Questions for the German Council's Hearing on Preimplantation Genetic Diagnosis (PGD)
Considerations on PGD

Prof Dr P Devroey

Centrum voor Reproductieve Geneeskunde

Universitair Ziekenhuis Brussel

Centrum voor Medische Genetica

Application

Application of PGD (Belgium)

- Centre for Medical Genetics (n: 7)
- Centre for Reproductive Medicine (regulated by law)
- Psychologist
- Ethics Committee
  - → Institutional
  - → Ad Hoc (psychologist, biologist, geneticist, lawyer, paramedical)

List of genetic diseases (PGD)

- According a rational approach (prenatal diagnosis)
- If an embryo is carrying a given disease
- Embryo is not replaced
- ≈ 100 indications
- Genetic normal embryos are replaced according to their morphology

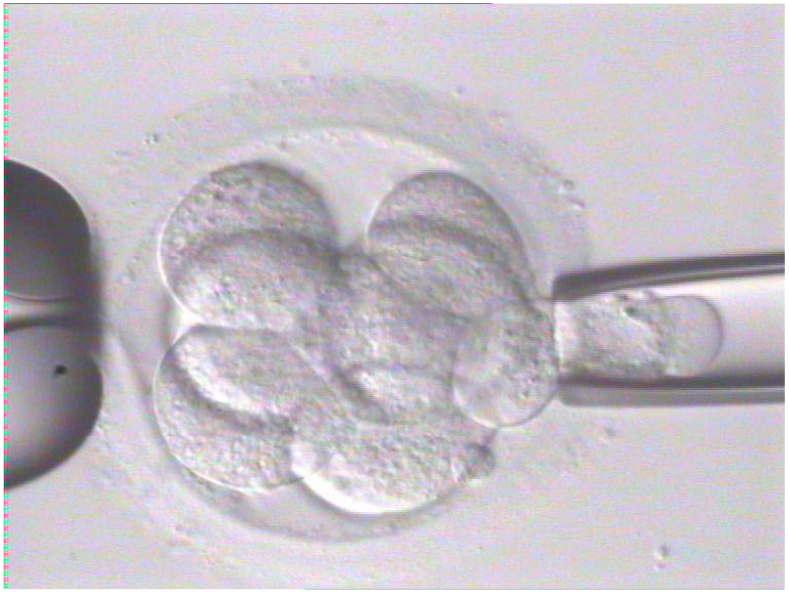
Rating : Decision process in transparent

