

Reproductive options and testing during pregnancy in case of a genetic disease

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Reproductive options in case of genetic disease

Avoid transmission of the disease

- ▶ Prenatal testing (w/out termination of pregnancy)
- ▶ IVF-PGT
- ▶ Gamete donation
- ▶ Adoption
- ▶ No children
- ▶ Risk acceptance

Reproductive options

Depending on time frame



Preconception

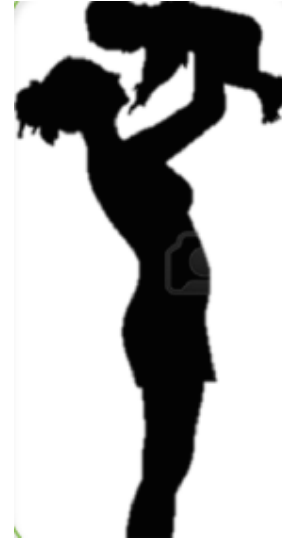
Preconception
counseling
(eg. PGT, gamete
donation, adoption)

Expanded Carrier
Screening



During pregnancy

CVS/AC

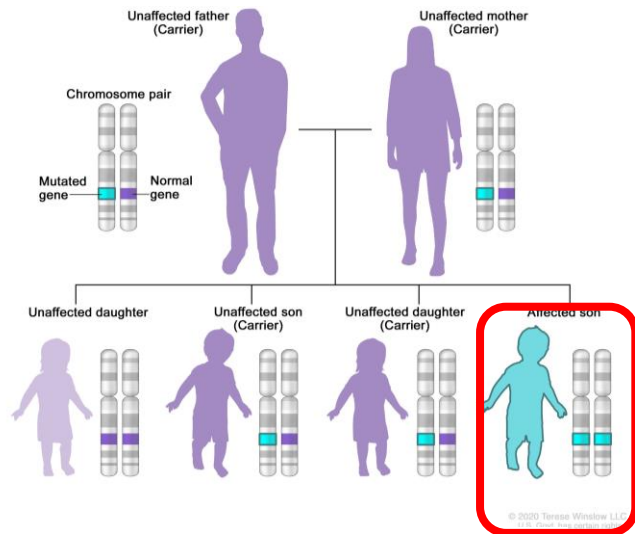


Birth

Postnatal
testing

Location	Phenotype	Inheritance	Phenotype mapping key	Phenotype MIM number	Gene/Locus	Gene/Locus MIM number
2p22.3	Cutis laxa, autosomal recessive, type IIE	AR	3	619451	LTBP1	150390
2p16.1	Cutis laxa, autosomal recessive, type ID	AR	3	620780	EFEMP1	601548
3q13.31	Cutis laxa, autosomal recessive, type IID	AR	3	617403	ATP6V1A	607027
7q11.23	Cutis laxa, autosomal dominant	AD	3	123700	ELN	130160
10q24.1	Cutis laxa, autosomal recessive, type IIIA	AR	3	219150	ALDH18A1	138250
10q24.1	Cutis laxa, autosomal dominant 3	AD	3	616603	ALDH18A1	138250
11q13.1	Cutis laxa, autosomal recessive, type IB	AR	3	614437	EFEMP2	604633
12q24.31	Cutis laxa, autosomal recessive, type IIA	AR	3	219200	ATP6V0A2	611716
14q32.12	Cutis laxa, autosomal recessive, type IA	AR	3	219100	FBLN5	604580
14q32.12	?Cutis laxa, autosomal dominant 2	AD	3	614434	FBLN5	604580
17q25.3	Cutis laxa, autosomal recessive, type IIIB	AR	3	614438	PYCR1	179035
17q25.3	Cutis laxa, autosomal recessive, type IIB	AR	3	612940	PYCR1	179035
19q13.2	Cutis laxa, autosomal recessive, type IC	AR	3	613177	LTBP4	604710
22q11.21	Cutis laxa, autosomal recessive, type IIC	AR	3	617402	ATP6V1E1	108746

