PRENATAL OR PGD – WHICH ONE TO CHOOSE?

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ESHRE 2010

Genetic Conditions for Which Prenatal but Not Preimplantation Genetic Diagnosis Applicable

- Fetal structural abnormalities detectable only by ultrasound
- Follow up noninvasive aneuploidy screening (maternal serum analytes) followed by need for definitive diagnosis

Genetic Conditions in Which PGD Possible but not Practical

- Advanced Maternal age absent need for ART

Age (y)	Aneuploidy
30	1/ 384
35	1/204
40	1/ 65

- Risk of Amniocentesis or CVS

~1/400 to 1/500 in experienced hands

GENETIC CONDITIONS FOR WHICH EITHER PREIMPLANTATION OR PRENATAL DIAGNOSIS APPLICABLE

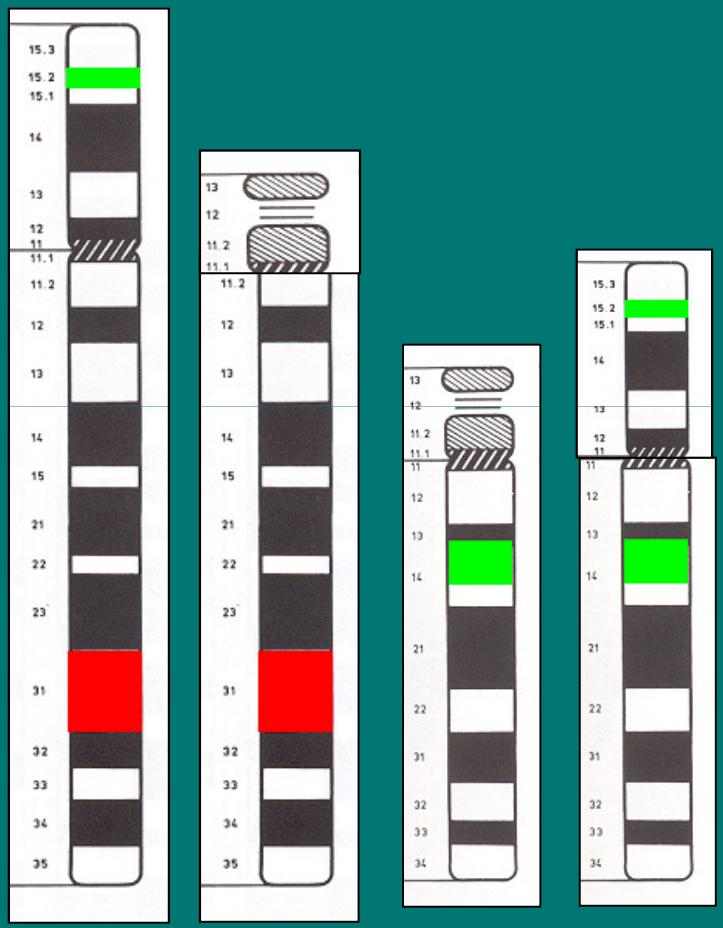
- Translocations
- Mendelian disorders
- Aneuploidy testing solely to exclude abnormal liveborn

Usually prenatal save extenuating situations

46,XY,t(5;13)(p10;q10)

