Assisted Reproduction Techniques for avoiding inherited diseases

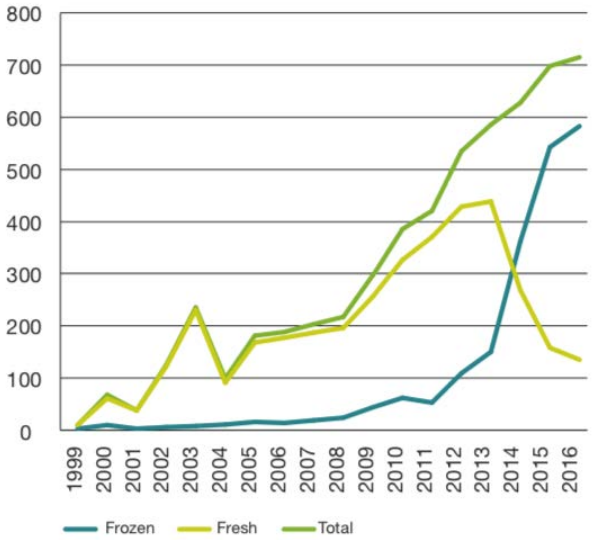
Practical aspects of PGD and Results

Peter Braude OBE FRCOG FMedSci
Emeritus Professor of Obstetrics and Gynaecology
Division of Women's Health
King's College London

Reporting Outcome of PGD

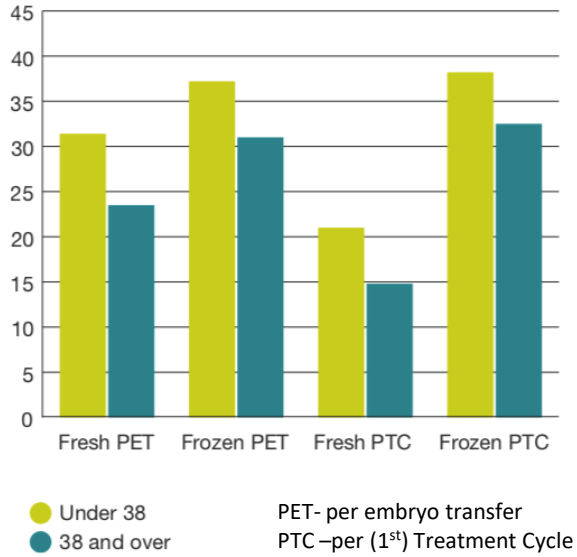
Most clinics and registries report outcome based on the IVF and the PGD as per 1st transfer cycle

Figure 42: PGD treatment numbers for UK



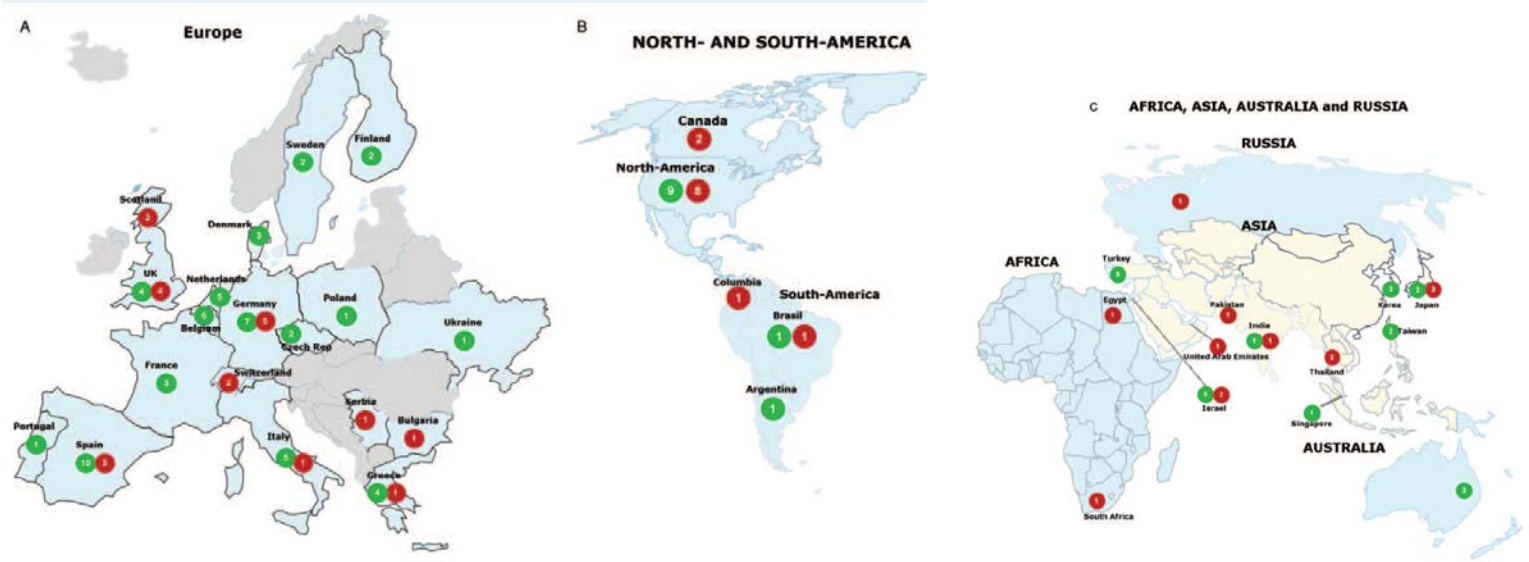
HFEA Fertility Treatment: 2014-2016 Trends and Figures

