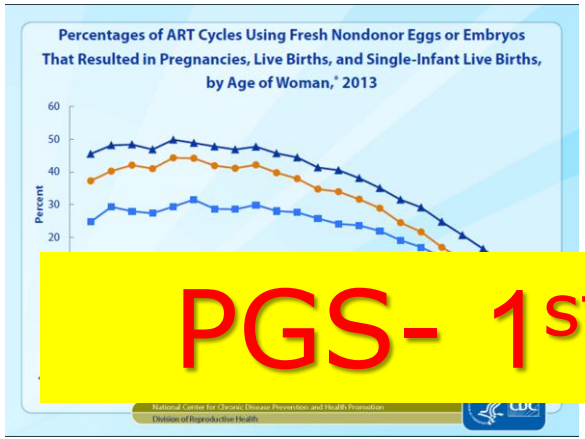
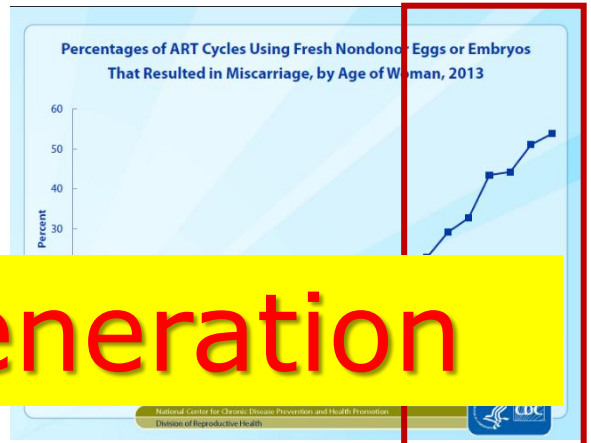
PGT CANNOT ADD TO THE MANAGEMENT OF INFERTILE COUPLES

Raoul Orvieto M.D.
Department of Obstetrics and Gynecology, Chaim Sheba Medical Center, Ramat Gan, Israel
The Tarnesby-Tarnowski Chair for Family Planning and Fertility Regulation, Faculty of Medical and Health Science, Tel-Aviv University, Israel.

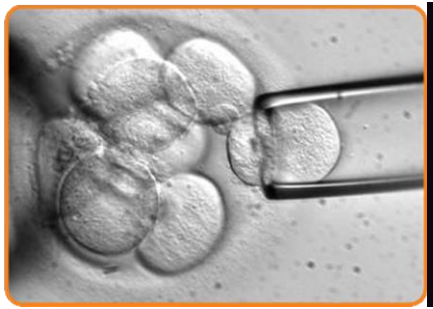
No relevant financial relationships to disclose

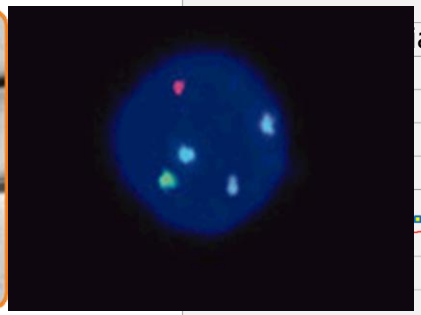




PGS- 1st generation

FISH Day3





Preimplantation genetic screening: a systematic review and meta-analysis of RCTs

S. Mastenbroek*, M. Twisk, F. van der Veen, and S. Repping

Human Reproduction Update, Vol.17, No.4 pp. 454–466, 2011

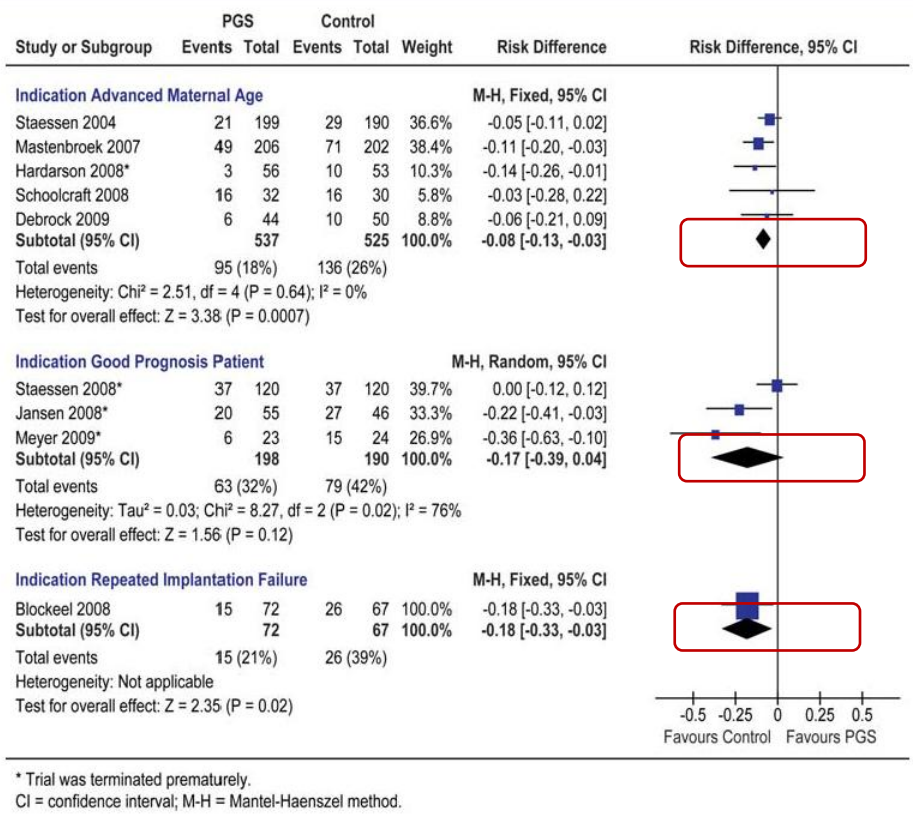
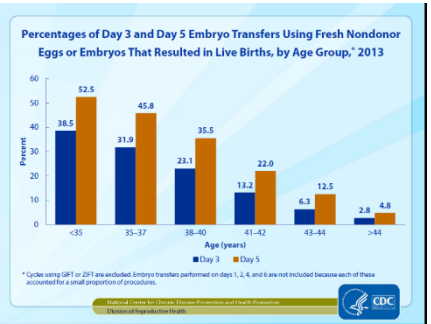


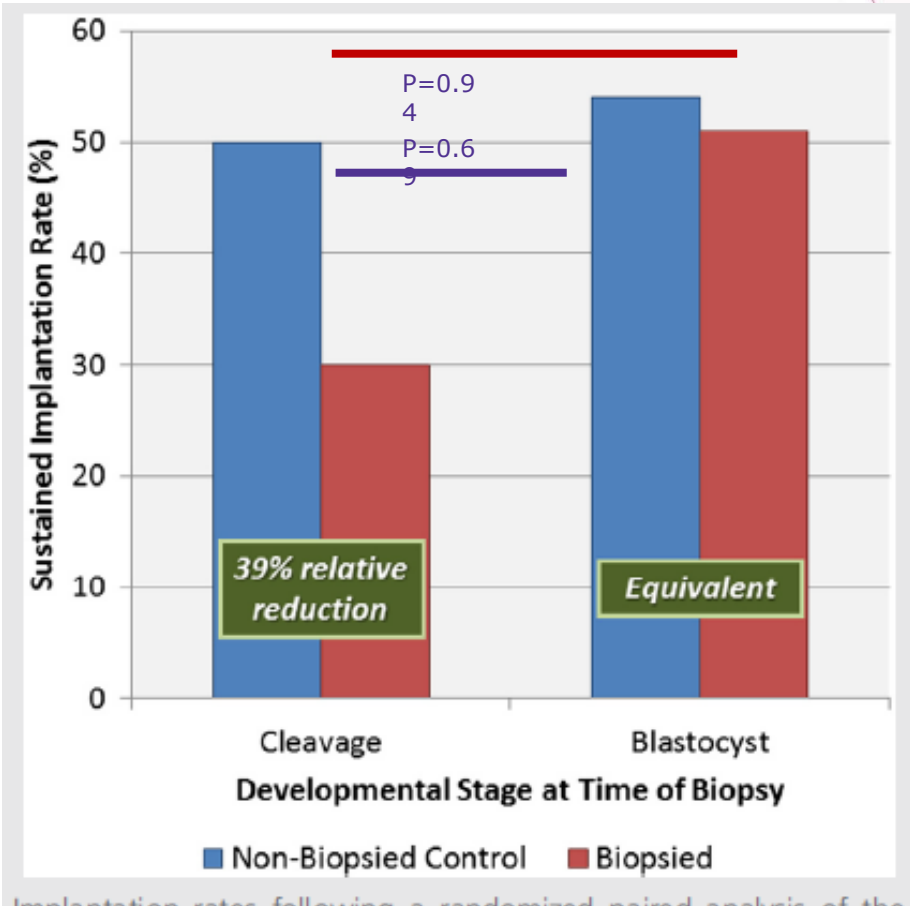
Figure 2 The effect of PGS on the live birth rate per patient.

