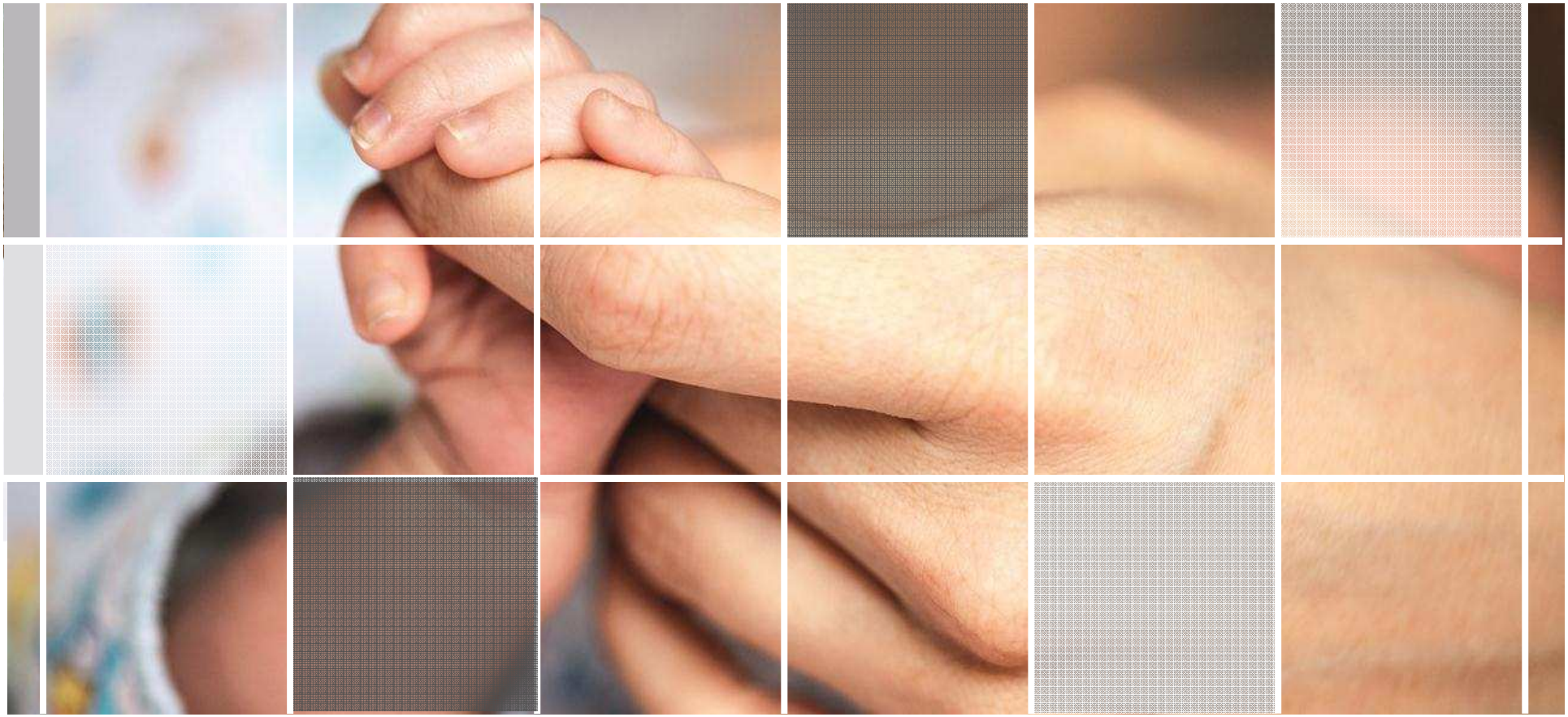


GENETICS AND REPRODUCTION:
Changing needs and possibilities

DR. MICHAEL MORRIS

synlab
lab services

Genetics and infertility

A. Age: chromosomal aneuploidy

B. Infertility: Genes and chromosomes

C. Treatment and screening

D. Recommendations and the Future

Human Reproduction, Vol.29, No.8 pp. 1603–1609, 2014
doi:10.1093/humrep/deu130

human reproduction ESHRE PAGES

Current issues in medically assisted reproduction and genetics in Europe: research, clinical practice, ethics, legal issues and policy†

EuroGentest eshre ESHG

Maternal age is increasing

María del Carmen Bousada de Lara (5.1.1940–11.7.2009)