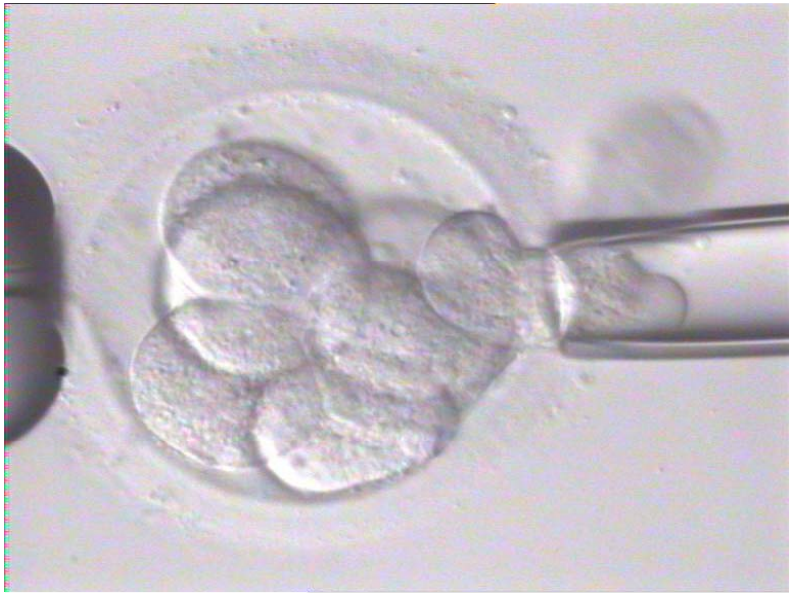
PGS versus PGD

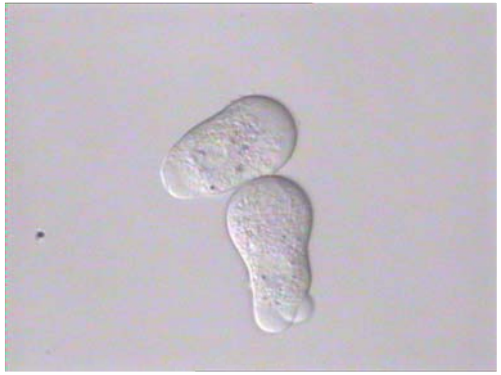
- Preimplantation Genetic Screening (PGS)
  - → Mosaicism
  - → Chromosomal rearrangement

Preimplantation aneuploidy screening: a research tool for now
Devroey, Lancet 2007

Biopsy of cleavage-stage embryo







PGS study < 36 years of age

	Control	PGS	
No of transfers	89	85	
Embryos / transfer mean ± SD	1.0 ± 0.0	1.0 ± 0.0	
No of positive HCG	52	47	
Positive HCG/OPU Positive HCG/ET	53.1 % 58.4 %	47.0 % 55.3 %	NS NS
No ongoing pregnancies (> 12 w)	37	37	
Ongoing preg/OPU Delivery rate/ET	37.7 % 41.6 %	37.0 % 43.5 %	NS NS
Embryos cryopreserved	2.2 ± 2.6	1.4 ± 2.2	P<0.01

Staessen HR 2008

Rating : PGS is research

Sequence of embryo replacement decision

- Genetic examination
- Morphological evaluation
- If genetically and morphological normal one embryo is replaced
- Supplementary day 5 blastocyst or vitrify for possible later use

Rating : decision process is simple

Psychological counseling (and ethical evaluation)

Meeting with geneticist (genetic disease) (A)
Meeting with infertility doctor (B)
Meeting with psychologist (C)
If needed ad hoc ethics committee (D)