(2013)

Cleavage-stage biopsy significantly impairs human embryonic implantation potential while blastocyst biopsy does not: a randomized and paired clinical trial

Richard T. Scott Jr., M.D.,[a,b] Kathleen M. Upham, B.S.,[a] Eric J. Forman, M.D.,[b] Tian Zhao, M.S.,[a] and Nathan R. Treff, Ph.D.[a,b,c]

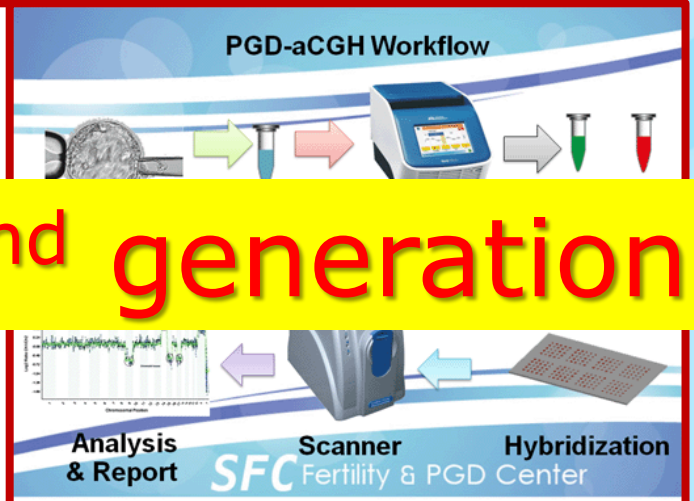




Implantation rates following a randomized paired analysis of the

Percentages of Day 3 and Day 5 Embryo Transfers Using Fresh Nondonor Eggs or Embryos That Resulted in Live Births, by Age Group,* 2013

60



PGS- 2nd generation

Age (years)

■ Day 3 ■ Day 5

* Cycles using GIFT or ZIFT are excluded. Embryo transfers performed on days 1, 2, 4, and 6 are not included because each of these accounted for a small proportion of procedures.

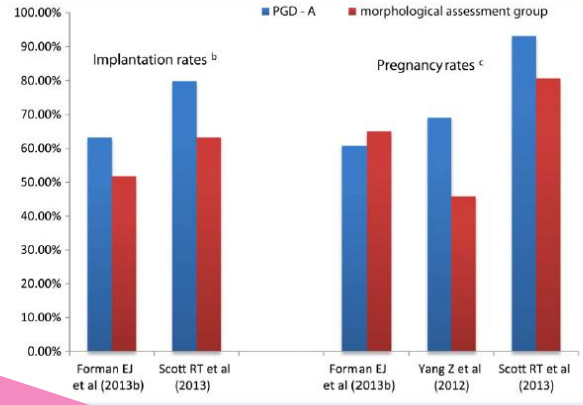
National Center for Chronic Disease Prevention and Health Promotion
Division of Reproductive Health

CDC

Human Reproduction, Vol.30, No.2 pp. 473–483, 2015

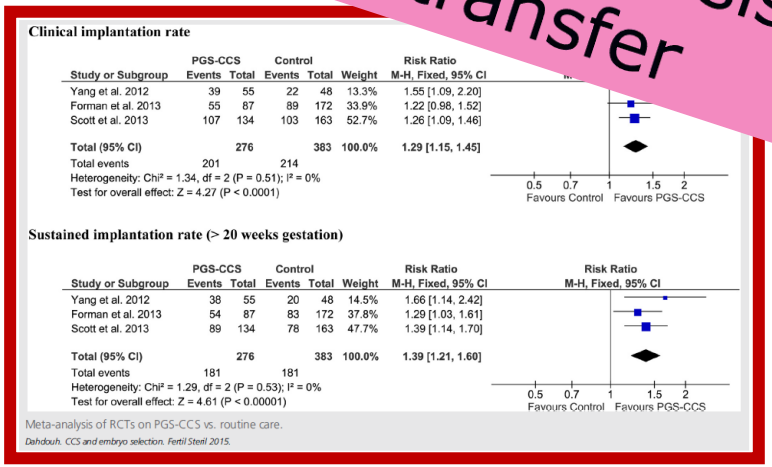
The clinical effectiveness of preimplantation genetic diagnosis for aneuploidy in all 24 chromosomes (PGD-A): systematic review

Evelyn Lee[1,*], Peter Illingworth[2], Leeanda Wilton[3], and Georgina Mary Chambers[1]



PGD-A randomized controlled trials of young patients with good prognosis[a]. [a]Data extracted from the

- Good prognosis patients
- Per transfer



Meta-analysis of RCTs on PGS-CCS vs. routine care.

Dahdouh. CCS and embryo selection. Fertil Steril 2015.

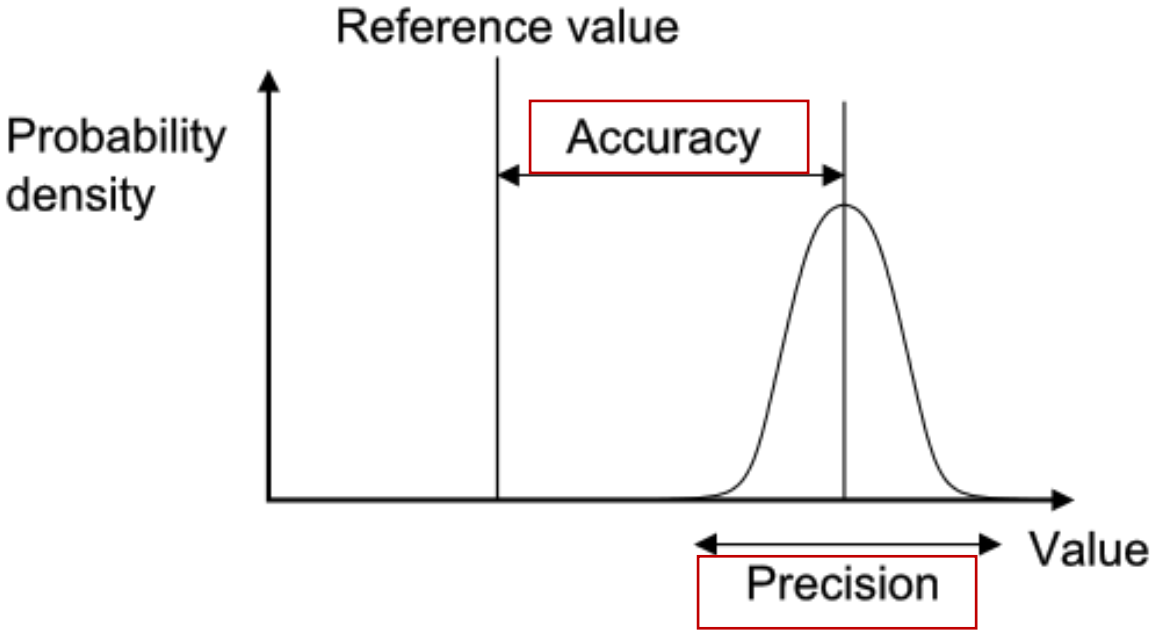
Scott (2013)-patients with two or more blastocyst were randomized
Forman (2013)-patients had to have at least two blastocysts suitable fo trophectoderm biopsy
Yang (2012)-<35yrs; Blast: 8±2

Day 5 blastocysts	8.3 ± 2.1	8.1 ± 2.4

Assumptions

- Every potentially viable embryo will develop to the blastocyst stage in vitro
- Mosaicism does not exist in embryos
- The biopsy procedure does not reduce the viability of the embryo
- Cryopreservation has no risks and does not reduce the viability of the embryo
- The testing is 100% accurate/precise without false (+)(-) results

PGS


Reference value
Probability
density
Accuracy
Value
Precision

Technical errors/ mosaicism

Should pre-implantation genetic screening be implemented to routine clinical practice?

