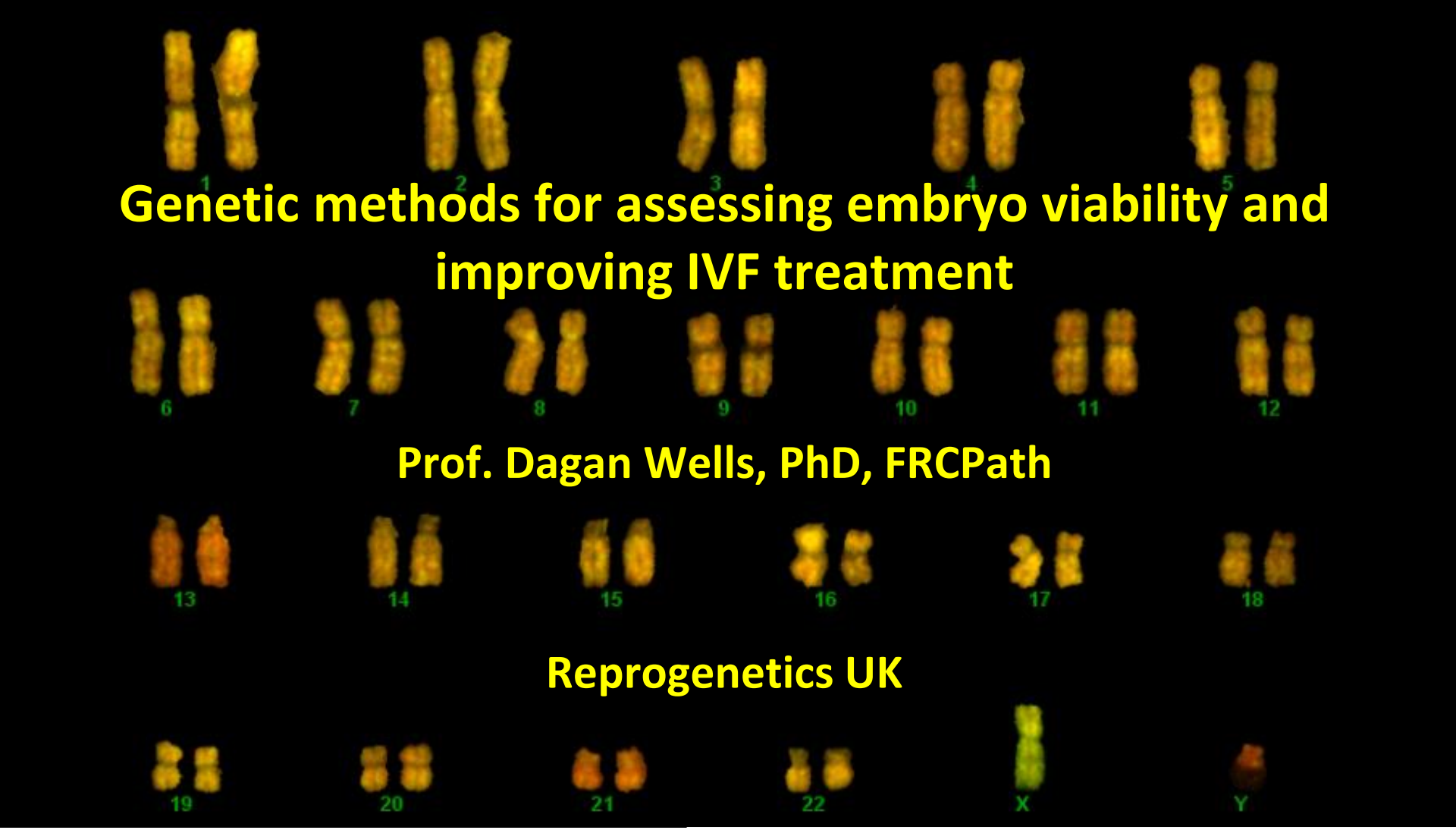


Genetic methods for assessing embryo viability and improving IVF treatment

Prof. Dagan Wells, PhD, FRCPath

Reprogenetics UK

Reprogenetics

Points for discussion

Diagnosis of inherited disorders in preimplantation embryos

Sampling DNA from embryos (embryo biopsy)

Frequency of chromosome abnormalities in human embryos

The use of aneuploidy screening to improve IVF treatment

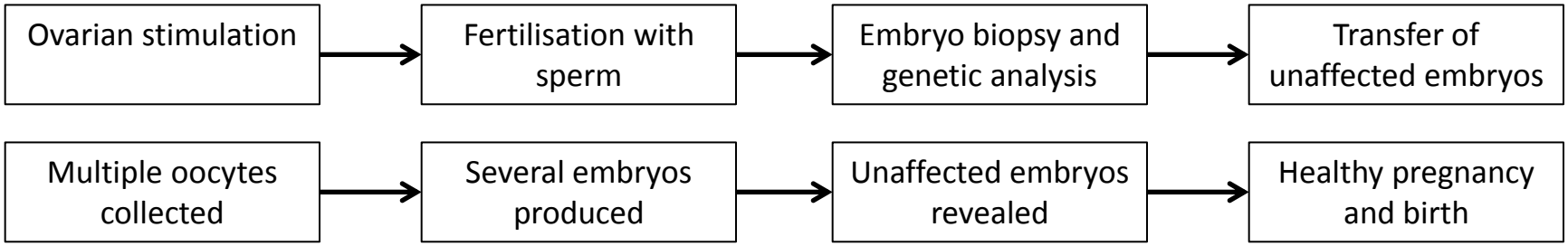
Clinical data from preimplantation genetic screening