Figure 45: PGD birth rates by age, 2016



PET- per embryo transfer
PTC –per (1st) Treatment Cycle

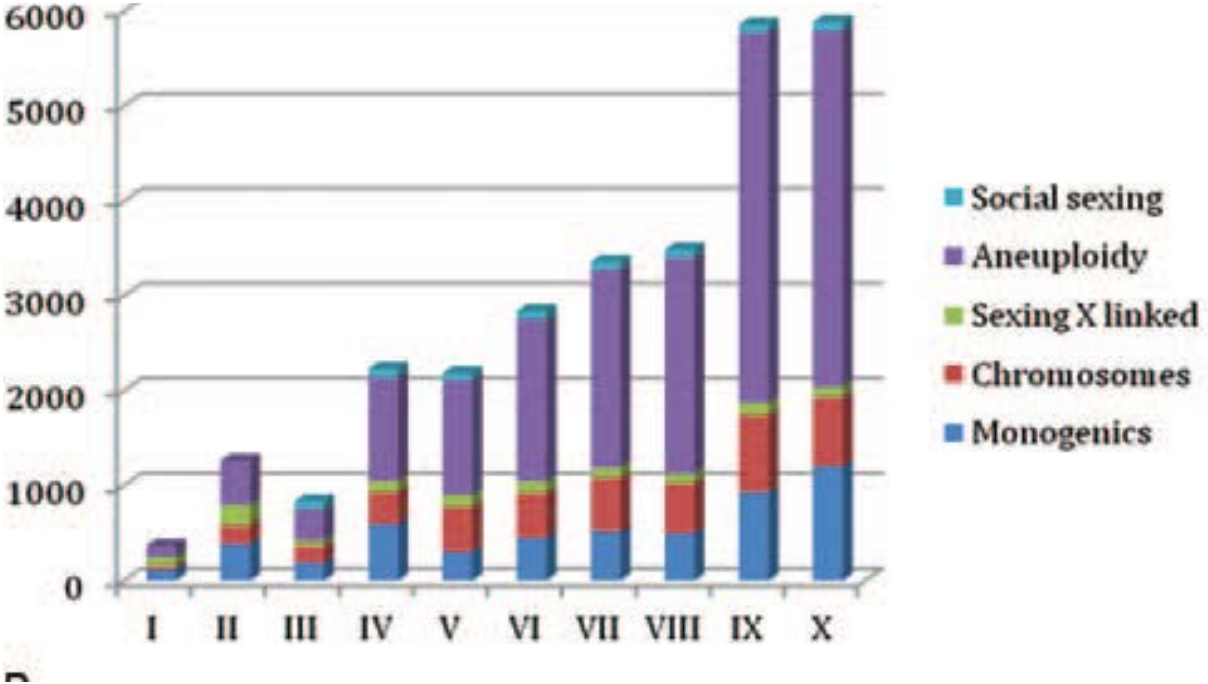
Data from ESHRE PGD Consortium



Human Reproduction Update, Vol.0, No.0 pp. 1–14, 2012
doi:10.1093/humupd/dmr052

human reproduction update

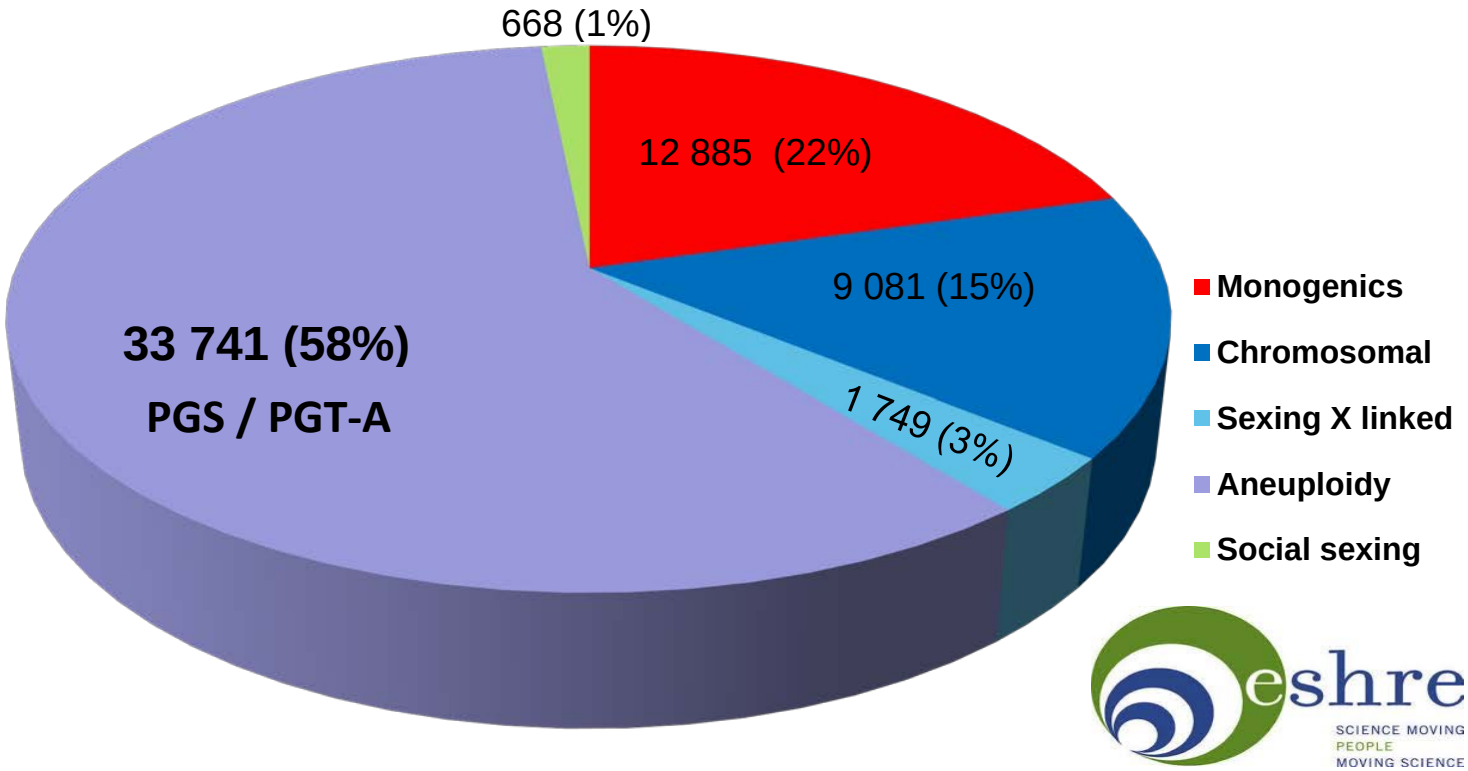
The ESHRE PGD Consortium: 10 years of data collection



