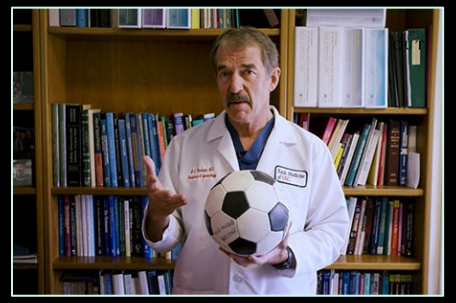
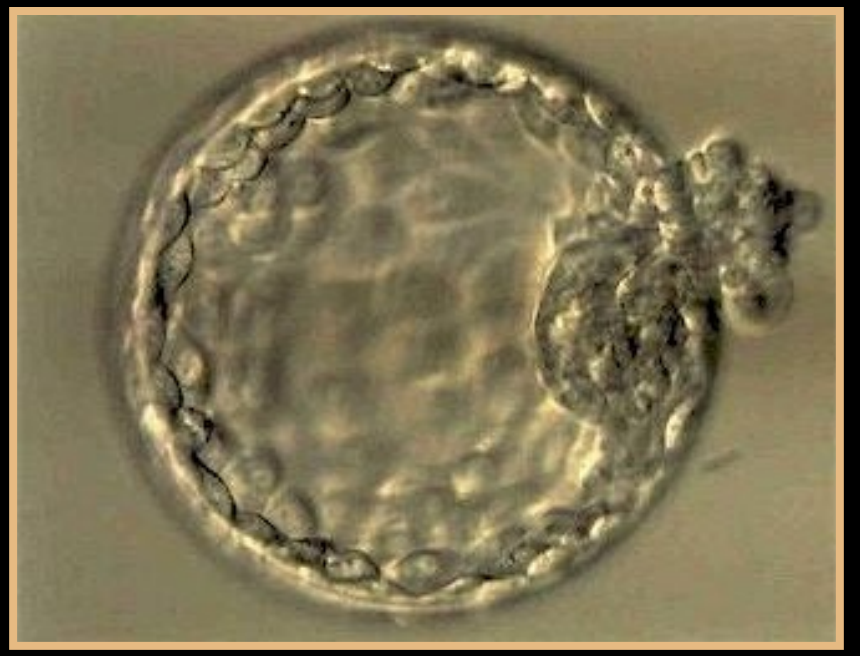
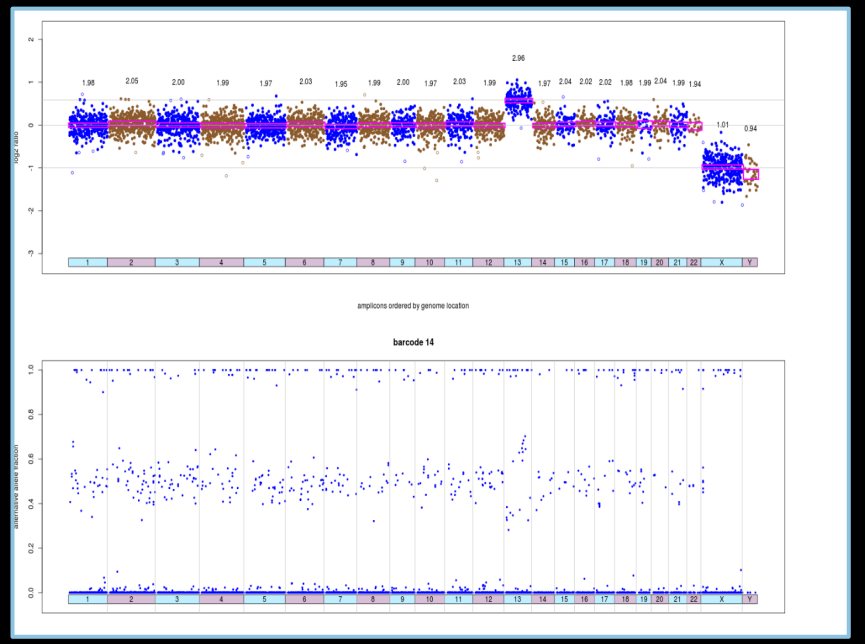
The Great Debate (ver8)
Is PGT-A a Useful Adjunct in IVF



vs Richard T. Scott, Jr, MD, HCLD/ALD



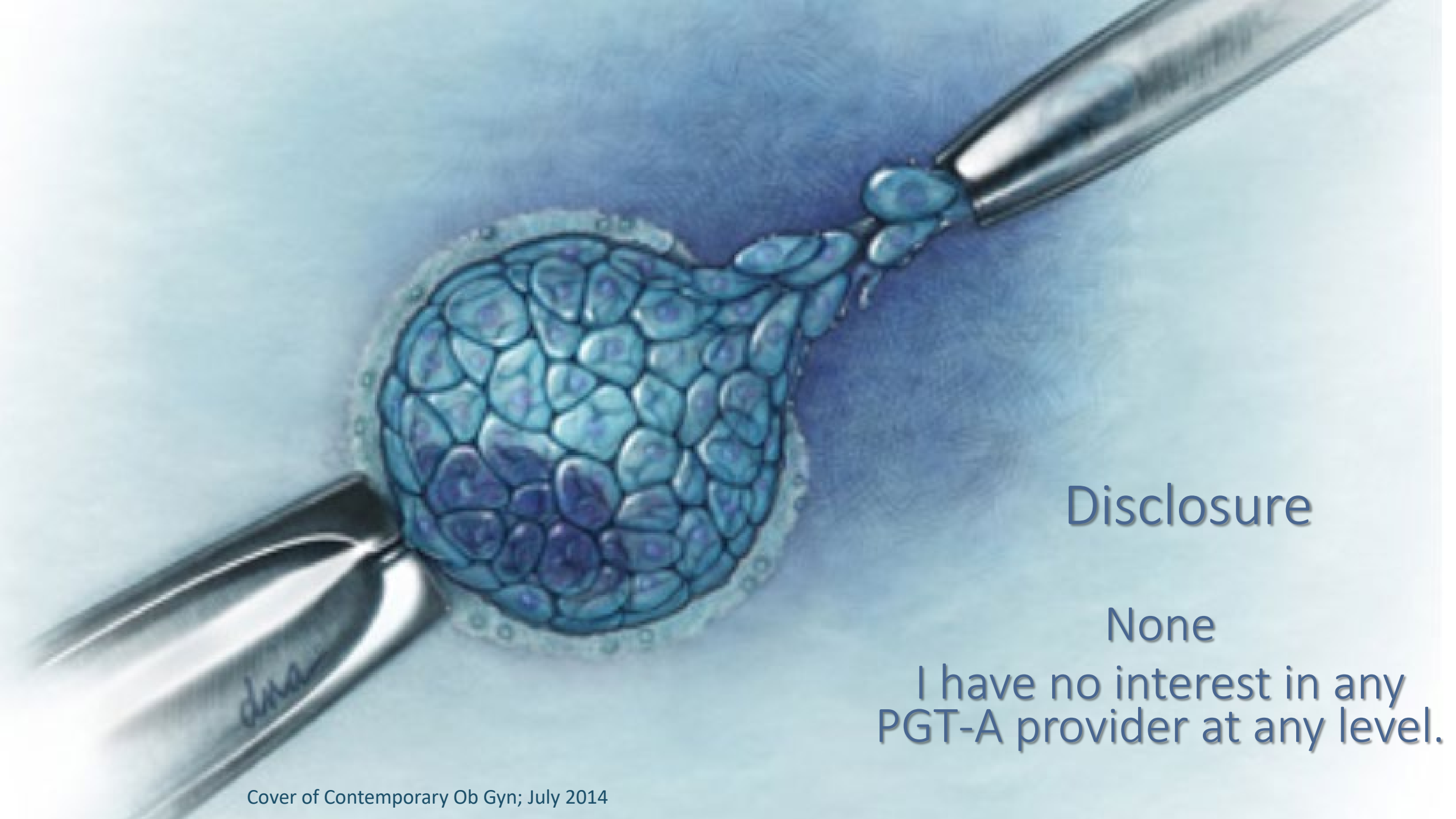
rtsjrmd@hotmail.com
richard.t.scott@yale.edu



THE FOUNDATION FOR EMBRYONIC COMPETENCE
ADVANCING KNOWLEDGE. ENHANCING OUTCOMES

Yale University School of Medicine

UofSC SCHOOL OF MEDICINE GREENVILLE



Disclosure

None

I have no interest in any PGT-A provider at any level.

Cover of Contemporary Ob Gyn; July 2014

Why is PGT-A 2.0 treated as one thing?

