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Scientific Director

Fertility Associates, Lecturer, University of Auckland

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Obstetrician and Gynaecologist

Medical Director, Fertility Associates Christchurch

Dr Michelle Bailey

Fertility Specialist

Fertility Associates, St Georges Hospital, Christchurch

Thursday, August 11, 2016 (Room 4)

14:00 - 16:00 WS #14: Fertility 101

16:30 - 18:30 WS #19: Fertility 101 (Repeated)

FERTILITY associates | a better understanding
TE RAUHANGA O TE WHARETANGATA

Evolving Technology in the IVF Laboratory

Dean E. Morbeck, PhD, HCLD, MBA
Scientific Director

Leaders in Fertility

Disclosures

None

Objectives

- Provide an introduction to embryo culture in the 21st century.
- Describe the various terms and acronyms in use for pre-implantation genetic testing.
- Explain the different stages of embryo development when testing can be performed and which is considered optimal.
- Understand the limitations and risks of pre-implantation genetic testing.
- Revisit basic biology “laws”

Apple Computer Design Evolution

with Base Prices

Apple I – $667
1976

Apple II – $1298
1977

Apple III – $7800
1980

Apple Lisa – $9995
1983

Macintosh – $1995
1984

Apple IIGS – $999
1986

Macintosh II – $5500
1987

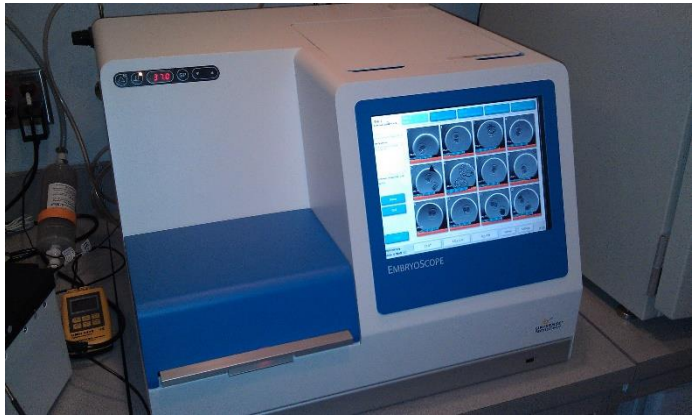
PowerMac 5200 – $1900
1995

iMac G3 – $1299
1998

iMac G4 – $1299
2002

iMac G5 – $1299
2004

iMac Unibody – $1199
2009



1978

1988

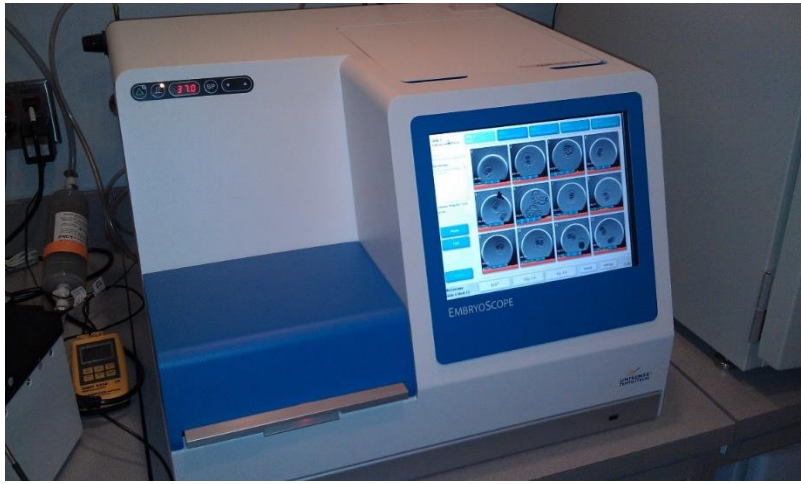
1998

2008

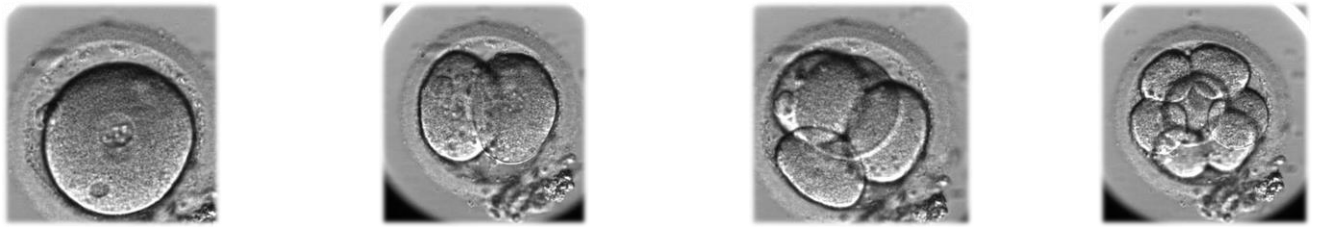
2011

2016

Quality and Safety



Why Time-Lapse?

