NIMGenetics
New Integrated Medical Genetics

SPAIN
Parque Científico de Madrid
Faraday, 7 (Campus de Cantoblanco)
28049 Madrid
Tel. +34 91 037 83 54
M. +34 672 060 393

BRASIL
Rua Elvira Ferraz, nº 250, Cj. 211
Itaim - Sao Pauolo, SP.
Postcode: 04552-040
Tel. +55 11 3044 1813

MÉXICO
World Trade Center
Montecito, 38 - Floor 35 - Office 10
Col. Nápoles - 03810 Mexico City
Tel. +52 55 68232076

PORTUGAL
Complexo Interdisciplinar da Universidade de Lisboa
Rooms 2.12 and 2.14
Avenida Prof. Gama Pinto nº 2,
1649-003 Lisboa
Tel. +351 932 34 80 32

La Suma de Todos
Comunidad de Madrid

NIMGenetics is a Genetic Diagnosis centre authorised by the Department of Health and Consumption of the Community of Madrid, registered in the corresponding Register under number CS 10673

CAT-26; Rev 02; 28/06/2021

www.nimgenetics.com

TrisoNIM® NEOSEQ

A revolution in Prenatal Diagnosis

NIMGenetics
New Integrated Medical Genetics

NIMGenetics - Leaders in non-invasive prenatal genetic diagnosis since 2011

TrisoNIM®

Trisomy 21

TrisoNIM®

Trisomy 21

+

Trisomy 13

Trisomy 18

TrisoNIM®

Trisomy 21, 13 y 18

+

Foetal sex

Sexual aneuploidies

TrisoNIM® ADVANCE

Trisomy 21, 13 y 18

Foetal sex

Sexual aneuploidies

+

3 microdeletion syndromes (≥ 10 Mb)

The first company that carries out a complete cell-free foetal DNA test in Spain

TrisoNIM® PREMIUM

Trisomy 21, 13 y 18

Foetal sex

Sexual aneuploidies

3 microdeletion syndromes (≥ 10 Mb)

+

Trisomy 9, 16 y 22

4 microdeletion syndromes (≥ 10 Mb)

TrisoNIM® EXCELLENCE

Trisomy 21, 13 y 18

Foetal sex

Sexual aneuploidies

+

24 chromosomes

38 microdeletion syndromes (≥ 5 Mb)

TrisoNIM® NEOSEQ

Trisomy 21, 13 y 18

Foetal sex

Sexual aneuploidies

24 chromosomes

38 **microdeletion syndromes** (≥ 5 Mb)

+

2038 pathogenic and probably pathogenic variants

We innovate for your well-being

Non-Invasive Prenatal Test - Detection of cell-free foetal DNA in maternal blood

Currently, **the most comprehensive non-invasive prenatal testing offers the following:**

- Detection of foetal aneuploidies on chromosomes 21, 13, and 18.
- Study of aneuploidies on all chromosomes.
- Information on the most common sexual aneuploidies and on the foetal sex.
- Study of a limited number of microdeletion syndromes.

The technical limitations in these studies prevent other alterations of a pathogenic nature from being considered, thus hindering a more comprehensive approach.

TrisoNIM® NEOSEQ **is a synonym of the great technological advance,** enabling the analysis of other pathogenic alterations, providing a global genetic approach, which includes:

- **A wide selection of microdeletion syndromes:** These alterations represent a large group of serious pathologies which, when identified in the first trimester, make it possible to receive appropriate genetic counselling early on.
- **Dominant monogenic diseases:** The variants analysed are located in genes associated with disabling, lethal, and/or serious pathologies. Most of these mutations are characterised for being *de novo* (healthy parents), that is, there is no family history compatible with the variant.

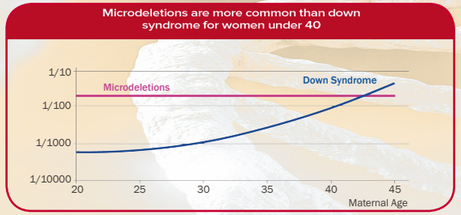
Key aspects in the study of microdeletion syndromes

NIMGenetics pffers the most competent study of microdeletion syndromes, selected for their clinical relevance in prenatal diagnosis, with a detection ≥ 5Mb

Why choose a comprehensive study of microdeletion syndromes?

They do not depend on maternal age.

Overall, they have a significant prevalence that is higher than the one of Down Syndrome in young women [1,2].



(1) Wapner RJ et al. N Engl J Med. 2012 Dec 6; 367(23):2175-2184
(2) Snijders, et al. Ultrasound Obstet Gynecol 1999;13:167–170

They allow for early diagnosis of pathologies that are not associated with echographic alterations during the first trimester [3,4].

The study of these genetic alterations does not significantly increase the number of amniocentesis [3].

The detection capacity is highly dependent on the foetal fraction and the size of these alterations.

