GENOMICA
Next Generation Genetics

An innovative genetic test to predict TESE outcome in non-obstructive azoospermia

Identifies the genetic causes of NOA and estimates the probability of sperm retrieval

FERTILADVANCE

TESE

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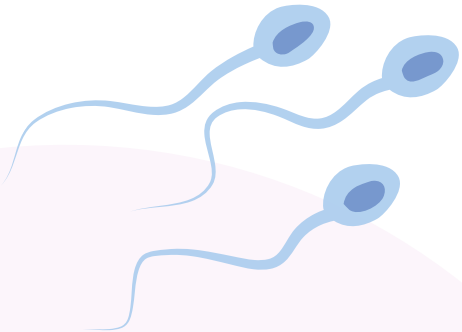
AZOOSPERMIA AND NOA

Azoospermia—defined as the absence of spermatozoa in the ejaculate—is the most severe form of male infertility and affects approximately **1%** of the male population.

Etiological classification:

- **Obstructive azoospermia (OA):** sperm production is preserved, but an obstruction of the seminal tract prevents sperm from reaching the ejaculate.
- **Non-obstructive azoospermia (NOA):** a primarily testicular disorder, with quantitative/qualitative impairment of spermatogenesis up to complete absence of spermatozoa in the ejaculate.



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NOA: WHY THIS MATTERS FOR THE SPECIALIST

In clinical practice, NOA is among the most challenging conditions in male infertility management. In many patients, the only option to obtain gametes suitable for ART (ICSI) is **surgical testicular sperm retrieval** via **TESE/micro-TESE**, which nevertheless fails in a substantial proportion of cases (≈**50%** in idiopathic series).

Clinical-hormonal parameters and first-line genetic tests (karyotype, Y-chromosome **AZF microdeletions**) provide limited prognostic value, except for selected conditions (e.g., complete **AZFa** or **AZFb/bc** deletions).

In recent years, *Next Generation Sequencing* (**NGS**) has enabled the identification of monogenic determinants of NOA and, crucially, the correlation of specific genes with the likelihood of sperm retrieval.

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WHAT IS FERTILADVANCE TESE

FERTILADVANCE TESE is an advanced genetic test designed to identify the genetic causes of NOA and to estimate the probability of sperm retrieval, providing prognostic stratification of TESE/micro-TESE outcome.

Main purposes

1. **Molecular diagnosis**
   Identification of **monogenic causes** associated with NOA/spermatogenic failure through the analysis of **200+ genes** involved in key spermatogenic pathways (meiosis, recombination, chromosomal synapsis, germ cell maturation, flagellar structure, etc.).

2. **TESE prognostic stratification** (pre-TESE or after failed TESE)
   In the presence of pathogenic variants in specific genes with evidence supporting TESE−/TESE+ association:

   - **TESE-negative (very unfavorable prognosis):** genes consistently associated with failed retrieval in carriers of pathogenic variants → may support avoiding repeated invasive procedures with an unfavorable risk/benefit ratio.
   - **TESE-positive:** genes compatible with residual sperm production and possible (variable) retrieval → TESE/micro-TESE may be clinically justified, with outcome influenced by the specific gene, phenotype, and/or histology.

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GENES ASSOCIATED WITH TESE-NEGATIVE OUTCOMES AND CLINICAL IMPLICATIONS

By integrating multicentre cohorts and the scientific literature, genes have been identified in which **pathogenic** variants are recurrently associated with **failed sperm retrieval** (**TESE-negative**).

Main genes associated with TESE-negative outcomes in carriers of pathogenic variants:

C1orf146, DMRT1, FANCA, KCTD19, LUZP4, MCM9, MEI1, MEIOB, MSH4, PSMC3IP, RAD21L1, SCML1, SHOC1, STAG3, SYCE1, TERB1, TEX11, TEX14, ZMYM5

Many of these genes encode proteins essential for **meiosis and recombination** (chromosomal synapsis, crossing-over, DNA repair) or for early **germ-cell progression**. Defects in these pathways may result in **severe maturation arrest** and absence of mature germ cells available for retrieval.

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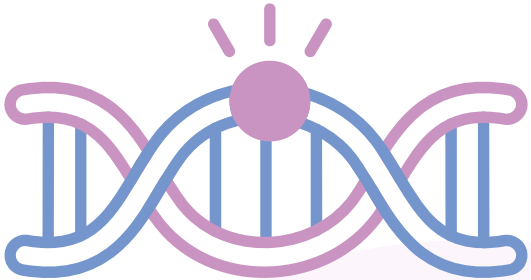
Clinical implications

A pathogenic variant in these genes is indicative of a **very low likelihood** of sperm retrieval by TESE—**close to zero** for some genes (e.g., **TEX11**, **SYCE1**, **MSH4**).