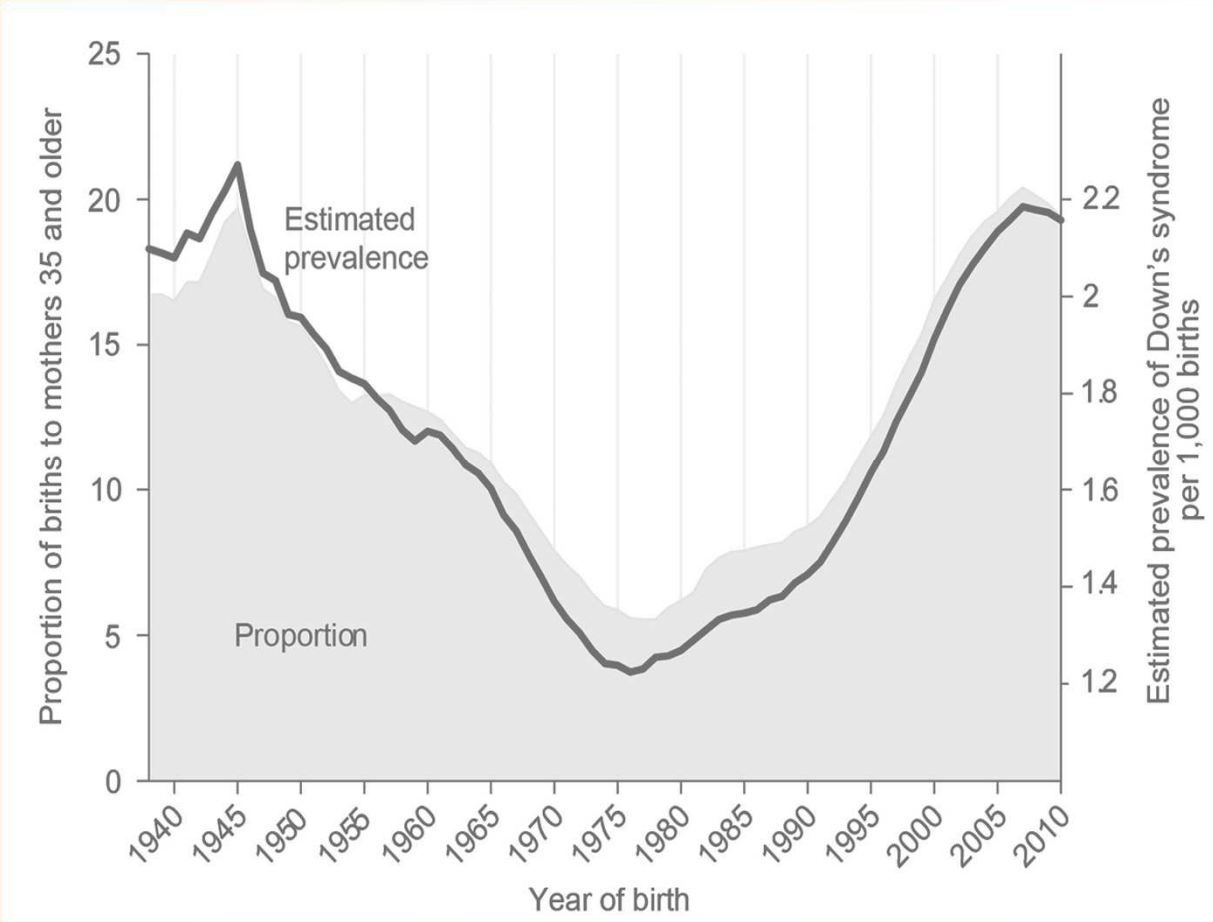
Maternal age is increasing

- Improved education
- Employment
- Insecurity

Delayed child-bearing is associated with increased risks and complications

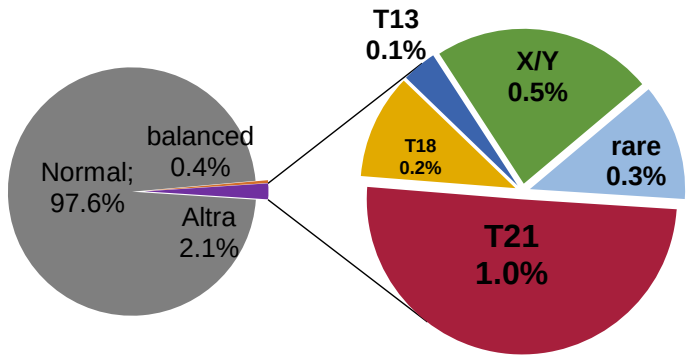
- Female fertility declines after 32 yrs
  - Live birth in 1 year: 75% at 30 yrs, 66% at 35
- Sperm quality declines with age
- Maternal and paternal age are risk factors for miscarriage
- Increased risk of aneuploidy

Or is it? Proportion of births ≥ 35 yrs



Wu & Morris, European Journal of Human Genetics (2013) 21, 943–947

Chromosomal anomalies and age

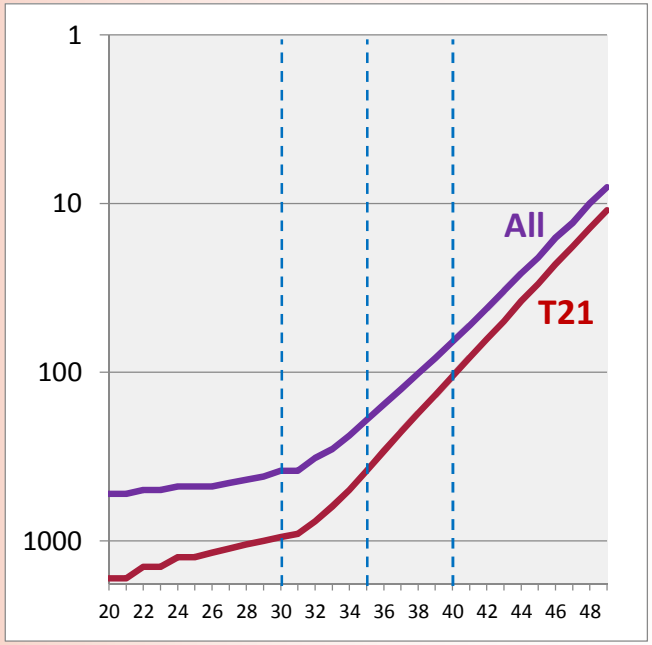


Incidence of non-age-dependent chromosomal abnormalities: a population-based study on 88965 amniocenteses