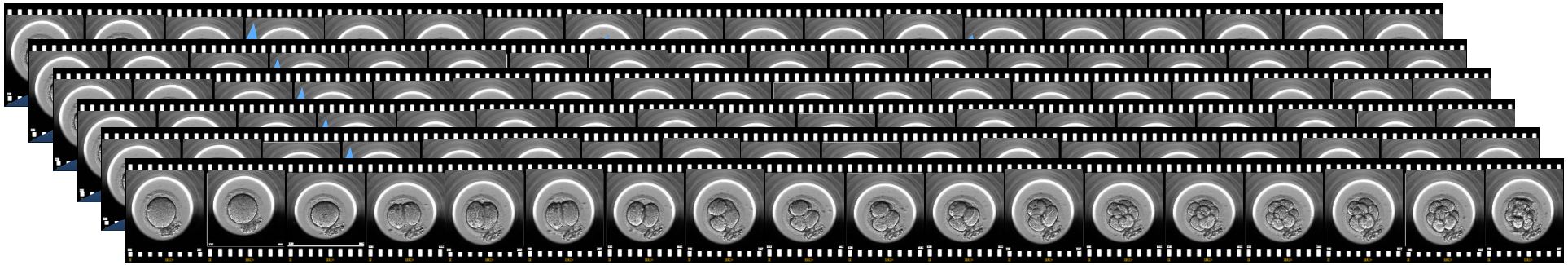


17 hrs 25 hrs 42 hrs 66 hrs

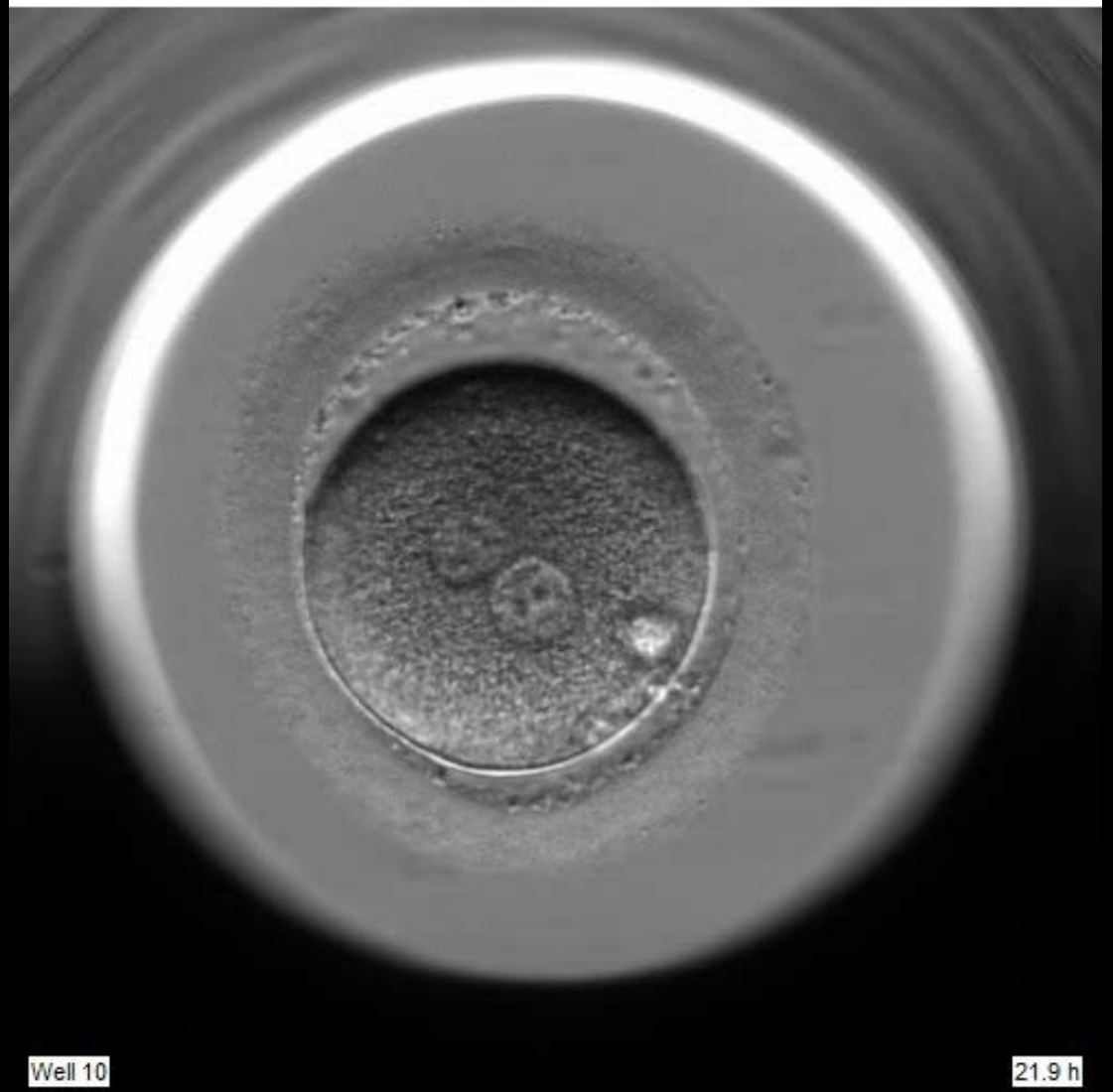
More Observations
Better Selection

Less Disturbance
Better Development

>1500 images over 3 days per embryo



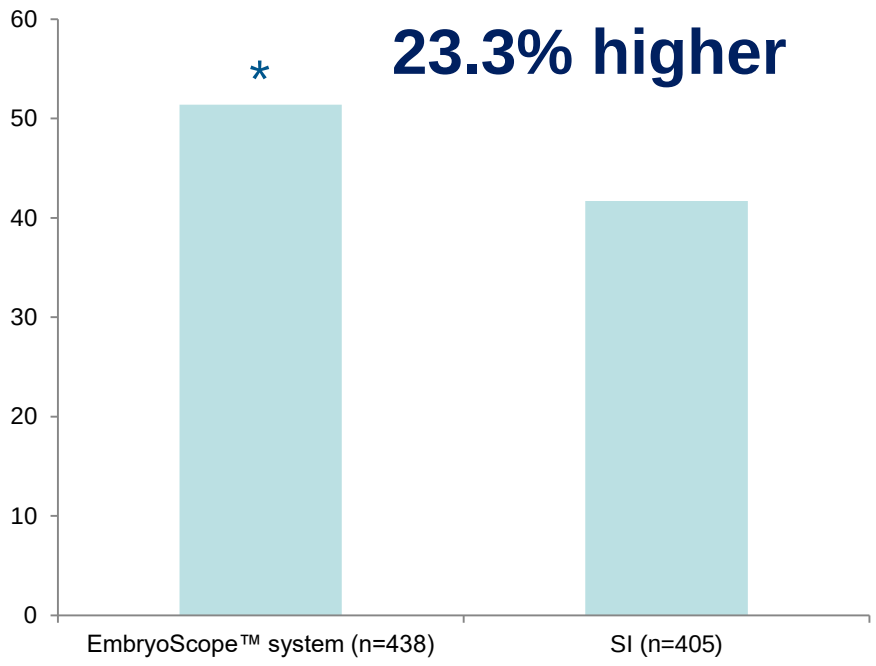
Typical Embryo Development



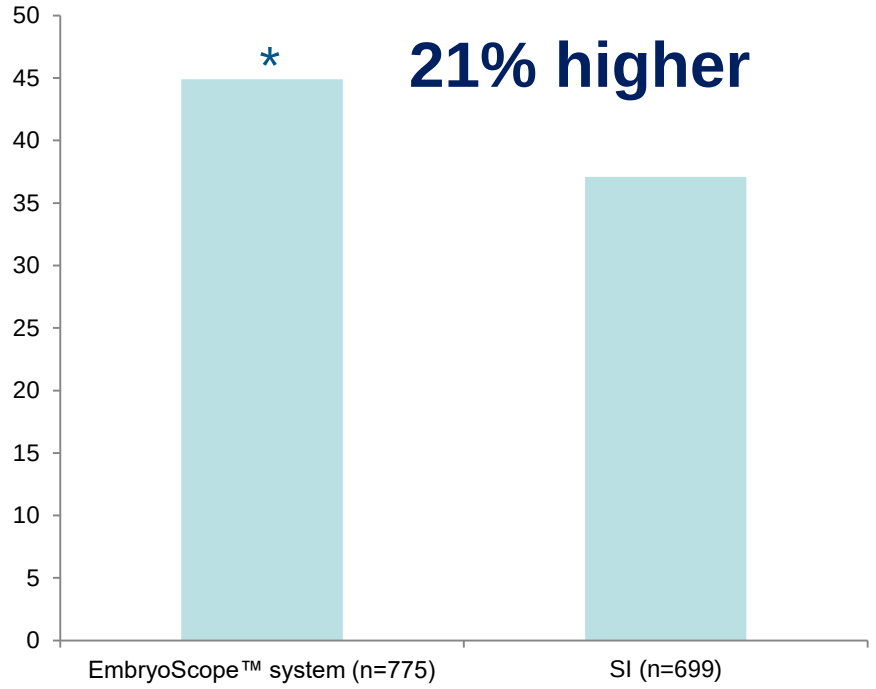
The Era of Time-Lapse

RCT Results

Ongoing pregnancy rate



Implantation rate

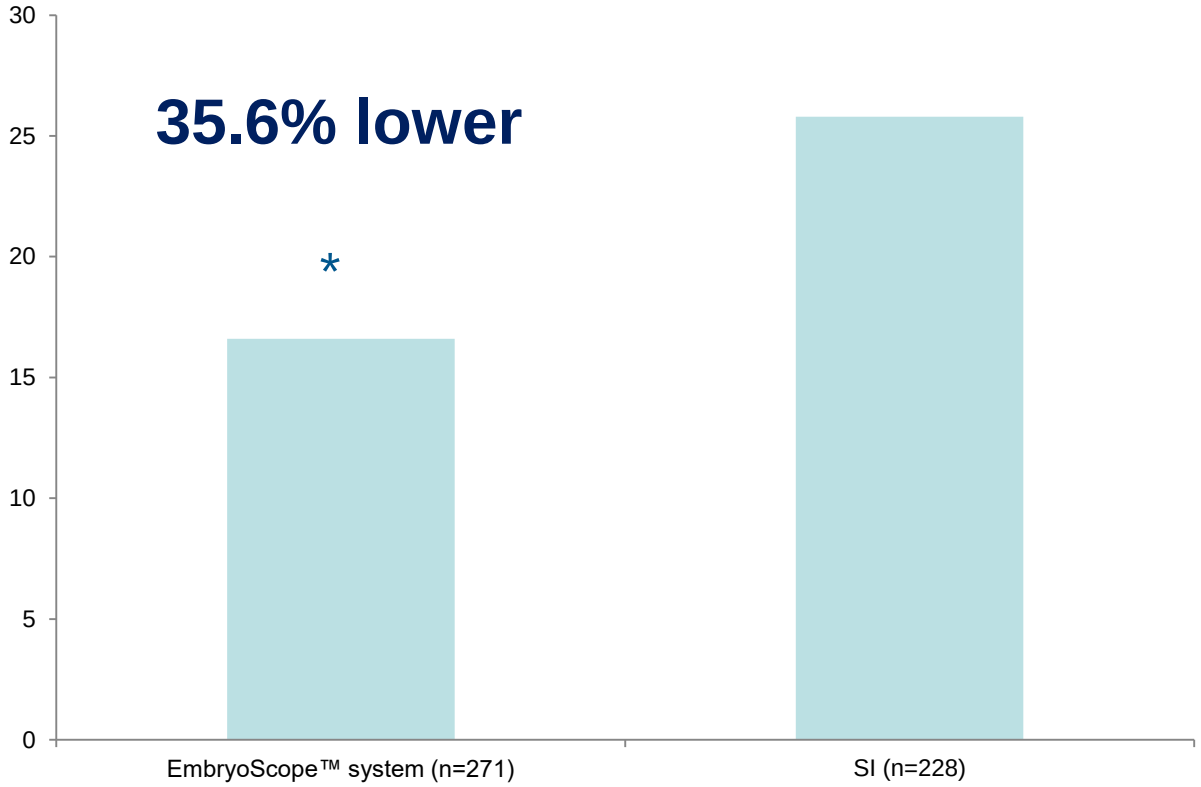


Time-lapse

VS

Data from Rubio et al (2014) Fertil Steril

Early Pregnancy Loss

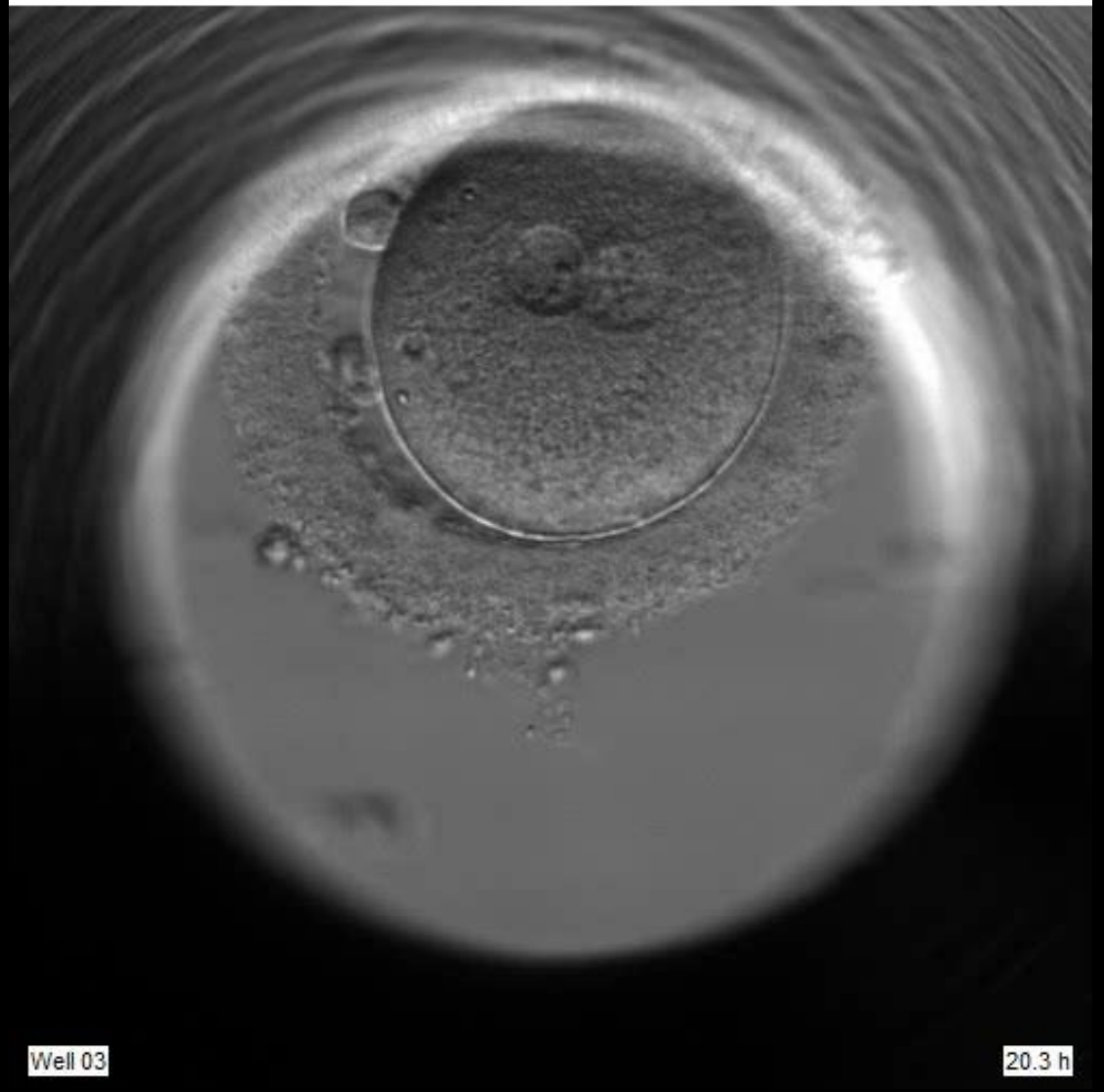


Time-lapse

VS

Data from Rubio et al (2014) Fertil Steril

Direct 1-3 Without Compaction



THE ORIGIN
OF
MALIGNANT TUMORS

By
THEODOR BOVERI
University of Würzburg

Translated by
MARCELLA BOVERI

25168

BALTIMORE
THE WILLIAMS & WILKINS COMPANY
1929

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Review

Tripolar mitosis in human cells and embryos: Occurrence, pathophysiology and medical implications

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Human papilloma virus
Chlamydia trachomatis

ABSTRACT

Tripolar mitosis is a specific case of cell division driven by typical molecular mechanisms of mitosis, but resulting in three daughter cells instead of the usual count of two. Other variants of multipolar mitosis