(3) Hong et al. Sci China Life Sci 62, 215-224 (2018)
(4) Van Opsal et al. Genet Med 2018 Apr; 20(5): 480-485

Key aspects in the study of mutations in dominant monogenic diseases

A new dimension in prenatal diagnosis through the identification of alterations in single gene DNA sequence.

TrisoNIM® NEOSEQ **offers a new diagnostic option that provides highly valuable information not covered by current approaches and without an alternative screening method.**

- A global incidence of approximately 1/600 individuals (higher than Down syndrome) [5].
- This study is aimed at pathogenic or probably pathogenic variants in genes that are associated with severe, disabling, and/or lethal dominant monogenic diseases.
- There is no suitable conventional screening method for these diseases and the ultrasound findings are inconclusive for their diagnosis.
- Within monogenic diseases, those associated with an autosomal dominant inheritance pattern represent 54%, and most of them appear in the absence of a family history, as more than 70% of the cases are *de novo variants* [6].
- Advanced paternal age is associated with a higher frequency of variants that cause monogenic diseases [7,8].

(5) McRae J et al. Nature 2017: 542:433-438

(6) Yang Y. et al. JAMA, 2014, 312(18):1870-1879

(7) Kong, Augustine, Frigge, et al. Nature. 2012, 488:471-475.

(8) Toriello H V , Meck J M. Genetics in Medicine, 2008, 10(6):457-460.

Beyond the limits of non-invasive prenatal diagnosis

Studies of cell-free foetal DNA in maternal blood reach their maximum potential with TrisoNIM® NEOSEQ, **which offers the most comprehensive study of clinically relevant syndromes during pregnancy.**

ANALYSES ALL CHROMOSOMES

▸ **STUDIES ANEUPLOIDY FOR ALL CHROMOSOMES**

IT DETECTS:

- Trisomy 21, associated with Down syndrome
- Trisomy 18, associated with Edwards syndrome
- Trisomy 13, associated with Patau syndrome

REPORTS:

- Aneuploidies for sex chromosomes and foetal sex
- Aneuploidies of the remaining autosomal chromosomes

REPORTS 38 MICRODELETION SYNDROMES

ANALYSES 2038 PATHOGENIC AND PROBABLY PATHOGENIC VARIANTS

- Located in 18 genes, associated with 27 genetic syndromes

LIST OF REPORTED MICRODELETION SYNDROMES

SYNDROME	#OMIM
1p36 Microdeletion	607872
1p32p31 Microdeletion	613735
2q33.1 Microdeletion	612313
2p12p11.2 Microdeletion	613564
3pterp25 Microdeletion	613792
4p16.3 Microdeletion	194190
4q21 Microdeletion	613509
5q12 Microdeletion	615668
Cri-du-chat Syndrome	123450
5q14.3q15 Microdeletion	612881
6pterp24 Microdeletion	612582
6q11q14 Microdeletion	613544
6q24q25 Microdeletion	612863
Langer-Giedion Syndrome	150230
9p Microdeletion	158170
DiGeorge 2 Syndrome	601362
10q26 Microdeletion	609625
11p11.2 Microdeletion	601224

SYNDROME	#OMIM
Jacobsen Syndrome	147791
WAGRO Syndrome	612469
WAGR Syndrome	194072
Frias Syndrome	609640
14q11q22 Microdeletion	613457
15q26qter Microdeletion	612626
15q26 Microdeletion	142340
15q11q13 Duplication	608636
Prader-Willi Syndrome	176270
Angelman Syndrome	105830
16p12p11 Microdeletion	613408
16q22 Microdeletion	614541
Yuan-Harel-Lupski Syndrome (combination of CMT1A and Potocki-Lupski)	616652
17p13.3 Microdeletion (Miller-Dieker Synd.)	247200
17p13.3 Duplication	613215
17p11.2 Microdeletion (Smith-Magenis Synd.)	182290
17p11.2 Duplication	610883
18q Microdeletion	601808
18p Microdeletion	146390
DiGeorge Syndrome	188400

TrisoNIM® NEOSEQ reports microdeletions sized ≥ 5 Mb, with the exception of DiGeorge Syndrome, where detection capability is up to 3 Mb.
In approximately 30% of cases, Angelman and Prader-Willi Syndromes are produced by genetic alterations not detectable by any foetal DNA in maternal blood test.