Gynecol Endocrinol, 2016

Raoul Orvieto, Yulia Shuly, Masha Brengauz, and Baruch Feldman

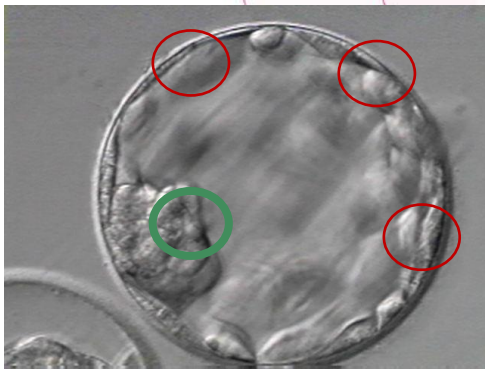


Table 1. Patients' NGS results.

Embryo number	Patient's age (yrs)	Trophectoderm biopsies 1	2	3	Biopsy of the rest of the embryo (including the inner cell mass)
1	34	Normal	Normal*	Inconclusive	-
2	31	Abnormal Trisomy 20*	Normal*	Abnormal* X0	-
3	31	Normal	Normal *	Normal	-
4	41	Normal	Abnormal Trisomy 16	Normal	-
5	32	Normal	Abnormal +5, +10, +19	Normal	Inconclusive
6	32	Normal	Normal	Inconclusive	Inconclusive
7	32	Normal	Normal	Inconclusive	Abnormal Chaotic
8	32	Abnormal Trisomy 13	Abnormal Trisomy 13*	Abnormal Trisomy 13	Abnormal Trisomy 13

*Overall noise (DLR-Derivative Log Ratio) > 0.4.
Shaded values indicate Abnormal/Inconclusive results.

10 (35.7%) of the 28 biopsies (24 trophectoderms and 4 inner cell masses) revealed mosaicism or inconclusive results.

Reanalysis of human blastocysts with different molecular genetic screening platforms reveals significant discordance in ploidy status

Drew V. Tortoriello[1] · Molina Dayal[1] · Zeki Beyhan[1] · Tahsin Yakut[2] · Levent Keskintepe[1,2]

(2016)

37 blastocyst-stage abnormal embryos from eight patients underwent re-biopsy.

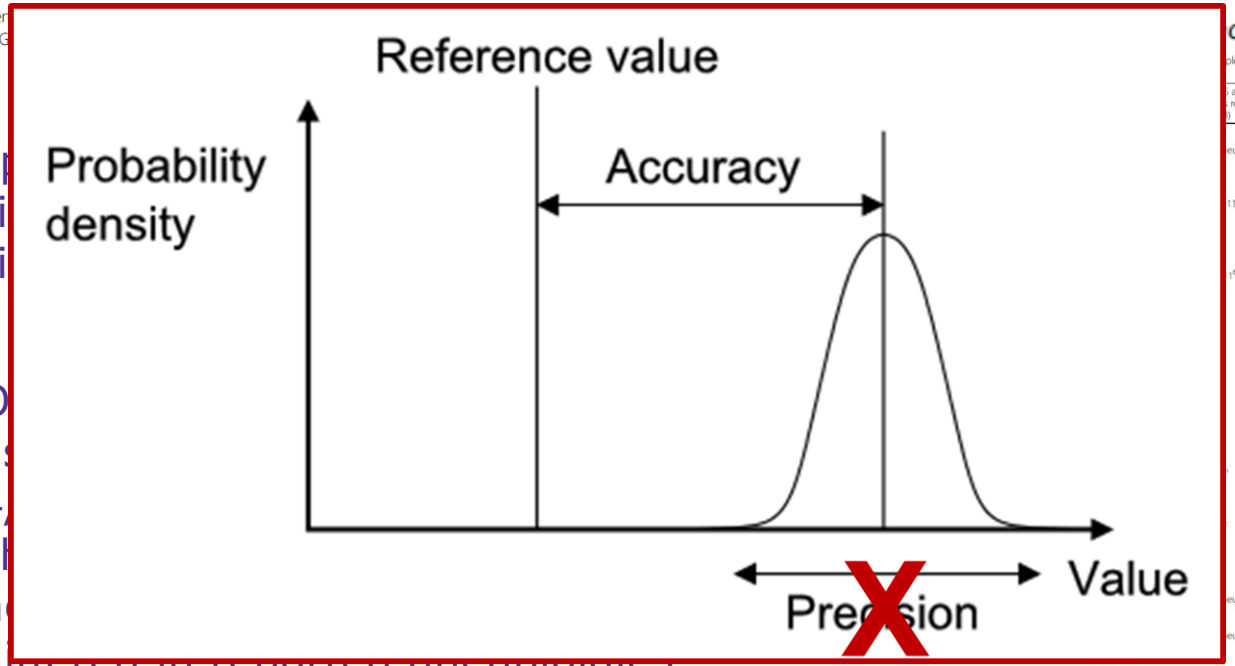
4 embryos were initially analyzed by aCGH then with SNP array; 6 of them were initially with SNP array then NGS; 27 of them were initially analyze by aCGH then with NGS.

9/27 (33 %) of embryos originally reported to be aneuploid, upon repeat assessment, were found to be euploid.

Embryo ID	Biopsy #	Sample #1	Gender	Original Testing	Sample #2	Gender	Repeat testing
SH-1-2	2	Tri 18	XY	aCGH	NL	XY	NGS
SH-1-8	2	Tri 21	XX	aCGH	NL	XX	NGS
SH-1-15	2	Mono 18	XX	aCGH	NL	XX	NGS
SH-2-1	2	Tri 16	XXY	aCGH	Tri 16	XY	NGS
SH-2-8	2	Tri 15, 17	XY	aCGH	Tri 15	XY	NGS
SH-3-1	2	Mono 21, Tri 13	XX	aCGH	NL	XX	NGS
SH-3-2	2	Tri 15, 18	XY	aCGH	NL	XY	NGS
SH-4-18	2	Mono 4	XX	SNP a	Mono 4	XX	NGS
SH-4-19	2	Tri 1	XY	SNP a	Tri 1	XY	NGS
SH-5-1	2	Mono 12	XX	aCGH	NL	XX	SNP a
SH-5-2	2	Tri 9, 13, 14, 17	XX	aCGH	NL	XX	SNP a
SH-5-4	2	No Result	N/A	aCGH	No Result	N/A	SNP a
SH-5-6	2	Tri 2, 20	XY	aCGH	NL	XY	SNP a
SH-6-2	2	Mono 21	XY	aCGH	Mono 21	XY	NGS
SH-6-4	2	Tri 9, 13	XY	aCGH	Tri 13	XY	NGS
SH-6-7	2	Mono 3, Tri 20, 21	XY	aCGH	NL	XY	NGS
SH-6-12	2	Partial Mono 18	XX	aCGH	Complex ABN	XX	NGS
SH-6-13	2	Tri XXY	XXY	aCGH	NL	XY	NGS
SH-6-15	2	Mono 7, 20	XY	aCGH	Tri 7, 20	XY	NGS
SH-6-17	2	Mono 8, Tri 12, 16, 22	XY	aCGH	Tri 8, 16	XY	NGS
SH-6-11	2	Mono 3, Tri 20, 21	XY	aCGH	Mono 3	XY	NGS
SH-7-1	2	Mono 13	XY	SNP a	Tri 14	XX	NGS
SH-7-2	2	Tri/polysomy 14	XX	SNP a	Mono 13	XY	NGS
SH-7-3	2	Tri 11,12,15,17,21	XXY	aCGH	Tri 7,8,10,11	XX	NGS
SH-7-4	2	Tri 5,6,11,17,18,21	XX	aCGH	Tri 5,13,17	XX	NGS
SH-7-5	2	Tri 21	XX	aCGH	Tri 2	XX	NGS
SH-7-6	2	Tri 2	XX	aCGH	Complex ABN	XX	NGS
SH-7-7	2	Del/Dup 5	XX	SNP a	NL	XY	NGS
SH-7-8	2	Tri/polysomy 13	XX	SNP a	Tri 13	XX	NGS
SH-8-1	2	Complex ABN	XY	aCGH	Complex ABN	XY	NGS
SH-8-2	2	Complex ABN	XY	aCGH	XO	XO	NGS
SH-8-3	2	Mono 13	XX	aCGH	Mono 13	XX	NGS
SH-8-4	2	Partial Tri 5	XY	aCGH	NL	XY	NGS
SH-8-5	2	Mono 16, Tri 3	XY	aCGH	NL	XY	NGS
SH-8-6	2	Tri 21	XX	aCGH	NL	XX	NGS
SH-8-7	2	Tri 13, 20	XX	aCGH	NL	XX	NGS
SH-8-8	2	Tri 13, 21	XX	aCGH	NL	XX	NGS