REASONS FOR EMBRYO BIOPSY

ESHRE Consortium data I-XV

Based on 54,589 cycles



eshre
SCIENCE MOVING PEOPLE MOVING SCIENCE

Human Reproduction Update, Vol.0, No.0 pp. 1–14, 2012
doi:10.1093/humupd/dmr052

human reproduction update

The ESHRE PGD Consortium: 10 years of data collection

Table I Ten years of PGD Consortium data.

	Cycles to OR	No. embryos biopsied	No. embryos transferred (mean/ET)	Embryo transfer procedures	Clinical pregnancy rate (per OR and per ET)
Single genes	4733	27980	7035 (1.9)	3727	22% per OR 29% per ET
Structural chromosome abnormalities	4253	27068	4775 (1.7)	2731	17% per OR 26% per ET
Sexing X-linked	1167	7317	1598 (1.8)	880	19% per OR 26% per ET
Aneuploidy	16806	90404	21543 (1.8)	12071	19% per OR 27% per ET
Social sexing	671	4285	993 (2.0)	492	21% per OR 29% per ET

OR, oocyte retrieval; ET, embryo transfer procedure.

ESHRE PGD Consortium data collection XIV–XV: cycles from January 2011 to December 2012 with pregnancy follow-up to October 2013† FREE
M De Rycke ✉, V Goossens, G Kokkali, M Meijer-Hoogeveen, E Coonen, C Moutou Author Notes
Human Reproduction, Volume 32, Issue 10, October 2017, Pages 1974–1994, https://doi.org/10.1093/humrep/dex265
Published: 30 August 2017 **Article history**

Table IVa

Cycles performed for single gene disorders, data collection I–XIII.

Indication	X-linked	Autosomal recessive	Autosomal dominant
Cycles to OR	1330	2838	3114
Clinical outcome			
Cycles to ET	1002	2396	2402
hCG positive	364	977	878
Positive heartbeat	294	776	684
Clinical pregnancy rate (% per OR/% per ET)	22/29	27/32	22/28

Reporting Outcome of PGD

- Most clinics and registries report outcome based on the IVF and the PGD as per 1st transfer cycle

- **This does not inform patients of the likelihood of having an unaffected child when they complete a full PGD cycle (including the transfer of any tested embryos that remain frozen)**

- **It is important for patients to know the chance of having an unaffected child after one hormonal stimulation for PGD (intention to treat – ITT)**

Cumulative Livebirth Rate

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The likelihood of attaining a live birth after completing a full stimulation, IVF, and PGD cycle

- **Includes fresh and related frozen transfers**
- **Number of frozen cycles may vary (1-6)**
- **Counted up to the first successful delivery**