What next for genetic methods of embryo viability assessment

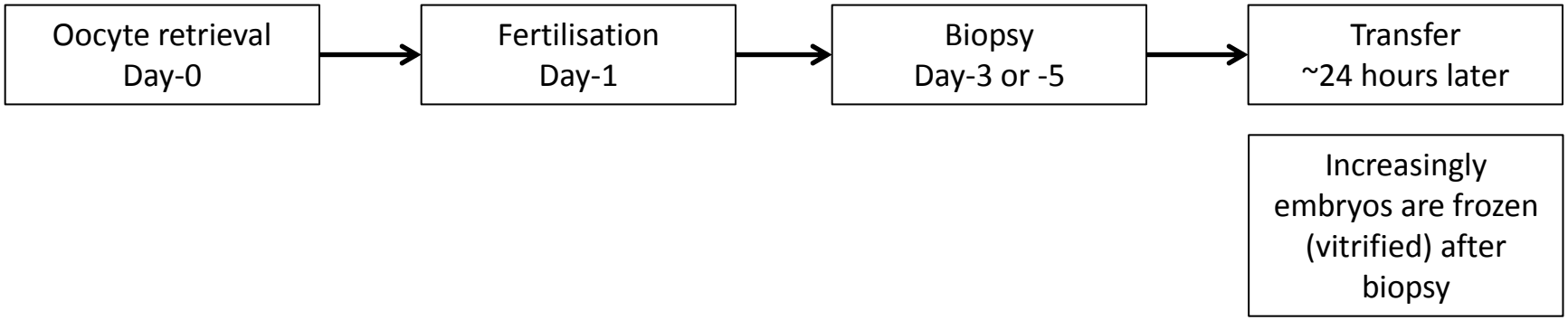
Genetic testing of embryos produced using IVF

Originally an alternative to prenatal testing for high-risk patients

Patients undergo in vitro fertilisation treatment

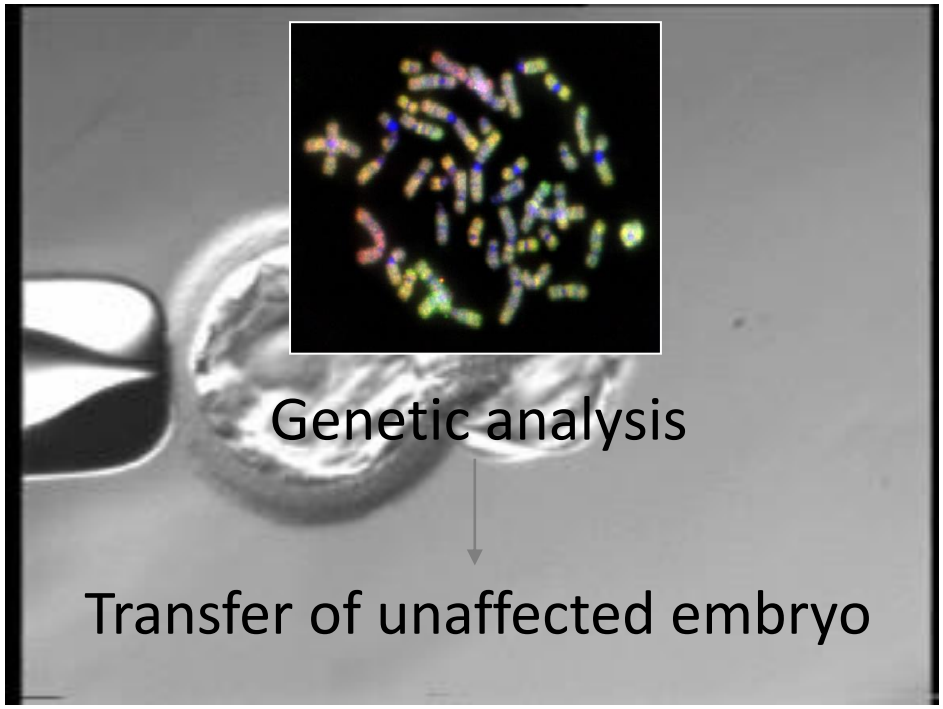


PGD is a rapid process



Genetic testing of embryos produced using IVF

Originally an alternative to prenatal testing for high-risk patients



Prevent affected pregnancy and avoid pregnancy termination

PGD of single gene disorders

To date diagnosis performed diagnosis of >300 disorders

Diagnosis possible for any disorder provided mutation is known

Tests are typically 99% accurate

Results within 24 hours

The use of genetics to improve IVF outcomes

Preimplantation genetic screening (PGS)

In vitro fertilisation (IVF)

A highly successful medical intervention

Infertility treatment revolutionised

Estimated that >5 million babies born following IVF

1-5% of all births in industrialised countries

But….

….the process is very inefficient

In vitro fertilisation (IVF)

Worldwide only 30% of IVF cycles produce a pregnancy

Choose most viable embryo - based (primarily) on morphology

Methods are subjective and provide only rough guide

85% of embryos transferred do not implant

Solution to poor embryo selection – transfer more embryos!

