# From Here to Fertility: Preconception Genetic Testing for The Infertile Couple

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N°1 FERTILITY

# Background

- Preconception genetic screening can vary significantly between countries, clinics and clinicians, impacting PGT pathways
- Many infertile couples are not routinely offered relevant preconception genetic testing options
- Clinical guidelines and recommendations vary regarding preconception genetic testing
- Objective: To highlight the clinical utility of baseline karyotype analysis and importance of routine reproductive genetic carrier screening to the infertile couple seeking ART treatment

# Preconception test types

Reproductive Genetic Carrier Screening (RGCS)

- Identifies carriers of genetic disorders within the general population
- Helps assess the risk of passing on genetic conditions to offspring

Karyotypes

- Examination of chromosomes to detect abnormalities
- Aids in diagnosing genetic disorders and infertility issues

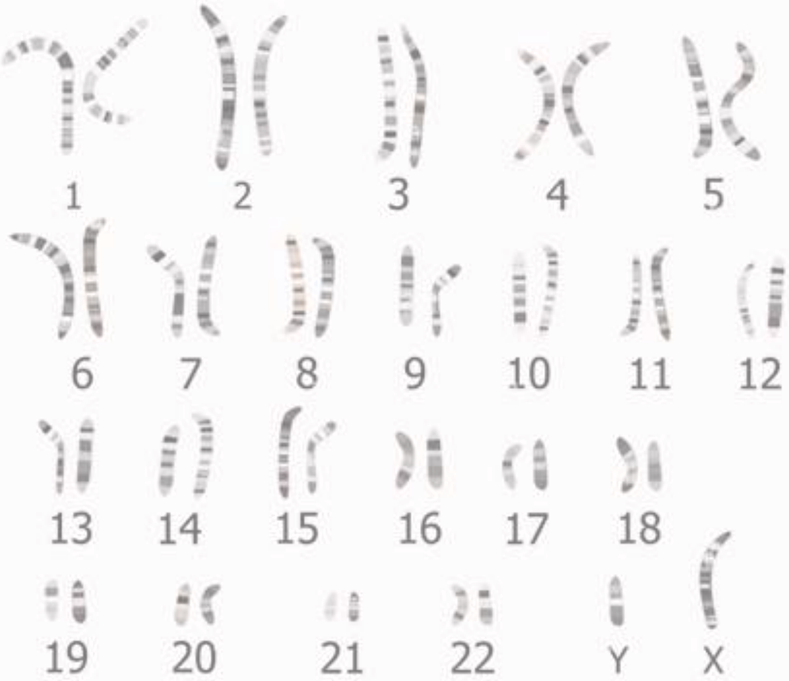
Targeted Investigations

- Tailored tests based on clinical presentation
- Examples:
  - Y chr microdeletions for non-obstructive azoospermia
  - CFTR for non-obstructive azoospermia
  - FXS for Primary Ovarian Insufficiency (POI)

# Reproductive genetic carrier screening

- Currently widely accessible in Australia
- The Australian Government introduced health care rebates for carrier screening of 3 genes (CF, SMA, FXS) for reproductive females from November 1, 2023, improving accessibility and awareness
- This has led to a higher occurrence of carrier and at-risk couple findings
- Research indicates that 2-4% of couples undergoing expanded panel screening may receive elevated risk outcomes, varying based on the gene panel and variant interpretation

# Karyotype analysis




- Commonly accepted indication: 3+ miscarriages (some variability)
- Traditional approach assumes conception capacity
- Overlooks balanced rearrangements hindering conception

> Patients with balanced rearrangements struggle to conceive

> Estimated 0.3-0.5% in general population

> Karyotype analysis often delayed until multiple failed transfers (RIF) or miscarriages (RPL)

Karyotypes as routine pre-treatment investigation

- Ensures early detection and tailored interventions
- Underscores importance of systematic screening
- Australian-specific experience: Cost of karyotype analysis is covered/significantly subsidised by Medicare

# What do the international guidelines say?

# Indications and management of preimplantation genetic testing for monogenic conditions: a committee opinion

Practice Committee and Genetic Counseling Professional Group of the American Society for Reproductive Medicine, American Society for Reproductive Medicine, Washington, D.C.