5p15.2
Spectrum
Green
450kb

EGR1-5q31
Spectrum
Orange
200kb



5p15.2
Spectrum
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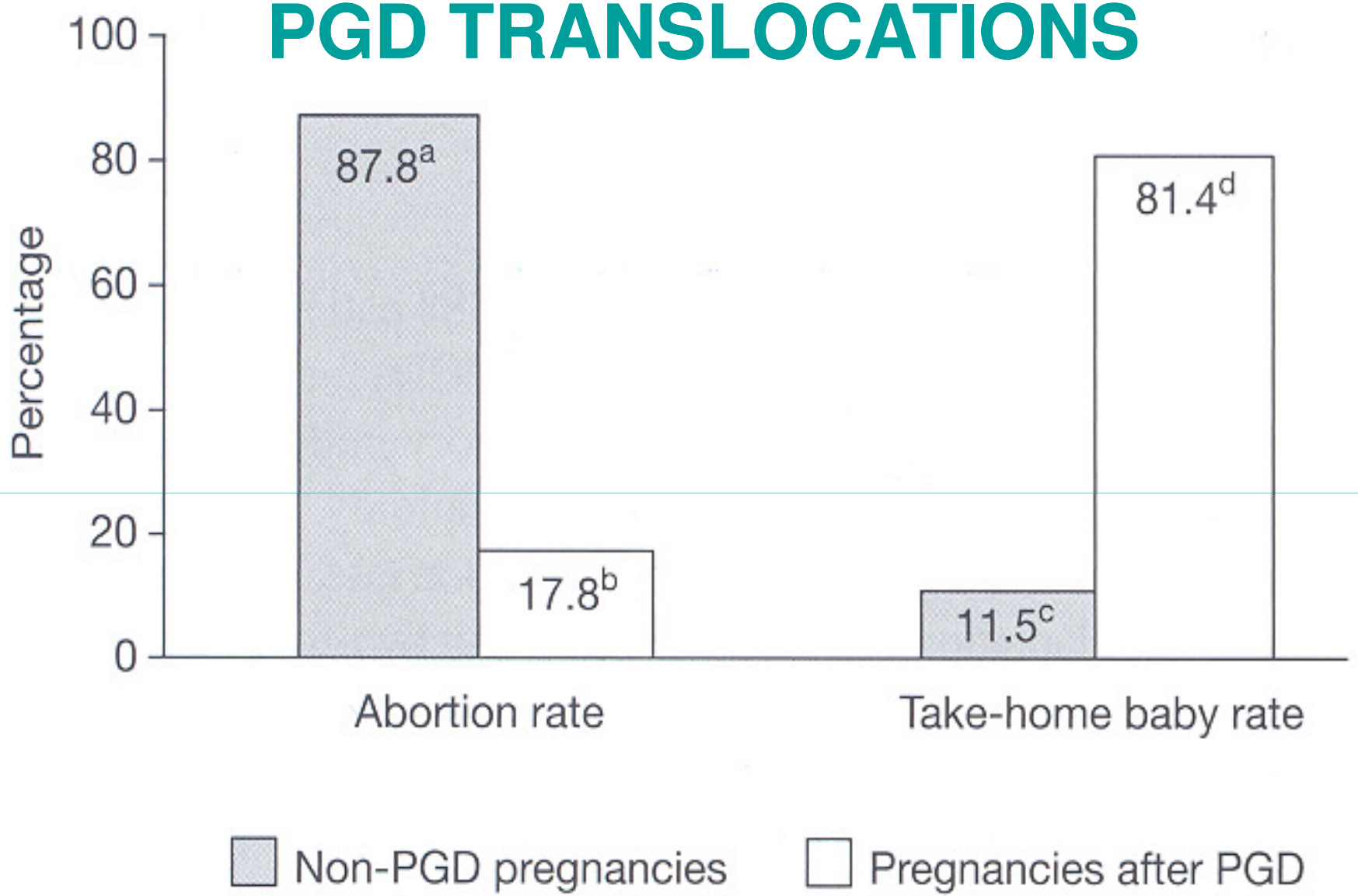
LSI13-Rb
Spectrum
Green; 160kb

5 der5 13 der13

- Cannot distinguish balanced normal from genetically normal

PGD TRANSLOCATIONS



Cumulative Results:

Verlinsky and Kuliev, 2005

RECIPROCAL TRANSLOCATIONS

Tissue	UNBALANCED
Chorionic Villi	10-12%
Blastomeres*	70-90%

GENETIC INDICATIONS FOR WHICH PGD PREFERENTIAL

- Translocations
- Transferring normal embryos without translocation
- Achieving livebirth more rapidly

LIKELIHOOD REPEATED PREGNANCY LOSS*: Applicable as well for Translocations

	Prior Abortions	Risk*
Prior Liveborns	0	5 - 10%
	1	20 - 25%
	2	25%
	3	30%
	4	30 - 35%
No Prior Liveborns	3	40%

** Maternal-age dependant*

Simpson, 2002

WHY USE PGD IF 60-70% EVENTUALLY BECOME PREGNANT?