The assay used by the FEC would be termed PGT-A 9.0

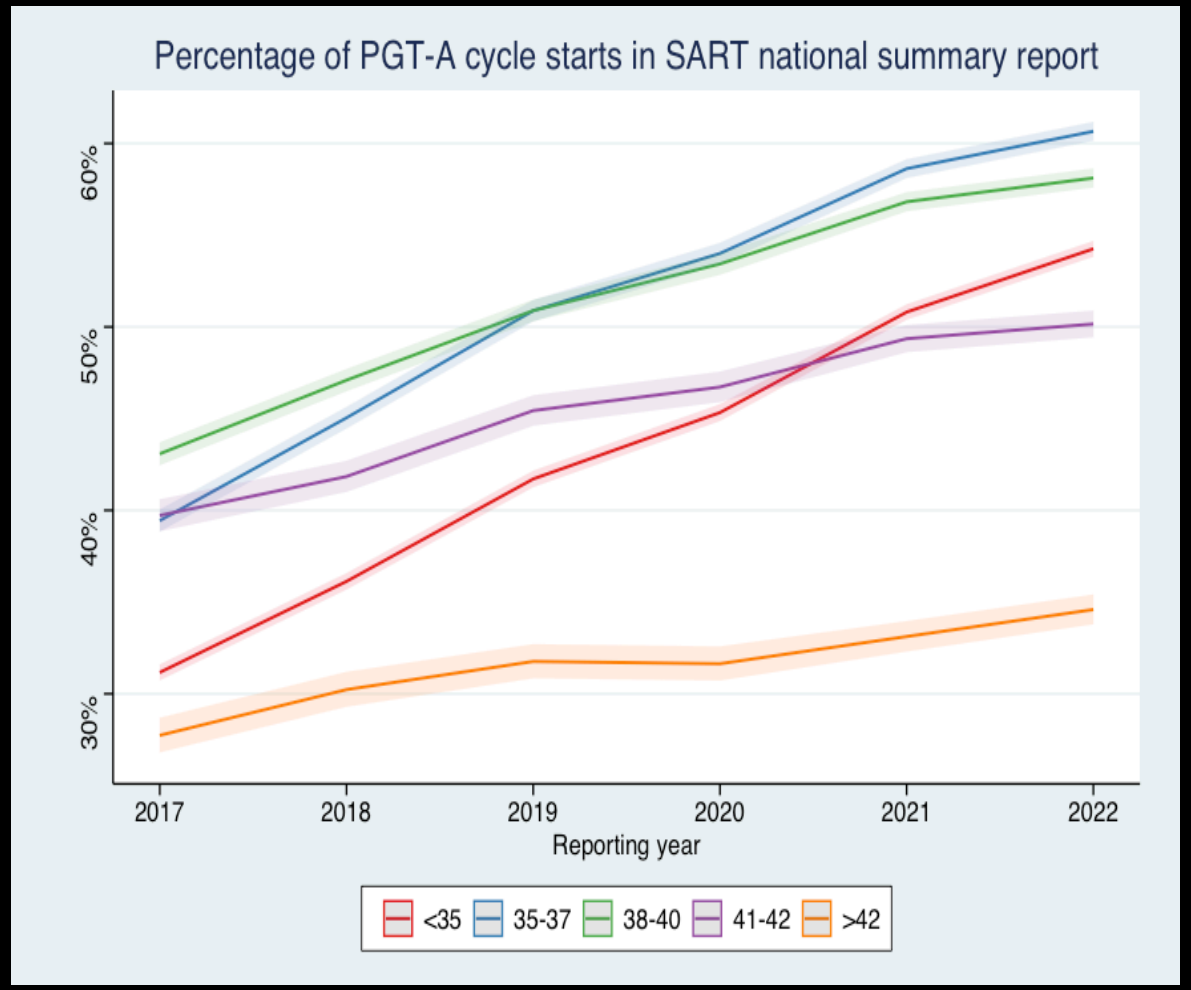
Others might be PGT 3.0 to 8.0

- Is there another clinical problem where all diagnostic screening paradigms are considered equivalent?
  - Of course not..

- Breast cancer
- Colon cancer
- Atherosclerotic heart disease

- The technologies lumped together for PGT-A 2.0 are vastly different in their safety, efficacy, and predictive values
- Each must be independently validated

PGT-A Utilization in the USA



- Clearly increasing as clinical experience increases
- Physicians see higher implantation rates
- ***No way they can know if they are discarding competent embryos***
  - ***MD's generally thankful that patients not subjected to a futile or pregnancy loss cycle***

Kalafan and Scott – in review 2024

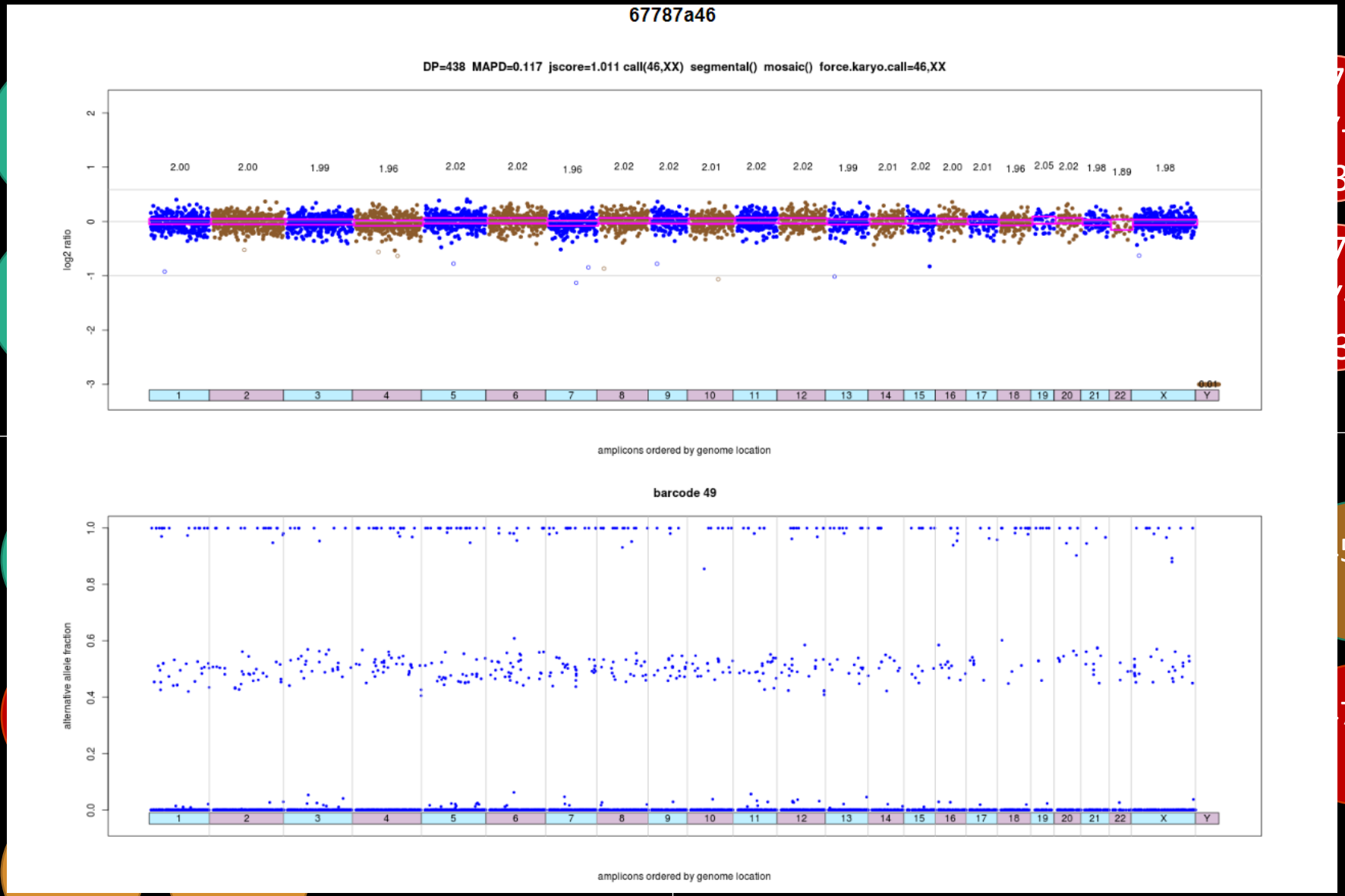
What is the GOAL of PGT-A?

A stringent definition of success is necessary for adequate validation of any embryo diagnostic

Sustained Implantation Rate is the only thing that counts

Everything is indexed per embryo – not per patient

TE Biopsies: What result would a perfect analytical platform provide (quantitative)



