Future of Genetic testing in fertility

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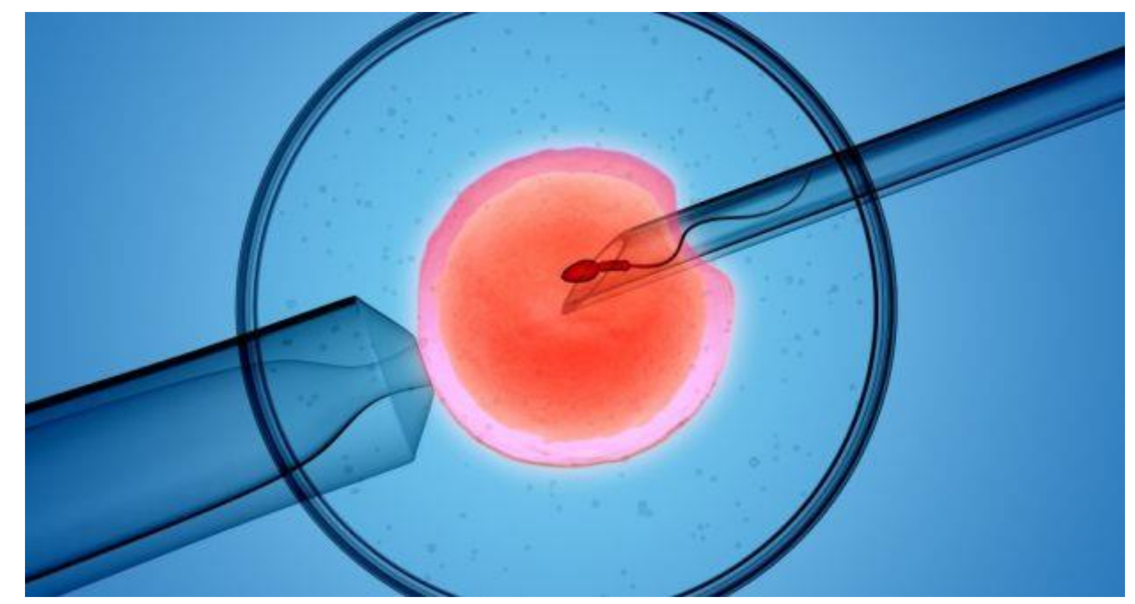
Why do we need genetic testing in fertility at all?

- In vitro fertilization has completely transformed the field of human infertility

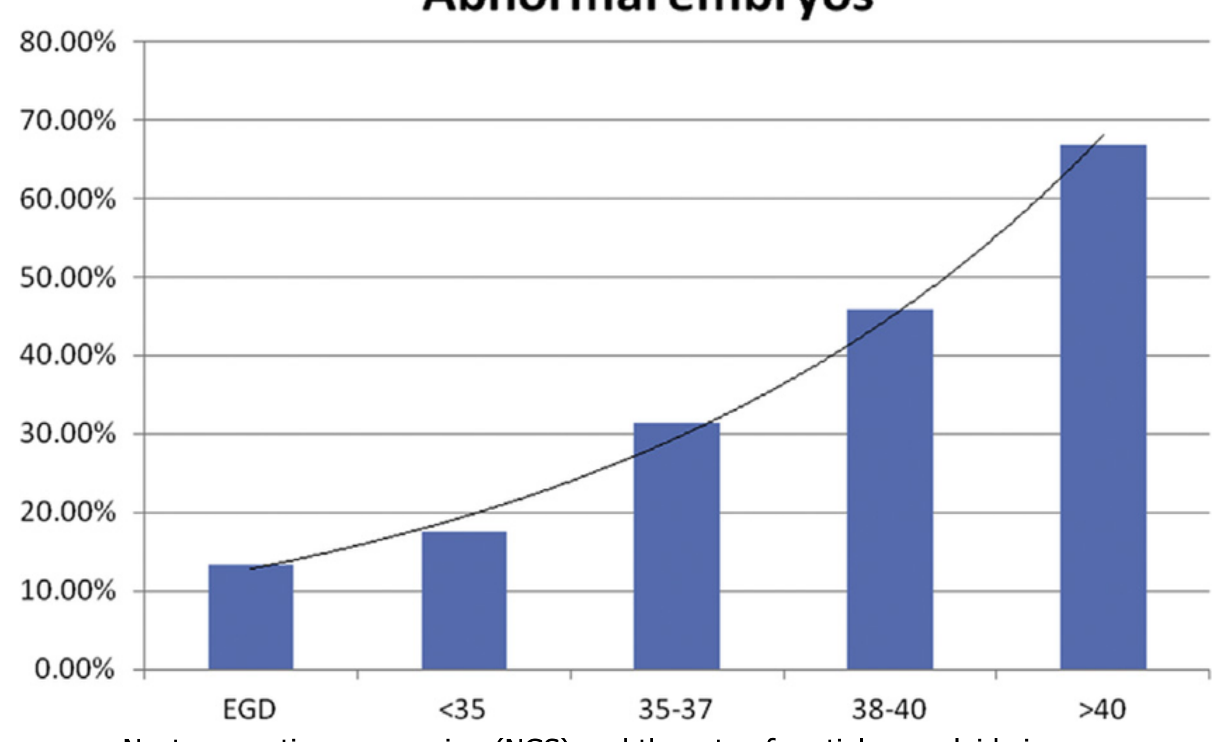
- Assisted reproductive technologies (ART) are available throughout the world

- Scientific developments and refinements in clinical and laboratory technologies have led to IVF evolving into a efficient, safe and accessible medical technique



Why do we need genetic testing at all?

- Greater than 50% cleavage and blastocyst stage embryos produced in-vitro are found to be chromosomally abnormal or aneuploid
- Aneuploidy numbers reach as high as 70% in women over 42 years of age
- Prevention of inherited diseases in future generations



Next generation sequencing (NGS) and the rate of partial aneuploidy in preimplantation genetic screening (PGS)
T. Escudero, L. Ribustello, M. Sumarroca, S Munne

Role of Genetic testing in improving implantation outcomes

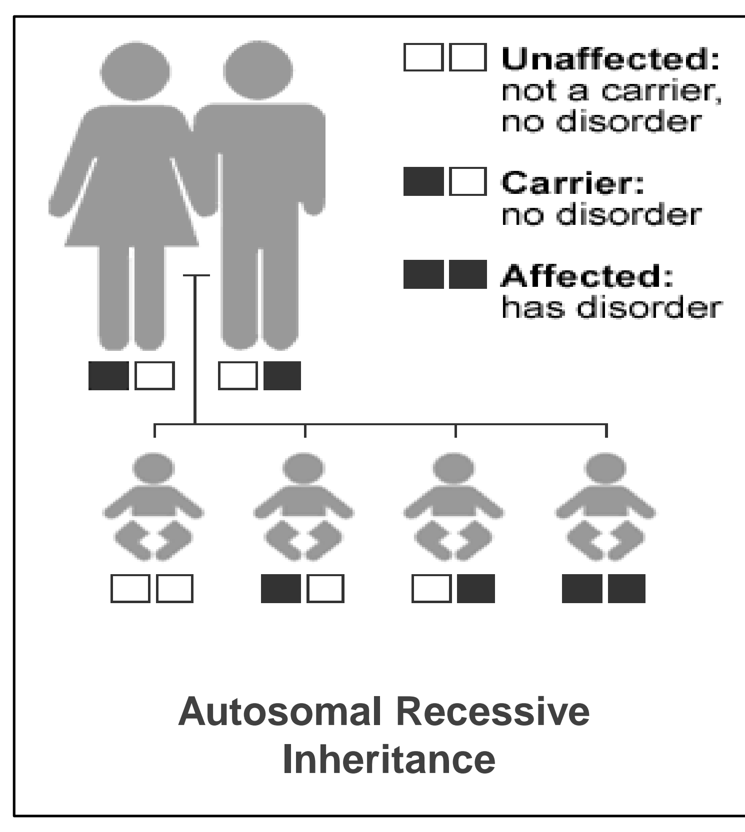
- Low success of artificial reproductive treatments is observed in embryos that are detected with numerical chromosomal abnormalities
- Aneuploidy clearly has detrimental effects on efficacy of ART
- Up to 70% of chromosomal abnormalities are often observed in cases which result in spontaneous abortions
- Selection of normal (euploid) embryos to transfer during IVF to improve the rates of success for the procedure is necessary

PGD for Gene Defects

Complexity of the human genome

- 3.500 million pairs of bases
- 88 million (2.5%) are different **single nucleotide polymorphisms (SNPs)** – they make us different from one another
- 3% are coding genes (about 35,000 genes)
- 97% is “junk” DNA with regulatory activity over genes

The Burden Of Genetic Disease



- **>6000 single gene disorders**
- **Combined incidence:** 1/300 births (U.S.)
- **Everyone carries 14-18 severe recessive mutations** that can cause genetic conditions
- **Carriers may not have a family history** or symptoms of a genetic disease
- Hence, **carrier screening is the only way to determine carrier status**

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Start with Carrier Screening

- Recommended for people who are planning a family or early in pregnancy, even without family history of genetic disease
- 80% children with conditions have no family history of disease
- Includes about 314 conditions categorized based on impact, inheritance, and/or availability of treatment
- About 3.5% of all couples are carriers of genetic disease

High Impact

These diseases have a significant effect on life expectancy and quality of life.

Moderate Impact

These diseases typically don't affect life expectancy but can affect quality of life.

Treatment Benefits

Treatment can lessen the impact of these diseases, especially with early intervention.

X-Linked

These diseases are passed down by female carriers. Carriers may have symptoms.

