Genetic tests for reproduction
Explained

2025

PRECONCEPTION

Karyotype (chromosomal analysis) examines the number and structure of chromosomes in cells. Individuals experiencing fertility issues have a higher chance of presenting numerical or structural chromosomal abnormalities.
Chromosomal analysis can be useful to identify the cause of infertility and provide couples with several reproductive options, including preimplantation genetic testing for aneuploidies (PGT-A) or structural rearrangements (PGT-SR), gamete donation, or adoption.

ESHRE Guideline Group on RPL; Bender Atik R, Christiansen OB, Elson J, Kolte AM, Lewis S, Middeldorp S, Mcheik S, Peramo B, Quenby S, Nielsen HS, van der Hoorn ML, Vermeulen N, Goddijn M. ESHRE guideline: recurrent pregnancy loss: an update in 2022. Hum Reprod Open. 2023 Mar 2;2023(1):hoad002. doi: 10.1093/hropen/hoad002. PMID: 36873081; PMCID: PMC9982362.

Carrier screening allows the assessment of the reproductive risk for a selection of autosomal recessive and X-linked conditions. Carriers for these conditions are generally asymptomatic and may have no previous family history, but may transmit the condition to their offspring in certain circumstances. It is estimated that 1–2 in 100 couples are at increased risk for these conditions. Carrier screening is recommended during the preconception stage to help couples or individuals make informed reproductive decisions when a risk is identified. Carrier screening tests can be targeted or universal. Targeted carrier screening is based on an individual's family history or for diseases with a higher prevalence in certain populations (i.e beta-thalassaemia in Cyprus or Tay-Sachs disease in Ashkenazi). Universal carrier screening, enables the simultaneous screening for multiple genetic disorders regardless of ancestry or geographic origin.

Henneman L et al., Responsible implementation of expanded carrier screening. Eur J Hum Genet. 2016 Jun;24(6):e1–e12. doi: 10.1038/ejhg.2015.271. Epub 2016 Mar 16. Erratum in: Eur J Hum Genet. 2017 Nov;25(11):1291.

Committee Opinion No. 690.Summary:. Carrier screening in the age of genomic medicine. Obstet Gynecol 2017;129:e35–40. doi:10.1097/AOG.0000000000001947Gregg AR et al., ACMG Professional Practice and Guidelines Committee. Screening for autosomal recessive and X-linked conditions during pregnancy and preconception: a practice resource of the American College of Medical Genetics and Genomics (ACMG). Genet Med. 2021 Oct;23(10):1793–1806).

Fragile X premutation testing analyses the FMR1 gene, located on the X chromosome, to assess the number of CGG repeats. Women who carry a premutation (55–200 CGG repeats) in FMR1 have an increased risk of developing a condition known as Fragile-X related primary ovarian insufficiency (FXPOI), characterised by a decreased ovarian function at a young age. About 20% of female premutation carriers may experience FXPOI. ESHRE's guidelines on the management of women with POI suggests that "Fragile-X premutation testing is indicated in all women diagnosed with POI".

European Society for Human Reproduction and Embryology (ESHRE) Guideline Group on POI; Webber L, Davies M, Anderson R, Bartlett J, Braat D, Cartwright B, Cifkova R, de Muinck Keizer-Schrama S, Hogervorst E, Janse F, Liao L, Vlaisavljevic V, Zillikens C, Vermeulen N. ESHRE Guideline: management of women with premature ovarian insufficiency. Hum Reprod. 2016 May;31(5):926–37. doi: 10.1093/humrep/dew027. Epub 2016 Mar 22. PMID: 27008889.

Cystic fibrosis (CF) testing is suggested for men with idiopathic obstructive azoospermia as recommended by the AUA/ASRM joint guideline. Moreover, patients with congenital bilateral absence of the vas deferens (CBAVD) can also benefit from this testing as variants in the cystic fibrosis transmembrane conductance (CFTR) gene are found in up to 80% of men with this condition.

