# Preimplantation Genetic Testing

SOFIE SYMOENS – ANNELIES DHEEDENE

12-10-2022

## Prenatal diagnosis techniques

## NIPT

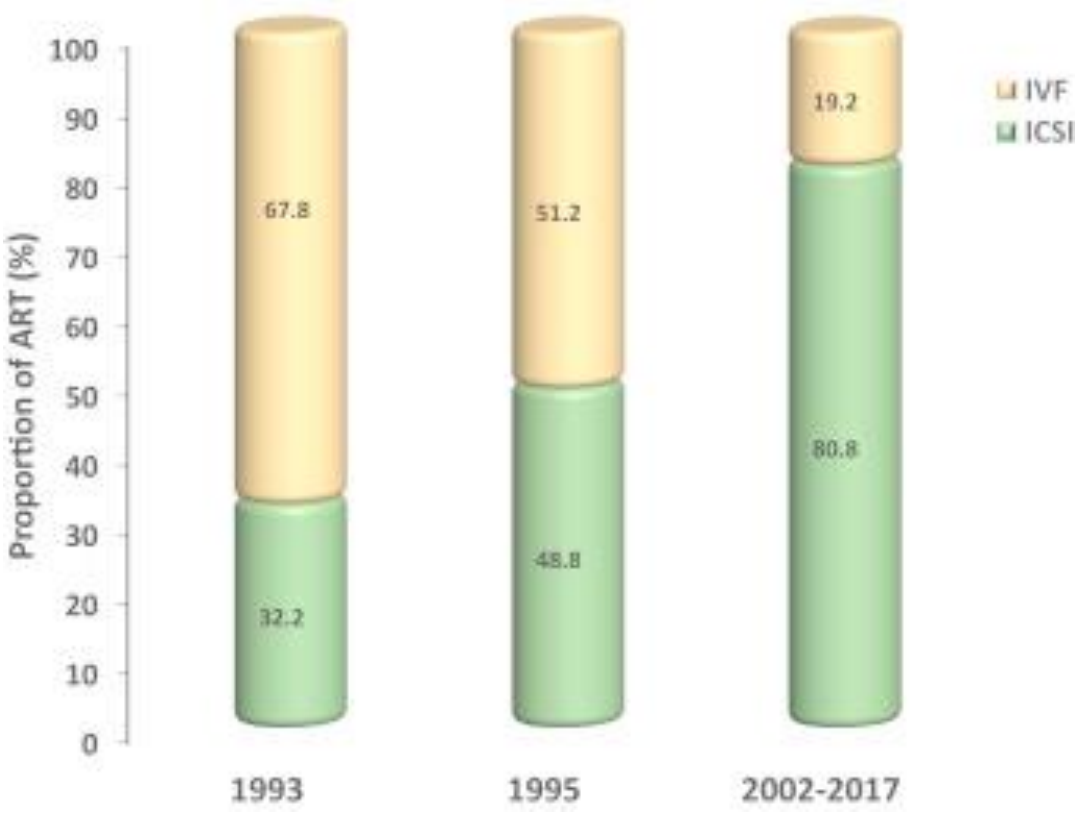
## Preimplantation Genetic Testing (PGT)

- PGT-A and PGT-SR
- PGT-M

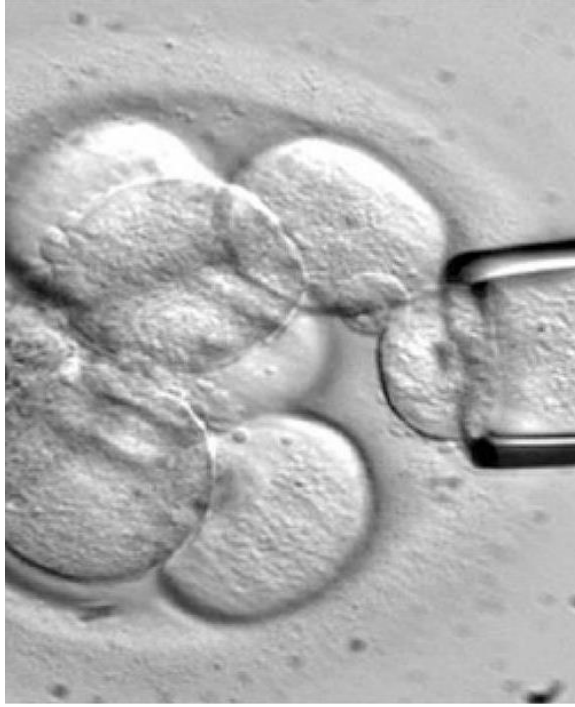
# IVF - ICSI

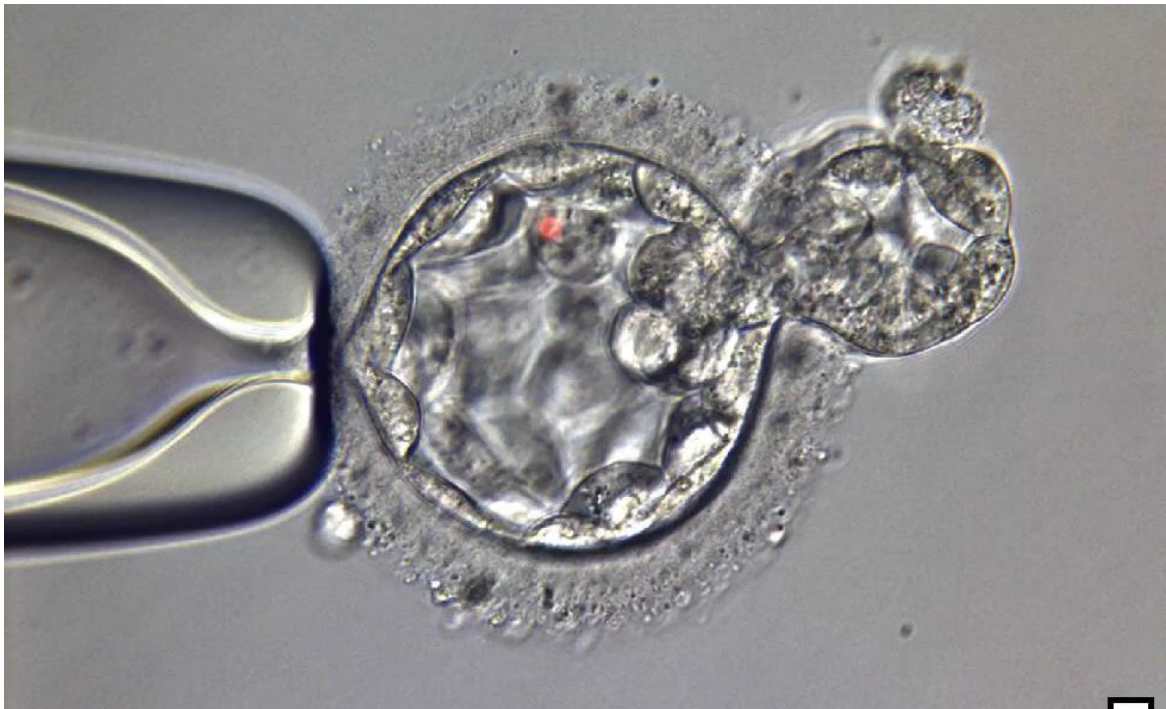
ICSI prevalence during 25 years (The Ronald O. Perelman and Claudia Cohen Center for Reproductive Medicine, Weill Cornell Medicine).

Niederberger C., Fertil Steril. 2018 Jul 15;110(2):185-324



# Preimplantation Genetic Testing (PGT)





MENU nature
International journal of science

Letter | Published: 19 April 1990

# Pregnancies from biopsied human preimplantation embryos sexed by Y-specific DNA amplification

A. H. Handyside, E. H. Kontogianni, K. Hardy & R. M. L. Winston

*Nature* **344**, 768–770 (1990) | Download Citation

## Abstract

OVER 200 recessive X chromosome-linked diseases, typically affecting only hemizygous males, have been identified. In many of these, prenatal diagnosis is possible by chorion villus sampling (CVS) or amniocentesis, followed by cytogenetic, bioc
recovered from the conceptu
determine the sex of the fetu

1990: Handyside et al: first PGD for X-linked disease

1992: Handyside et al.: baby after PGD for Cystic Fibrosis

ORIGINAL ARTICLE

# Birth of a Normal Girl after in Vitro Fertilization and Preimplantation Diagnostic Testing for Cystic Fibrosis

Alan H. Handyside, Ph.D., John G. Lesko, M.S., Juan J. Tarín, Ph.D., Robert M.L. Winston, M.D., and Mark R. Hughes, M.D., Ph.D.

Article Figures/Media

19 References 326 Citing Articles

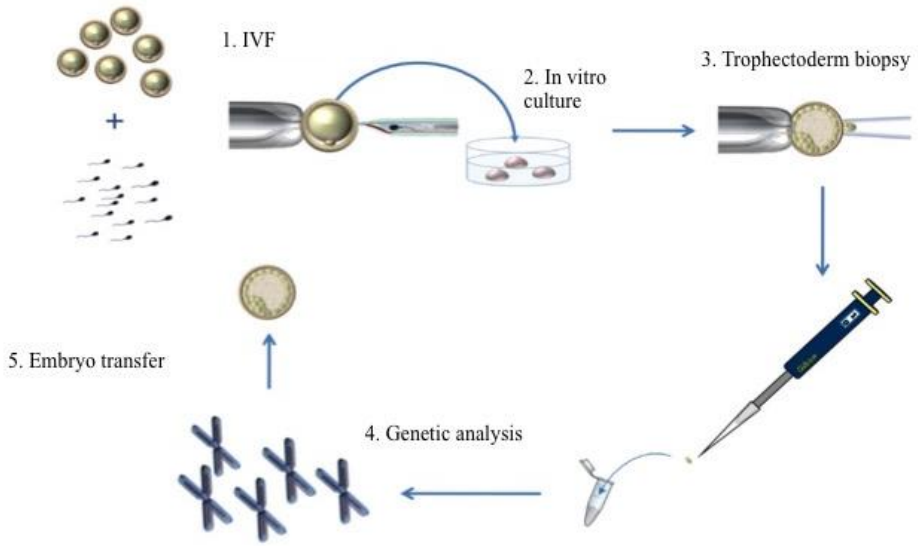
September 24, 1992
N Engl J Med 1992; 327:905-909
DOI: 10.1056/NEJM199209243271301

## Abstract

BACKGROUND.
Cystic fibrosis is a common, severe autosomal recessive disease caused in a majority of cases by a three-nucleotide deletion (ΔF508) in the cystic fibrosis transmembrane regulator gene. Current methods of prenatal diagnosis involve chorionic-villus sampling or amniocentesis. In vitro fertilization and diagnosis during embryonic development before implantation would allow only unaffected embryos to be selected for transfer to the uterus, thereby avoiding the need to terminate a pregnancy.

# Preimplantation Genetic Testing (PGT)

PGT is a state-of-the-art procedure used to identify familial genetic defects in embryos obtained through *in vitro fertilization* (IVF) before pregnancy.



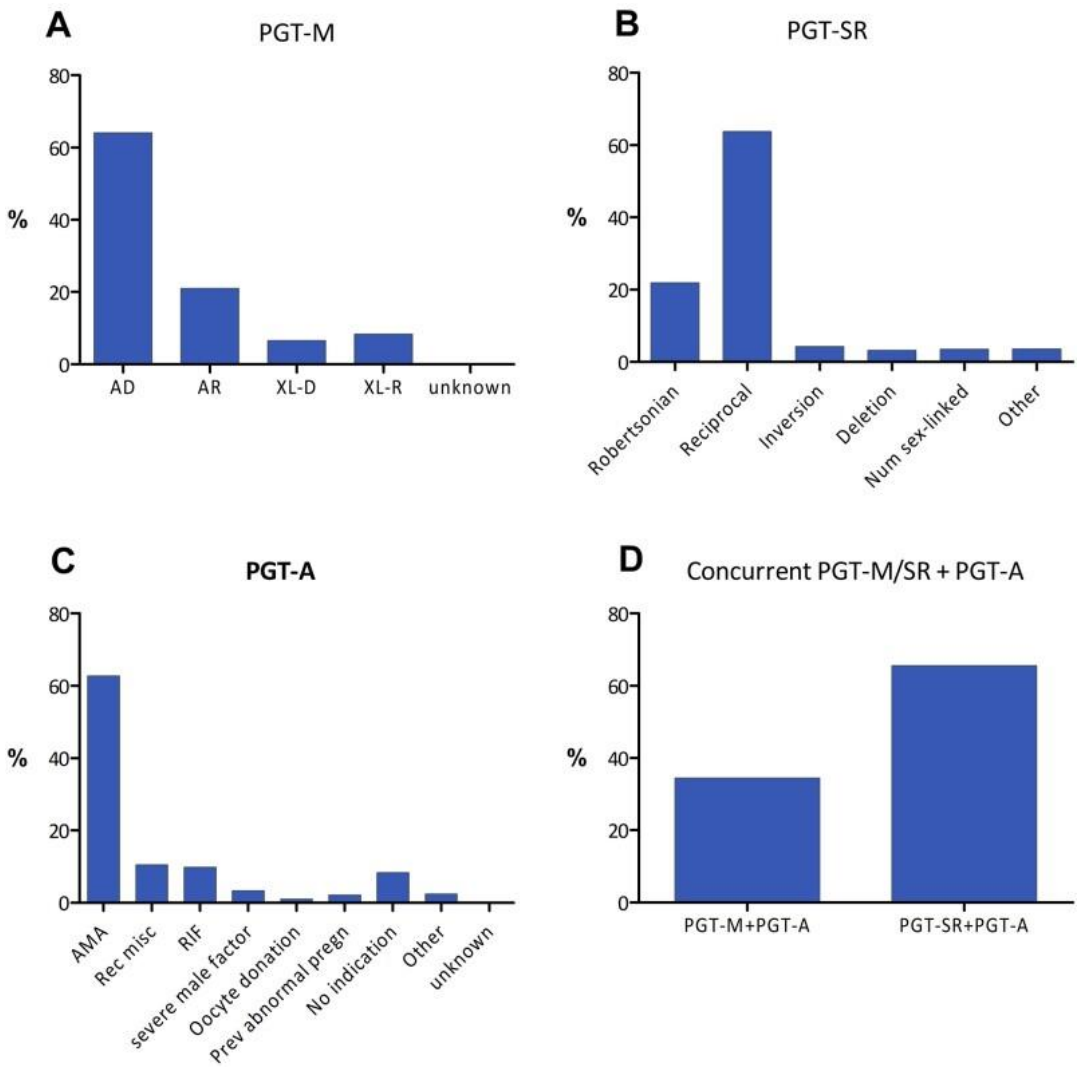

https://www.generaroma.it/assisted-reproductive-techniques-art/pgdpgs-diagnosi-genetica-pre-impianto/?lang=en

**Distribution of PGT indications in 2016-2017.**

Hum Reprod Open. 2021 Jul 27;2021(3):hoab024. doi: 10.1093/hropen/hoab024. eCollection 2021.
ESHRE PGT Consortium data collection XIX-XX: PGT analyses from 2016 to 2017
A van Montfoort , F Carvalho, E Coonen, G Kokkali, C Moutou, C Rubio , V Goossens, M De Rycke

Relative contributions

- PGT-M 35%
- PGT-SR 13%
- PGT-A 47%
- concurrent PGT-M/SR/A 7%

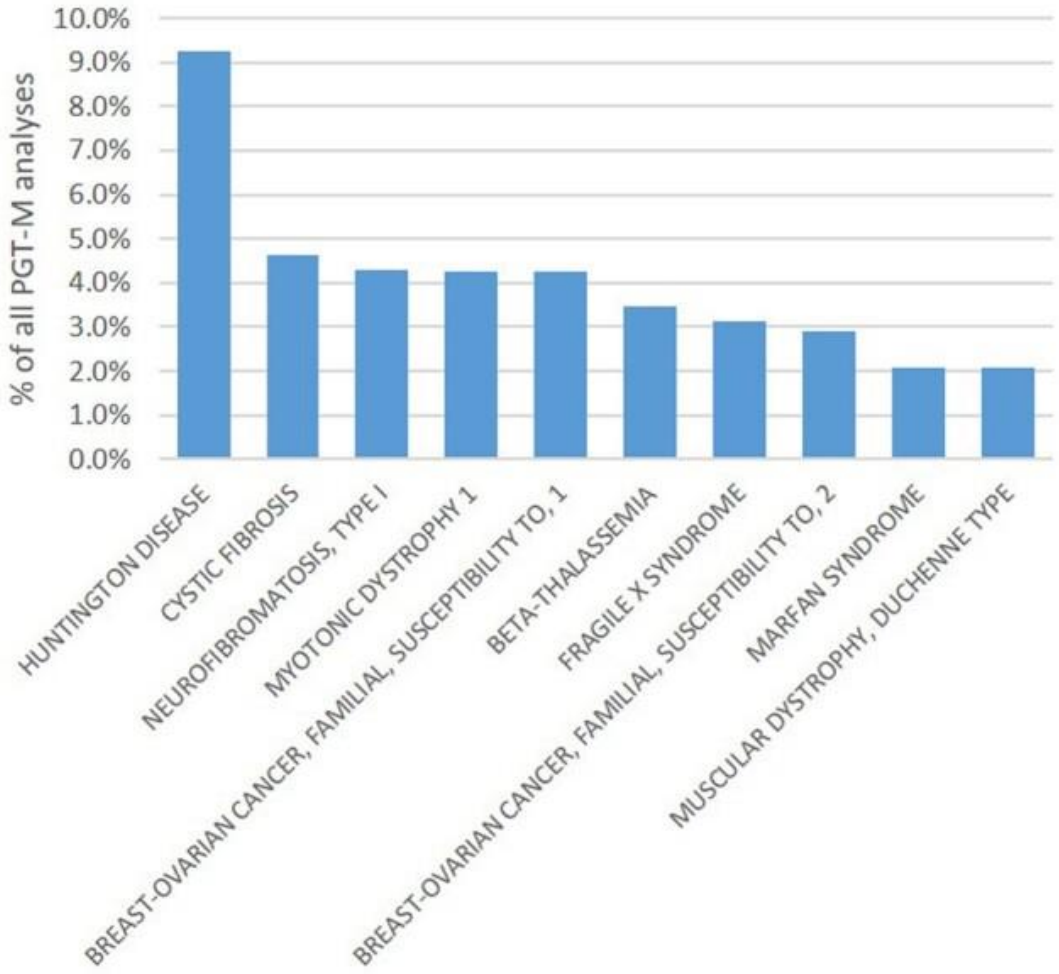


| PGT-M analysis method | | |
|---|---|---|
| | Total | % |
| PCR | 2536 | 82 |
| FISH | 22 | 1 |
| qPCR | 3 | 0 |
| WGA total | 455 | 15 |
| WGA+PCR | 58 | 2 |
| WGA+qPCR | 2 | 0 |
| WGA+SNP array | 332 | 11 |
| WGA+CGH array | 11 | 0 |
| WGA+NGS | 52 | 2 |
| WGA+other | 0 | 0 |
| combi | 50 | 2 |
| Not reported | 32 | 1 |

ESHRE PGT Consortium data collection XIX-XX: PGT analyses from 2016 to 2017 , A van Montfoort et al., 2021

**Top 10 of the indications for which PGT-M was applied in 2016–2017**.

Hum Reprod Open. 2021 Jul 27;2021(3):hoab024. doi: 10.1093/hropen/hoab024. eCollection 2021.
ESHRE PGT Consortium data collection XIX-XX: PGT analyses from 2016 to 2017
A van Montfoort , F Carvalho, E Coonen, G Kokkali, C Moutou, C Rubio , V Goossens, M De Rycke



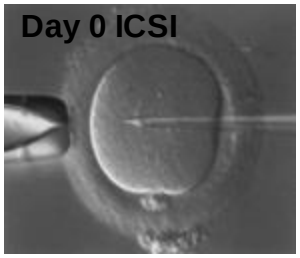
# Belgian law

Art. 67. Verboden zijn :

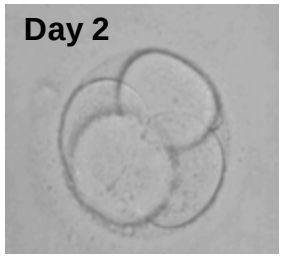
1° Genetische pre-implantatiediagnostiek met het oog op eugenetische selectie, zoals gedefinieerd in artikel 5, 4°, van de wet van 11 mei 2003 betreffende het onderzoek op embryo's in vitro, dat wil zeggen gericht op de selectie of de verbetering van **niet-pathologische** genetische kenmerken van de menselijke soort;

2° Genetische pre-implantatiediagnostiek met het oog op geslachtsselectie, zoals gedefinieerd in artikel 5, 5°, van de wet van 11 mei 2003 betreffende het onderzoek op embryo's in vitro, dat wil zeggen gericht op geslachtsselectie, met uitzondering van de selectie ter voorkoming van geslachtsgebonden ziekten.