Antonino Forabosco*,[1], Antonio Percesepe[1] and Sandra Santucci[1]

The risk of aneuploidy increases with age

(ovocytes suspended for years in meiosis I)



Genetic anomalies in infertility

	Female	Male
Chromosomal anomalies		
• Numerical	XO, XXX, mosaicism	XXY
• **Structural**	X chromosome rearrangements Translocations (RPL)	Translocations (Azoo, oligo, OAT)
Genetic anomalies		
• ***AZF*** (Y microdeletions)	-	Azoo, severe oligospermia
• ***CFTR***	-	CBAVD obstructive azoo/oligospermia
• ***FMR1***	Premature ovarian insufficiency (POI)	-
• Thrombophilia	RPL	-
• Rare	FOXL2, GLAT, POLG, FSHR, LHCGR, KAL, AR, CAH	FSHR, LHCGR, KAL, AR
• Unsolved	PCOS, endometriosis	gr/gr, other azoospermia

Genetic testing

Genetic tests

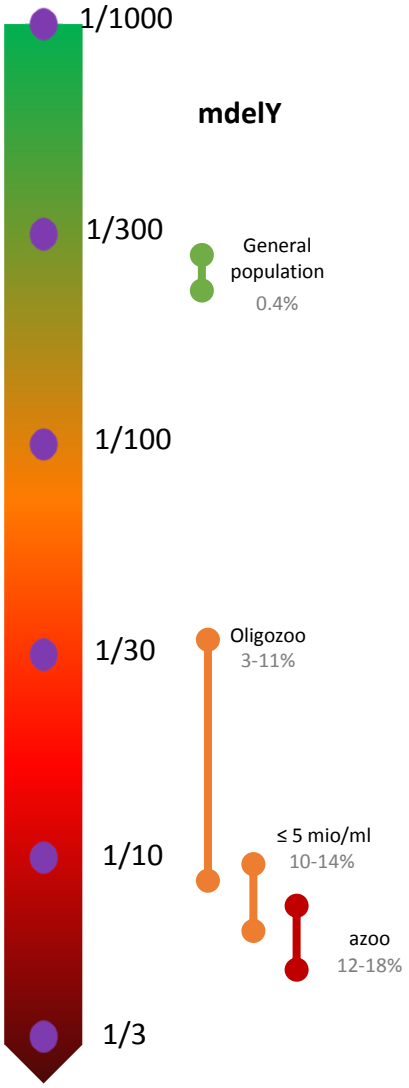
Treatment choice

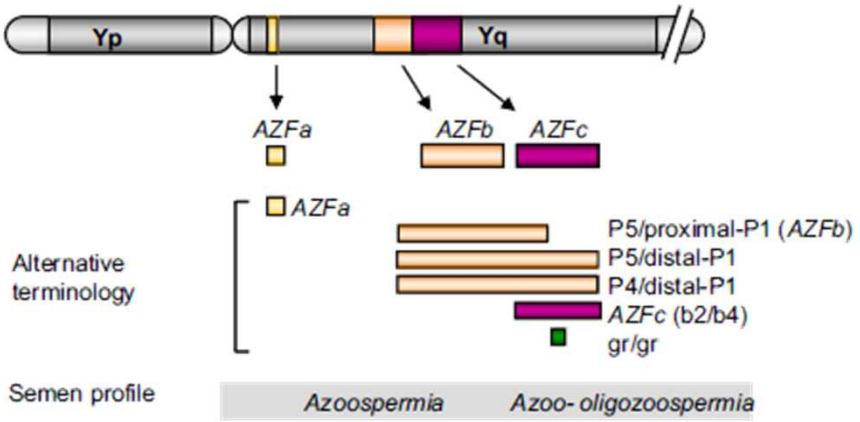
- Karyotype
- *AZF*
  HLAG
- Thrombophilia
  FSHR

Risk for offspring

- Karyotype
- *FMR1*
  Fragile X syndrome
- *CFTR*
  Cystic fibrosis

AZF (Y chromosome microdeletions)





Treatment outcome:

Del AZFc

70% chance to recover fertile sperm by TESE

Del AZFb OU AZFb+AZFc

1° spermatocyte arrest

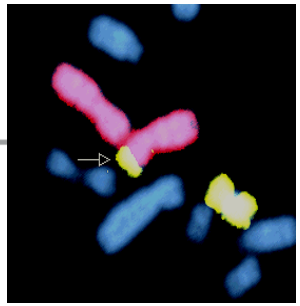
Chance virtually zero

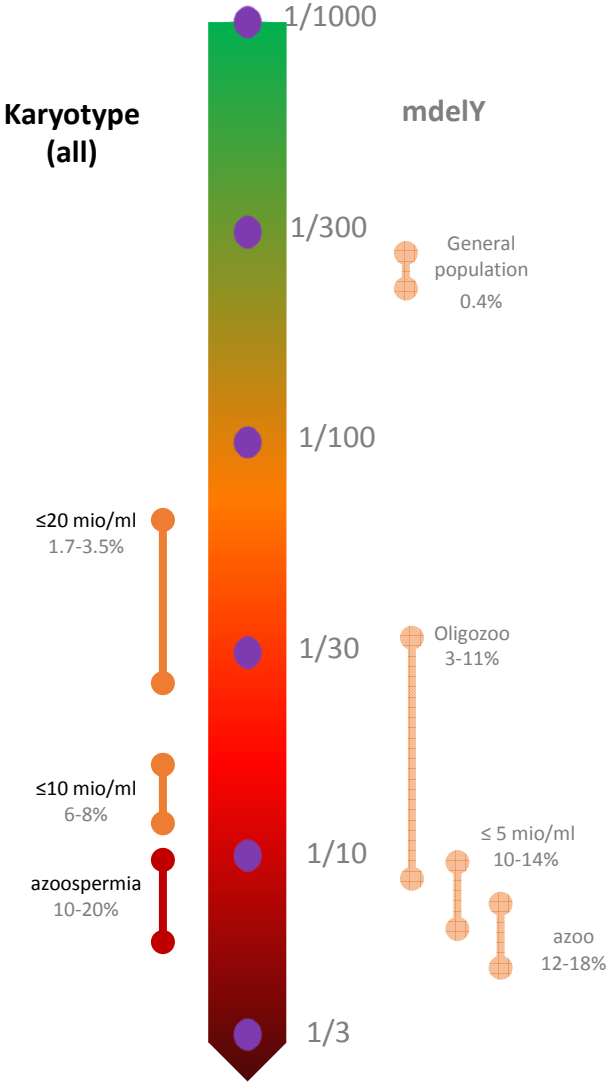
Del AZFa

Sertoli-cell only syndrome

Chance virtually zero

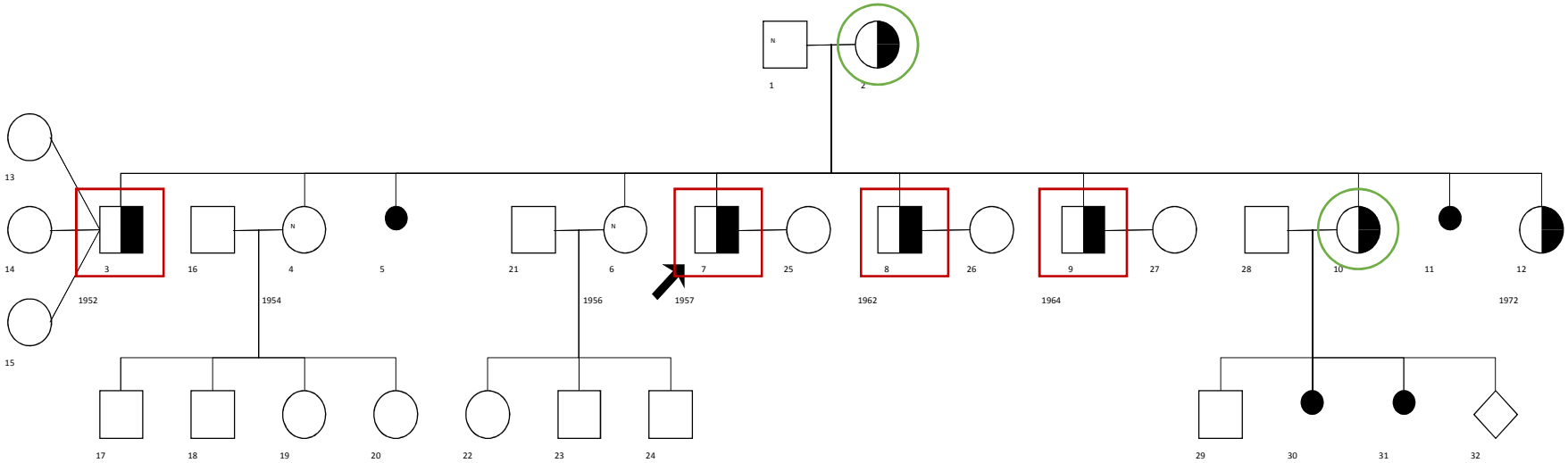
Chromosomal anomalies



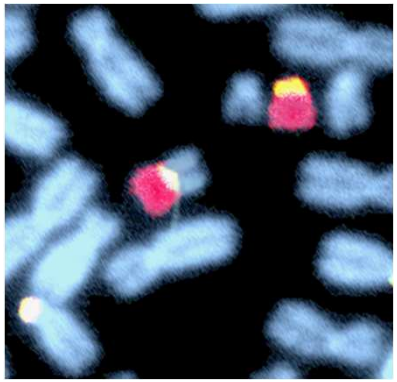


Male translocation (1/250)	**Female translocation** (1/250)
Severe OAT or azoospermia	Spontaneous abortion
Risk of aneuploidy ≈ 1%	Risk of aneuploidy ≈ 10%
Risk UPD (6,7,11,14,15) ≈ 0.8%	Risk UPD (6,7,11,14,15) ≈ 0.8%