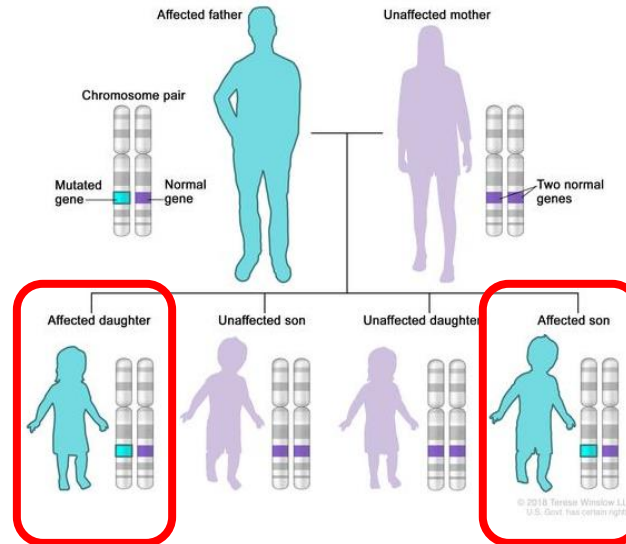
Autosomal recessive



Risk of 25% for an affected child

LTBP4
(AR)

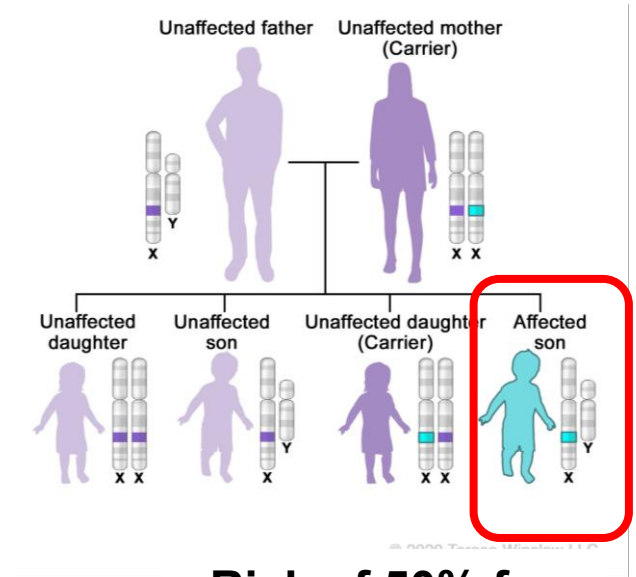
Autosomal dominant



Risk of 50% for an affected child

ELN
(AD)

X-linked



Risk of 50% for an affected son

ATP7A
(XL)

Reproductive options

Depending on time frame



Preconception

Preconception
counseling
(eg. PGT)

Expanded Carrier
Screening



During pregnancy

CVS/AC



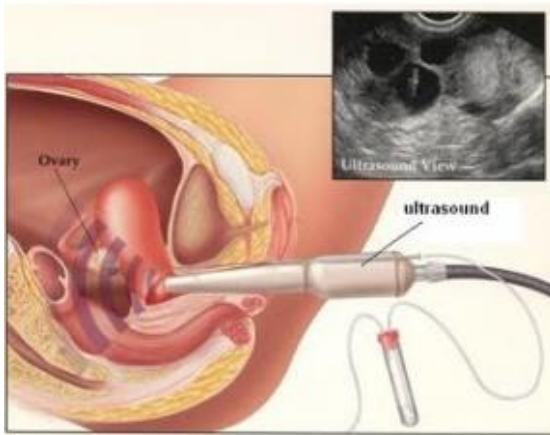
Birth

Postnatal
testing

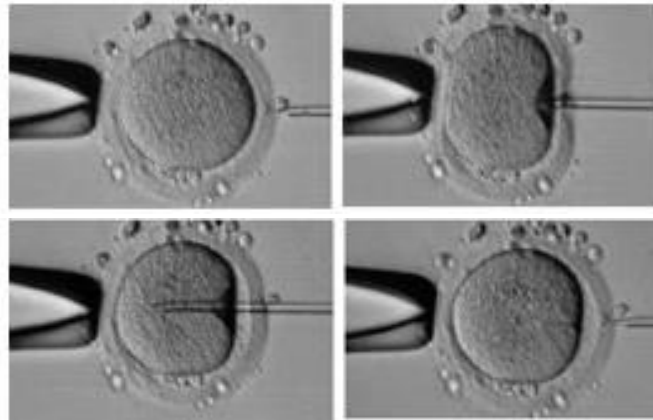
Pre-implantation genetic testing (PGT)

- ▶ For couples whose future children are *at risk* for a genetic disease
- ▶ If the gene defect is known
- ▶ If no PND with pregnancy interruption is desirable