20-25% of IVF pregnancies are multiple gestations

Significant risks of complications for mother and child

In vitro fertilization (IVF)

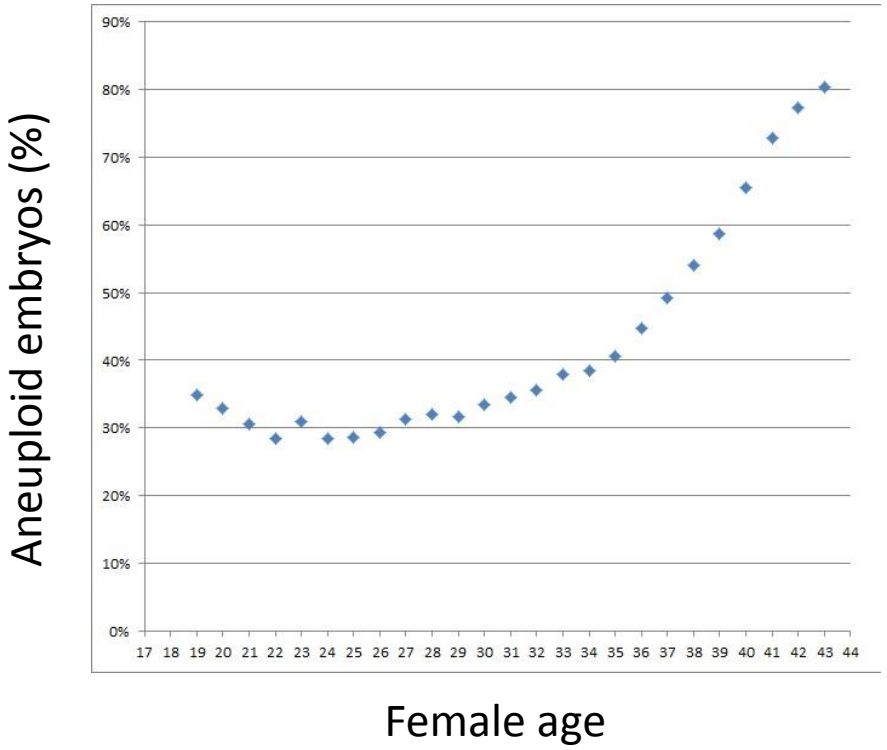
Improved methods needed for embryo selection (eSET)

Could genetic tests provide a more definitive, less subjective assessment?

Genetic abnormalities explain most implantation failures and miscarriages

Chromosome abnormality is extremely common in oocytes

Problem increases with advancing maternal age

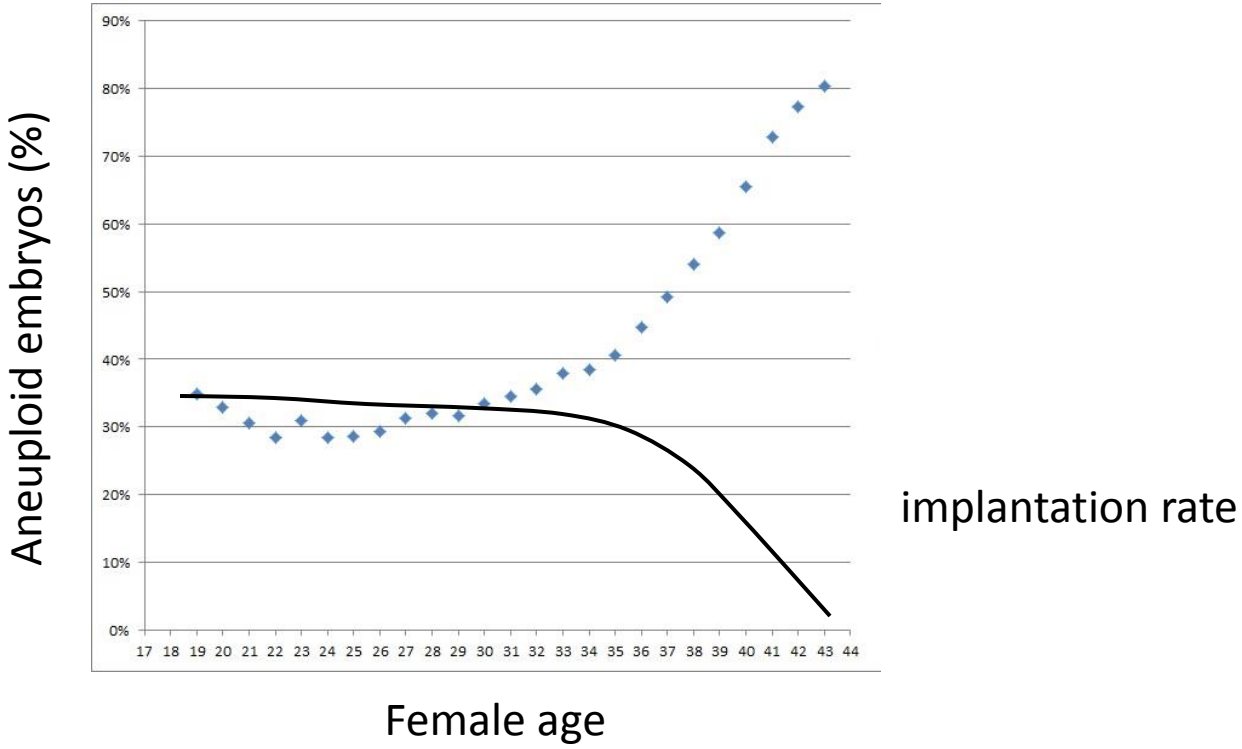


Data from >50,000 embryos analyzed by Reprogenetics

Genetic abnormalities explain most implantation failures and miscarriages

Aneuploidy is almost always lethal (failed implantation/miscarriage)

While aneuploidy increases with age, implantation rate decreases

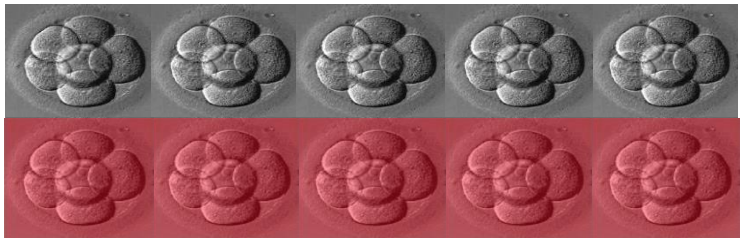


Data from >50,000 embryos analyzed by Reprogenetics

Concept of PGS

Standard embryo evaluations do not reveal embryos with the wrong number of chromosomes