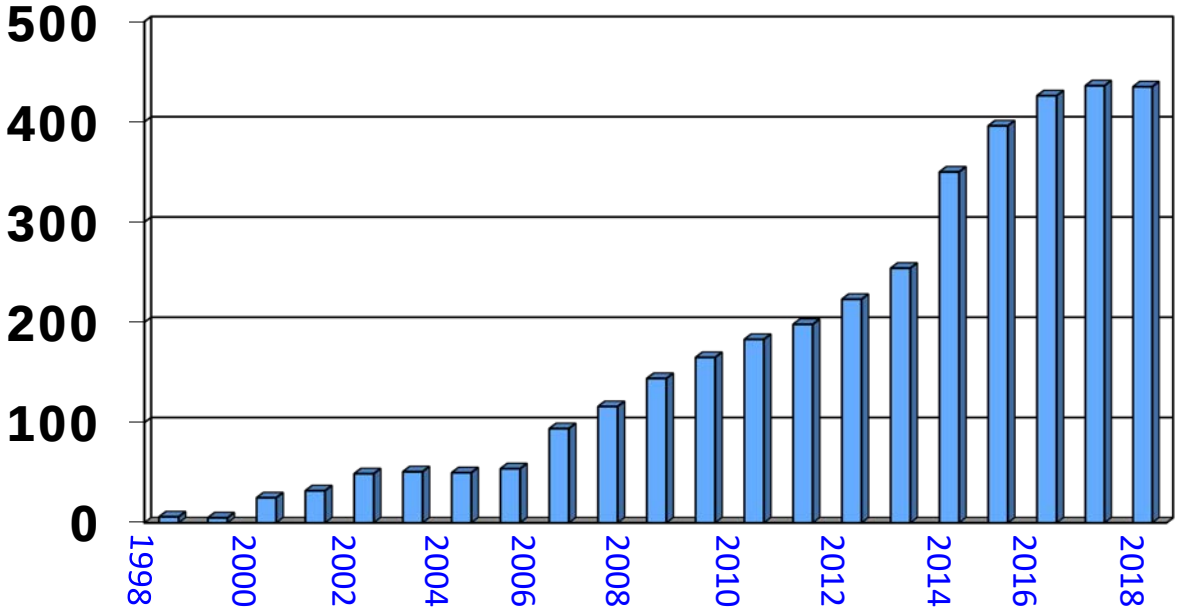
Value of Cumulative Rate

- Improves patient counselling (realistic expectations)
- Better awareness of possible reasons for a cycle not progressing or the need for multiple transfer cycles
- Better control of multiple pregnancy (one at a time)
- Clear target for funding and service provision
- Needed for comparison of other modalities of avoiding genetic disease

Likelihood of success

- Type of genetic inheritance
- Age of woman
- Response to stimulation
- Number and quality of embryos that develop
- Number of blastocysts available for biopsy
- Quality of the laboratory handling ICSI, biopsy, and cryopreservation and thaw
- Veracity of the molecular testing result

Annual number of stimulation cycles started for PGD at one UK centre



UK PGD cycles

HFEA 3 year aggregate data

ACU, Guy's Hospital

UCH, London

CARE, Nottingham

The Bridge Centre, London

Glasgow Royal Infirmary

IVF Hammersmith, London

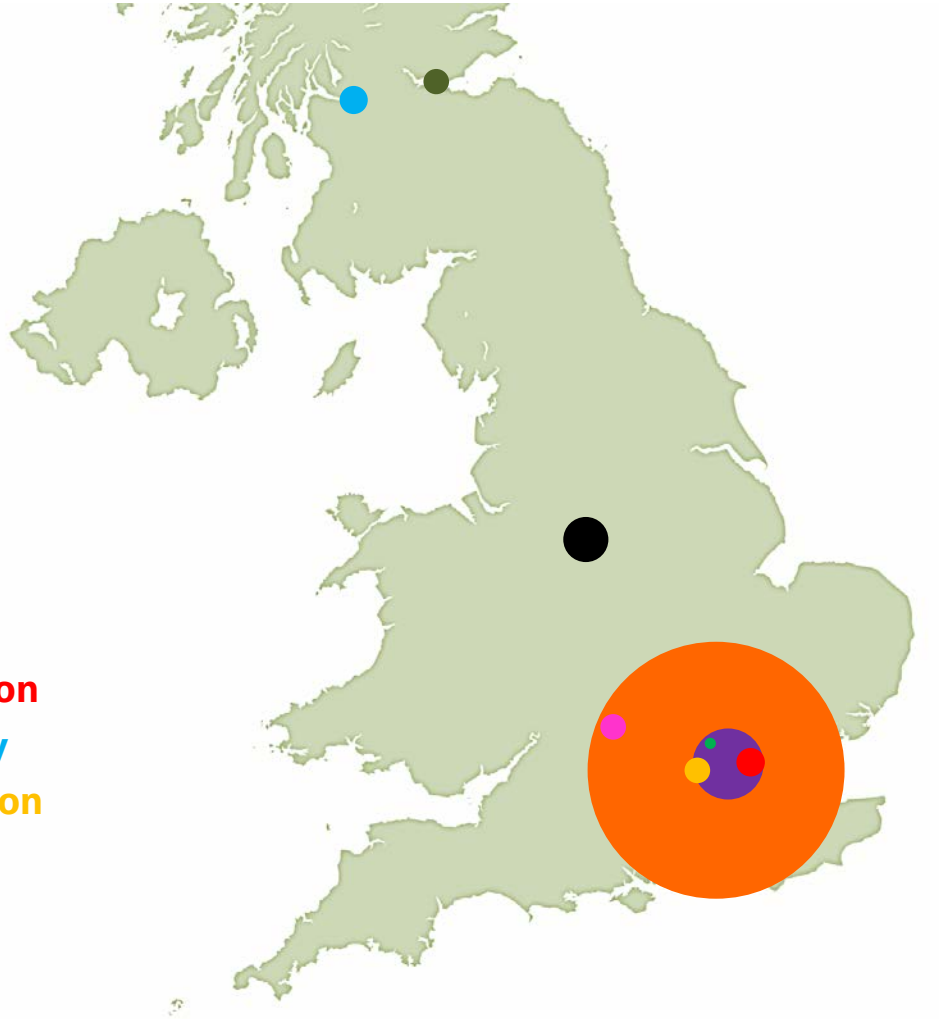
Oxford Fertility Unit

Edinburgh ACU

ARGC, London

UK PGD cycles

HFEA 3 year aggregate data



ACU, Guy's Hospital

UCH, London

CARE, Nottingham

The Bridge Centre, London

Glasgow Royal Infirmary

IVF Hammersmith, London

Oxford Fertility Unit

Edinburgh ACU

ARGC, London

Types of PGD cases

NO PGS (PGT-A) undertaken

No (%)	2010	2011	2012	2013	2014	2015	2016	2017	2018
Rearrang (FISH)	75 (41)	75 (37)	74 (33)	79 (32)	28 (8)	14 (4)	10	0	0
Rearrang (CGH)					73 (21)	73 (18)	90	102 (23)	84 (19)
Single Gene PGH	106 (58)	120 (61)	144 (65)	167 (65)	240 (69)	303 (76)	323	300 (69)	351 (81)