The Royal Australian and New Zealand College of Obstetricians and Gynaecologists

*Excellence in Women's Health*

# Genetic carrier screening

eshre

SCIENCE MOVING PEOPLE MOVING SCIENCE

# Management of women with premature ovarian insufficiency

**Human Reproduction Open, pp. 1–15, 2021**
doi:10.1093/hropen/hoaa063

human reproduction open

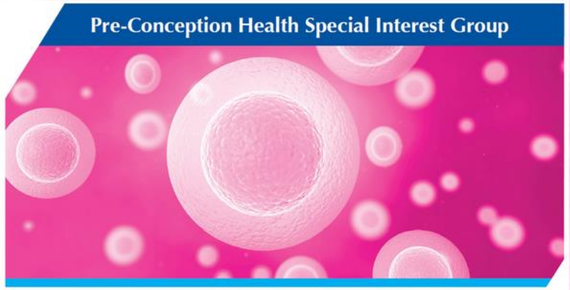
ESHRE PAGES

# The ethics of preconception expanded carrier screening in patients seeking assisted reproduction

**Guido de Wert [1,*,†], Sanne van der Hout [1,†], Mariëtte Goddijn[2], Rita Vassena [3], Lucy Frith [4], Nathalie Vermeulen [5], Ursula Eichenlaub-Ritter[6], on behalf of the ESHRE Ethics Committee[‡]**

The Fertility Society of Australia


Genetics and genomics




Reproductive carrier screening

# Diagnosis and treatment of infertility in men: AUA/ASRM guideline part I

Peter N. Schlegel, M.D.,[a] Mark Sigman, M.D.,[b] Barbara Collura,[c] Christopher J. De Jonge, Ph.D., H.C.L.D.(A.B.B.),[d] Michael L. Eisenberg, M.D.,[e] Dolores J. Lamb, Ph.D., H.C.L.D.(A.B.B.),[f] John P. Mulhall, M.D.,[g] Craig Niederberger, M.D., F.A.C.S.,[h] Jay I. Sandlow, M.D.,[i] Rebecca Z. Sokol, M.D., M.P.H.,[j] Steven D. Spandorfer, M.D.,[f] Cigdem Tanrikut, M.D., F.A.C.S.,[k] Jonathan R. Treadwell, Ph.D.,[l] Jeffrey T. Oristaglio, Ph.D.,[l] and Armand Zini, M.D.[m]

[a] New York Presbyterian Hospital-Weill Cornell Medical College; [b] Brown University; [c] RESOLVE; [d] University of Minnesota School of Medicine; [e] Stanford University School of Medicine; [f] Weill Cornell Medical College; [g] Memorial-Sloan Kettering Cancer Center; [h] Weill Cornell Medicine, University of Illinois-Chicago School of Medicine; [i] Medical College of Wisconsin; [j] University of Southern California School of Medicine; [k] Georgetown University School of Medicine; [l] ECRI; and [m] McGill University School of Medicine

# Evaluation and treatment of recurrent pregnancy loss: a committee opinion

The Practice Committee of the American Society for Reproductive Medicine
American Society for Reproductive Medicine, Birmingham, Alabama

# Recurrent Pregnancy Loss

Guideline of European Society of Human Reproduction and Embryology

Update 2022
**ESHRE Recurrent Pregnancy Loss Guideline Development Group**

# Fertility evaluation of infertile women: a committee opinion

Practice Committee of the American Society for Reproductive Medicine
American Society for Reproductive Medicine, Birmingham, Alabama

- Genetic or acquired conditions that predispose to diminished ovarian reserve (e.g., chemotherapy, radiation exposure, FMR1 premutation)

An evaluation may also be indicated in some women who do not have infertility to optimize assisted reproductive technology treatments for other indications, such as recurrent pregnancy loss or genetic carrier status of an individual or couple where preimplantation genetic testing (for aneuploidy, monogenic disorders, and structural chromosomal rearrangements) is warranted. A fertility evaluation before treatment in these situations is useful.

