Current status of PGD

Johnny Hindkjær

CENTRE OF

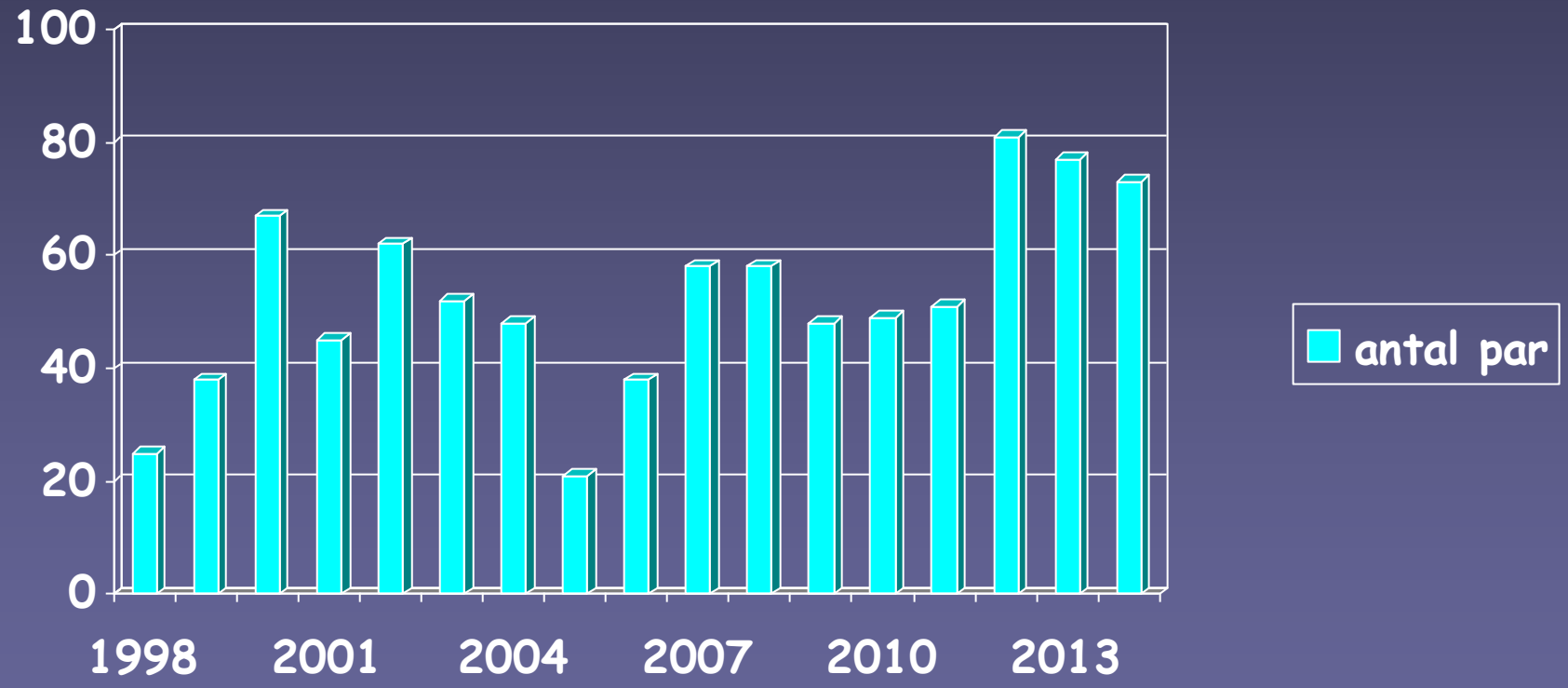
PREIMPLANTATION GENETIC DIAGNOSIS

AARHUS UNIVERSITY HOSPITAL

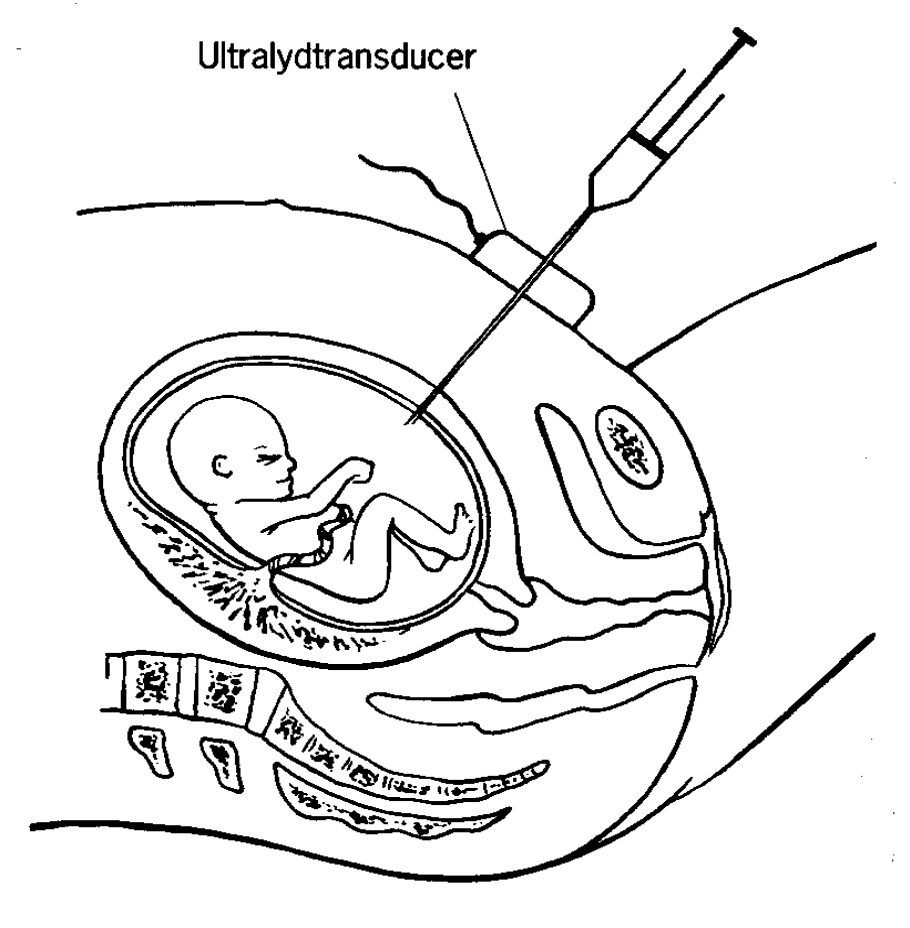
REPRODUKTIVE CHOISES IN GENETIC DISEASES

- No children
- Adoption
- Oocyte or semen donation
- Take the chance
- Prenatal diagnosis and possible abortion.
- Preimplantation genetic diagnosis

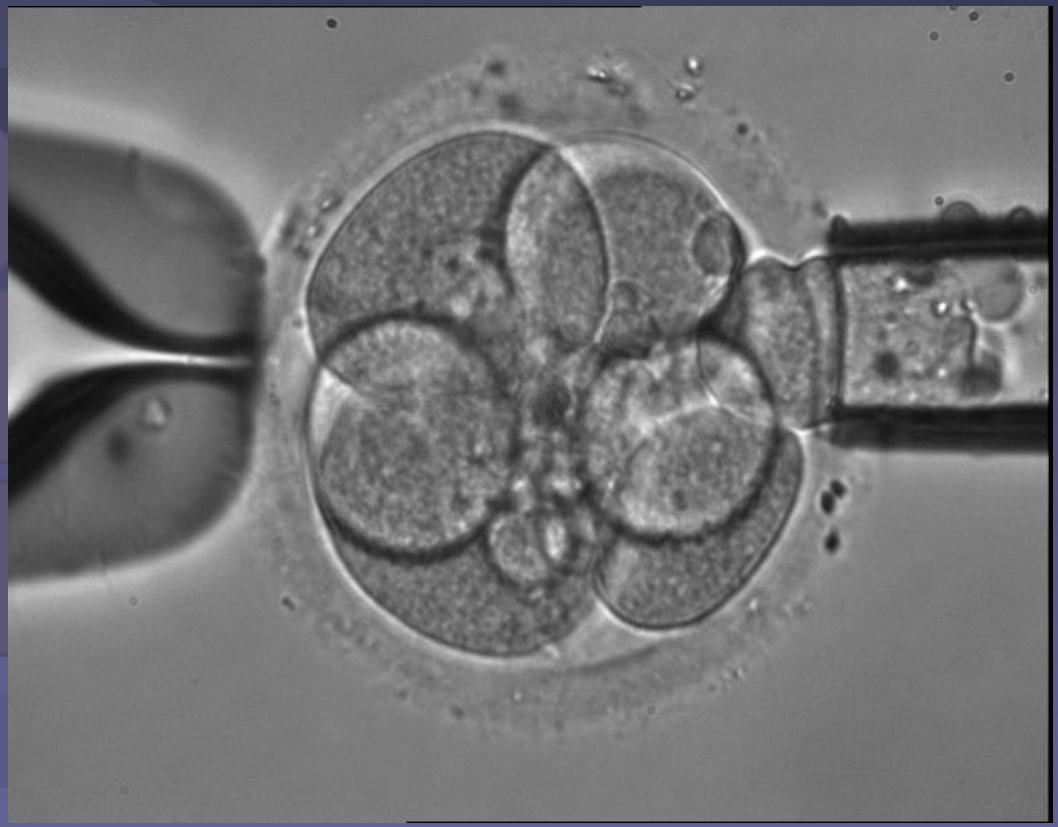
% of referred pt. that want PGD



CVS/amnio 10. - 16. week



PGD 3-6. days



Law (DK) on artificial insemination 10. June 1997

- Scientific protocol proved by a scientific comity

§7 part 1
- High risk of having a child with an serious inherited disease

§7 part 2
-In combination with IVF to look for chromosome abnormalities

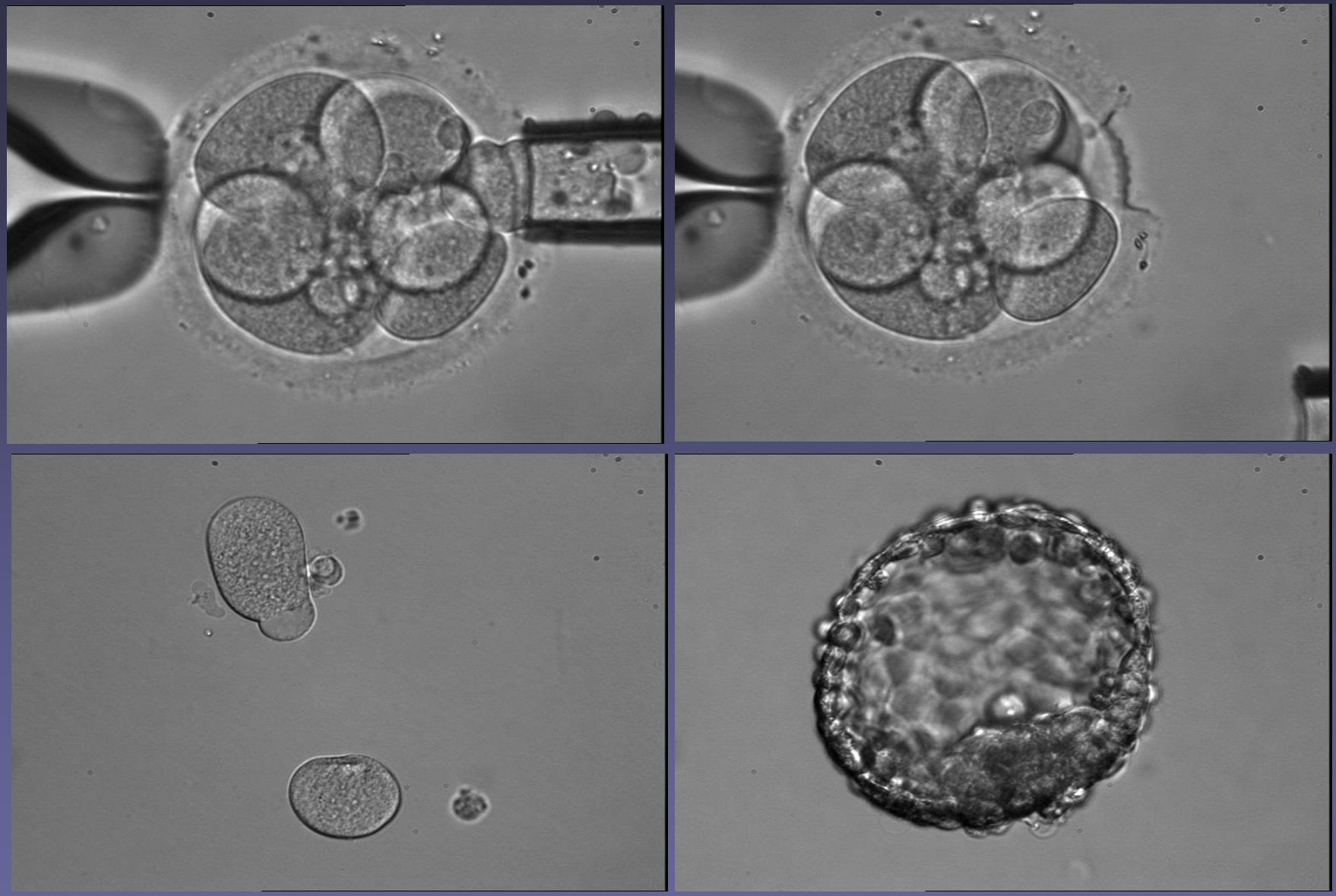
-PGD with HLA match to save a sibling who needs new stem cells (March 2004)