Familial translocation associated with male-only sterility



Clin Genet. 2000 Oct;58(4):324-8

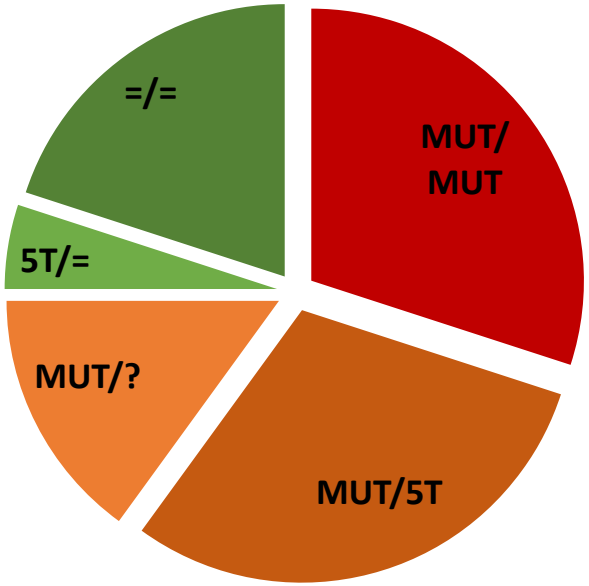


t(6;21)

CFTR (“cystic fibrosis gene”)

- CBAVD

  Congenital bilateral absence of vas deferens



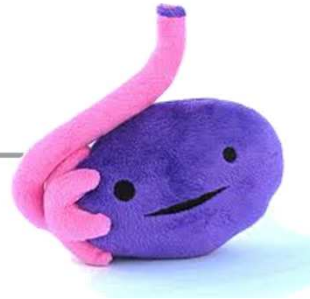
1 cystic-fibrosis mutation;

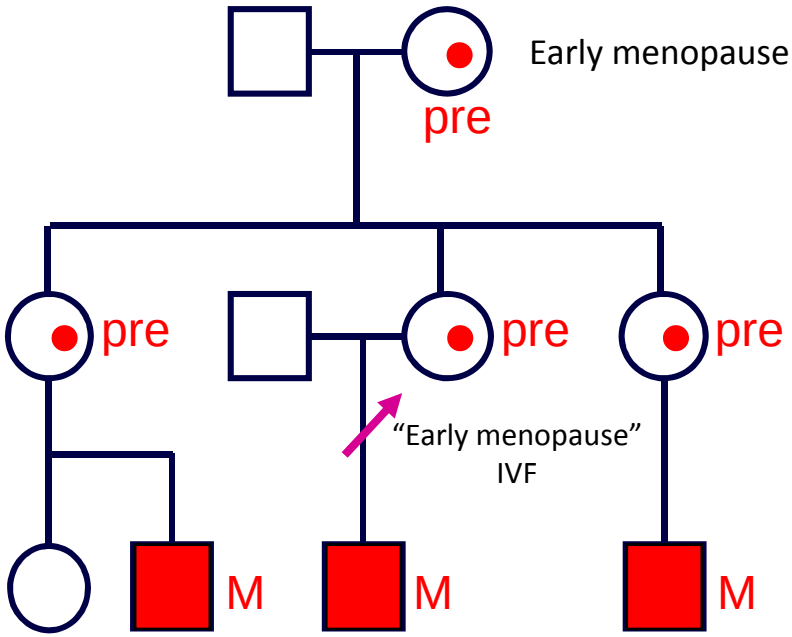
1 “mild” non-CF-causing mutation

- CFTR mutations:
  - Azoospermic, non CBAVD: 16-31%
  - Oligospermic: 6-22%

  - Tomaiuolo et al 2011:
- “All subjects affected by **obstructive or secretory azoospermia** should undergo molecular analysis and counselling for CF”.

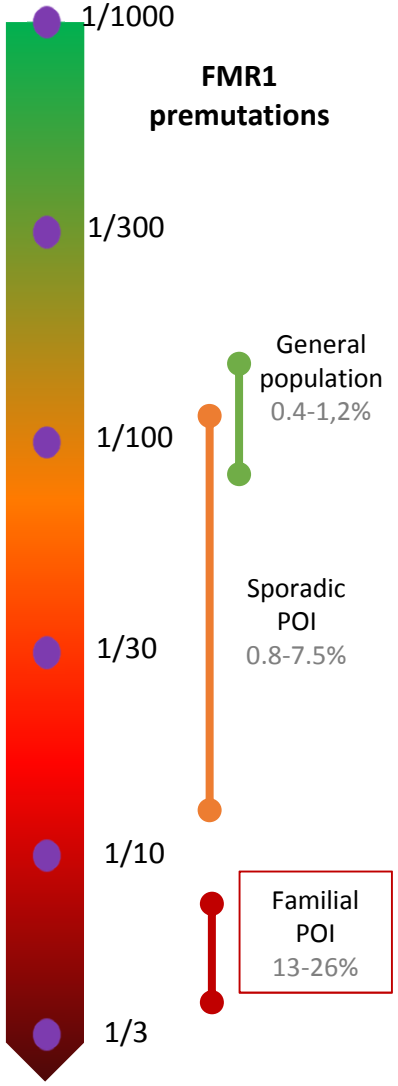
Premature ovarian insufficiency and FRAXA