In these cases, clinical counseling may include:

- discussion of whether to avoid repeated invasive procedures with low expected benefit;
- consideration of **alternative strategies** (e.g., **male donor sperm**), according to patient preferences and the clinical-legal context.



Riera-Escamilla et al. Genetic determinants of testicular sperm extraction outcomes: insights from a large multicentre study of men with non-obstructive azoospermia. Hum Reprod Open. 2025 Aug 29;2025(3):hoaf049.

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GENES ASSOCIATED WITH TESE-POSITIVE OUTCOMES AND CLINICAL IMPLICATIONS

Genes have also been identified in which pathogenic variants are compatible with **residual sperm production** and therefore with a possibility of retrieval (**TESE-positive**).

Main genes associated with TESE-positive outcomes in carriers of pathogenic variants:

ADAD2, AR, BCORL1,
DCAF12L1, FATE1, M1AP, MLH3,
PASD1, RBBP7, SYCP3, UBR2

Clinical implications

- A pathogenic variant in these genes does not rule out sperm retrieval and suggests partially preserved or intermittent spermatogenesis: **TESE/micro-TESE may be clinically justified**, with variable success.
- Retrieval probability may be **gene-dependent** and influenced by clinical/histological factors: for some genes, success has been reported in up to approximately **half of cases**, whereas for others the probability remains **low but not null**.

Riera-Escamilla et al. Genetic determinants of testicular sperm extraction outcomes: insights from a large multicentre study of men with non-obstructive azoospermia. Hum Reprod Open. 2025 Aug 29;2025(3):hoaf049.

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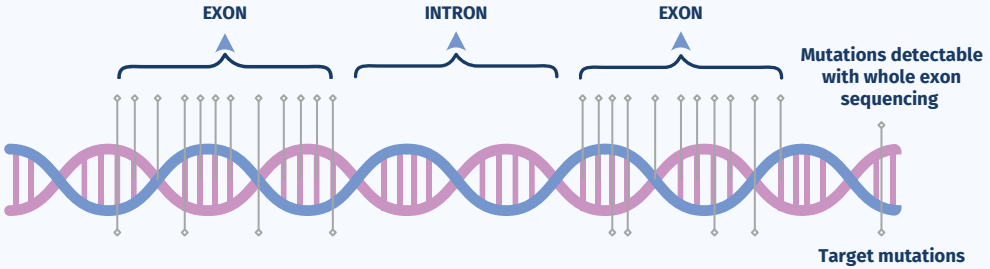
TECHNOLOGY: HIGH-RESOLUTION SEQUENCING AND ADVANCED BIOINFORMATICS

FERTILADVANCE TESE everages next-generation **NGS** with **whole exon sequencing** of the investigated genes, followed by advanced bioinformatic analysis.

Advantage over "target" tests: it does not focus only on selected mutations, but enables identification of **any variant** within the sequenced regions.



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TEST RESULTS

Positive: pathogenic variant detected

- Supports the molecular diagnosis of NOA/spermatogenic failure.
- If detected in TESE−/TESE+ genes, contributes to prognostic assessment and clinical decision-making.

Negative: no pathogenic variant detected

- Does not exclude a genetic basis for NOA, given its high genetic heterogeneity and the possibility of variants in regions not interrogated.
- Clinical decisions should be based on the overall andrological evaluation.

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INDICATIONS FOR TESTING

- **NOA** after comprehensive andrological work-up and exclusion of obstructive causes.
- NOA with non-informative first-line testing (**karyotype**, **AZF**).
- **Pre-TESE evaluation** for prognostic counseling and clinical decision-making.
- **Previous TESE-negative result** for etiologic reassessment and re-definition of reproductive strategy.
- Severe oligozoospermia/cryptozoospermia when considering surgical retrieval and/or fertility preservation.
- Need for **reproductive genetic counseling** (TESE/ICSI, cryopreservation, alternatives).

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A SIMPLE, STEP-BY-STEP WORKFLOW

Kit request

Completion of kit documentation

Sample collection

Sample shipment

Report delivery

Turnaround time **15 days**

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Leading diagnostic laboratory and research center of excellence specializing in genetics and molecular diagnostics.

GENOMICA is a highly innovative company with extensive technical and scientific expertise, active in both clinical applications and research. Supported by a team with over 20 years of experience in molecular diagnostics, GENOMICA combines cutting-edge technology with a strong commitment to innovation, delivering increasingly accurate and accessible diagnostic services.

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Dedicated **R&D Team**

International **Partnerships**

Personalized genetic counseling with genetic counselors experts in discussing genetic test results and familial risks

20+ years experience in prenatal molecular diagnostics

FertilAdvance TESE ENG rev.00

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