: _____

MEDICAL PRACTITIONER DATA

Name:	Telephone Number:
Clinic /Hospital /Laboratory:	E-mail address:

1. I have received information on the indication, purpose, characteristics, scope, times, and limitations of TrisoNIM®, and I have had the opportunity to read the information provided about the test through the information sheet attached to this document, and my questions have been answered satisfactorily.
2. I declare that the personal and medical information I have provided is true and reliable.
3. I understand that I may be asked for a new sample if the collected sample is not optimal in terms of quality or quantity and that I may be contacted if additional clinical data are required.
4. I understand that TrisoNIM® is a screening and not a diagnostic test.
5. I understand that, despite the high sensitivity of the test, a low-risk result does not exclude the possibility of foetal alterations of genetic origin.
6. I understand that a high-risk result must be confirmed by an invasive prenatal diagnostic test.
7. I understand the limitations of this test described in the attached information sheet and confirm that I have informed my physician of circumstances that may affect the reliability of the test, should any of them occur. I also understand that this request has been made within the recommended period of pregnancy weeks.
8. I understand that the results of this test do not replace the medical diagnosis made within a medical visit, nor the genetic counselling given by your doctor, recommending that these results be shared in a medical visit, where, in addition, the genetic counselling described in the attached information sheet should be carried out. NIMGenetics, S.L. shall not be liable for any use made by you or your doctor of the results obtained, nor for any harmful consequences that may derive from the use of such information.
9. I understand that this study will provide information on the foetal sex.
10. I understand that, by performing this test, genetic information not related to the medical concern for which this test has been requested may be obtained on the foetus or the mother. These findings, which would be included as an informational note in the report of results, may require additional testing. I check this box to indicate that **I DO NOT WANT** this information to be disclosed to me. ☐
11. I understand that the information obtained may also have implications for other family members, as well as the desirability of transmitting such information to them myself in this case.

For all the reasons above, I declare the aforementioned to be true and accurate and I give my consent to carry out the TrisoNIM® test in the contracted modality.

Signature Patient/Legal Guardian: _____ **Signature Medical Practitioner:** _____

Date: _____

☐ I consent to the use of my clinical data and the obtained results under a pseudonym (i.e. without name or surname) for research purposes, scientific publications, quality studies, and databases in the healthcare field, in which strict confidentiality shall be preserved regarding my identity.

☐ I consent to the assignment of my clinical data and results under a pseudonym (i.e. without your name or surname) to third parties for scientific research.

☐ I authorise NIMGenetics, or its affiliates, to send me information related to its products and services.

Signature Patient/Legal Guardian: _____ **Date:** _____

NIMGenetics S.L. - Parque científico de Madrid - C/Faraday, 7 (Campus de Cantoblanco) 28049 Madrid - CIF B-85332138

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Purpose, indications, and categories of TrisoNIM®

TrisoNIM® is a prenatal screening test that is performed by analysing the foetal DNA in the maternal blood through which the risk that the foetus may be a carrier of certain genetic and/or chromosomal alterations is assessed according to the selected modality.

For **single foetus pregnancies**, NIMGenetics carries out four categories of TrisoNIM® prenatal screening tests: Advance 24, Premium 24, Excellence, and NeoSeq. In all of them, this test assesses the risk of foetal trisomy for chromosomes 21 (Down Syndrome), 18 (Edwards Syndrome), or 13 (Patau Syndrome) with a detection accuracy of approximately 99% for these trisomies, as well as the risk that the foetus may be a carrier of aneuploidies (alterations in the number) in the rest of the chromosomes. The analysis of the sex chromosomes will make it possible to know the sex of the foetus, as well as screening for the following numerical alterations: X, XXX, XXY and XYY.

In addition, the various TrisoNIM® categories will make it possible to assess the risk of the foetus suffering from other syndromes, as described below for each of them:

- **Advance 24:** This category also assesses the risk of the foetus suffering from the microdeletion syndromes 1p36, 2q33.1, and 5p15 (Cri-du-Chat Syndrome).

- **Premium 24:** This category also assesses the risk of a foetus suffering from microdeletion syndromes 1q32-q41, 10p14-13, 11q23-qter (Jacobsen syndrome), or 16p12-p11.