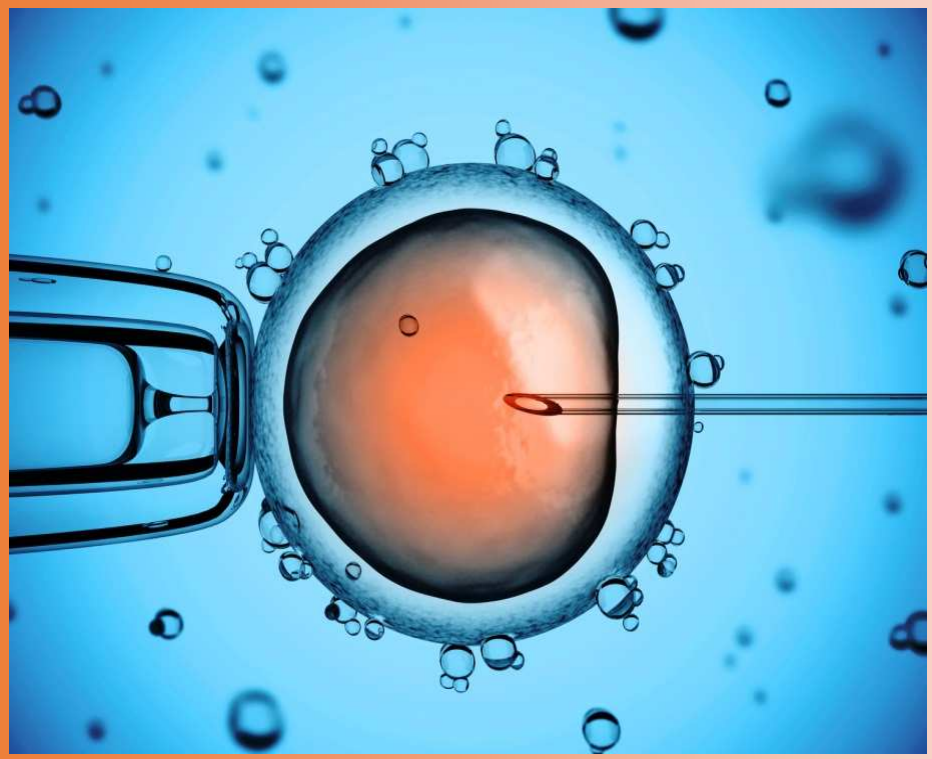


1-2 yrs: developmental delay

4 yrs: fragile X mental retardation syndrome



Assisted reproductive technologies



www.princetonivf.com

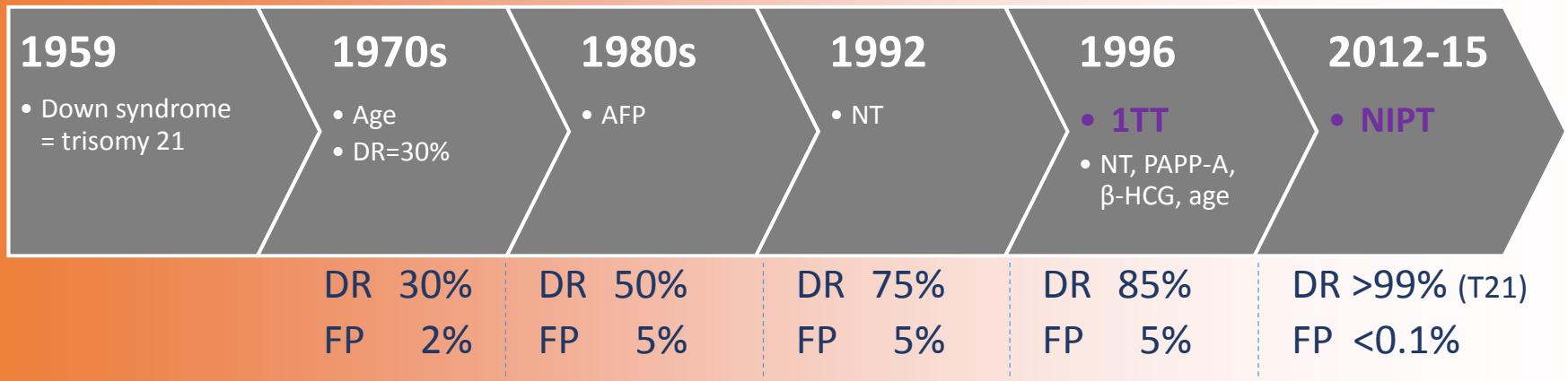
ART delivers successful pregnancies to otherwise infertile couples