show even more mitotic poles and are relatively rare. In nature, this phenomenon was frequently observed or suspected in multiple common cancers, infected cells, the placenta, and in early human embryos with impaired pregnancy-yielding potential. Artificial causes include radiation and various toxins. Here we combine several pieces of the most recent evidence for the existence of different types of multipolar mitosis in preimplantation embryos together with a detailed review of the literature. The related molecular and cellular mechanisms are discussed, including the regulation of centriole duplication, mitotic spindle biology, centromere functions, cell cycle checkpoints, mitotic autocorrection mechanisms, and the related complicating factors in healthy and affected cells, including post-mitotic cell–cell fusion often associated with multipolar cell division. Clinical relevance for oncology and embryo selection in assisted reproduction is also briefly discussed in this context.

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Introduction

origination of a near triploid DNA stem line, while tetrapolar mitoses are more correlated with an increased DNA content, but

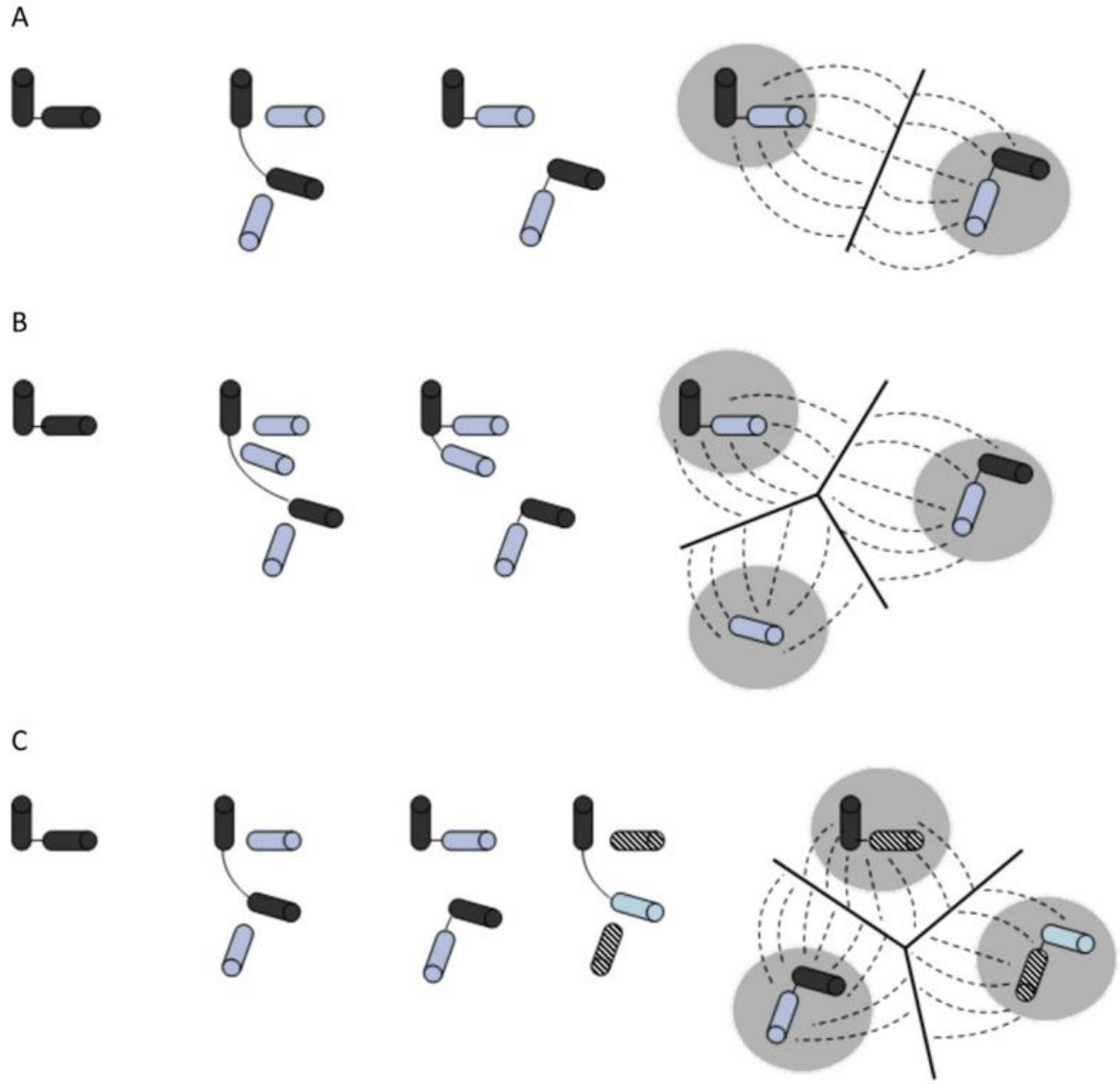
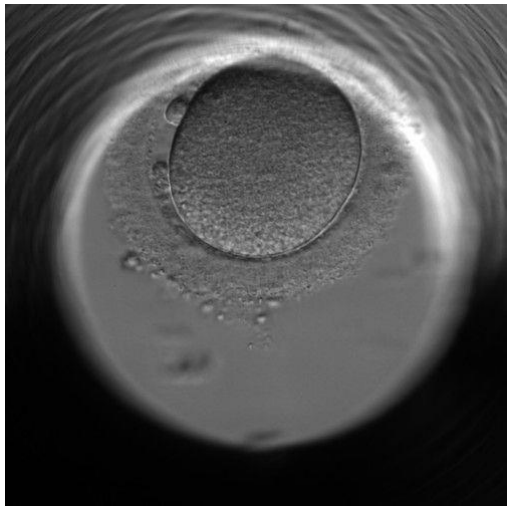
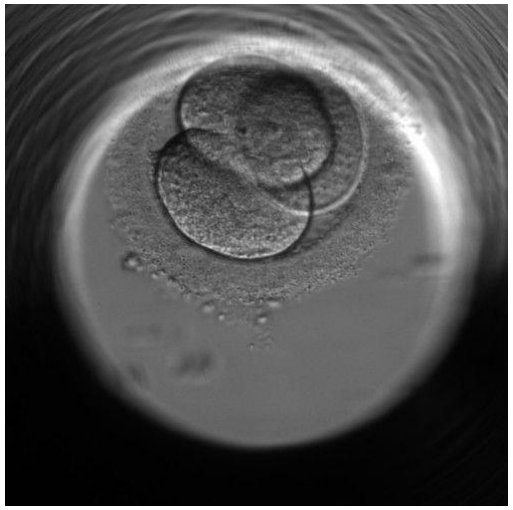