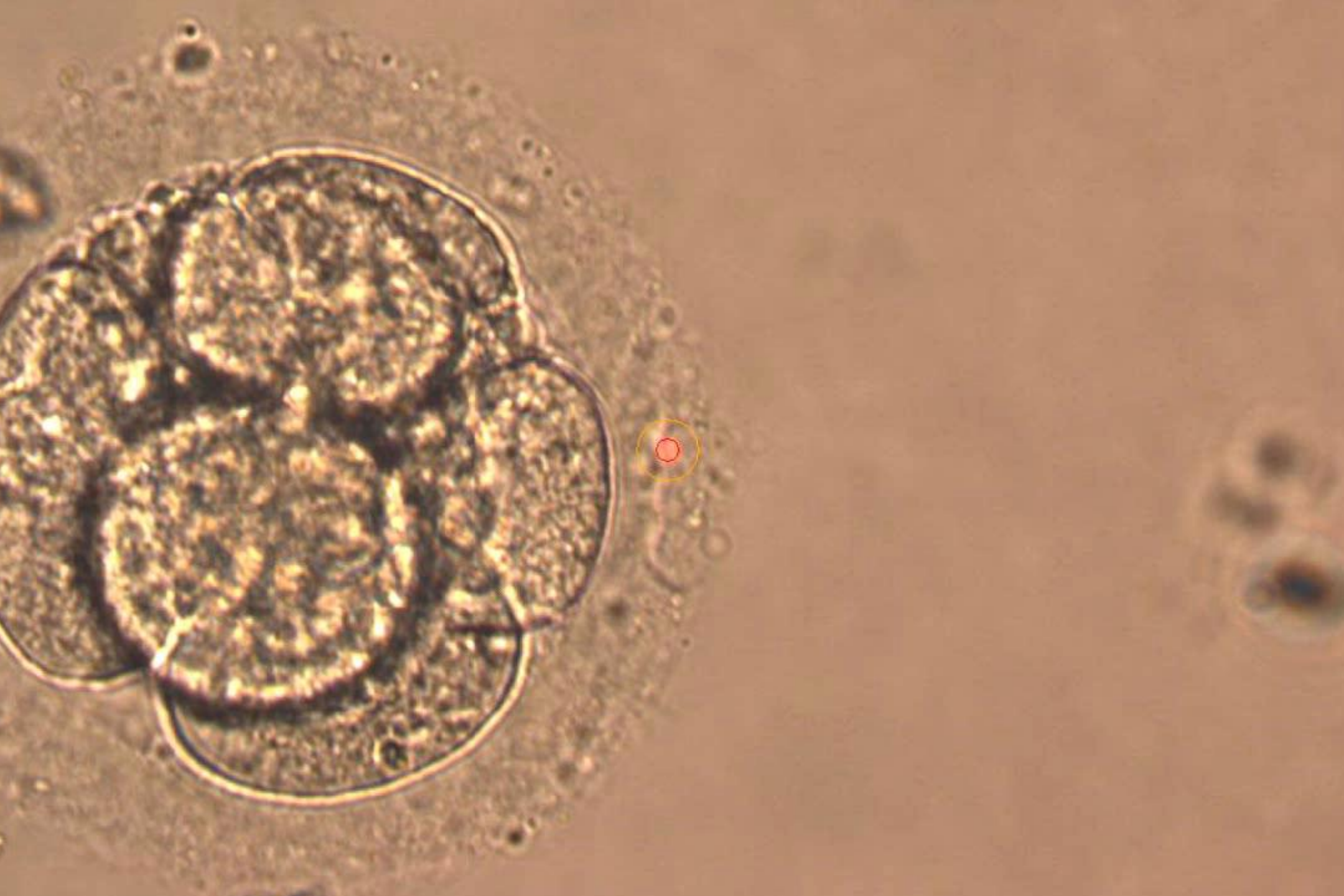
PRÆIMPLANTATION DIAGNOSIS

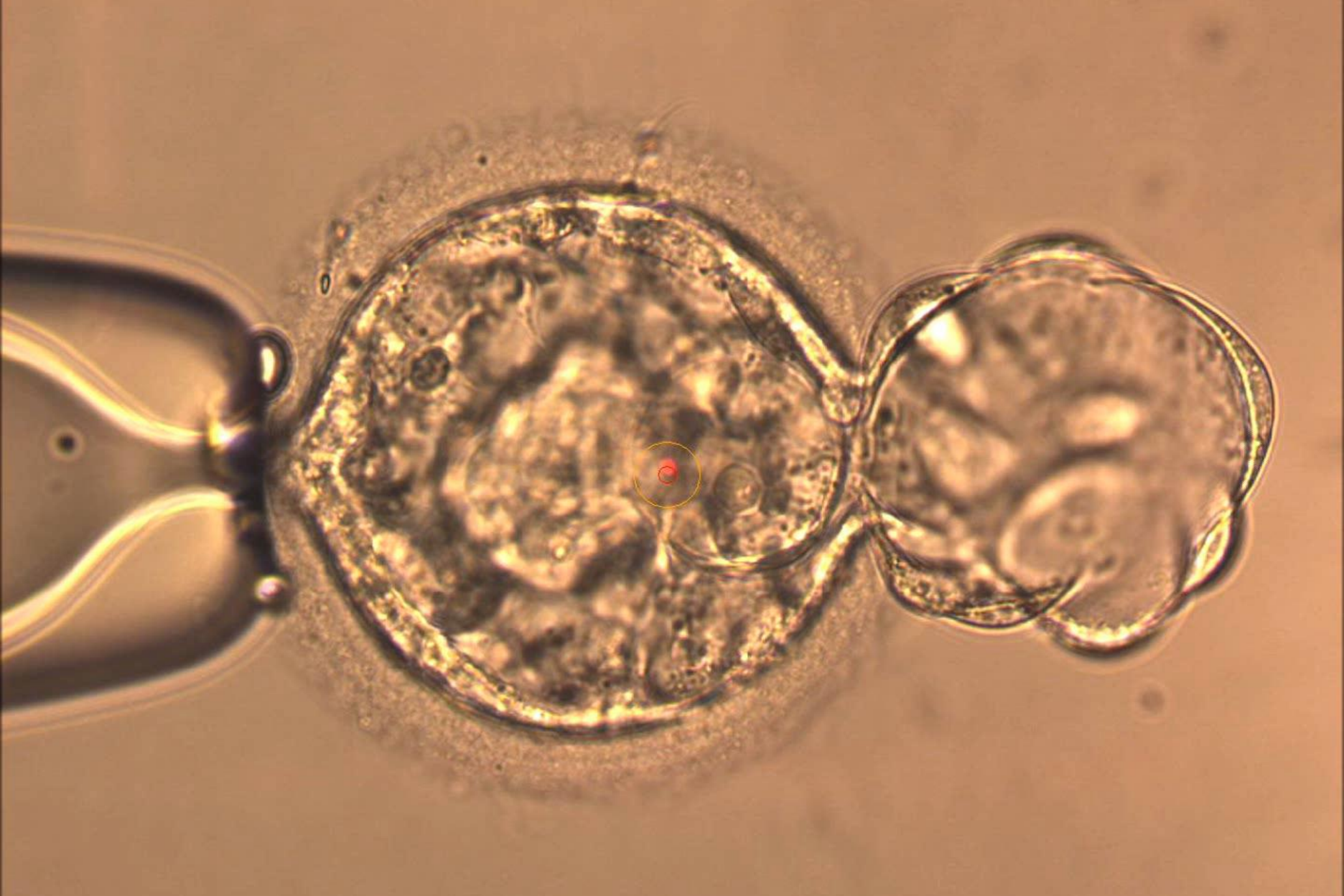
IVF-treatment

- Hormonal down regulation and stimulation
- Oocyte retrieval
- Fertilization
- Embryo development
  - Embryo biopsy and genetic diagnosis
- Transfer of 1 or 2 healthy embryos

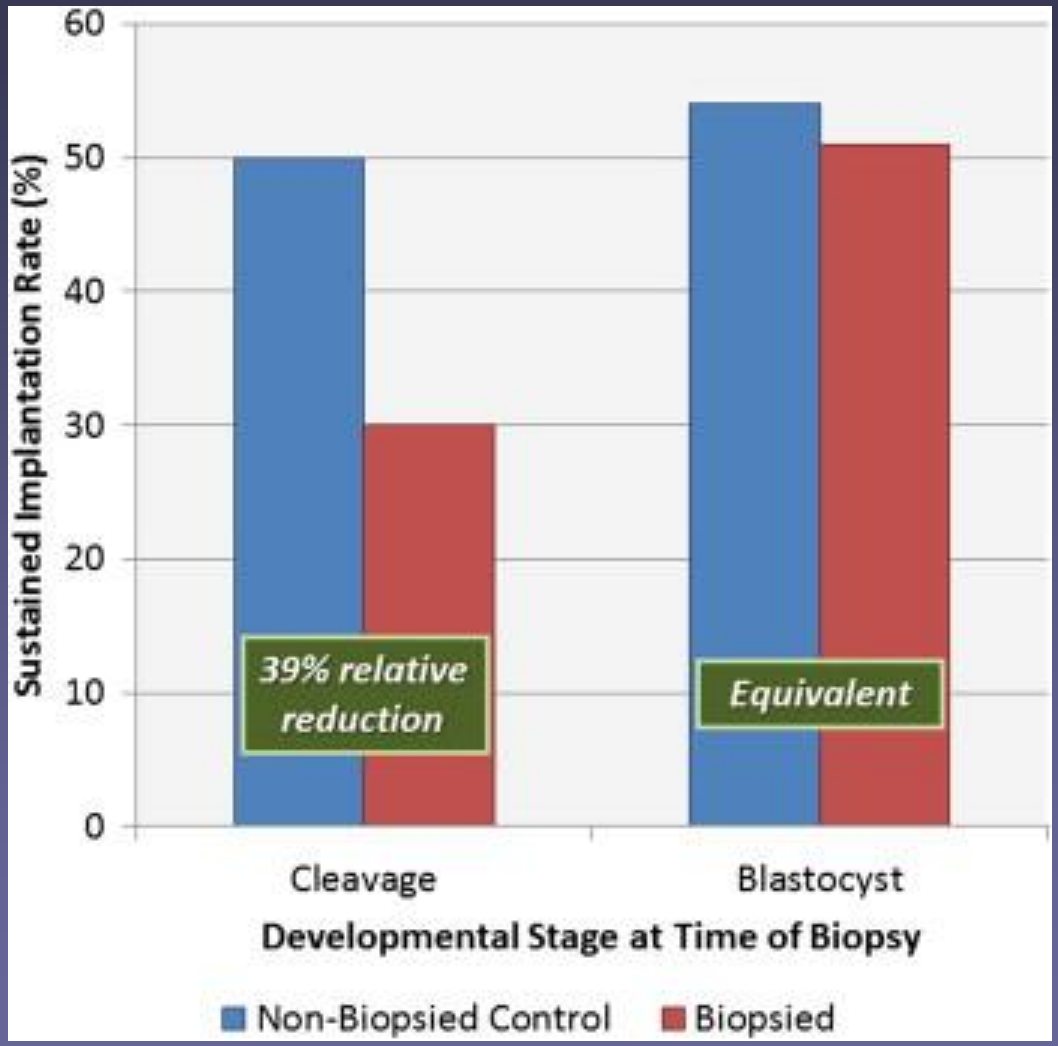
Microscope with laser and micromanipulation equipment