46, XX

46, XX

47, XY+ 13

47, XY+ 13

46, XX

47, XX+ 13

45, XX -13

-13

-13

45,XX -4

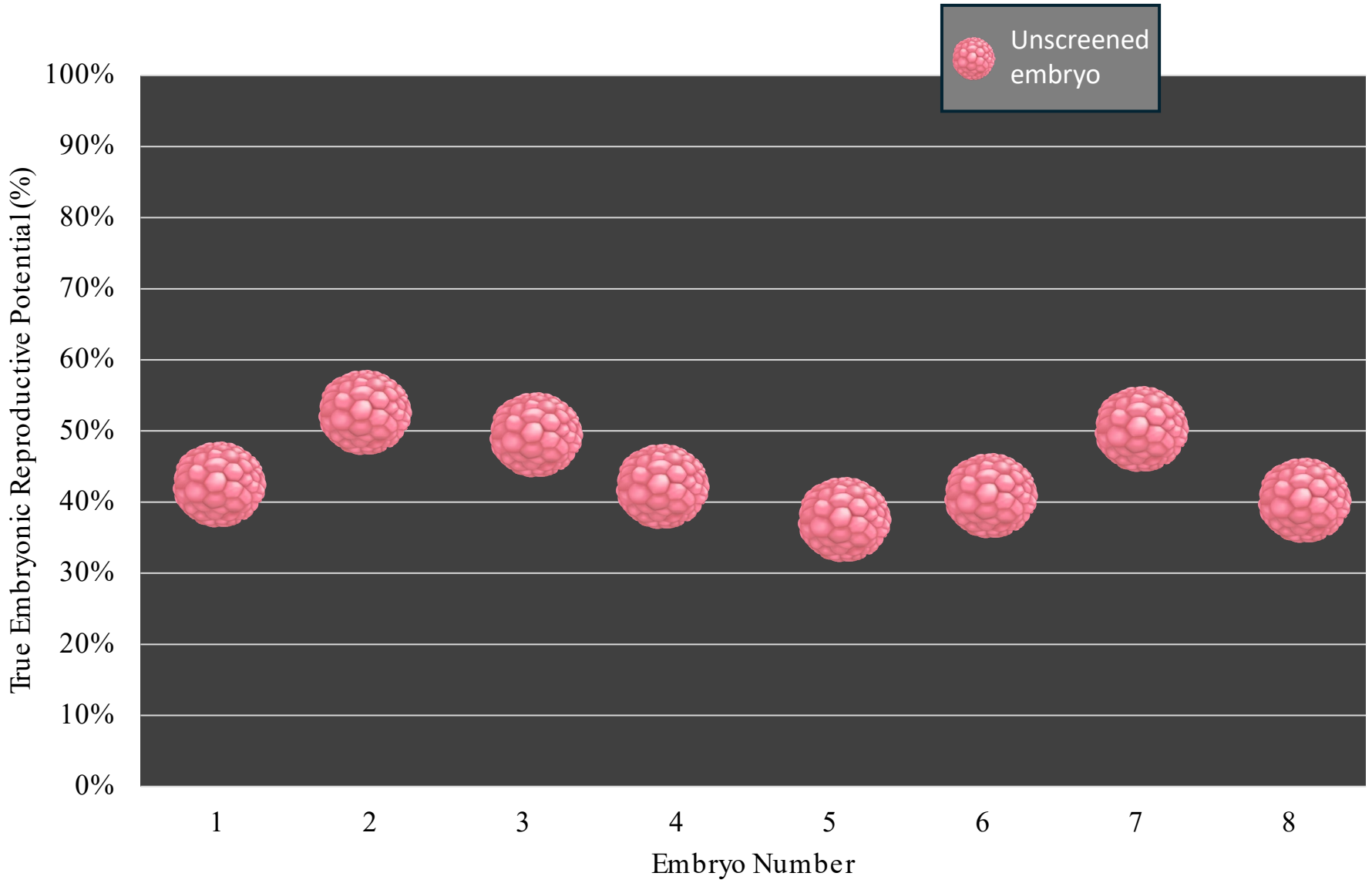
45,XX -4

47,XX +4

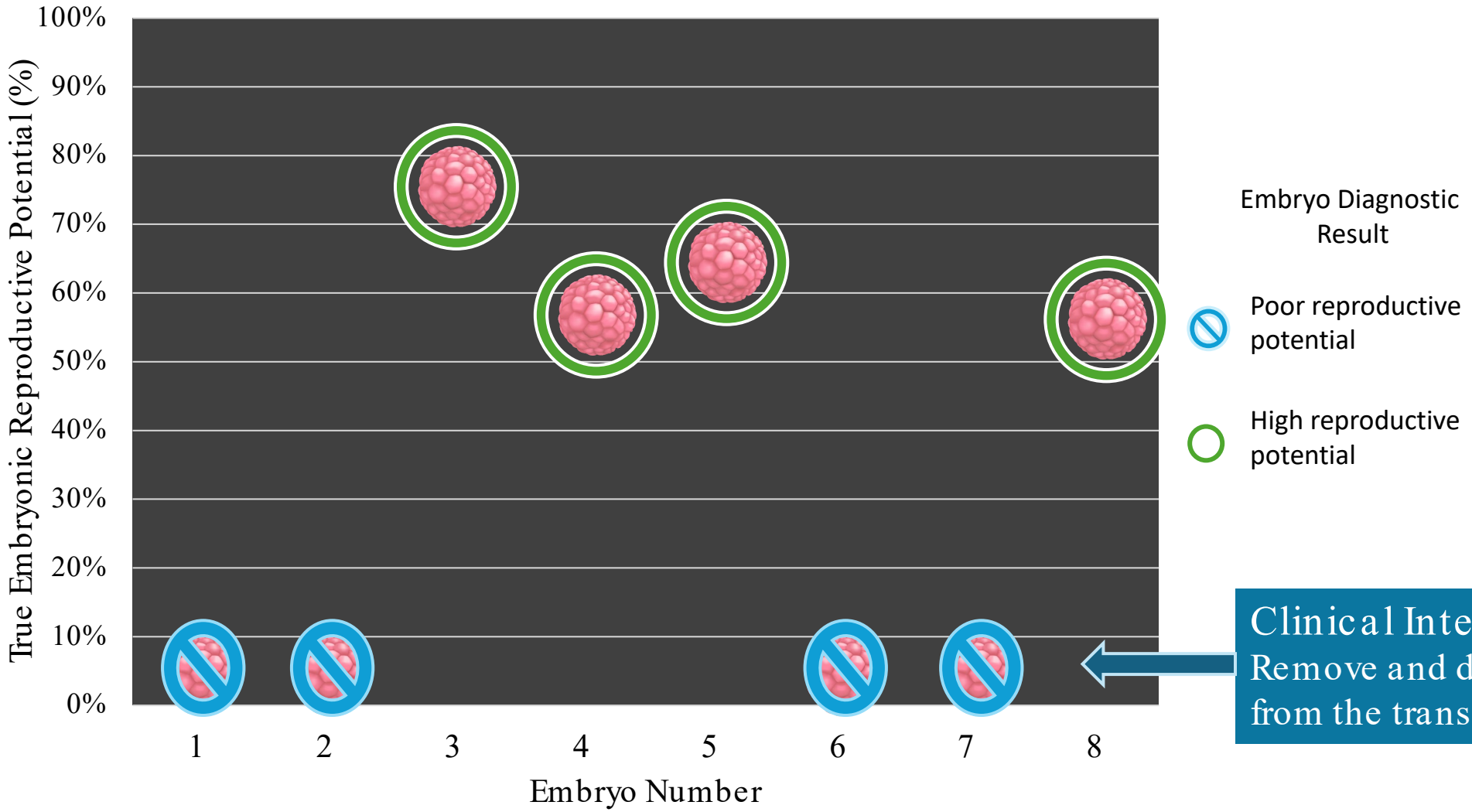
47,XX +4

Making the Case for Embryo Diagnostics

Blastocyst implantation rates based on morphology



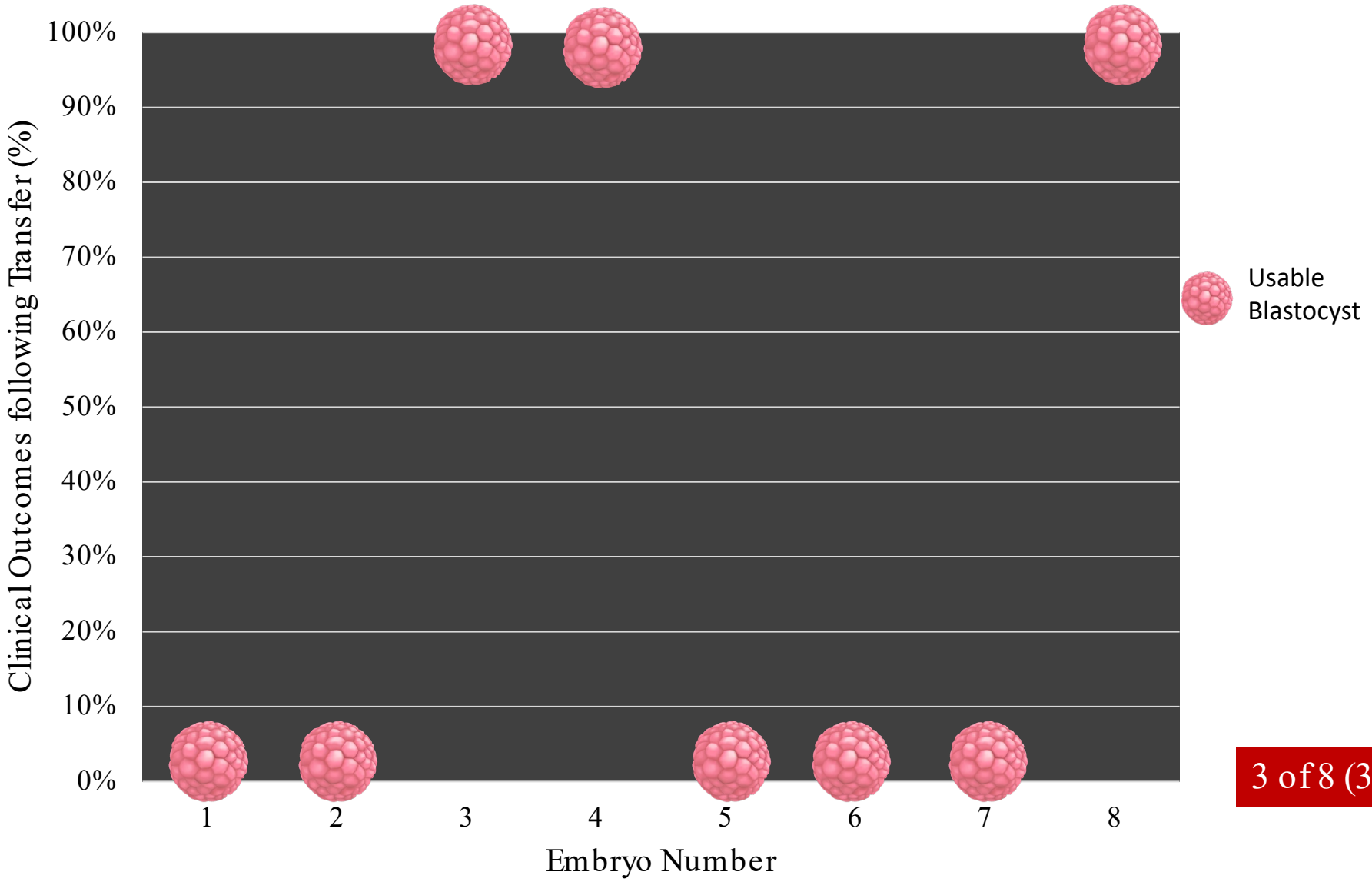
Blastocyst Reproductive Potential –
Application of an Embryo Diagnostic / Prognostic



Clinical Intervention
Remove and discard these embryos from the transferrable pool