IVF treatment usually results in the production of several embryos

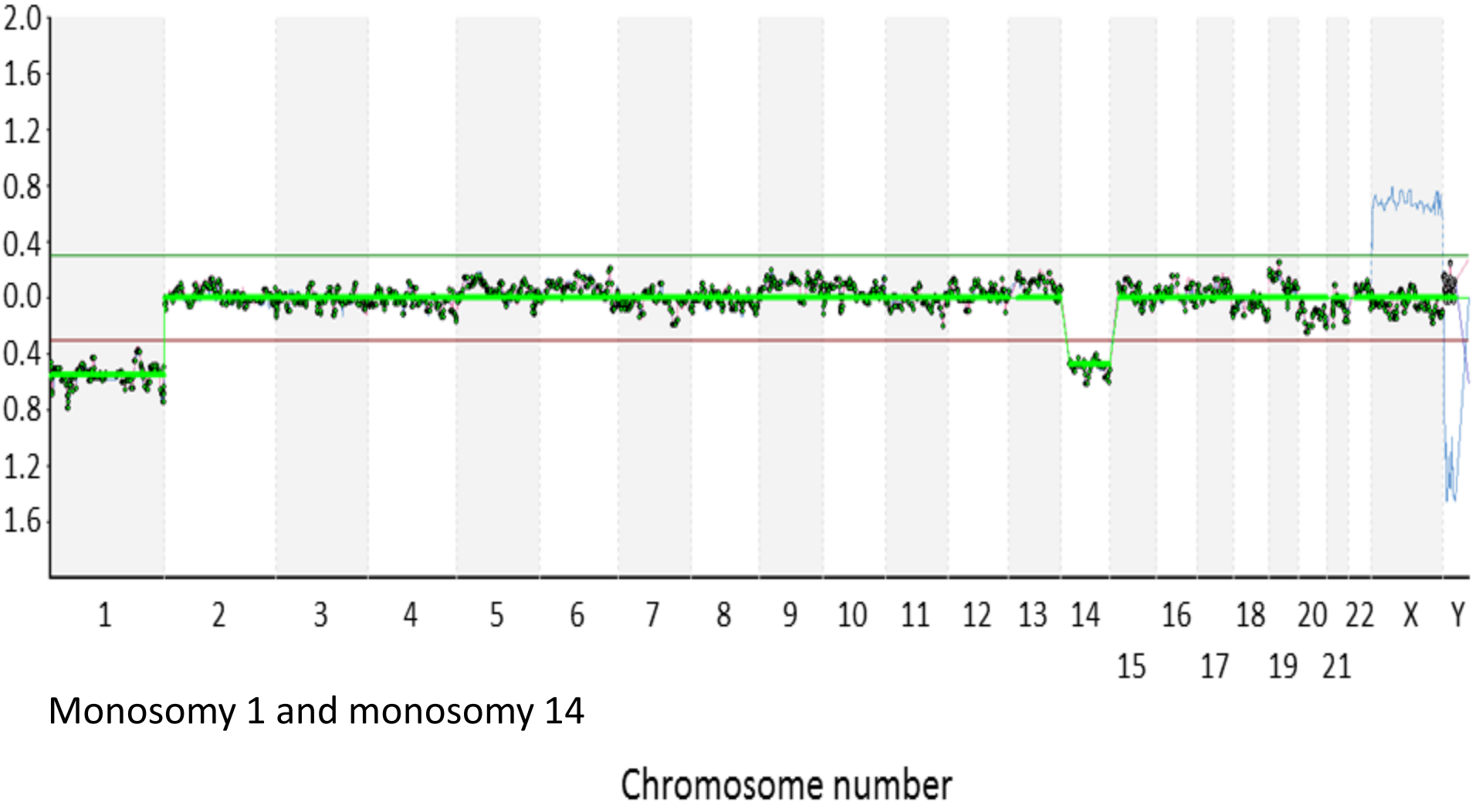


Ideally, one embryo is transferred to the uterus

after chromosome screening

Munne et al., 1993

Microarray comparative genomic hybridization



Monosomy 1 and monosomy 14

Does PGS work?

Evidence that PGS has clinical value

New comprehensive methods shown to be highly accurate: ~98%

Highly predictive:
<2% of aneuploid embryos transferred produced a viable pregnancy
(Scott et al., Fertil Steril 2012)

RCTs have now been carried out using the modern PGS methods

All show that PGS provides a significant advantage

None have presented any negative findings

1st Randomized trial: aCGH + single embryo transfer, <35 years old

	Control	PGS	
patients	48	55	
age	<35	<35	
replacement	Day 6	Day 6	
replaced	48 (1)	55 (1)	
pregnancy rate	45.8%	70.9%	**P<0.05**
ongoing preg rate	41.7%	69.1%	**P<0.05**
multiples	0	0	

Yang et al. (2012)

2nd randomized trial: qPCR, <42 years old

	PGS	Control	
age	32.2	32.2	
N	72	83	
embryos replaced	1.9	2.0	
implantation	79.8%	63.2%	P=0.002
sustained implant	66.4%	47.9%	P=0.03
delivery rate	84.7%	67.5%	P=0.01