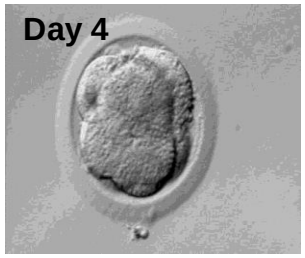
Art. 68. In afwijking van artikel 67 is pre-implantatie genetische diagnostiek uitzonderlijk toegestaan in het therapeutisch belang van een reeds geboren kind van de wensouder(s).Het geraadpleegde fertiliteitscentrum moet, in het geval bedoeld in het eerste lid van dit artikel, beoordelen of de kinderwens niet uitsluitend ten dienste staat van dat therapeutisch belang.



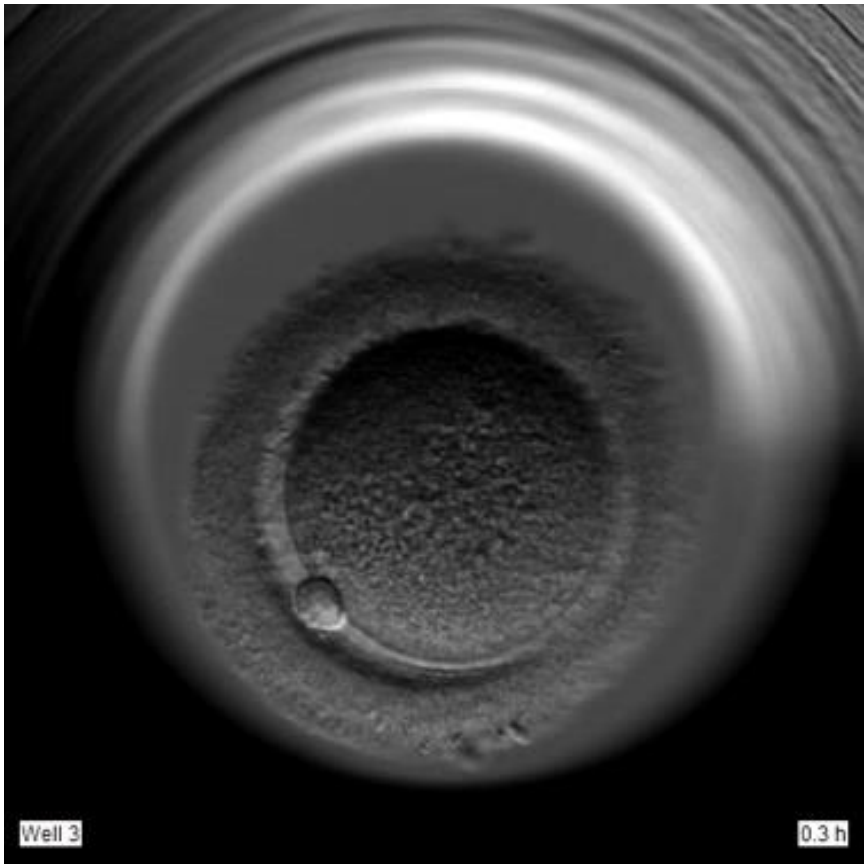












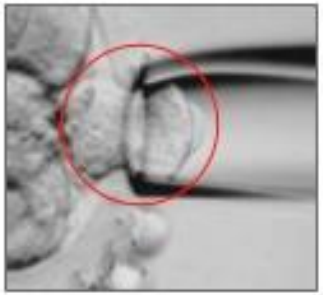

Vrouwenkliniek
Afdeling Reproductieve Geneeskunde

# Early embryonic development

# Possible Biopsy Stages

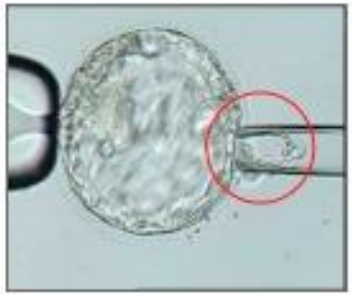
**Polar body biopsy**

- 30% postmeiotic abnormalities undetected
- Triple amount of cells to analyze vs blastocysts



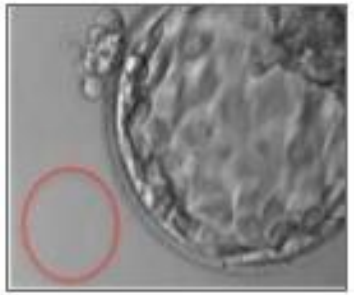
**Embryo biopsy**

- 30%[a] to 60%[b] loss of implantation potential
- PGT-A can compensate the damage but does not reach its potential



**Blastocyst biopsy**

- "not" detrimental (single study) [a]
- Not standardized



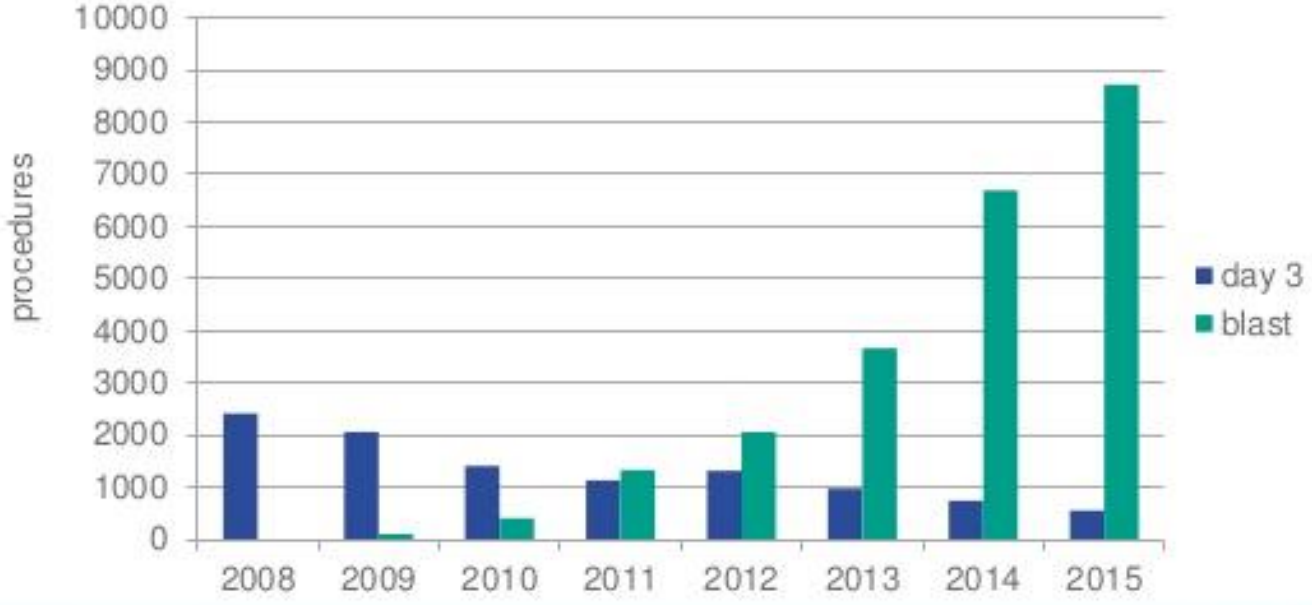
**Spent media analysis**

- Non-invasive
- Concordance with TE biopsy >90% [c,d]

[a] Scott et al (2013), [b] Mastenbroek et al. (2007) [c] Xu et al. (2016), [d] Babariya et al. (2017) ESHRE

CooperGenomics

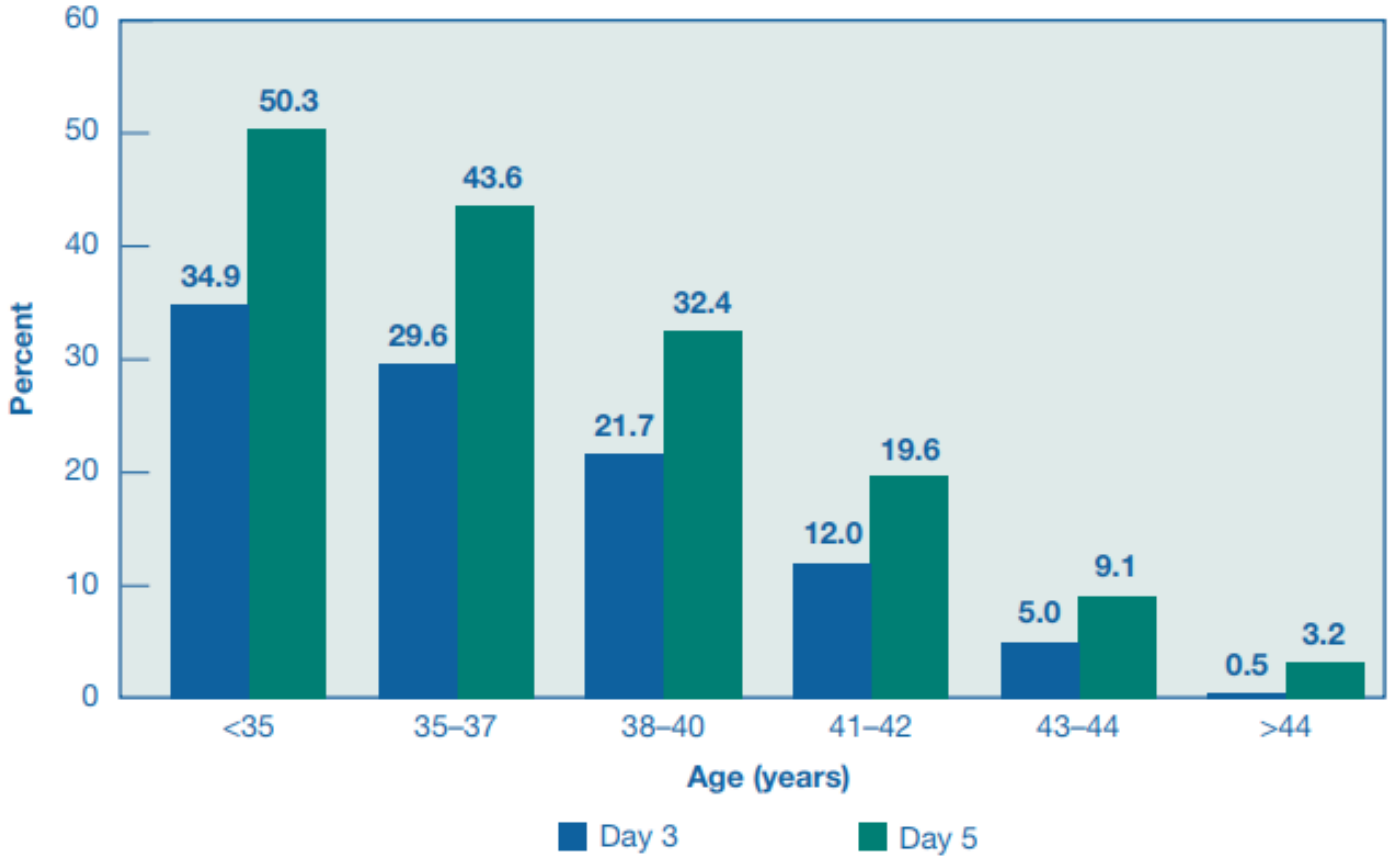
# Evolution of biopsy techniques: About 100% of biopsies in US are blastocyst

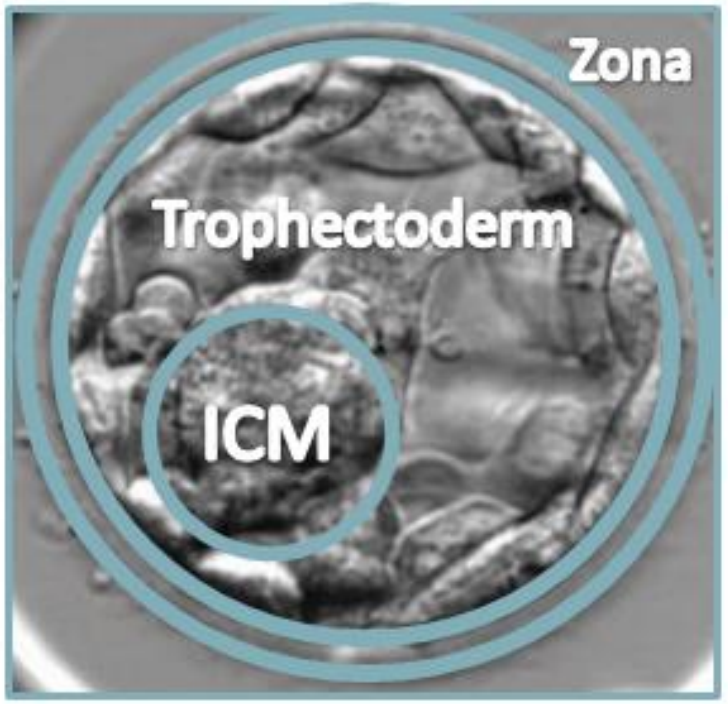



Reprogenetics US procedures

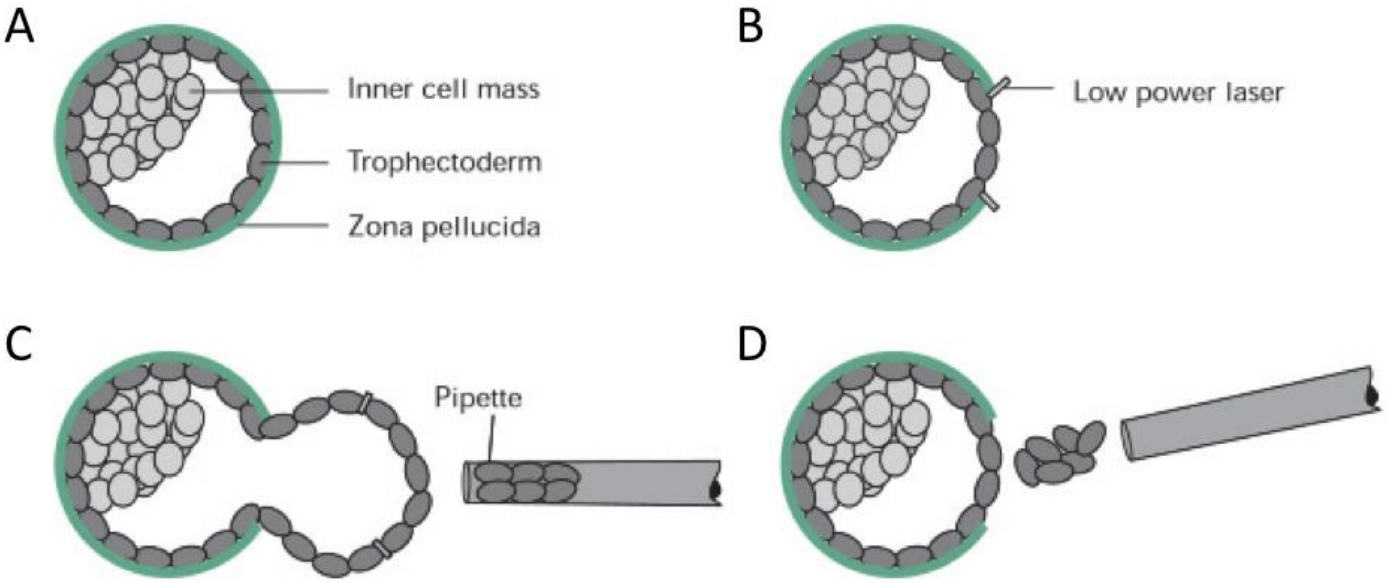
CooperGenomics

## Percentages of Day 3 and Day 5 Embryo Transfers Using Fresh Nondonor Eggs or Embryos That Resulted in Live Births, by Age Group,* 2015






# Blastocyst grading



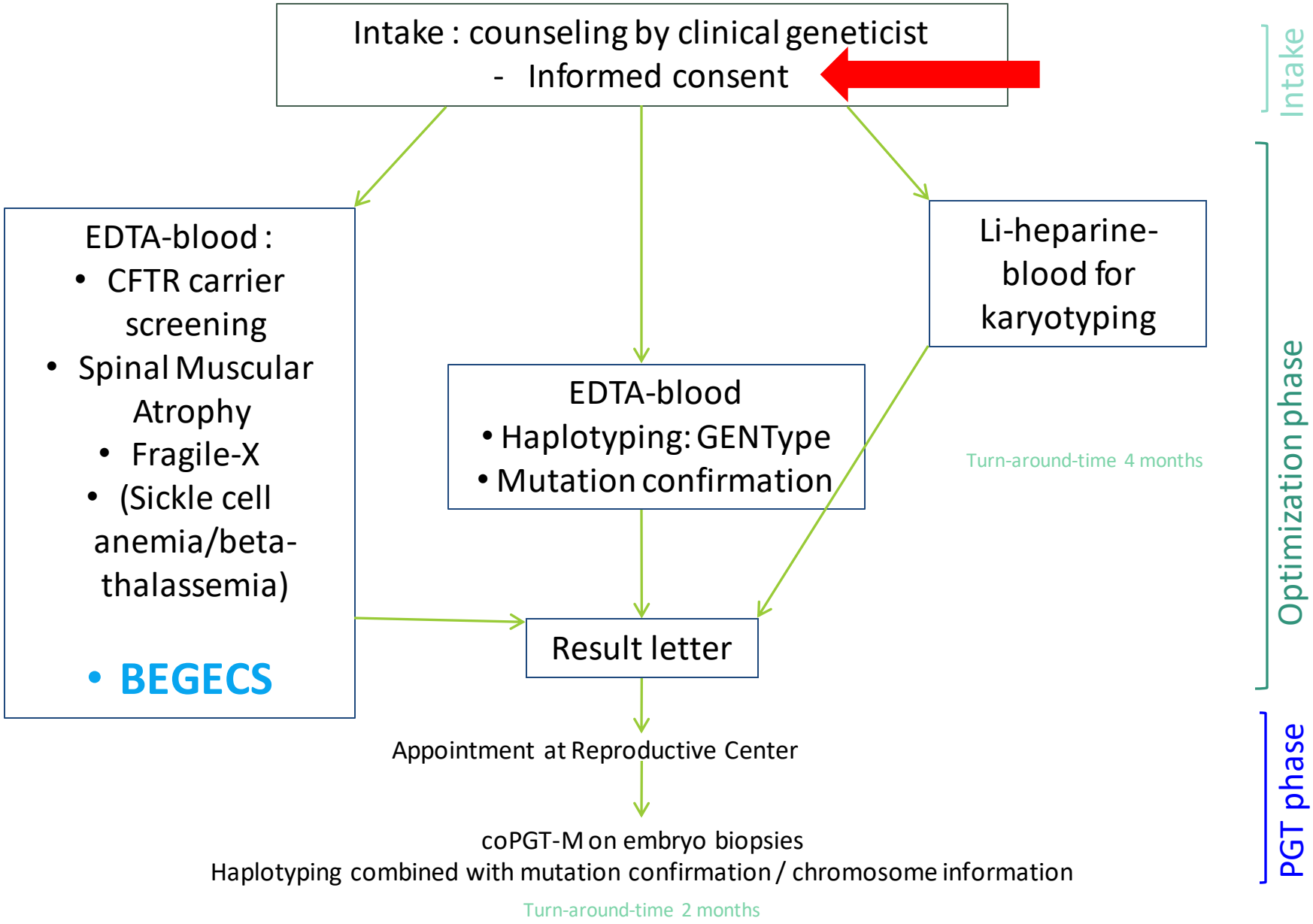
# Indications for PGT

- ***PGT for aneuploidy***: select for embryos with a normal number of chromosomes.
- ***PGT for (unbalanced) structural chromosomal rearrangments***: for example for chromosomal translocations.
- ***PGT for monogenic diseases --> coPGT-M***: monogenic/single-gene disorders.