Blastocyst Reproductive Potential

The True State of Nature if Everyone Embryo were Transferred



3 succeed
8 total

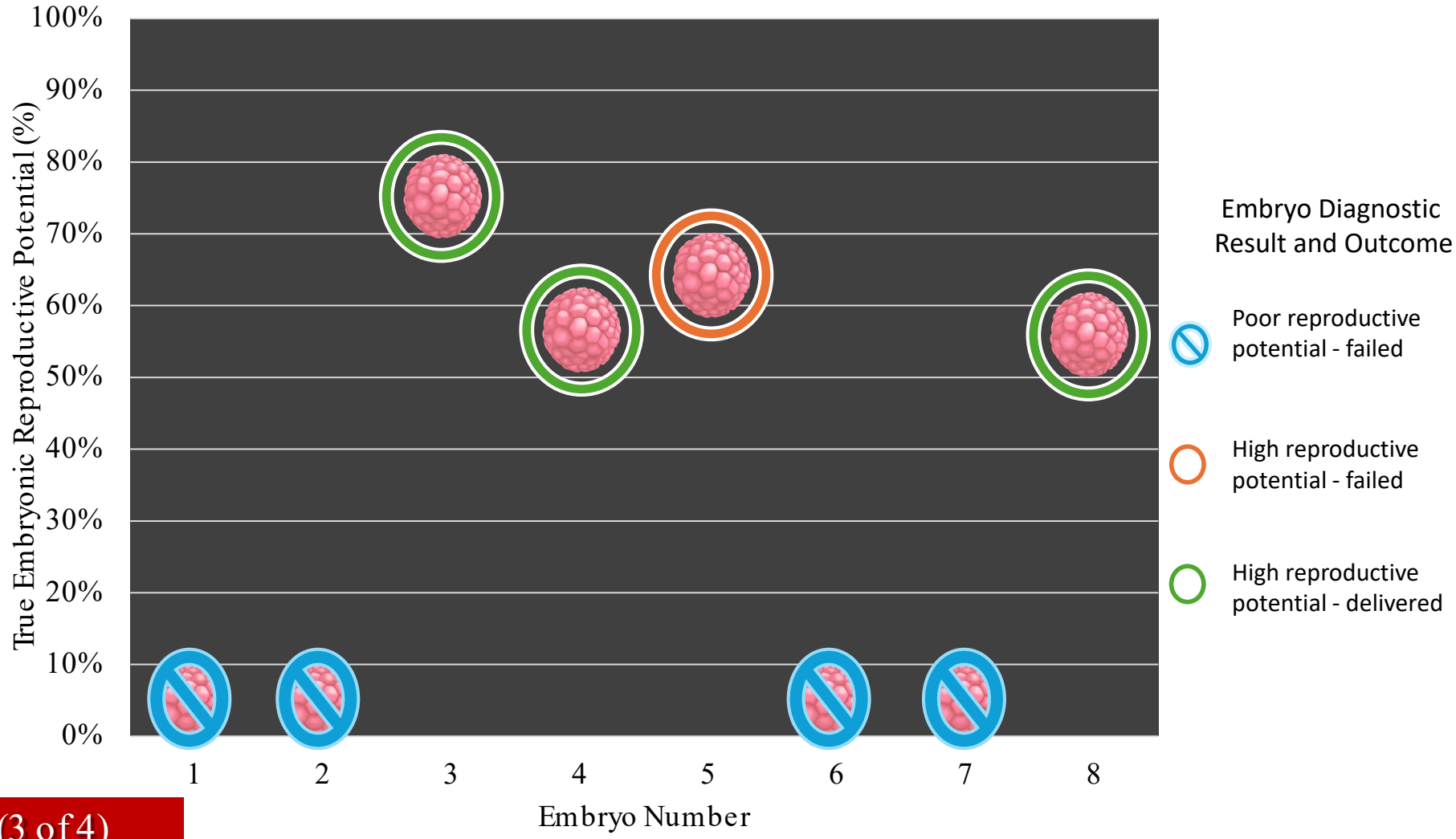
3 of 8 (37.5%) deliver

Blastocyst Selection
What if you discard a competent embryo from the transferrable pool?

3 succeed
8 total

Remove 4 from
the denominator

3 succeed
4 total



After screening, 75% (3 of 4)
in transferrable pool will deliver

Major Teaching Point

PGT-A works by taking embryos with zero or near zero reproductive potential out of the transferrable pool.

It does not identify which embryos are specifically capable of sustained implantation

What is a Predictive Vale or Non-Selection Study

BLINDED

BIOPSIES (OR SAMPLES) COLLECTED AND CRYOPRESERVED WITHOUT ANALYSIS

ALL CLINICAL CARE PROVIDED

CLINICAL OUTCOME DETERMINED

SAMPLES ANALYZED

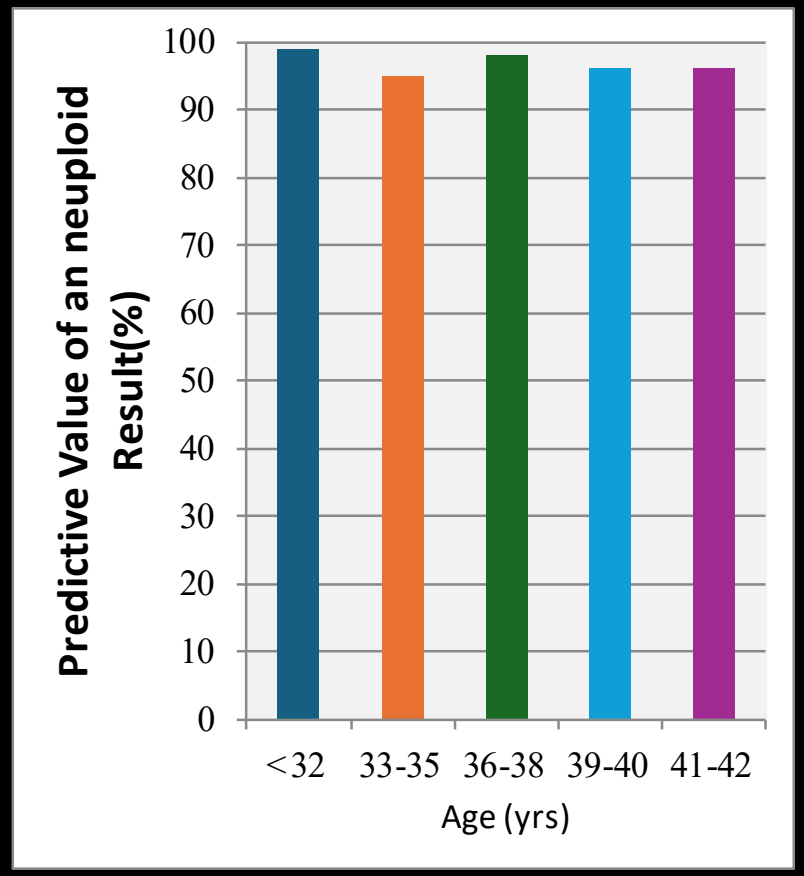
PREDICTIVE VALUES CALCULATED

One Step At A Time

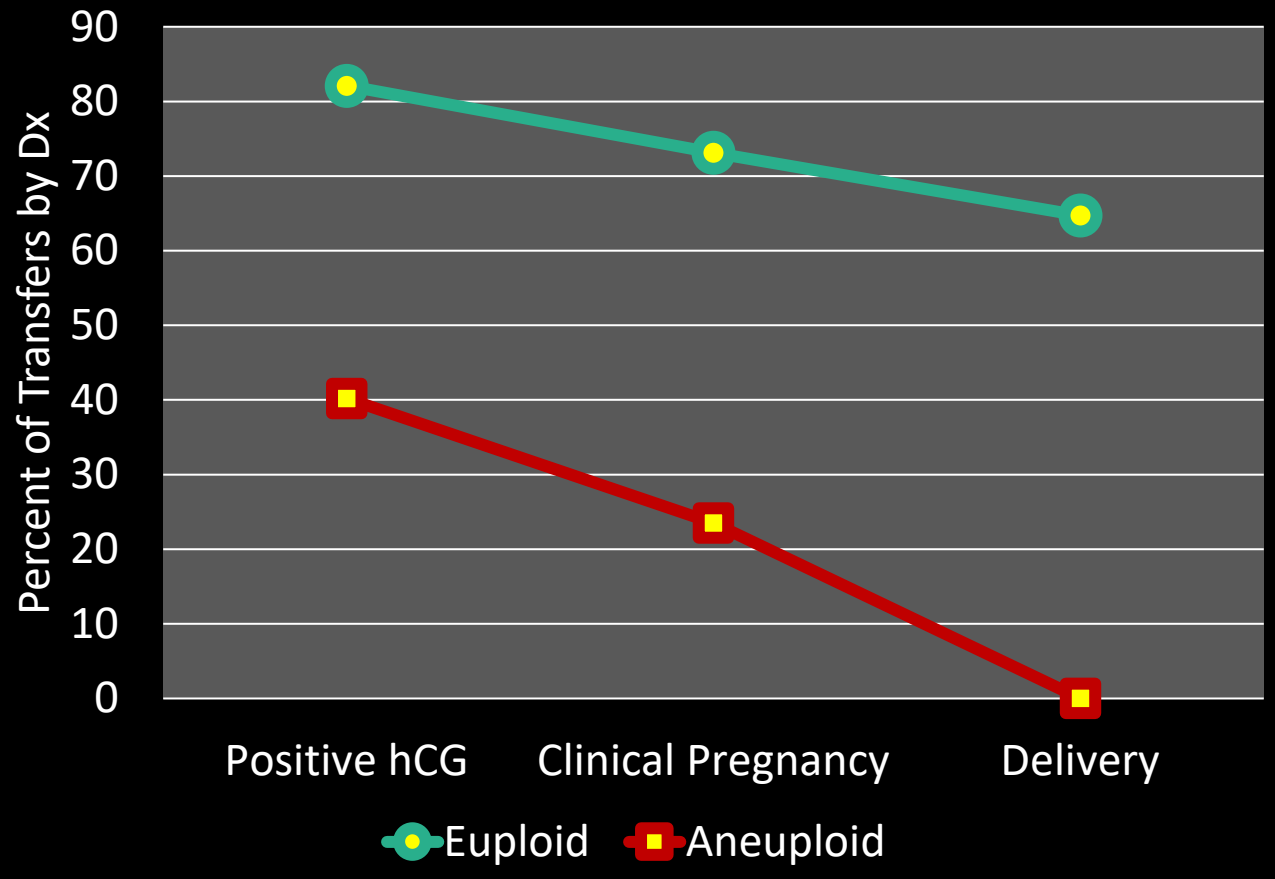
What Do you Learn from a Predictive Value Study?