Fig. 2. Mechanisms of pathological multiplication of centrioles and mitotic poles. (A) Normal mitosis: a pair of mother centrioles (dark) splits in two parts and each of them grows its own duplicate (light blue), resulting in two pairs of centrioles. Centriole distribution in mitosis = 2:2. (B) Tripolar mitosis – scenario 1 (surplus duplication of mother centriole): one of the two mother centrioles replicates normally, while the other one gives rise to two daughter centrioles, thus forming a tripolar spindle. Centriole distribution in mitosis = 2:2:1. (C) Tripolar mitosis – scenario 2 (surplus duplication of daughter centriole): one of the normally duplicated centrioles duplicates again during the S phase, thus forming a tripolar spindle. Centriole distribution in mitosis = 2:2:2. (D) Tripolar mitosis – scenario 3 (surplus single-centrioled centrosome): centrioles duplicate normally, but one resulting pair does not hold together, and two spindle poles are organized around the two orphan centrioles in addition to a normal centrosome, resulting in a tripolar spindle. Centriole distribution in mitosis = 2:1:1. (E) Tripolar mitosis – scenario 4 (surplus MTOC without centrioles – "empty centrosome"): centrioles duplicate normally, but an additional microtubule-organizing center (MTOC) emerges as a standalone body of pure "empty" pericentriolar matrix (*i.e.*, without centrioles) in addition to two normal centrosomes, resulting in a tripolar spindle. Centriole distribution in mitosis = 2:2:0. (F) Rescue mechanism for reverting tripolar mitosis into normal – scenario 1 (centrosome clustering): Bipolar spindle is formed in a presence of multiple centrosomes. Centriole distribution in mitosis = 2:4 (may vary in other cases, *e.g.*

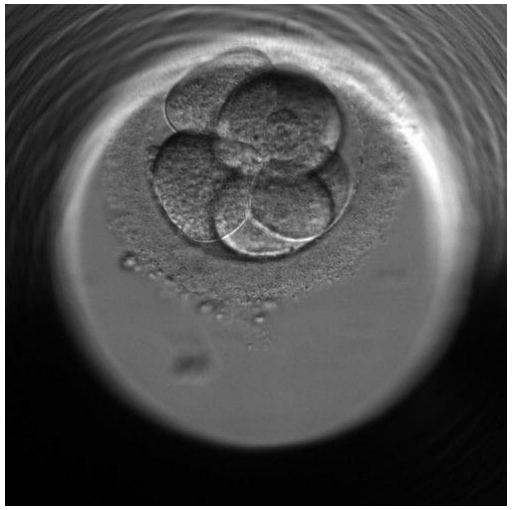
Abnormal Cleavage Events



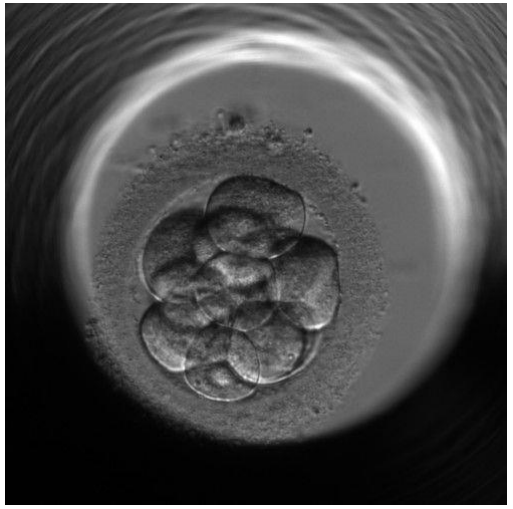
32h



44h



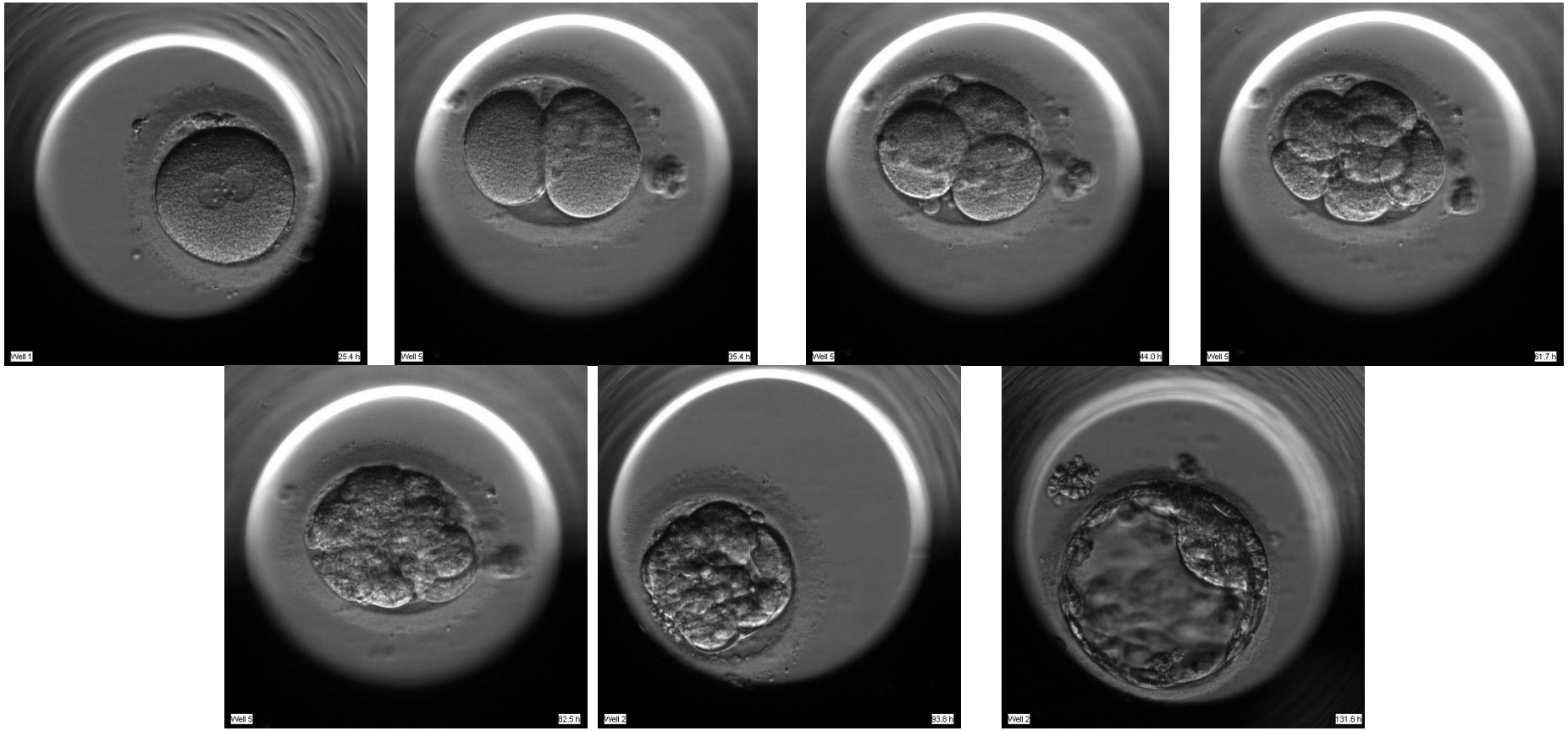
- Direct cleavage from 1 to 3 cells
  - Rubio et al., 2012
- Reverse cleavage
  - Campbell et al., 2013