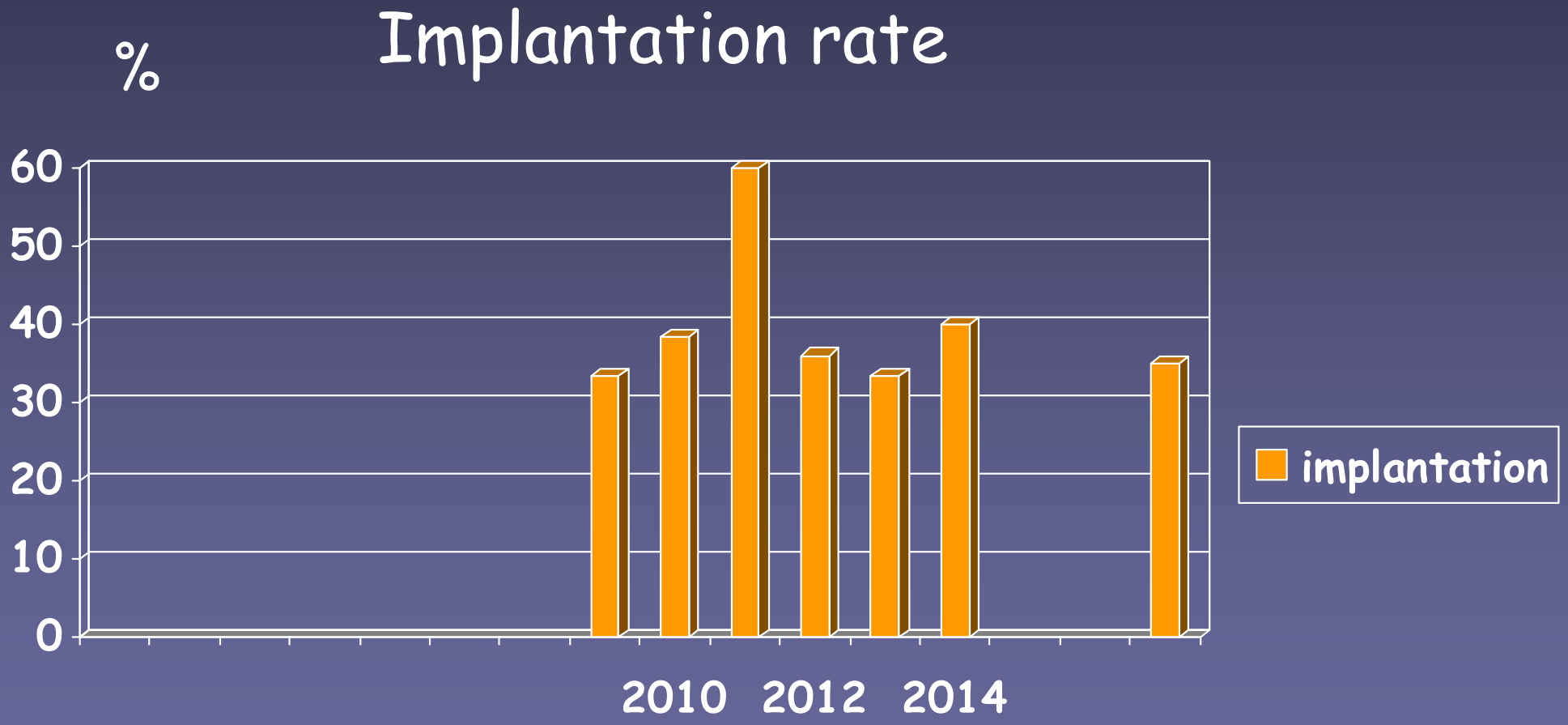


Cleavage-stage biopsy significantly impairs human embryonic implantation potential while blastocyst biopsy does not: a randomized and paired clinical trial
Scott et al, fertil steril sep 2013



Preimplantation genetic diagnosis

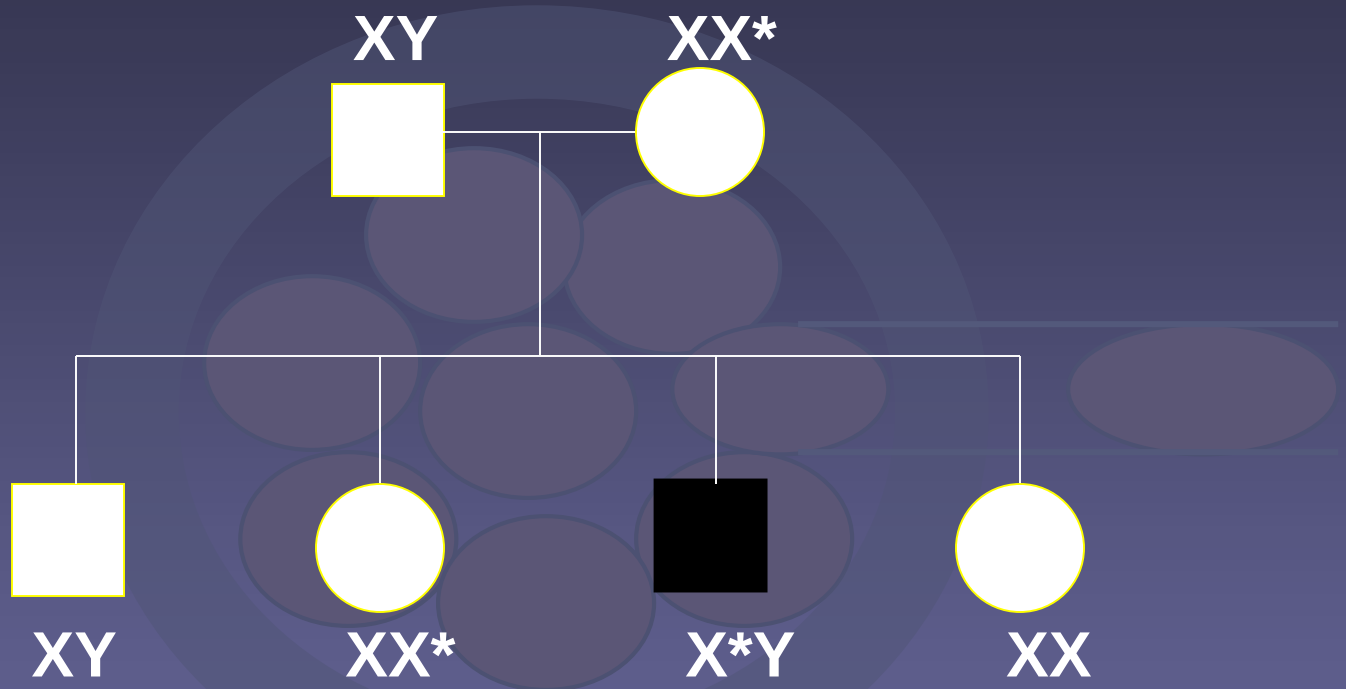
Aarhus University hospital

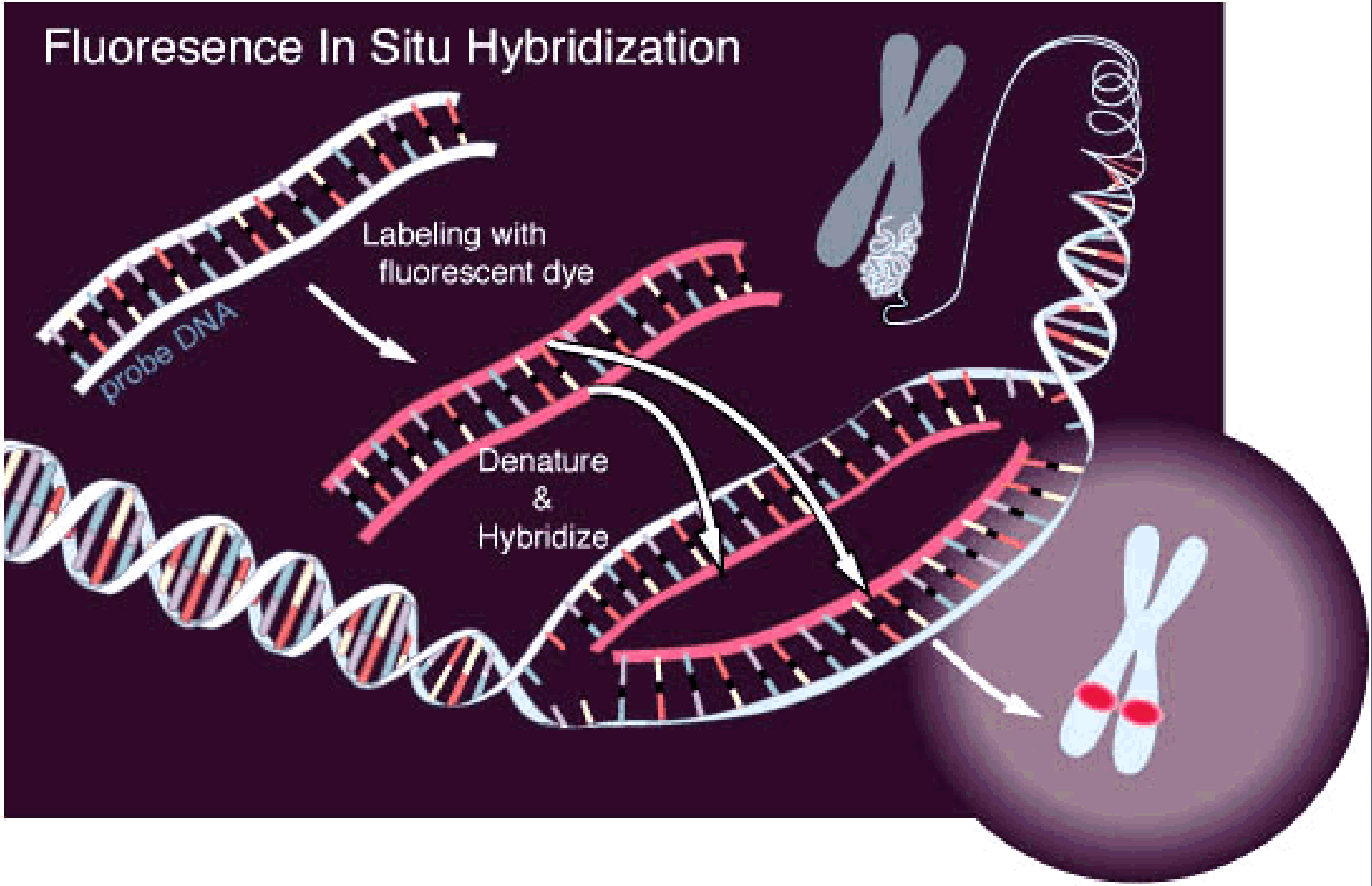


Preimplantation genetic diagnosis

- FISH ANALYSIS
  SEXING
  Translocations
- CCS (CGH, NGS, RT-qPCR)
  Aneuploidy screening/translocations
- PCR ANALYSIS
  Gene specific diagnosis