- Predictive Value of an Abnormal Result
- Predictive Value of a Normal Result
- Estimation of transfer rate for chromosomally abnormal embryos
- Calculation of age specific changes in clinical outcomes

Non-Selection Studies utilizing PGT-A



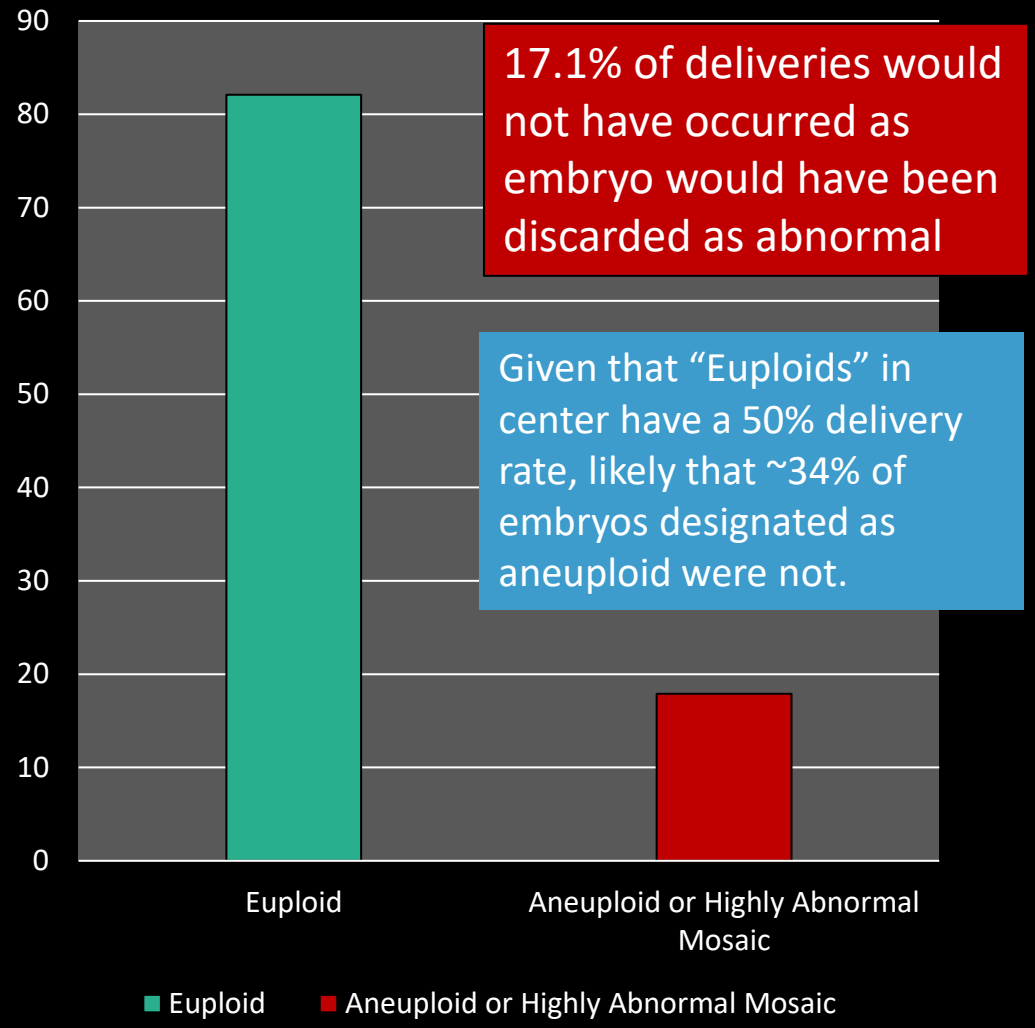
Scott *et al Fertil Steril* 2012; 97:870-5



Adapted from Tiegs et al Fertil Steril 2021

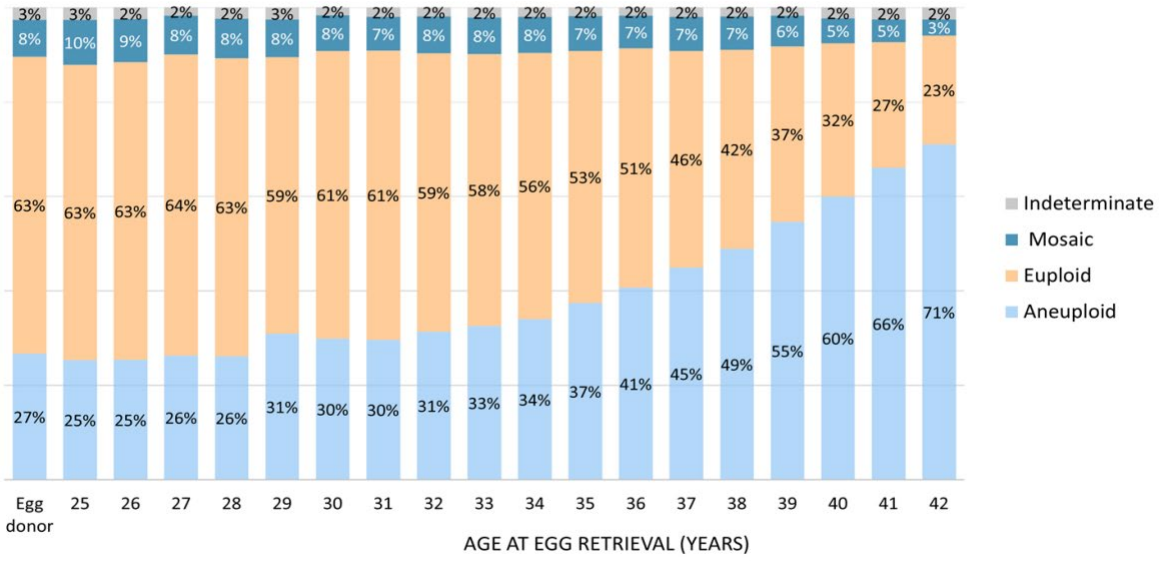
PGT-A using prior samples from embryos undergoing PGT-M using MDA based amplification

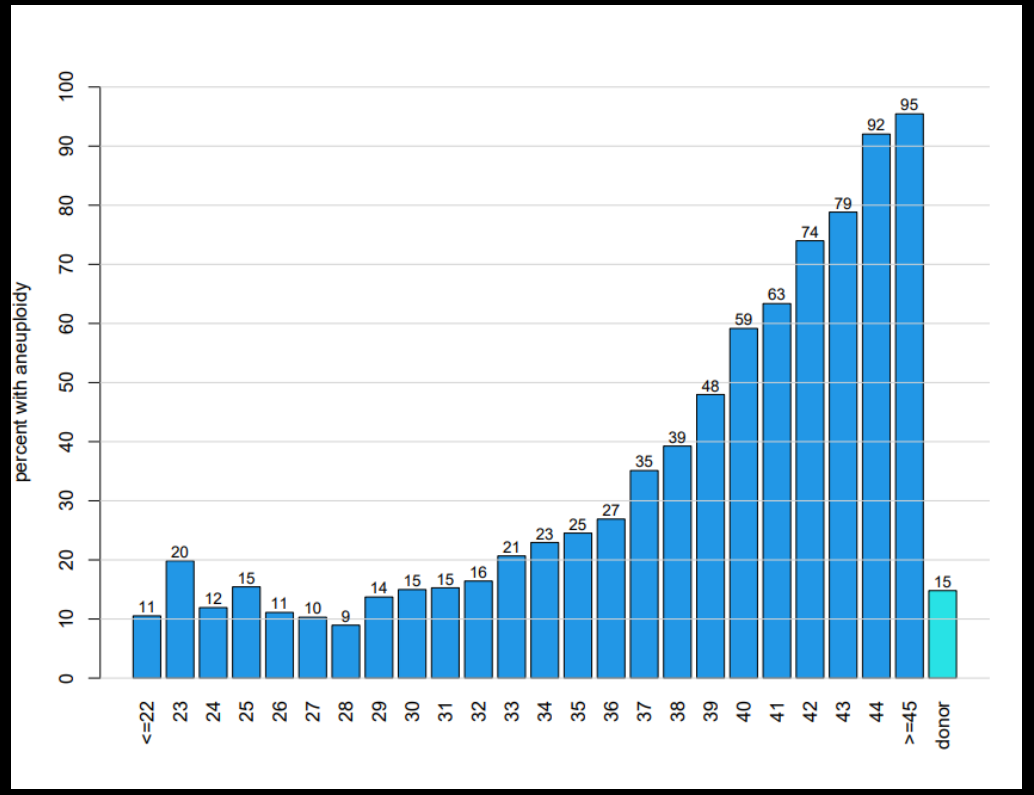
- Not a true non-selection study – but very close
- Only considered those embryos with clinical implantation
- All had initially done PGT-M using MDA for WGA
- Went back and did the math on the amplification and aligned data
- Still allows the ability to look at the presence of meiotic aneuploidy calls amongst live born infants