GENES AND GENETIC SYNDROMES ASSOCIATED WITH THE GENETIC VARIANTS ANALYSED

Skeletal abnormalities	
GENE	SYNDROME
COL1A1	Osteogenesis Imperfecta, Type I
	Osteogenesis Imperfecta, Type II
	Osteogenesis Imperfecta, Type III
	Osteogenesis Imperfecta, Type IV
COL1A2	Osteogenesis Imperfecta, Type II
	Osteogenesis Imperfecta, Type III
	Osteogenesis Imperfecta, Type IV
FGFR3	Achondroplasia
	Thanatophoric dysplasia, type I
	Thanatophoric dysplasia, type II
	Crouzon syndrome with acanthosis nigricans

Craniosynostosis	
GENE	SYNDROME
FGFR2	Crouzon syndrome
	Apert Syndrome
	Jackson-Weiss syndrome
	Pfeiffer syndrome
FGFR1	Pfeiffer syndrome

Syndromic phenotype	
GENE	SYNDROME
BRAF	Cardiofasciocutaneous syndrome
KRAS	Cardiofaciocutaneous syndrome II
MAP2K1	Cardiofaciocutaneous syndrome II
MAP2K2	Cardiofaciocutaneous syndrome IV
HRAS	Costello Syndrome
CHD7	CHARGE Syndrome
TSC1	Tuberous Sclerosis I
TSC2	Tuberous Sclerosis II
COL2A1	Stickler syndrome, type I
COL11A1	Type II Stickler syndrome
STAT3	Hyper IgE recurrent infection syndrome
LMNA	Hutchinson-Gilford Progeria

TrisoNIM® NEOSEQ analyses 2038 pathogenic and probably pathogenic variants in 18 genes that are associated with 27 genetic syndromes.
The complete list of variants included in this study (with #OMIM) is available at: https://bit.ly/neoseq-variants

TrisoNIM® NEOSEQ

Combination of genome and exome studies for prenatal diagnosis

Cutting edge technology

Two combined technologies that enable for the most innovative approach:

- High-depth NGS for the detection of mutations.
- Low-depth whole-genome for variants detection in the number of copies (CNVs).

With the best prenatal diagnosis platform

A high risk result after a foetal DNA test must be confirmed by an invasive test. Therefore, NIMGenetics offers, free of charge, the validation of these cases:

- **Chromosomal aneuploidies and CNVs:** KaryoNIM® Prenatal, enabling to quickly and efficiently establish a genetic diagnosis through the analysis of 124 syndromes.
- **Dominant monogenic diseases:** Validation by Sanger sequencing technology.

Reliability

Risk prediction and foetal fraction calculation are performed using a double algorithm*, increasing the accuracy of the analysis.

CHROMOSOMAL ALTERATION	SENSITIVITY	SPECIFICITY
T21 (Down syndrome)	99,17%	99,95%
T18 (Edwards syndrome)	98,24%	99,95%
T13 (Patau syndrome)	99,99%	99,96%
X0 (Turner Syndrome)	>95%	-
Y Chromosome Detection	>98%	-

Published data: Zhang H et al. Ultrasound Obstet Gynecol 2015; 45: 530-538

(*): Analysis algorithm with CE-IVD marking for trisomy 21, tested on more than 3 million pregnant women.

Quality parameters associated with genetic variants detection:

PARAMETER	RESULT
Sensitivity	97,5%
Specificity	99,7%
Positive Predictive Value	95,9%
Negative Predictive Value	99,8%

BGI technology validation study inner data

Parameters associated with the detection of copy number variants (CNVs):

PARAMETER	RESULT
Sensitivity	>99,99%
Specificity	99,99%

Hong et al. Sci China Life Sci 62, 215-224 (2018)

Tailored to your needs

TrisoNIM® NEOSEQ

Reliability, safety and innovation

Hand in hand with the most qualified experts

Endorsed by the world's most relevant genomic company (BGI), the NIMGenetics team, made up of experts in Medical Genetics, members of the AEDP (1) and the AEGH (2), is recognised for its specialisation in the area of prenatal genetic diagnosis.

Certified quality

- The **UNE-EN ISO 15189:2013** accreditation for **screening** foetal aneuploidies (13, 18, 21, X, and Y chromosomes) and for foetal sex determination in maternal blood by massive sequencing (NGS).
- The **ISO 9001:2015** accreditation for the provision of analysis services for genetic diagnosis in the pre-analytical, analytical, and post-analytical stages for the specialities of genomics, non-invasive prenatal testing and molecular diagnosis.

Limitations

- Recommended for pregnant women at 12 weeks or more confirmed by ultrasound.
- For pregnant women with over 22 weeks of pregnancy, special informed consent is required.
- Not suitable for egg donation.
- Not suitable for twin pregnancy.

Result report time

The result will be reported within 15 business days as of the sample reception in the laboratory.

Your TrisoNIM® NEOSEQ step by step

1. Consult your specialist. Based on the specialist's advice, sign the informed consent
2. Contact us to schedule the sample extraction and collection
3. At NIMGenetics, the sample will be analysed and a report will be drawn up
4. See your specialist for report interpretation

(1): AEDP: Spanish Association of Prenatal Diagnosis
(2): AEGH: Spanish Association of Human Genetics

TrisoNIM® NEOSEQ