Schlegel, P. N., Sigman, M., Collura, B., De Jonge, C. J., Eisenberg, M. L., Lamb, D. J., Mulhall, J. P., Niederberger, C., Sandlow, J. I., Sokol, R. Z., Spandorfer, S. D., Tanrikut, C., Treadwell, J. R., Oristaglio, J. T., & Zini, A. Diagnosis and treatment of infertility in men: AUA/ASRM guideline part I,. Fertility and Sterility, 2021, Volume 115, Issue 1, 54 – 61.

Y chromosome microdeletion testing examines a region within the Y chromosome, known as the azoospermia factor (AZF), which contains genes that are responsible for the production of spermatozoa in men. Y chromosome microdeletions have a high incidence in infertile men and testing is recommended for individuals with azoospermia (absence of sperm) or oligozoospermia (low sperm count).

Krausz C, Navarro-Costa P, Wilke M, Tüttelmann F. EAA/EMQN best practice guidelines for molecular diagnosis of Y-chromosomal microdeletions: State of the art 2023. Andrology. 2023 Sep 6. doi: 10.1111/andr.13514. Epub ahead of print. PMID: 37674303.

PREIMPLANTION

Preimplantation genetic testing (PGT) allows the genetic analysis of embryos that have been generated through medically assisted reproduction (MAR) procedures. Usually, PGT examines a small number of cells biopsied from the extra-embryonic portion of developing embryos at day 5–7 post fertilization. PGT can have different purposes:

1. **Aneuploidies (PGT-A):** PGT-A is used to identify numerical chromosomal abnormalities (aneuploidies) in embryos before they are transferred to the uterus. This testing helps detect abnormalities that could compromise developmental potential or result in chromosomally abnormal pregnancies, potentially leading to miscarriages. Indications for PGT-A include advanced maternal age (AMA), recurrent implantation failure (RIF), severe male factor (SMF) and couples with normal karyotypes who have experienced recurrent miscarriage (RM).

   ESHRE PGT-SR/PGT-A Working Group; Coonen E, Rubio C, Christopikou D, Dimitriadou E, Gontar J, Goossens V, Maurer M, Spinella F, Vermeulen N, De Rycke M. ESHRE PGT Consortium good practice recommendations for the detection of structural and numerical chromosomal aberrations. Hum Reprod Open. 2020 May 29;2020(3):hoaa017. doi: 10.1093/hropen/hoaa017. PMID: 32500102; PMCID: PMC7257111.,

   ESHRE Working Group on Recurrent Implantation Failure; Cimadomo D, de Los Santos MJ, Griesinger G, Lainas G, Le Clef N, McLernon DJ, Montjean D, Toth B, Vermeulen N, Macklon N. ESHRE good practice recommendations on recurrent implantation failure. Hum Reprod Open. 2023 Jun 15;2023(3):hoad023. doi: 10.1093/hropen/hoad023. PMID: 37332387; PMCID: PMC10270320.

2. **Structural rearrangements (PGT-SR):** PGT-SR is used to test embryos resulting from couples where one or both partners carry a structural rearrangement. The most frequent structural rearrangements include: reciprocal translocations, Robertsonian translocations and inversions. The purpose of this test is to identify embryos that are chromosomally normal or have inherited the balanced rearrangement from their parent.

   ESHRE PGT-SR/PGT-A Working Group; Coonen E, Rubio C, Christopikou D, Dimitriadou E, Gontar J, Goossens V, Maurer M, Spinella F, Vermeulen N, De Rycke M. ESHRE PGT Consortium good practice recommendations for the detection of structural and numerical chromosomal aberrations. Hum Reprod Open. 2020 May 29;2020(3):hoaa017. doi: 10.1093/hropen/hoaa017. PMID: 32500102; PMCID: PMC7257111.

3. **Monogenic disorders (PGT-M):** PGT-M is used to test for the transmission of inherited genetic conditions in the embryos. PGT-M is an option for those patients at risk of transmitting an autosomal dominant, autosomal recessive or X-linked condition to their children. PGT-M is also used to test for pathogenic variants in mitochondrial DNA (mtDNA), as well as for human leukocyte antigen (HLA) typing.