Change to Trophoblast Biopsy

Main conditions in 2011-2018

	2011	2012	2013	2014	2015	2016	2017	2018
CF	39	28	29	28	25	44	39	34
HD	32	26	39	40	40	39	38	44
DMD	5	9	16	12	13	6	6	8
Fragile X	5	10	11	12	11	6	5	5
Hb'pathy	4	11	9	9	22	29	25	16
MD	3	8	6	9	13	7	19	14

Range of SGD cases

2018: 272 biopsy cases

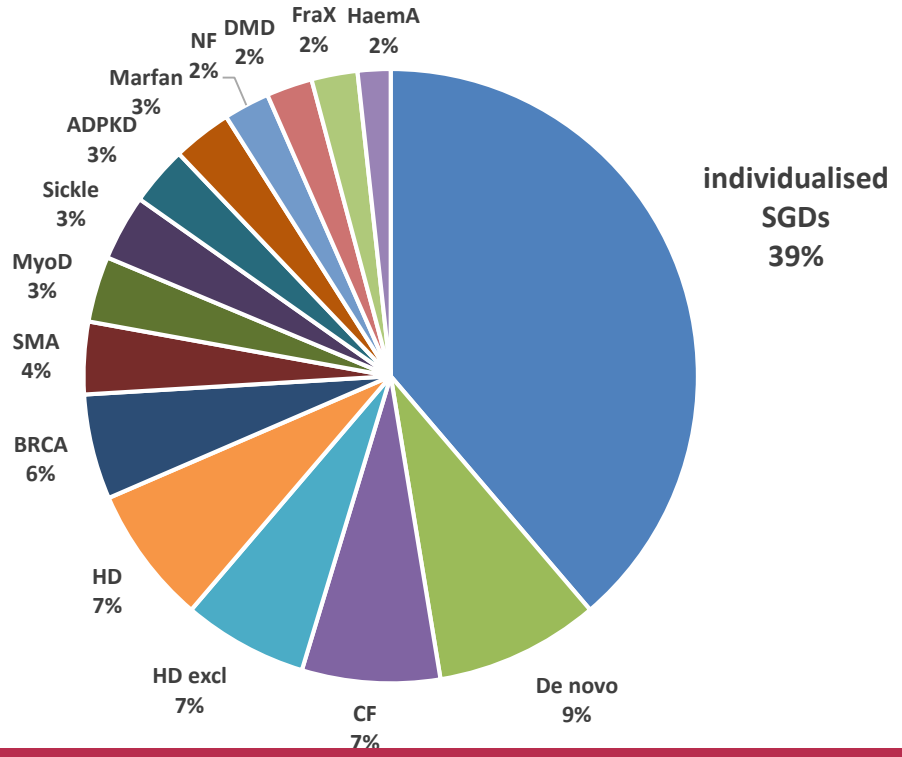
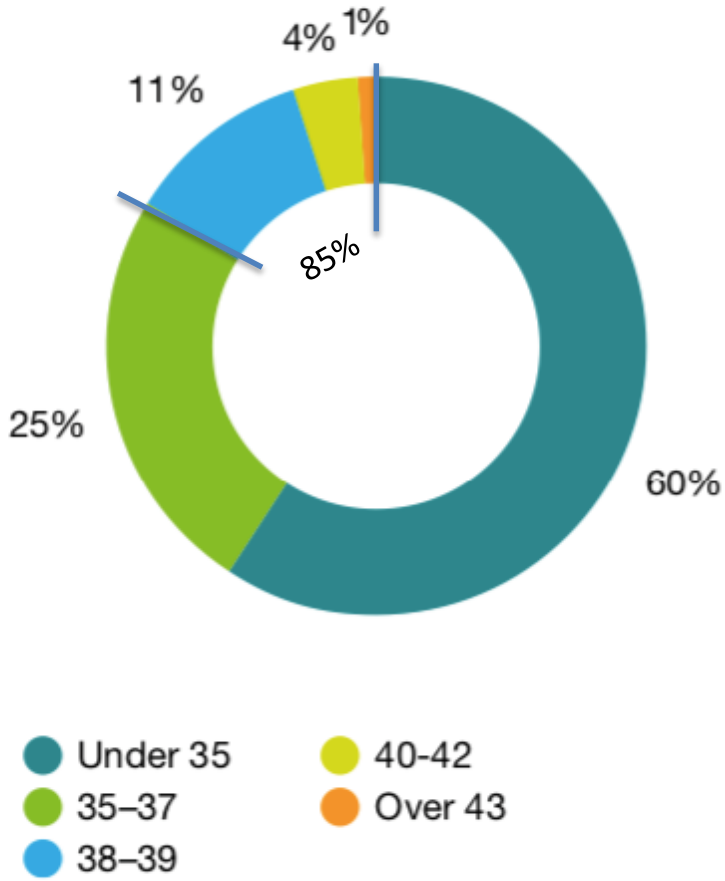
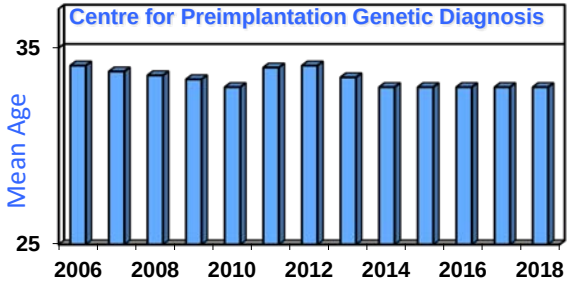