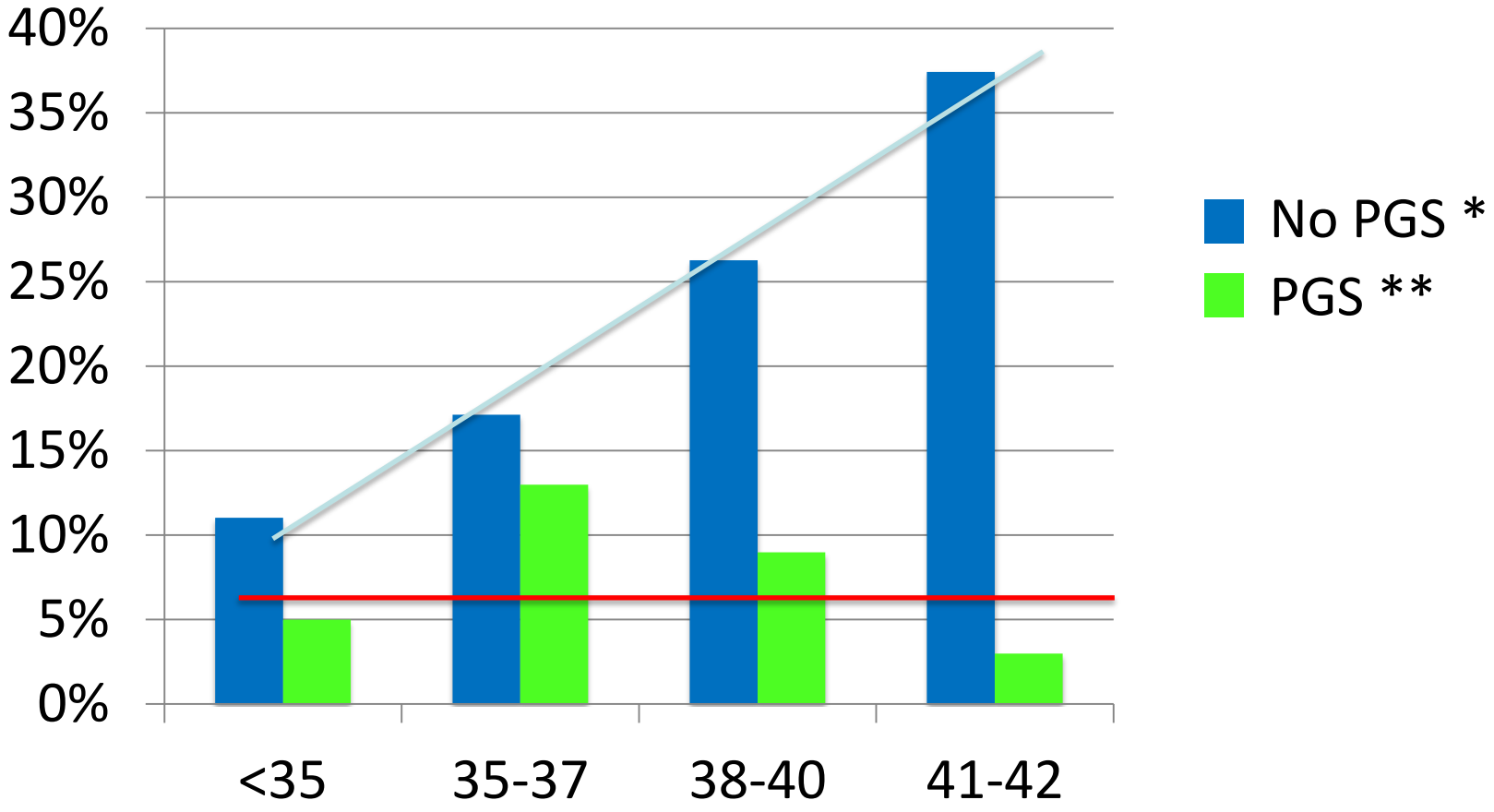
Scott et al., 2013 Fertil Steril.

3rd randomized trial:
Transfer of 1 euploid embryo vs. 2 untested

	ongoing pregnancy rate		
	1 euploid blastocyst (PGS)	2 untested blastocysts	
Fresh transfer	65%	70%	**NS**
Twins/triplets	0%	53%	**P<0.001**

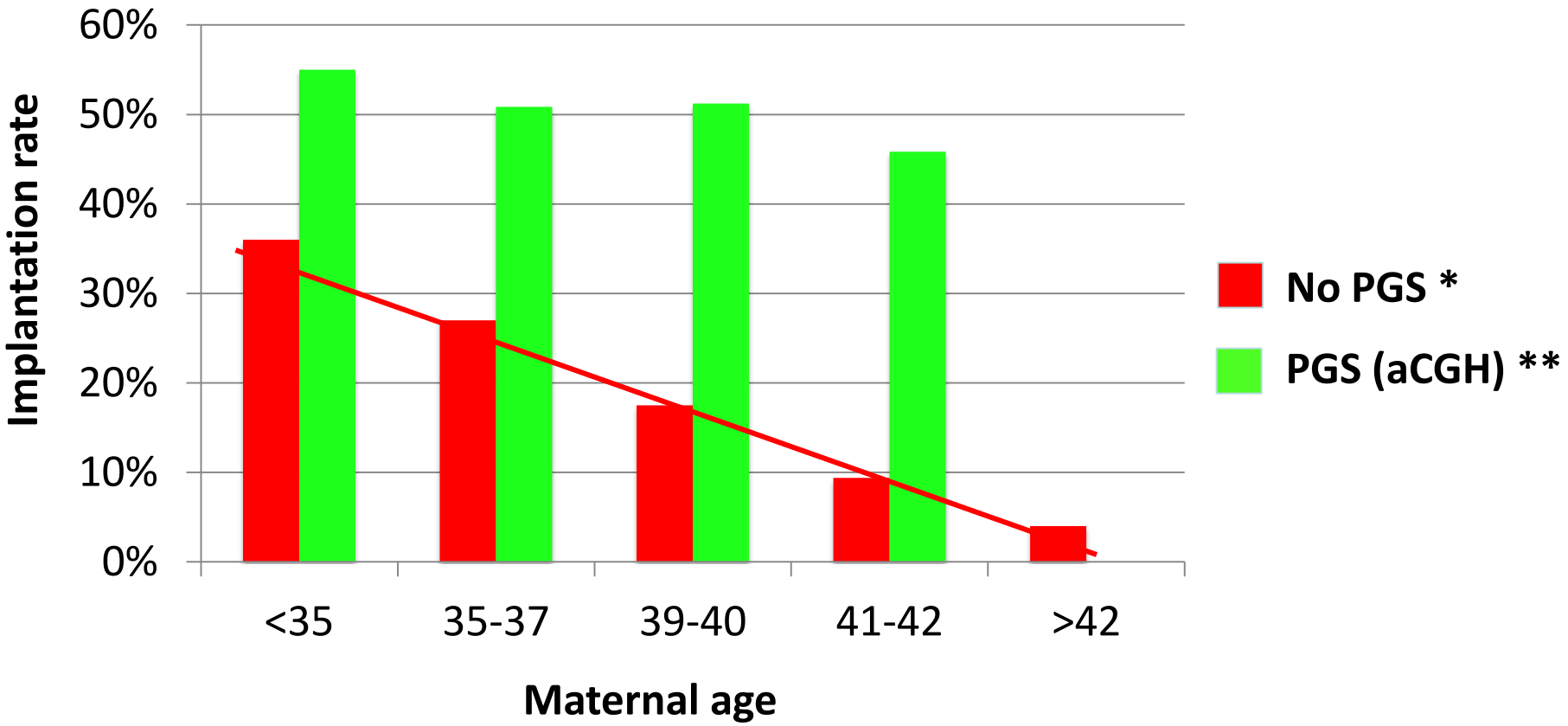
Forman et al. (2013) Fertil Steril
Mean maternal age 35 (patients <43)