PGD for gene disorders

We can do PGD for any monogenic disease provided the mutation is known

Disease tested: Acetil Co Oxidase type I defficiency, Adrenoleucodistrophy, Alpha-thalassemia, Alport syndrome, Autosomal Dominant Polycystic Kidney Disease (ADPKD), Autosomal Recesive Polycystic Kidney Disease (ARPKD), Beta-thalassemia, Branchio-Oto-Renal syndrome (BOR), BRCA1 breast cancer predisposition, BRCA2 breast cancer predisposition, CanavanCharcot-Marie-Tooth type IA (CMT1a), Choroideremia, Congenital adrenal hyperplasia (CAH), Congenital neutropenia, Connexin 26 hearing loss, Cystic fibrosis, Duchenne/Becker Muscular Dystrophy (DMD), Ectrodactyly, Ectodermal dysplasia, and Cleft lip/palate syndrome (EEC1), Fabry Disease, Familial adenomatous poliposis coli (FAP), Familial dysautonomia, Familial intrahepatic cholestasis 2, Fanconi anemia, Fragile site mental retardation , Gangliosidosis type 1 (GM1), Gaucher disease, Glomuvenous malformations (GVM), Glycogen-storage disease type I (GSD1), Glycosylation type 1C, Hemoglobin SC disease, Hemophilia A, Hemophilia B, Hereditary nonpolyposis colon cancer (HNPCC), Hereditary pancreatitis, HLA matching Huntington disease, Hurler syndrome, Hypophosphatasia, Incontinential pigmenti, Krabbe disease (Globoid cell leukodystrophy), Long QT syndrome, Marfan syndrome, Meckle gruber, Metachromatic leukodystrophy (MLD), Methylmalonic aciduria cblC type (MMACHC), Myotonic Dystrophy 1, Myotubular myopathy, Neurofibromatosis 1, Neurofibromatosis 2, Niemann-Pick Disease, Noonan syndrome, Oculocutaneous albinism 1 (OCA1), Ornithine carbamoyltransferase deficiency (OTC), Osteogenesis Imperfecta 1, Rapp Hodgkin ectodermal dysplasia, Retinitis pigmentosa, Retinoblastoma, Sickle Cell Anemia, Smith-Lemli-Opitz syndrome (SLOS), Spinal bulbar muscular atrophy (SBMA), Spinal Muscular Atrophy Type 1 (SMA1), Tay Sachs, Tuberous sclerosis 1 (TSC1), Tuberous sclerosis 2 (TSC2), Von Hippel-Lindau Syndrome (vHL), X-linked dominant Charcot–Marie–Tooth (CMTX), etc…… *(see review Gutierrez et al. (2008))*

PGD procedures performed

Cases performed: >10,000

Disease genes tested: 778

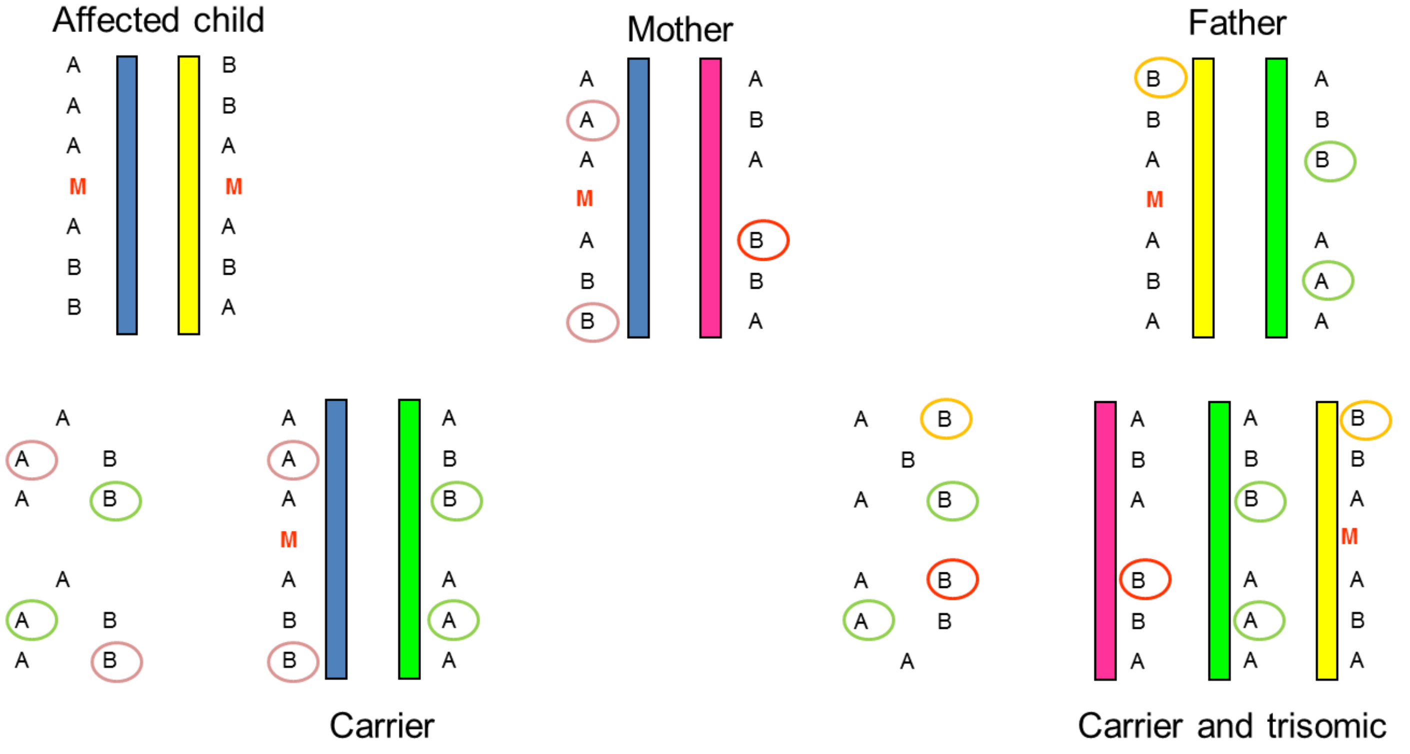
Top 10 diseases:

- Cystic fibrosis
- Fragile X
- Huntington disease
- Sickle cell anemia
- Spinal Muscular atrophy
- Neurofibromatosis type 1
- Beta Thalassemia
- Breast cancer (BRCA1, BRCA2)
- Myotonic dystrophy
- Polycystic Kidney Disease (PKD1)

Faster work-up time for PGD: Karyomapping

Thousands of polymorphisms on each chromosomes

Each chromosome (region) has a unique DNA fingerprint



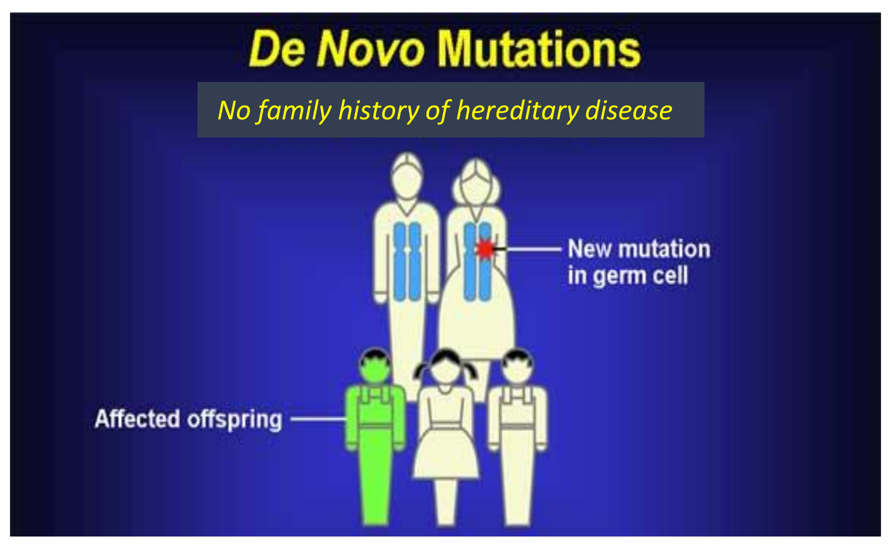
Advantages of Karyomapping

	Karyomapping	PCR
Work-up time	2-4 weeks	8-12 weeks
Embryos correctly diagnosed	99.6%	96.8%
Clinical error rate	0%	Lab dependent
Aneuploidy meiotic	Yes	No
Aneuploidy mitotic	No	No
Parental origin / fingerprint	Yes	No
Affected by ADO	No	Yes (3.6%)

Konstantinidis et al (2015) RBO and Reprogenetics data

What is next: De novo mutations

- De novo mutations occur during gametogenesis and post-zygotically
- De novo mutations contribute to almost every known genetic disorder
- Increased paternal age known to contribute towards de novo mutations
- Autism, Schizophrenia, Familial adenomatous polyposis, Multiple endocrine neoplasia 2B, retinoblastoma, Schinzel-Giedion syndrome, CFTR, Bohring-Opitz syndrome



Kong, A., et al., *Rate of de novo mutations and the importance of father/'s age to disease risk.* Nature, 2012. **488**(7412): p. 471-475.
Sanders, S,. et al,. *De novo* mutations revealed by whole-exome sequencing are strongly associated with autism. Nature, 2012. 485(7397):237-41

Role of de novo mutations in pregnancy and outcomes

- No evidence exists regarding de novo mutations (SNVs and CNVs) in IVF generated embryos

- Increased load of Copy Number Variations seem to have an increasing role in ASD, Schizophrenia, Bipolar Disorder etc.