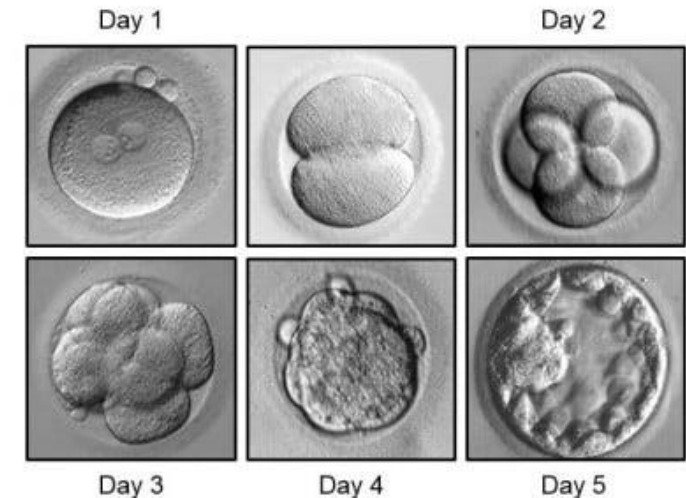
IVF



Hormone stimulation
Oocyte retrieval

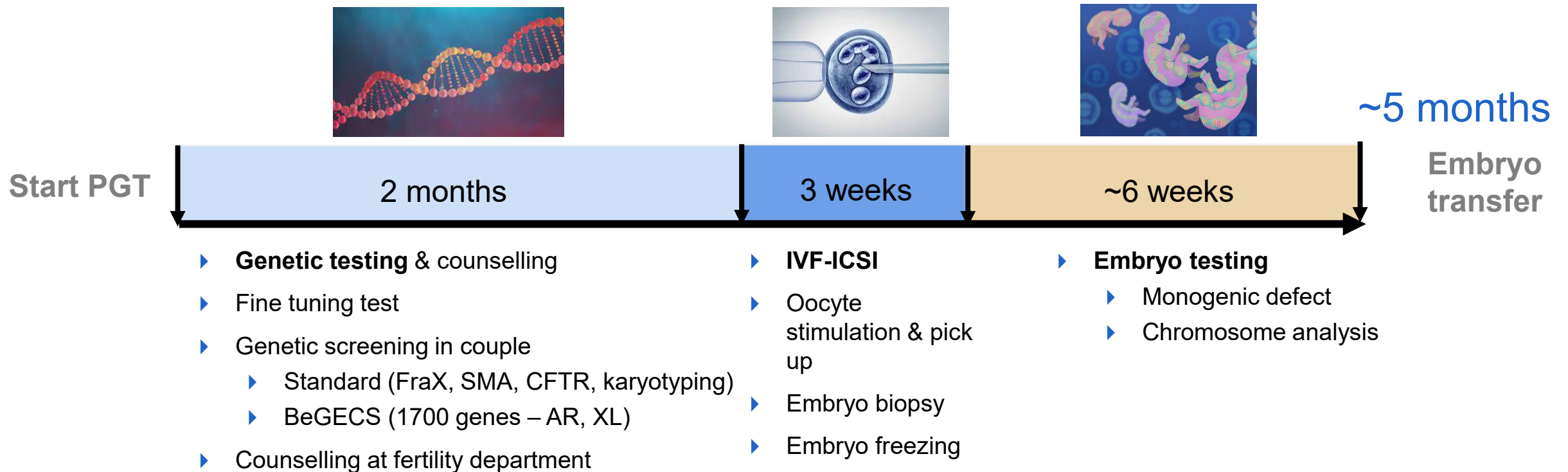


Intracytoplasmic sperm
injection (ICSI)



Embryo development
Embryo biopsy

PGT: Trajectory in case of a known genetic defect



Success rate for live birth after transfer: ~40%

PGT: Costs

▶ Consultatie genetica beide partners	€ 93,38
▶ Karyotype beide partners	€ 664,00
▶ Dragerschapsonderzoek	
▶ Mucoviscidose beide partners	€ 349,24 (eventueel eerst ♂)
▶ Spinale musculaire atrofie ♀	€ 402,08
▶ Fragile X syndroom ♀	€ 174,62
▶ coPGT-M: oppuntstelling test	€ 2 297,60
▶ PGT analyse (per IVF cyclus)	€ 1 723,20
▶ Totale kostprijs	€ 5 629,50/ 5704,12 – € 6206,20
▶ Belgische patiënten	
▶ Remgeld / analyse	€ 8,68
▶ Remgeld consultatie beide partners	€ 24