- Hormonal stimulation
- TESE
- Insemination
- IVF
- ICSI

Risks

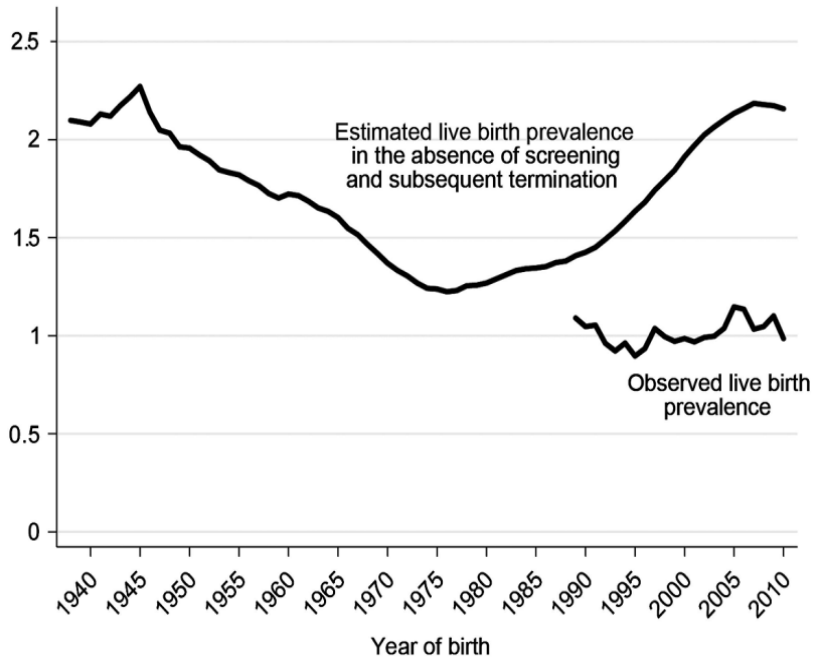
- **Age-related aneuploidy**
- **Transmission of genetic disease**

Progression of prenatal screening for T21



Performance of prenatal screening

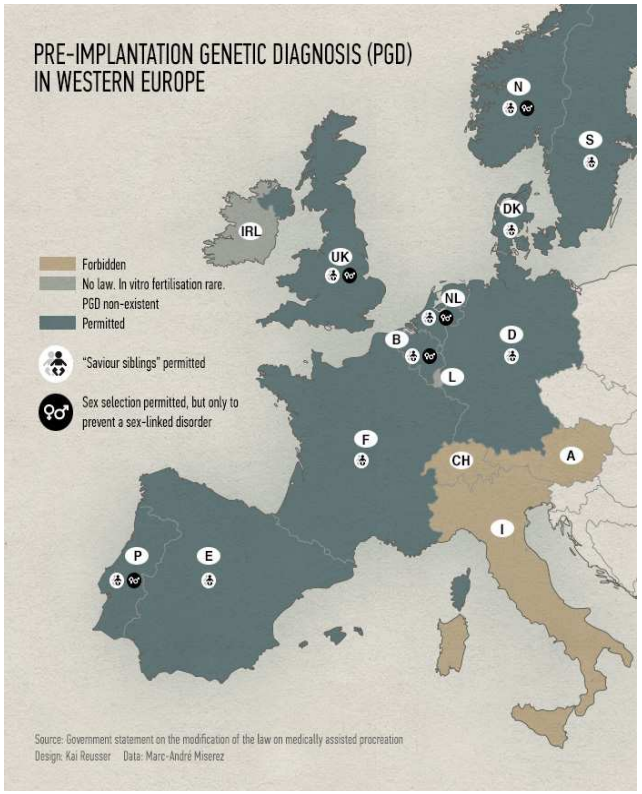
85'000 preg/yr	1TT	NIPT
Detection Rate (T21)	190 (85%)	220 (99%)
False-Positive Rate	4250 (5%)	85 (0.1%)
Potential Pregnancy loss	**21**	**0-1**
PPV	**4.3%**	**72%**
NPV	99.96%	>99.99%



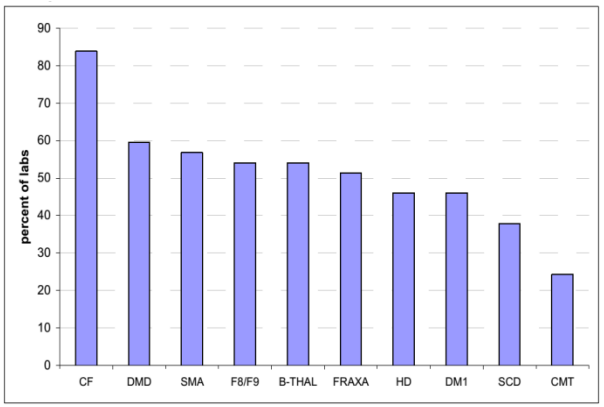
Wu & Morris, *European Journal of Human Genetics* (2013) 21, 943–947

“Treatment” options for genetic anomalies

Prenatal diagnosis **PND**	Preimplantation Genetic Diagnosis **PGD**	Preimplantation Genetic Screening **PGS**
High accuracy Disease-specific (DNA) Aneuploidy (karyotype)	Disease-specific Chromosome-specific	Age-related aneuploidy (≥38 years)
Chorionic villus Amniotic fluid	Single-cell testing ▪ Polar body ▪ Blastomere ▪ Trophoblast	Single-cell testing ▪ Polar body ▪ Blastomere ▪ Trophoblast
Pregnancy loss (0.5%) TOP	Requires IVF Legal constraints Cost	Requires IVF Legal constraints Cost