Decision is accepted if A B C D are positive

Rating : transparent but delicate and difficult human decision process

Research and monitoring of PGD

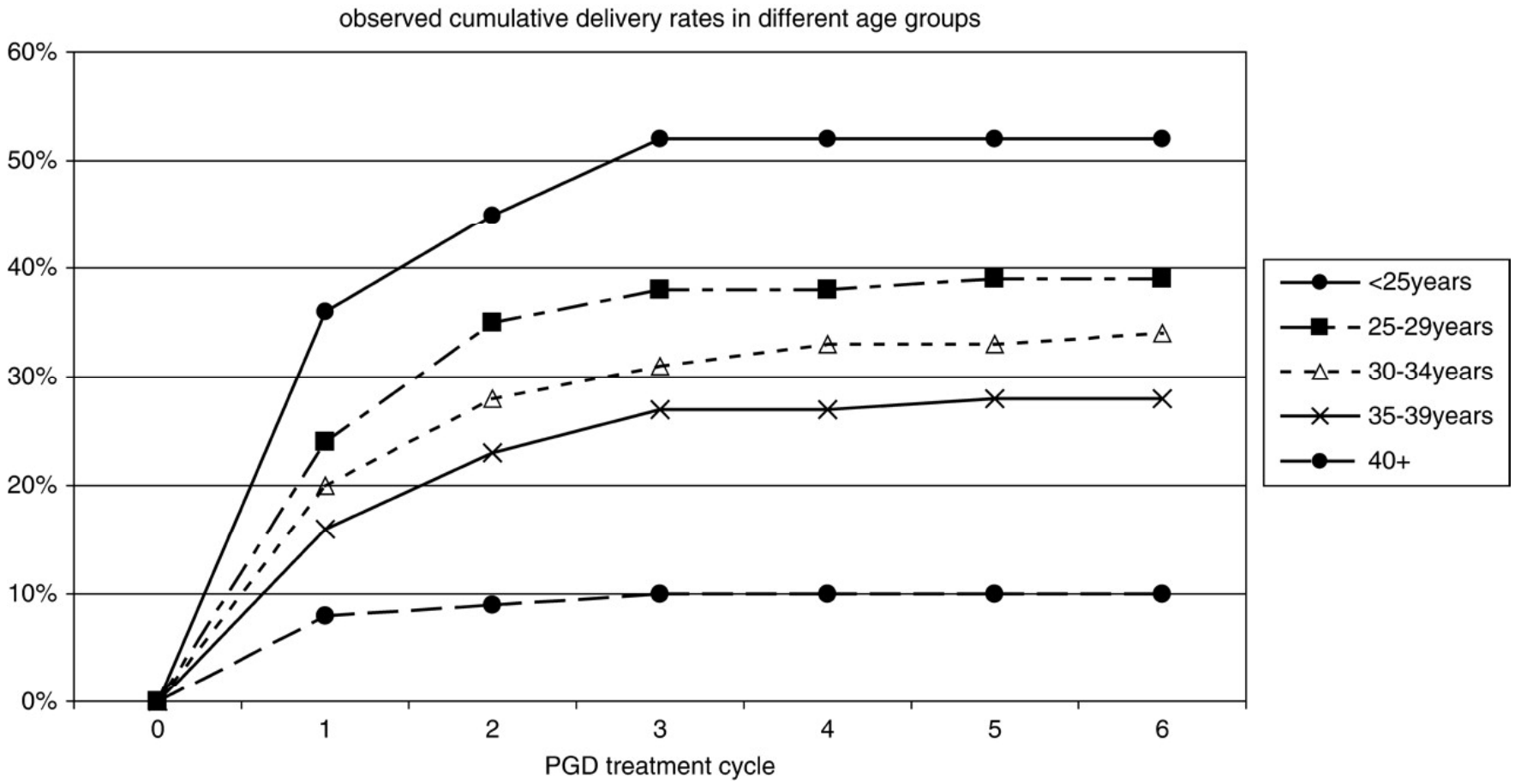
- Research on embryos regulated by embryo law
  - → Institutional local Ethics Committee
  - → National Belgian Bio-Ethics Committee
- Monitoring
  - → Prospective online organized by Belgian Ministry of Health (Belgian Registry)
  - → EHSRE Consortium (yearly and retrospective)
  - → Institutional report