## Requirements:

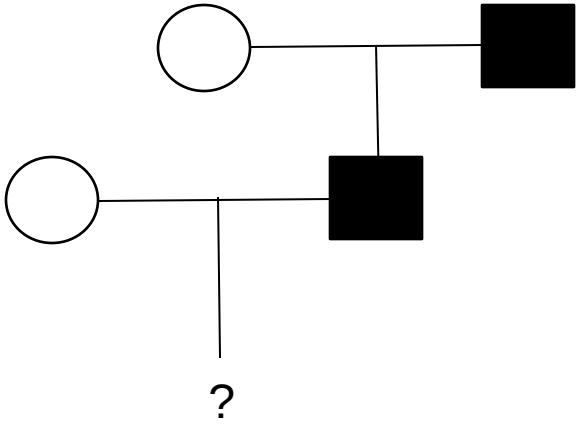
- ✧The (familial) genetic defect needs to be known, prior to the PGT procedure.
- ✧The (familial) genetic defect can be single nucleotide substitutions, small genomic insertions/deletions.
- ✧The (familial) genetic defect needs to be a variant that is likely pathogenic (class 4) or pathogenic (class 5).

| Classes | ACMG Interpretation |
|---|---|
| Class 1 | Benign |
| Class 2 | Likely benign |
| Class 3 | Variant of Unknown Significance |
| Class 4 | Likely Pathogenic |
| Class 5 | Pathogenic |



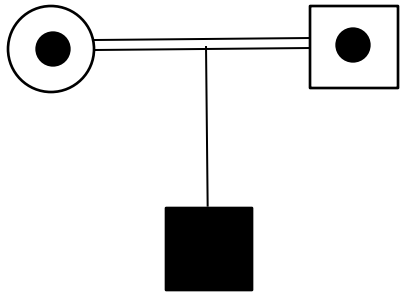

# Strategy at the CMGG for **coPGT-M**

## Autosomal dominant inheritance




Sample from an additional affected family member needed for phasing of the haplotype

## Autosomal recessive inheritance



Sample from parents and affected child needed for phasing of the haplotype

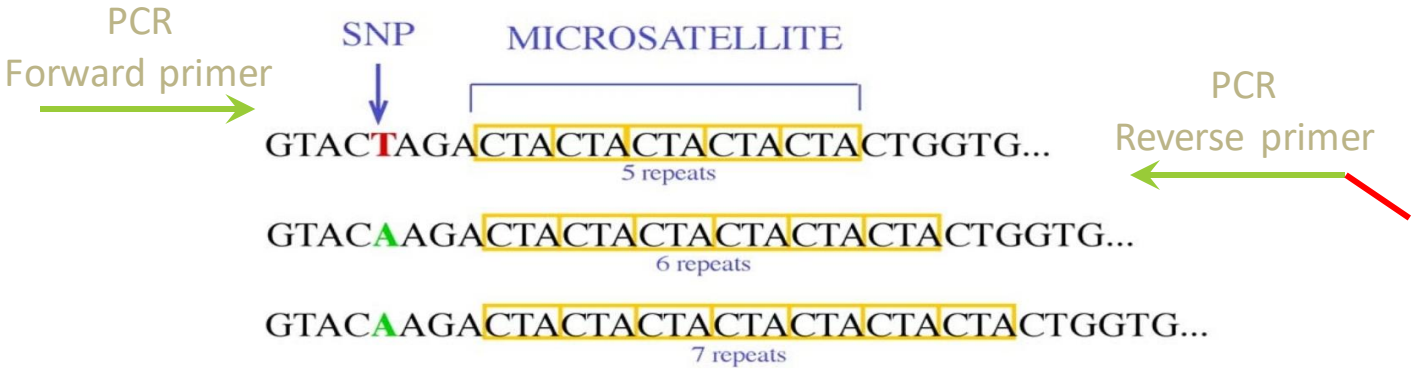
# PGT-M and haplotyping

A haplotype is a particular pattern of sequential SNPs and/or STRs (short tandem repeats) found on a single chromosome.

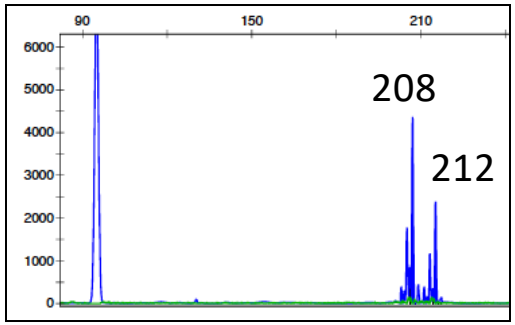
Disease genes can be associated with SNPs/STRs because they come together in a haplotype.

Haplotypes have been succesfully used to identify disease genes.

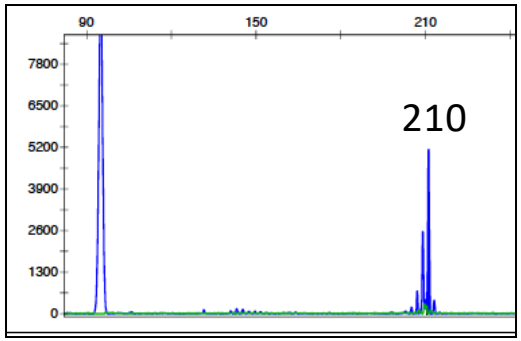
Necessary STRs for haplotyping: at least 2 upstream and 2 downstream of the familial disease locus (1-2 Mb) → more STRs make the test more robust.