Cost for patient +/- € 1000-1500

6 cycles reimbursed

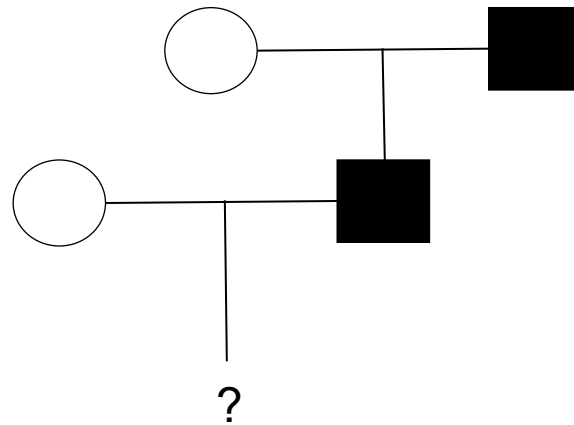
PGT in the lab

Procedure:

- Step 1: fine tuning of the coPGT-M test, genetic carrier screening and karyotyping
 - Prerequisites for coPGT-M:
 - The familial variant is known and is causally linked to the clinical phenotype
 - It is possible to (Sanger) sequence this variant
 - Purpose of the fine tuning phase: phasing of the haplotype, is the available genetic information informative enough: can we reliably detect the “affected allele”?

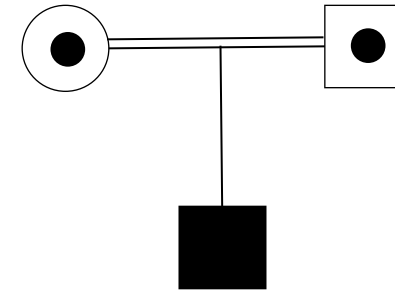
PGT in the lab

Autosomal dominant inheritance



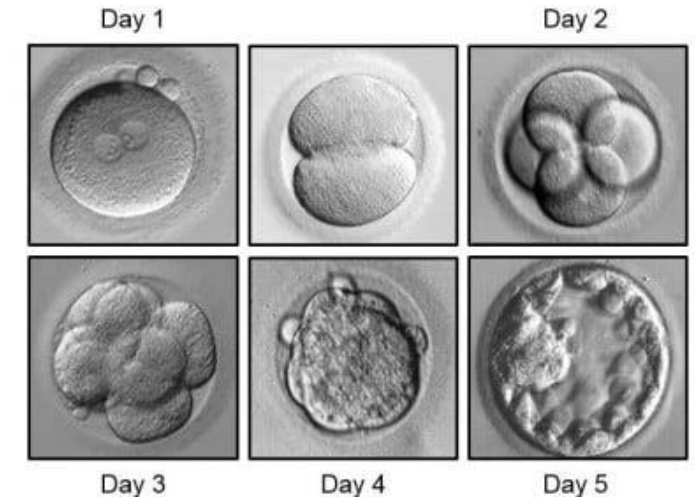
Sample from an additional affected family member needed for phasing of the haplotype