15 years of PGD in Europe



2005

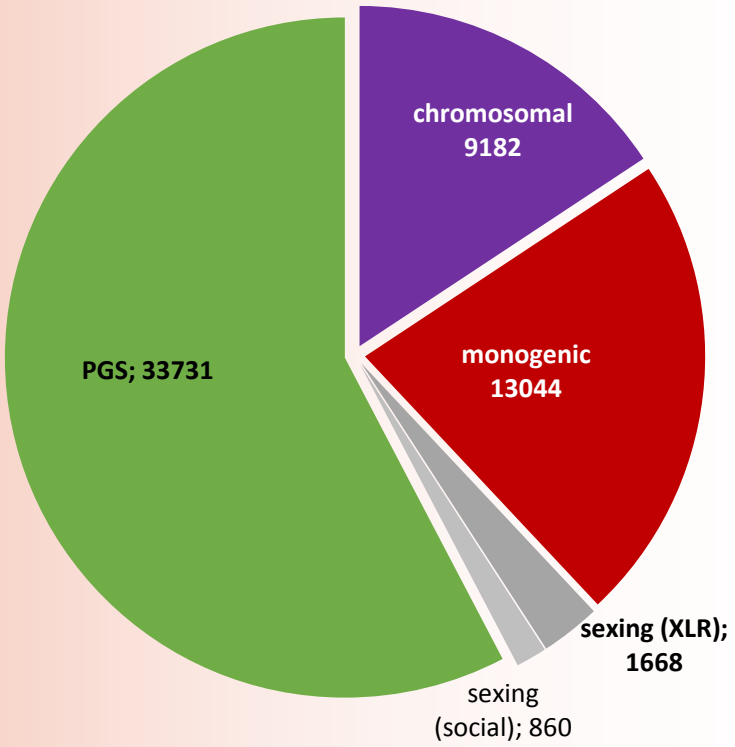
JRC Scientific and Technical Reports

Preimplantation Genetic Diagnosis in Europe

Anniek Corveleyn, Eleni Zika, Michael Morris, Elisabeth Dequeker, James Lawford Davies, Karen Sermon, Guillermo Antiñolo, Andreas Schmutzler, Jiri Vanecek, Fransesc Palau, Dolores Ibarreta

JRC EUROPEAN COMMISSION

ESHRE 2015 (58485 cycles)



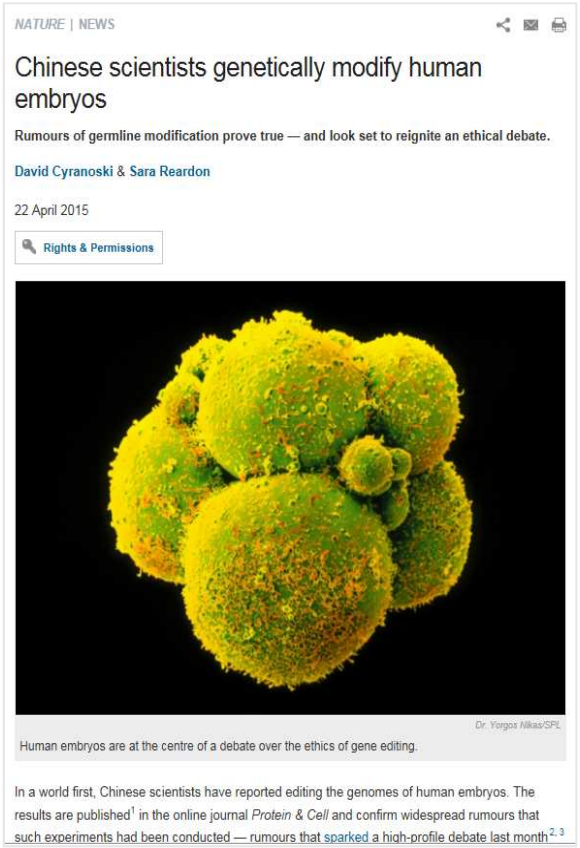
Recommendations

	Male Infertility	Female infertility	RPL
Karyotype	✓	✓	couple
FMR1		FSH⇧ / AMH⇩ <40a Sporadic POI Family history POI	
CFTR	CBAVD Azoospermia Severe oligospermia		
AZF (Y microdeletions)	≤5 mio/ml		
Thrombophilia			✓ Female (?)

What does the future hold?

PND	PGD	PGS
NIPT effect ▪ Numbers will drop ▪ Pure diagnosis ▪ Karyotype still gold standard	**Remove legal constraints** Improve access	**Remove legal constraints** Improve access - Reduce costs
Technology ▪ Microarray, BACs on beads ▪ NIPT for paternal mutations	Technological convergence ▪ Today: personalized tests ▪ Tomorrow: karyomapping	Technological evolution ▪ Microarray > NGS ▪ Mitochondrial DNA ?

Designer babies?



NATURE | NEWS

Chinese scientists genetically modify human embryos

Rumours of germline modification prove true — and look set to reignite an ethical debate.

David Cyranoski & Sara Reardon

22 April 2015

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Dr. Yorgos Nikas/SPL

Human embryos are at the centre of a debate over the ethics of gene editing.

In a world first, Chinese scientists have reported editing the genomes of human embryos. The results are published[1] in the online journal *Protein & Cell* and confirm widespread rumours that such experiments had been conducted — rumours that sparked a high-profile debate last month[2,3]

Designer babies NO

YES to babies

- To infertile couples
- To older couples
- With fewer chromosomal anomalies
- With less inherited disease.

Thank you!

G·E·N·E·T·I·C·S

THIS IS HOW IT WORKS

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