Rating : easy to organize

Research

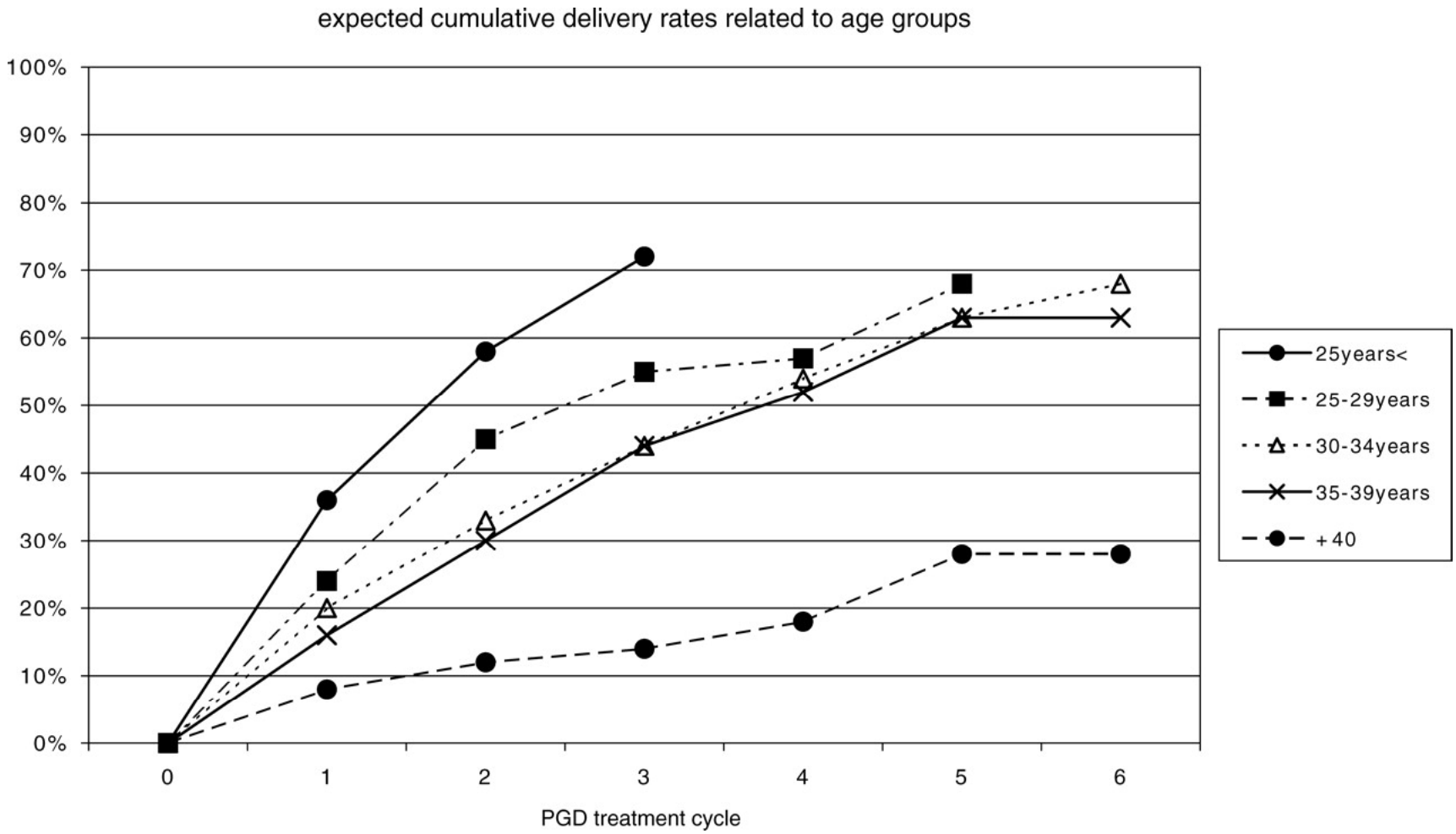
- Publications of the Centre for Reproductive Medicine and Human Genetics
  → N : 52 peer reviewed publications
- Grants
  → National Research Council
  → European Research Council
- Ph thesis

