GENOMICA
Next Generation Genetics

Genetic testing for predisposition to preeclampsia and hypertensive disorders of pregnancy



PREECLARISK

NEXT GENERATION
GENETICS

PREECLARISK

01 BACKGROUND

Preeclampsia and early risk assessment

Hypertensive disorders of pregnancy are a leading cause of complications for mothers and babies around the time of birth. **Preeclampsia** warrants particular attention. Identifying women at higher risk early helps clinicians plan appropriate monitoring.

2–8%
of pregnancies are affected by preeclampsia

4 milion
women worldwide are affected by preeclampsia each year

Up to 15%
of women develop a hypertensive disorder in at least one pregnancy

14%
of maternal deaths worldwide are attributed to hypertensive disorders of pregnancy

Key conditions in pregnancy

Chronic hypertension	High blood pressure present before pregnancy or first detected before 20 weeks of gestation.
Gestational hypertension	High blood pressure that develops from 20 weeks of gestation without other signs of preeclampsia. Monitoring is needed because it can progress to preeclampsia.
Preeclampsia	From 20 weeks of gestation, high blood pressure is accompanied by proteinuria, signs of maternal organ or placental dysfunction, or both. Preeclampsia can also develop in women with chronic hypertension.
Eclampsia	Seizures in a woman with preeclampsia that cannot be attributed to another cause.

CARDIOVASCULAR HEALTH AFTER PREGNANCY

After preeclampsia, the risk of **ischemic heart disease**, **stroke and cardiovascular death** is about twice as high. The risk of **chronic hypertension and heart failure** is three to four times as high. Pregnancy history can therefore help guide cardiovascular prevention and follow-up in the years after delivery.

02 THE CONDITION

Preeclampsia and its complications

Once known as *gestosis*, **preeclampsia** is a pregnancy complication that can affect multiple organs. From 20 weeks of gestation, it presents with high blood pressure accompanied by protein in the urine (proteinuria), signs of maternal organ or placental dysfunction, or both.

The role of the placenta

Abnormal placental development can reduce blood flow to the placenta.

A poorly functioning placenta can release antiangiogenic factors such as **sFlt-1** and **soluble endoglin** into the mother's bloodstream. These factors impair blood vessel function and contribute to high blood pressure and proteinuria.

Complications for the mother

Possible complications include kidney and liver damage, pulmonary edema, clotting problems and cerebrovascular complications.

Serious complications include **HELLP syndrome** and **eclampsia**, which involves seizures.

Effects on the baby

Impaired placental function can restrict fetal growth and compromise the baby's well-being. Placental abruption and, in the most severe cases, fetal death can occur.

Preeclampsia can also require preterm delivery and is associated with low birth weight.

< 34

EARLY AND LATE ONSET

Early and late onset

Early-onset preeclampsia develops before 34 weeks. It is more often associated with severe complications and abnormal placental development. Maternal cardiovascular and metabolic predisposition may play a greater role in **late-onset preeclampsia**. The mechanisms vary and involve both maternal and fetal factors.

Key clinical risk factors

Pre-existing conditions

- chronic hypertension
- autoimmune disease
- kidney disease
- diabetes
- obesity

Pregnancy history and characteristics

- previous pregnancy complicated by a hypertensive disorder
- family history of preeclampsia
- first pregnancy
- advanced maternal age
- multiple pregnancy

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03 SCIENTIFIC EVIDENCE

Genetic contributions to risk

Preeclampsia is a multifactorial condition. Heritable factors also contribute substantially to individual susceptibility. Family studies attribute approximately **31–35%** of the predisposition to preeclampsia to **maternal genetic factors**.[2]

Genetic predisposition adds to clinical and placental factors in shaping an individual's risk profile. Early risk assessment makes it possible to plan obstetric surveillance in good time.