Autosomal recessive inheritance



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

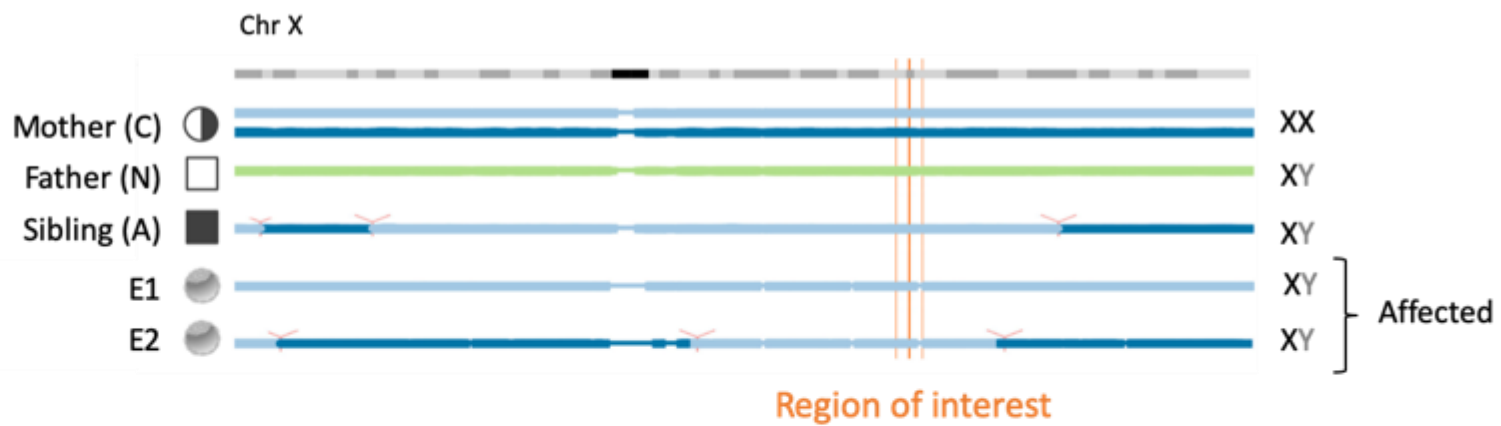
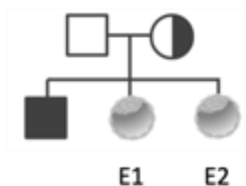
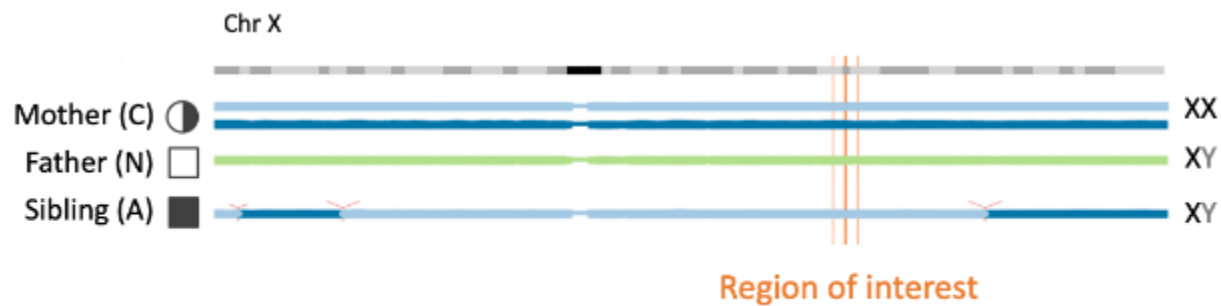
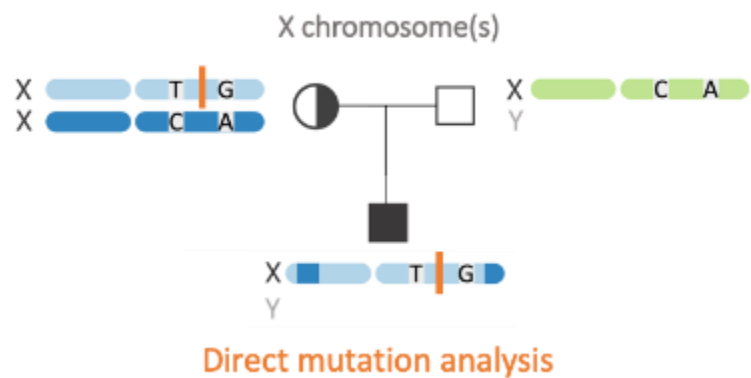
PGT in the lab