- **Excellence:** This category also assesses the risk of a foetus suffering from microdeletion syndromes, 1p32p31, 2p12p11.2, 3pter-p25, 4p16.3, 4q21, 5q12, 5q14.3q15, 6pterp24, 6q11q14, 6q24q25, 8q24.11-q24.13 (Langer-Giedion Syndrome), 9p, 10q26, 11p11.2, 11p13p12 (WAGRO and WAGR Syndromes), 14q11-22, 14q22 (including Frias Syndrome), 15q26qter (Congenital Diaphragmatic Hernia Type I and Drayer's Syndrome), 15q11-q13 (Angelman and Prader Willi Syndromes), 16q22, 17p13-p11.2 (Miller-Dieker and Smith-Magenis), 18q, 18p and 22q11.2 (DiGeorge Syndrome) and microduplication syndromes in 15q11-q13, 17p12-p11 (Yuan-Harel-Lupski and Potocki-Lupski Syndromes), and 17p13.3.

- **NeoSeq:** This category also assesses, with 99% of sensitivity and specificity, the presence of 2038 pathogenic or probably pathogenic de novo variants in 18 genes associated with 27 pathologies of monogenic origin with an autosomal dominant inheritance pattern. The included genes are BRAF, CHD7, COL1A1, COL1A2, COL2A1, COL11A1, FGFR1, FGFR2, FGFR3, HRAS, KRAS, LMNA, MAP2K1, MAP2K2, SOX9, STAT3, TSC1, TSC2. Exceptionally, some variants detected could come from the biological father. The complete list of variants included in this study is available at **https://bit.ly/neoseq-variants**

For **pregnancies with two foetuses**, only the Twin category is recommended. This test is restricted to foetal trisomy risk assessment for chromosomes 21 (Down syndrome), 18 (Edwards syndrome), or 13 (Patau syndrome). The test cannot be carried out in case of individual foetuses. If a Y chromosome is detected, the test cannot determine the foetal sex of each twin. **In these cases, the presence of microdeletions or alterations for other chromosomes than the specified ones will not be reported.**

In the event that one of the foetuses is lost (vanishing twin), the pregnancy will continue to be considered, as far as foetal DNA is concerned, as a twin pregnancy.

In order to start processing the sample, the first page of this consent must correctly indicate the category of the test to be performed. The study will be retained until this information is completed. The TrisoNIM® test can be carried out as of the 10th week of pregnancy, **except in the case of the NeoSeq category, which must be performed as of the 12th week onward.**

Risks and disadvantages

These studies do not pose a risk to the foetus since only 10 ml of maternal blood is required to perform them. Blood will be drawn from the mother by venipuncture, involving a possible series of risks for her that are usually minor and infrequent, including excessive bleeding, fainting or dizziness, haematoma, infection, and multiple punctures to locate veins.

If the collected sample is not optimal regarding quality or quantity, or if the diagnosis complexity requires other tests, NIMGenetics may require a new sample. You may also be contacted if additional clinical data are required.

Location where the analysis will be carried out and use of the biological sample at the end of the analysis

The sample analysis will be performed by technical personnel from NIMGenetics in the laboratory owned by this company, located in Madrid or, depending on the type of test, in a collaborating laboratory with whom a partnership agreement has been signed in accordance with the terms and legal requirements by current legislation.

Only authorised NIMGenetics personnel and collaborating laboratories will have access to the connection between your biological sample, your DNA and the information obtained by processing it, and the code assigned in each case.

If there is sufficient sample quantity left after the test, an aliquot of the excess sample and/or extracted DNA shall be stored in a coded form at NIMGenetics' laboratories, for a maximum period of 3 months. Such surplus may be used when a new study is necessary to confirm the result since it will only be suitable for prenatal screening, but not for additional or confirmatory diagnostic tests.

Additional or confirmatory tests should be performed on the foetal sample. The material generated from the DNA collected from the samples, called *genomic libraries*, shall also be kept in a coded form for a period of one year to ensure its preservation until the end of the pregnancy.

Test results and implications

TrisoNIM® is a screening test, not a diagnostic test, although it is very accurate to identify foetal chromosomal abnormalities (with a detection accuracy of approximately 99% for trisomies 21, 18, and 13). However, the implications of the potential results must be considered before carrying out the test.

- **Implications of a positive result:**

  False positives have occurred, therefore, if a high-risk result is obtained, the alteration must be confirmed by an invasive prenatal diagnostic test (amniocentesis or chorionic villus biopsy). In some cases, this will have to be associated with specific studies on the parents.