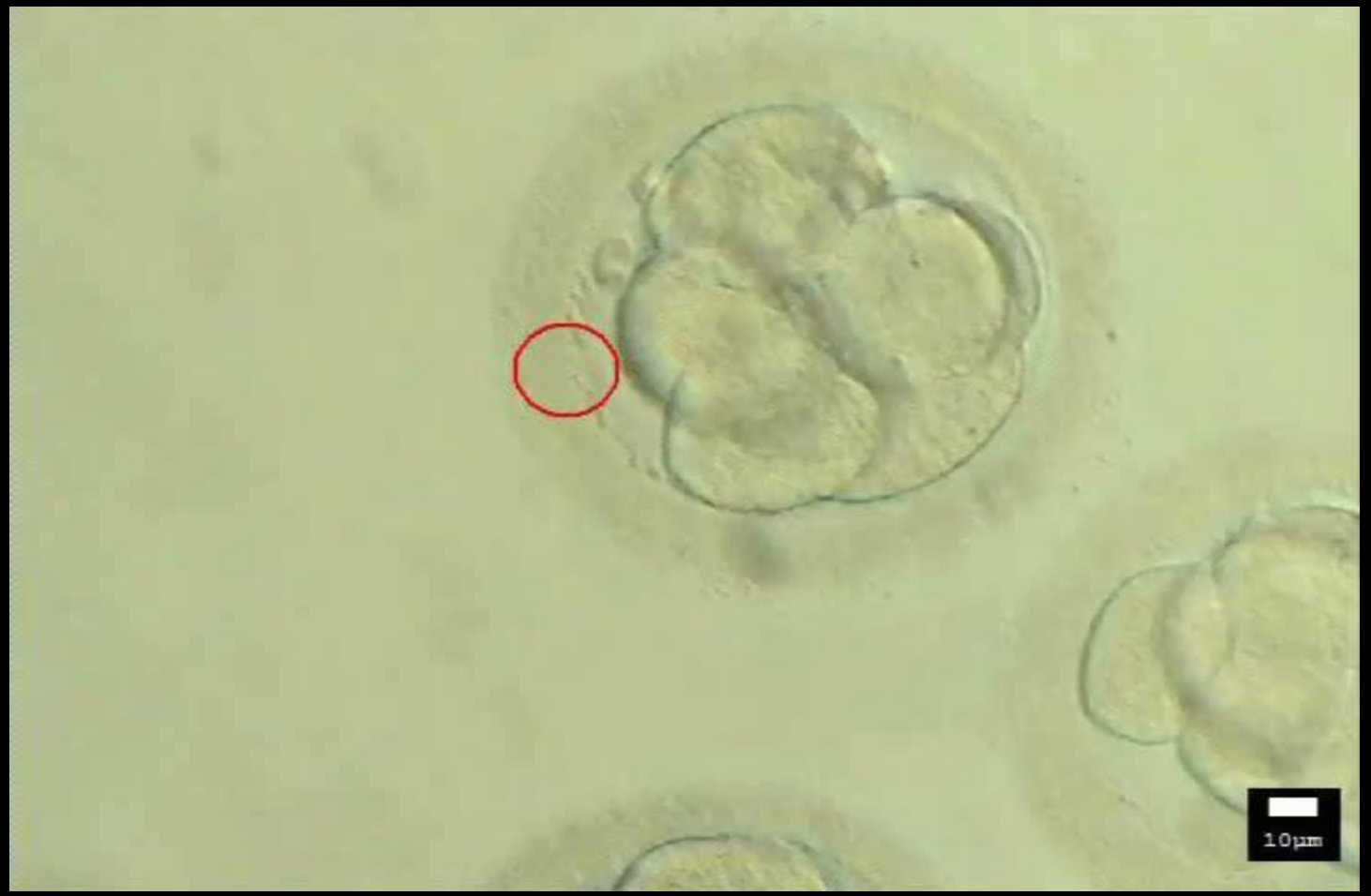


PGDefinitions

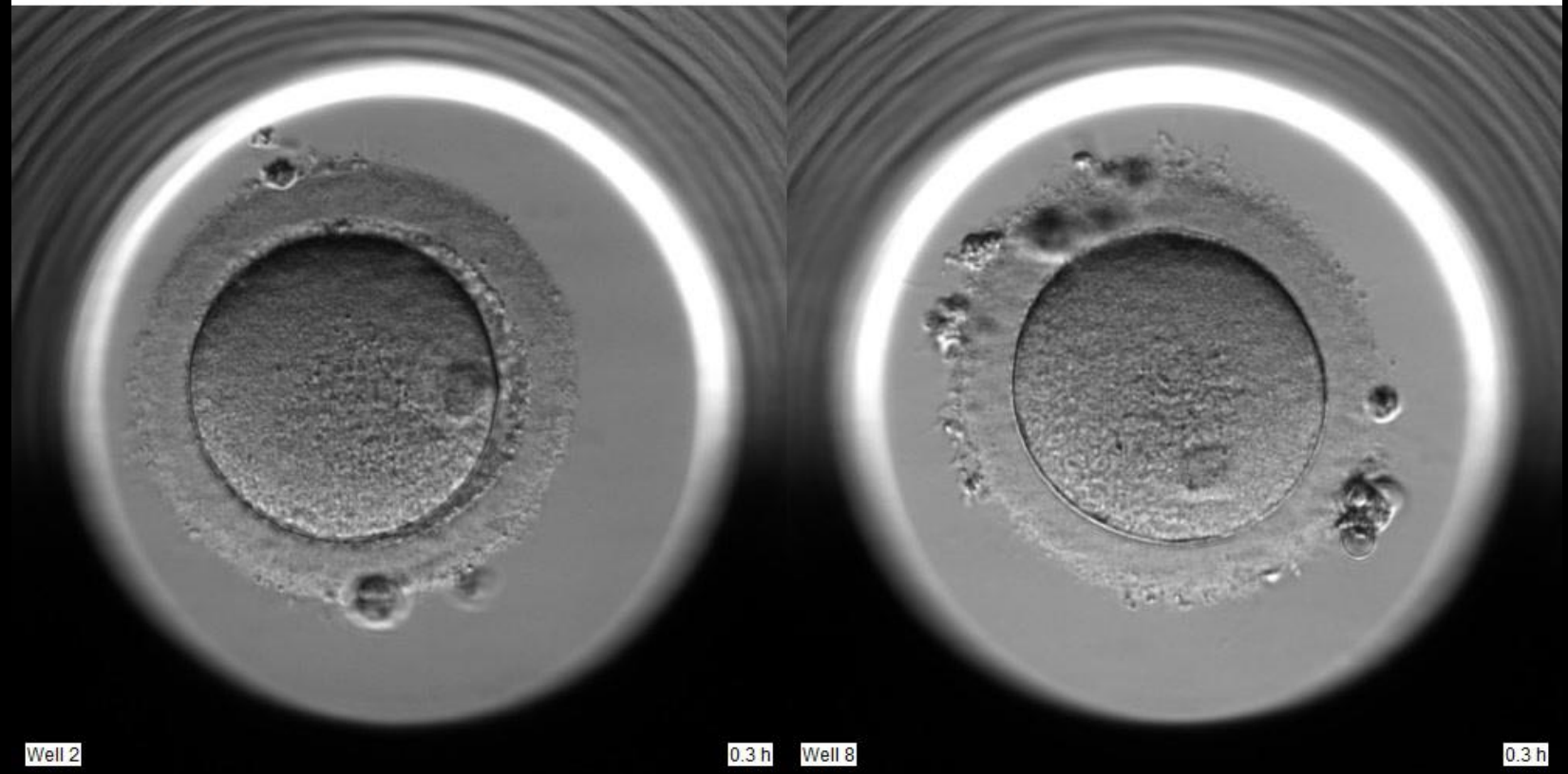
- PGT: Pre-Implantation Genetic Testing
  - PGD: Genetic Diagnosis
  - PGS: Genetic Screening
  - CCS: Comprehensive Chromosome Screening
  - PGS-A: Aneuploidy Screening