Figure 43: PGD treatments by age, 2016

HFEA Report





PGD Cycle Dislocation

Ovarian stimulation (GnRH agonist trigger)

1

Culture to blastocyst and biopsy

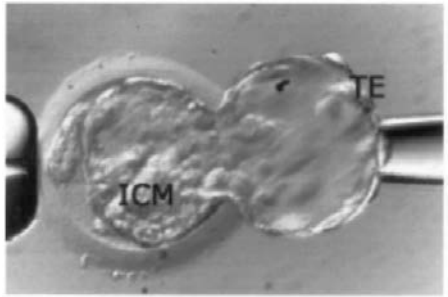
2

3

Blastocyst Vitrification

Batch genetic testing

4

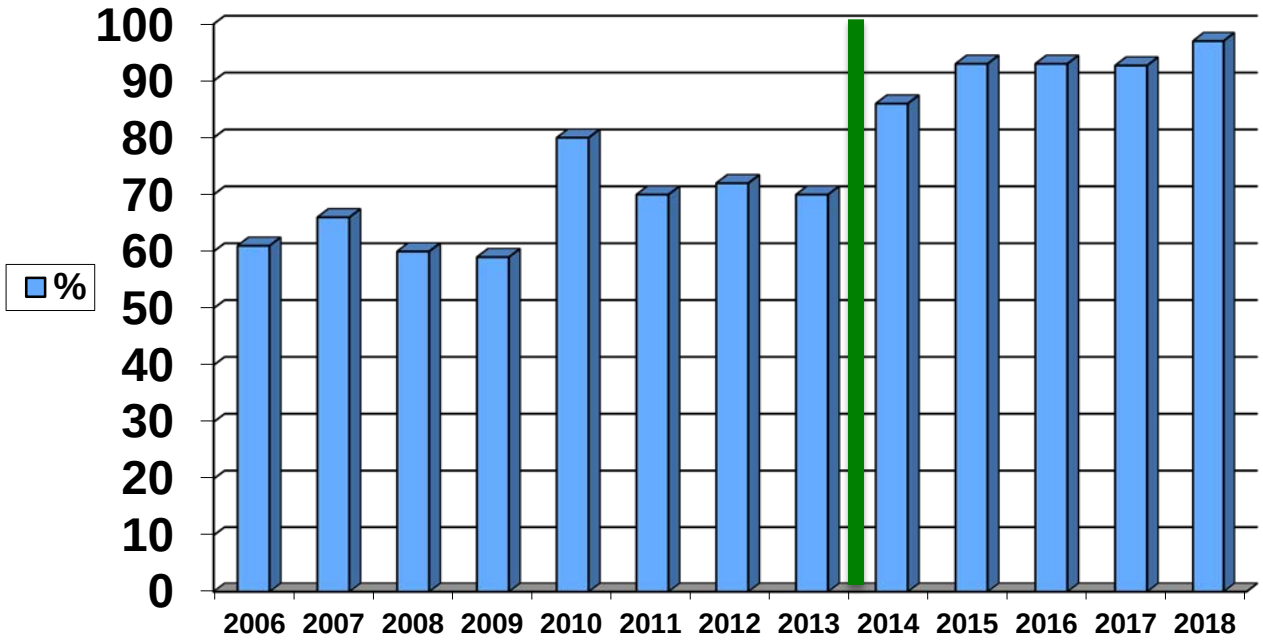


Blastocyst Thaw

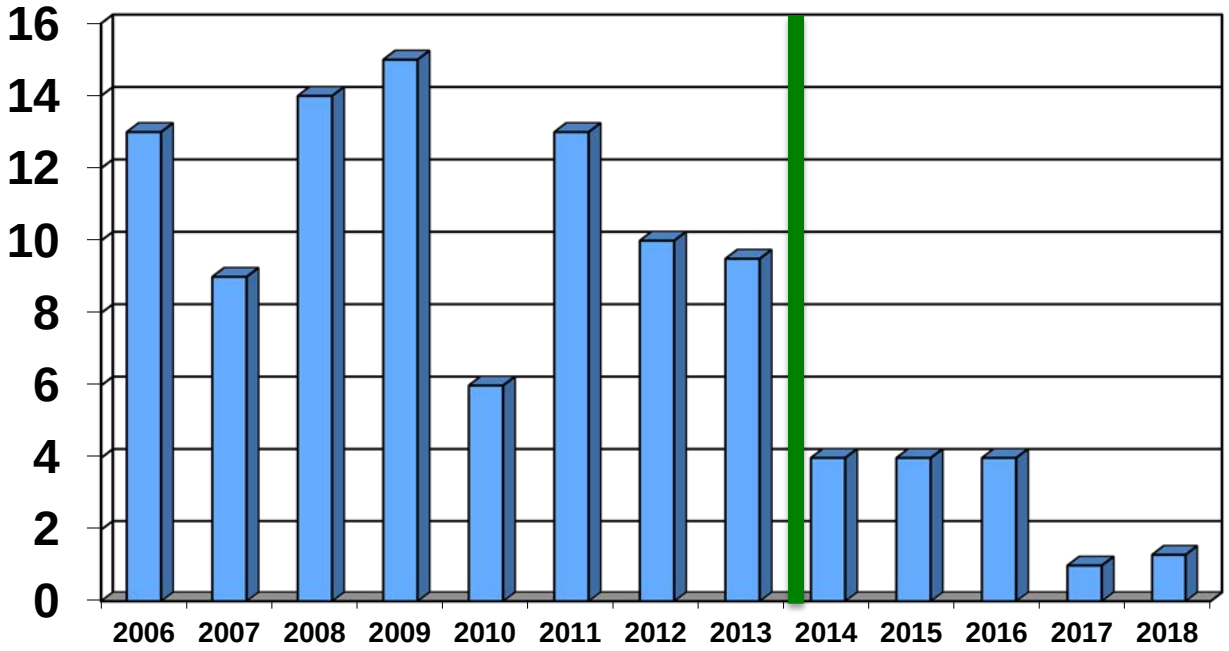
5

Single embryo transfer

SET is the norm at Guy's



Multiple pregnancy rate has fallen dramatically



PGD Cycle Dislocation

Ovarian stimulation (GnRH agonist trigger)

1 Few eggs Poor quality

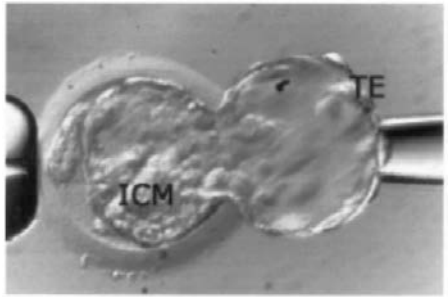
Culture to blastocyst and biopsy 2

Poor fertilisation
No blastocysts
Biopsy failure

3

Blastocyst Vitrification

What can go wrong



Inadequate for cryopreservation

Batch genetic testing

Test failure
Uninterpretable result

4

Blastocyst Thaw

5 Fail to survive thaw

Single embryo transfer

Cumulative LBR after TBx FOR SGD

In 2016, 319 couples started treatment

- **89 couples had no ET (28%)**
- **82 couples had one FET** → **20 had a LB (27%)**
- **148 couples Had two or more FET** → **103 had an LB (70%)**

Total no. of LB = 123

39% per couple starting
54% per couple reaching transfer

PGD Cycle Dislocation

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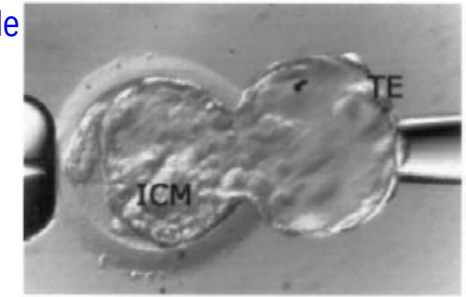
Ovarian stimulation (GnRH agonist trigger)

319 couples started

89 (28%) no ET

Single embryo transfer

1 — 3 no response
2 no eggs suitable for ICSI



5 — 4 Failed to survive thaw

Culture to blastocyst and biopsy (2)