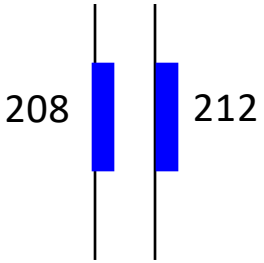

Patient 1



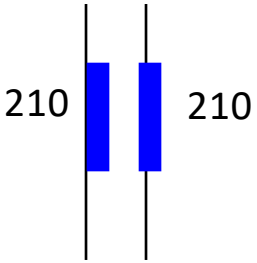

Patient 2




Patient 1

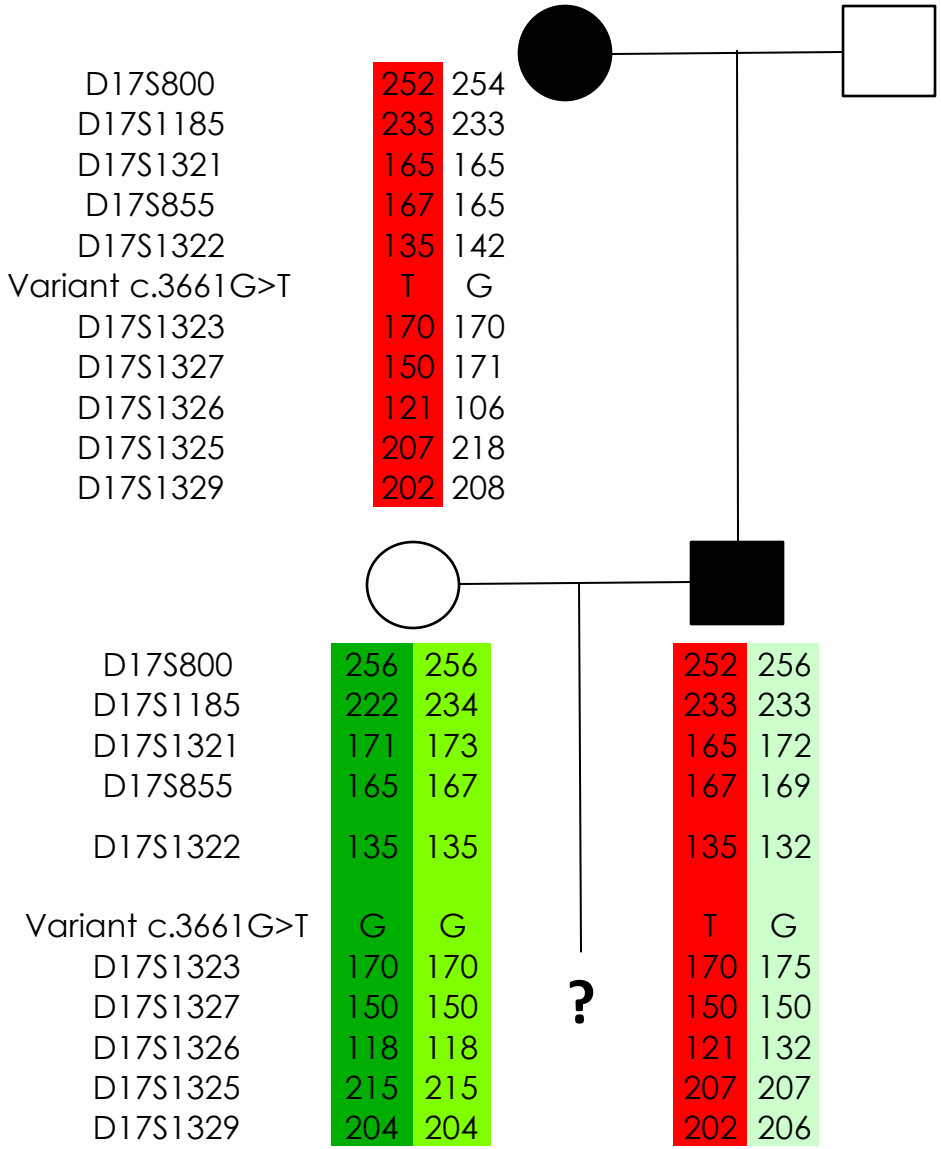


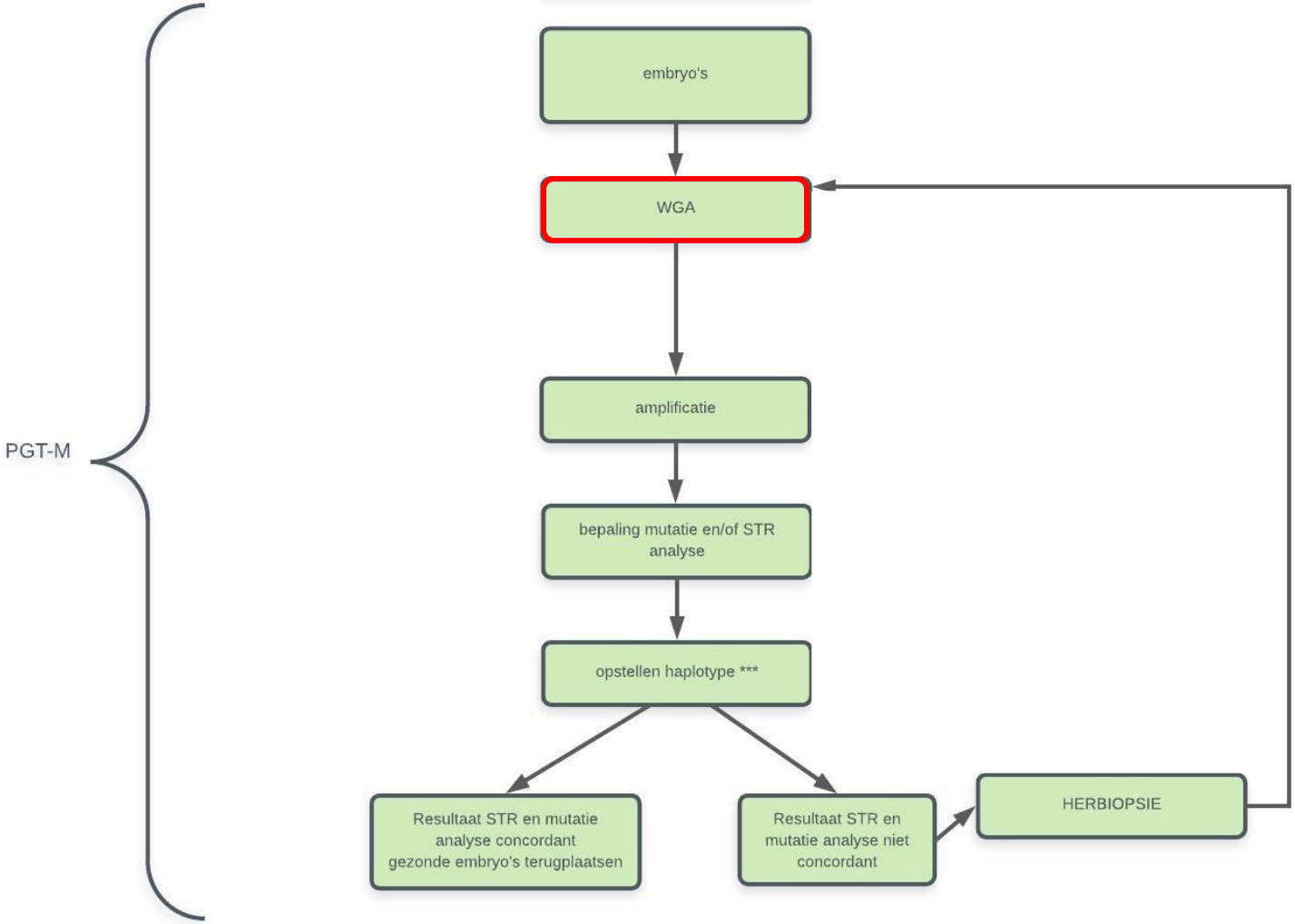

Patient 2

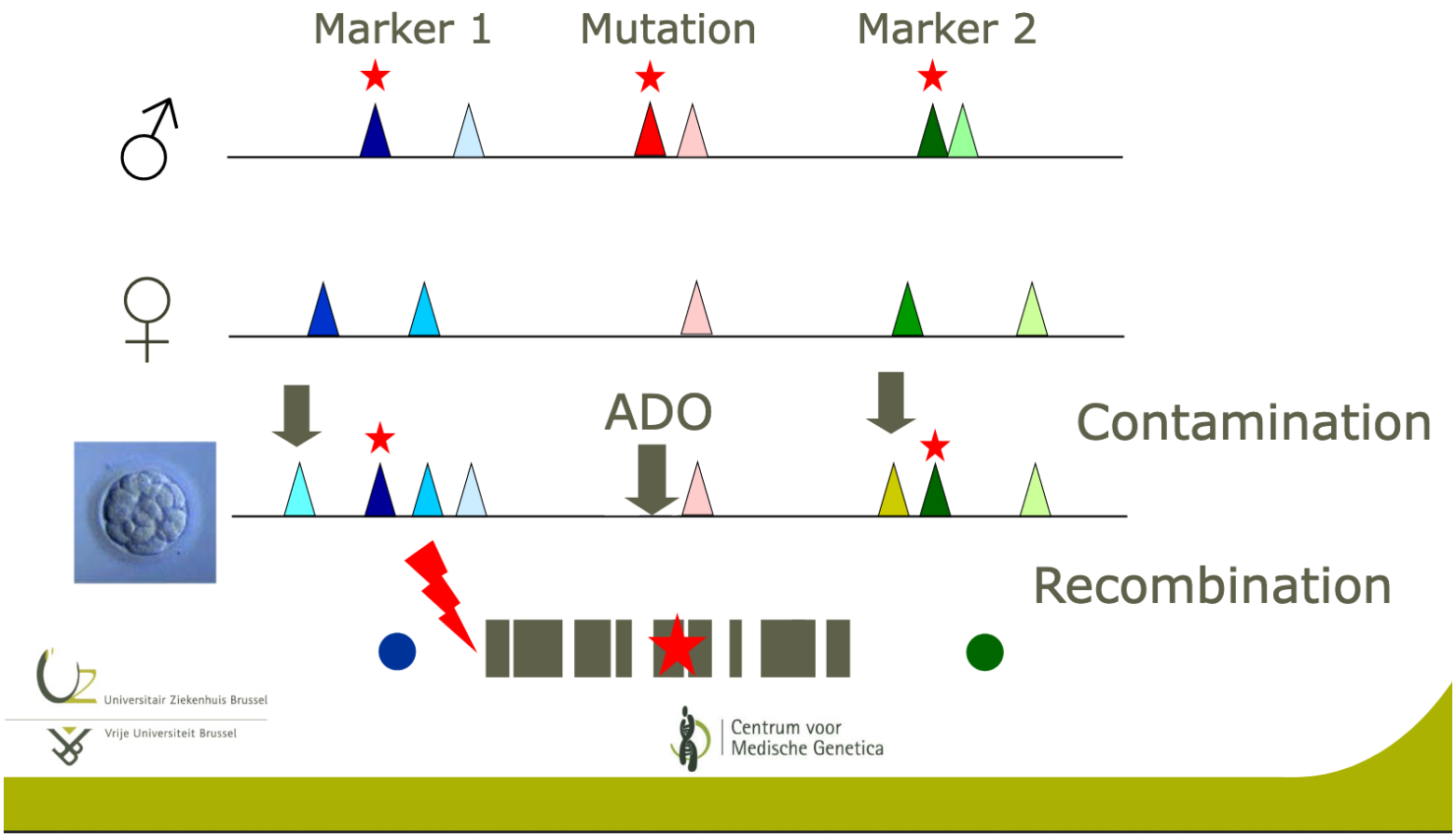



# STR profiling - haplotyping

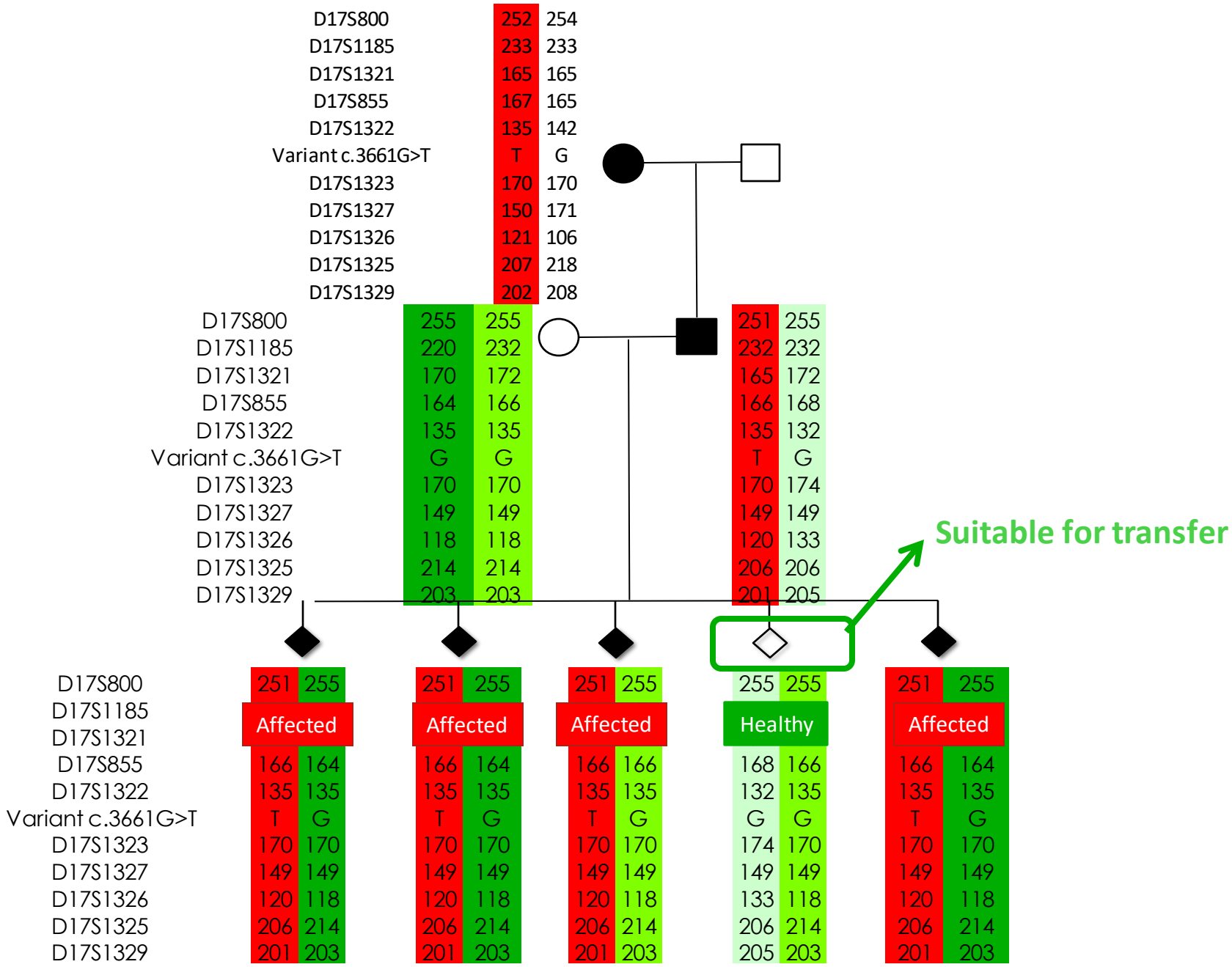
# Optimization phase for PGT-M AD disease



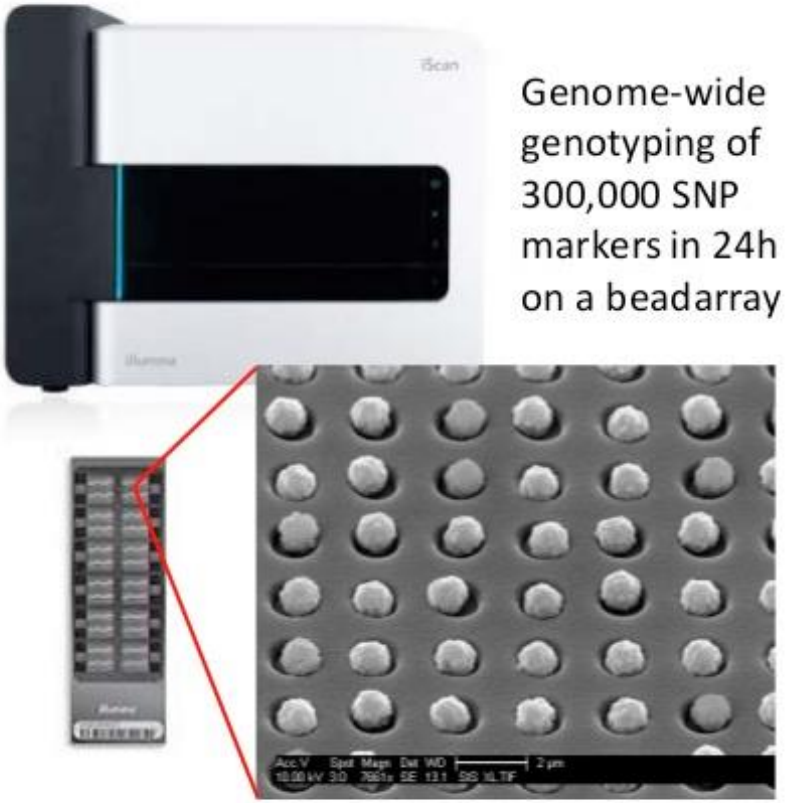

PGT-M
embryo's
WGA
amplificatie
bepaling mutatie en/of STR analyse
opstellen haplotype ***
Resultaat STR en mutatie analyse concordant gezonde embryo's terugplaatsen
Resultaat STR en mutatie analyse niet concordant
HERBIOPSIE



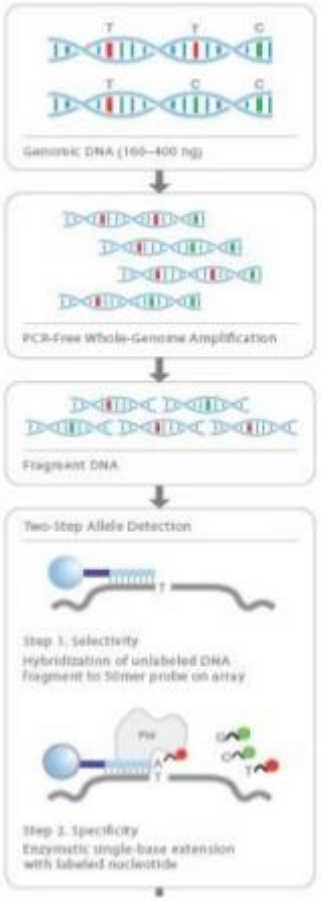

# WGA – ADO – RISKS




# PGT Phase – AD disease



Genome-wide genotyping of 300,000 SNP markers in 24h on a beadarray

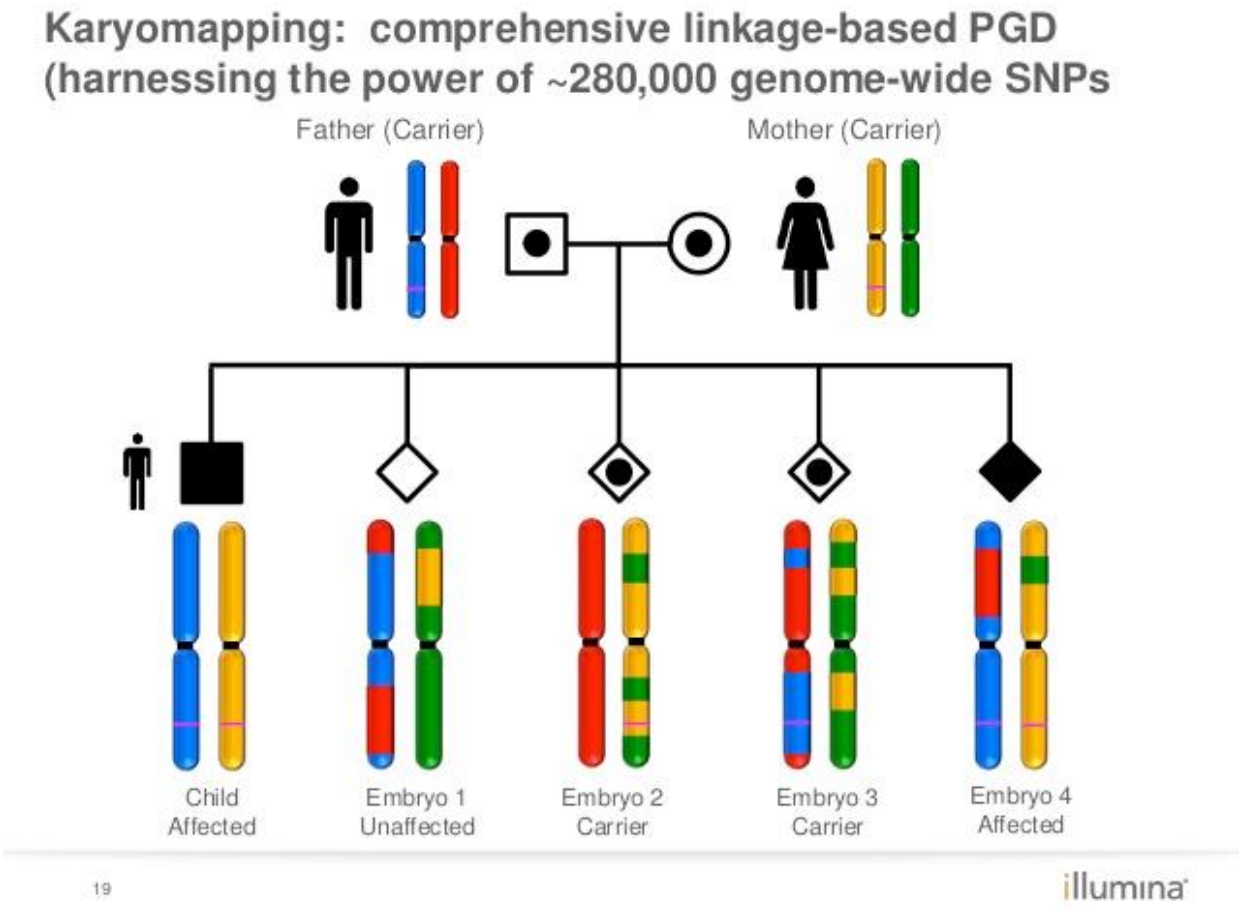



# PGT-M and karyomapping

Table 1 Parental genotype combinations – informative SNPs

| Example | Father | Mother | Informative? |
|---|---|---|---|
| 1 | AB | AA | Informative for father |
| 2 | AB | BB | Informative for father |
| 3 | AA | AB | Informative for mother |
| 4 | BB | AB | Informative for mother |
| 5 | AA | AA | Not informative |
| 6 | AA | BB | Not informative |
| 7 | AB | AB | Not informative |
| 8 | BB | BB | Not informative |
| 9 | BB | AA | Not informative |

# PGT-M and karyomapping




# PGT-M and karyomapping

# CoPGT-M

Genoomwijde haplotypering (ddRADseq – GENType)

GENType: all-in-one preimplantation genetic testing by pedigree haplotyping and copy number profiling suitable for third-party reproduction

De Witte L, Raman L, Baetens M, De Koker A, Callewaert N, Symoens S, Tilleman K, Vanden Meerschaut F, Dheedene A, Menten B. Hum Reprod. 2022;37(7):1678-1691.

PMID: 35552408

PGT-M

PGT-A(-SR)

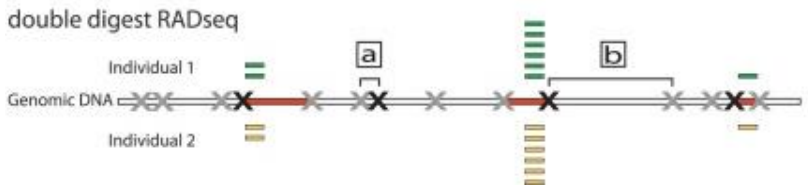
WGA

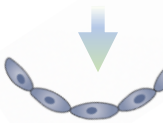
Sequencing technology

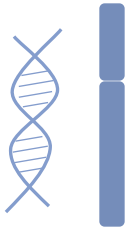
## GENType (ddRADseq)

One flow:

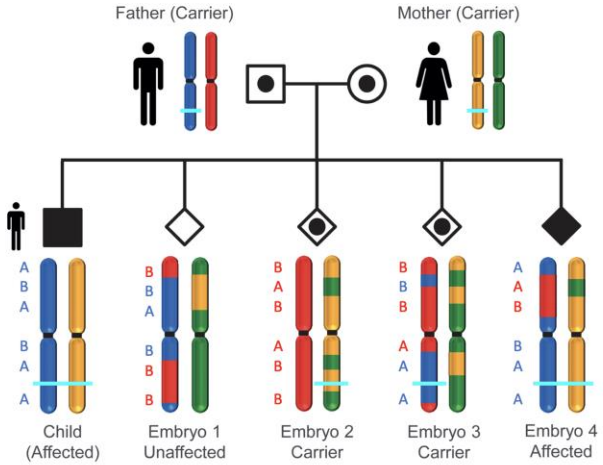
- PGT-M + chromosome screening
- Alternative sWGS



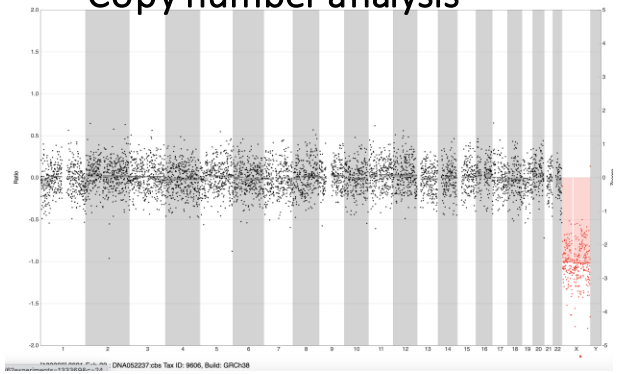





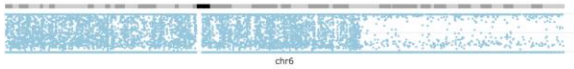
### Genome-wide haplotyping




### Copy number analysis



### B-allele frequencies



GENType - De Witte et al., 2022, Hum Reprod.

# Tricky cases for PGT-M

Saviour baby

When screening for two different disorders

When one of the parents is the index case

Those couples for whom PGT-M can not be performed

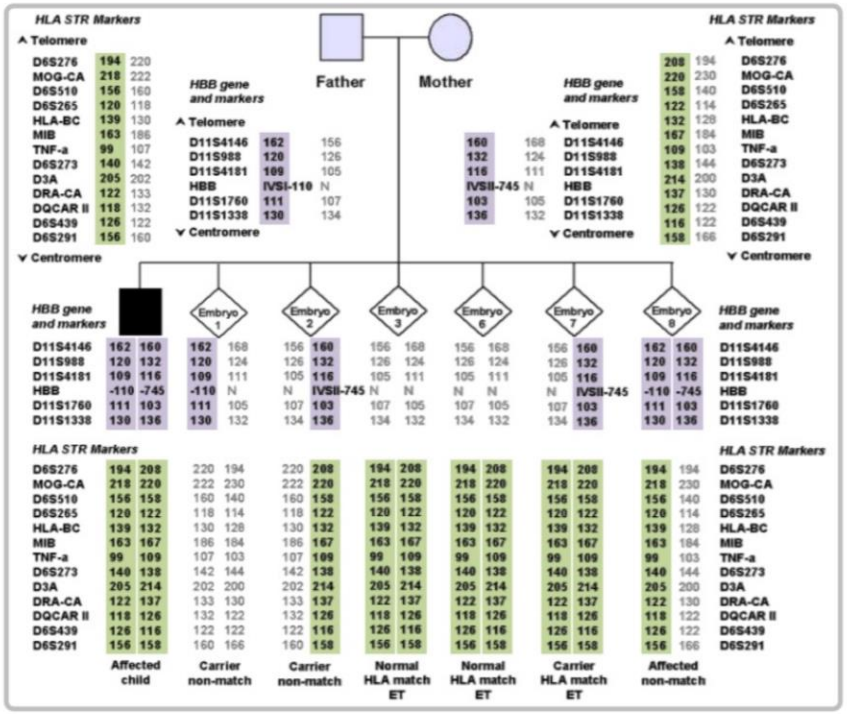
Mosaicism in one of the parents

# Tricky cases for PGT-M

**Solutions**

- Saviour baby
- When screening for two different disorders

Combined PGD for Beta Thalassaemia and HLA matching




Fiorentino et al. (2005) *Eur J Hum Genet* 13, 953

**PGT-M for HLA alone:**
only **25% of biopsied embryos** are HLA match and thus genetically **transferable**

**PGT-M for HLA match + monogenic disorders** (immunodeficiencies or hemoglobinopathies)
**18,8%** (¼x ¾) for **AR or X-linked R disorder of biopsied embryos** are genetically **transferable**

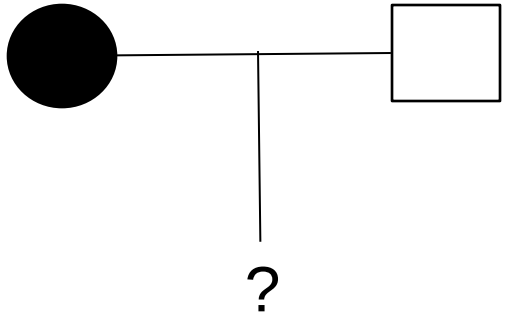
**12,5%** ( ¼ x ½) for **AD disorder of biopsied embryos** are genetically **transferable**

# Tricky cases for PGT-M

- When one of the parents is the index case
  - phasing relies on embryos
  - single sperm isolation
  - polar biopsy