X-linked Recessiv inheritage

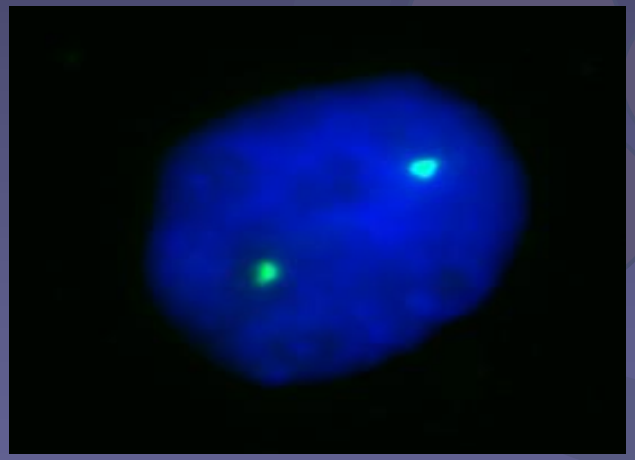



Fluoresence In Situ Hybridization
Labeling with
fluorescent dye
Probe DNA
Denature
&
Hybridize

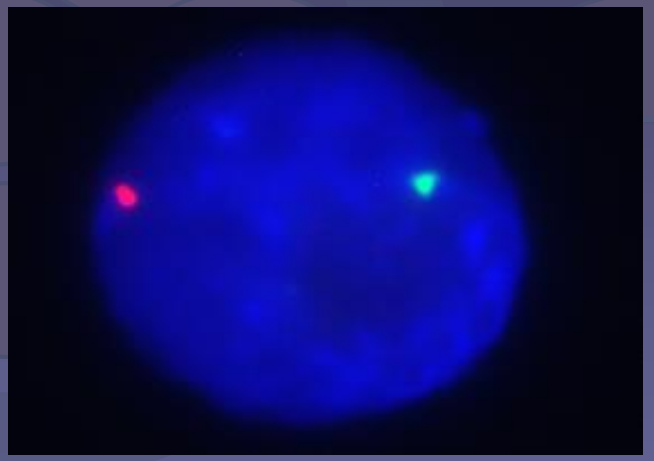
Preimplantation diagnosis

FISH ANALYSIS

sexing

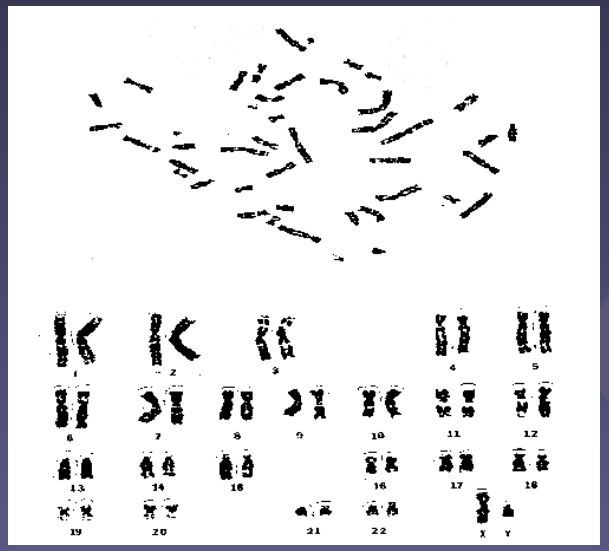


A: XX (female)

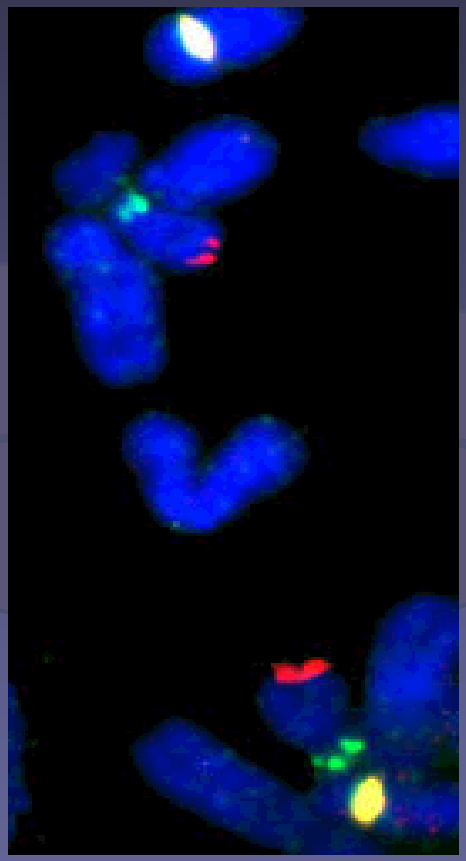


B: XY (male)