Accuracy of preimplantation genetic screening (PGS) is compromised by degree of mosaicism of human embryos

Norber
Yang-G



1
sp
(i
(i

O
a
4
cl
n
differed in reported aneuploidies.

In intra-embryo analyses, 5/10 (50 %) differed between biopsy sites.

ology (2016)

loidy between two PGS 2.0

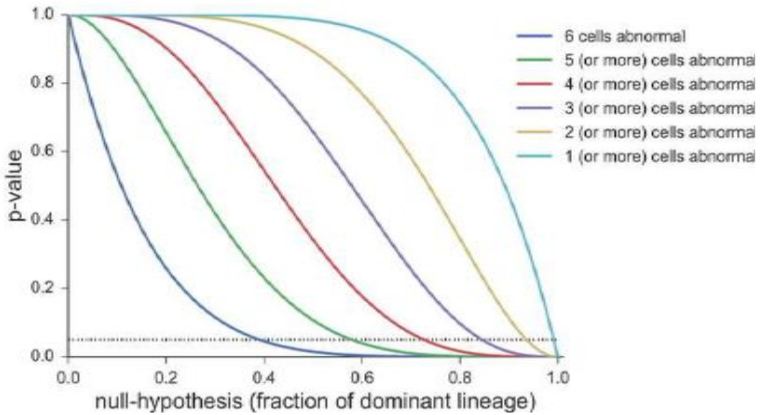
			analysis reported	Repeat PGS analysis[a] (multiple biopsies)
				Normal 46, XX
			euploid[b]	XY, +10, -18q
				XY, +11, +16, -21
				XX, -3q
			11, +15, -14[b]	XX, -2
				Normal 46\XX
				45, XY, -18
				Normal 46,XX
			[b]	45, XY, -14
				45, XY, -14
				45, XY, -14
				45, XY, -14
				47, XY, +3
				47, XY, +3
				47, XY, +3
				Normal 46, XY
				Normal 46, XX
				Normal 46, XX
				Normal 46, XX
				Normal 46, XY
				Normal 46, XY
				Normal 46, XY
				Normal 46, XY
				Normal 46, XY
				Normal 46, XY
				Normal 46, XY
			euploid[c]	Normal 46, XY
				47, +18
			euploid[c]	47, XY, +8q, -15, +16
	D5	3		46, XY, -15, +16
	D6	4		46, XY, -15, +16
	D7	5		46, XY, -15, +16
11	D8	1	46, XX, +14, -15[c]	46, XX, +14, -15
	D9	2		46, XX, +14, -15
	D10	3		46, XX, +14, -15
	D11	4		46, XX, +14, -15

Pat# patient number, *Emb#* embryo number; The diagnostic platforms utilized by the various PGS laboratories are described under Methods: [a]aCGH, [b]qPCR and [c]array CGH

A single trophectoderm biopsy at blastocyst stage is mathematically unable to determine embryo ploidy accurately enough for clinical use

Norbert Gleicher,[1,2,3,4*] Jacob Metzger,[5] Gist Croft,[4] Vitaly A. Kushnir,[1,6] David F. Albertini,[1,3] David H Barad, [1,2]

$$p(n, n, N_1, N) = \binom{N_1}{k} / \binom{N}{n},$$



The probability that a biopsy shows no mosaicism as a function of the fraction of euploid cells r = $N1/N$

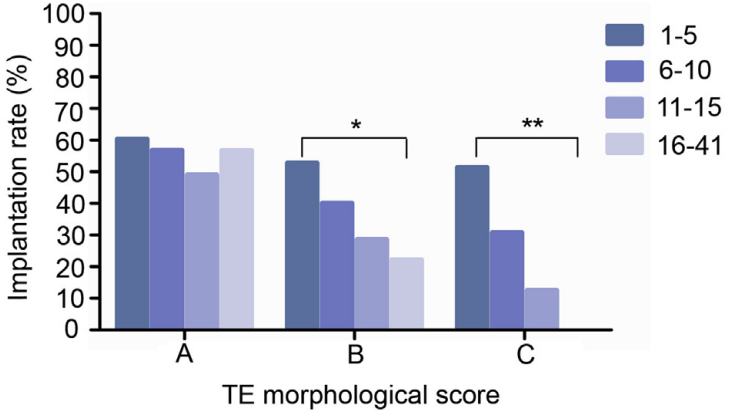
($N1$ is the number of euploid cells, and N the total number of cells)

One would need a biopsy of 27 cells to assure that the probability of obtaining only euploid cells in a biopsy is less than 5% if the fraction of euploid cells in the embryo is r=0.9

Biopsy Impact on embryo development

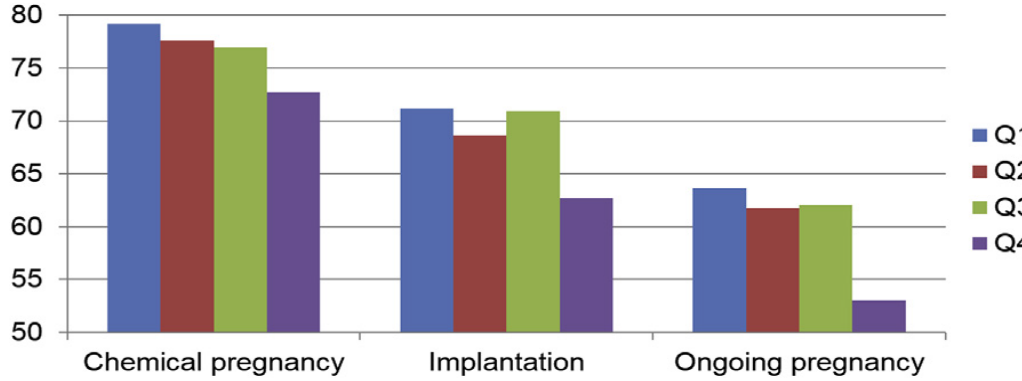
Number of biopsied trophectoderm cells is likely to affect the implantation potential of blastocysts with poor trophectoderm quality (2016)

Shuoping Zhang, M.Sc.,[a,b] Keli Luo, M.D., Ph.D.,[a,b,c] Dehua Cheng, M.Sc.,[a,b] Yueqiu Tan, Ph.D.,[a,b,c] Changfu Lu, Ph.D.,[a,b,c] Hui He, M.Sc.,[a,c] Yifan Gu, Ph.D.,[a,b,c] Guangxiu Lu, M.D.,[a,b,c,d] Fei Gong, M.D., Ph.D.,[a,b,c] and Ge Lin, M.D., Ph.D.[a,b,c,d]



High relative deoxyribonucleic acid content of trophectoderm biopsy adversely affects pregnancy outcomes (2017)

Shelby A. Neal, M.D.,[a,b] Jason M. Franasiak, M.D.,[a,b] Eric J. Forman, M.D., H.C.L.D.,[a,b] Marie D. Werner, M.D.,[a,b] Scott J. Morin, M.D.,[a,b] Xin Tao, M.S.,[a] Nathan R. Treff, Ph.D.,[a,b] and Richard T. Scott Jr., M.D., H.C.L.D.[a,b]