31–35%
of variation in susceptibility has been attributed to maternal genetics in family studies

38%
estimated heritability from common maternal variants in European populations

18
independent risk loci identified by studying over 20,000 cases and 700,000 controls. [3-4]

Findings from genome-wide studies

Genome-wide association studies (GWAS) have identified several genetic associations with susceptibility.[3-4]

FETAL GENOME
Variants near **FLT1**, a gene that also gives rise to the placental protein sFlt-1.[1-2]

MATERNAL GENOME
Associations near **ZNF831**, **FTO**, **MECOM**, **FGF5** and **SH2B3**, in regions previously linked to blood pressure or body mass index

META-ANALYSIS
in large meta-analyses, **18 independent loci** associated with preeclampsia and/or gestational hypertension, as well as additional markers related to the full spectrum of maternal hypertensive disorders of pregnancy[3-4]

How variants form a polygenic score

A **polygenic risk score** (**PRS**) summarizes the combined contribution of multiple variants. In research using genome-wide scores, women in the top 10% had about **twice the odds** of preeclampsia compared with the rest of the group, even after accounting for key clinical factors.

Six biological processes

Studies have linked maternal predisposition to these processes:

- blood pressure regulation;
- endothelial function and blood vessel formation;
- glomerular and kidney function;
- placental development and function;
- maternal–fetal immune tolerance;
- cardiometabolic predisposition.

From single variants to the polygenic score

The polygenic score adds up the contributions of the individual variants, based on the number of allele copies and on the weight estimated in the reference studies.

Genotype
Number of copies of the effect allele (0, 1 or 2 copies)

×

Variant weight
effect estimated in the reference study

=

Polygenic score
sum of the contributions of all variants

Polygenic information helps describe individual predisposition and is interpreted alongside the clinical assessment..

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04 THE TEST

PREECLARISK and genetic predisposition

PREECLARISK analyzes maternal DNA to identify the **genetic predisposition to preeclampsia** and **gestational hypertension**. The test combines the contribution of the variants investigated into a **polygenic risk score** (**PRS**). The result describes one component of an individual's susceptibility and should be interpreted together with the clinical and obstetric history, blood pressure values, and the other assessments provided for in the standard care pathway.

What the test analyzes

22 single-nucleotide polymorphisms (SNPs) in maternal constitutional DNA across **18 genes** or genomic regions linked to processes involved in hypertensive disorders of pregnancy.

Marker selection is based on associations documented in large population studies.

What the report shows

A report that places the maternal profile in one of three predisposition categories

Increased risk

Intermediate risk

Low risk

The report is accompanied by a dedicated technical document that explains the scientific basis of the test, the interpretation criteria, and its limitations.

How the result is used

Maternal genetic predisposition adds to the risk assessment alongside medical and pregnancy history, blood pressure and other clinical findings.

The result may help identify women who could benefit from individualized monitoring early in pregnancy.

Test features at a glance

Maternal DNA
The test assesses the woman's genetic predisposition using a maternal sample.

Simple sample collection
A sample of cells from the oral mucosa, collected via a swab, is sufficient.

Lasting information
Constitutional DNA is stable, so testing generally needs to be done only once.

Scientific basis
Markers selected from large genome-wide studies and meta-analyses.

Clear results
Three risk categories with an accompanying technical report.

Part of prenatal care
The result complements routine screening and prenatal checkups.

UNDERSTANDING THE RESULT

PREECLARISK assesses genetic predisposition and does not establish a diagnosis. The result complements clinical screening models that consider medical history, mean arterial pressure, uterine artery pulsatility index and first-trimester biomarkers such as PlGF and PAPP-A..

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05 THE PANEL

22 variants across 18 genes

The panel covers genomic regions linked to six biological processes relevant to maternal adaptation to pregnancy and placental function.

Blood pressure and cardiovascular adaptation

MECOM · FGF5 · RGL3 · ZNF831/ZBTB46 · PREX1

Associations in these regions link susceptibility to blood pressure control and blood vessel function. Pregnancy can bring an existing cardiovascular vulnerability to light.

Natriuretic peptides and fluid balance

NPR3 · FURIN/FES

These genes are involved in regulating and processing natriuretic peptides, hormones that help the kidneys excrete sodium and regulate blood vessel tone.

Blood vessel development and placental function

FLT1 · WNT3A

FLT1 also gives rise to sFlt-1, a protein that can impair maternal blood vessel function when present in excess. WNT3A is involved in cell development signaling and is expressed in the placenta.