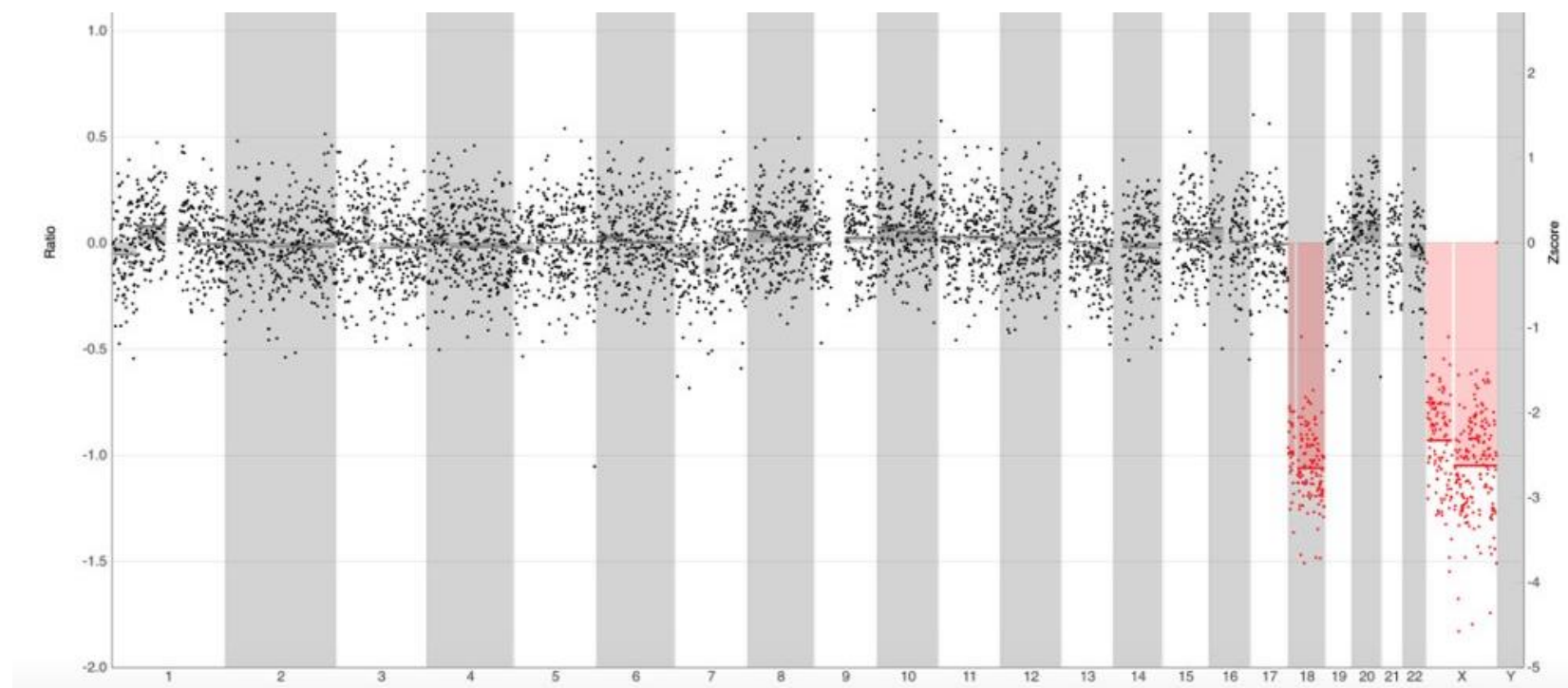
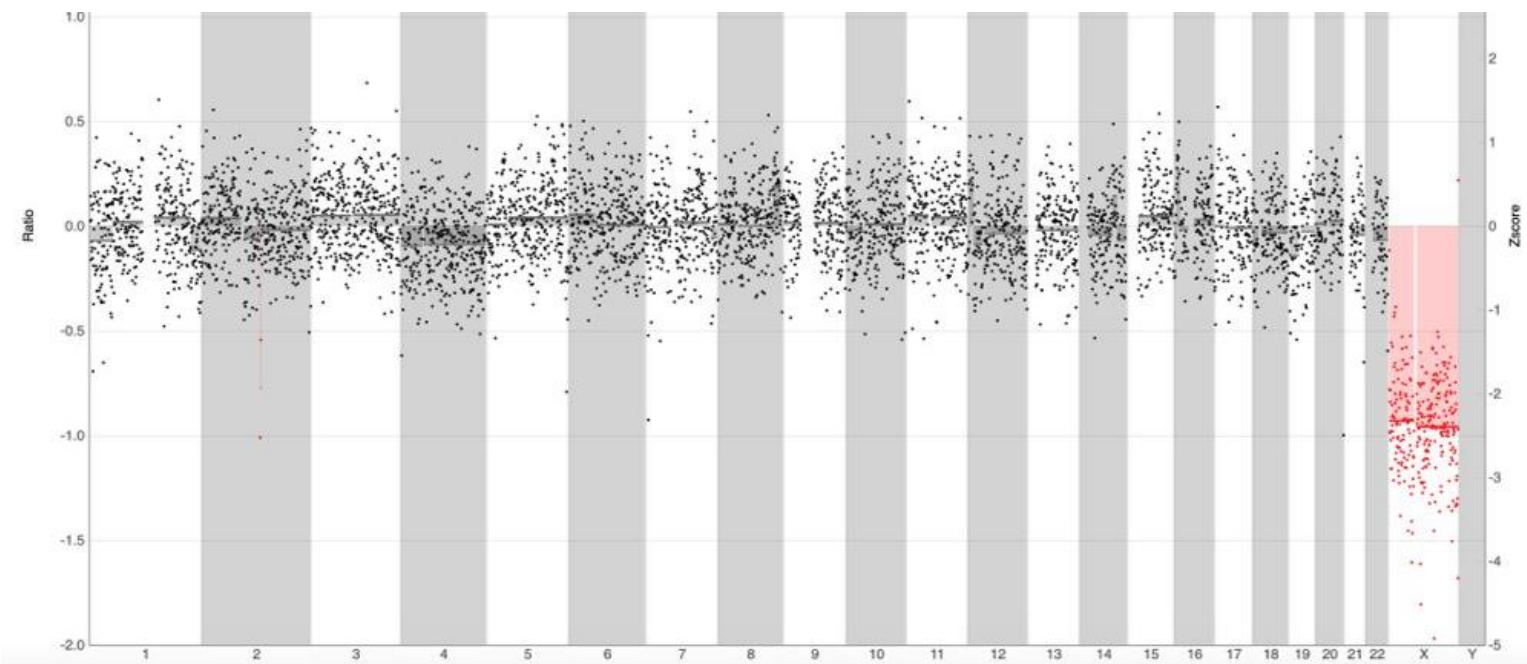