- **Implications of a negative result:**

  Although this test has a high sensitivity to detect alterations, a low-risk/non-detection result does not entirely exclude the possibility of a chromosomal or foetal alteration.

- **Implications of a non-informative result:**

  In some cases (less than 0.1% of the studies carried out), it will not be possible to obtain a clear result because the blood sample does not contain enough foetal DNA, due to various clinical reasons such as early gestational age or high maternal weight, among others. It may be necessary to take a new blood sample in these cases so that the test can be repeated, or to resort to invasive prenatal diagnostic tests.

The response time for the selected test category is available at www.nimgenetics.com. On occasions (less than 1%), this period may be extended due to different methodological causes.

Test limitations

The following situations make it impossible to obtain a reliable test result:

- Genetic changes in the placenta (confined placental mosaicism) or in the mother (in the presence or not of chromosomal mosaicism) mean that test results may not reflect genetic changes in the foetus.
- A limited number of foetal cells carry one of the genomic alterations analysed (foetal mosaicism).
- Chromosomal alteration in untested regions or the presence of chromosomal alterations in the parents.
- Complete triploidies/tetrasomies or chromosomal microdeletions in the analysed regions of a size lower than the resolution limit of the technique, which is currently considered to be approximately 10Mb, except in the Excellence and NeoSeq categories which is 5Mb.
- Blood transfusions within one year, transplant, immune therapy in which exogenous DNA is introduced within four months, or stem cell therapy prior to the drawing of the blood sample.
- Gestational age earlier than the 10th week or later than the 25th week. For the NeoSeq category, it is not recommended that the study be carried out before 12 weeks and after 22 weeks.

- Triplets or pregnancies with a higher number of foetuses.
- This study is not recommended as a diagnostic test in the presence of foetal ultrasound alterations or in patients with malignant tumours.
- The no-information rate may be increased in morbidly obese patients (BMI≥35) or in patients being treated with low molecular weight heparin.
- Also, the technology used will not enable the detection of other genetic alterations such as other unspecified numeric alterations, large deletions, rearrangements (such as translocations, inversions, or ring chromosomes), uniparental disomies, sequence changes, repetitive expansions of trinucleotides or epigenetic alterations (such as alterations in imprinting centres), which could cause the same or similar pathologies as those secondary to some microdeletions or microduplications included in this test.

Additionally, in the NeoSeq category, the following elements must be taken into account:

1. It is not indicated in pregnancies with foetuses from egg donation, family history of genetic disease or in patients with known monogenic diseases.

2. In cases where no sample can be obtained from the biological father (e.g., in pregnancies resulting from sperm donations), the origin of the genetic alteration cannot be established with certainty.

3. Mutations present in mosaic, located in repetitive genomic regions or regions of high homology (pseudogenes) may not be identified. In exceptional cases, the presence of individual variations in the genomics sequence might prevent the identification of any of the variants evaluated in this study (allele drop-out effect). Pathologies associated with autosomal, recessive or polygenic inheritance are not included in this study. Pathologies associated with dominant autosomal inheritance outside the genes selected in this test are not analysed in this test.

You are responsible for informing your doctor about any of these circumstances.

No genetic study technique is capable of identifying all the possible genetic or epigenetic alterations associated with a certain pathology. Therefore, each technology has its own specific instructions and limitations that will be reflected in the report of results.

Incidental Findings

TrisoNIM® analyses other regions of the genome outside those included in the lists of alterations subject to these studies. It is important to understand that, on exceptional cases, we can identify genetic alterations in the foetus or mother in these regions. This incidental finding will be included in the report of results as an informative note, if you give your consent, because the analysis of these regions cannot be carried out with the same statistical accuracy as the genetic regions that are the subject of this study. These findings may require additional invasive or imaging tests. You must decide whether or not you wish to receive this additional information by completing the appropriate section at the beginning of the document.

In addition, the information obtained may also have implications for other family members and, in this case, it is advisable that you share this information with them so that, if they wish, they can make arrangements for a genetic consultation where they will be informed about their personal risk and their future healthcare options.

Genetic Counselling

The medical practitioner who requests/advises this test undertakes to provide information about the purpose of the analysis and provide genetic counselling once the analysis results have been obtained and evaluated. NIMGenetics is available to this professional to clarify any questions that may arise.