Maternal–placental interface and kidney function

PGR/TRPC6 · PLCE1 · TNS2 · ACTN4

Candidate genes involved in progesterone response, endometrial adaptation and the structure and function of the kidney's filtering cells.

Immune regulation and protein homeostasis

HLA/PSORS1C2 · SH2B3/ATXN2 · PZP · AUH/LINC00484

These regions include candidate genes involved in immune regulation, cell-to-cell signaling and maintaining protein balance outside cells.

Metabolic factors

FTO

This locus is associated with body mass index and body fat, linking metabolic predisposition to one component of obstetric risk.

18 MARKERS

with evidence of association in the **maternal genome** across the regions covered by the panel.

4 MARKERS

in the **FLT1** region with associations first reported in the **fetal genome**. Testing the mother does not determine the fetal genotype.

The technical report lists all variants, effect alleles, odds ratios and references.

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06 WHO IT IS FOR

Who may consider the test

PREECLARISK is designed for women planning a pregnancy or in the early weeks of pregnancy and for the healthcare professionals who care for them.

For women

Women may wish to discuss testing with their clinician if they

- want to learn about their genetic predisposition before conception or in early pregnancy
- have a family history of preeclampsia or hypertension
- have had a previous pregnancy complicated by a hypertensive disorder
- have clinical risk factors such as chronic hypertension, diabetes, obesity, kidney disease or autoimmune disease
- are in their first pregnancy, are of advanced maternal age or are expecting more than one baby

For clinicians and specialists

Il test consente di:

- affiancare ai fattori clinici un'informazione sulla componente genetica materna del rischio;
- approfondire il colloquio preconcezionale e la valutazione del primo trimestre;
- considerare il profilo genetico, insieme ai dati clinici, nella pianificazione della sorveglianza;
- discutere con la paziente un risultato chiaro, supportato da una documentazione tecnica dedicata.

When to consider testing

Before conception

During pregnancy planning, to gain further insight into the mother's genetic predisposition—even before conception.

In early pregnancy

During the first few weeks, as part of the obstetric assessment and first-trimester screening.

After a complicated pregnancy

In preparation for a new pregnancy, following a previous hypertensive disorder of pregnancy.

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07 THE TESTING PROCESS

From sample to report

From sample collection to discussing the result with the specialist, every stage follows a defined process.

1	**Consultation**	The clinician explains the purpose and limitations of the test and obtains informed consent for genetic analysis.
2	**Sample collection**	Collection of buccal mucosa cells or a peripheral blood sample from the patient.
3	**DNA extraction and preparation**	Genomic DNA is extracted and checked for quality. Target regions containing the variants are amplified by PCR.
4	**Sequencing and genotyping**	The selected regions are analyzed by next-generation sequencing (NGS) to determine the genotypes.
5	**Bioinformatics analysis**	The laboratory aligns the sequence data to the reference genome, verifies the genotypes and calculates the risk score using a proprietary algorithm.
6	**Report and technical report**	The predisposition profile is presented in a personalized report for discussion with an obstetrician or maternal–fetal medicine specialist.

What you receive

Test report

The report presents the test result and assigned risk category in an easy-to-read format.

Technical report

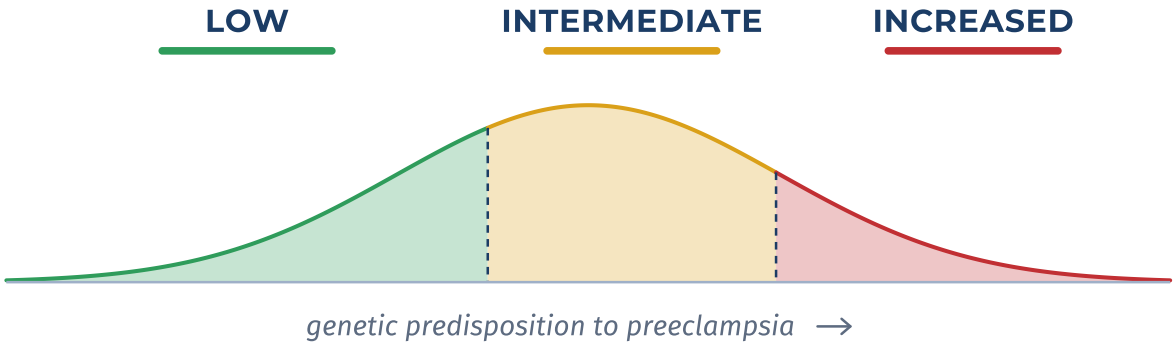
It explains the clinical context, scientific evidence, genes and variants analyzed, interpretation criteria and test limitations.