The biopsy quartile with highest DNA content (Q4) demonstrated poorer outcomes across all measured outcomes

Healthy Babies after Intrauterine Transfer of Mosaic Aneuploid Blastocysts

Ermanno Greco, M.D.
Maria Giulia Minasi, M.Sc. N ENGL J MED 373;21 NEJM.ORG NOVEMBER 19, 2015

Table 1. Clinical Outcomes of Single Mosaic Blastocysts Transferred.*

Patient No.	Chromosomal Constitution	Mosaicism†	Karyotype‡	Clinical Outcome
		percent		
1	arr(4)x1,(10)x1	40	46,XX	Baby healthy at birth
2	arr(6)x1,(15)x1	50	46,XX	Baby healthy at birth
3	arr(2)x1	40	46,XX	Baby healthy at birth
4	arr(2)x1	35	46,XY	Baby healthy at birth
5	arr(5)x1	50	46,XX	Baby healthy at birth
6	arr(5)x1,(7)x1	40	46,XX	Baby healthy at birth
7	arr(11)x1,(20)x3,(21)x3	30	NA	No pregnancy
8	arr(1)x1,(6)x3,(10)x3,(12)x3,(13)x3,(14)x3,(21)x3	50	NA	No pregnancy
9	arr(3)x1,(10)x3,(21)x3	35	NA	No pregnancy
10	arr(1)x3	50	NA	Biochemical pregnancy§
11	arr 9p21.2q34.3(26,609,645-140,499,771)x3	45	NA	Biochemical pregnancy§
12	arr(15)x3	30	NA	No pregnancy
13	arr(18)x1	50	NA	No pregnancy
14	arr(18)x1	50	NA	No pregnancy
15	arr(18)x1	40	NA	No pregnancy
16	arr(4)x1	50	NA	No pregnancy
17	arr(5)x3	40	NA	No pregnancy
18	arr 10q21.3q26.3(67,216,644-134,326,648)x3	50	NA	No pregnancy

Table 2 Characteristics of aneuploid embryos transferred that led to implantation

Patient	n Embryos transferred	Embryos transferred	Outcome
1	1	43, XY, -13, -15, -18	Normal birth, 46, XY
2	1	45, XY, -21	Normal birth, 46, XY
3	2[a]	45, XY, -21 46, XX	Normal birth, 46, XY
4	2[b]	Partial 47, XX,17p11.2-pter 45, XY, -22	Normal ongoing 46, XX
5	2[c]	47, XY, +22 Partial 45, XY,-1plar-p36, 12	Normal ongoing 46, XY
6	1[d]	45, XY, -21	Chemical pregnancy

CrossMark

Accuracy of preimplantation genetic screening (PGS) is compromised by degree of mosaicism of human embryos

Norbert Gleicher[1,2,3*], Andrea Vidali[1,4], Jeffrey Braverman[5], Vitaly A. Kushnir[1,6], David H. Barad[1,2,7], Cynthia Hudson[1], Yang-Guan Wu[1], Qi Wang[1], Lin Zhang[1], David F. Albertini[1,8] and the International PGS Consortium Study Group

Reproductive Biology and Endocrinology (2016)

PGS- 2nd generation

Criticism of PGS

Publication of growing evidence of an unacceptably high false-positive rate for PGS

(Gleicher et al. 2015/6; Greco et al., 2015; Morales et al., 2016)

PGDIS Newsletter, July 19, 2016

ITION STATEMENT ON CHROMOSOME MOSAICISM AND
PLOIDY TESTING AT THE BLASTOCYST STAGE

PGS- 3rd generation PGT-A

For reporting e… …t for definition of mosaicism is >20%, so lowe… …% abnormal (aneuploid), a… …id mosaics).

pregnancies and healthy live… …e however, suggests that pregnancy rate…

How does this affect aneu…

Most trophectoderm biopsy resu… …changes for one or more chromosomes, which may ind… …mosaic aneuploidies are detected, and these may be the only… …y have clinical implications for the pregnancy, including effects on placental fu… …hen there is no alternative and preferably only after appropriate genetic counseling of the p…

Recommendations for the laboratory (if reporting mosaic aneuploidies)

1. For reliable detection of mosaicism, ideally 5 cells should be biopsied, with as little cell damage as pos… …l be minimal and preferably at cell junctions. Overly aggressive use of the laser may result in cell damage and partial destruction of ce…
2. Only a validated NGS platform that can quantitatively measure copy number should be used for measurement of mosaicism … …an accurately and reproducibly measure 20% mosaicism in a known sample.
3. For reporting embryo results, the suggested cut-off point for definition of mosaicism is >20%, so lower levels should be treated as normal (euploid), … …d the remaining ones between 20-80% mosaic (euploid-aneuploid mosaics).

Mosaic human preimplantation embryos and their developmental potential in a prospective, non-selection clinical trial

Antonio Capalbo,[1,*] Maurizio Poli,[1] Laura Rienzi,[2] Laura Girardi,[1] Cristina Patassini,[1] Marco Fabiani,[1] Danilo Cimadomo,[2] Francesca Benini,[3] Alessio Farcomeni,[4] Juliana Cuzzi,[5] Carmen Rubio,[6,7] Elena Albani,[8] Laura Sacchi,[8] Alberto Vaiarelli,[2] Matteo Figliuzzi,[1] Necati Findikli,[9,10] Onder Coban,[11] Fazilet K. Boynukalin,[12] Ivan Vogel,[13] Eva Hoffmann,[13] Claudia Livi,[3] Paolo E. Levi-Setti,[8] Filippo M. Ubaldi,[2] and Carlos Simón[6,7,14,15]

The American Journal of Human Genetics *108*, 2238–2247, December 2, 2021

Three main categories:

"euploid"

"low-grade mosaic" (20–30% aneuploid cells),

"medium-grade mosaic" (30–50% aneuploid cells).

Table 1. Reproductive outcomes of euploid and mosaic embryos

	Group A: Euploid	Group B: Low-grade mosaic (20–30% variation)	Group C: Medium-grade mosaic (30–50% variation)	Adjusted OR (95% CI; p value)
Test sets, n	484	282	131	-
Positive pregnancy test, % (n)	55.8% (270/484)	55.0% (155/282)	55.7% (73/131)	0.98 (0.75–1.27; 0.86)
Biochemical pregnancy loss, % (n)	10.7% (29/270)	12.3% (19/155)	13.7% (10/73)	1.18 (0.69–2.02; 0.53)
Miscarriage, % (n)	12.0% (29/241)	11.0% (15/136)	12.7% (8/63)	0.89 (0.50–1.55; 0.69)
Live birth, % (n)	43.4% (210/484)	42.9% (121/282)	42.0% (55/131)	0.97 (0.74–1.26; 0.82)

Detailed investigation into the cytogenetic constitution and pregnancy outcome of replacing mosaic blastocysts detected with the use of high-resolution next-generation sequencing

Fertil Steril® 2017

Santiago Munné, Ph.D.,[a] Joshua Blazek, Ph.D.,[b] Michael Large, Ph.D.,[b] Pedro A. Martinez-Ortiz, Ph.D.,[c] Haley Nisson, B.S.,[a] Emmeline Liu, M.Sc.,[a] Nicoletta Tarozzi, Ph.D.,[d] Andrea Borini, M.D.,[d] Amie Becker,[e] John Zhang, M.D.,[e] Susan Maxwell, M.D.,[f] James Grifo, M.D., Ph.D.,[f] Dhruti Babariya, M.Sc.,[g] Dagan Wells, Ph.D.,[g] and Elpida Fragouli, Ph.D.[g]

False Positive

Pregnancy outcome of mosaic embryos according to mosaicism type, percentage

Mosaic type	% Abnormal	No. of cycles	Implanted n	Implanted %	n			
Complex	20–40	17	2	12	0	0		
	>40–80	4	0	0	0	0		
Double	20–40	22	11	50	2	18	9	
	>40–80	7	5	71	1	20	4	
Monosomic	20–40	28	20	71	6	30	14	50
	>40–80	6	2	33	0	0	2	33
Trisomic	20–40	17	11	65	0	0	11	65
	>40–80	3	1	33	1	100	0	0
Segmental	20–40	25	17	68	7	41	10	40
	>40–80	14	7	50	1	14	6	43
	20–40, all	109	61	56	15	25	46	42
	>40–80, all	34	15	44	3	20	12	35
Single aneuploid	20–40	45	31	69	6	19	25	56
	>40–80	9	3	33	1	33	2	22
Complex, all		21	2	10	0	0	2	10
Double, all		29	16	55	3	19	13	45
Aneuploid, all		54	34	63	7	21	27	50
Segmental, all		39	24	62	8	33	16	41
No. of chromosomes involved								
1		93	58	62	15	26	43	46
2		29	16	55	3	19	13	45
>3		21	2	10	0	0	2	10
Total		143	76	53	18	24	58	41

Note: NS = not significant.