**TABLE 3**

**Infertility tests that should not be routinely ordered, unless specifically indicated (33).**

- Laparoscopy for unexplained infertility
- Advance sperm function testing (e.g., DNA fragmentation testing)
- Postcoital testing
- Thrombophilia testing
- Immunologic testing
- Karyotype
- Endometrial biopsy
- Prolactin
- Progesterone
- Estradiol
- Follicle-stimulating hormone
- Luteinizing hormone

*ASRM. Fertility evaluation of infertile women. Fertil Steril 2021.*

OXFORD hro

*Human Reproduction Open*, 2023, **2023(3)**, hoad023
https://doi.org/10.1093/hropen/hoad023
ESHRE Pages

# ESHRE good practice recommendations on recurrent implantation failure†

ESHRE Working Group on Recurrent Implantation Failure, D. Cimadomo [1], M.J. de los Santos [2], G. Griesinger [3,4], G. Lainas [5], N. Le Clef [6], D.J. McLernon [7], D. Montjean [8], B. Toth[9], N. Vermeulen [6], and N. Macklon [10,*]

Published Online 19 June 2023
DOI: 10.1111/1471-0528.17515

RCOG GREEN-TOP GUIDELINES

BJOG An International Journal of Obstetrics and Gynaecology

# Recurrent Miscarriage

Green-top Guideline No. 17

**Lesley Regan | Rajendra Rai | Sotirios Saravelos | Tin-Chiu Li | on behalf of the Royal College of Obstetricians and Gynaecologists**

# Recurrent implantation failure: reality or a statistical mirage?

## Consensus statement from the July 1, 2022 Lugano Workshop on recurrent implantation failure

(The writing group) for the participants to the 2022 Lugano RIF Workshop, Paul Pirtea, M.D.,[a] Marcelle I. Cedars, M.D.,[b] Kate Devine, M.D.,[c] Baris Ata, M.D., M.Sc.,[d,e] Jason Franasiak, M.D.,[f] Catherine Racowsky, Ph.D.,[a] Jim Toner, M.D., Ph.D.,[g] Richard T. Scott, M.D.,[f] Dominique de Ziegler, M.D.,[a] and Kurt T. Barnhart, M.D., M.S.C.E.[h]

# Diagnosis and treatment of infertility in men: AUA/ASRM guideline part I

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# Unexplained infertility

Guideline of European Society of Human Reproduction and Embryology

2023

**Unexplained infertility Guideline Development Group**

Developed in collaboration with the Monash University led NHMRC Centre of Research Excellence in Women's Health in Reproductive Life (CREWHIRL).

CREWHiRL Centre for Research Excellence in Women's Health in Reproductive Life

Recommendation

| | | |
|---|---|---|
| Genetic or genomic tests are currently not recommended in couples with unexplained infertility. | Strong | ⊕OOO |

# International Guidelines : Carrier screening

| | Targeted | Population |
|---|---|---|
| **ASRM** | Yes<br>(CF/FMR1) | No comment |
| **ESHRE** | Yes<br>(FMR1) | Yes<br>(with ethical caution) |
| **FSANZ** | Yes | Yes |
| **ACOG** | Yes | Yes |
| **RANZCOG** | Yes<br>(ethnic) | Yes<br>(shared HGSA) |

# International Guidelines : Karyotypes

| | RPL | RIF | Infertility |
|---|---|---|---|
| ASRM | Yes | No comment | No |
| ESHRE | Yes | Yes | No |
| FSANZ | Yes | Yes | No comment |
| ACOG | Yes | No comment | No (shared ASRM) |
| RANZCOG | Yes (shared RCOG) | No comment | No comment |

# The experience at No.1 Fertility

Retrospective cohort study at No.1 Fertility

Duration: Data collected from 2018 to 2023 (n=293)