TURNAROUND TIME — **approximately 10 working days**

08 THE REPORT

Possible results

The polygenic score combines the genotypes identified and assigns the individual profile to one of three risk categories defined by the model.



RESULT	WHAT THE RESULT MEANS
INCREASED RISK	Indicates a higher-than-average genetic predisposition, associated with an increased risk of preeclampsia or gestational hypertension. The result should be discussed with a specialist to determine the most appropriate monitoring based on the overall risk profile.
INTERMEDIATE RISK	Indicates a moderate increase in risk, to be interpreted in conjunction with the medical history and other individual risk factors.
LOW RISK	Indicates a below-average risk. Routine obstetric check-ups recommended as part of standard prenatal care remain necessary. This result does not rule out preeclampsia or other pregnancy complications.

HOW TO READ THE RESULT

The **PREECLARISK** result should be interpreted in conjunction with the patient's medical and obstetric history, blood pressure readings and, when available, first-trimester screening results. Decisions regarding monitoring should be based on an overall risk assessment.

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09 USE IN CLINICAL CARE

PREECLARISK in the obstetric care pathway

PREECLARISK provides genetic information alongside standard prenatal assessments.

Medical history and clinical factors

Pregnancy and family history, maternal age, body mass index, blood pressure and pre-existing conditions.

First-trimester screening

When indicated and available, screening uses mean arterial pressure, uterine artery Doppler, PlGF and, in some models, PAPP-A.

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Maternal genetic predisposition summarized in a polygenic score and reported in one of three categories.

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Assessment by an obstetrician or maternal–fetal medicine specialist

↓

Prenatal monitoring based on the overall risk profile

Clinical management during pregnancy

Angiogenic biomarkers

When preeclampsia is suspected, sFlt-1 and PlGF measurements can help guide clinical assessment according to applicable protocols. They provide information that complements the genetic result.

Preventive treatment

In women at high risk, low-dose aspirin started early in pregnancy reduces the incidence of preterm preeclampsia. Prescribing follows clinical assessment and guidelines. A genetic result alone cannot guide a decision to start, stop or change treatment.

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10 TEST BENEFITS

Why choose PREECLARISK

A clear genetic risk profile with supporting information to discuss with your specialist.

For clinicians and specialists

- **A more complete assessment.** Maternal genetic predisposition to consider alongside clinical risk factors.
- **Scientific evidence.** Markers selected from large genome-wide studies and meta-analyses of hypertensive disorders of pregnancy.
- **Clear results.** Three risk categories and a technical report to guide interpretation.
- **Transparent reporting.** The documentation lists genes, variants, interpretation criteria and limitations.
- **Clinical context.** Results to consider alongside screening, follow-up and specialist assessment.

For patients

- **Simple collection.** Sample of epithelial cells via buccal swab, or a sample of peripheral blood.
- **Maternal sample only.** Testing requires no invasive fetal procedures.
- **Lasting information.** Constitutional DNA is generally stable, so the test usually needs to be performed only once.
- **Better understanding.** Knowing your genetic predisposition helps you discuss your risk profile with your clinician.
- **Care planning together.** Your specialist interprets the result and considers it when planning follow-up.

Key features

Evidence
Markers drawn from studies of hundreds of thousands of women.

Simplicity
Can be performed using a buccal mucosa cell sample or a peripheral blood sample

Clear results
Three risk categories for a clear interpretation of the results.

Transparency
Documented interpretation criteria and limitations.

REFERENCES

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GENOMICA
Next Generation Genetics

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Genetic testing for predisposition to preeclampsia and hypertensive disorders of pregnancy

PreeclaRisk M A4 ENG rev.00

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Visit the website dedicated to the test