PGS eliminates the effect of maternal age on miscarriage



*SART, ** Harton et al. (2013) Fertil Steril, and unpublished data

PGS eliminates the negative effect of maternal age on implantation



*SART, ** Harton et al. (2013) Fertil Steril, and unpublished data

Chromosome screening conclusions

What can PGS potentially offer?

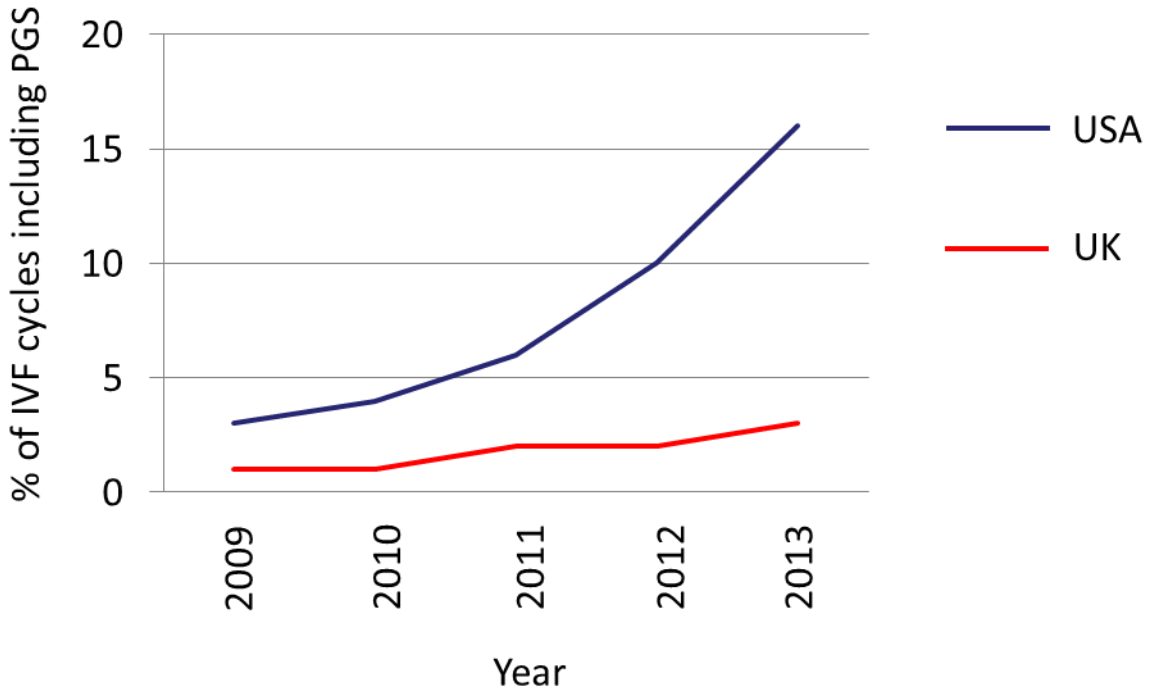
Achieve very high efficiency eSET
Faster time to pregnancy

Avoid unnecessary embryo transfers
Avoid cryopreservation of non-viable embryos

Reduce miscarriage rate
Reduce risk of Down syndrome

Future of perspectives on PGS

In USA - growing acceptance that PGS should be widely applied



European medical community waiting for further evidence?