(Balanced Translocation Heterozygotes)

	Cumulative Live birth rate	Time to pregnancy
Sugiura-Ogasawa (2004)	68%	- 16 year follow up
Goddijn (2004)	70%	- 6 year (mean)
Stephenson & Sierra (2006)	71%	- 4 year (mean)

PGD recommended given time to achieve pregnancies naturally. ASRM/SART Practice Committees *Fritz & Schattman, Fertil Steril 90: 892, 2008.*

GENETIC INDICATIONS FOR WHICH PGD PREFERENTIAL

- Mendelian Disorders
  - Adult onset disorders (family dynamics and high risk)
  - Testing more than one disorder (high likelihood abnormal fetus)
  - De novo mutation
- PGD can determine phase for linkage analysis)

DETERMINE PHASE IN DE NOVO DOMINANT MUTATIONS OR RECESSIVE HETEROZYGOSITY

Male

- Single sperm (haplotype) analysis in absence other affected family members
- Determining phase in gonadal mosaicism

  – Excluding affected can utilize prenatal or PGD approaches

PGD TO DETERMINE PHASE IN DE NOVO MATERNAL MUTATIONS

Female

- Polar Body (haplotype 1st versus 2nd polar body)
- establish phase in de novo germinal mutation

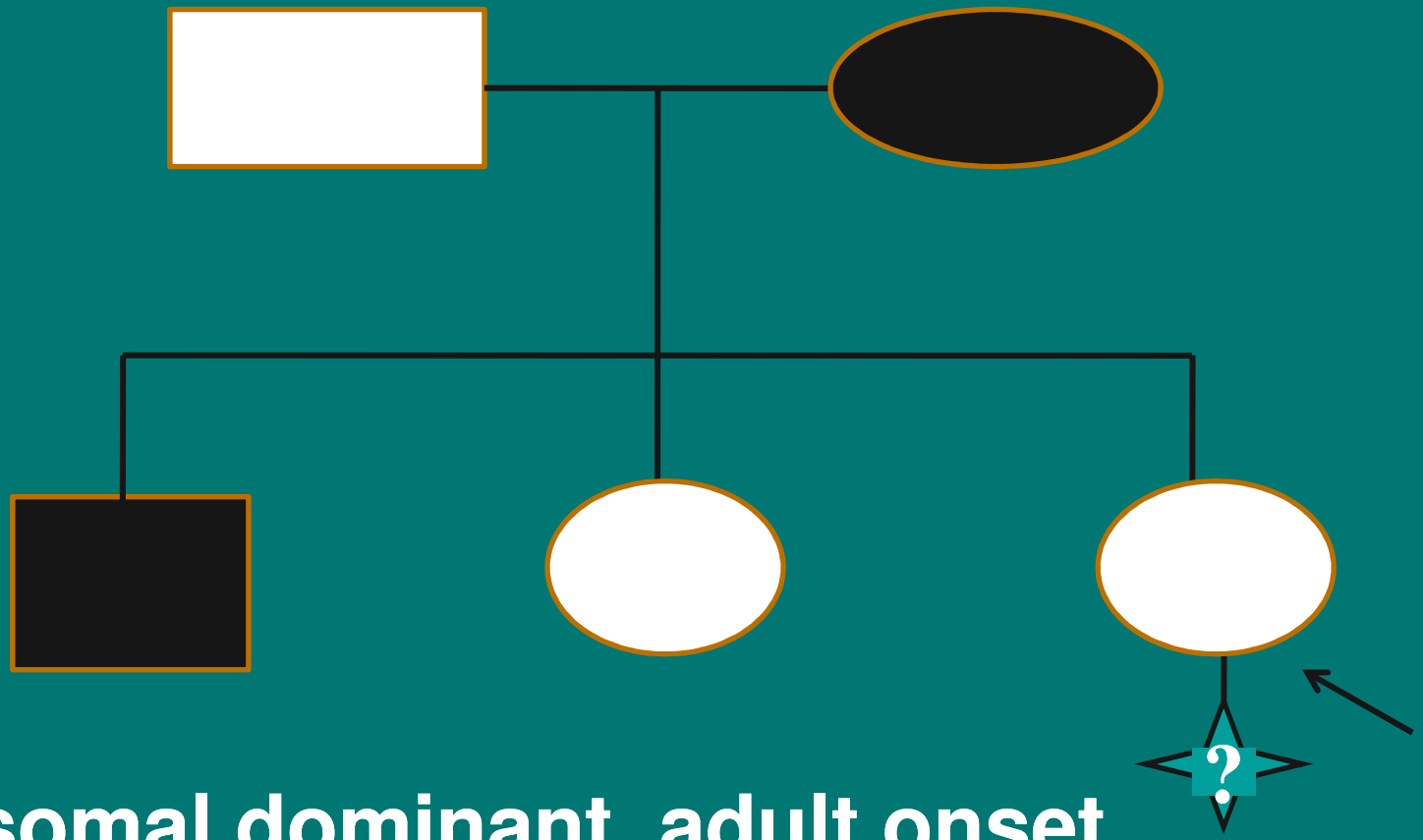
Cycle (Embryo)