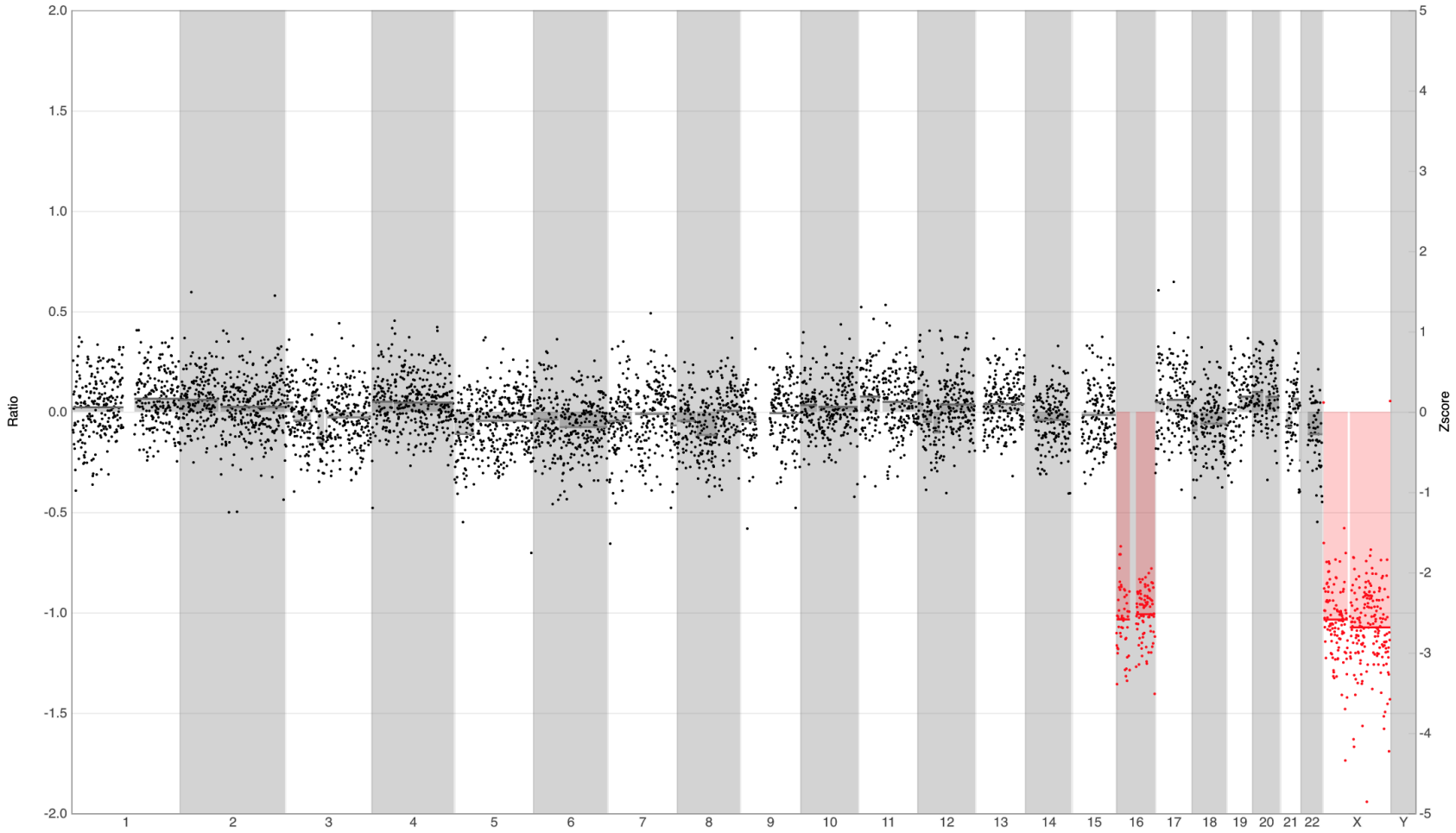
- (Suspected) Mosaicism in one of the parents (eg multiple affected previous pregnancies, segmental NF1)

- Those couples for whom PGT-M cannot be performed
  - when mutation analysis is not possible (region too large for amplification (eg DMD deletion, FSHD), pseudogene interference (PKD1), MLPA, *triplet diseases*, ...)
  - Informativity STR markers/SNPs



# Tricky cases: mosaicism

| CLASS A: TRANSFER | CLASS B: TRANSFER WITH RANKING and/or AFTER COUNSELING | CLASS C: NO TRANSFER |
| --- | --- | --- |
| Euploid embryos | chr X and Y, except for Turner (SCA'S) no transfer unless counseling<br>chr 6, 7, 11, 14 and 15 (UPD chr)<br>chr 2 and 22<br>chr 1, 3, 4, 5, 10, 12, 17, 19 and 20 | chr 8 and 9<br>chr 13, 18 and 21<br>chr 16<br>Turner (monosomy X) |

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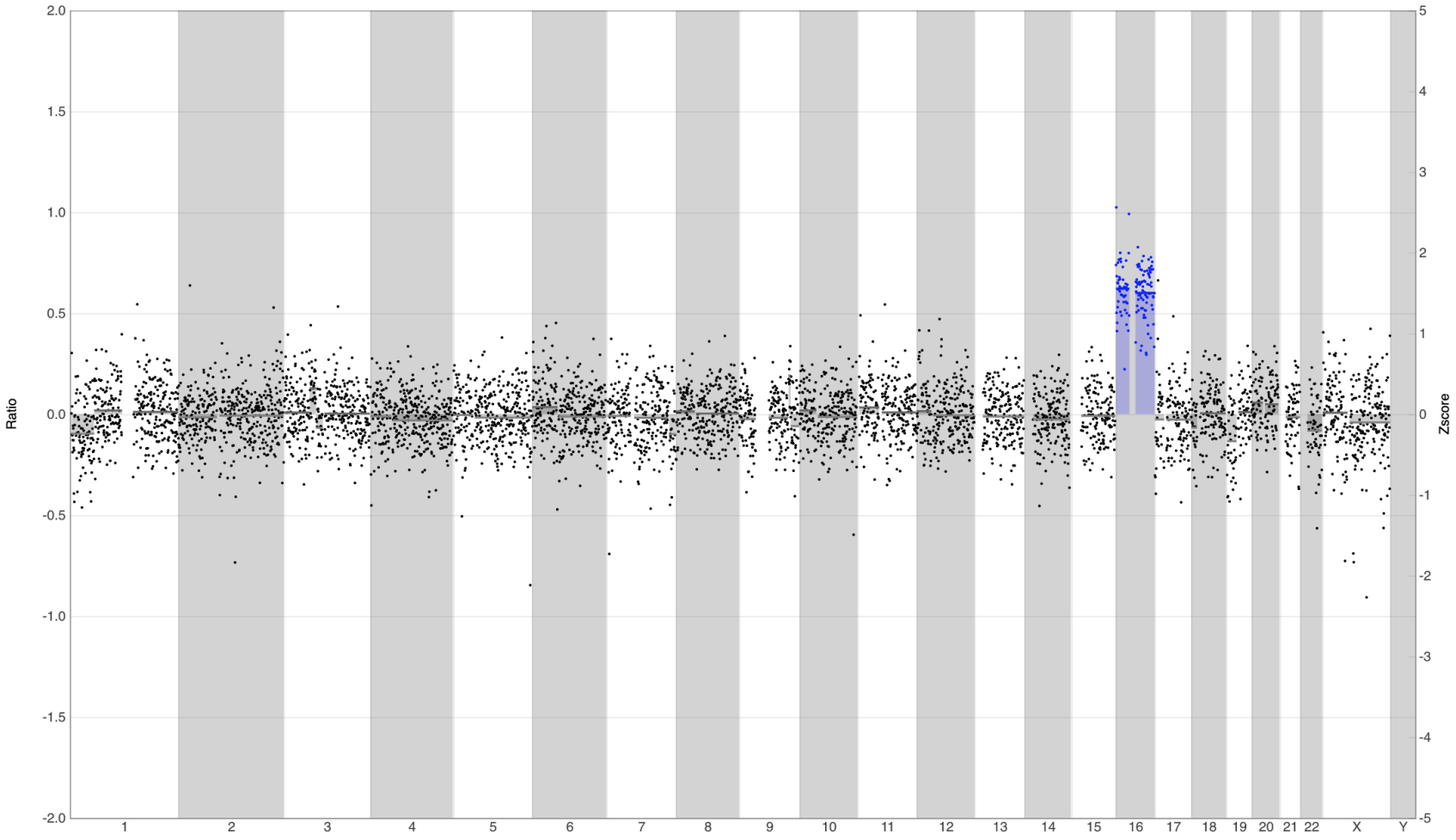


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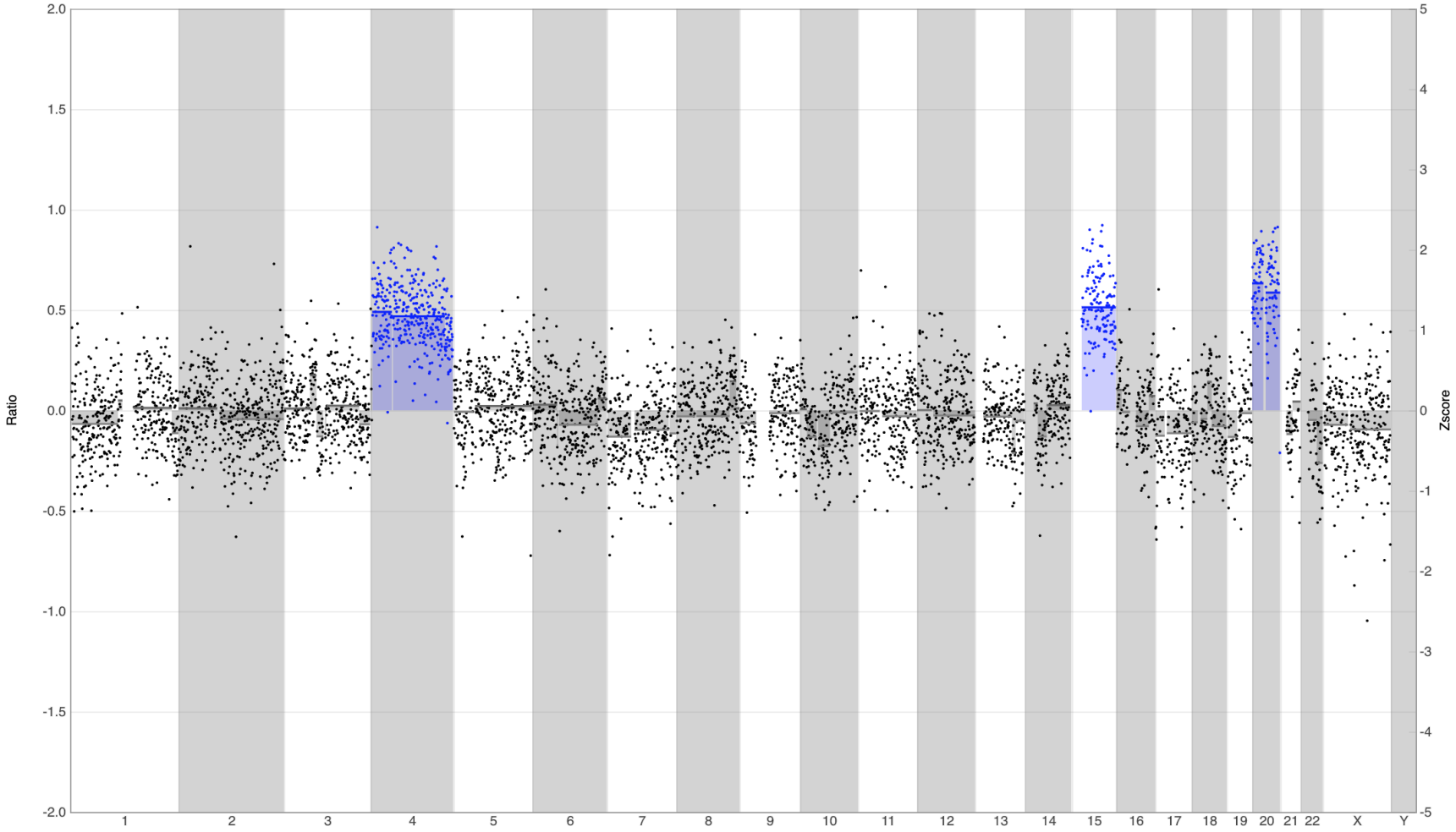


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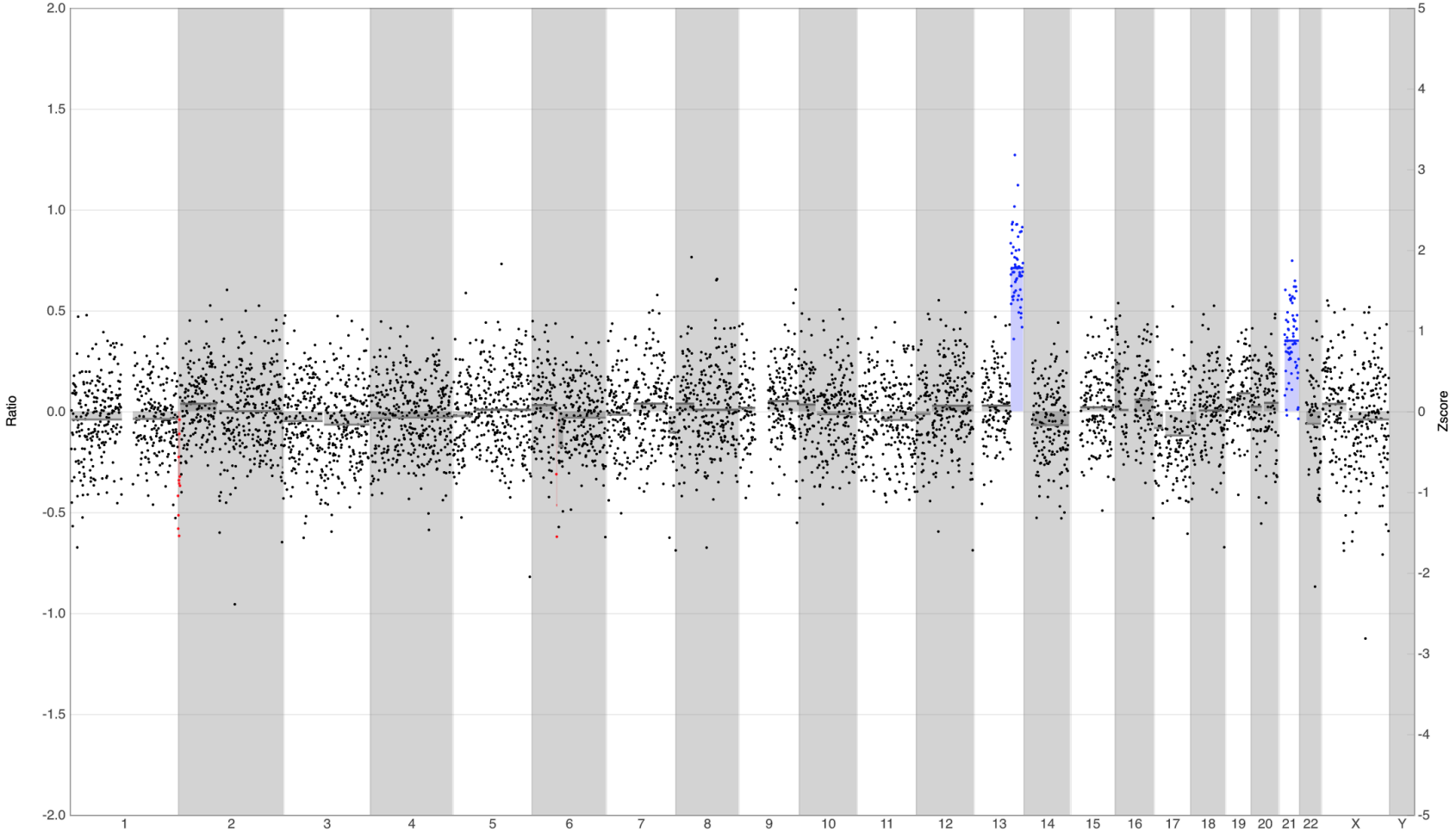
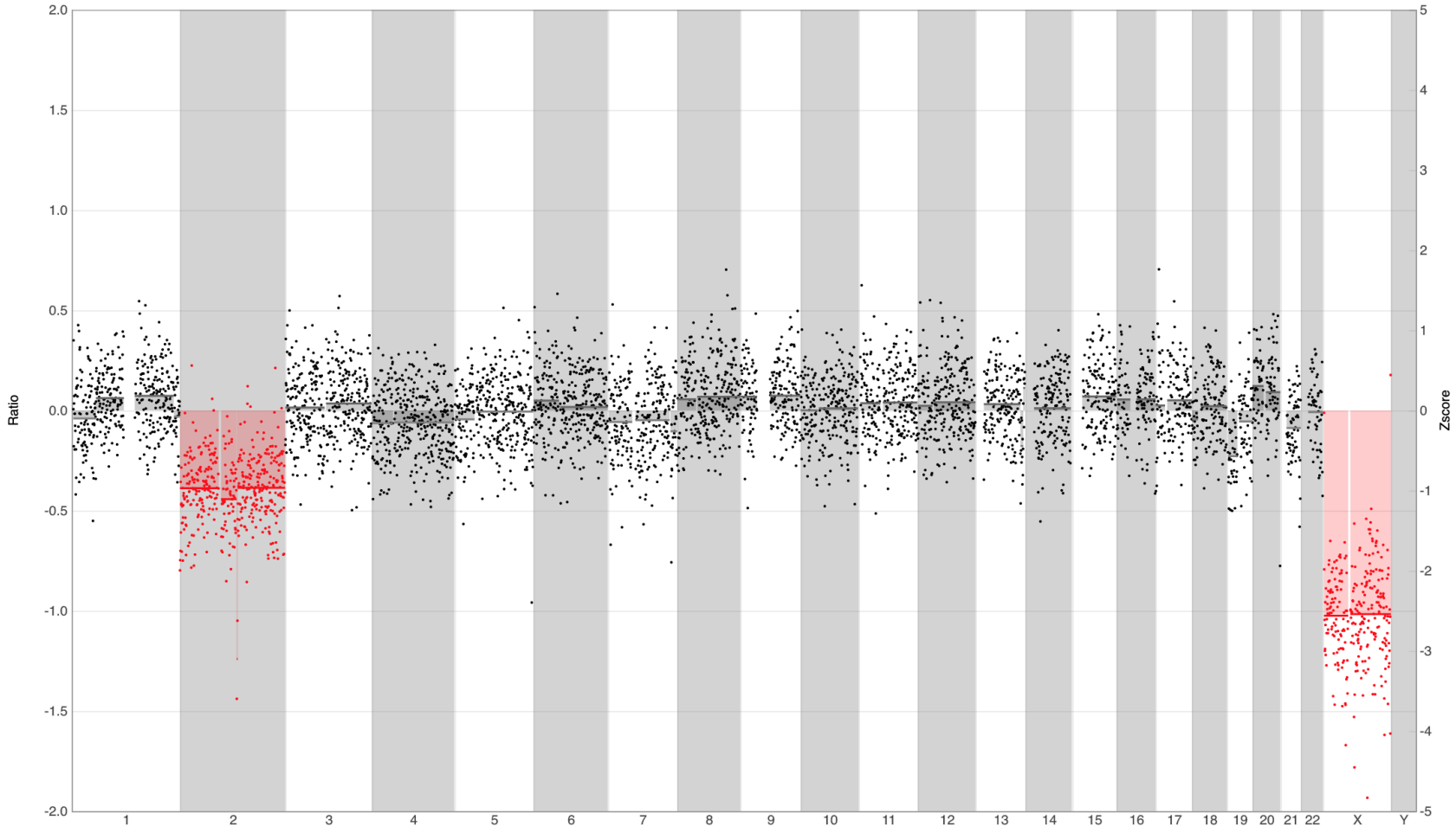
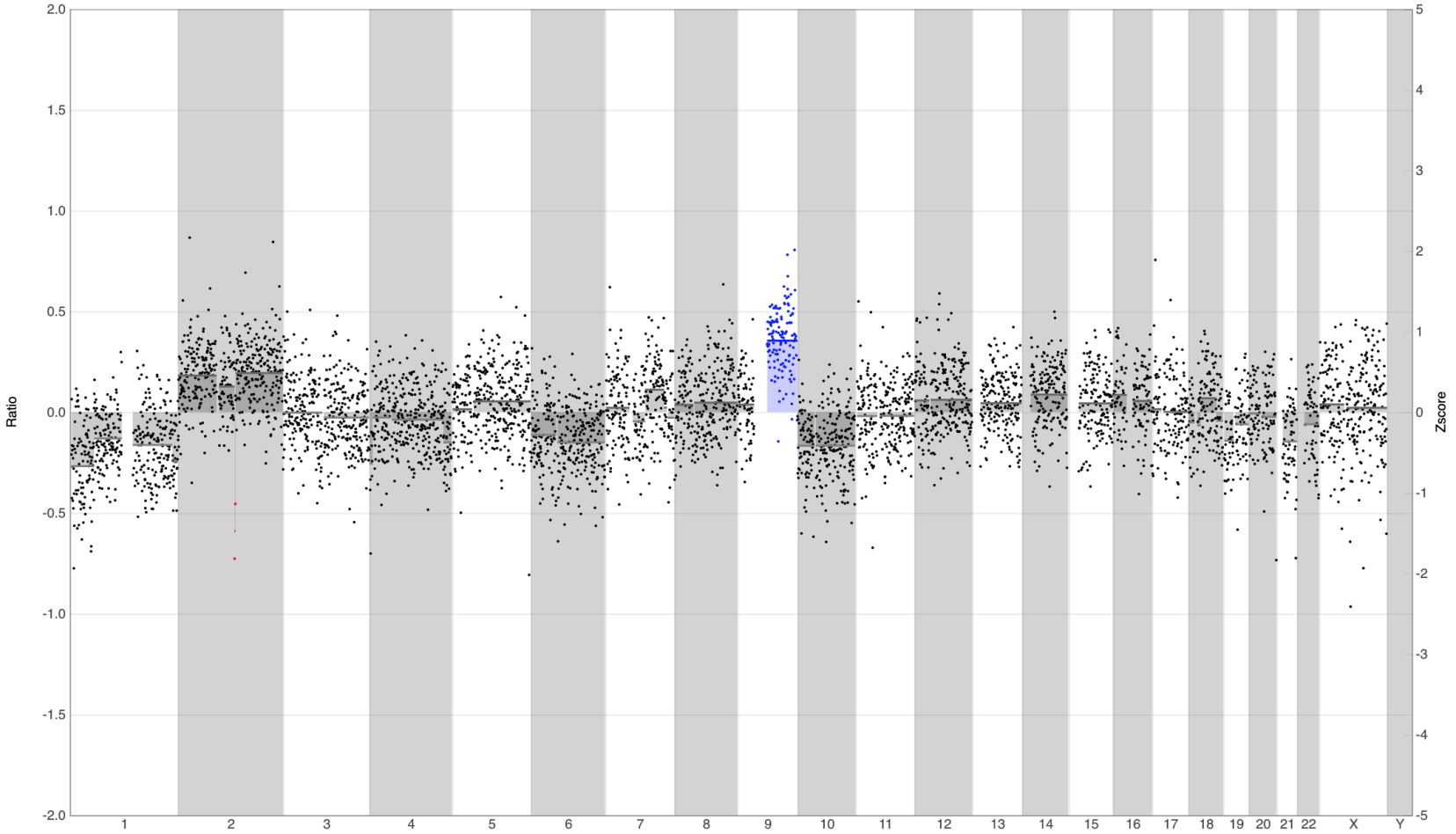