Embryo development
Embryo biopsy

Procedure:

- Step 2: coPGT-M test (= genomewide sequencing) on embryo biopsies
 - Embryos are tested for the familial pathogenic variant linked to the monogenic disease (cutis laxa)
 - And for aneuploidies (and for large chromosomal structural variants)





Reproductive options

Depending on time frame



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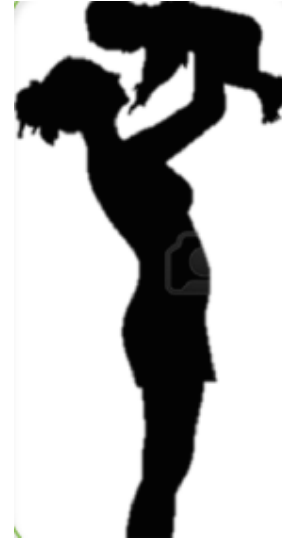
Preconception
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(eg. PGT)

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During pregnancy

CVS/AC



Birth

Postnatal
testing

Invasive prenatal testing

CVS (Chorion Villi Sampling)

- ▶ 11-12w
- ▶ Transvaginal/abdominal
- ▶ Placenta

AC (Amniocentesis)

- ▶ >15w
- ▶ Transabdominal
- ▶ Amniocytes (fetal cells)

- ▶ Risk miscarriage: 1/400
- ▶ Genetic tests: CNV/exome/...
- ▶ Diagnostic with US abnormalities/
known genetic risk
- ▶ TOP (termination of pregnancy)