Munné. Pregnancy outcome of mosaic blastocysts. Fertil Steril 2017.

Mosaic group	Implantation per embryo transfer	Ongoing pregnancy or birth per embryo transfer	Spontaneous abortions per implanted embryo	*P* value
l (n = 5,561)	57.2%	52.3%	8.6%	
= 1,000)	46.5%	37.0%	20.4%	<.0001
some (n = 517)	41.8%	31.3%	25.0%	<.0001
	44.1%	35.3%	20.4%	<.0001
	55.5%	37.2%	33.0%	<.0001
	50.9%	43.9%	13.8%	
		41.5%	20.3%	
		39.5%	19.2%	
Mosaic lo		39.8%	11.9%	
Mosaic low comp		25.0%	26.7%	<.0001
Mosaic high 1 chromoso		22.4%	31.7%	
Mosaic high 2 chromosomes (n		20.0%	40.0%	
Mosaic high complex (n = 38)		13.2%	44.0%	

Summary of results of the 1,000 mosaic embryo transfer study. *Note:* Columns indicate the measured clinical outcomes, and rows indicate the (sub) category of result obtained with preimplantation genetic testing for aneuploidy (PGT-A). Low, <50%; high, ≥50%; complex, >2 aberrant chromosomes. Compared with the euploid group, the following mosaic groups had significantly lower likelihood of achieving ongoing pregnancy or birth per embryo transfer: mosaic all, mosaic whole chromosome, mosaic no selection, and mosaic no knowledge (χ^2 test, *P*<.0001). The subgroups are statistically significant (Cochran-Armitage test for trend, *P*<.0001). For each clinical outcome, the colored shading indicates the relative success rate of each (sub) category, from best (white) to worst (red).

Viotti. Mosaicism in PGT-A matters. Fertil Steril 2021.

The reproducibility of trophectoderm biopsies in euploid, aneuploid, and mosaic embryos using independently verified next-generation sequencing (NGS): a pilot study (2020)

Nidhee M. Sachdev [1,2] · David H. McCulloh [1] · Yael Kramer [1] · David Keefe [1] · James A. Grifo [1]

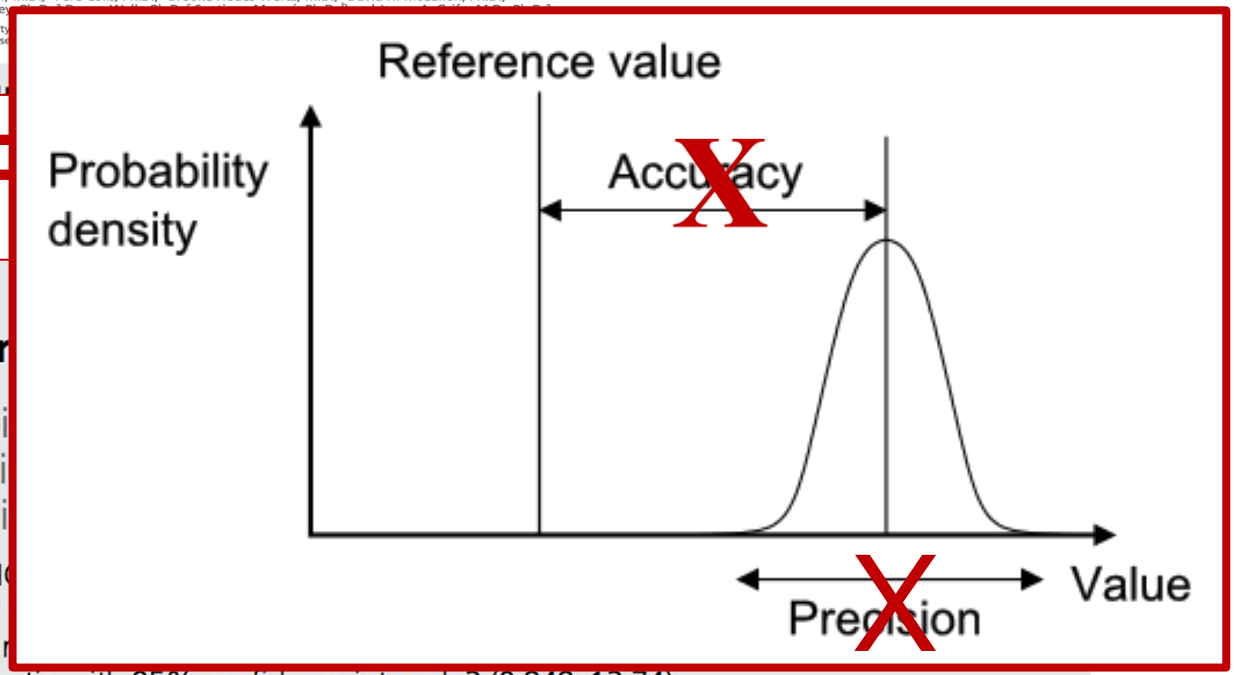
The reproducibility of trophectoderm biopsies – The chaos behind preimplantation genetic testing for aneuploidy

Raoul Orvieto[a,b]

European Journal of Obstetrics & Gynecology and Reproductive Biology 254 (2020) 57–58

Why do euploid embryos miscarry? A case-control study comparing the rate of aneuploidy within presumed euploid embryos that resulted in miscarriage or live birth using next-generation sequencing

Susan M. Maxwell, M.D.,[a] Pere Colls, Ph.D.,[b] Brooke Hodes-Wertz, M.D.,[a] David H. McCulloh, Ph.D.,[a] Caroline McCaffrey
[a] New York University
Livingston, New Jers



Re
ge

NGS r

Euploi
Mosai
Triploi

Note: N
[a] Mid-P
[b] Odds r
[c] Odds ratio with 95% confidence interval: 3 (0.848–13.74).

Maxwell. NGS reanalysis of aCGH euploid embryos. Fertil Steril 2016.

(2016)

Preimplantation genetic screening: who benefits?

Hey-Joo Kang, M.D., Alexis P. Melnick, M.D., Joshua D. Stewart, M.D., Kangpu Xu, Ph.D., D.V.M., and Zev Rosenwaks, M.D.

	PGS	Controls	P
Cycle (all)	191	216	
All aneuploid embryos	105		
No Blastocysts	26		
41/60 (68%) per transfer			
Age (yrs)	41.7+1.8	39.7+1.3	**<0.001**
Clinical intrauterine gestation	21.5% (41/191)	49.5%	**<0.001**
41/191 (21.5%) per started cycle			
LBR	19.9	39.8	**<0.001**

Kang. PGS and IVF outcomes. Fertil Steril 2016.