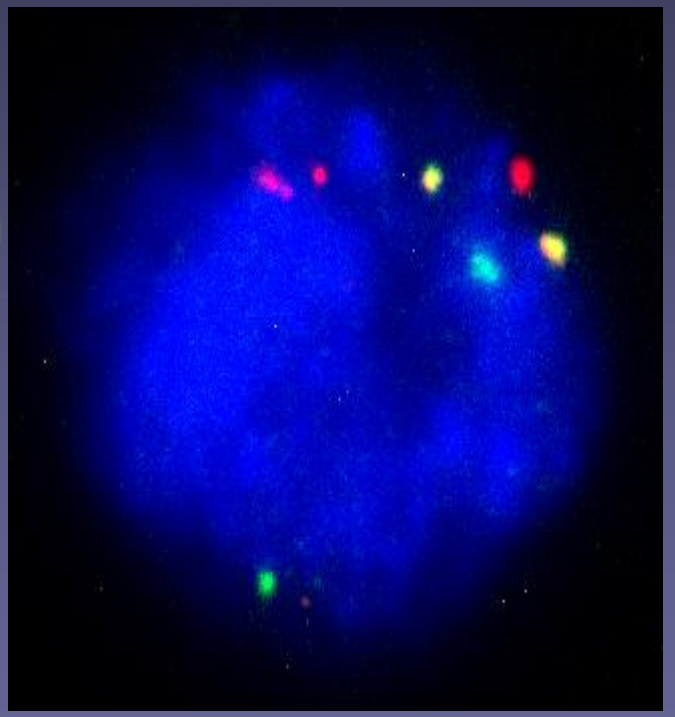
Translocations



Translokation

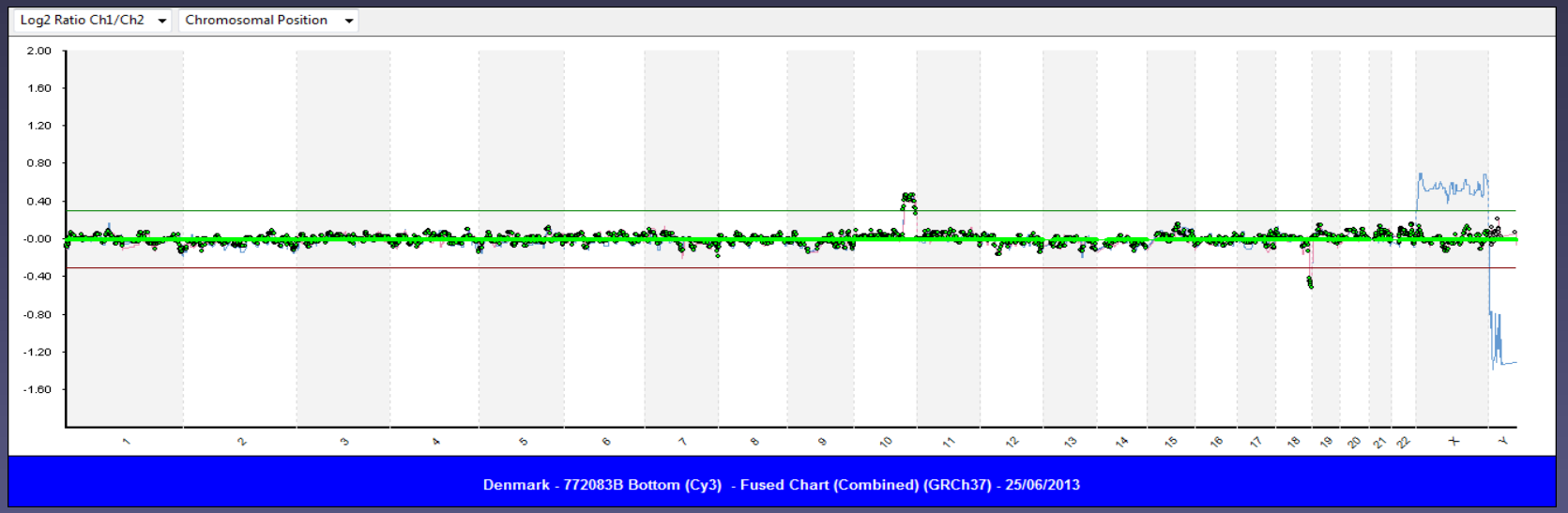


Blastomér

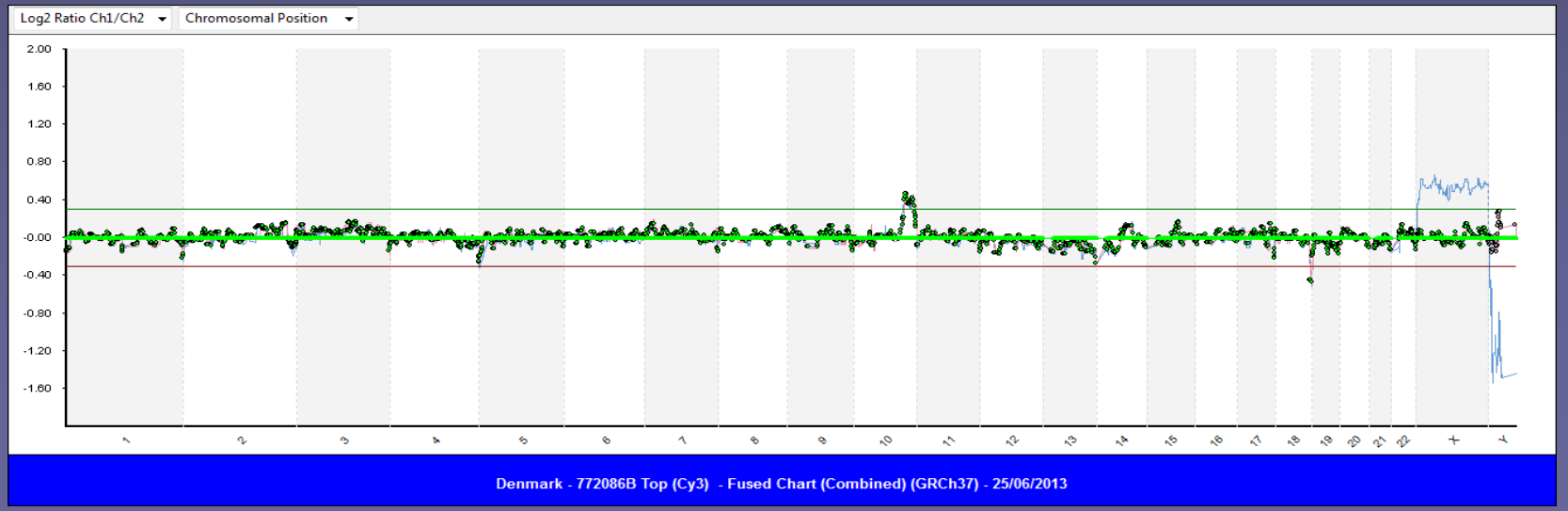


Sample 7, Translocation 10, 18

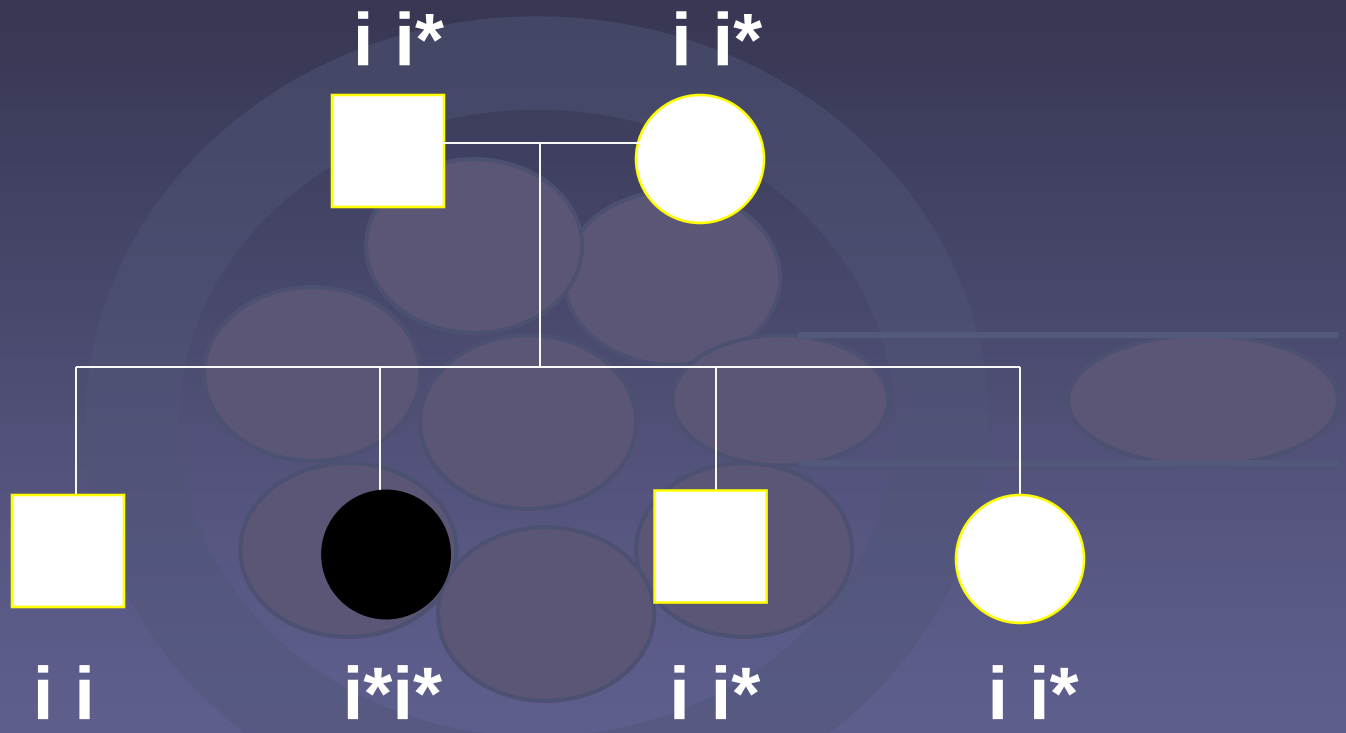
ICM_7



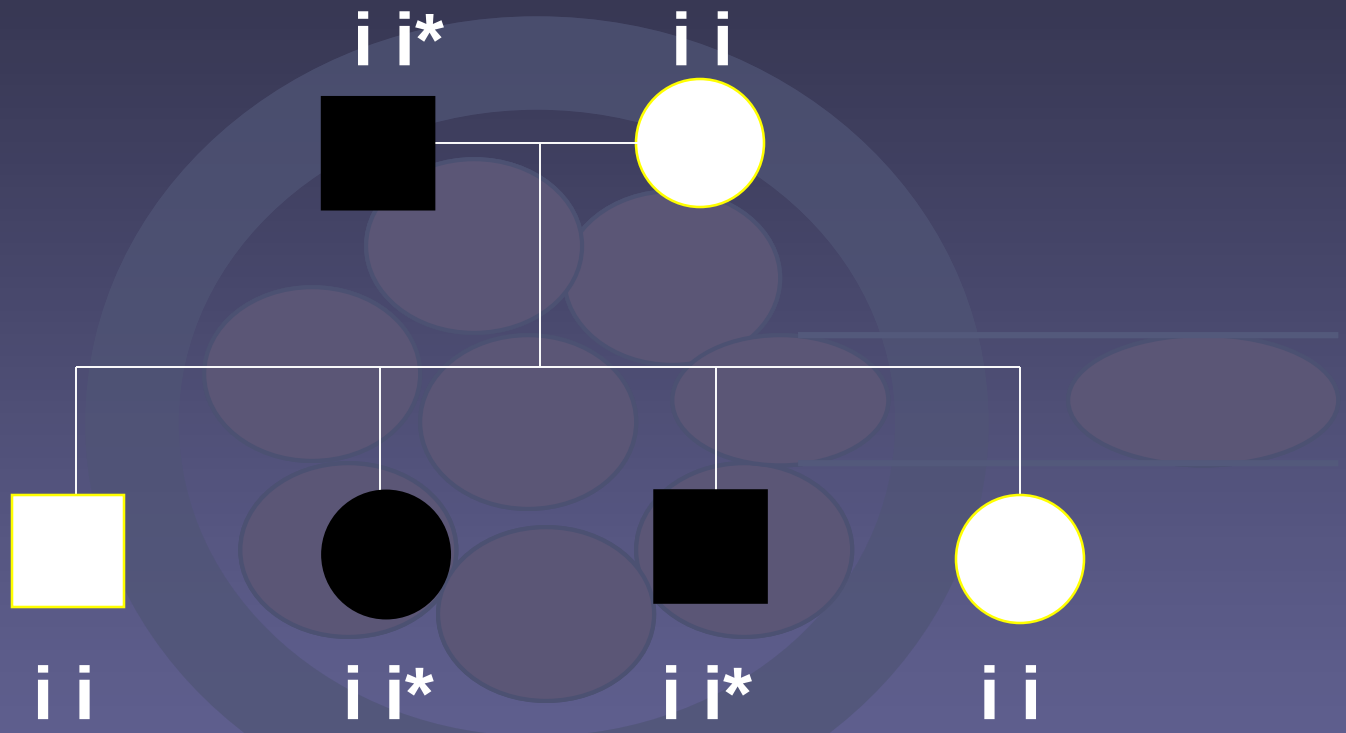
TE_7



Autosomal Recessive inheritage

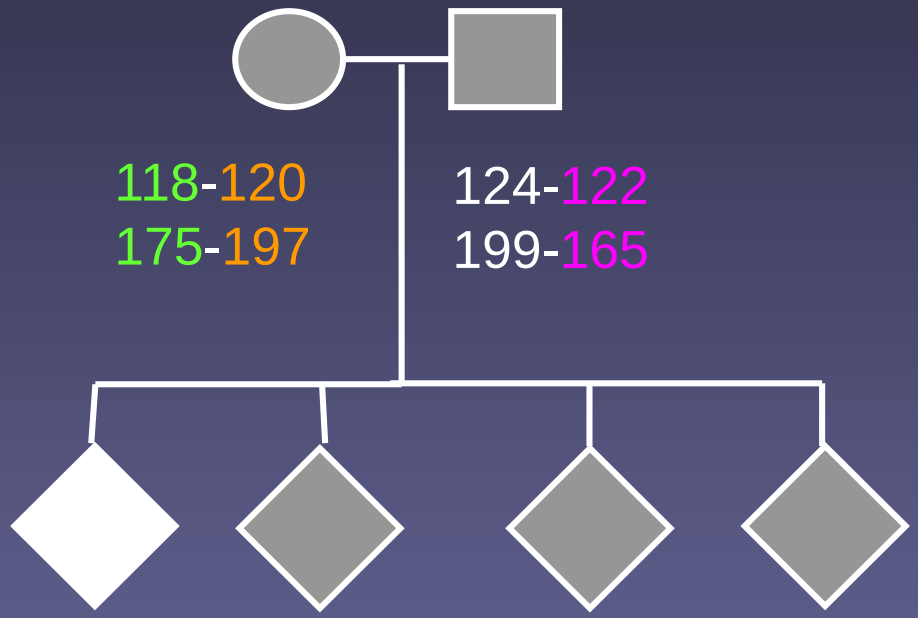


Autosomal Dominant inheritage



HLA-match

D6S105
4.855 kbp - 1.8 cM
D6S2443



D6S105
4.855 kbp - 1.8 cM
D6S2443

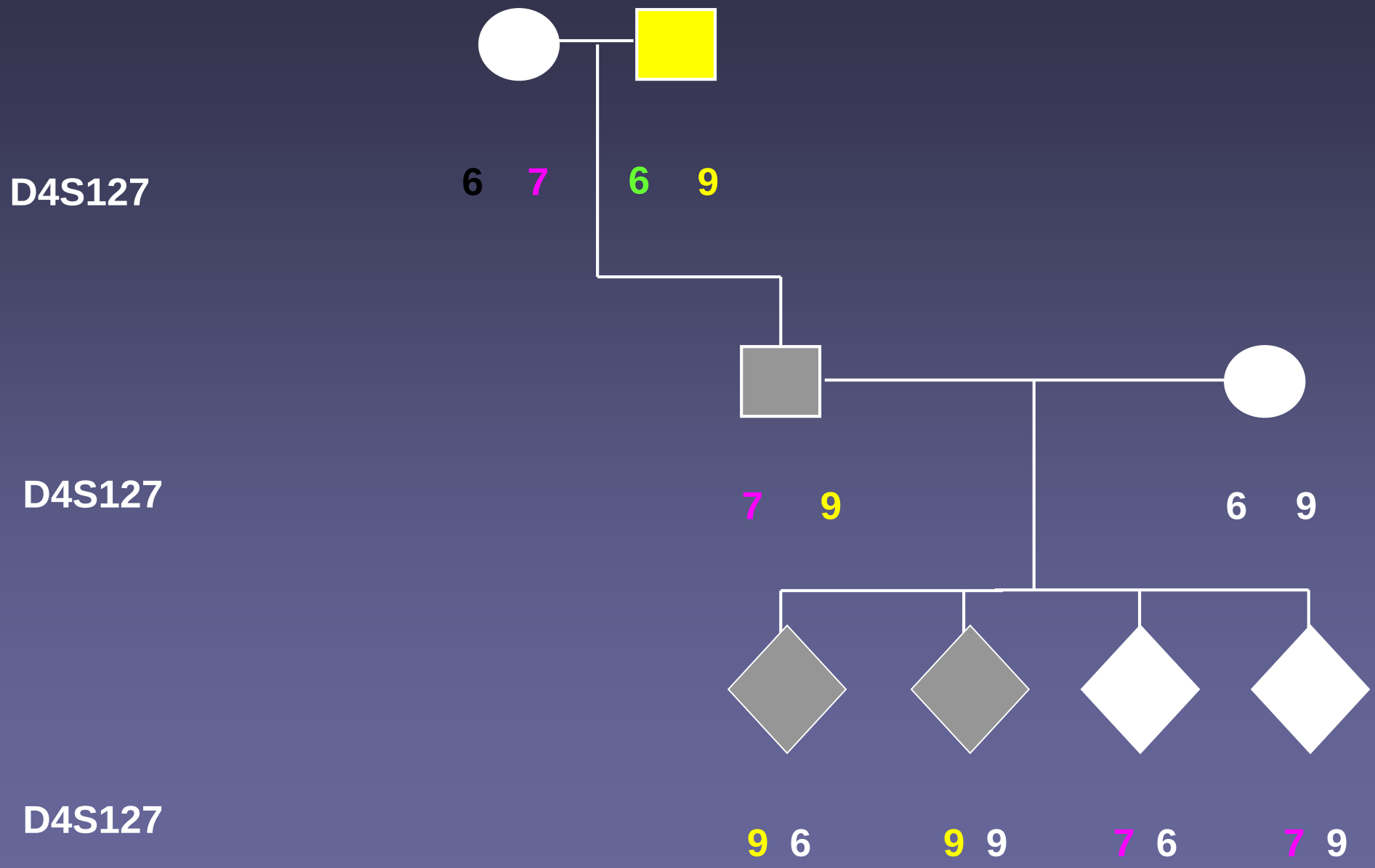
118-122
175-165

120-122
197-165

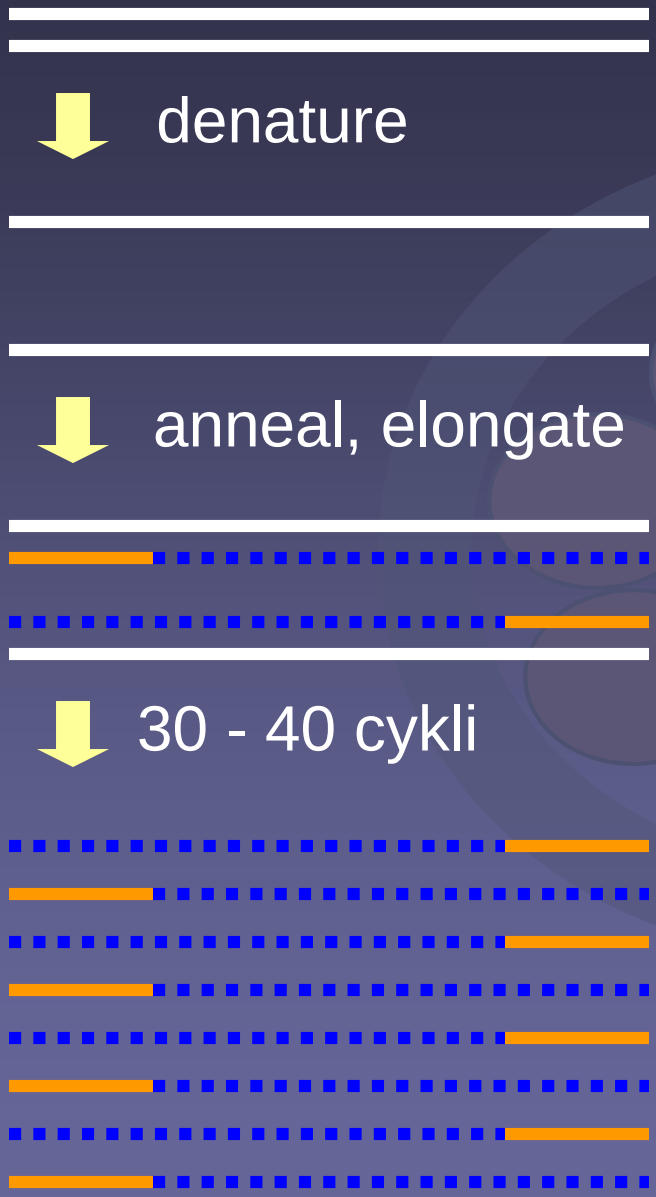
118-124
175-199

120-124
197-199

HD exclusion test



PCR

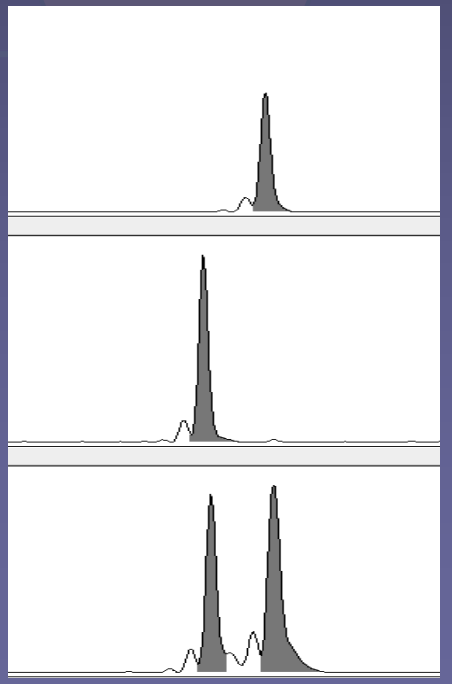


Healthy

Sick

Carrier/

Sick