Cumulative reproductive outcome after PGD



Verpoest … Devroey HR 2009

Cumulative reproductive outcome after PGD



Verpoest … Devroey HR 2009

Indications for PGD 1993-2005

indication	OMIM reference number(s) disorder	OMIM nr. + name of gene / genetic region tested	method	N patients
Autosomal Dominant				
achondroplasia	#100800	*134934 (FGFR3)	PCR	2
autosomal dominant polycystic kidney disease (ADPKD)	#173900	+601313 (PKD1)	PCR	3
breast cancer 1 gene (BRCA1)	#114480	*113705 (BRCA1)	PCR	2
Charcot Marie Tooth (CMT) type 1A	#118220	*601097 (PMP22)	PCR	9
Dystonia Musculorum Deformans 1	#128100	*605204 (DYT1)	PCR	1
Ectrodactyly Ectodermal Dysplasia and orofacial clefts (EEC3)	#604292	*603273 (TP63)	PCR	1
Epidermolysis Bullosa Simplex DOWLING-MEARA TYPE	#131760	*148066 (KRT14)	PCR	1
Familial Adenomatous Polyposis of the Colon (FAP)	#175100	*611731 (APC)	PCR	2
Facioscapulohumeral dystrophy (FSHD)	158900%	No Omim Reference (4q35)	PCR	4
Huntington Disease exclusion	+143100	+143100 (HD)	PCR	16
Huntington Disease (HD)	+143100	+143100 (HD)	PCR	37
Hypokalemic periodic paralysis (HOKPP)	#170400	*114208 (CACNA1S)	PCR	2
Marfan syndrome	#154700	*134797 (FBN1)	PCR	8
Multiple Endocrine Neoplasia type 2A (MEN2A)	#171400	+164761 (RET)	PCR	1
Multiple Exostoses (EXT1)	#133700	*608177 (EXT1)	PCR	1
Myotonic Dystrophy 1 (DM1)	#160900	*605377 (DMPK)	PCR	78
Neurofibromatosis type 1 (NF1)	+162200	+162200 (NF1)	PCR	8
Neurofibromatosis type 2 (NF2)	#101000	*607379 (NF2)	PCR	1
Osteogenesis Imperfecta (OI) type I	#166200	+120150 (COL1A1)	PCR	3
Osteogenesis Imperfecta (OI) type IV	#166220	*120160 (COL1A2)	PCR	2
Retinoblastoma	+180200	+180200 (RB1)	PCR	1
Spinocerebellar Ataxia 1 (SCA1)	#164400	*601556 (ATXN1)	PCR	1
Spinocerebellar Ataxia 7 (SCA7)	#164500	*607640 (ATXN7)	PCR	3
Stickler syndrome type I	#108300	+120140 (COL2A1)	PCR	1
Tuberous Sclerosis type 1	#191100	*605284 (TSC1)	PCR	4
Tuberous Sclerosis type 2	#191100	*191092 (TSC2)	PCR	1

Indications for PGD 1993-2005 (continued)

Autosomal Recessive				
ARPKD	#263200	*606702 (PKHD1)	PCR	2
21 hydroxylase deficiency	+201910	+201910 (CYP21)	PCR	1
Beta-thalassemia	+141900	+141900 (HBB)	PCR	5
Canavan disease	#271900	*608034 (ASPA)	PCR	1
Carbohydrate Deficient Glycoprotein syndrome (CDG) type Ia	#212065	*601785 (PMM2)	PCR	1
Carbohydrate Deficient Glycoprotein syndrome (CDG) type Ic	#603147	*604566 (ALG6)	PCR	1
Cystic fibrosis (CF)	#219700	*602421 (CFTR)	PCR	64
Connexin 26 deafness	#220290	*121011 (GJB2)	PCR	2
Familial Dysautonomia (DYS)	#223900	*603722 (IKBKAP)	PCR	1
Gaucher disease type II	#230900	*606463 (GBA)	PCR	2
Glutaric Acidemia type I	#231670	*608801 (GCDH)	PCR	1
Glycogenosis	+232200	+232200 (G6PC)	PCR	1
Medium Chain AcetylCoA dehydrogenase (MCAD) deficiency	#201450	*607008 (ACADM)	PCR	1
Pompe disease	#232300	*606800 (GAA)	PCR	1
Rhizomelic Chondrodysplasia Punctata type 1	#215100	+601757 (PEX7)	PCR	1
Sickle Cell Anaemia	#603903	+141900 (HBB)	PCR	6
Spinal Muscular Atrophy (SMA) types I, II, III	#253300, #253550, #253400	*600354 (SMN1)	PCR	17
Non-Mendelian				
Leber hereditary optic neuropathy (LHON)	#535000		FISH-sexing	1
Renal Agenesis	undefined		FISH-sexing	1

Indications for PGD 1993-2005 (continued)