- Sequencing based methods capable of detecting both SNV/CNV and aneuploidy simultaneously could be the future of genetic testing

Possible limitations and challenges

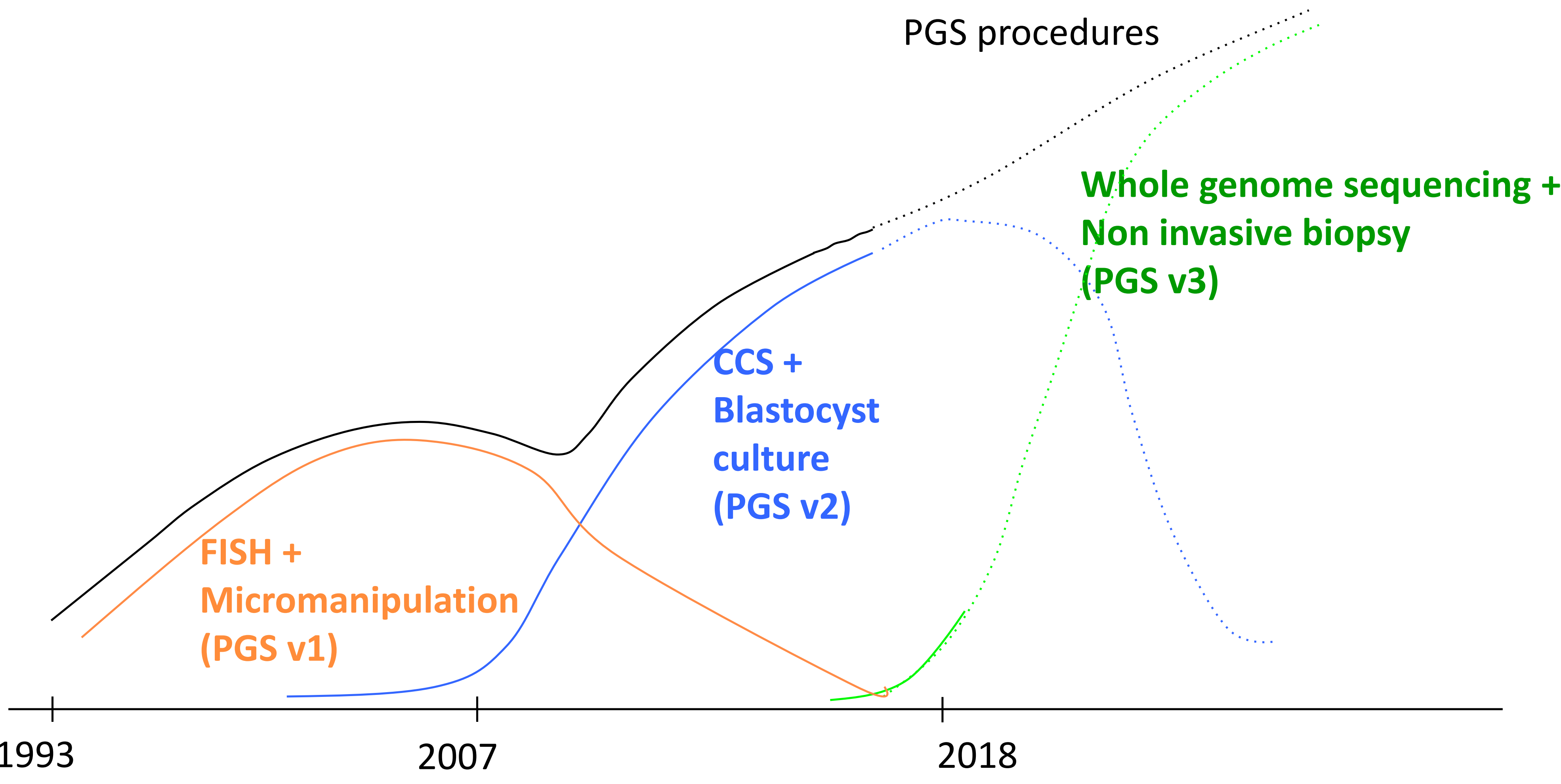
- Large number of variants will be detected
- Would require immense automation of variant curation and additional variant curators
- Genetic counselling would be big challenge: What is the new normal?

PGS for aneuploidy

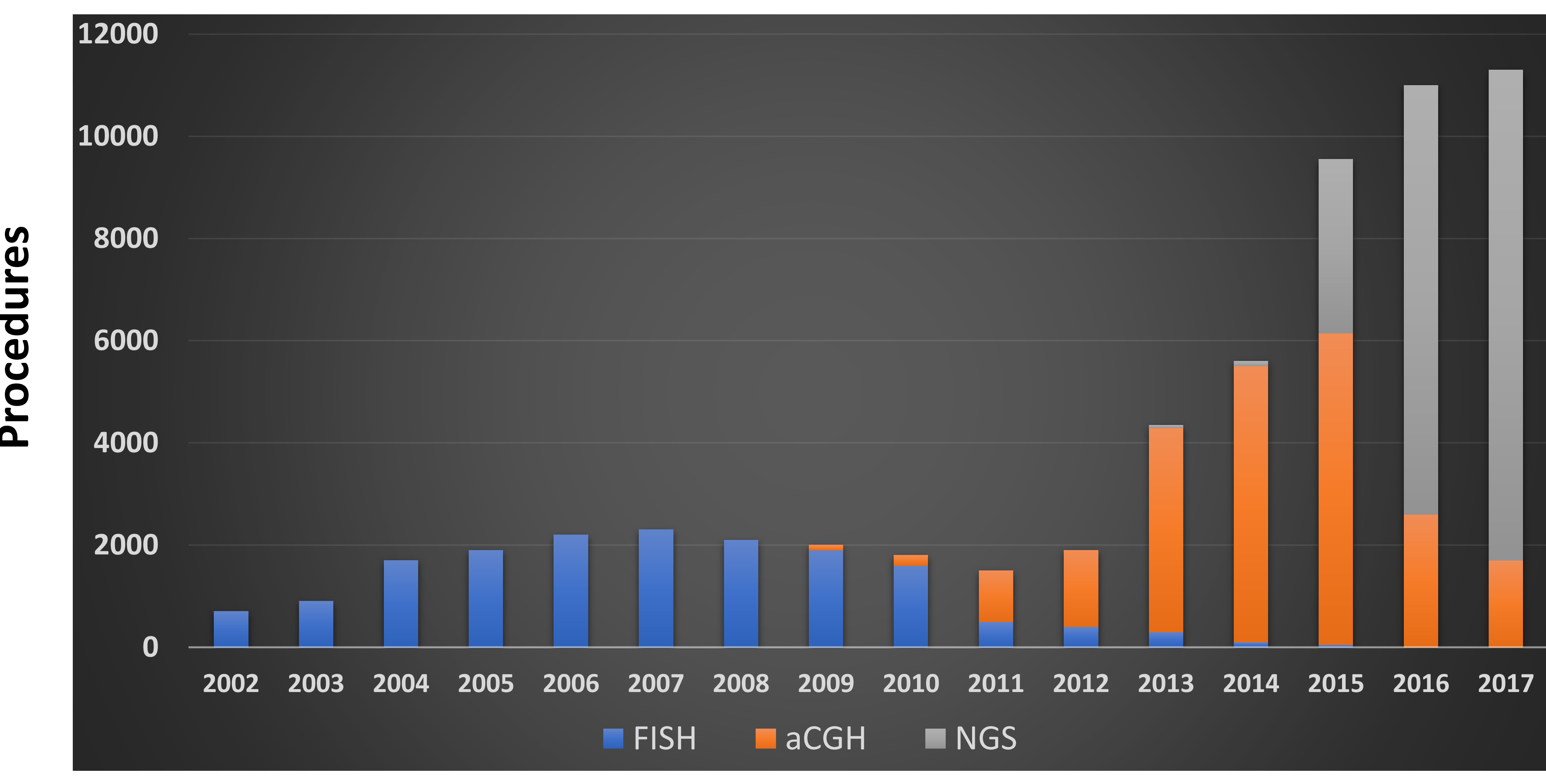
Pre-implantation genetic screening

- Aneuploidy increase is the major cause of reduced fertility with increasing maternal age
- One can use genetic material from embryos to determine ploidy of the embryo
- PGS can test abnormal number of chromosomes and disorders associated with it like Down's syndrome, Edward's syndrome , Trisomy 21 and etc.

Waves of technology



Evolution of PGS techniques



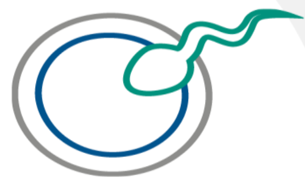
PGS data from Reprogenetics US, (*) annualized

Preimplantation Genetics Screening (PGS)

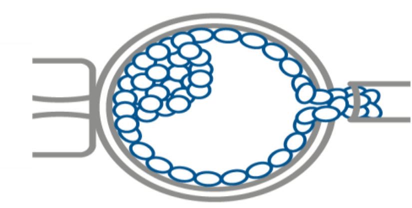
CASE REVIEW
Prospective parents meet with genetic counselor and discuss if additional genetic testing of the couple or other family members is required.

PGD TEST PREPARATION
The PGD lab designs a test unique to each family.

IVF/ICSI
In vitro fertilization is performed and the resulting embryos are incubated.



EMBRYO BIOPSY
An embryologist carefully removes one or several cells from each embryo.



PGD
Samples are sent to the PGD laboratory, and testing is performed.

EMBRYO TRANSFER
An unaffected embryo is transferred. Remaining embryos can be frozen for future use.