ESHRE PGD Consortium data collection XII: cycles from January to December 2009 with pregnancy follow-up to October 2010

C Moutou et al, Hum Reprod vol 5, 2014

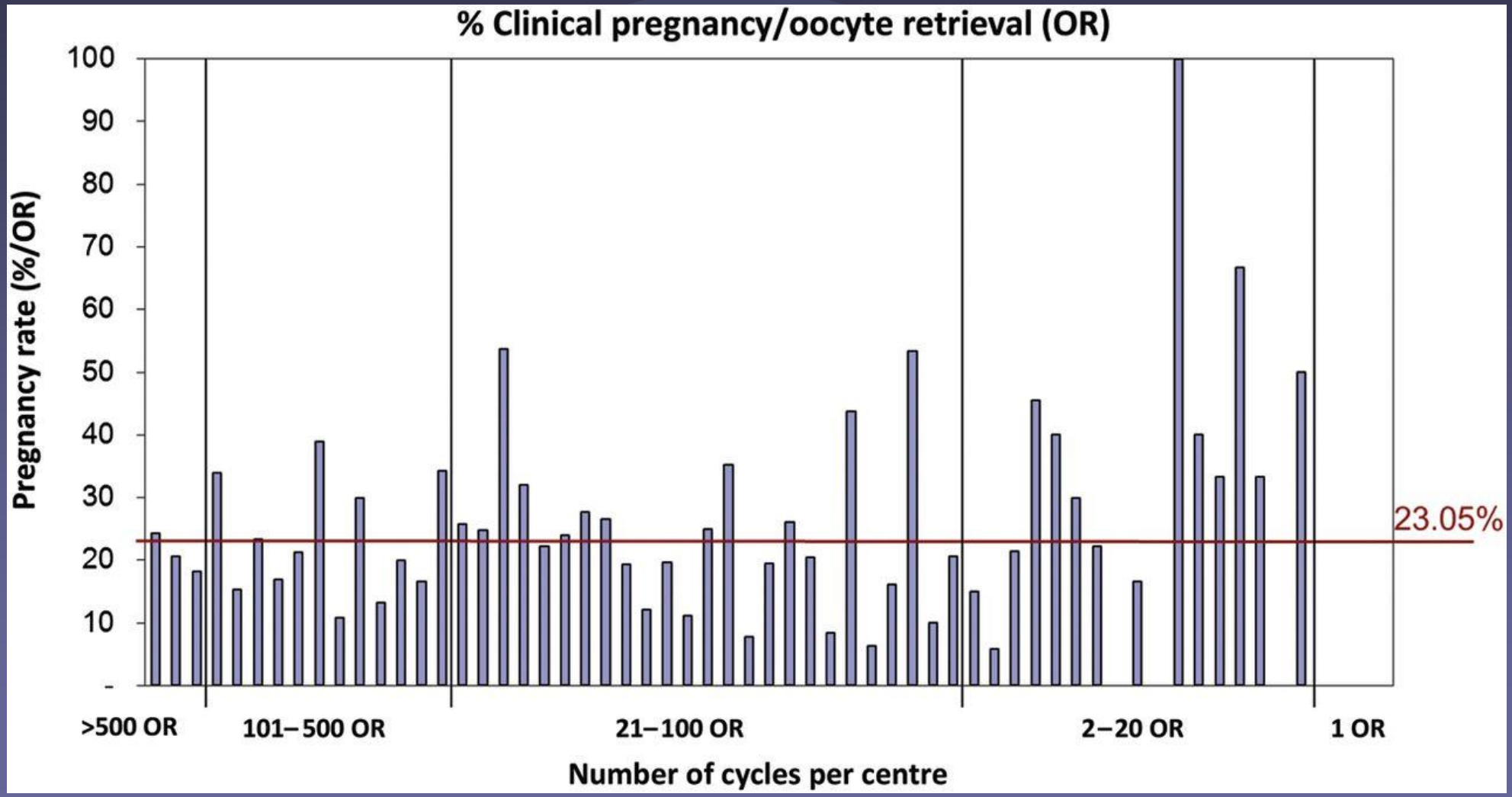
MAIN RESULTS for data collection XII, 60 centres reported data for 6160 cycles with oocyte retrieval (OR), along with details of the follow-up on 1607 pregnancies and 1238 babies born.

A total of 870 OR were reported for chromosomal abnormalities, 113 OR for sexing for X-linked diseases, 1597 OR for monogenic diseases, 3551 OR for preimplantation genetic screening and 29 OR for social sexing.

3 known with misdiagnosis all FISH based.

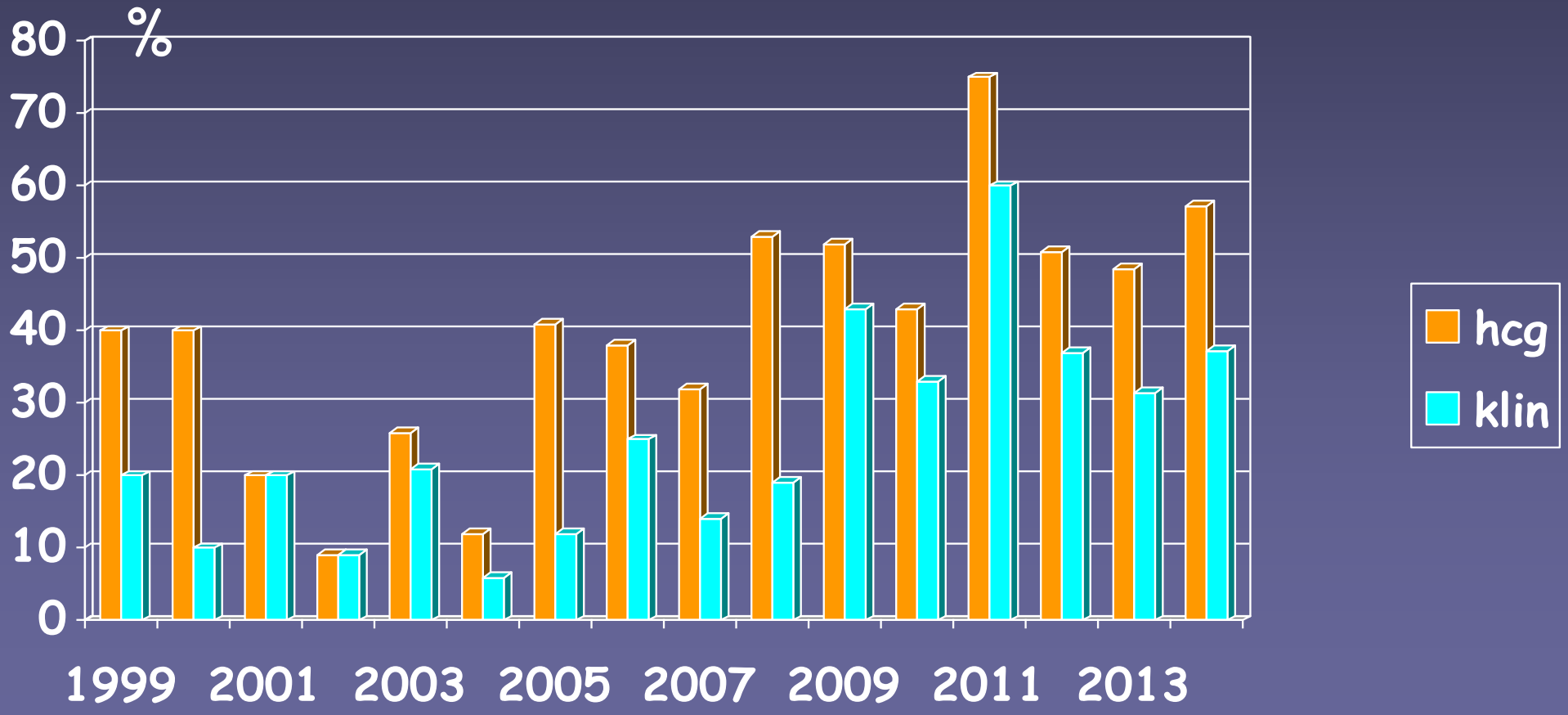
ESHRE PGD Consortium data collection XII: cycles from January to December 2009 with pregnancy follow-up to October 2010