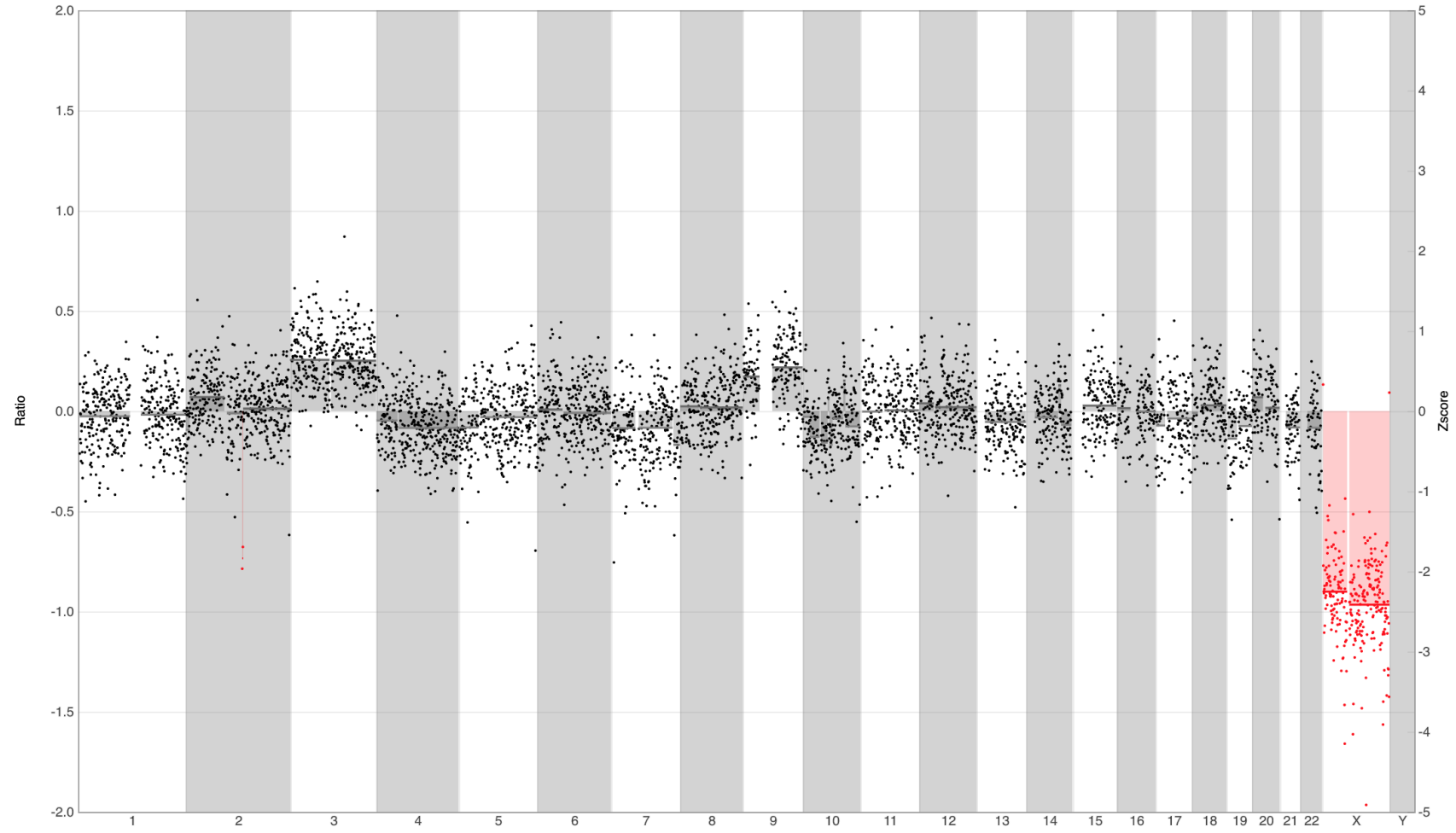

[146060] 2021-Dec-22 : K2100942:cbs Tax ID: 9606, Build: GRCh38




[145319] 2021-Nov-29 : K2100866:cbs Tax ID: 9606, Build: GRCh38




[145325] 2021-Nov-29 : K2100872:cbs Tax ID: 9606, Build: GRCh38




[148438] 2022-Mar-14 : K2200142:cbs Tax ID: 9606, Build: GRCh38

igg.be/view/6?experiments=148438&c=3

# BeGECS

- **Gene panel: ECS_mandatory_AR:**

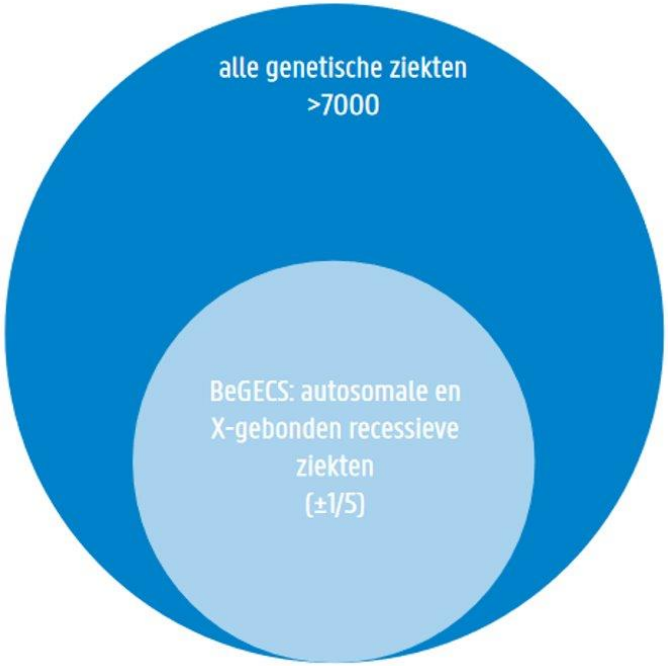
7 diseases with highest carrier frequency. Whenever a (likely) pathogenic variant is found in these genes --> report in result letter.

- **Gene panel: ECS_mandatory_optional:**

All autosomal recessive genes that are known to cause severe disorders during childhood. (Likely) pathogenic variants are only reported when the partner also carries a variant in this gene.

- **Gene panel: ECS_mandatory_X:**

All X-linked recessive genes that are known to cause severe disorders. Whenever a (likely) pathogenic variant is found in the female and/or in the EFNB1 and PCDH19 genes in the male --> report in the result letter.



| Genes | Disorder |
|---|---|
| ACADM | Acyl-CoA dehydrogenase, medium chain, deficiency of, 201450 (3), Autosomal recessive |
| CFTR | {Bronchiectasis with or without elevated sweat chloride 1, modifier of}, 211400 (3), Autosomal dominant; Congenital bilateral absence of vas deferens, 277180 (3), Autosomal recessive; Cystic fibrosis, 219700 (3), Autosomal recessive; {Hypertrypsinemia, neonatal} (3); {Pancreatitis, hereditary}, 167800 (3), Autosomal dominant; Sweat chloride elevation without CF (3) |
| DHCR7 | Smith-Lemli-Opitz syndrome, 270400 (3), Autosomal recessive |
| GJB2 | Bart-Pumphrey syndrome, 149200 (3), Autosomal dominant; Deafness, autosomal dominant 3A, 601544 (3), Autosomal dominant; Deafness, autosomal recessive 1A, 220290 (3), Autosomal recessive; Hystrix-like ichthyosis with deafness, 602540 (3), Autosomal dominant; Keratitis-ichthyosis-deafness syndrome, 148210 (3), Autosomal dominant; Keratoderma, palmoplantar, with deafness, 148350 (3), Autosomal dominant; Vohwinkel syndrome, 124500 (3), Autosomal dominant |
| GJB6 | Deafness, autosomal dominant 3B, 612643 (3), Autosomal dominant; Deafness, autosomal recessive 1B, 612645 (3), Autosomal recessive; Deafness, digenic GJB2/GJB6, 220290 (3), Autosomal recessive; Ectodermal dysplasia 2, Clouston type, 129500 (3), Autosomal dominant |
| HBB | Delta-beta thalassemia, 141749 (3), Autosomal dominant; Erythrocytosis 6, 617980 (3); Heinz body anemia, 140700 (3), Autosomal dominant; Hereditary persistence of fetal hemoglobin, 141749 (3), Autosomal dominant; {Malaria, resistance to}, 611162 (3); Methmoglobinemia, beta type, 617971 (3); Sickle cell anemia, 603903 (3), Autosomal recessive; Thalassemia, beta, 613985 (3); Thalassemia-beta, dominant inclusion-body, 603902 (3) |
| PAH | [Hyperphenylalaninemia, non-PKU mild], 261600 (3), Autosomal recessive; Phenylketonuria, 261600 (3), Autosomal recessive |
| SMN1 | Spinal muscular atrophy-1, 253300 (3), Autosomal recessive; Spinal muscular atrophy-2, 253550 (3), Autosomal recessive; Spinal muscular atrophy-3, 253400 (3), Autosomal recessive; Spinal muscular atrophy-4, 271150 (3), Autosomal recessive |

# BeGECS

ECS_MANDATORY_AR

# BeGECS

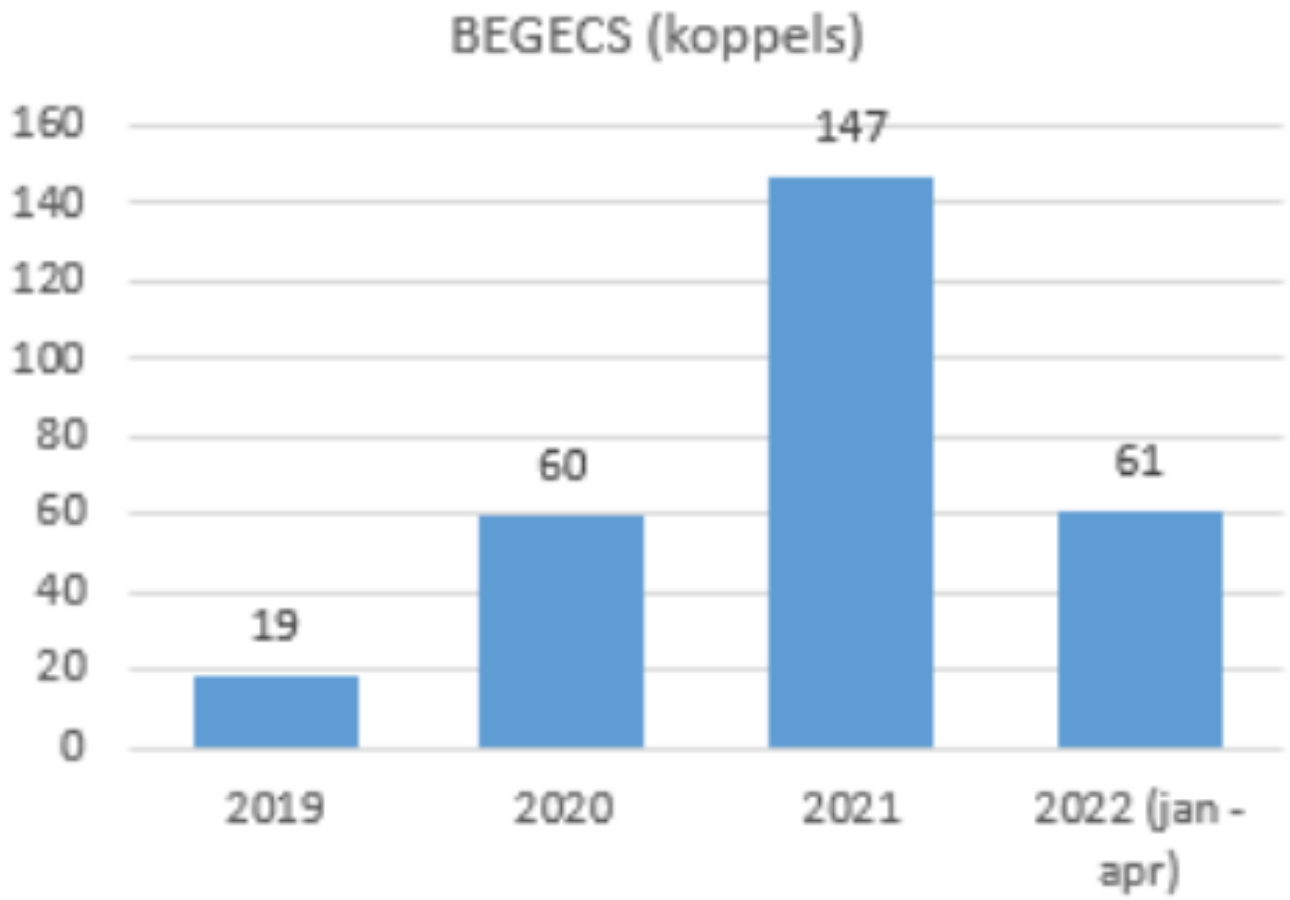
How is it performed in the lab?