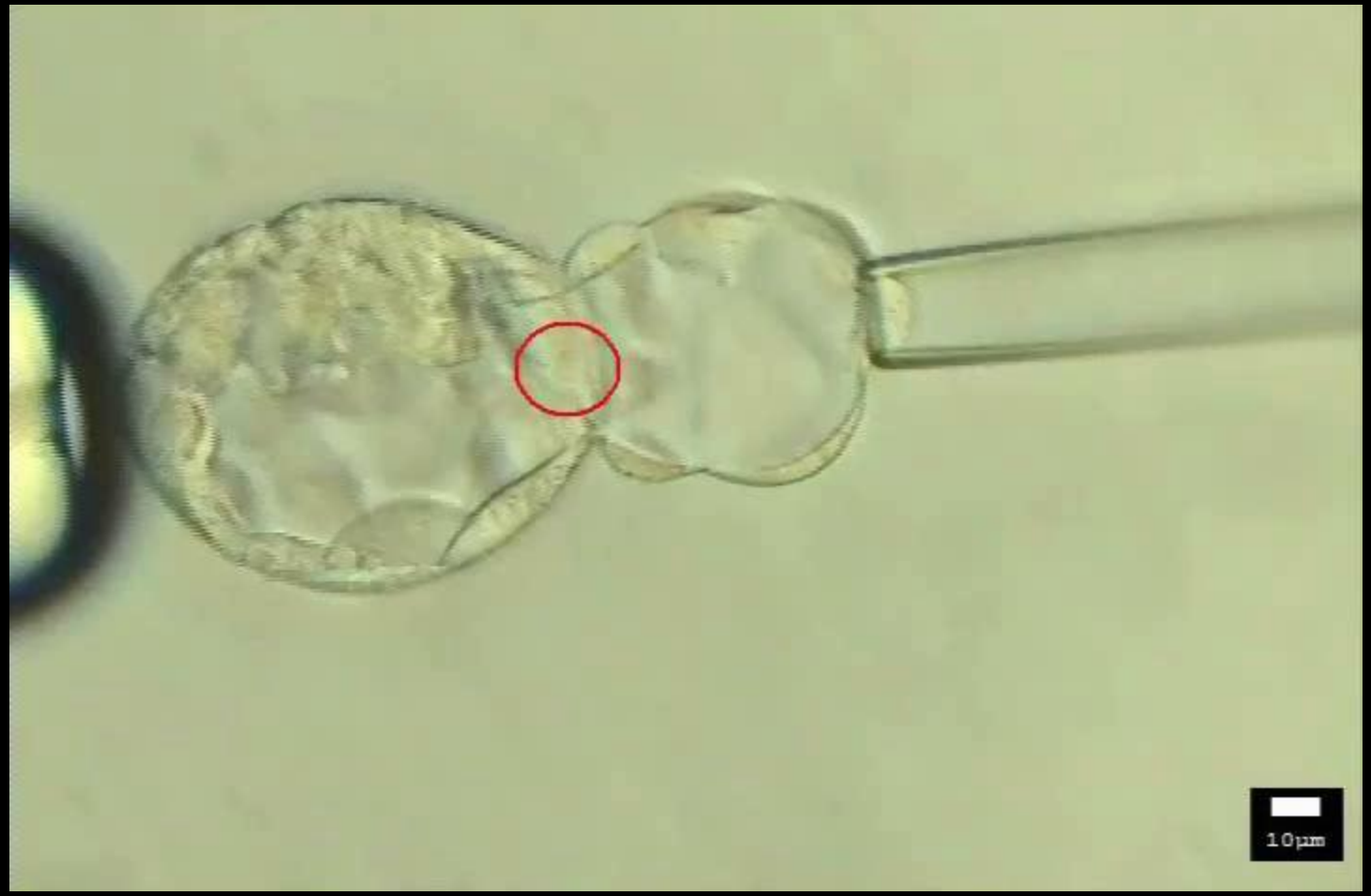
Stages to Biopsy

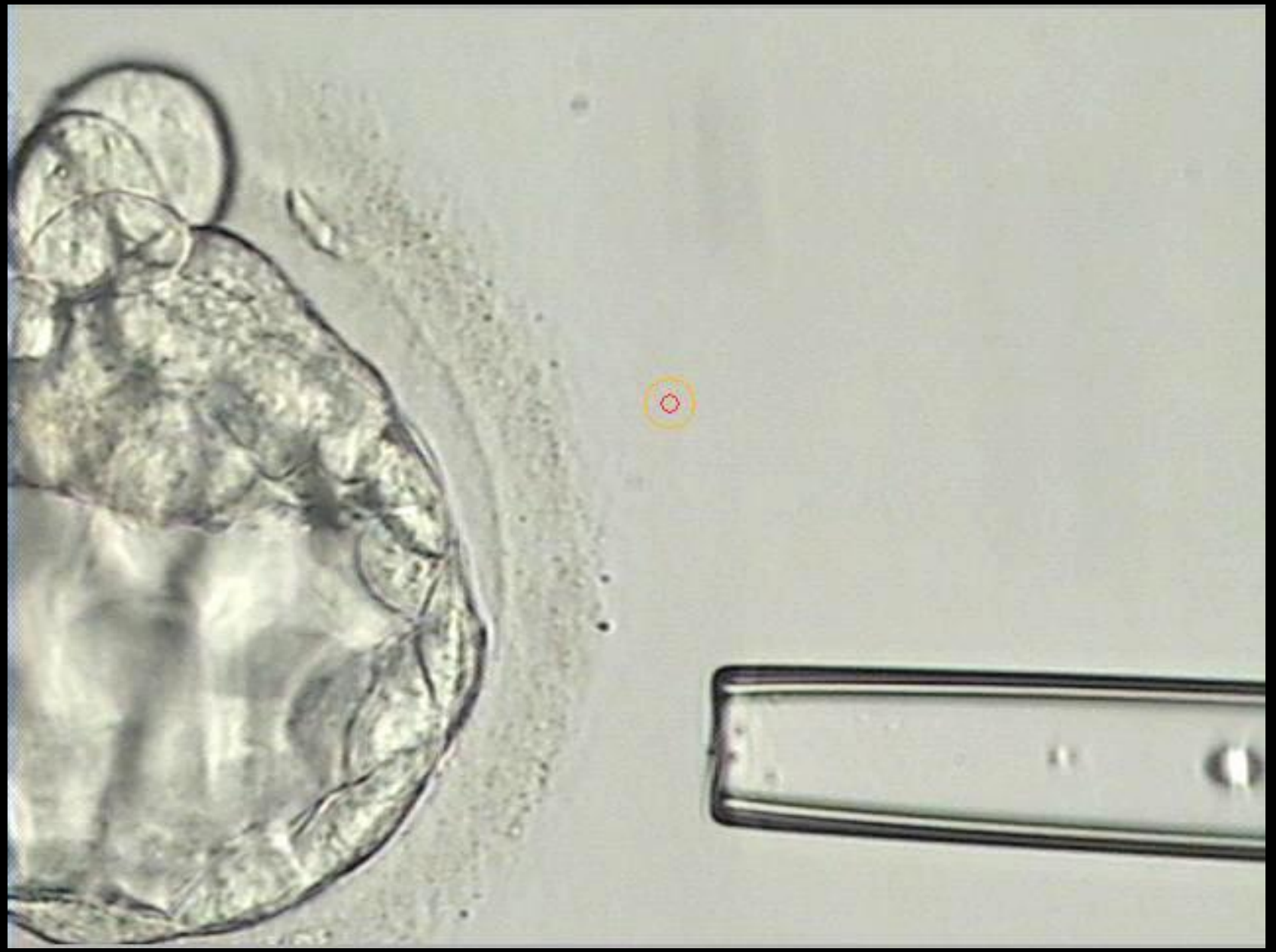



10µm

TE Biopsy



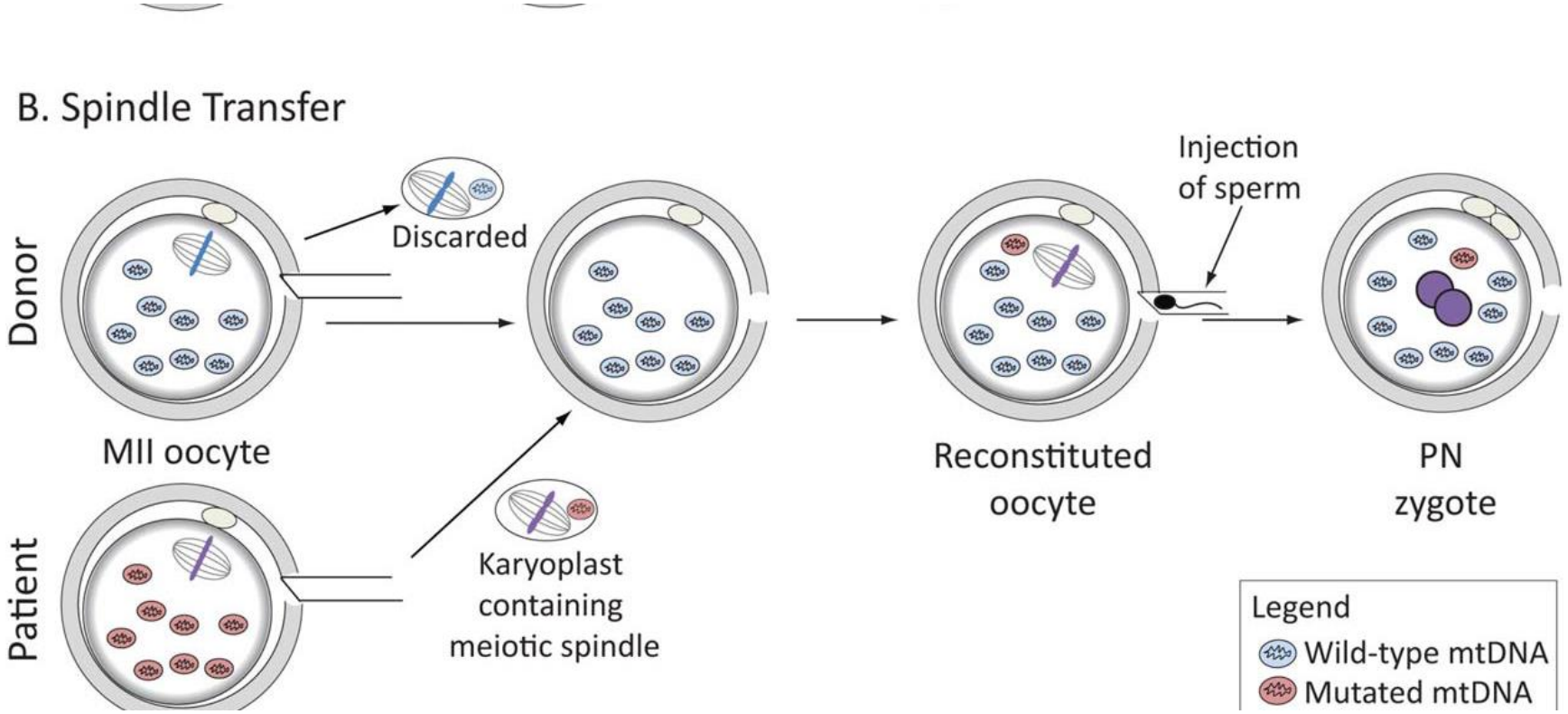

10µm



Why PGT?

- PGD
  - Eliminate gene mutations from germ-line
  - Select against unbalanced translocations
  - HLA Matching
- PGS/CCS
  - Recurrent miscarriage
  - Advanced maternal age
  - Recurrent implantation failure
  - Improve implantation potential?