C Moutou et al, Hum Reprod vol 5, 2014



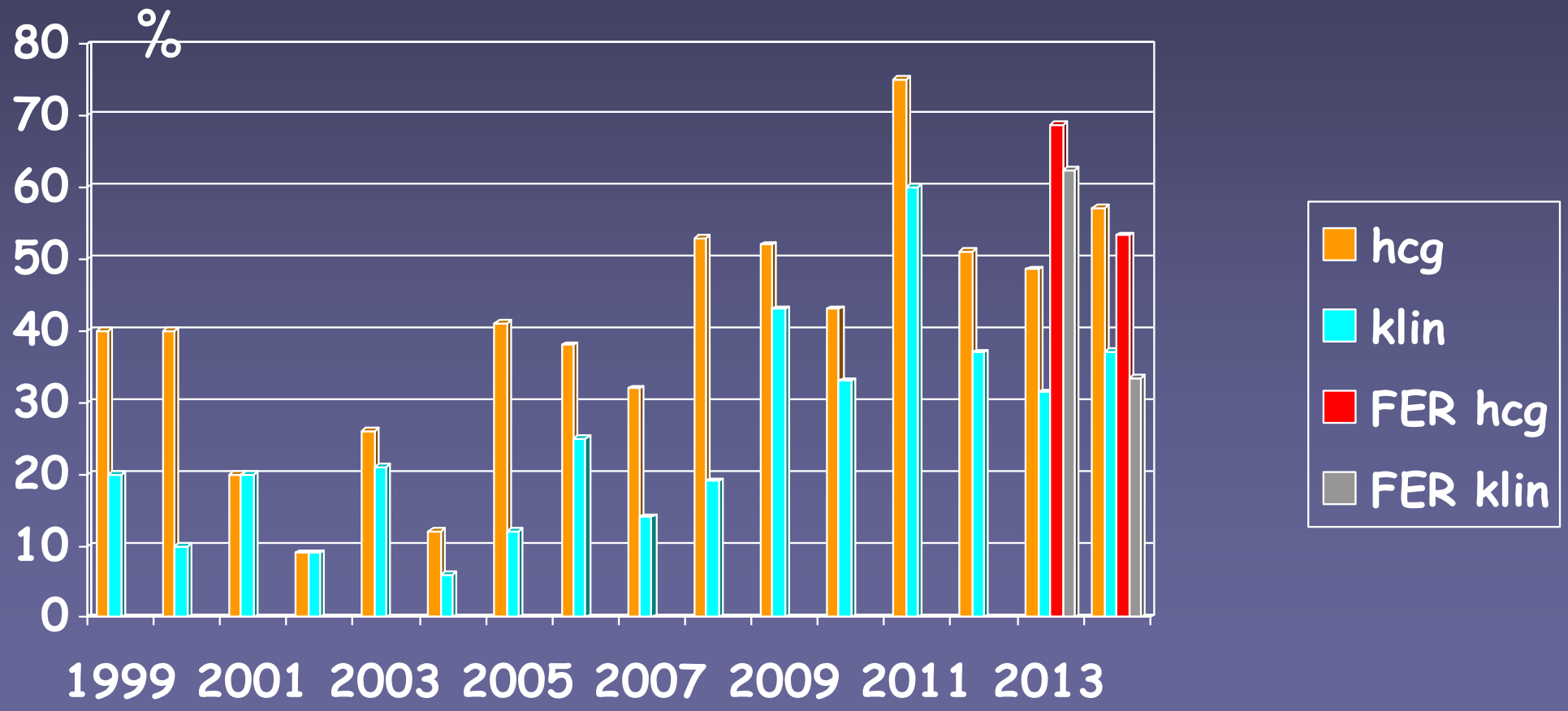
Preimplantation genetic diagnosis

Aarhus University hospital
Biochemical/clinical pregnancy rate per ET 1999-2014



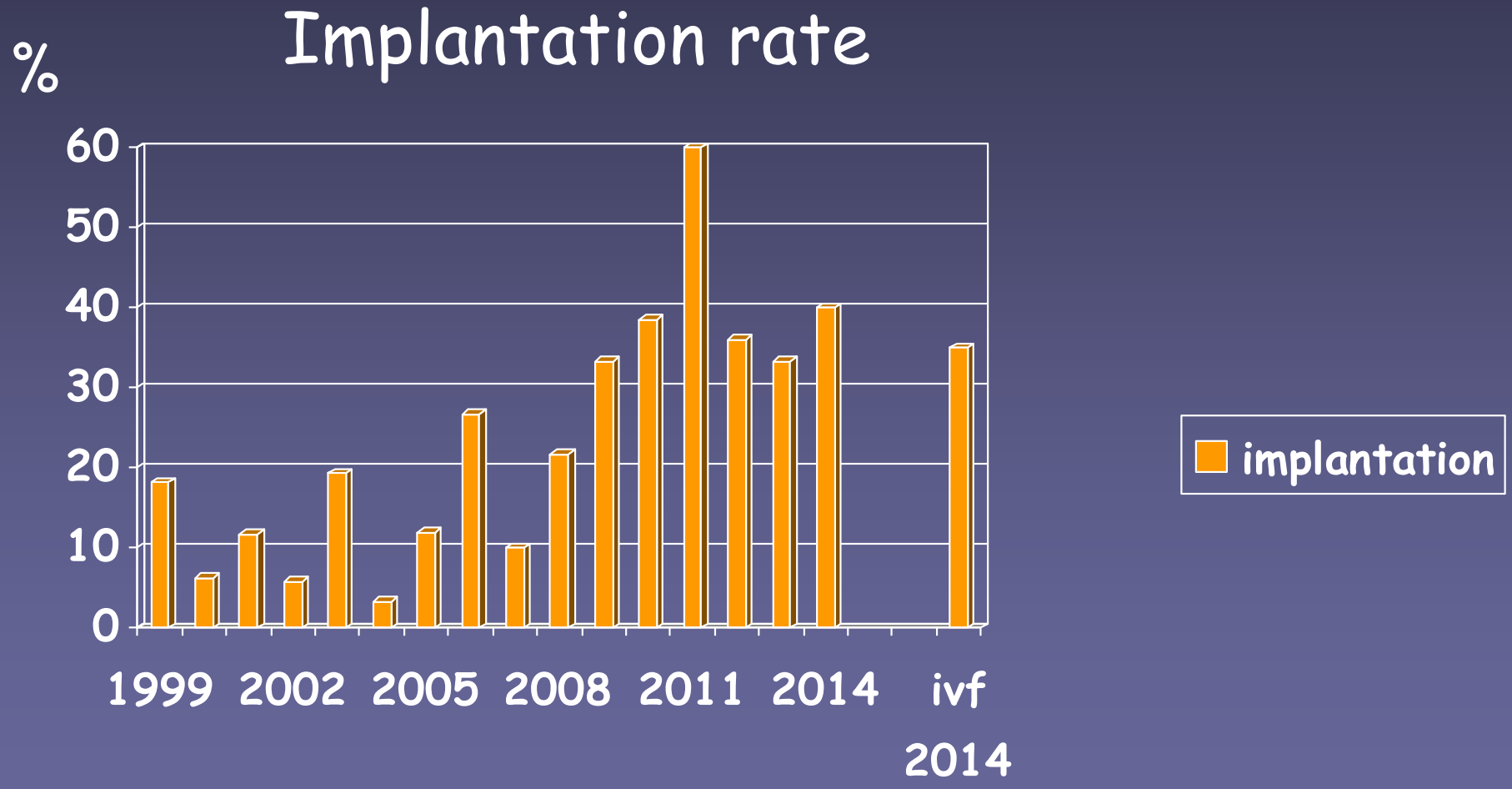
Preimplantation genetic diagnosis

Aarhus University hospital
Biochemical/clinical pregnancy rate per ET 1999-2014



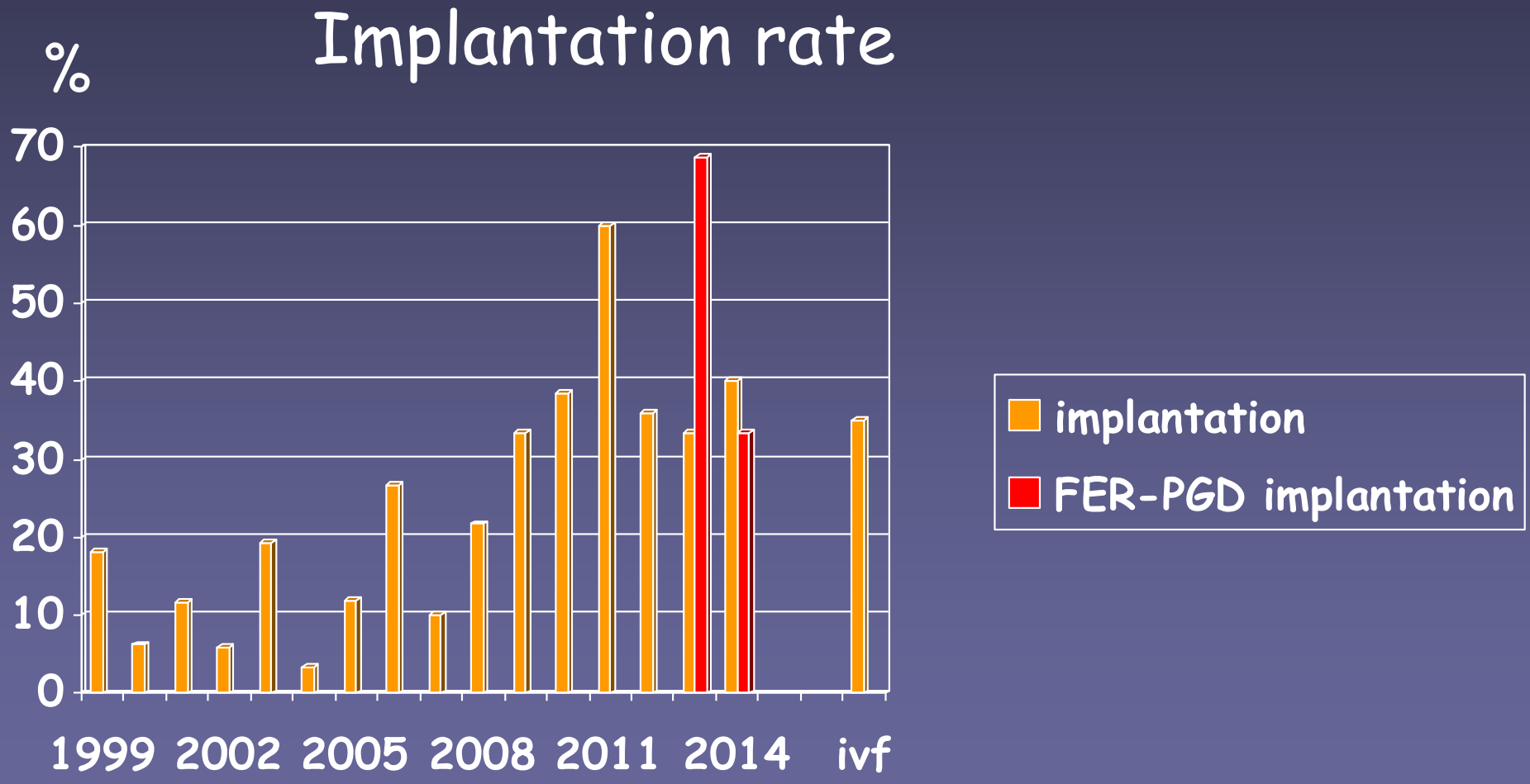
Preimplantation genetic diagnosis

Aarhus University hospital



Preimplantation genetic diagnosis

Aarhus University hospital

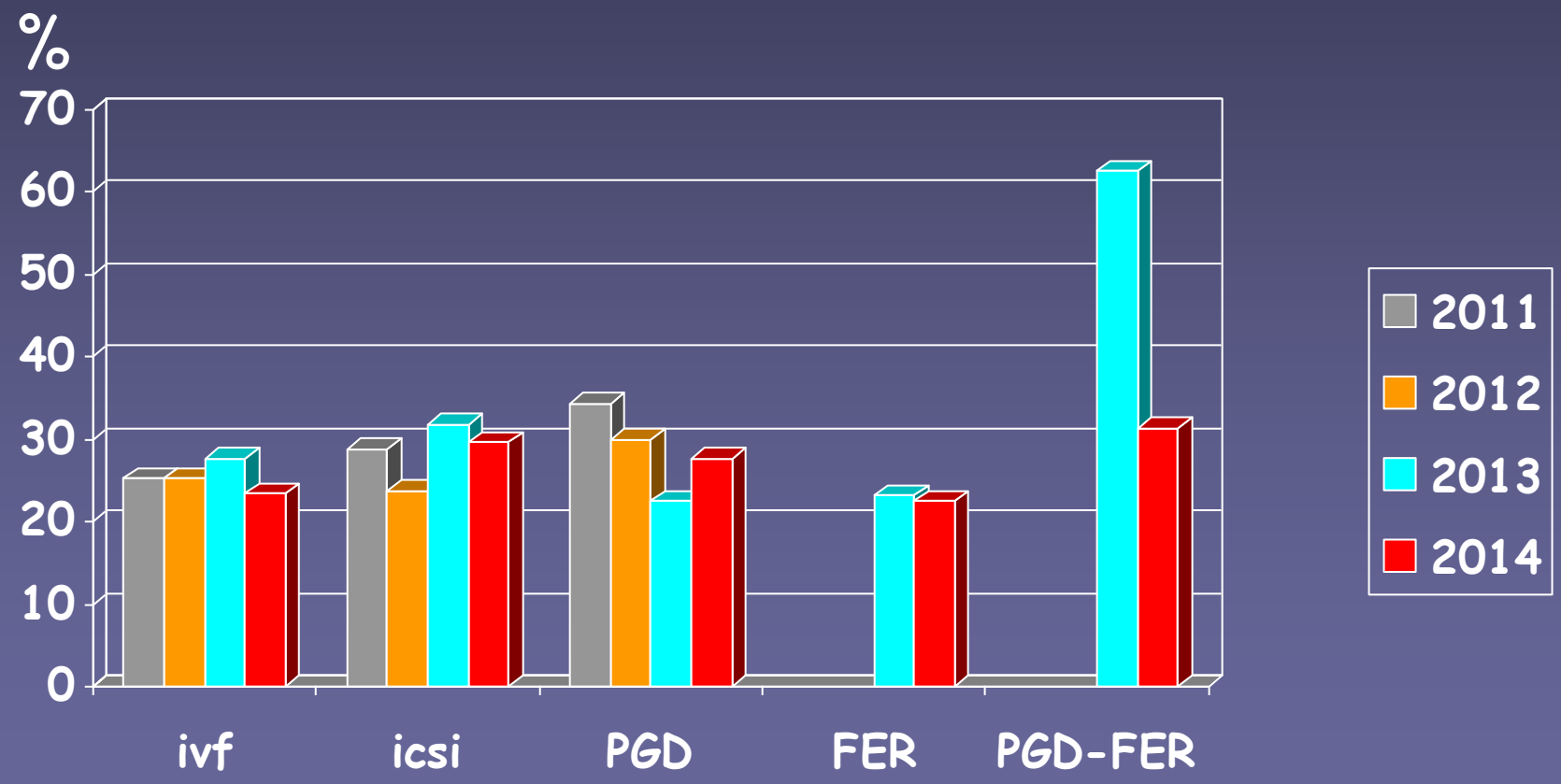


PGD results: Laser/no cells:	07/08 old/2	09/10 old/1	11/12 13/14 new/1/e-scope
Total cycles	94	85	181
Cycles to OR	90	85	181
Cycles to trans	40 (44%)	42 (49%)	131 (72%)
Pos hcg/cycle	24 (26%)	20 (24%)	73 (40%)
Clinical preg/cycle	9 (10%)	16 (19%)	51 (28%)
Pos hcg/trans	44 %	48 %	56%
Clin preg/trans	17 %	38 %	39%
implantationrate	17 %	36 %	40%

Preimplantation genetic diagnosis

Aarhus University hospital

Clinical prenancy rate per started cycle (<40 yrs)



Neonatal outcome after preimplantation genetic diagnosis

Talia Eldar-Geva et al. Fertil Steril, Vol 102 2014

Patient(s)

242 children born after PGD, 242 children born after intracytoplasmic sperm injection (ICSI) (158 singletons and 42 twins pairs in each group), and 733 children born after a spontaneous conception (SC) (493 singletons, 120 twins pairs), matched for maternal age, parity, and body mass index.

Conclusion(s)

Embryo biopsy itself did not cause intrauterine growth restriction or low birth weight compared with SC, despite lower gestational ages with PGD. The worsened outcomes in ICSI compared with PGD pregnancies may be due to the infertility itself.

Growth and health outcome of 102 2-year-old children conceived after preimplantation genetic diagnosis or screening

Sonja Desmytterea et al, early Hum Dev, Vol 85, 2009.

Study design

Auxological data and physical findings were compared at birth and age 2 for 102 children (70 singletons and 32 twins) born after PGD/PGS and 102 matched children born after intracytoplasmic sperm injection (ICSI) in a prospective study.

Conclusion

Children born after embryo biopsy applied in PGD/PGS present similar prenatal and postnatal growth and health outcome in the first two years of life compared to ICSI children. Up till now, PGD and PGS appear not to be associated with a higher risk for health problems.

Near Future.

I think that more and more PDG cycles will be combined with PGS analysis, which most likely will improve the implantation rate and the clinical pregnancy rate.

NGS could be the technique of choise

Top 10 inherited diseases

	couples		
t(13;14)	21	fragile X	6
CF	18	IP	5
DMD	10	DM	5
HD	16	FAP	5
NF1	10	hemophilia A	5

Diseases treated with PGD AUH

	Par
CYSTIC FIBROSIS	18
HUNTINGTON DISEASE; HD	16
MUSCULAR DYSTROPHY, DUCHENNE TYPE; DMD	10
NEUROFIBROMATOSIS, TYPE I; NF1	10
FRAGILE X MENTAL RETARDATION SYNDROME	6
ADENOMATOUS POLYPOSIS OF THE COLON; APC	5
HEMOPHILIA A	5
INCONTINENTIA PIGMENTI; IP	5
BREAST CANCER 1 GENE; BRCA1	4
MARFAN SYNDROME; MFS	4

Liste over årsager til PGD

	Par
BREAST CANCER 1 GENE; BRCA1	3
CHARCOT-MARIE-TOOTH DISEASE, DEMYELINATING, TYPE 1A; CMT1A	3
DARIER-WHITE DISEASE; DAR	3