(2019)

Preimplantation genetic testing for aneuploidy versus morphology as selection criteria for single frozen-thawed embryo transfer in good-prognosis patients: a multicenter randomized clinical trial

Santiago Munné, Ph.D.,[a,b,c] Brian Kaplan, M.D.,[d] John L. Frattarelli, M.D., H.C.L.D.,[e] Tim Child, M.D.,[f] Gary Nakhuda, M.D.,[g] F. Nicholas Shamma, M.D.,[h] Kaylen Silverberg, M.D.,[i,j] Tasha Kalista, M.A.,[k] Alan H. Handyside, Ph.D.,[l] Mandy Katz-Jaffe, M.D.,[m] Dagan Wells, Ph.D.,[n] Tony Gordon, Ph.D.,[o] Sharyn Stock-Myer, Ph.D.,[p] and Susan Willman, M.D.,[q] on behalf of the STAR Study Group

STAR

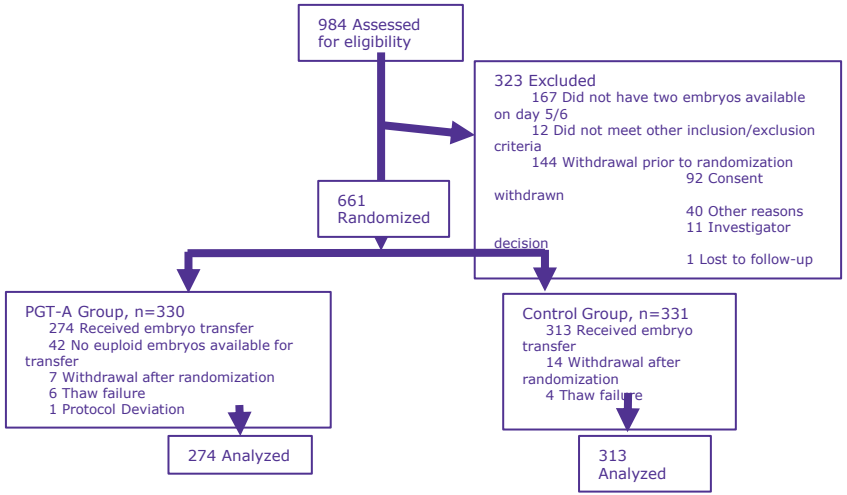
Inclusion criteria were female age 25–40 years undergoing IVF with autologous oocytes with at least two blastocysts of sufficient quality for biopsy and vitrification by day 6.

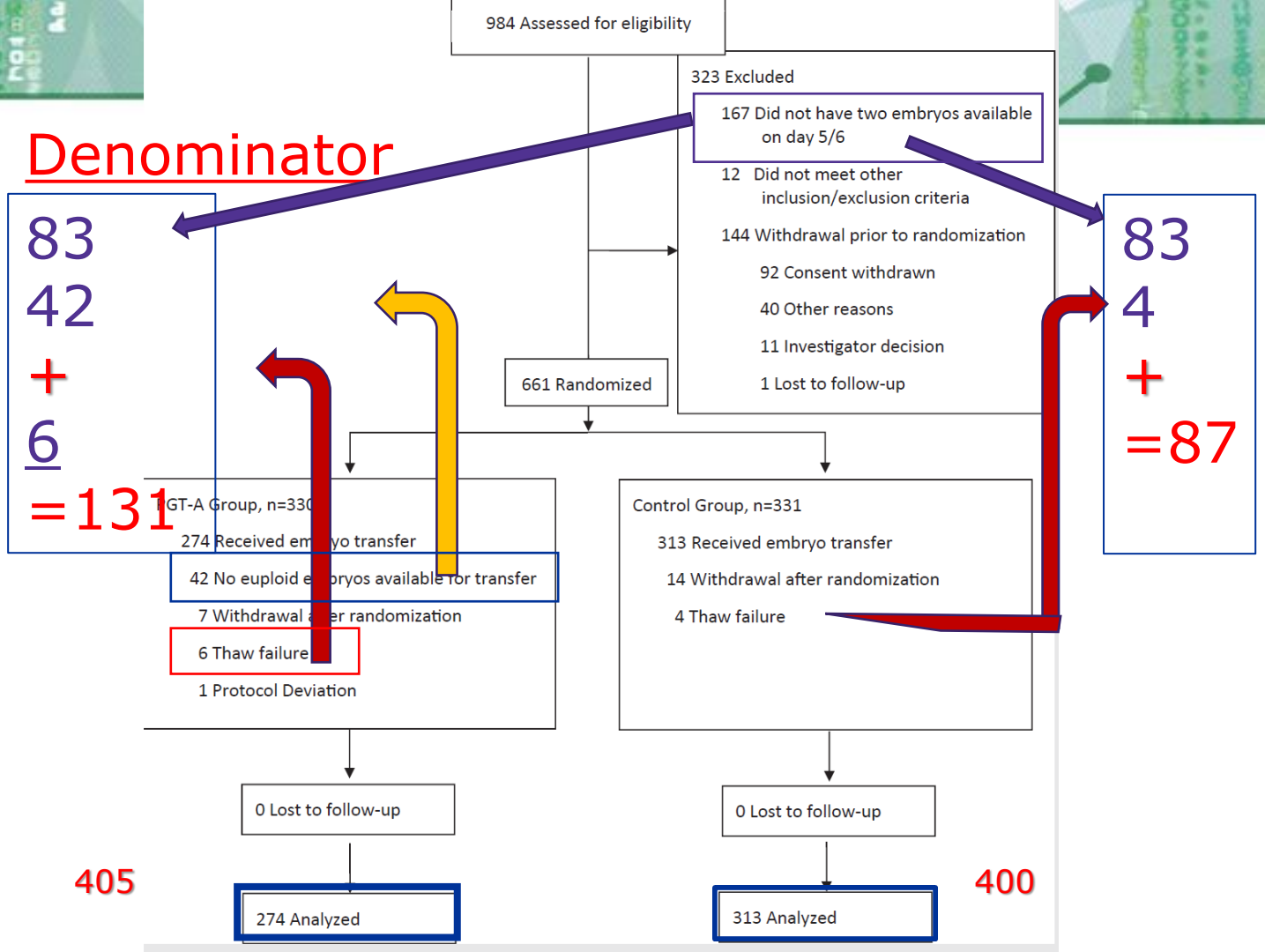
An average of 7.4 day-5/6 blastocysts were obtained per patient in both arms.

Outcomes in patients undergoing an embryo transfer with embryo selection by means of preimplantation genetic testing for aneuploidy (PGT-A) versus morphology (Control), n (%).

	< 35 y		35–40 y		All patients		
Outcome	PGT-A (n = 152)	Control (n = 168)	PGT-A (n = 122)	Control (n = 145)	PGT-A (n = 274)	Control (n = 313)	*P* value[a]
Negative β-hCG	46 (30.3)	53 (31.5)	34 (27.9)	59 (40.7)	80 (29.2)	112 (35.8)	.0934
Positive β-hCG	106 (69.7)	115 (68.5)	88 (72.1)	86 (59.3)	194 (70.8)	201 (64.2)	ND
Biochemical pregnancy	14 (9.2)	10 (6.0)	15 (12.3)	16 (11.0)	29 (10.6)	26 (8.3)	.3315
Miscarriage	17 (11.2)	14 (8.3)	10 (8.2)	16 (11.0)	27 (9.9)	30 (9.6)	.8979
Elective termination	0	2 (1.2)	1 (0.8)	0	1 (0.4)	2 (0.6)	.6603
Ongoing pregnancy at 20 weeks' gestation	75 (49.3)	89 (53.0)	62 (50.8)	54 (37.2)	137 (50.0)	143 (45.7)	.3177
P value for age subgroups	*P* = .5757		*P* = .0349				

Figure 1: Enrollment, assignment, treatment, and analysis process of study and control patients.
1a- Original STAR study
1b- Corrected analysis in this submission.
PGT-A - preimplantation genetic testing for aneuploidy.