X-linked recessive				
Adrenoleukodystrophy	#300100	X-chromosome (sexing) or *300371 (ABCD1)	FISH or PCR	4
Adrenoleukomyeloneuropathy	#300100	X-chromosome (sexing)	FISH	1
Agammaglobulinemia	#300755	*300300 (BTK)	PCR	1
Alport syndrome	#301050	X-chromosome (sexing)	FISH	4
Androgen insensitivity syndrome	#300068	*313700 (AR)	PCR	1
Choroideremia	#303100	*300390 (CHM)	PCR	1
Duchenne Muscular Dystrophy	#310200	X-chromosome (sexing) or *300377 (DMD)	FISH or PCR	25
Ectodermal dysplasia, Hypohydrotic, x-linked	#305100, #300291	X-chromosome (sexing)	FISH	2
Fabry Disease	#301500	X-chromosome (sexing)	FISH	1
FG syndrome	not defined for this patient	X-chromosome (sexing)	FISH	1
Hemophilia A	+306700	X-chromosome (sexing)	FISH	11
Hydrocephaly	#307000	X-chromosome (sexing)	FISH	3
Kallmann syndrome	+308700	X-chromosome (sexing)	FISH	1
Kennedy disease	#313200	*313700 (AR)	PCR	2
Menkes disease	#309400	X-chromosome (sexing)	FISH	2
Myotubular Myopathy	#310400	X-chromosome (sexing)	FISH	1
Ornithine Transcarbamylase Deficiency (OTC)	#311250	X-chromosome (sexing)	FISH	1
Retinitis Pigmentosa type III	#300389	X-chromosome (sexing)	FISH	8
Retinoschisis 1	+312700	X-chromosome (sexing)	FISH	1
Severe Combined Immunodeficiency (SCID)	#300400	*308380 (IL2RG)	PCR	1
Wiskott-Aldrich syndrome (WAS)	#301000	X-chromosome (sexing)	FISH	2
X-linked mental retardation (MR)	Heterogeneous group	X-chromosome (sexing)	FISH	7
Charcot Marie Tooth X linked	not defined for this patient	X-chromosome (sexing)	FISH	1
Chondrodysplasia punctata	not defined for this patient	X-chromosome (sexing)	FISH	1

Indications for PGD 1993-2005 (continued)

X-linked dominant				
Incontinentia Pigmenti (IP)	#308300	*300248 (IKBKG; =NEMO)	PCR	3
Oro facial Digital Syndrome I (OFD 1)	#311200	X-chromosome (sexing)	FISH	2
Fragile X syndrome	#300624	*309550 (FMR1)	PCR	37
Fragile X syndrome + Mental retardation	#300624 + X-linked MR	*309550 (FMR1) + Unknown	FISH + PCR	1
HLA typing				
Beta-thalassemia + HLA	+141900	+141900 (HBB), HLA	PCR	3
Chronic septic granulomatosis + HLA	#306400	X-chromosome (sexing), HLA	FISH + PCR	1
Fanconi anaemia + HLA	#227650	*607139 (FANCA), HLA	PCR	2
Leukemia + HLA	Not relevant	HLA	PCR	5
Sickle Cell Anaemia + HLA	#603903	+141900 (HBB), HLA	PCR	5
Wiskott-Aldrich syndrome (WAS) + HLA	#301000	*300392 (WAS), HLA	PCR	1
Robertsonian translocations				57
reciprocal translocations				90
other chromosomal abnormalities				68
PGS				837

Results on a consecutive series of 581 children born after blastomere biopsy for PGD

	PGD	ICSI
Malformation rate	2.13 %	3.38 %

Embryo biopsy does not add risk factors for the health of singleton children after PGD

The perinatal death rate in multiple pregnancies is such that both caution and long term follow-up are required

Liebaers HR 2010

Future trends of PGD

- Increase the number of genetic diseases which can be tested
- Improve vitrification of blastocyst
- Singleton pregnancies and deliveries after fresh replacement of 1 blastocyst
- Single pregnancies and deliveries after replacement of frozen – thawed vitrified embryos, replacement of one blastocyst
- Children follow-up

Donoso HR 2008

Discussion on PGD

	Controversial	Not controversial
Indications		X
Methodology		X
Results		X
Children		X

Avoiding prenatal diagnosis

Rating : transparent and straight forward

CODA

- Transparent request
- Correct and safe methodology
- Avoiding interruption of pregnancy
- Leading to singleton deliveries (one by one)
- Vitrification of day 5 blastocyst leading to singleton deliveries (one by one)
- Avoiding cross border medical care