DMD, SMA: MLPA-based

Targeted, customized gene panel, 1100 genes: NGS

FraX: TP-PCR (TP = triplet primed, triplet disease)

GJB6 multiplex PCR


BEGECS (koppels)
160
140
120
100
80
60
40
20
0
19
60
147
61
2019
2020
2021
2022 (jan - apr)

| Dragerschap AR mutatie met dragerschapsfrequentie ≤ 1/50 | | | |
|---|---|---|---|
| **Gen** | **Aandoening** | **Dragerschap op 138 personen** | **Dragerschapsfrequentie** |
| SMA | Spinale Musculaire Atrofie | 6 | 1/23 |
| GJB2-6 | Doofheid | 6 | 1/23 |
| CFTR | mucoviscidose | 11→7 | 1/20 |
| DHCR7 | Smith-Lemli Opitz syndroom | 5 | 1/28 |
| HBB - HBS | hemoglobinopathie | 1 | 1/138 |
| ACADM | Medium-Chain Acyl-CoA Dehydrogenase Deficiëntie | 4 | 1/35 |
| PAH | Fenylketonurie | 5 | 1/28 |

CFTR: correctie dragerschap, 2 koppels met gekend dragerschap (PGT)

| Dragerschap XL mutatie in DMD – FMR1 | | | |
|---|---|---|---|
| Gen | Aandoening | Aantal/ 69 vrouwen | Dragerschapsfrequentie |
| DMD | Duchenne / Becker spierdystrofie | 0 | |
| FMR1 grijze zone | | 4 | 1/17 |
| FMR1 premutatie | POF - FXTAS | 0 | |
| FMR1 mutatie | Fragile X syndroom | 0 | |

| Dragerschap XL mutatie in DMD – FMR1 | | | |
|---|---|---|---|
| Gen | Aandoening | Aantal/ 69 vrouwen | Dragerschapsfrequentie |
| DMD | Duchenne / Becker spierdystrofie | 0 | |
| FMR1 grijze zone | | 4 | 1/17 |
| FMR1 premutatie | POF - FXTAS | 0 | |
| FMR1 mutatie | Fragile X syndroom | 0 | |

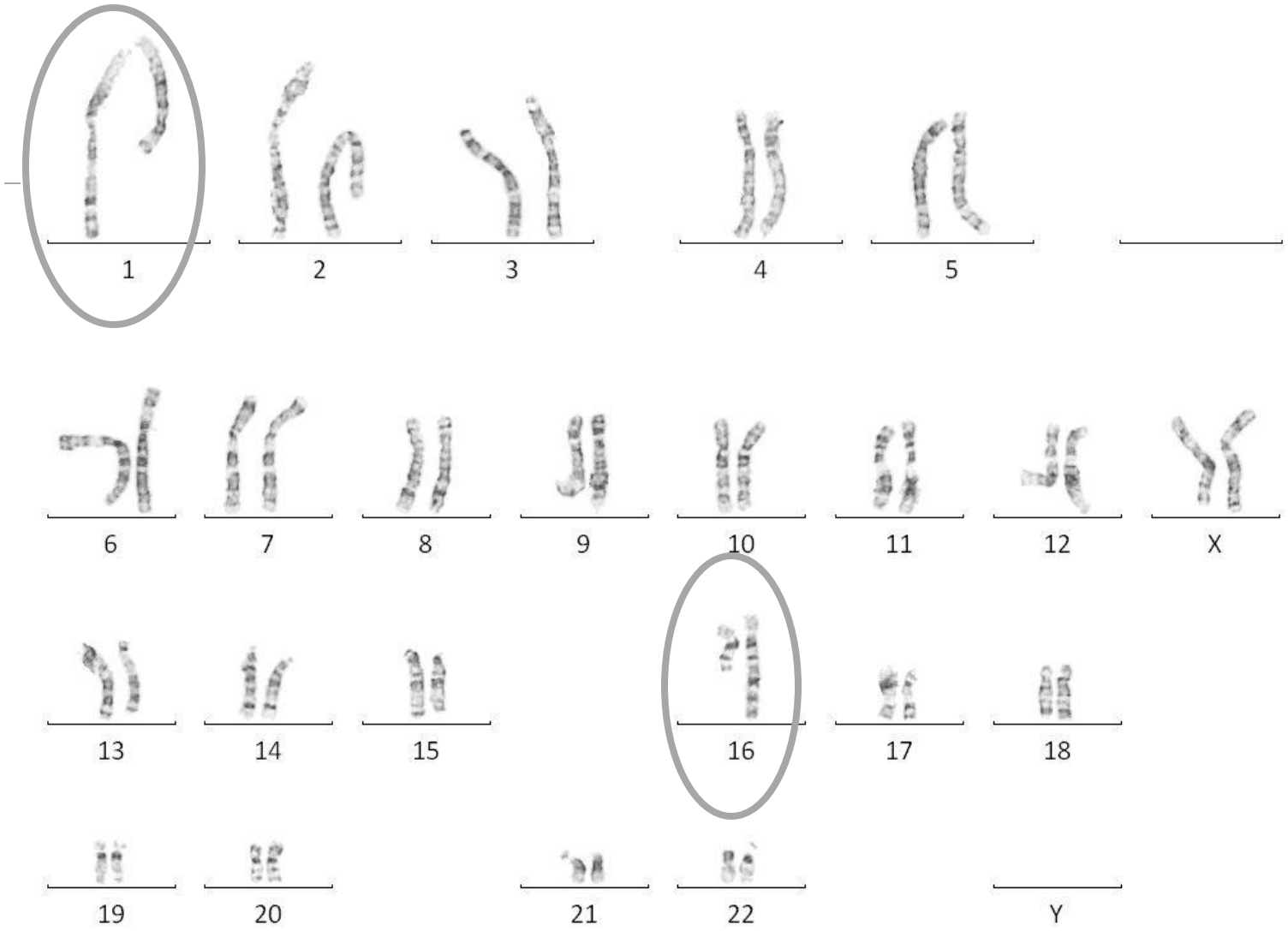
| Dragerkoppels van AR mutatie (niet eerder gekend) | | | |
|---|---|---|---|
| **Gen** | **Fenotype** | **Aantal / 69 koppels** | **Consanguien** |
| ABCC6 | PXE | 1 | + |
| MUTYH | MUTYH associated polyposis | 1 | + |
| TYR | Oculocutaan albinisme | 1 | + |

| Dragerschap XL mutatie (niet eerder gekend) | | | |
|---|---|---|---|
| **Gen** | **Fenotype** | **Aantal/ 138 personen** | **implicatie** |
| G6PD | Favisme | 1 (♂) | Vermijden tuinbonen, bepaalde medicatie |

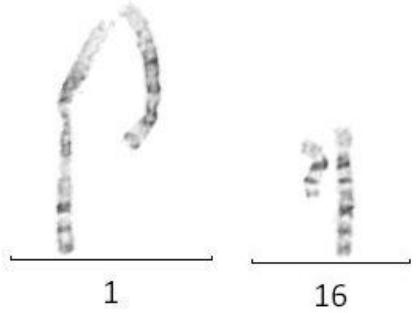
# PGT-SR

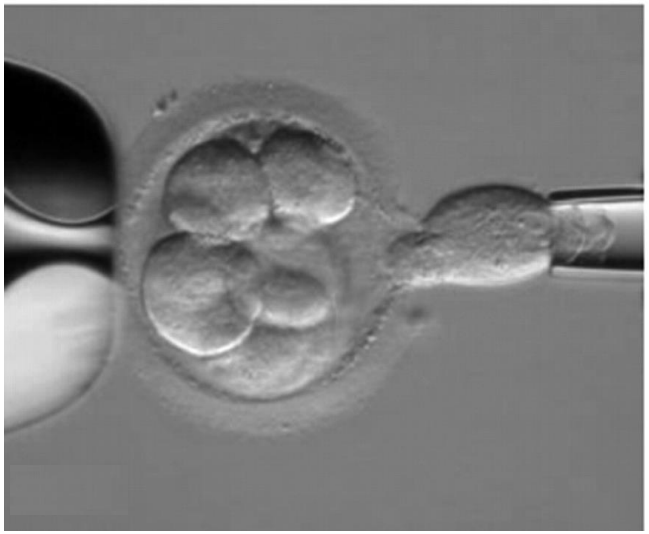
- Structural rearrangements: translocation, (pericentric) inversions, insertions, deletions, …
- blastomere (day 3) + FISH or comprehensive chromosome screening (CCS)
- trophectoderm (day 5) + CCS
- resolution CCS:
  - ~ 10 Mb microarrays
  - ~ 5 Mb NGS

46,XX,t(1;16)(q24;q23)

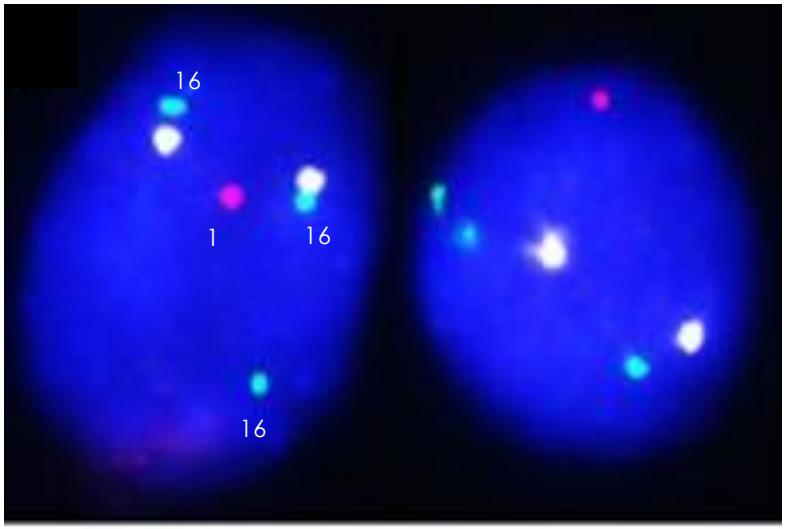


# day 3



FISH

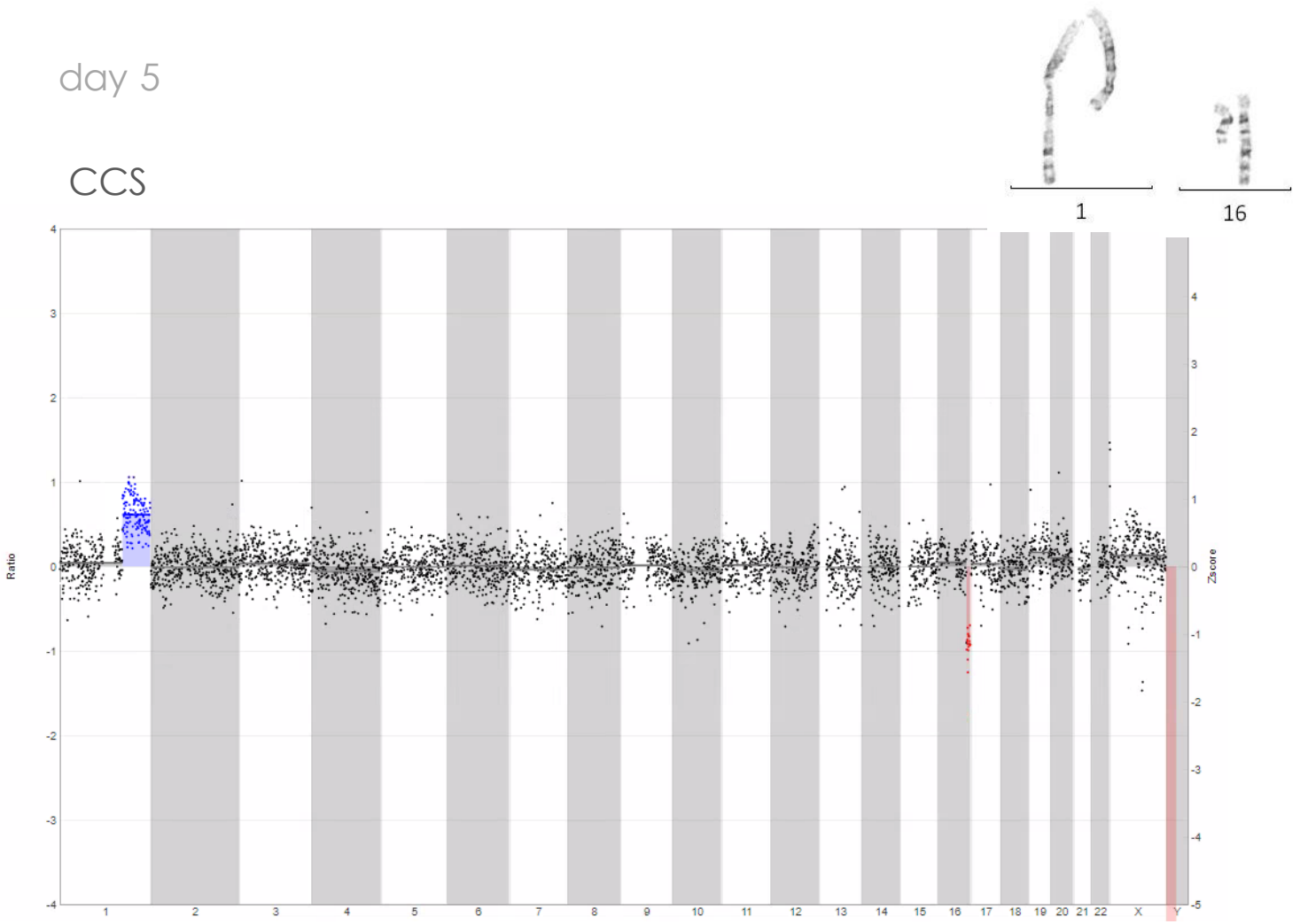


# FISH

- Strengths:
  - Structural rearrangements with small exchanged segments can be diagnosed.
  - Haploidy and polyploidy can be detected
- Limitations:
  - Patient-specific workup required
  - Often subjective interpretation (low signal to background).
  - Frequent FISH errors (splitting or overlapping signals)
  - Few chromosomes are tested (probemix)
  - Not useful for duplications
  - Normal and balanced segregations are not distinguishable

day 5

CCS


1
16
Ratio
Zscore
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 X Y

# CCS: arrayCGH and sWGS

- Strengths:
  - No patient-specific workup required
  - All chromosomes are tested
  - Straightforward interpretation

- Limitations:
  - Structural rearrangements with small exchanged segments (<5 Mb/ 10 Mb) cannot be diagnosed
  - Normal and balanced segregations are not distinguishable
  - Haploidy and polyploidy cannot be detected
  - Uniparental disomy (UPD) is not detected

# PGT-A

- Couple has a normal karyotype
  - Recurrent implantation failure
  - Recurrent abortion
  - Advanced maternal age
  - Antecedents trisomy

ESTABLISHED IN 1812 JULY 5, 2007 VOL. 357 NO. 1

# In Vitro Fertilization with Preimplantation Genetic Screening

Sebastiaan Mastenbroek, M.Sc., Moniek Twisk, M.D., Jannie van Echten-Arends, Ph.D., Birgit Sikkema-Raddatz, Ph.D., Johanna C. Korevaar, Ph.D., Harold R. Verhoeve, M.D., Niels E.A. Vogel, M.D, Eus G.J.M. Arts, Ph.D., Jan W.A. de Vries, Ph.D., Patrick M. Bossuyt, Ph.D., Charles H.C.M. Buys, Ph.D., Maas Jan Heineman, M.D., Ph.D., Sjoerd Repping, Ph.D., and Fulco van der Veen, M.D., Ph.D.

NEJM

**Letter**

## Response: how PGS/PGT-a laboratories succeeded in losing all credibility

Munné et al. 2018 Reprod Biomed Online

*To the Editor*

We commend the passion with which Dr Gleicher et al. [2018] defend their business model, denouncing preimplantation genetic screening (PGS) as their marketing differentiator from other centres. It would be idealistic if this was a purely academic discussion, however there are commercial interests on both sides and whilst the authors discuss theories and opinions, this reply reports facts and data supporting PGS.

decision between the patient and t
error rate was higher and well kno
clearly in reports and consents. Fo
ogy and adding mosaicism screenin
euploid and fully aneuploid embryos
sify an intermediate group as mos
pregnancy potential (Fragouli et al.,
Greco et al., 2015; Grifo et al., 2015
et al., 2016, 2017b; Spinella et al.,

Human Reproduction, Vol.29, No.9 pp. 1846–1850, 2014
Advanced Access publication on July 8, 2014 doi:10.1093/humrep/deu163

human reproduction OPINION

## Preimplantation genetic screening: back to the future

**Sebastiaan Mastenbroek* and Sjoerd Repping**

Center for Reproductive Medicine, Academic Medical Center, University of Amsterdam, Q3-119, Meibergdreef 9, 1105 AZ, Amsterdam, The Netherlands

*Correspondence address. E-mail: s.mastenbroek@amc.uva.nl

*Submitted on April 1, 2014; resubmitted on May 9, 2014; accepted on June 3, 2014*

**ABSTRACT:** All agree that in hindsight the rapid adoption of preimplantation genetic screening (PGS) using cleavage stage biopsy and fluorescence *in situ* hybridization (FISH) in routine clinical practice without proper evaluation of (cost-)effectiveness basically resulted in couples paying more money for a less effective treatment. Now, almost 20 years later, we are on the verge of a new era of PGS. But have things really changed or are we simply going back to the future?

**Key words:** IVF/ICSI / PGS / aneuploidy / efficacy / randomized controlled trials

**Human Reproduction, pp. 1–5, 2022**
https://doi.org/10.1093/humrep/deac052

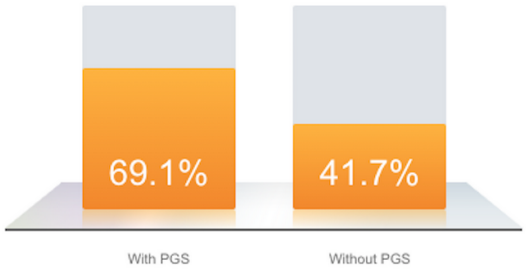
human reproduction OPINION

## We have reached a dead end for preimplantation genetic testing for aneuploidy

**Norbert Gleicher[1,2,3,4], David H. Barad [1], Pasquale Patrizio[5], and Raoul Orvieto [6,7,*]**

# Improving IVF outcomes with PGS



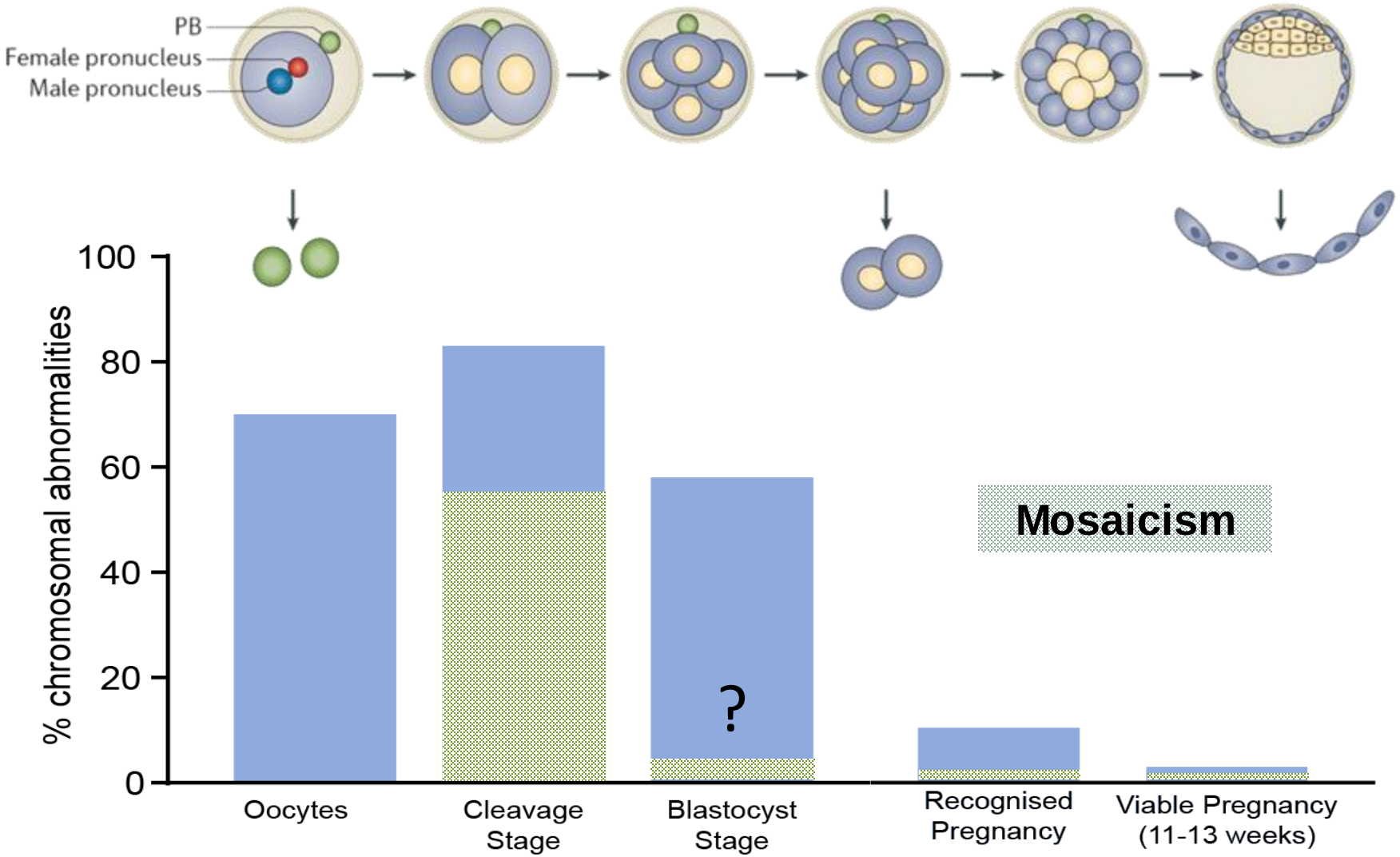



## Significantly Higher Rate of Pregnancy May Be Possible with PGS

The pregnancy rate shown for embryos analyzed using preimplantation genetic screening and morphology is 69.1%, much higher than the 41.7% achieved using morphology screening alone.[5]

Pilot study of young, good prognosis patients (age < 35, first-time IVF, no history of prior miscarriage, n = 103)

# Human preimplantation development is vulnerable to error




*Adapted from Fragouli et al. 2013, Human Genetics, Los et al. 2004, Human Reproduction Update, Vermeesch et al. 2016, Nat Rev Genet.*

**Human Reproduction, pp. 1–13, 2018**
doi:10.1093/humrep/dey106

human reproduction

ORIGINAL ARTICLE *Reproductive genetics*

# Chromosomal mosaicism in human blastocysts: the ultimate challenge of preimplantation genetic testing?

**M. Popovic[1,*], A. Dheedene[2], C. Christodoulou[1], J. Taelman[1], L. Dhaenens[1], F. Van Nieuwerburgh[3], D. Deforce[3], E. Van den Abbeel[1], P. De Sutter[1], B. Menten[2,†], and B. Heindryckx[1,†]**

[1]Ghent Fertility and Stem cell Team (G-FaST), Department for Reproductive Medicine, Ghent University Hospital, Corneel Heymanslaan 10, Ghent 9000, Belgium [2]Center for Medical Genetics, Ghent University Hospital, Corneel Heymanslaan 10, Ghent 9000, Belgium [3]Laboratory of Pharmaceutical Biotechnology, Ghent University, Ottergemsesteenweg 460, Ghent 9000, Belgium

Case: Woman, 36 years of age, **R**epeated **I**mplantation **F**ailure

→ PGT for aneuploidy testing

→ 5 embryo's for genetic testing

→ Which one to transfer (first)?