Reproductive options

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Preconception

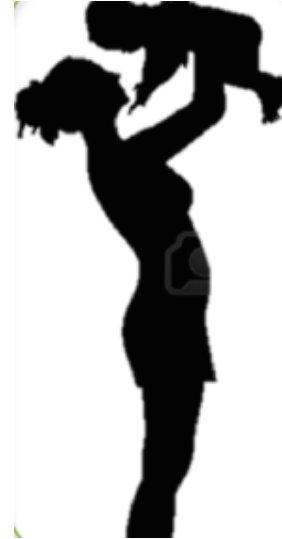
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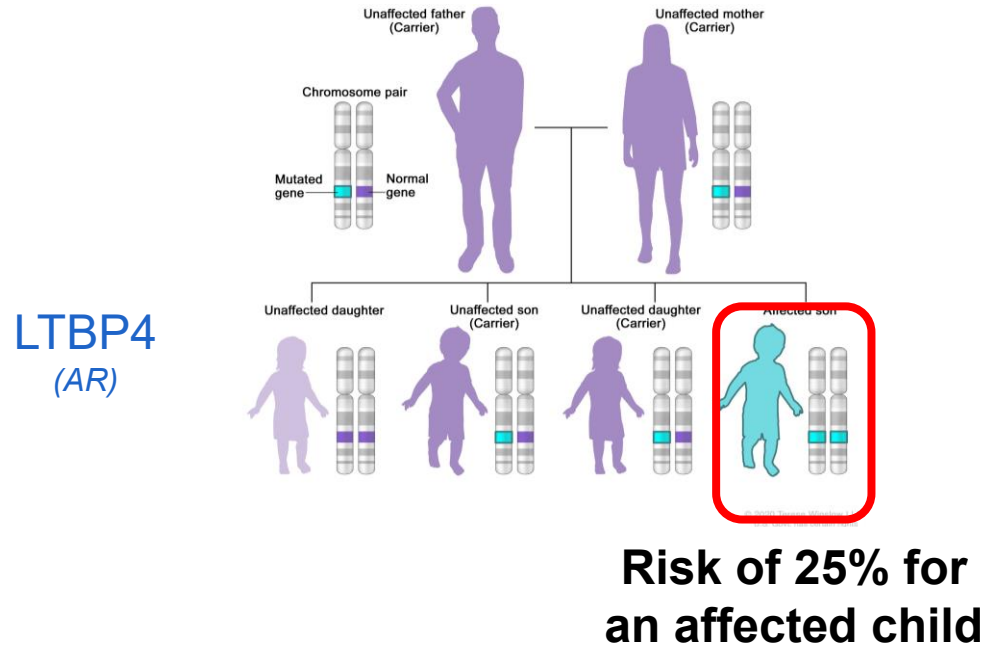
BeGECS – Expanded carrier screening

Couple test

Goal: Reduce occurrence of severe recessive/X-linked disorders

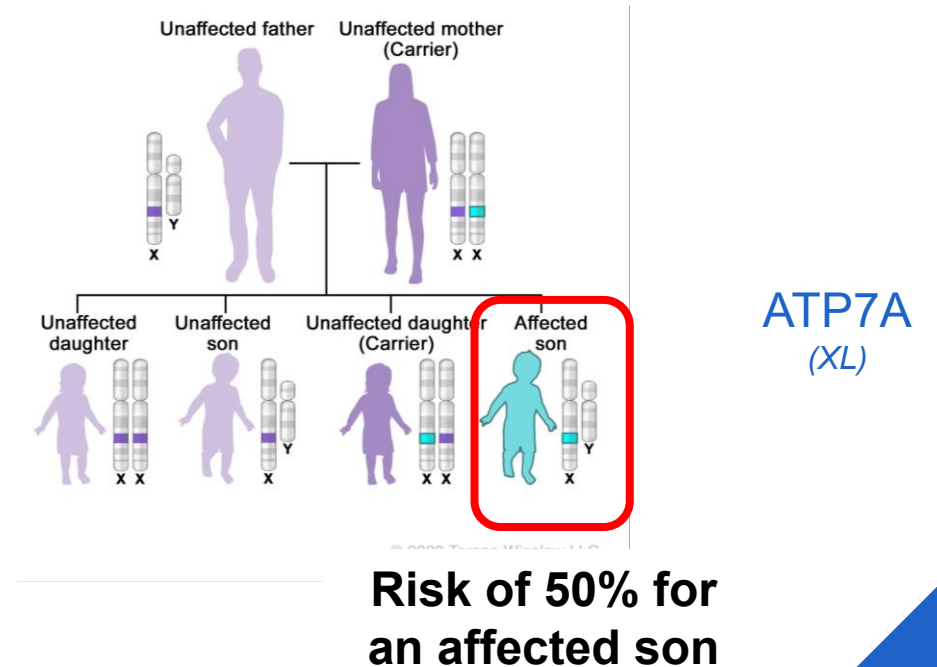
Autosomal recessive disease

- Identify (unaffected) carriers of a genetic defect in the same gene



X-linked disease

- Identify (unaffected) carriers of an X-linked disease



BeGECS – Expanded carrier screening

Couple test

- ▶ Blood test
- ▶ Goal: Reduce occurrence of severe recessive/X-linked disorders
- ▶ 2017: Positive advice “Hoge Gezondheidsraad” concerning expanded carrier screening
- ▶ >2019: BeGECS

- ▶ 1700 genetic diseases
- ▶ Yield: ~3-5%
- ▶ Turn around time: 2 months
- ▶ Cost: 1500 euro
 - ▶ 250-300 euro reimbursement

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Volg ons op



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