- Establish basis of unequivocally normal or affected embryo

Genetic Indications Uniquely Addressed Through PGD

- Avoiding clinical terminations
- Single gene disorders in which nondisclosure is required
- Single gene disorders in which identifying HLA compatible embryos required

PRENATAL DIAGNOSIS WITHOUT DISCLOSURE OF PARENTAL GENOTYPE



Autosomal dominant, adult onset

AVOIDING UNNECESSARY TRANSFERS IN NONDISCLOSURE PGD

- Provide no information on status or number of oocytes
- Perform aneuploidy testing concurrently. Failure to transfer could be far more than a single reason.

Genetic Indications Uniquely Addressed Through PGD

- Avoiding clinical terminations
- Single gene disorders in which nondisclosure is required
- Single gene disorders in which identifying HLA compatible embryos also required

PGD FOR STEM CELL TRANSPLANTATION

Genetic Disorders *(25% risk)*

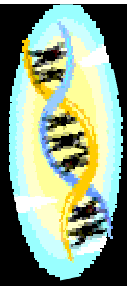
- **Fanconi anemia**
- **β-thalassemia**
  - **Non-functioning bone marrow treated with stem cells from normal bone marrow or umbilical cord blood**
  - **HLA match ~95% successful**
  - **Non HLA match ~60% successful**

LIKELIHOOD OF TRANSFERRABLE EMBRYO

Autosomal Recessive

HLA Compatible = 1/4
Normal (Autosomal Recessive): ¾
Thus, 1/4 • 3/4 = 3/16

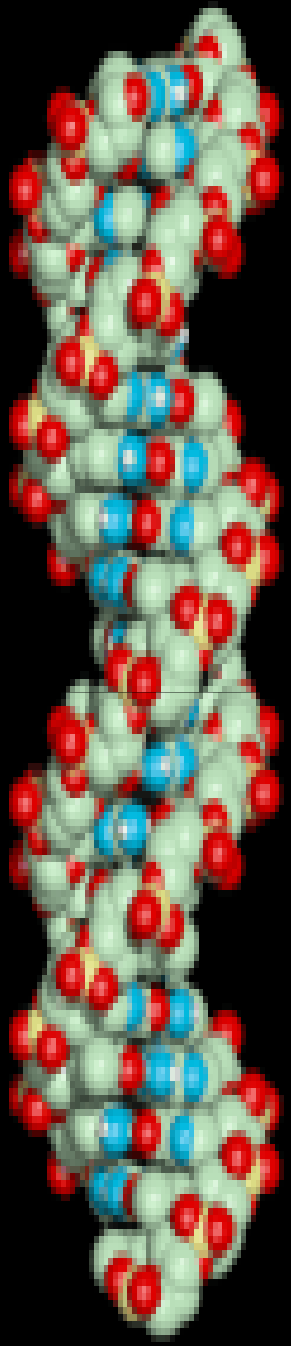
Overall Results and outcome of PGD for Single Gene Disorders & Preimplantation HLA testing



Testing	Patient/ Cycle	# of Transfer	# Embryos Transferred	Pregnancy / Birth
HLA	127/ 297	194	301	58 / 47 (3)* 30 %
Single Gene Disorders	1012 / 1731	1490	2958	619 / 592 (51)* 41.5%
TOTAL	1139 / 2028	1684	3259	677 / 639 (54)* 40.2%