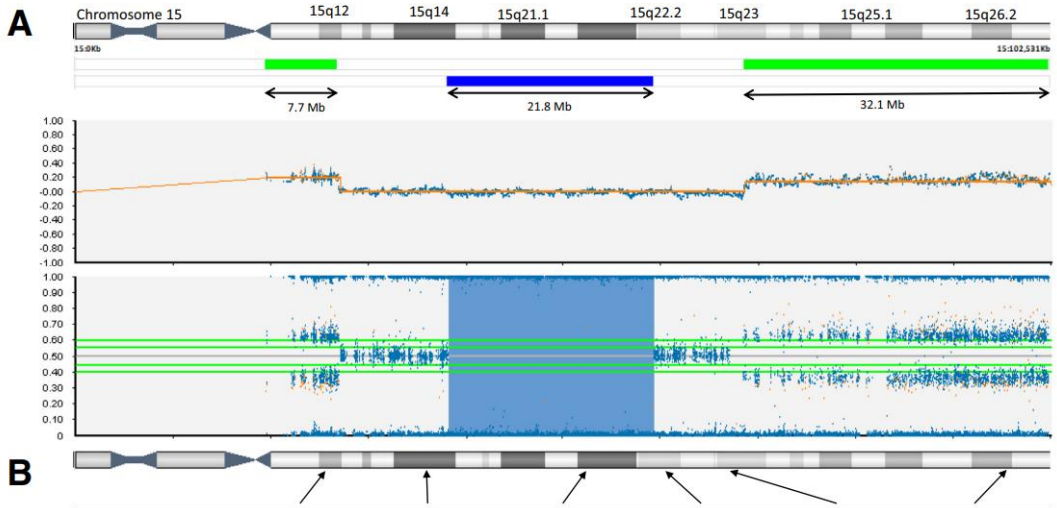
| A | B | C | D | E |
|---|---|---|---|---|
| trisomy 16 | results not interpretable | mosaic monosomy 2 | trisomy 21 | did not survive the procedure |

F: we shouldn't have performed PGT in the first place, and selected on best morphology

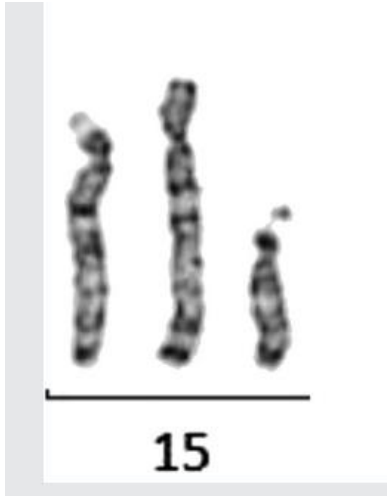
# Mosaic embryo transfer—first report of a live born with nonmosaic partial aneuploidy and uniparental disomy 15

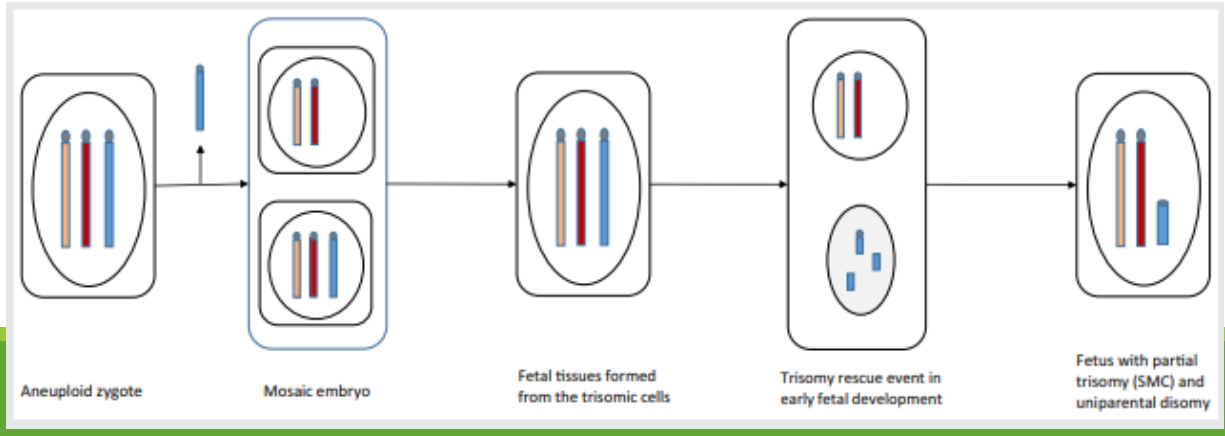


Kamilla Schlade-Bartusiak, Ph.D.,[a,b] Emma Strong, Ph.D.,[a,b] Olive Zhu, M.Sc.,[c] Jessica Mackie, M.Sc.,[c] Diane Salema, M.Sc.,[c] Michael Volodarsky, Ph.D.,[a] Jeffrey Roberts, M.D.,[c] and Michelle Steinraths, M.D.[d]




| Microsatellite marker | D15S986 | D15S118 | D15S1016 | D15S1036 | D15S988 | D15S1014 |
|---|---|---|---|---|---|---|
| Proband | 183,187 | 221,230 | 288 | 121,126 | 99 | 191,193,199 |
| Mother | 183 | 221,230 | 288,299 | 121,126 | 99 | 193,199 |
| Father | 187 | 230 | 278,290 | 119,123 | 97,101 | 191,195 |
| Result interpretation | Uninformative | Uninformative | Maternal UPD, isodisomy | Maternal UPD, heterodisomy | Maternal UPD | 2 maternal markers, 1 paternal marker |



# What will the future bring for PGT?

- Complete (genome) sequencing for de novo mutations (eg long read sequencing)
- Mitochondrial PGT-M
- Non-invasive PGT

--> BUT: where does it stop? How many "suitable" embryo's will there be left? Should parents be given a ranking of disorders when screening for multiple disorders?

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Taking advantage of the ever-expanding role of modern genetics

Introduction | Enrollment | Testing Genetics | Latest News

### Announcing Eye Color Selection!

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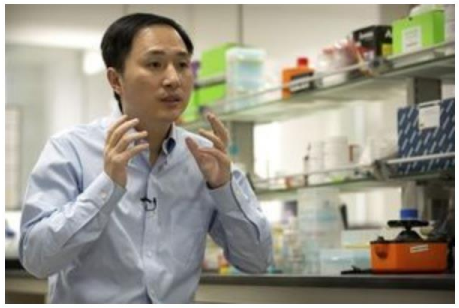
212-725-1177 New York
801-523-7573 Utah

# Chinese wetenschapper claimt eerste CRISPR-baby gemaakt te hebben

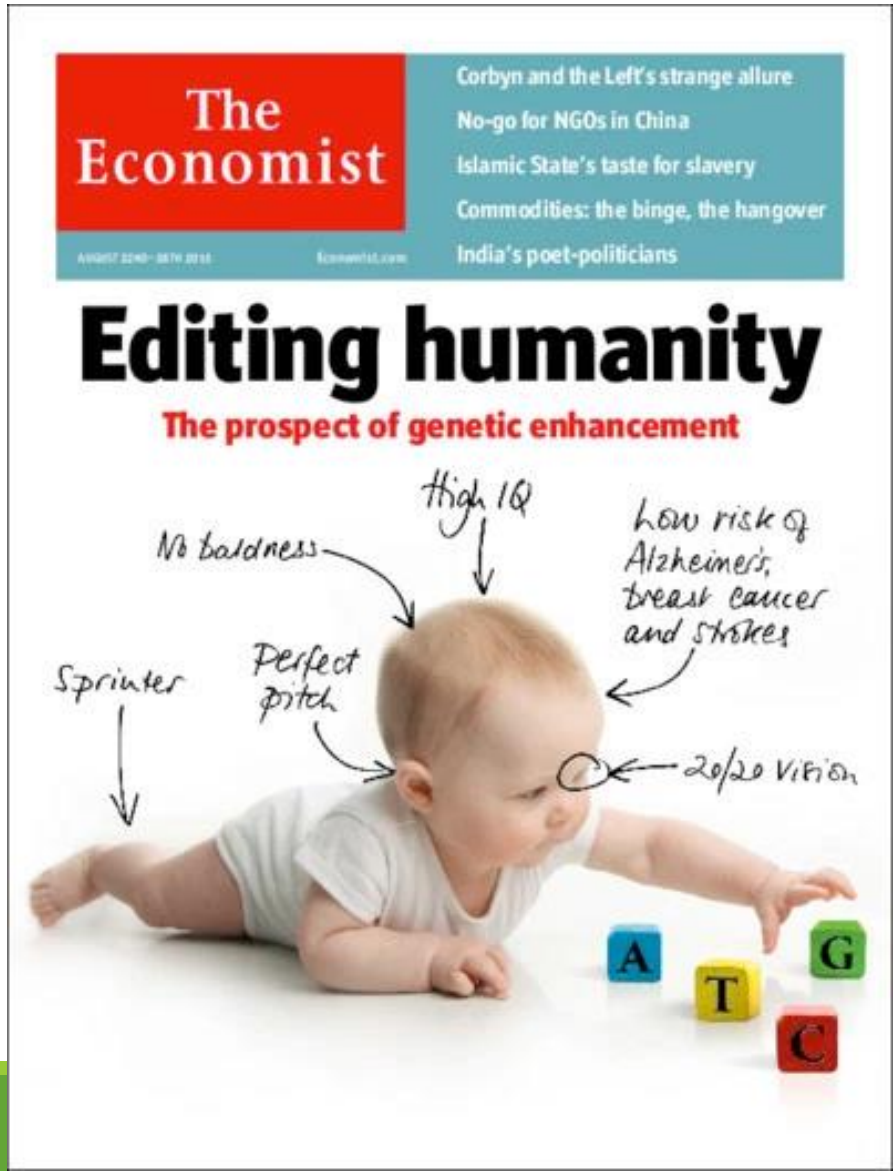
26/11/18 om 16:12 Bijgewerkt op 27/11/18 om 15:27 Bron : Belga

**De Chinese wetenschapper He Jiankui beweert de genen van een IVF-tweeling zo te hebben aangepast dat ze niet met HIV kunnen worden geïnfecteerd, zo blijkt uit een video die zondag op YouTube werd gezet. Zijn universiteit zegt weliswaar geen weet te hebben van het experiment.**



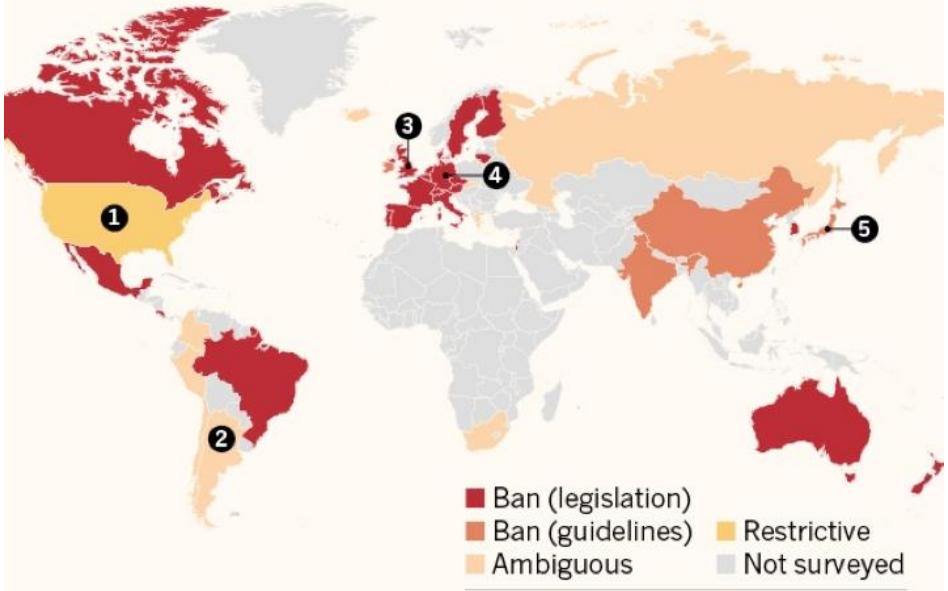
© .

De Chinese meisjes, Lulu en Nana, "kwamen enkele weken geleden wenend ter



# CRISPR EMBRYOS AND THE LAW

Regulations governing genetic modification in human embryos vary. Some countries ban the practice through legislation that carries criminal penalties; others have unenforceable guidelines.



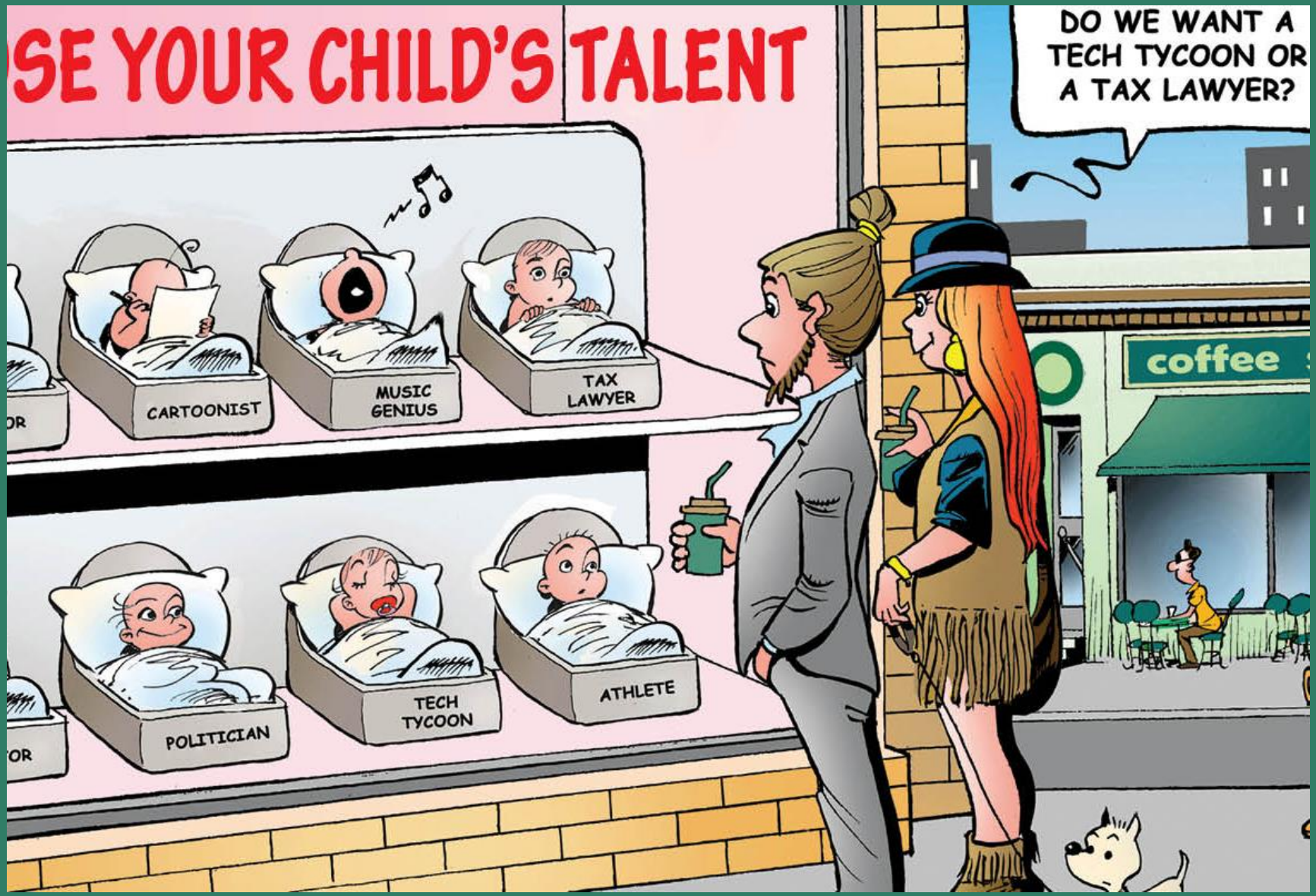

**1. THE UNITED STATES** does not allow the use of federal funds to modify human embryos, but there are no outright genome-editing bans. Clinical development may require approval.

**2. ARGENTINA** bans reproductive cloning, but research applications of human-genome editing are not clearly regulated.

**3. THE UNITED KINGDOM**'s independent Human Fertilisation and Embryology Authority may permit human-genome editing for research, but the practice is banned in the clinic.

**4. GERMANY** has strict laws on the use of embryos in assisted reproduction. It also limits research on human embryos, and violations could result in criminal charges.

**5. JAPAN**, like China, India and Ireland, has unenforceable guidelines that restrict the editing of a human embryo's genome.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