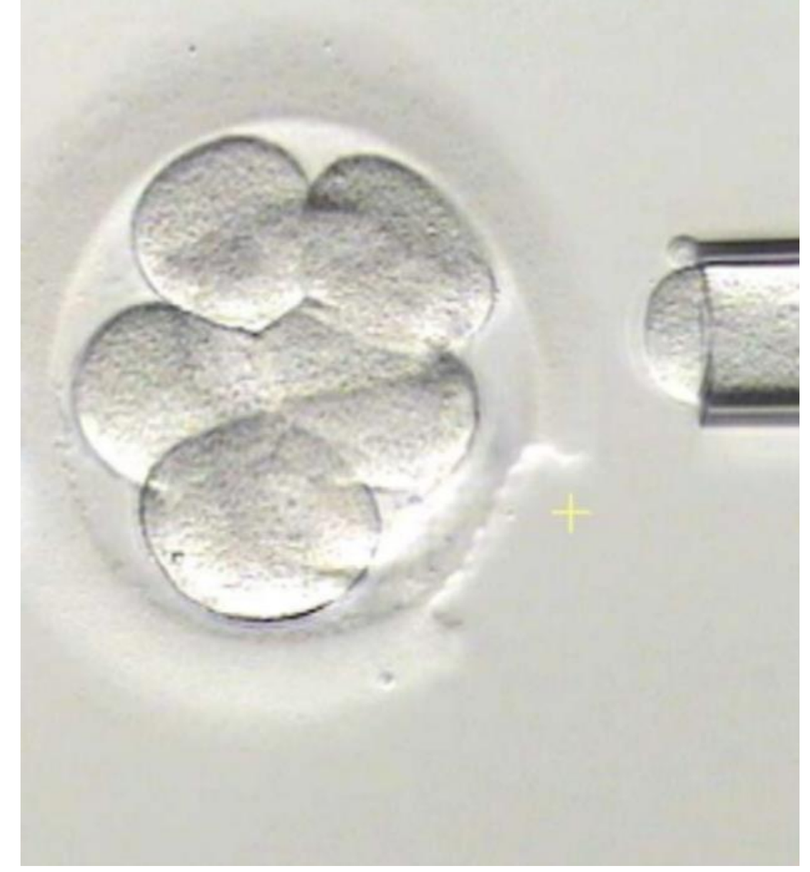
PGS Version 2

Blastocyst biopsy

Comprehensive chromosome screening

Biopsy Techniques- Cleavage stage biopsy

- Cleavage stage biopsy involves obtaining genetic material for PGS by performing biopsy on cleavage stage embryos on day-3 post-fertilization
- However recently it has been replaced by day- 5 blastocyst biopsy
- Mosaicism is one of the typical problems that occur during the screening of cleavage stage embryos for chromosomal anomalies

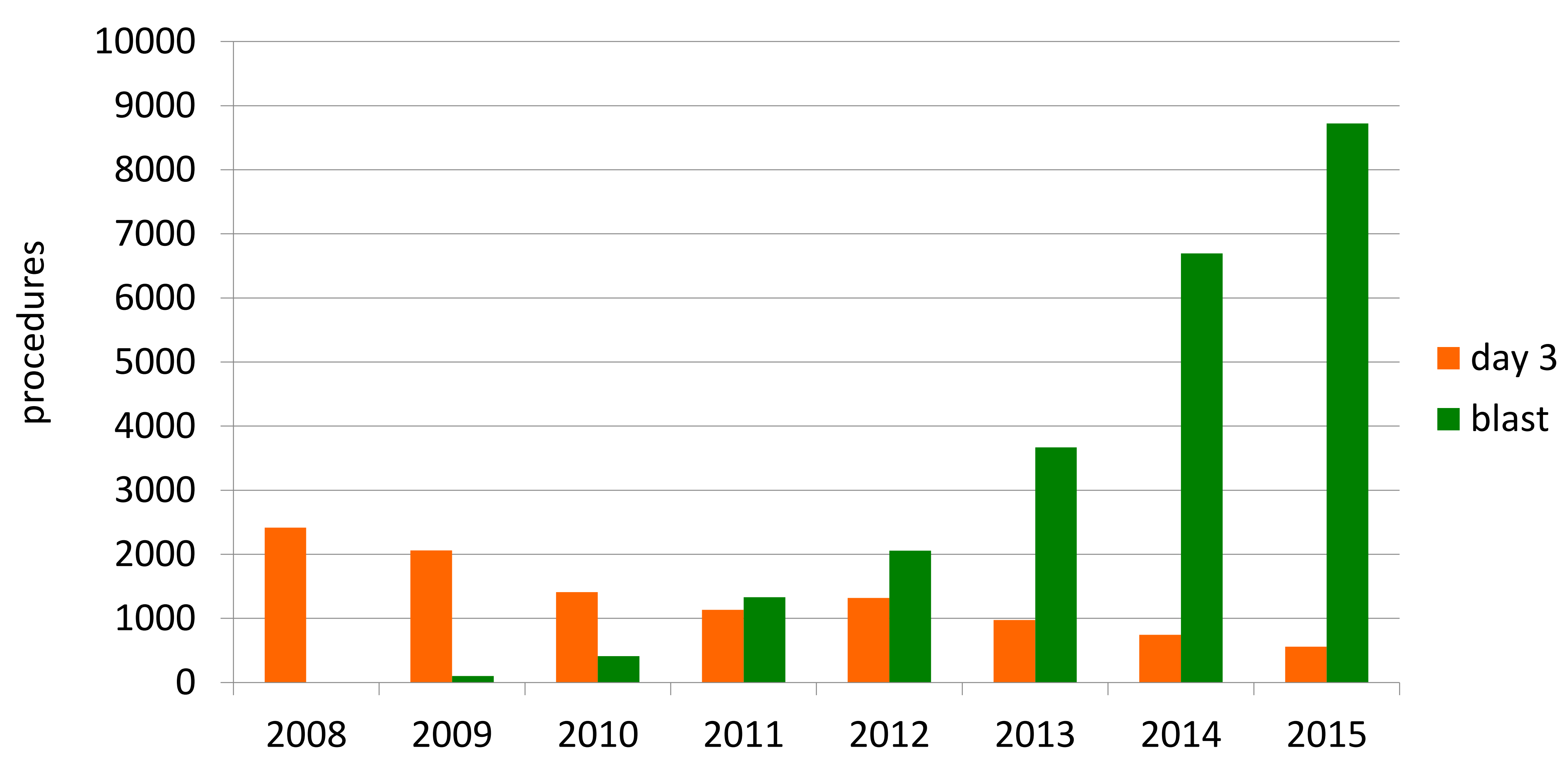


Biopsy Techniques- Blastocyst biopsy

- The most prevalent option nowadays for obtaining genetic material from the embryo

- Trophectoderm biopsy obtains multiple cells for carrying out PGD/PGS. This leads to an overall improved accuracy of the test

Evolution of biopsy techniques: About 100% of biopsies in US are blastocyst

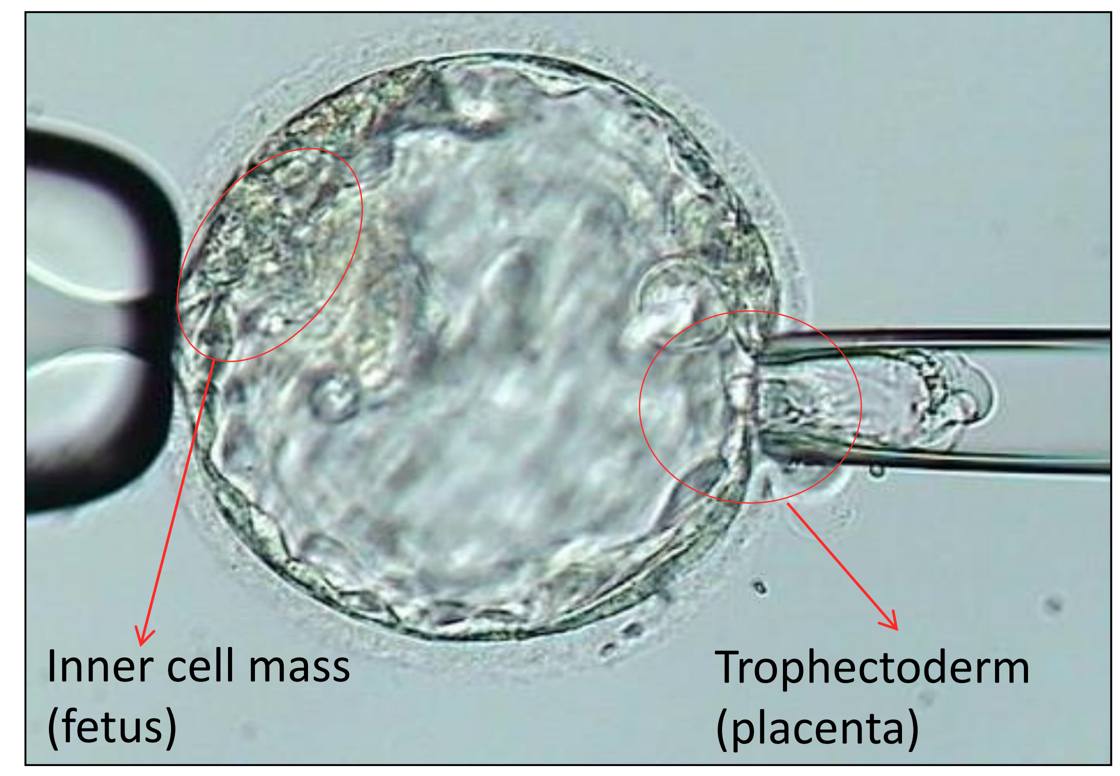


Reprogenetics US procedures

Blastocyst biopsy: Advantages

Advantages:

- More DNA: fewer no results
- Fewer mosaics (21%) than day 3 (33%)
- Reduced impact of embryo biopsy *
- Less embryos to process
- Facilitates single embryo transfer



Risks:

- Every center biopsies differently: Some variations are detrimental
- Manipulator dependent

** Scott et al. (2013) Fertil Steril*

Comparison of PGS platforms

	% embryos	FISH	aCGH	NGS
Labs Performing Test		100s	180	5
Total Independent Data Signals*		11	2,700	700,000
Resolution in Mb		arm	6Mb	3Mb
Misdiagnosis aneuploides (a-f)		7%	2%	0%
Unbalanced translocations (g)	2%	custom	yes	yes
Partial aneuploidies	5%	no	yes	yes
Polyploidy	2%	yes	no	yes
Mosaicism (h, i)	20%	20%	4%	20%
Miscarriage rate (j, k)		10-20%	13%	11%

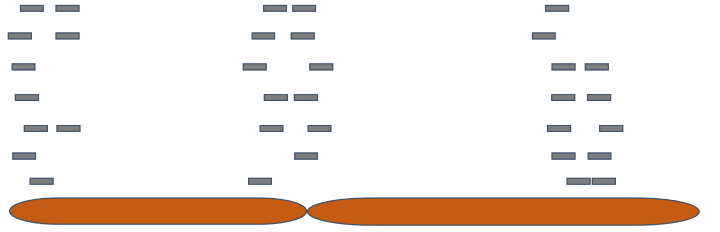
*a Gutierrez-Mateo et al (2011) Fertil Steril, b Scott et al. (2012), c Treff et al. (2012) Fertil Steril 97:819–24, dGood Start Genetics: unpublished 7 misdiagnoses of 265 samples; e Kung et al. (2015) Reprod Biomed Online, , f Wells et al. (2014) J Med Genet, g Yeobah et al. (2015) ASRM, h Greco et al (2016) NEJM, i Tormasi et al (2015) PGDIS, ASRM. J Rodriguez-Purata et al. (2016) JARG; k Friedenthal et al. (2017) ESHRE * 24M reads per run, 24 samples per run, 30% reads lost = 700,000 reads per sample*