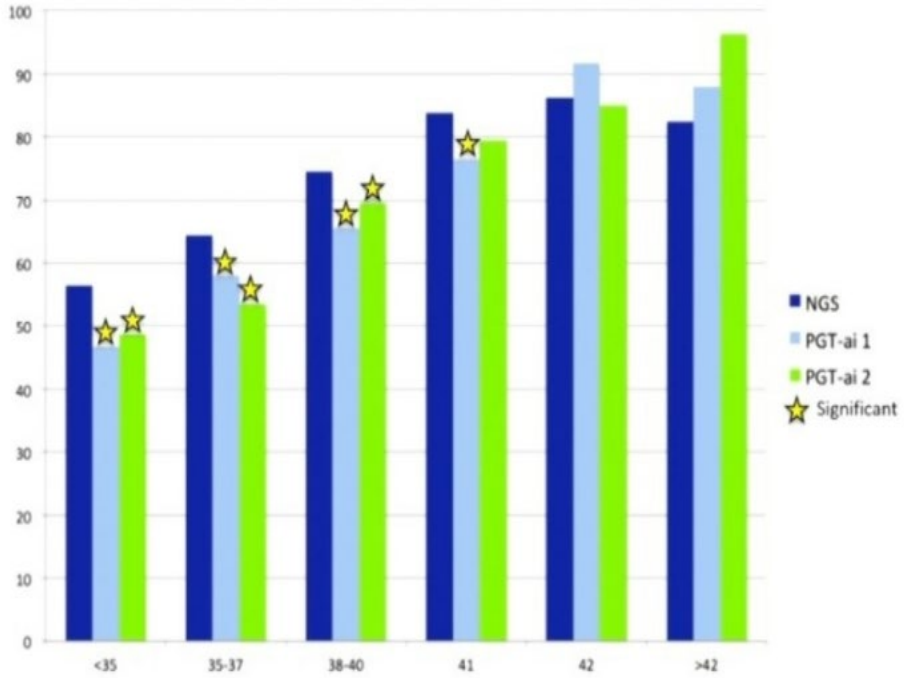
Shen et al JARG 2022; 39: 1323-31

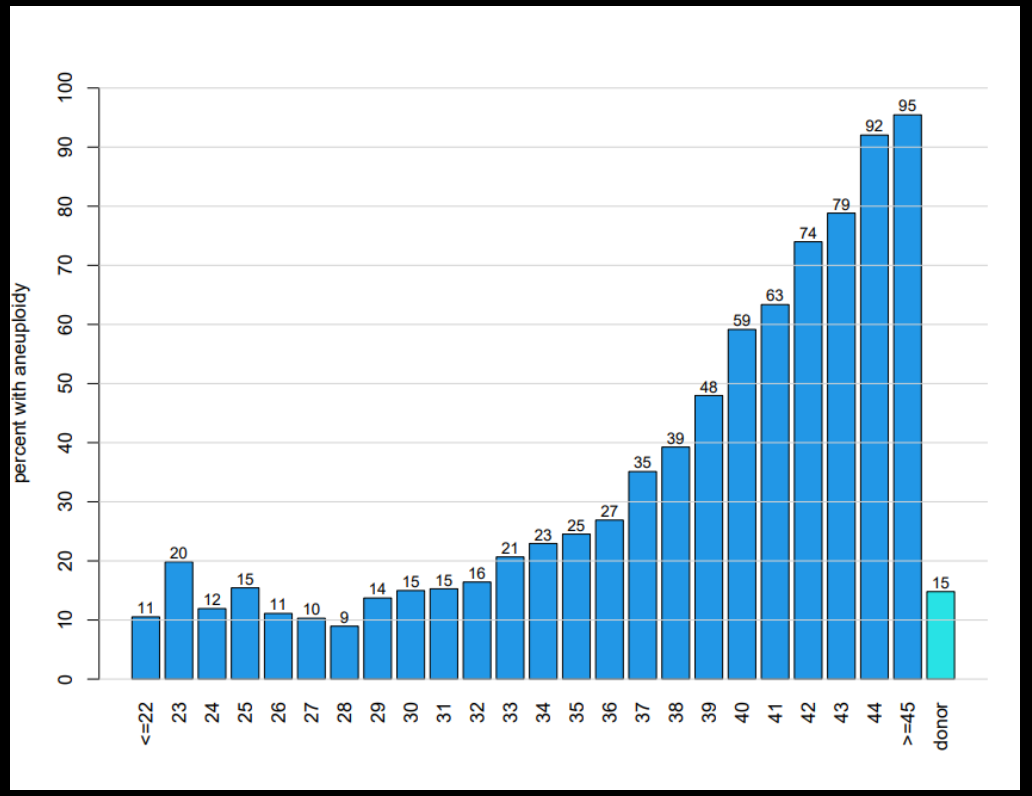
ANEUPLOIDY IN EMBRYOS BY AGE AT EGG RETRIEVAL

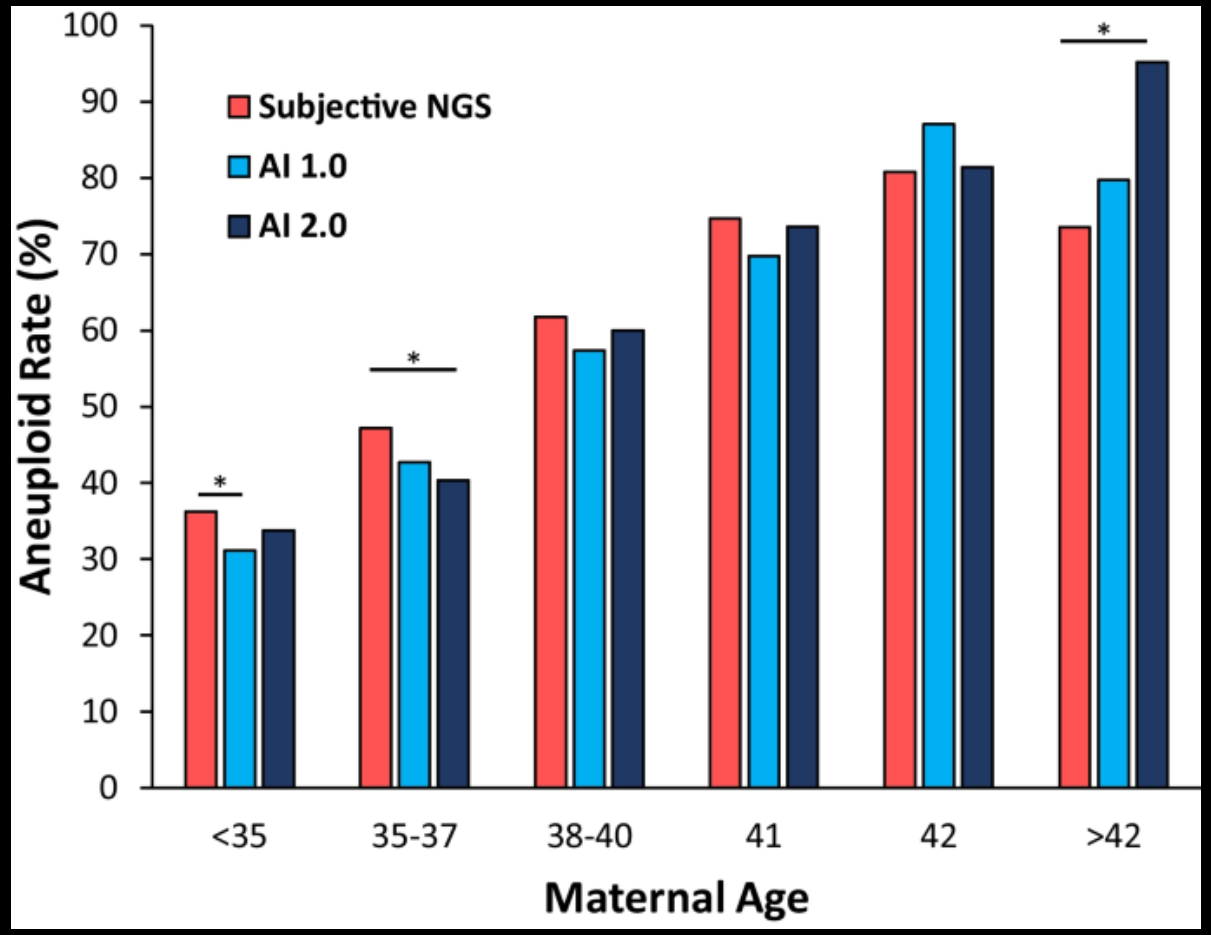


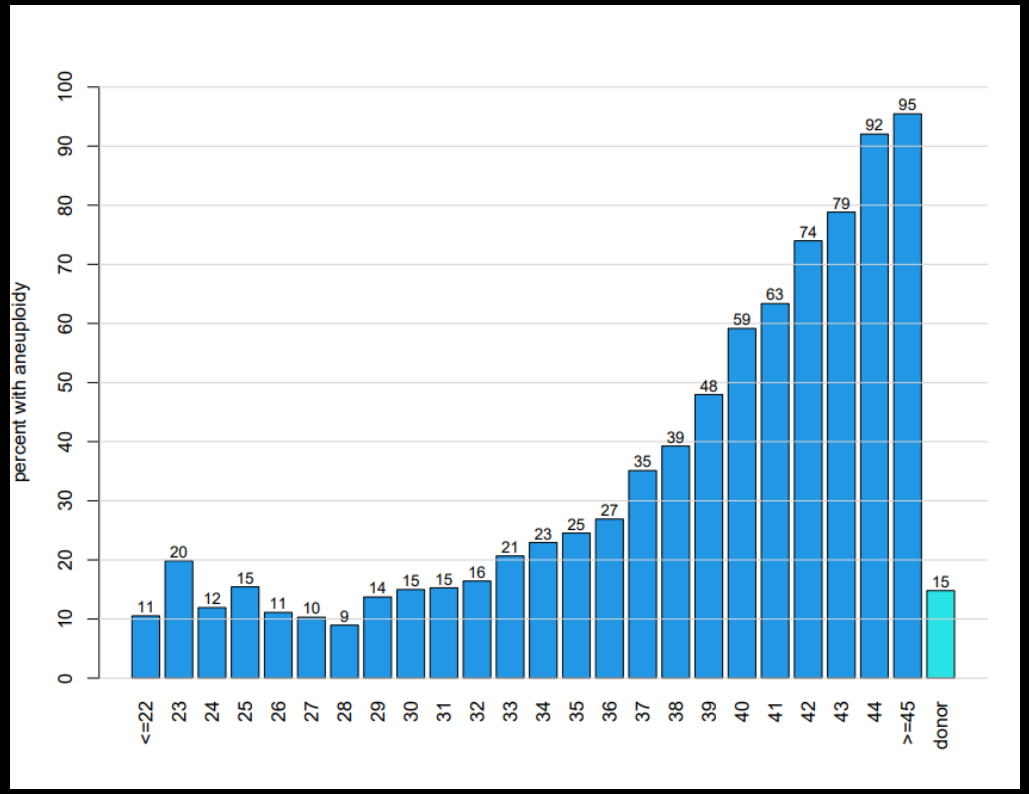


Primary Outcomes: % Aneuploid





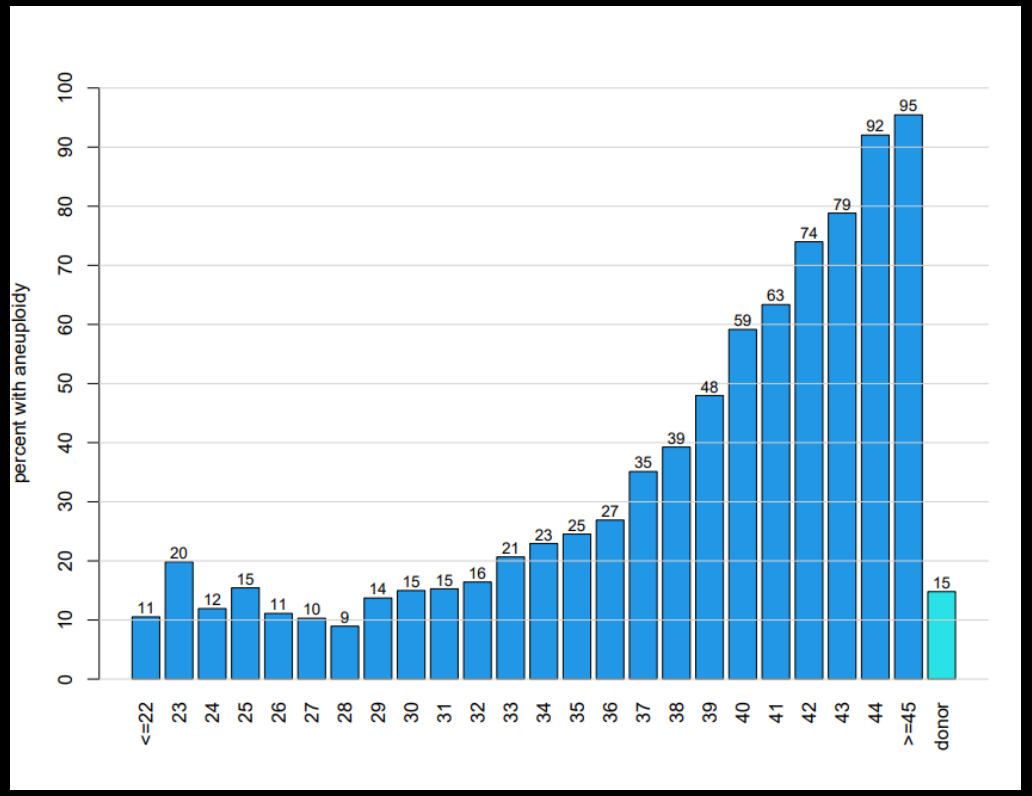

Subjective NGS
AI 1.0
AI 2.0
Aneuploid Rate (%)
100
90
80
70
60
50
40
30
20
10
0
*
*
*
<35
35-37
38-40
41
42
>42
Maternal Age