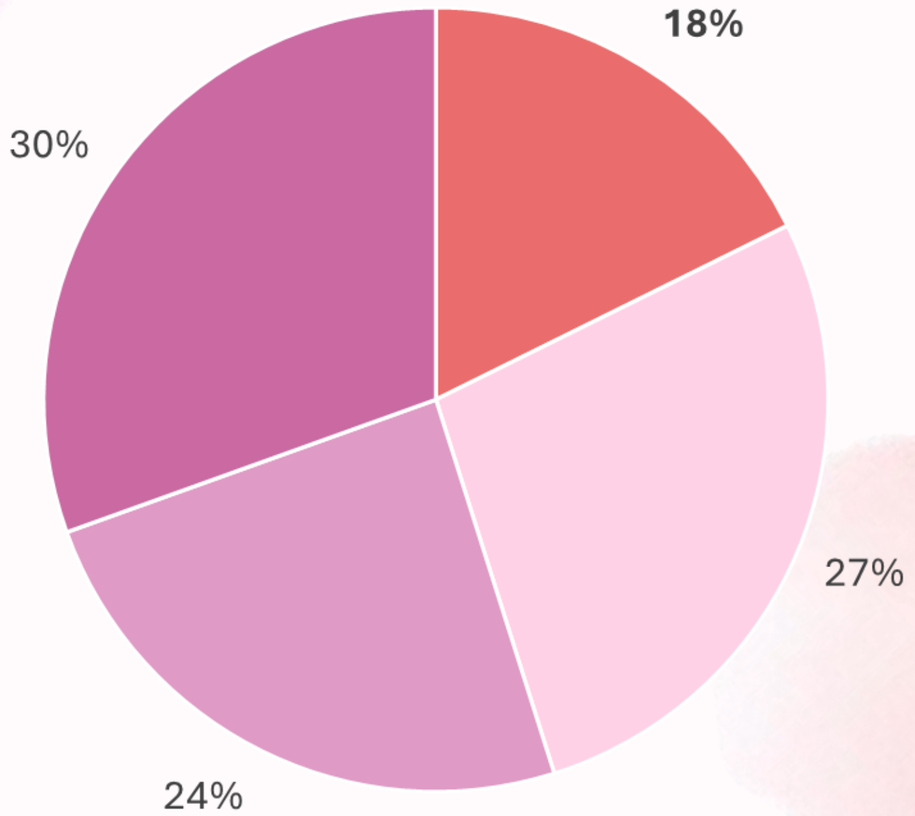
Main Cohorts:

- Patients seeking PGT-SR
- Patients seeking PGT-M

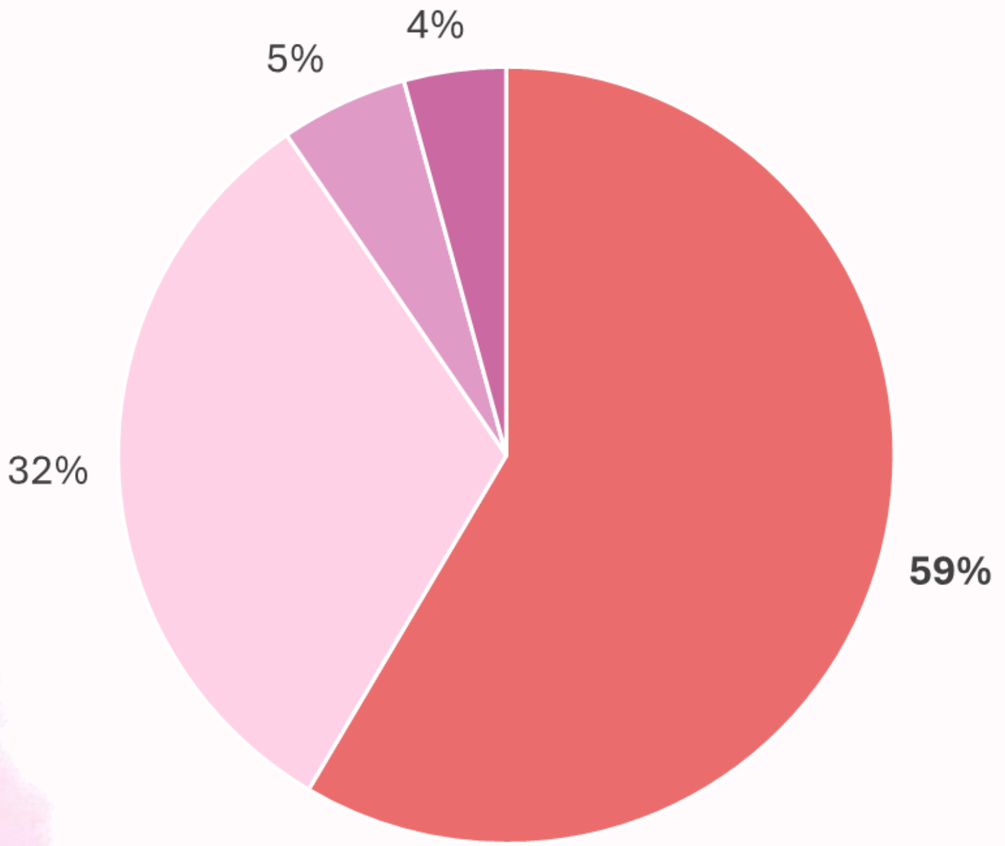
Analysis Methods:

- Descriptive statistics for variation measures
- Chi-square test for proportions ($P < 0.05$ significance level)

# Indications for PGT-M (n=164)



# Indications for PGT-SR (n=129)



| | |
|---|---|
| 45,XX,der(13;14)(q10;q10) | routine karyotype |
| 46,XX,t(12;14)(q22;p10) | affected pregnancy/child |
| 46,XX,t(2;9)(q32.2;q32) | personal history |
| 46,XX,t(2;7)(q13;p13) | personal history |
| 46,XY,t(8;10)(p23.3;p11.2) | routine karyotype |
| 45,XY,der(13;14)(q10;q10) | family history |
| 46,XY,t(1;5)(q21;q13.1) | personal history |
| 46,XX,t(9;15)(p24;q21.3) | personal history |
| 45,XY,der(13;14)(q10;q10) | routine karyotype |
| 46,XX,t(4;8)(p12;q24.1) | personal history |
| 45,XY,rob(13;14)(q10;q10) | family history |
| 46,XY,t(3;11)(p25;p15.3) | routine karyotype |
| 45,XY,der(13;14)(q10;q10) | personal history |
| 46,XY,t(9;15)(q32;q25) | routine karyotype |
| | |
| 46,XX,t(3;6)(q25.3;q21) | routine karyotype |
| 45,XX,der(13;14)(q10;q10) | personal history |
| 46,XX,t(7;11)(q32;p13) | routine karyotype |
| 46,XX,t(1;10)(q32.3;q22.3) | routine karyotype |

| | |
|---|---|
| 46,Y,t(X;10)(q27;q24.3) | personal history |
| 46,XX,t(5;7)(q35.1;q32) | routine karyotype |
| 46,XX,t(4;18)(q31.23;q21.2) | affected pregnancy/child |
| 46,XX,t(7;18)(p13;q21.1) | personal history |
| 46,Y,t(X;4)(p11.23;p14) | personal history |
| | |
| 46,XY,t(19;21)(q12;p12) | personal history |
| 46,XX,der(13;14)(q10;q10) | personal history |
| 46,XX,t(11;19)(p15.5;p13.1) | personal history |
| 46,XX,t(5;14)(q11.2;q11.2) | routine karyotype |
| 46,XX,inv(3)(p25q23) | personal history |
| 46,XY,inv(17)(p11.2q21.3) | routine karyotype |
| 46,XX,t(12;16)(q24.33;q11.1) | routine karyotype |
| 46,XY,t(14;22)(q13;q13.3) | routine karyotype |
| 45,XY,der(13;15)(q10;q10) | routine karyotype |
| 45,XY,der(13;14)(q10;q10) | routine karyotype |
| 46,XY,t(4;13)(q31.2;q21.2) | personal history |

| | |
|---|---|
| 46,XY,t(4;13)(q31.2;q21.2) | personal history |
| 46,XX,t(4;8)(q23;q21.2) | routine karyotype |
| 46,XX,t(5;17)(q33.3;p12) | routine karyotype |
| 46,XY,t(2;17)(p23;q11.2) | routine karyotype |
| 46, XX, t(3;9)(q25.3;q13) | family history |
| 46,XY,t(15;18)(q26.3;q12.1) | affected pregnancy/child |
| 46,XY,t(3;4)(q26.2;q33) | personal history |
| 46,XX,t(19;22)(q13.3;q11.2) | personal history |
| 46,XY,t(4;9)(q27;q22.3) | personal history |
| 45,XY,der(13;14)(q10;q10) | family history |
| | |
| 46,XX,inv(5)(q22;q31.1) | routine karyotype |
| 45,XY,der(13;14)(q10;q10) | routine karyotype |
| 46,XX,t(12;20)(q24.1;p13) | personal history |
| 45,XX,der(13;14)(q10;q10) | routine karyotype |
| 46,XX,t(4;9)(q25;q32) | routine karyotype |
| 46,XX,t(2;11)(q11.2;q13.3) | routine karyotype |
| 46,XX,t(8;11)(q24.13;q23.3) | personal history |
| 46,XX,t(4;9)(q31.3;p24) | personal history |