Data Protection and Confidentiality

Only health and technical personnel duly authorised by NIMGenetics and collaborating laboratories may access personal data and results of genetic tests. Such data shall be processed in a strictly confidential manner in accordance with current regulations on personal data protection.

In accordance with the provisions of Regulation (EU) 2016/679 on the protection of personal data of natural persons (GDRP) and with Organic Law 3/2018 on Personal Data Protection and guarantee of digital rights, we inform you that your personal data will be registered and incorporated into the data processing systems under the responsibility of NIMGenetics for the diagnostic purpose (and, where appropriate, research purposes) described herein. Data processing is necessary for carrying out the diagnostic test. Therefore, if you do not agree with this processing, we cannot carry out the requested analysis. We also inform you that your personal data will not be shared with any recipient outside NIMGenetics, except with those authorised by you as requested in the following heading "Further use of data" or as required by law. Your personal data will not be used for any other purpose than the one stated herein or others that are not compatible with it.

The personal information that NIMGenetics processes for performing the test, as well as the results, will be stored by NIMGenetics for 5 years as of the issue of the report. After this period, if you have not exercised your right of erasure, your data will be pseudonymised and used for research purposes.

The results of your sample sequencing may be transferred to service suppliers of NIMGenetics that are outside the European Economic Area. However, NIMGenetics guarantees that such transfer will be carried out in accordance with the warranties provided for in Regulation (EU) 2016/679 without including identification data.

You may exercise your rights of access, rectification, erasure, limitation of specific processing, portability, and objection to the processing described at the following address: NIMGenetics GENÓMICA Y MEDICINA S.L.: C/de Anabel Segura, 16 - Vega Norte Building, tower 3 - 1st floor 28108 Alcobendas (Madrid) Parque Científico de Madrid, C/Faraday, 7 Campus Cantoblanco, 28049 Madrid or by contacting the Data Protection Officer at the following e-mail address: **dpo@nimgenetics.com**

For additional information on your personal data processing, please check the Privacy Policy on our website:
https://www.nimgenetics.com/en/privacy-policy/

Further use of the data

The results may contribute to increasing the analytical capacity of the test and the current state of knowledge, providing benefits for new studies. Therefore, NIMGenetics requests your consent to use your clinical data and results under a pseudonym, (i.e. without your name or surname) for research purposes, scientific publications, quality studies, and databases in the healthcare field, maintaining strict confidentiality regarding your identity, which will not be revealed under any circumstances.

Furthermore, NIMGenetics requests your consent for the assignment of your clinical data and results under a pseudonym (i.e. without your name or surname) to third parties for scientific research.

NIMGenetics contact details

Feel free to contact NIMGenetics by calling +34 91 037 83 54 to clarify any doubts that may arise in connection with the content of this informed consent.

In order to carry out the requested prenatal screening test, you must sign and date the informed consent form.

NIMGenetics
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TEST INSTRUCTIONS

1. Complete the Informed Consent.

Personal data:

- Include the patient's personal data, the sample identification code, and the reason for consultation.
- The COD field located at the top right of this consent will be assigned by NIMGenetics.

Data for sending the report:

- Specify the name and e-mail address of the medical practitioner to whom the report will be sent.
- The informed consent must be signed by the patient or legal guardian once they have been informed by the medical practitioner, who acts as a witness.

2. Follow the instructions for the Extraction, Conservation, and Transport of samples.

The sample collection will be carried out at the hospital centre or extraction laboratory. Instructions for conservation and shipment are included inside the Extraction Kit.

Warning: In the TrisoNIM® NeoSeq category, two 10 ml Streck tubes must be sent.

3. Sample sending

The sample will be collected at the hospital centre or extraction laboratory after prior notification to NIMGenetics.
The sample and attached documents (informed consent and invoicing information) will be sent to the following address:
C/ Faraday nº 7. 28049 Madrid (Spain)
If you have any questions, please, call at +34 91 037 83 54

PAYMENT METHODS

This test must be paid by means of a bank deposit or transfer made on the same day or the day after the blood is drawn.

The DESCRIPTION on the transfer should read as follows: "TrisoNIM" and its category (Advance 24/Premium 24/Excellence/ NeoSeq/ Twin) along with the **NAME** and **SURNAME** of the **PATIENT.**

The **bank transfer receipt should be sent by e-mail to: miprueba@nimgenetics.com**

Bank details: Banco Santander
CC-IBAN No.: ES53 0075 0436 7206 00134861
Account holder: NIMGenetics, S.L.