Treating Mitochondrial Disease: 3 Parent IVF



Richardson et al., Stem Cells 2015

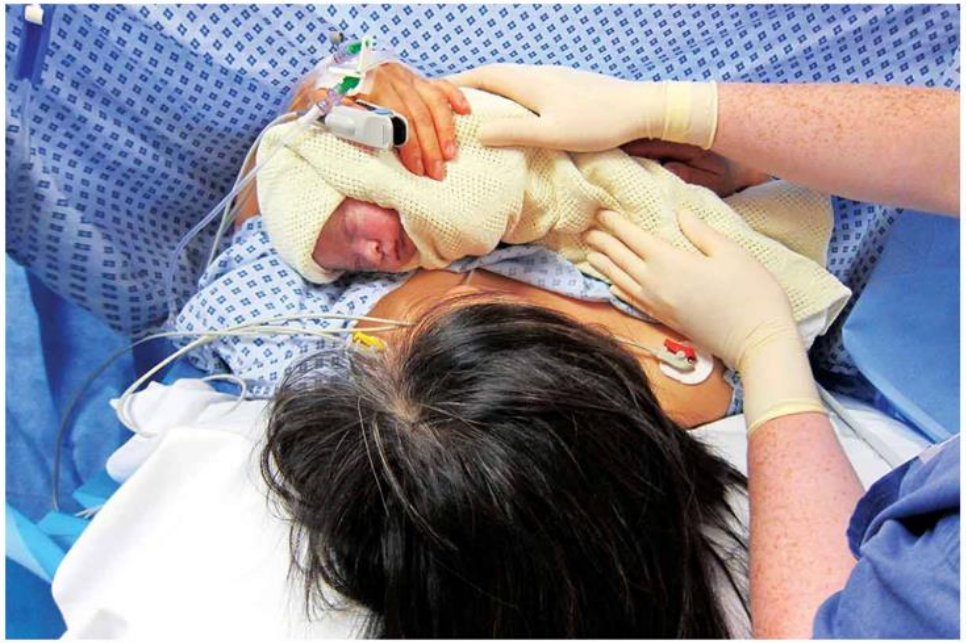
Egg number is set at birth and decreases until menopause.

Ovarian Stem Cells?

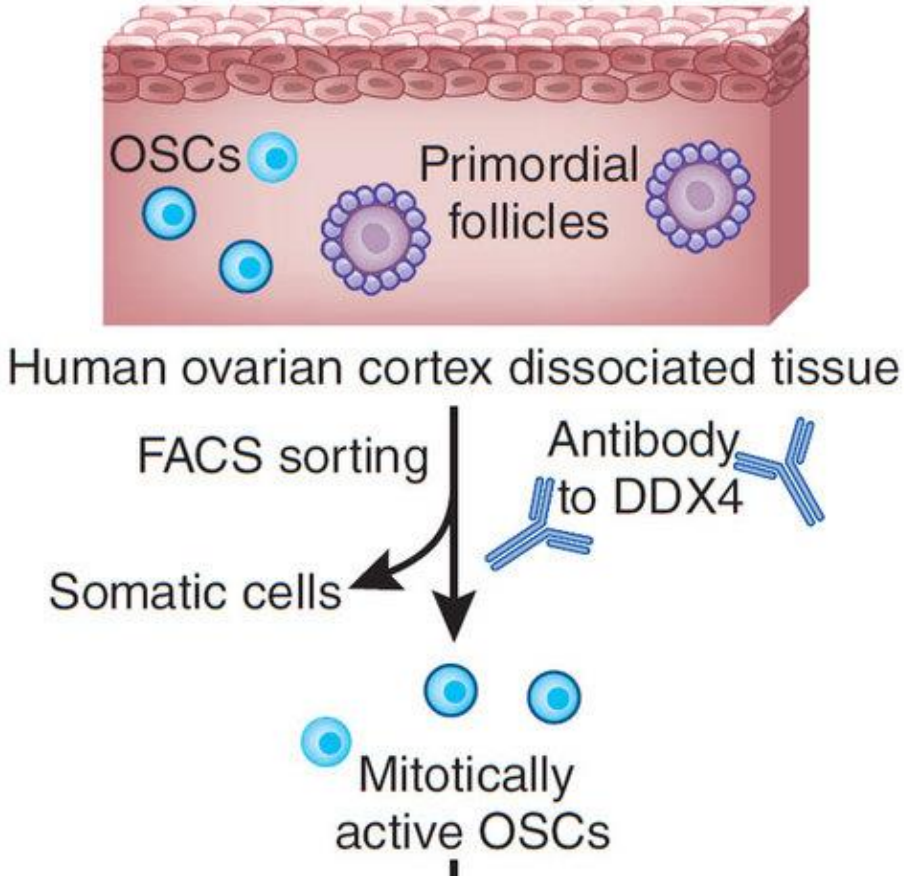
THIS WEEK 20 July 2016

Menopause reversal restores periods and produces fertile eggs

Women who have already passed through the menopause may be able to have children following a blood treatment usually used to heal wounds



Never too old?
Peter Dazeley/Getty

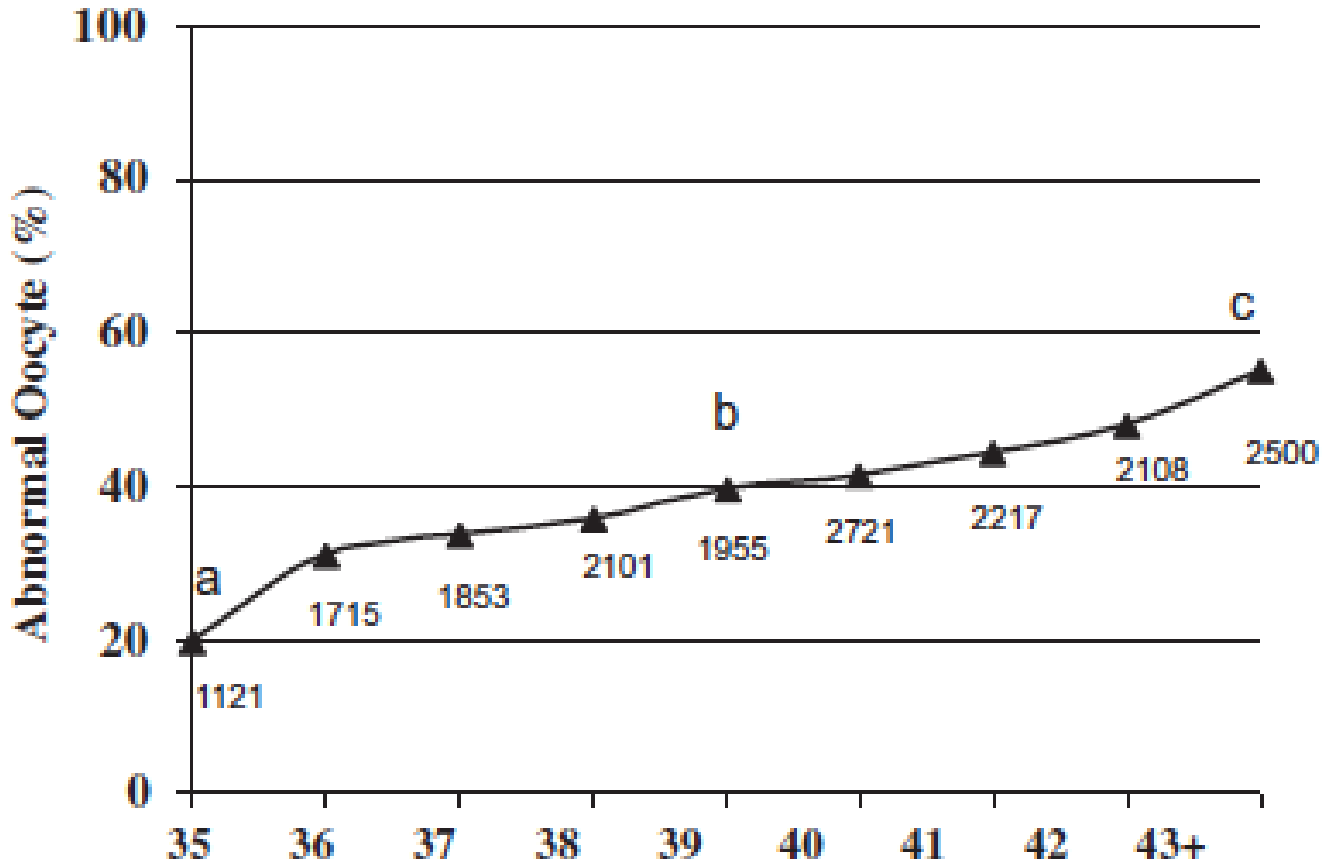


Find a clinic

Looking for where the AUGMENT℠ treatment is offered? In 2014, the AUGMENT treatment was introduced at select IVF clinics around the world through the AUGMENT Centers of Excellence (ACE) access program.