Cost of PGS - in Europe usually adds >30% to the cost of IVF cycle

- in USA adds <20% to the cost

Lower cost PGS

Next generation sequencing now allows cheaper PGS

NGS is revolutionizing genetic research and diagnostics (basis of noninvasive prenatal testing)

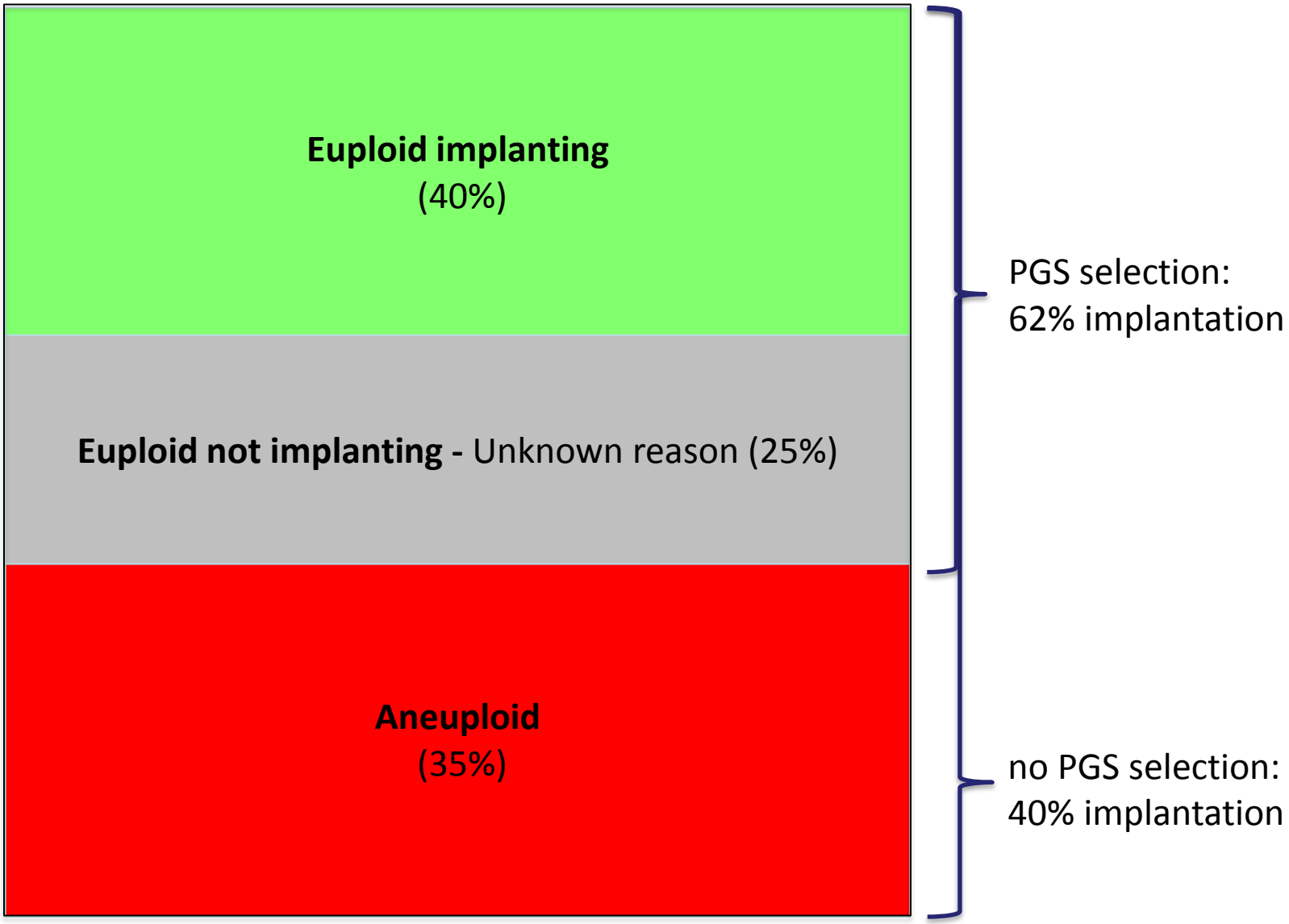
Vast quantities of DNA sequence information at low cost

Cost of PGS reduced by 25% this year using NGS

Wells et al., 2014 Journal of Medical Genetics

Additional genetic information relevant to viability

Example: patient 35 year old, blastocyst transfer



Additional genetic information relevant to viability

Approximately 35% of euploid embryos fail to implant. Why?

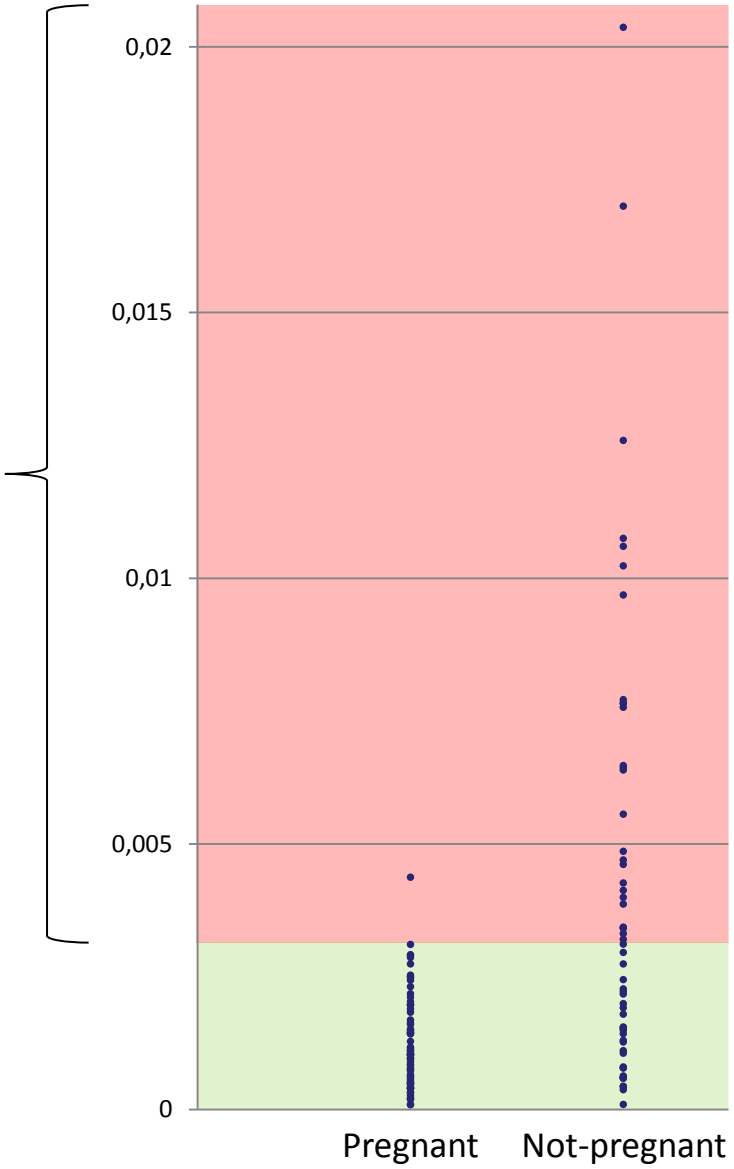
Chromosomally normal blastocysts with elevated mtDNA levels do not implant