   ESHRE PGT-M Working Group; Carvalho F, Moutou C, Dimitriadou E, Dreesen J, Giménez C, Goossens V, Kakourou G, Vermeulen N, Zuccarello D, De Rycke M. ESHRE PGT Consortium good practice recommendations for the detection of monogenic disorders. Hum Reprod Open. 2020 May 29;2020(3):hoaa018. doi:10.1093/hropen/hoaa018. PMID: 32500103; PMCID: PMC7257022.

   ESHRE PGT Consortium Steering Committee; Carvalho F, Coonen E, Goossens V, Kokkali G, Rubio C, Meijer-Hoogeveen M, Moutou C, Vermeulen N, De Rycke M. ESHRE PGT Consortium good practice recommendations for the organisation of PGT. Hum Reprod Open. 2020 May 29;2020(3):hoaa021. doi: 10.1093/hropen/hoaa021. PMID: 32524036; PMCID: PMC7257038.

PRENATAL

Fetal genetic evaluation during pregnancy is especially relevant for high-risk cases or following MAR procedures. Prenatal testing can be divided into:

Non-invasive prenatal testing (NIPT): It is applied on fetal DNA (cell free DNA) that circulates in the maternal blood. Sampling can be performed as early as the 10th week of pregnancy. NIPT can be used to examine the numeric chromosomal alterations that might lead to the birth of babies with certain chromosome syndromes (like Down Syndrome, which occurs when a baby gets three copies of chromosome 21). NIPT may also be used to test for certain monogenic disorders or for the confirmation of PGT-A results. Despite NIPT's high sensitivity and specificity, this is a screening test for common fetal aneuploidies and it is not considered a diagnostic test.

American College of Obstetricians and Gynecologists' (ACOG) clinical recommendations for Screening for Fetal Chromosomal Abnormalities (ACOG Practice Bulletin No. 226. American College of Obstetricians and Gynecologists. Obstet Gynecol 2020;136:e48–69, Hui, L., Ellis, K., Mayen, D., Pertile, M.D., Reimers, R., Sun, L., Vermeesch, J., Vora, N.L. and Chitty, L.S. (2023)

Position statement from the International Society for Prenatal Diagnosis on the use of non-invasive prenatal testing for the detection of fetal chromosomal conditions in singleton pregnancies. Prenatal Diagnosis, 43: 814–828. https://doi.org/10.1002/pd.6357

Invasive prenatal testing: genetic test performed on fetal samples obtained via invasive techniques, which include: chorionic villus sampling (CVS) performed between the 11th and 14th week of gestation on placental tissue (chorionic villi); amniocentesis, performed between the 15th and 20th week of gestation on amniotic fluid surrounding the fetus; and fetal blood (FB) sampling, performed after the 18th week of gestation. Indications for invasive prenatal testing may include increased risk in NIPT, couples' medical history, AMA, parental anxiety and pregnancies conceived through MAR. Depending on the medical indication, various genetic tests can be performed on the obtained prenatal sample:

1. **Chromosomal analysis:** It can be performed by two separate tests: Quantitative fluorescent PCR (QF-PCR) and karyotyping. More specifically, QF-PCR allows rapid detection of the most frequent chromosomal number alterations (involving chromosomes 13, 18, 21, X and Y). These numeric abnormalities are often compatible with life but can lead to severe genetic disorders. Karyotyping assesses both numerical and structural variations in all 46 chromosomes.
2. **Copy number variations and single nucleotide polymorphisms (SNP):** Array-comparative genome hybridization (array-CGH) for the detection of submicroscopic copy number or SNP-array o identify SNPs which can also be causative of severe genetic disorders.
3. **Gene sequencing:** direct mutation testing, gene panels, exome sequencing or genome sequencing for the investigation of gene mutations that are linked to malformations in the fetus and are associated with genetic conditions.

Van den Veyver IB, Chandler N, Wilkins-Haug LE, Wapner RJ, Chitty LS. International Society for Prenatal Diagnosis Updated Position Statement on the use of genome-wide sequencing for prenatal diagnosis. Prenat Diagn. 2022; 42(6): 796–803. https://doi.org/10.1002/pd.6157

Note: Due to national regulations, test availability and characteristics may vary. A referral letter from a specialist or scientific board approval might be necessary.