IVF Japan
Horac Grand Front Osaka Clinic
15th Floor Tower B
Grand Front Osaka
3-1 Ofuka-cho Kita-ku Osaka-shi
Osaka, Japan 530-0011
Contact Us Today

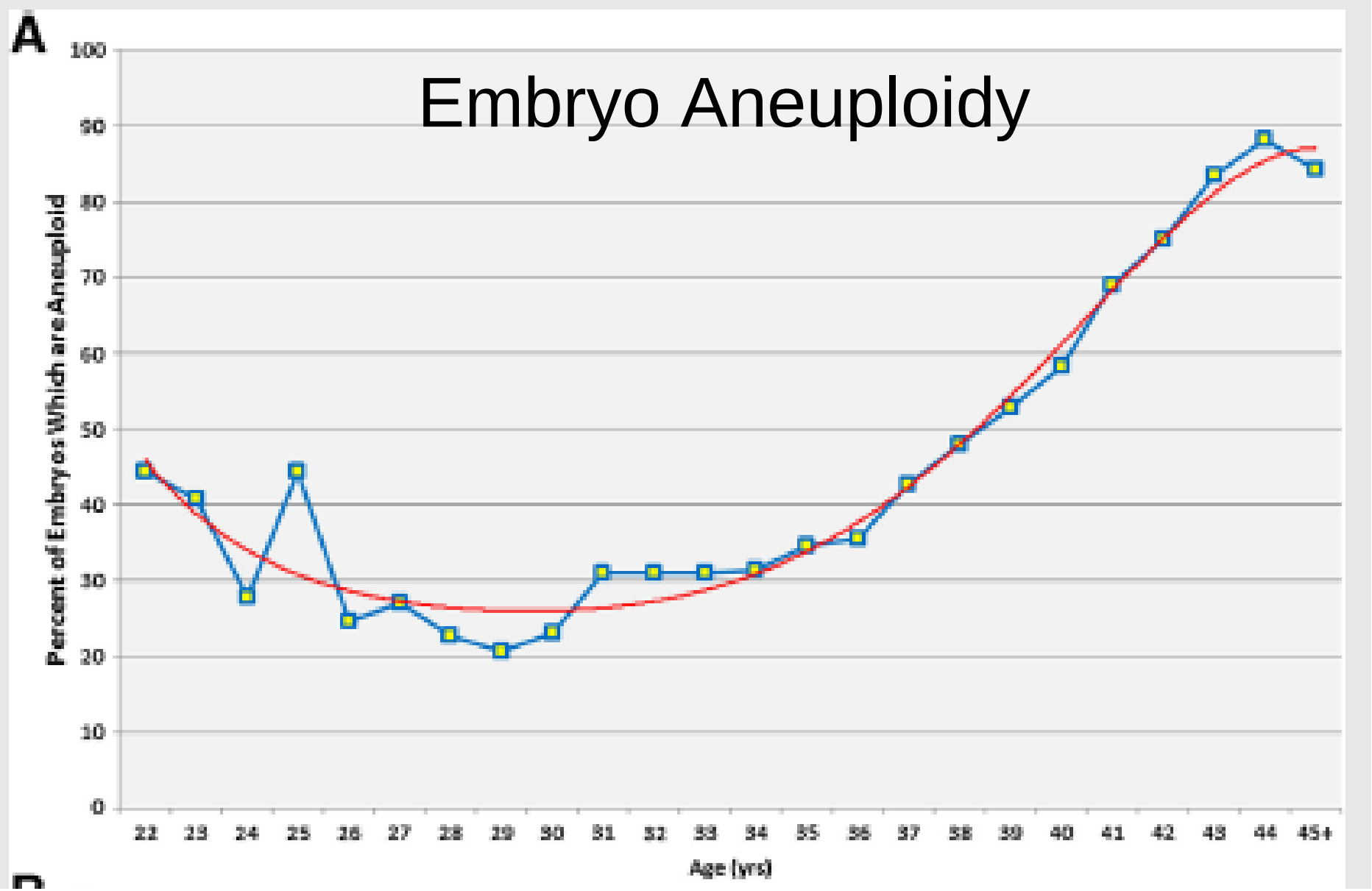
Why PGS?



a,b : $P < 0.001$
b,c : $P < 0.001$
a,c : $P < 0.001$

Predicted aneuploid by PB1 PB2 testing
Denominator = oocytes with results based on PB1 and PB2 testing

Kuliev et al., RBMOnline 2011



Franasiak et al., 2014 **Fertility and Sterility**

Why Not PGT?

- Invasive – waiting on non-invasive test!
- Requires blastocysts and frozen embryo transfer
  - False negatives
- PGS/CCS
  - False positives
  - Mosaicism
  - Unnecessary intervention?
  - RCTs but only in select populations

Case Report #1 – Recurrent Pregnancy Loss

- 39 yo G5P0
  - 1st and 2nd trimester losses over the previous 5 years
  - Recurrent pregnancy loss (RPL)
- FSH 9.0, AMH 14
- Cycle 1: 23 embryos 4 euploid
- Term 8 lb male

Case Report #2 – False Negative?

- 37yo G2P0
- FSH 9.5, AMH 21
- Cycle 1: 11 oocytes, 11 mature, 9 embryos, 0 blastocysts to biopsy
- Cycle 2: no PGS – day 3 embryo transfer/1 implanted
  - Delivered healthy female

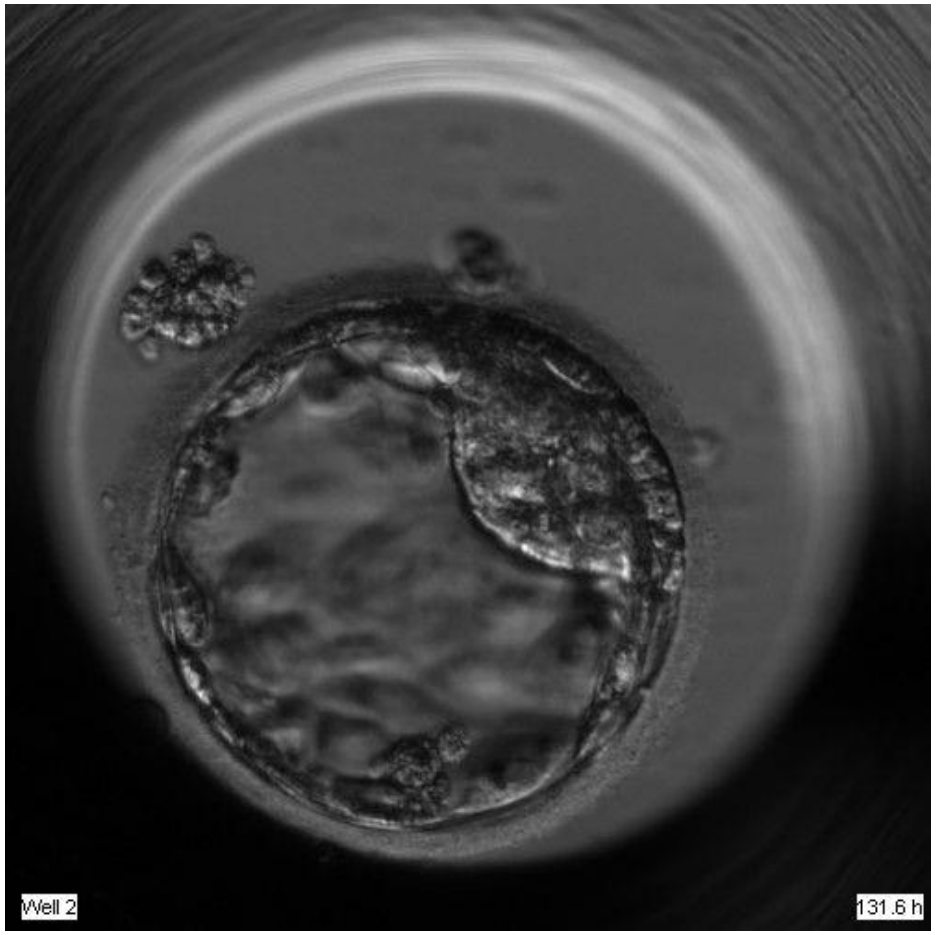
Case Report #3 – PGS Indicated?

- G0P0, 35 yo, Diminished ovarian reserve
- FSH 8.1, AMH 5.1
- Cycle 1: 4 embryos, 3 blastocysts, 1 euploid, 1 no result
- Cycle 2: 4 embryos, 2 blastocysts, 2 euploid
- Total: 8 embryos, 5 blastocysts (62%), 4 euploid (80%/blastocyst; 50%/embryo)
- Normal singleton delivery

Case Report #4 – Age, Eggs and False Positives

- 43 yo G4P0
  - trisomy 21, trisomy 22 (42yo)
- AMH 60.1, FSH 10.8
- Cycle 1: 10 embryos, 5 blastocysts, 1 euploid
- Cycle 2: 18 embryos, 10 blastocysts, 0 euploid
- Cycle 3: 10 embryos, 9 blastocysts, 1 euploid
- Cycle 4: 14 embryos, 7 blastocysts, 1 euploid
- eSET + singleton
- Total: 52 embryos, 31 blastocysts (60%), 3 euploid (9.7%/blastocyst, 5.7%/embryo)

PGT Conclusions



- PGD
  - Single genes ✓
  - Translocations ✓
  - HLA Matching ✓
  - Mitochondrial disease ✓
- PGS/CCS
  - AMA + eggs ✓
  - AMA ?
  - RPL ✓
  - Elective ?
  - Reduce risk of trisomy ✓

- False negative rate?
- False positive rate?
- Individualized plan

Questions?