Targeted Next Generation Sequencing

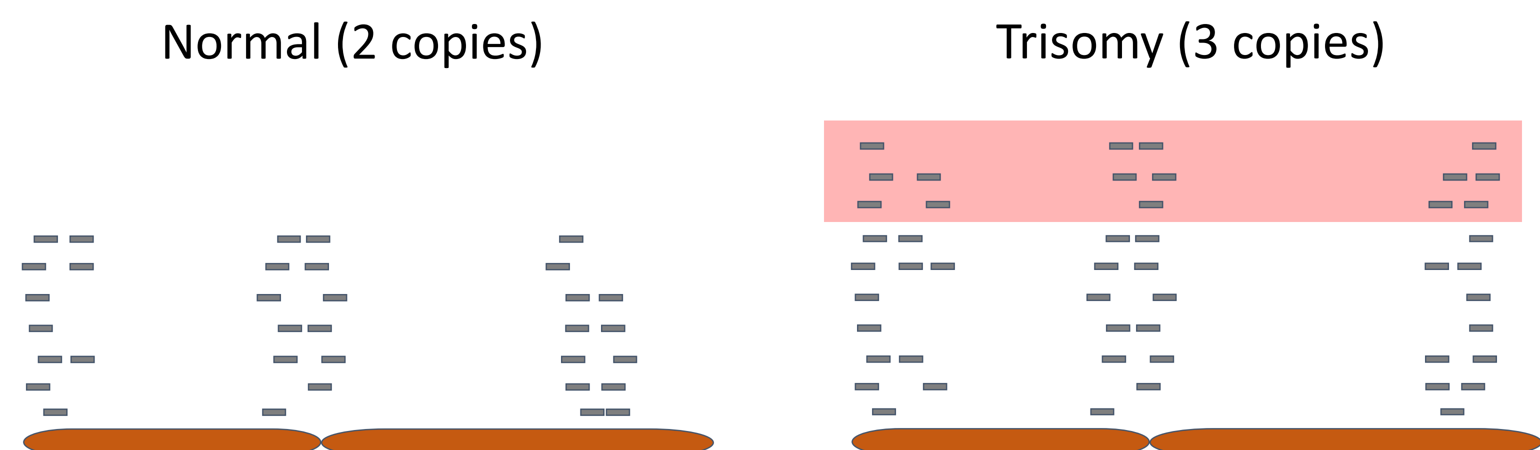
Targeted Next Generation Sequencing (NGS)

Targeted NGS

No WGA. Instead defined pieces of the genome are amplified and sequenced



Targeted Next generation sequencing (NGS)



- Targeted strategies are generally of lower resolution
- However, they have a couple of key advantages:

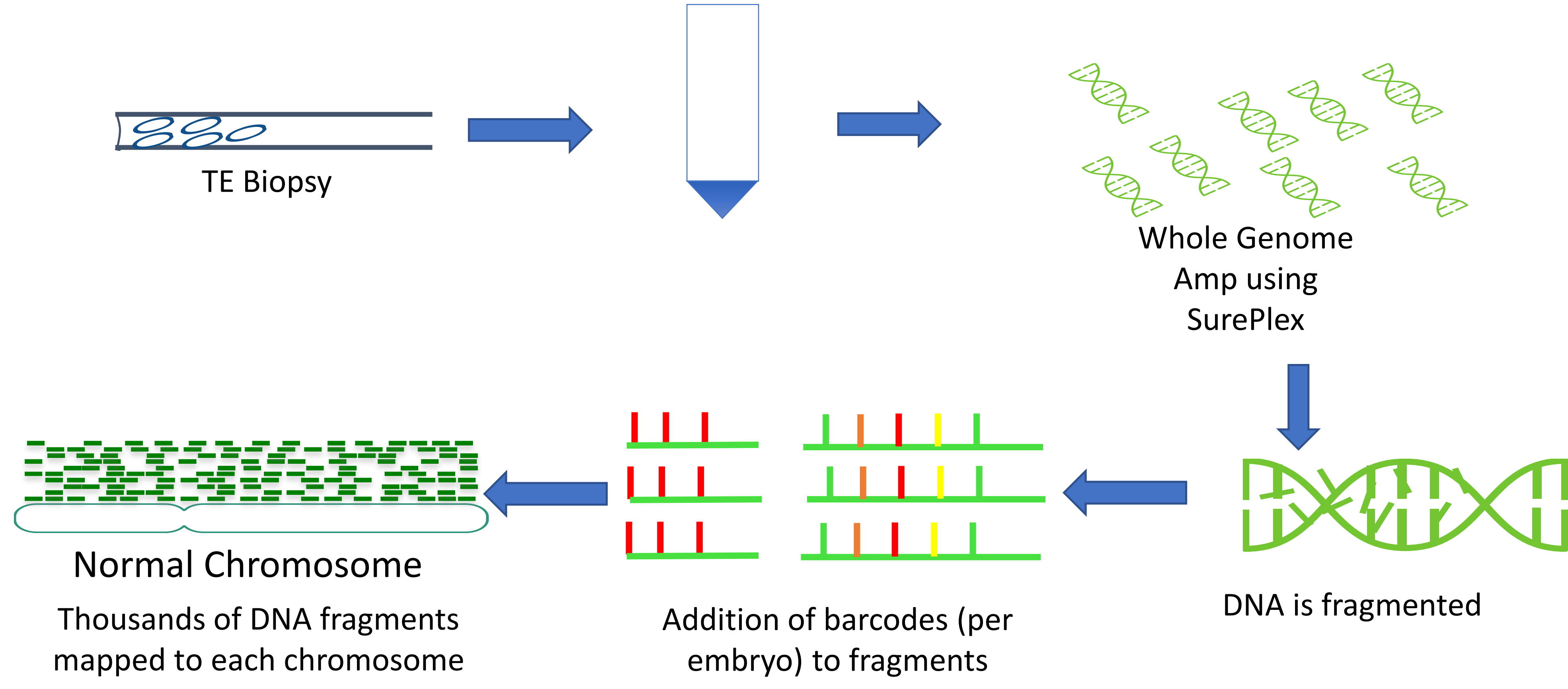
  Guaranteed coverage of specified sequences (genes or polymorphisms)

  Lower costs and higher throughput

Next Generation Sequencing

Whole genome amplification based

Protocol used for NGS



Abnormality rates by NGS :Data from >100,000 embryos

	Egg donor	<35	35-37	38-40	41-42	>42
Normal	59%	53%	44%	31%	19%	14%
Mosaic	16%	18%	17%	13%	10%	8%
Aneuploid (± mosaic)	18%	20%	28%	38%	41%	33%
Complex (*)	7%	8%	10%	17%	28%	44%
Polyploid	1%	1%	1%	1%	1%	1%

- Mosaics are MITOTIC and therefore do not increase with age
- Mosaics + Aneuploid and Mosaic show constant rates through age

N = **103,405 embryos**. Reprogenetics and Genesis Genetics data to 1/2017

* Complex: >2 full abnormalities

Validation of NGS

	Original Analysis method	Reanalysis method	Sample	Confirmed Euploid	Confirmed abnormal	TOTAL
Kung et al. 2015 (Reprogenetics)	aCGH	NGS	Same biopsy	44/44	108/108	152/152
Fiorentino et al. 2014	aCGH	NGS	Same biopsy	67/67	141/141	208/208
Wells et al. 2014 (Reprogenetics)	aCGH	NGS	Separate biopsy	13/13	28/28	41/41
Total				**100% Sensitivity**	**100% Specificity**	**0% Error rate**

Criteria for classification of samples

Observation	Categorization
Zero Aneuploid Chro	Normal/Euploid
1 or 2 Aneuploid Chro	Aneuploid
1 Aneuploid and 1 Mosaic Chro	Aneuploid
≥3 Chromosomal Abnormalities	Complex Abnormal
Up to 20-80% abnormal cells	Mosaic
80% and greater abnormal cells	Aneuploid
20% and lesser abnormal cells	Euploid

Comparison between NGS and aCGH: by Type of Abnormality

	Reanalysis by aCGH			
Original (NGS)	**Euploid**	**Aneuploid**	**Segmental**	**Ref**
Euploid	196	0	0	1,2
Aneuploid	0	222	0	1,2
Mosaic	16	4	0	2
Polyploid	6	4	0	2
Segmental Translocation	0	0	69	3

(1) Ribustello et al. 2016, PGDIS, (2) Ribustello (2015) ESHRE (3) Bauckman (2016) ESHRE