Reproductive Genetics Institute

* Ongoing pregnancies



Impact of Aneuploidy Testing on Preimplantation HLA Typing Efficiency & Outcome

	HLA	HLA + Aneuploidy	TOTAL
Mean Age	36.5	37.2	
Patient / Cycle	13 / 35	30 / 57	43 / 92
Total Embryos	319	428	747
Matched Embryos	65	85 (58 N + 27A) 66%	150
Non-matched Embryos		343 (181 N+162A) 53%	597
Transfers	254	35 (61.4%)	61
# Embryos transferred	26 (74%)	53 (.9)	94
Pregnancy	41 (1.6)	17 (48.5%)	24
Birth	7 (27%)	11 (2)*	17(2)*
	6		

Reproductive Genetics Institute

PGD FOR PURPOSES OTHER THEN PND

- Social sexing
- HLA identical embryos at risk for genetic disorder (e.g., prior child with leukemia): 1/4 likelihood)
- PGD aneuploidy testing (PGS)

PGD CYCLES FOR SOCIAL SEXING (ESHRE)

	Social Sexing	Total
1997-2004 (Collections I-VII)	412 (3.3%)	12,397
2005 (Collections VIII)	85 (2.4%)	3,488

Goosens at al, 2008

PGD CYCLES FOR SOCIAL SEXING (ESHRE)

Social Sexing Cycles	85
Sex Preference (Male: Female)	55:30
Embryo Transfer	65/85 (78%)
Implantation Rate	21/108 (19%)
Delivery Rate (per oocyte retrieval)	13/85 (15%)

Goosens at al, 2008

CHARACTERISTICS OF COUPLES SEEKING FAMILY BALANCING (Baylor College of Medicine)

- Determine attitudes and beliefs of couple desiring family balancing (after first child) through ART (interview by bioethicist)

Inquiries	169
Offered Interviews	47
Interviewed	18

- Interviews revealed logical reasons

McAdoo, Sharp, McGowan, Carson, Simpson; PGDIS, 2009

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Reproductive Genetics Institute HLA Alone Typing

	1990-2004*		2005-2009	
• HLA and Genetic Testing	47	63	125	201
• HLA alone	16		76	
• Other	499		974	
Total single gene	562		1175	

* All HLA 1999-2004

Rechitsky et al., 2009, PGDIS

PGD ANEUPLOIDY TESTING (PGS)

- **Rationale:**
  - High frequency aneuploidy even in morphologically normal embryos (50%)
- **Strategy:**
  - Transfer only euploid embryos
- **Goals:**
  - Reduce abortions
  - Increase livebirths

REDUCTION IN MISCARRIAGES IN RECURRENT PREGNANCY LOSS

maternal age	cycles	★% loss expected	% loss after PGD	
<35	85	26%	13%	p=0.09
≥35	143	39%	13%	p<0.001
Total	228	33%	13%	p<0.001

★ Logistic regression that takes into account maternal age, number, prior abortions
Brigham Hum Reprod 14: 2868, 1999

Munné et al. (2008)

PGD Aneuploidy Testing To Increase Livebirth Rate (CONTROVERSY)

- Impressive data from most experienced 3 centers, but no randomized clinical trials conducted in those centers
- RCTs in other centers have not shown benefit, but some unwittingly show embryo biopsy per se is harmful.