Blastocyst Thaw

13 No fert/cleavage
28 None suitable Bx

3

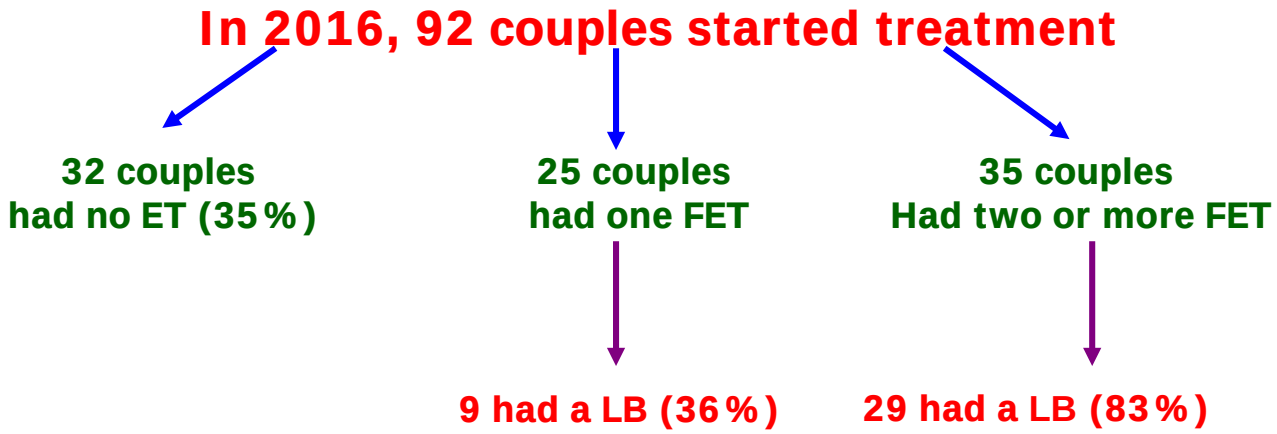
Blastocyst Vitrification

33 none suitable for ET

Batch genetic testing

4

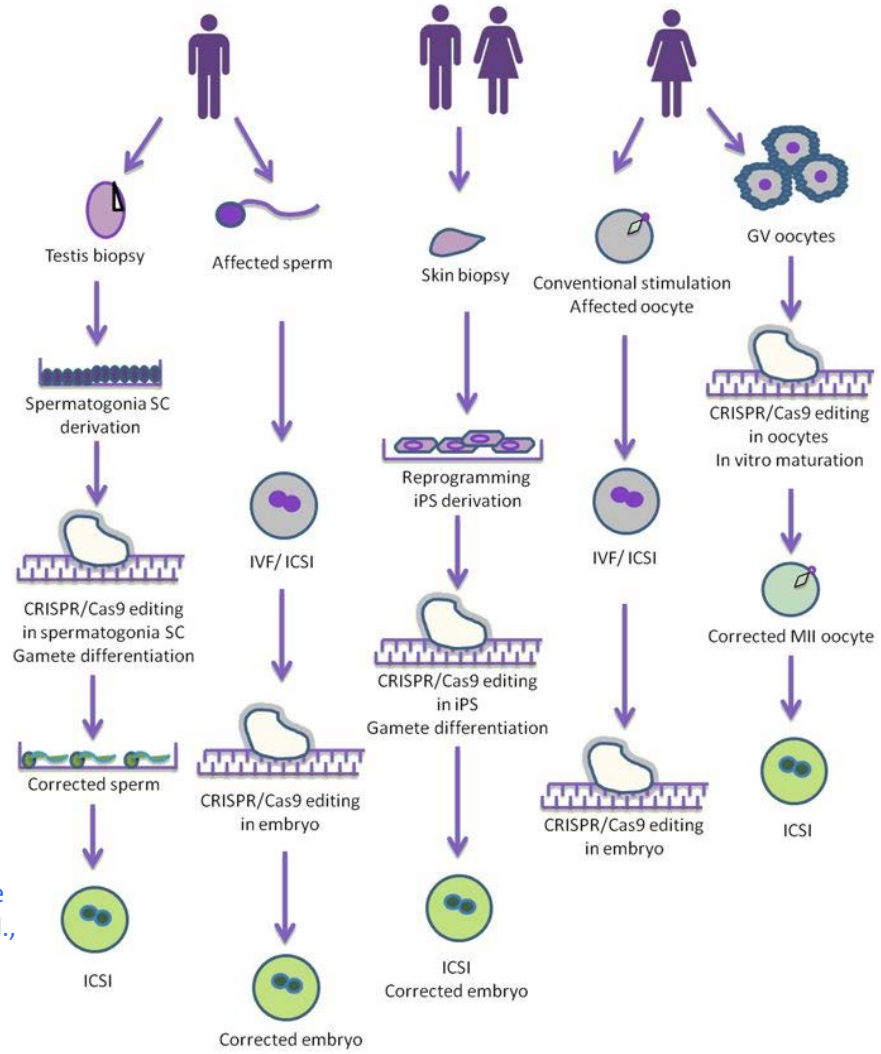
Cumulative LBR for rearrangements



Total no. of LB = 38

42 % per couple starting
63 % per couple reaching transfer

Using Genome Editing in ART



From:
Responsible innovation in Human Germline Gene Editing: ESHG & ESHRE. De Wert et al., Eur J Human Genetics 26, 450-470 (2018)

Gene Editing Cycle

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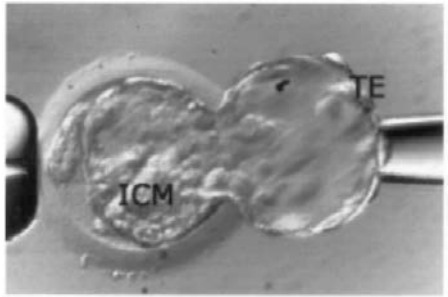
Ovarian stimulation (GnRH agonist trigger)

EDITING HERE
Sperm
Oocytes/embryos

Single embryo transfer

1 Few eggs
Poor quality



Fail to survive thaw 5

Culture to blastocyst and biopsy 2

Blastocyst Thaw

Inadequate for cryopreservation

Poor fertilisation
No blastocysts
Biopsy failure

3

Blastocyst Vitrification

Perhaps more unaffected

Batch genetic testing

Testing / Editing failure
Uninterpretable results
Off target effects / mosaics

4

Balance of Editing over PGD

Advantages of editing:

- **Perhaps more embryos to biopsy**
- **Perhaps more unaffected for transfer**

Disadvantages of editing

- **Efficiency of editing will have to be checked**
- **Reliability of the edit will have to be confirmed**
- **Off target effects will have to measured and controlled**

Precision & Reliability

Genome Editongue

Summary: PGD vs Editing

- **There are very few inherited conditions where PGD does not offer hope of an unaffected livebirth**
- **At present PGD can be effective if done well and using modern testing methods and without PGS**
- **Factors limiting PGD success generally will be the same as those encountered if gene edited ART undertaken**
- **The possibility of more edited unaffected embryos at the start is likely to be outweighed by the unknown or unintended effects of the edit and risks to the child and future generations**