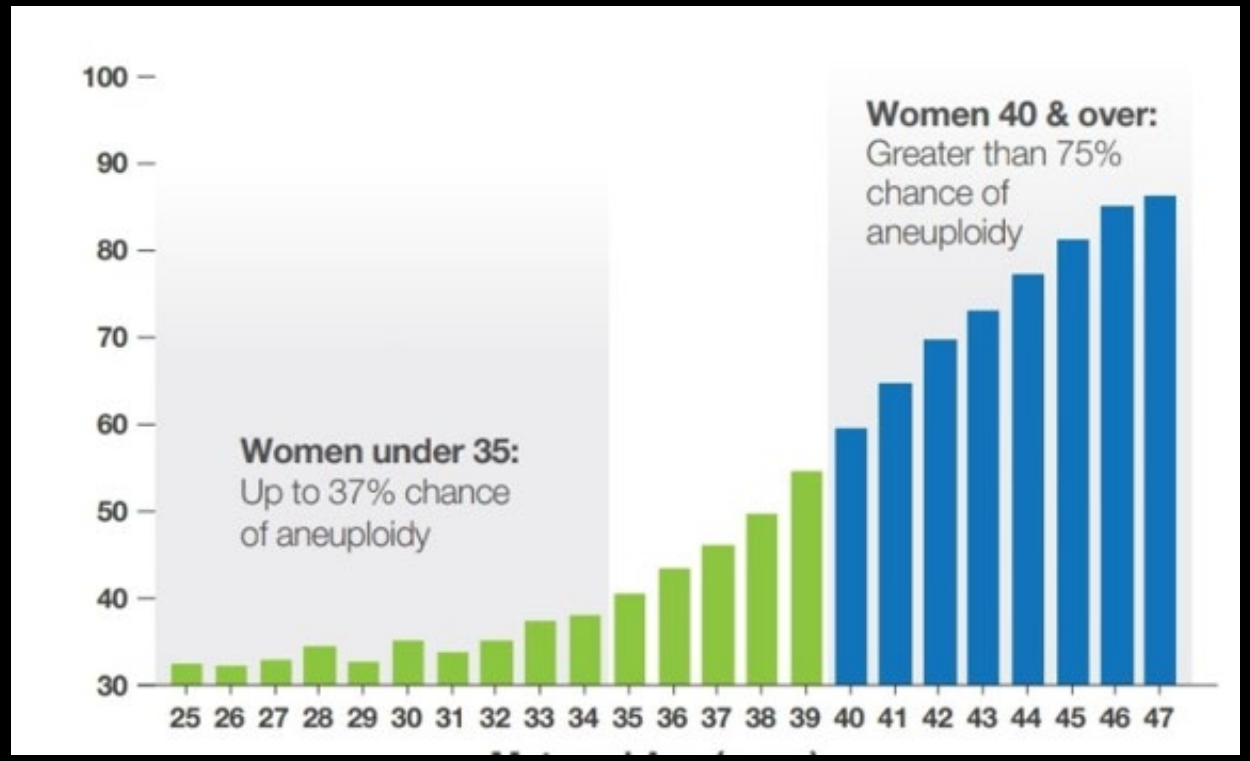

percent with aneuploidy
0
10
20
30
40
50
60
70
80
90
100
11
20
12
15
11
10
9
14
15
15
16
21
23
25
27
35
39
48
59
63
74
79
92
95
15
<=22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
>=45
donor

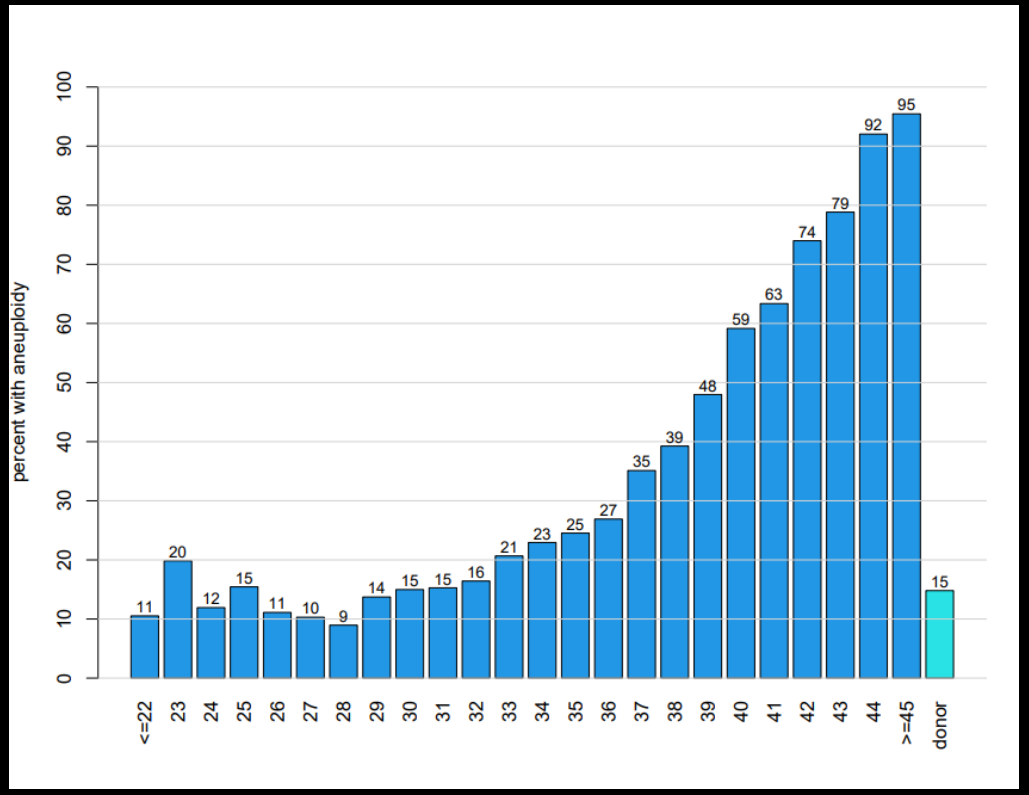
Maternal age and aneuploidy

Percentage of embryos with an abnormal number of chromosomes

Adapted from internal data; 2018.




100
90
80
70
60
50
40
30
Women 40 & over:
Greater than 75%
chance of
aneuploidy
Women under 35:
Up to 37% chance
of aneuploidy
25 26 27 28 29 30 31 32 33 34 35 36 37 38 39 40 41 42 43 44 45 46 47


percent with aneuploidy
0 10 20 30 40 50 60 70 80 90 100
11 20 12 15 11 10 9 14 15 15 16 21 23 25 27 35 39 48 59 63 74 79 92 95 15
<=22 23 24 25 26 27 28 29 30 31 32 33 34 35 36 37 38 39 40 41 42 43 44 >=45 donor

ARTICLE IN PRESS

ORIGINAL ARTICLE: ASSISTED REPRODUCTION

Reproductive genetics laboratory may impact euploid blastocyst and live birth rates: a comparison of 4 national laboratories' PGT-A results from vitrified donor oocytes

Jonah Bardos, M.D., M.B.E.,[a,b] Jaclyn Kwal, M.D.,[c] Wayne Caswell, M.S.,[d] Samad Jahandideh, Ph.D.,[e] Melissa Stratton, B.S.,[d] Michael Tucker, Ph.D.,[e] Alan Decherney, M.D.,[a] Kae Devine, M.D.,[e] Micah Hill, D.O.,[b] and Jeanne E. O'Brien, M.D., M.Sc.[d]

[a] National Institutes of Health, Bethesda, Maryland; [b] Walter Reed National Military Medical Center, Bethesda, Maryland; [c] Department of Obstetrics and Gynecology, University of Miami Miller School of Medicine, Miami, Florida; [d] Donor Egg Bank USA, Rockville, Maryland; and [e] Shady Grove Fertility, Rockville, Maryland

- The analytical lab matters
- No paradoxical effect of lowest aneuploidy rate also had best clinical outcomes
- The lower aneuploidy rate is not because that lab is not missing aneuploidy

TABLE 2

Biopsy results and pregnancy outcomes by laboratory

	Laboratory A	Laboratory B	Laboratory C	Laboratory D	*P* value (between 4 laboratories)	*P* Value (pairwise comparison)
Reproductive outcomes	N (%)	N (%)	N (%)	N (%)		
Euploid	661/898 (73.6%)	583/921 (63.3%)	142/233 (60.9%)	314/581 (52.3%)	<0.001	<0.001 all vs. A
Aneuploid	128/898 (14.2%)	303/921 (32.8%)	64/233 (27.4%)	184/581 (31.6%)	<0.001	<0.001 all vs. A
Mosaic	89/898 (9.9%)	26/921 (2.8%)	13/233 (5.5%)	67/581 (11.5%)	<0.001	NS
No call rate	20/898 (2.2%)	9/921 (1.0%)	14/233 (6.0%)	16/581 (2.8%)	<0.001	NS
Live birth rate	143/247 (57.8)	122/230 (53.0%)	31/67 (46.3%)	71/150 (47.3%)	0.14	0.04, A vs. D
Biochemical Pregnancy Loss rate	22/247 (8.9%)	18/230 (0.8%)	5/67 (7.5%)	11/150 (7.3%)	0.50	NS
Miscarriage rate	26/247 (10.5%)	22/230 (9.6%)	7/67 (10.4%)	17/150 (11.3%)	0.80	NS
Induced abortion	2/247 (0.8%)	2/230 (0.9%)	0/67 (0.0%)	0/150 (0.0%)	0.20	NS
Not pregnant	54/247 (21.8%)	66/230 (28.6%)	24/67 (35.8%)	51/150 (34%)	0.1	NS

NS = not significant.