| | |
|---|---|
| 46,XY,t(9;20)(p22,p12.2) | personal history |
| 46,XY,t(6;9)(p21.1;q21.2) | routine karyotype |
| 46,XY,t(11;20)(p11.2;q13.3) | routine karyotype |
| 46,XX, t(2;18)(p10;q10) | routine karyotype |
| 46,XY,t(9;20)(q34.2;q11.1) | personal history |
| 46,XX,t(1;10)(p13.3;p13) | routine karyotype |
| | |
| 46,XX,t(3;9)(q25.3;q13) | personal history |
| 46,XY,t(6;22)(q12;q11.21) | personal history |
| 46,XY,t(2;20)(q13;p13) | routine karyotype |
| 45,XY,der(13;14)(q10;q10) | personal history |
| 46,XY,t(1;4)(q24;q28) | routine karyotype |
| 45,XY,der(13;14)(q10;q10) | routine karyotype |
| 46,XX,t(10;13)(p12.2;q14.3) | routine karyotype |
| 46,XY,t(11;22)(q23.3;q11.2) | routine karyotype |
| 46,XX,t(19;22)(q13.3;q12.2) | personal history |
| 46,XX,t(2;17)(q21.1;q23.1) | routine kayrotype |
| 45,XY,der(14;21)(q10;q10) | routine karyotype |

| | |
|---|---|
| Mosaic - 46,X,del(X)(p22.1)[24 | routine karyotype |
| 45,XX,der(13;14)(q10;q10) | routine karyotype |
| 46,XX,inv(10)(q22.1q25.2) | routine karyotype |
| 46,XX,t(3;14)(p22.2;q32.1) | personal history |
| 45,XX,der(14;15)(q10;q10) | routine karyotype |
| 46, XX,t(5;6)(q33.3;q23.3) | routine karyotype |
| 46,XY,t(3;6)(q21;p23) | routine karyotype |
| 46,XX,t(3;6)(q21;p25) | routine karyotype |
| 46,XY,t(8;9)(q21.2;q21.2) | routine karyotype |
| 46,XY,t(9;20)(q34.3;p11.2) | family history |
| 46,XX,t(3;4)(p13;q21.1) | routine karyotype |
| 46,XX,t(2;18)(q33;q21.1) | routine karyotype |
| 46,XY,t(17;22)(q11.2q11.2) | personal history |
| 46,XX,t(8;29)(q24.22;p13.3) | routine karyotype |
| 45,XX,der(13;14) | personal history |
| 46,XY,t(9;19)(q34.1;q13.1) | routine karyotype |
| 46, XX, t(4;20)(q21.1;p11.2) | routine karyotype |
| | |
| Mosaic - 46,XY,t(16;22)(q24;q1 | routine karyotype |

| | |
|---|---|
| 46,XY,t(6;20)(p12;q12 | routine karyotype |
| 46,XX,t(1;17)(p34.1;p12) | routine karyotype |
| 46,XX,inv(2)(p15q23) | routine karyotype |
| 46,XY,t(1;11)(p36.2;q24.2) | routine karyotype |
| 45,XY,der(13;14)(q10;q10) | routine karyotype |
| 46,XY,t(9;10)(q22.3;q24.1) | routine karyotype |
| 46,X,t(X;18)(q28;p11.2) | affected pregnancy/child |
| 45,XX,der(13;15)(q10;q10) | routine karyotype |
| | |
| 46,XY,t(9;13)(q31;q22) | routine karyotype |
| 46,XY,t(6;9)(q25.1;q32) | routine karyotype |
| 46,XY,t(8;21)(p21.1;q22.1) | routine karyotype |
| 46,XX,t(11;20)(q23.3;p12.1) | affected pregnancy/child |
| 46,XY,t(6;20)(p21.3;q11.2) | routine karyotype |
| 46,XY,inv(4)(p14q12) | routine karyotype |
| 46,XY, t(5;9)(q35.3;q22.1) | routine karyotype |
| 46,XY,inv(3)(p24.1p14. 3) | routine karyotype |

# Conclusions

- Karyotypes and Genetic Carrier Screening are vital preconception genetic tests for infertile couples exploring reproductive pathways

- Karyotype analysis should be considered as a baseline investigation for infertility

- Results from karyotypes and genetic carrier screening can drastically change the reproductive journey for these patients
  - through the identification of additional or alternate PGT options
  - may also offer a probable cause for infertility, which can be beneficial for providing closure to patients seeking reproductive treatment

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Genetic carrier screening laboratory
Reproductive genetic counselling team

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Nº1 FERTILITY