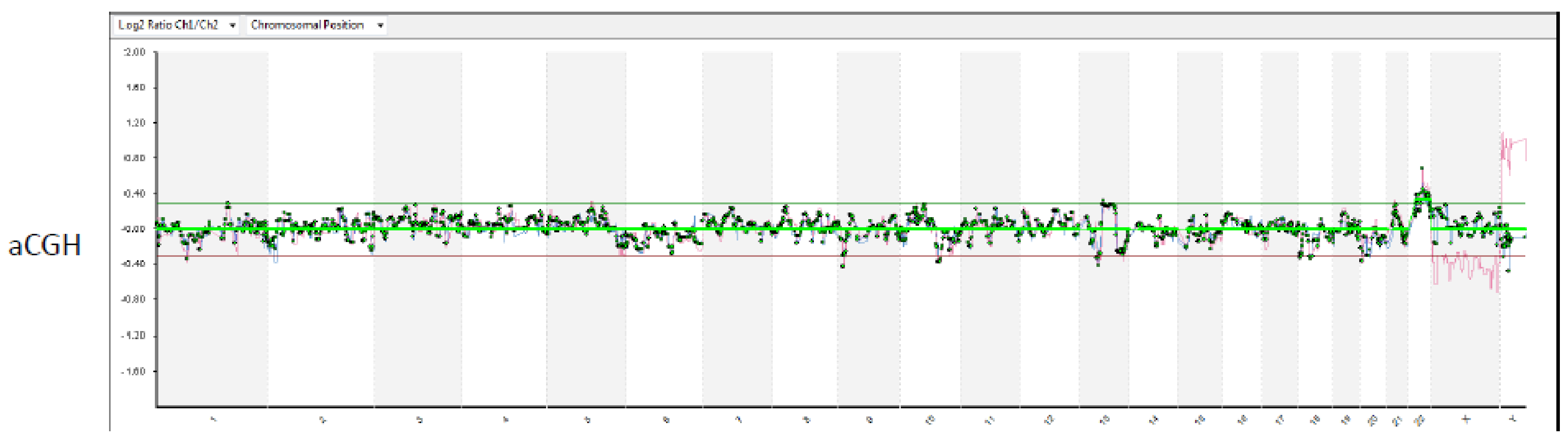
NGS advantages

Higher dynamic range than other techniques allows:

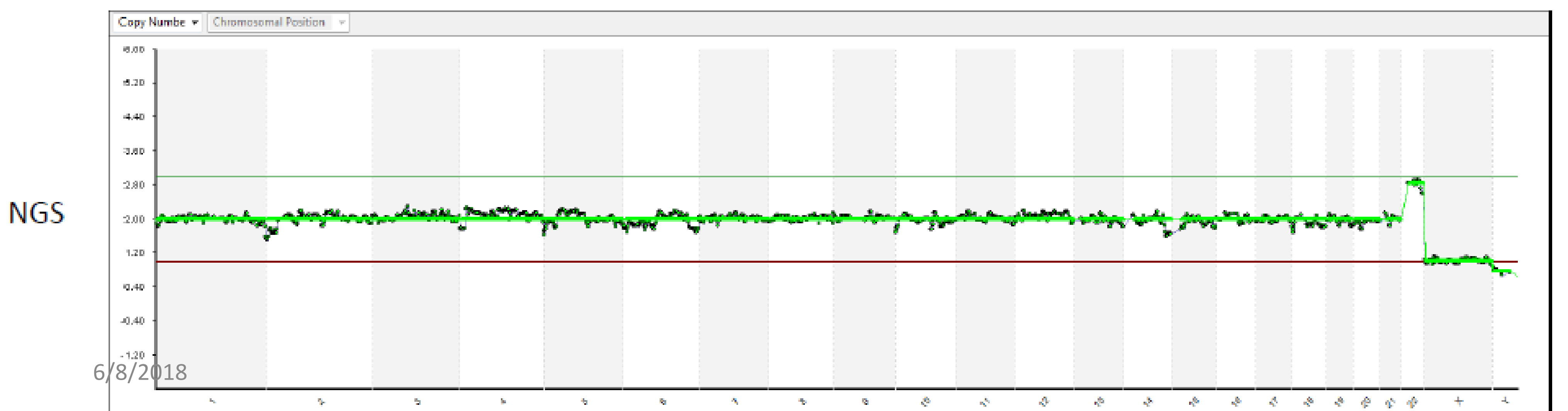
- Detection of **triploidy** 69,XYY and 69,XXY
- Detection of **mosaics** (20-80% range of abnormal cells or 1/5)
- **Higher resolution** than other techniques (1.5Mb)

Higher dynamic range, Less noise than aCGH

aCGH



NGS

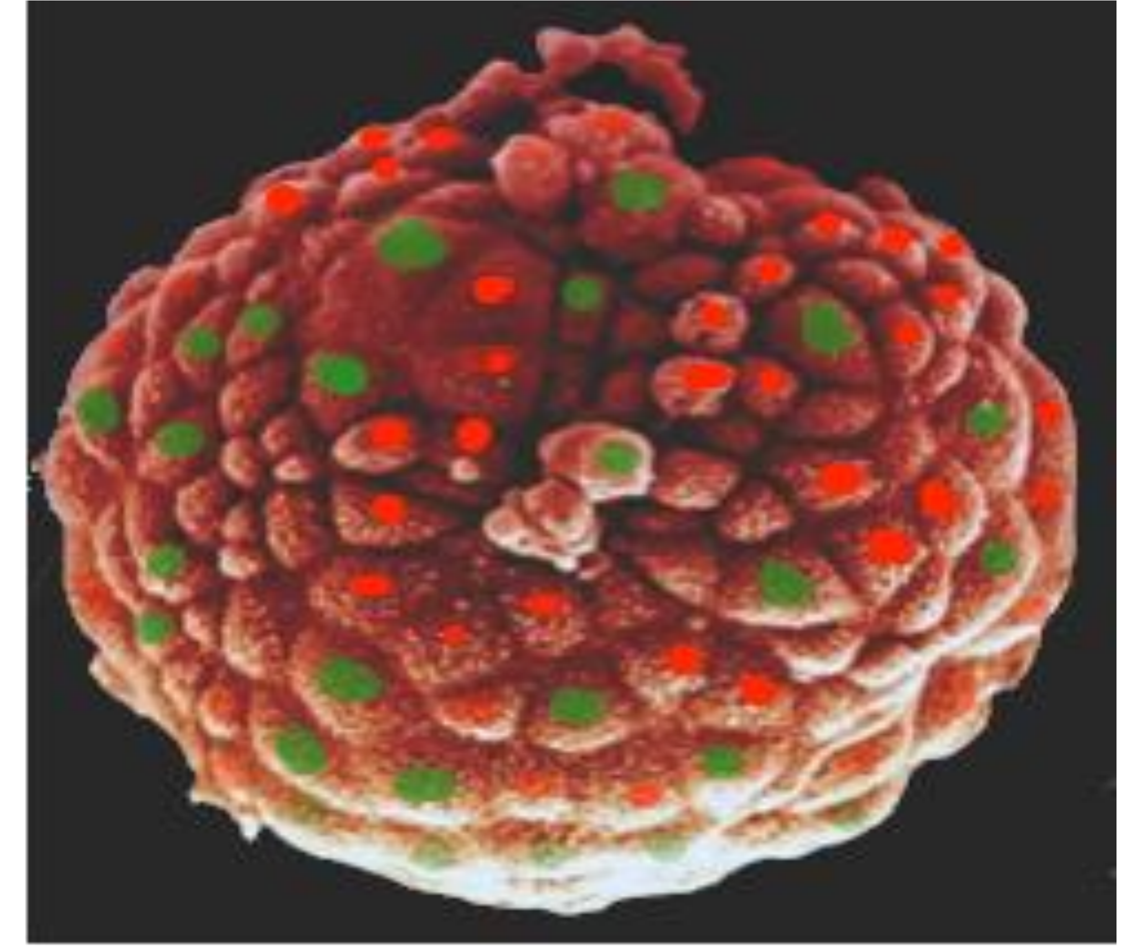


Trisomy 22

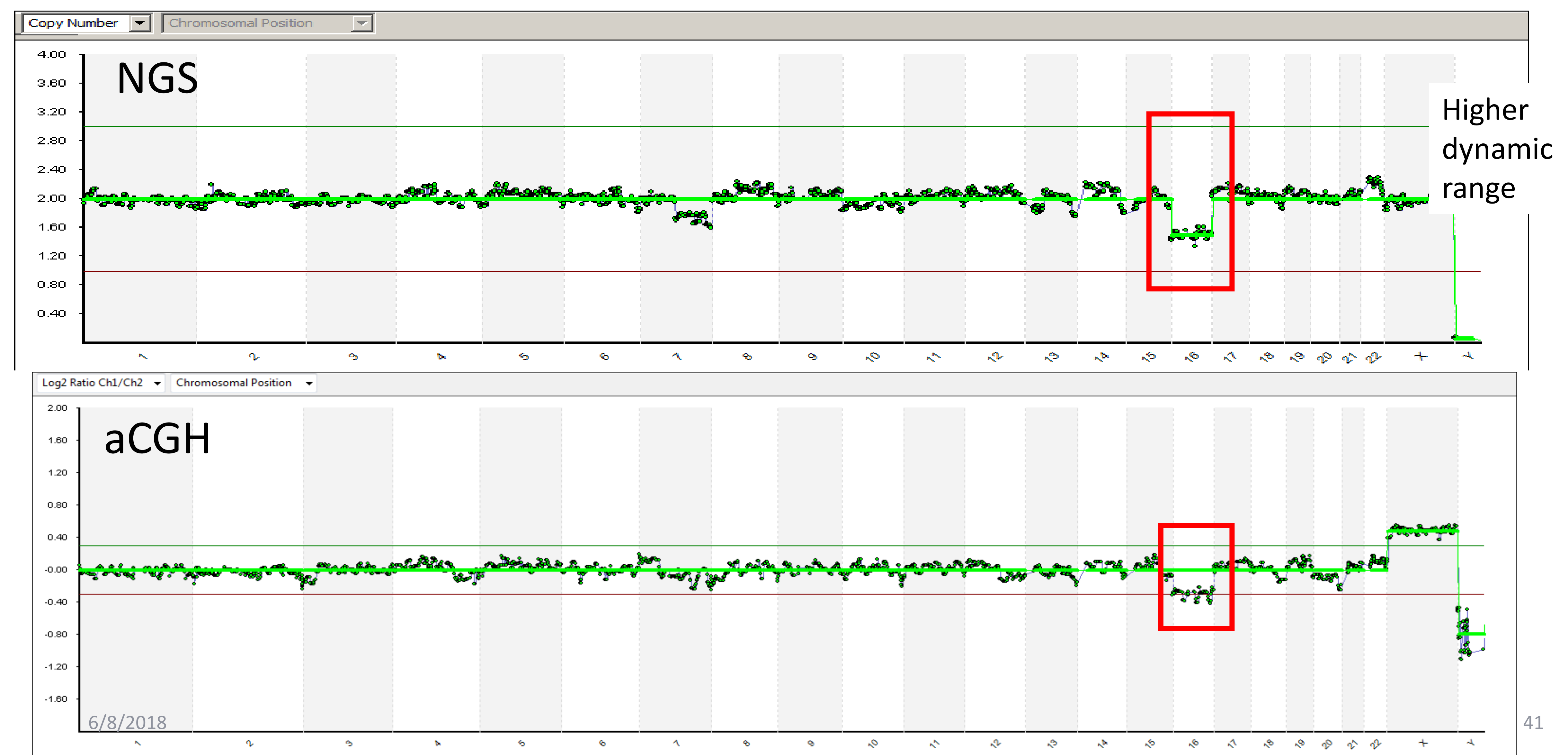
Mosacism

Mosaicism

- Chromosomal mosaicism is the presence of two or more cytogenetically distinct cell lines
- Unlike aneuploidy (meiotic origin), mosaicism caused by mitotic errors occurring after fertilization
- Mosaicism derived from : chromosome non-disjunction, anaphase lagging and endoreduplication