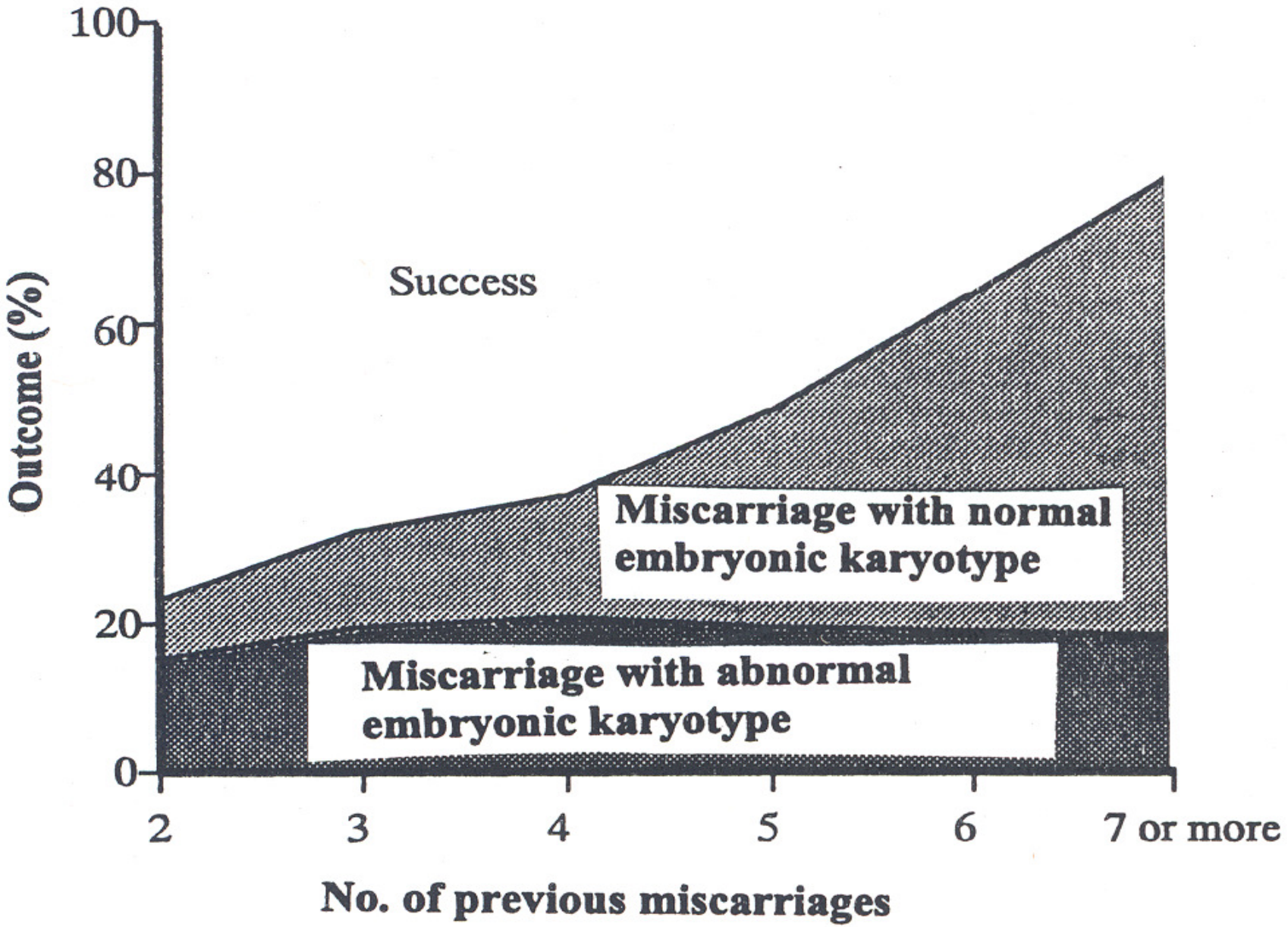
CLINICAL INDICATIONS FOR PGD ANEUPLOIDY

- Not just any maternal age but perhaps maternal age ≥ 38
- Not just any stimulated cycle but only those with sufficient number of morphologically normal embryos (≥6?)
- Not just any recurrent loss cases but those with 3-5 and with prior aneuploidy confirmed (recurrent aneuploidy)

RECURRENT ANEUPLOIDY

First Abortion	Second Abortion Normal	Mono	Tri	Poly	Trans
Normal	69	2	6	5	0
Monosomy	7	1	3	1	0
Trisomy	10	1	27	2	0
Polyploidy	7	1	3	2	0
Translocation	0	1	0	0	6

Hassold, 1984



Ogasawara et al., 2000

PREDICTIONS REGARDING PGD ANEUPLOIDY TESTING (JLS)

- Will be efficacious with precise indications (maternal age, prior aneuploidy in recurrent losses, sufficient morphologically normal embryos)
- Will prove efficacious with skilled embryo biopsy
- Will be efficacious with 24 chromosome assessment

PRENATAL OR PGD

1. PGD has accepted but still limited place overall in reproductive medicine and prenatal genetic diagnosis

2. PGD is possible but PND more practical for certain traditional indications

PRENATAL OR PGD

3. PGD may be preferable to PND in certain indications (translocations especially with advanced maternal age; single gene adult onset disorders)
4. PGD uniquely applicable for avoiding clinical terminations, nondisclosure, HLA typing

PRENATAL OR PGD

5. PGD alone applicable for selected non-genetic indications (HLA solely for matching; improving livebirth rates in ART)