Bardos. Euploidy rate varies by PGT-A lab. Fertil Steril 2022.

		Percentage of Transferred Blastocysts	Number if had 1000 Blastocysts	Observed Sustained Implantation Rate	Total Babies Delivered
PGT-A	Euploid	60.2%	602	64.7%	389
	Mosaic	3.5%	35	68.8%	27
	Segmental	8.8%	88	30.8%	24
	Aneuploid	24.6%	246	0%	0
	No Result	2.8%	28	46.6%	13
				Total =	**453**
No PGT-A		100%	1000	47.9%	**Total = 479**

How is it that Professor Paulson finds that embryos are missing? Is he wrong?

PGT-A leads to 26 (2.6%) fewer deliveries

Klimczak et al 2022

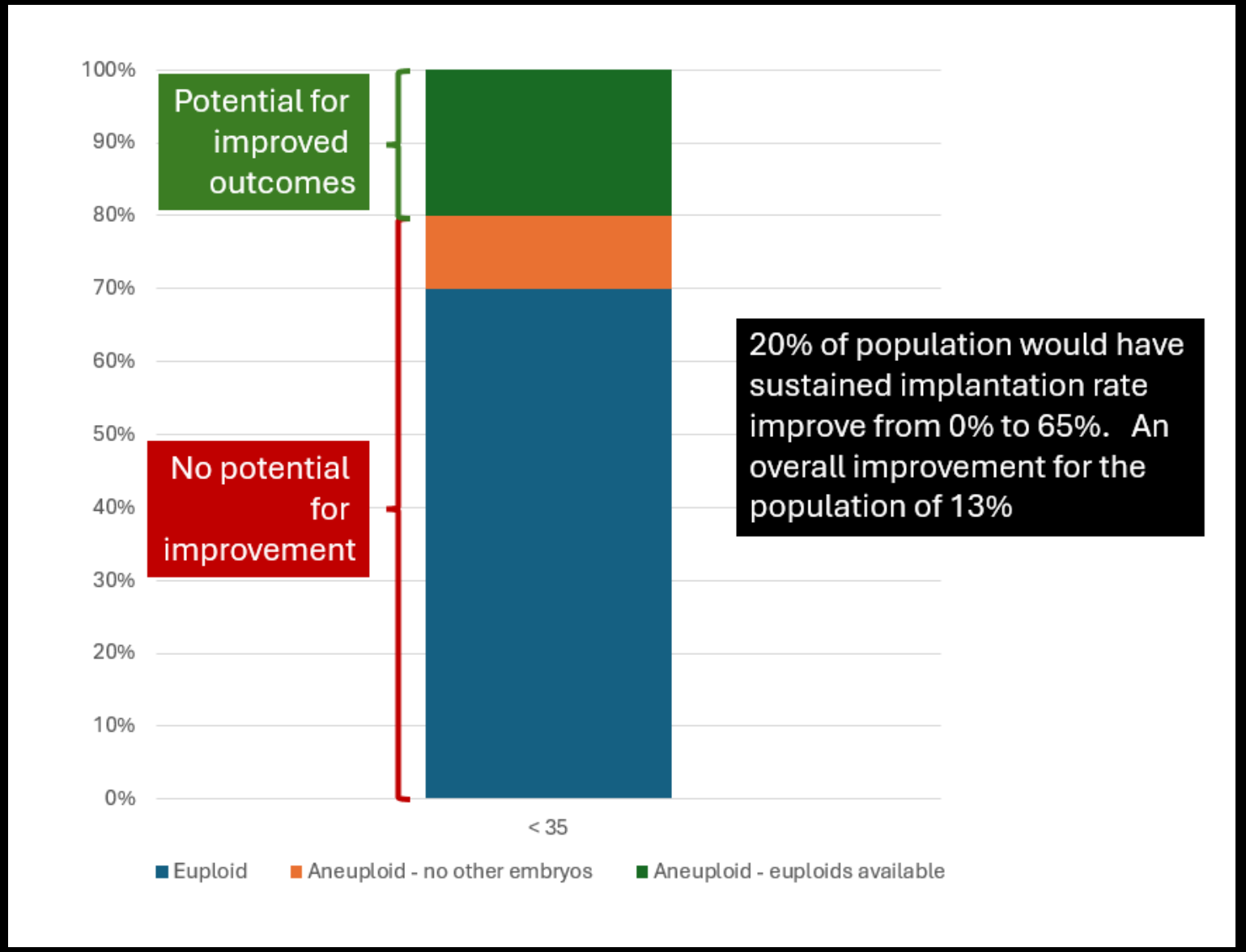
		Percentage of Transferred Blastocysts	Number if had 1000 Blastocysts	Observed Sustained Implantation Rate	Total Babies Delivered
PGT-A	Euploid	64.5%	645	64.7%	389
	Mosaic	3.3%	33	68.8%	27
	Segmental	8.1%	81	30.8%	24
	Aneuploid	21.1%	211	0%	0
	No Result	3.1%	31	46.6%	13
				Total =	**479**
No PGT-A		100%	1000	47.9%	**Total = 479**

PGT-A leads to an equivalent number of deliveries

Klimczak et al 2022

When should we do PGT-A?

Calculating the Putative Benefit



The lawsuit

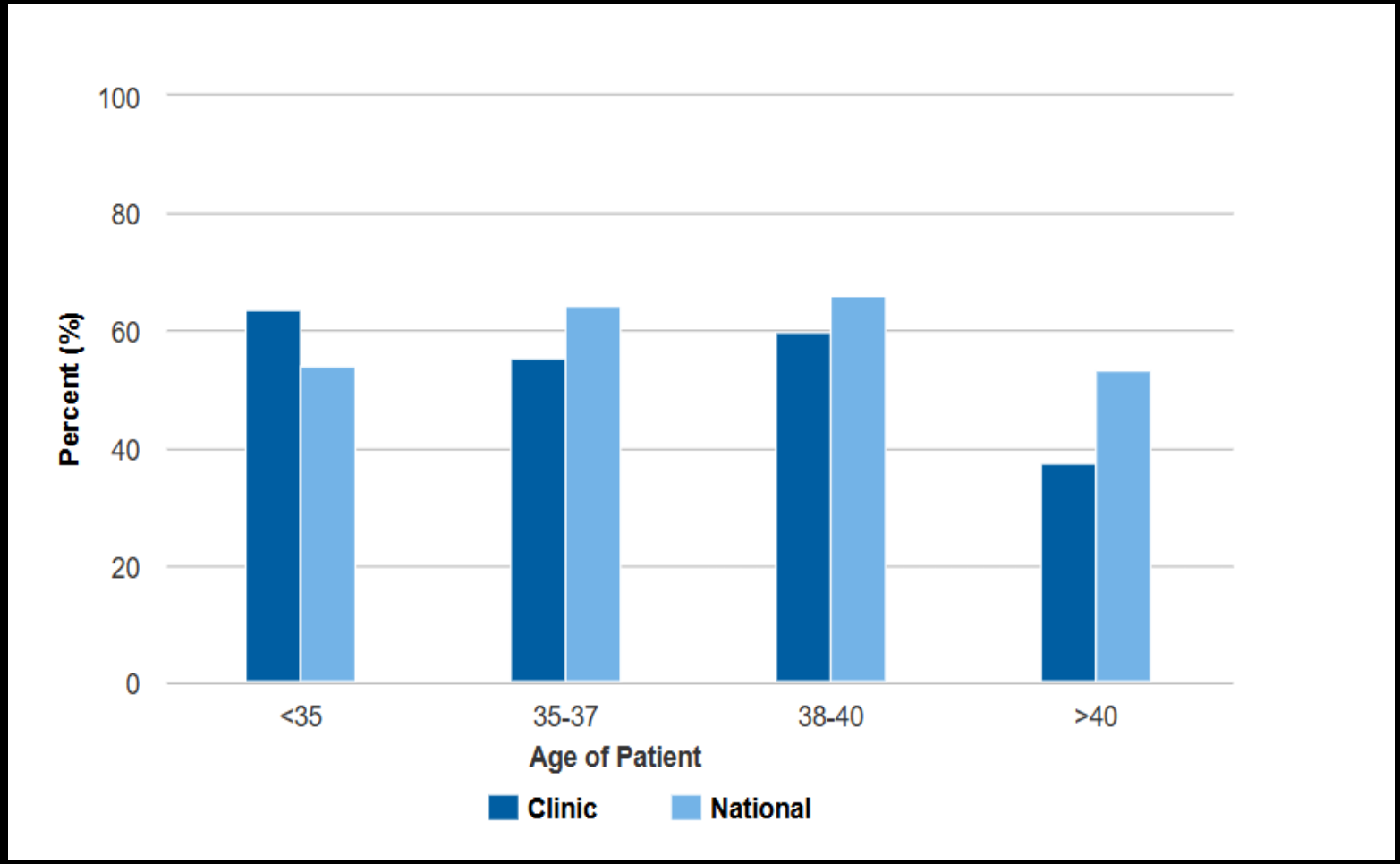
- How do you counsel your patients about the risks of clinical PGT-A?

- Many of us will have an opportunity to answer that question in a very serious way….

PGT Utilization at USC Fertility

What does Professor Paulson actually think about PGT-A?

Actions speak louder than words…



March 20, 2025; https://art.cdc.gov/

Thank you to those who did much of this research..

Thank you…

- It is a privilege to have the opportunity to attend this meeting

  and to debate
  Rick Paulson….