MUSCULAR DYSTROPHY, BECKER TYPE; BMD	3
RETINITIS PIGMENTOSA, X-LINKED	3
BETA-THALASSEMIAS	2
EPIPHYSEAL DYSPLASIA, MULTIPLE, 1; EDM1	2
GRANULOMATOUS DISEASE, CHRONIC, X-LINKED; CGD	2
MULTIPLE ENDOCRINE NEOPLASIA, TYPE I; MEN1	2
MUSCULAR DYSTROPHY, CONGENITAL MEROSIN-DEFICIENT, 1A; MDC1A	2

Liste over årsager til PGD

	Par
MUSCULAR DYSTROPHY, LIMB-GIRDLE, TYPE 1B	2
POLYCYSTIC KIDNEY DISEASE 1; PKD1	2
PROTEASE INHIBITOR 1; PI, ALPHA-1-ANTITRYPSIN DEFICIENCY	2
RETINOBLASTOMA; RB1	2
SPINAL MUSCULAR ATROPHY, TYPE I; SMA1	2
VON HIPPEL-LINDAU SYNDROME; VHL	2
ADRENOLEUKODYSTROPHY; ALD	1
ALPHA-THALASSEMIA/MENTAL RETARDATION SYNDROME, DELETION-TYPE	1
ALPORT SYNDROME, X-LINKED; ATS	1
AMYLOIDOSIS I; TTR	1

Liste over årsager til PGD

	Par
BARTTER SYNDROME, ANTENATAL, TYPE 1	1
CARNEY COMPLEX, TYPE 1; CNC1	1
CENTRAL CORE DISEASE OF MUSCLE	1
CEROID LIPOFUSCINOSIS, NEURONAL, 3; CLN3	1
CHARCOT-MARIE-TOOTH DISEASE, X-LINKED, 1; CMTX1	1
CROUZON SYNDROME	1
DEAFNESS, AUTOSOMAL RECESSIVE 1A; DFNB1A	1
DIGEORGE SYNDROME; DGS	1
DYSTROPHIA MYOTONICA 1/ t(6;14)	1
ECTODERMAL DYSPLASIA 1; ED1	1

Liste over årsager til PGD

	Par
ECTODERMAL DYSPLASIA, X-LINKED	1
EPIDERMOLYSIS BULLOSA PRURIGINOSA	1
EPILEPTIC ENCEPHALOPATHY, EARLY INFANTILE, 9; EIEE9	1
FACIOGENITAL DYSPLASIA	1
GAUCHER DISEASE, TYPE III	1
HEMOPHILIA B	1
HYDROCEPHALUS DUE TO CONGENITAL STENOSIS OF AQUEDUCT OF SYLVIUS; HSAS	1
Hyper-IgE recurrent infection syndrome	1
LEUKEMIA, ACUTE MYELOID; AML	1
LYMPHEDEMA-DISTICHIASIS SYNDROME	1

Liste over årsager til PGD

	Par
LYMPHOPROLIFERATIVE SYNDROME, X-LINKED, 1; XLP1	1
MATURITY-ONSET DIABETES OF THE YOUNG, TYPE 3; MODY3	1
MENKES DISEASE; ATP7	1
MORQUIO SYNDROME A	1
MULTIPLE ENDOCRINE NEOPLASIA, TYPE IIA; MEN2A	1
MYOTUBULAR MYOPATHY 1; MTM1	1
NAIL-PATELLA SYNDROME; NPS	1
NOONAN SYNDROME 1; NS1	1
OSTEOGENESIS IMPERFECTA, TYPE III	1
OSTEOPETROSIS, AUTOSOMAL DOMINANT 2; OPTA2	1

Liste over årsager til PGD

	Par
PALMOPLANTAR KERATODERMA, EPIDERMOLYTIC; EPPK	1
RETINITIS PIGMENTOSA 18; RP18	1
RETINOSCHISIS 1, X-LINKED, JUVENILE; RS1	1
SIMPSON-GOLABI-BEHMEL SYNDROME, TYPE 1; SGBS1	1
SPINOCEREBELLAR ATAXIA 2; SCA2	1
SPONDYLOCOSTAL DYSOSTOSIS 1, AUTOSOMAL RECESSIVE; SCDO1 JARCHO-LEVIN SYNDROME	1
SPONDYLOEPIPHYSEAL DYSPLASIA CONGENITA Retinitis pigmentosa 4,	1
TUBEROUS SCLEROSIS; TSC1	1
TUBEROUS SCLEROSIS; TSC2	1

Liste over årsager til PGD

	Par
VENTRICULAR TACHYCARDIA, CATECHOLAMINERGIC POLYMORPHIC, 1; CPVT1	1
WEBER-COCKAYNE TYPE EPIDERMOLYSIS BULLOSA SIMPLEX	1
WISKOTT-ALDRICH SYNDROME; WAS	1
X-LINKED MENTAL RETARDATION SYNDROME	1
ZELLWEGER SYNDROME; ZS	1
VENTRICULAR TACHYCARDIA, CATECHOLAMINERGIC POLYMORPHIC, 1; CPVT1	1
WEBER-COCKAYNE TYPE EPIDERMOLYSIS BULLOSA SIMPLEX	1
WISKOTT-ALDRICH SYNDROME; WAS	1
X-LINKED MENTAL RETARDATION SYNDROME	1
ZELLWEGER SYNDROME; ZS	1

Liste over årsager til PGD

	Par
t(1;11)	1
t(1;21)	1
t(1;6)	1
t(1;7)	1
t(1;8)	1
t(1;X)	1
t(10;18)	2
t(11;22)	5
t(13;14)	21
t(13;15)	1

Liste over årsager til PGD

	Par
t(13;21)	1
t(14;15)	2
t(14;21)	3
t(15;16)	1
t(15;22)	2
t(17;19)	1
t(3;11)	1
t(3;14)	1
t(3;22)	3
t(4;10)	2

Liste over årsager til PGD

	Par
t(4;20)	1
t(4;7)	1
t(4;8)	2
t(5;17)	1
t(6;10)	1
t(6;11)	1
t(6;13)	1
t(6;9)	1
t(7;17)	1
t(8;11)	1

Liste over årsager til PGD

	Par
t(8;14)	1
t(9;19)	1

Thank you