Higher dynamic range allows NGS to detect mosaics



Mosaics: a third category

aCGH	hr-NGS	impact
Normal **(61%)**	Normal (43%)	100% concordance
	Mosaic (18%)	Improved selection against low implantation, high miscarriage risk embryos
Abnormal **(39%)**	**Mosaic (3%)**	some chance of making a baby
	Abnormal (36%)	100% concordance

21%

PGDIS, COGEN Recommendations

- Report **<20% as normal** and **>80% as abnormal** (resolution limit)
- **High priority** mosaics: those with **<40% abnormal cells**
- **Low priority** mosaics: **chaotic mosaics** or those with **>40% abnormal cells**
- **Low priority** mosaics: - with chromosomes **X, Y, 13, 18, 21** (live born viability)
  - with chromosomes **14, 15** (risk of UPD)
  - with chromosomes **2, 7, 16** (intrauterine growth retardati

But there is **no evidence** that mosaics at blastocyst level have the same impact as mosaics in first trimester

Next frontier in PGS : Non Invasive

Challenges to conventional PGS

- Requirement of highly skilled personnel for polar body/ embryo biopsy
- Biopsy requires purchase and maintenance of a laser
- Time consuming and costly
- Potentially increases the risk to the embryo and might decrease the overall efficacy of PGT

ARTICLE

Genomic DNA in human blastocoele fluid

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[*] Corresponding author. *E-mail address:* simonepalini@yahoo.it (S Palini). [1] These authors contributed equally to this work.

Noninvasive chromosome screening of human embryos by genome sequencing of embryo culture medium for in vitro fertilization

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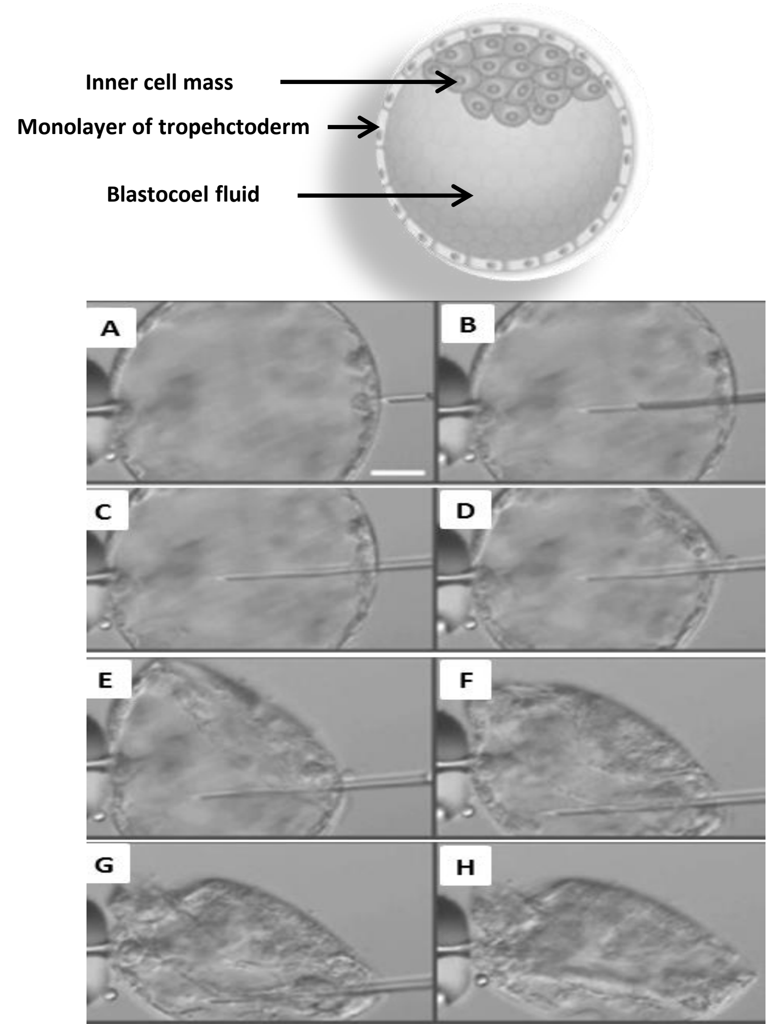
Non-invasive preimplantation genetic screening using array comparative genomic hybridization on spent culture media: a proof-of-concept pilot study

Michael Feichtinger [a,b], Enrico Vaccari [a], Luca Carli [a], Elisabeth Wallner [a], Ulrike Mädel [a], Katharina Figl [a], Simone Palini [c], Wilfried Feichtinger [a,]*

Sources of DNA for NI-PGS: Blastocoel fluid and spent culture media

- Blastocoel fluid present in the blastocyst cavity, 120-144 hours post fertilisation
- Media collected after embryo in culture till cleavage or blastocyst stage
- Both sources of extruded DNA and proteins by embryo
- Potential source of biomarkers for embryo viability
- If successful, these would be less intrusive than embryo biopsy
- Aim: To explore blastocoel fluid and spent media as a potential source of NI-PGT



Initial hypothesis and challenges for NI-PGS assay development

- DNA is likely to be degraded
  - Highly fragmented DNA is difficult to amplify using standard methods
  - Can we successfully amplify DNA from spent culture medium/blastocoel?

- Is the DNA similar to circulating cfDNA found in blood?
  - cfDNA is around ~160bp
  - Source of cell free DNA in blastocoel fluid and spent culture media?
  - Apoptotic cells? → fragmentation of DNA into nucleosome-sized fragments
  - Necrotic cells? → random fragmentation; variable DNA fragment sizes

Summary of some published results

Published study	Year	Journal	Method	Number of samples	Amplification rate	Ploidy concordance rate
Non-invasive preimplantation genetic screening using array comparative genomic hybridization on spent culture media: a proof-of-concept pilot study	2017	RBMO	Sureplex amplification +aCGH	22 spent media samples after blastocyst culture compared to PB results; SM collected after ssisted hatching	18/22 = 81.8%	13/18 (72.2%)
Noninvasive chromosome screening of human embryos by genome sequencing of embryo culture medium for in vitro fertilization	2016	PNAS	MALBAC + NGS	42 spent media samples	42/42 = 100%	Euploidy: 21/25= 84%; Aneuploidy: 15/17=88.2%
Non-invasive preimplantation genetic screening of human blastocysts	2017	Conference abstract ASRM-Fert Ster	Sureplex + NGS	25 spent media samples	25/25 = 100%	overall: 85% (75/20) with respect to TE biopsy
Monash University	2017	Conference abstract ASRM-Fert Ster	DOPlify + NGS	178 spent media samples	94% amplification	for day4 to day5/6 culture: 95%; for day3 to day5/6 culture: 65.4%

Summary of our results

- Spent culture media seems to be a better source for cell-free embryonic DNA as compared to blastocoel fluid

- Preliminary data analysis demonstrates our in-house modified method to be a superior amplification strategy for spent media samples as compared to existing WGA methods (Sureplex, MDA)

- Spent media can be potentially used as a source of DNA for non-invasive PGT, however extensive clinical validation is necessary to determine its efficacy.

- If successful, this can increase patient access to PGT and might be more cost effective compared to the current PGT techniques available.

Beyond the embryo

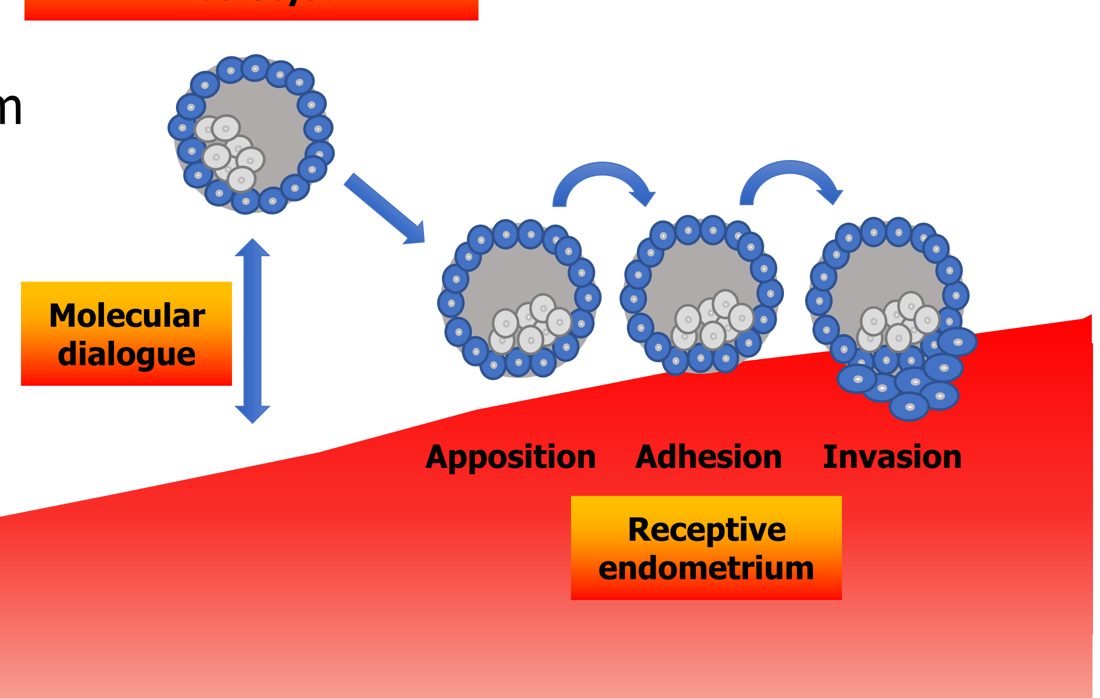
Endometrial receptivity

Embryo Implantation

Key process for the establishment of a successful pregnancy

- Complex: - apposition
  - adhesion
  - invasion
- Crucial: - dialogue between embryo and endometrium
  - implantation-competent blastocyst
  - receptive endometrium