Fragouli et al., 2015 PLoS Genetics

Explains ~1/3 of implantation failures involving euploid embryos

Data obtained using the MitoGrade test

28% of euploid blastocysts have elevated mtDNA



Normal mtDNA levels

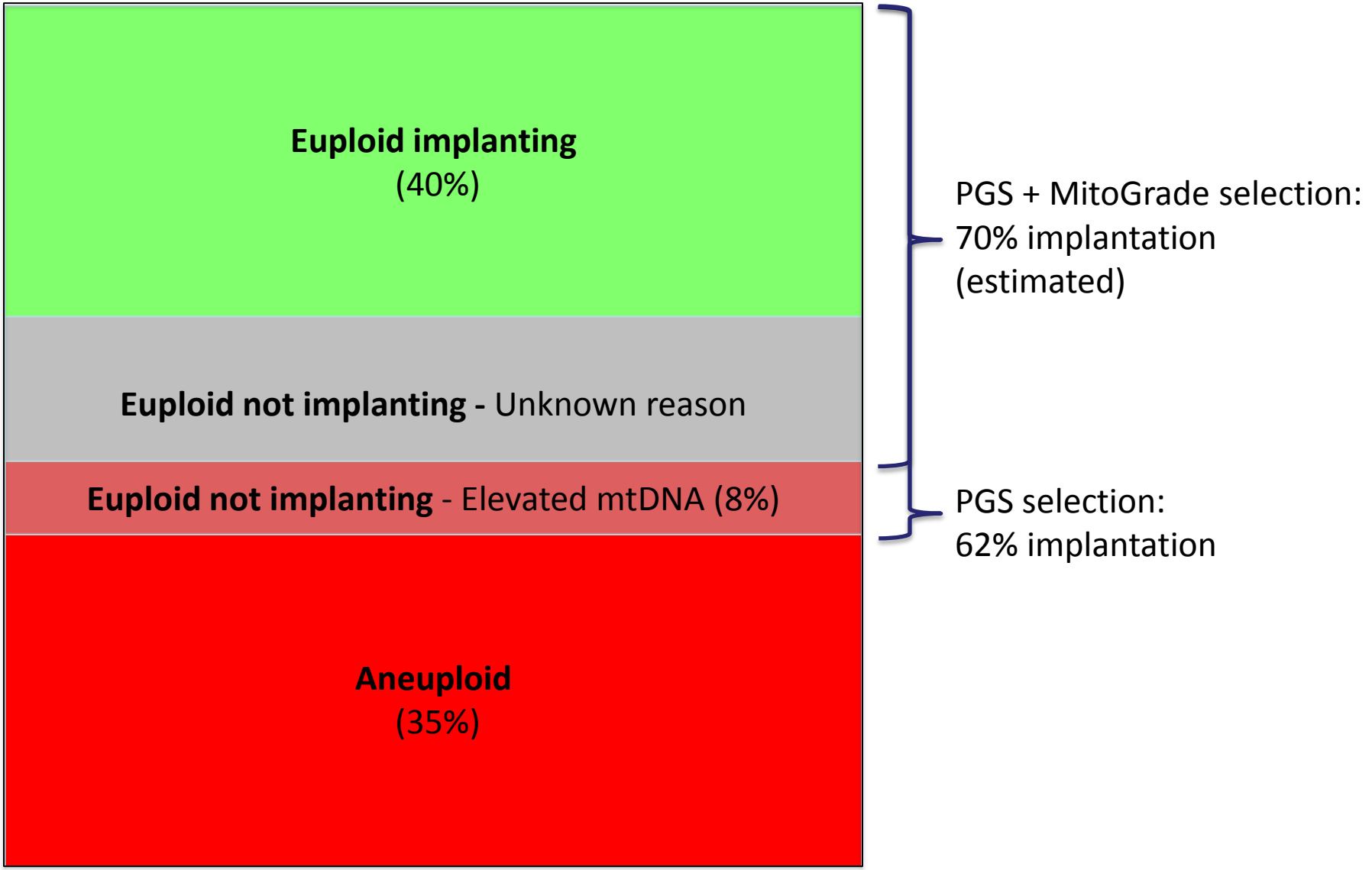
Elevated mtDNA levels

n=100 chromosomally normal blastocysts

Fragouli et al., 2015 PLoS Genetics

Added information from NGS - mtDNA

Example: patient 35 year old, blastocyst transfer



Key point

There is increasing evidence that genetic screening of embryos is of value to the majority of patients undergoing IVF

Has the use of genetics to select embryos reached its zenith?

No! The best is still to come…

Methods will become cheaper

Viable embryos will be revealed with more certainty

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