Synchrony between embryo and endometrium

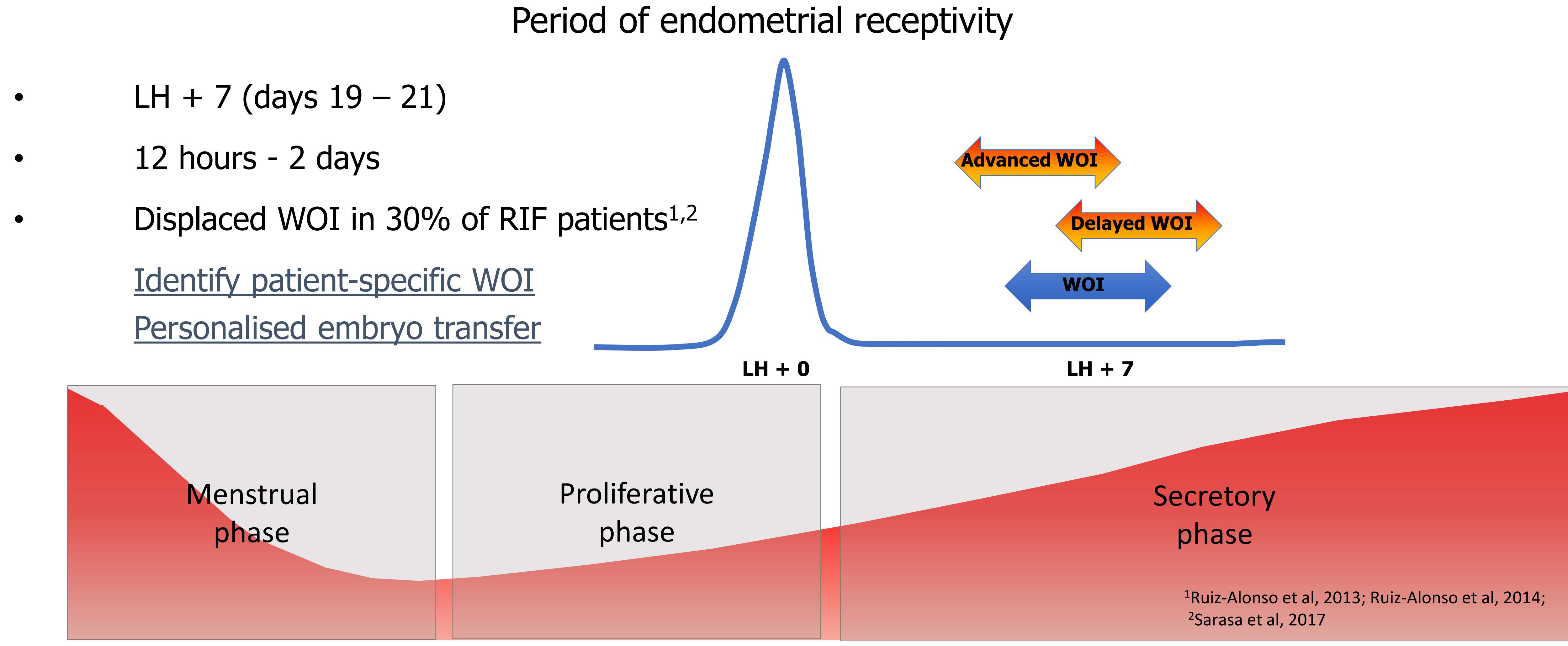


Window of Implantation (WOI)

- LH + 7 (days 19 – 21)
- 12 hours - 2 days
- Displaced WOI in 30% of RIF patients[1,2]

Identify patient-specific WOI

Personalised embryo transfer



[1]Ruiz-Alonso et al, 2013; Ruiz-Alonso et al, 2014;
[2]Sarasa et al, 2017

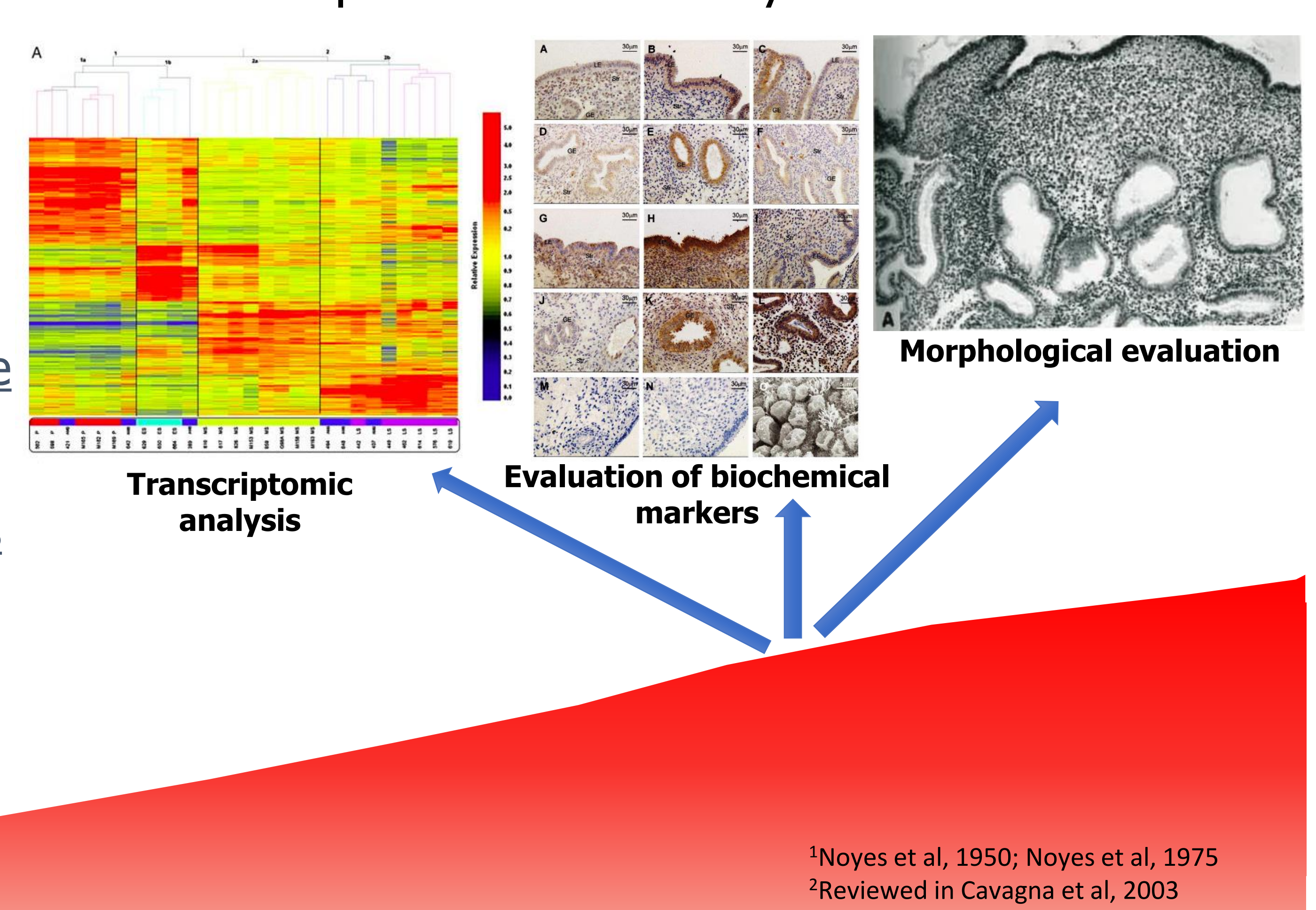
Evaluation of Endometrial Receptivity

Enables identification of a personalised WOI and personalised embryo transfer

- Histologic evaluation[1]
- Evaluation of biochemical markers[2]
- Analysis of gene expression[3]

Identification of transcriptomic signature specific to the WOI

Development of accurat diagnostic tools



[1]Noyes et al, 1950; Noyes et al, 1975
[2]Reviewed in Cavagna et al, 2003
[3]Reviewed in Horcajadas et al, 2006

Scientific data

Studies reporting on accuracy and treatment outcomes

- High accuracy in receptivity status assignment
- Displaced WOI in >25% of RIF patients
- Personal embryo transfer results in improved IVF outcomes

Personalised scheduling of embryo transfer at the moment of highest endometrial receptivity according to ER Map® test significantly improves clinical outcomes

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The accuracy and reproducibility of the endometrial receptivity array is superior to histology as a diagnostic method for endometrial receptivity

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O-113 ER map: a new comprehensive and reliable endometrial receptivity test

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The endometrial receptivity array for diagnosis and personalized embryo transfer as a treatment for patients with repeated implantation failure

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What a difference two days make: "personalized" embryo transfer (pET) paradigm: A case report and pilot study

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ER Map allow the reliable determination of the window of implantation in infertile women

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Advantages of ER Testing based on gene expression

Endometrial receptivity testing based on gene expression...

- Provides objective molecular diagnosis test
- Enables personal embryo transfer
- Shows high accuracy and reproducibility
- Provides evidence of a frequently displaced WOI in RIF patients
- Provides an effective strategy to improve clinical outcomes in RIF patients

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