Denominator
83
42
+
6
=131
984 Assessed for eligibility
323 Excluded
167 Did not have two embryos available on day 5/6
12 Did not meet other inclusion/exclusion criteria
144 Withdrawal prior to randomization
92 Consent withdrawn
40 Other reasons
11 Investigator decision
1 Lost to follow-up
661 Randomized
83
4
+
=87
GT-A Group, n=330
274 Received embryo transfer
42 No euploid embryos available for transfer
7 Withdrawal after randomization
6 Thaw failure
1 Protocol Deviation
Control Group, n=331
313 Received embryo transfer
14 Withdrawal after randomization
4 Thaw failure
0 Lost to follow-up
0 Lost to follow-up
405
400
274 Analyzed
313 Analyzed

	All patients		35-40y	
p-value	0.91		0.43	
OPR	137(50.0)	143(45.7)	62(50.8)	54(37.2)
p-value	0.29			

PGS- 3rd generation

Live Birth with or without Preimplantation Genetic Testing for Aneuploidy (2021)

J. Yan, Y. Qin, H. Zhao, Y. Sun, F. Gong, R. Li, X. Sun, X. Ling, H. Li, C. Hao, J. Tan, J. Yang, Y. Zhu, F. Liu, D. Chen, D. Wei, J. Lu, T. Ni, W. Zhou, K. Wu, Y. Gao, Y. Shi, Y. Lu, T. Zhang, W. Wu, X. Ma, H. Ma, J. Fu, J. Zhang, Q. Meng, H. Zhang, R.S. Legro, and Z.-J. Chen

Eligible couples: 1st IVF cycle; Woman's age of 20 to 37 years; ≥3 good-quality blastocysts.

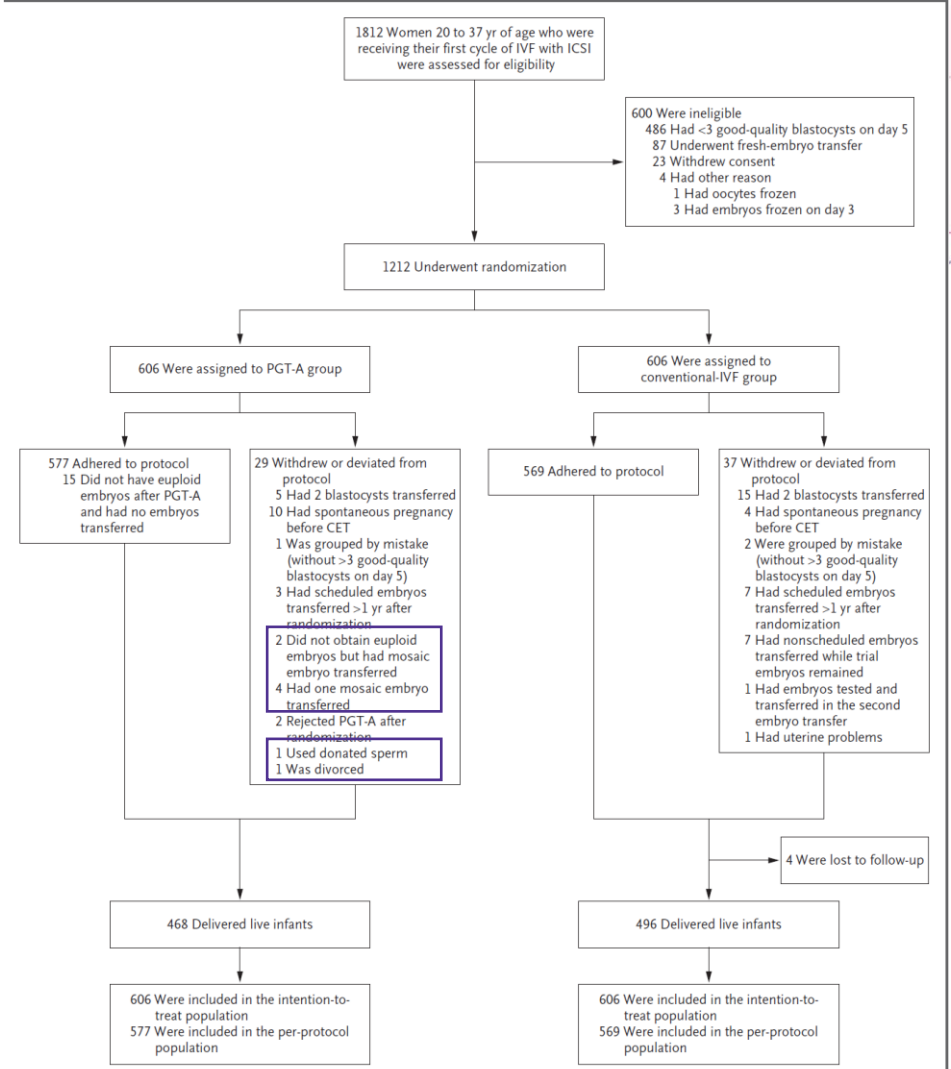


Table 3. Cumulative Live-Birth Rate and Secondary Outcomes.*

Outcome	PGT-A Group (N=606)	Conventional-IVF Group (N=606)	Absolute Difference (95% CI)	Rate Ratio (95% CI)
Primary outcome				
Cumulative live-birth rate — no. (%)†	468 (77.2)	496 (81.8)	−4.6 (−9.2 to −0.0)	0.94 (0.89 to 1.00)
Singleton	462 (76.2)	478 (78.9)	−2.6 (−7.3 to 2.1)	0.97 (0.91 to 1.03)
Twin	6 (1.0)	18 (3.0)	−2.0 (−3.5 to −0.4)	0.33 (0.13 to 0.83)
Secondary outcomes				
Cumulative biochemical pregnancy — no. (%)	526 (86.8)	571 (94.2)	−7.4 (−10.7 to −4.2)	0.92 (0.89 to 0.96)
Cumulative clinical pregnancy — no. (%)	505 (83.3)	556 (91.7)	−8.4 (−12.1 to −4.7)	0.91 (0.87 to 0.95)
Cumulative ongoing pregnancy — no. (%)	479 (79.0)	514 (84.8)	−5.8 (−10.1 to −1.5)	0.93 (0.88 to 0.98)
Birth weight				
Singleton				
No. of observations	462	478		
Mean weight — g	3417±488	3449±488	−32 (−95 to 30)	
Twin				
No. of observations	12	36		
Mean weight — g	2500±714	2605±420	−105 (−444 to 235)	
Cumulative pregnancy loss — no./total no. (%)				
Biochemical	31/526 (5.9)	41/571 (7.2)	−1.3 (−4.2 to 1.6)	0.82 (0.52 to 1.29)
Clinical	46/526 (8.7)	72/571 (12.6)	−3.9 (−7.5 to −0.2)	0.69 (0.49 to 0.98)
First trimester	37/526 (7.0)	60/571 (10.5)	−3.5 (−6.8 to −0.1)	0.67 (0.45 to 0.99)
Second trimester	9/526 (1.7)	12/571 (2.1)	−0.4 (−2.0 to 1.2)	0.81 (0.35 to 1.92)

What to advise to patients with only one good quality blastocyst, PGT-A or not? Outcomes of 2064 cycles

Semra Kahraman[1] · Ipek Nur Balin Duzguner[1] · Yucel Sahin[1] · Tulay Irez[2]

Journal of Assisted Reproduction and Genetics (2022) 39:2555–2562

Conclusion: PGT-A in the presence of a single blastocyst significantly increases clinical pregnancy and live birth rates and decreases total pregnancy losses regardless of age.

	Single blastocyst with PGT-A (n:1126)	Single blastocyst without PGT-A (n:938)	*P*-value
Biochemical pregnancy/ET, *n* (%)	158/225 (71%)		<0.001*
Clinical pregnancy/ET, *n* (%)	131/225 (63%)		<0.001*
Implantation rate, *n* (%)	131/225 (63%)	369/938 (39.3%)	<0.001*
Total pregnancy losses, *n* (%)	40/158 (25.3%)	131/420 (31.2%)	0.493
Live birth/ET, *n* (%)	115/225 (51.1%)	278/938 (29.6%)	<0.001*
Total gonadotrophin dosage used (IU)	2210.52 ± 58.15	2381.12 ± 48.47	0.018
Estradiol level on trigger day (ng/L)	994.18 ± 27.99	1179.36 ± 29.95	**<0.001***
Number of aspirated oocytes, *n*	4.44 ± 0.14	5.76 ± 0.14	**<0.001***
MII, *n*	3.58 ± 0.11	4.51 ± 0.11	**<0.001***
PN2, *n*	2.66 ± 0.08	3.35 ± 0.08	**<0.001***
Maturation rate, %	87.49 ± 0.58	83.74 ± 0.63	**<0.001***
Fertilization rate, %	82.40 ± 0.75	80.20 ± 0.80	**0.045***

10.2% 115/1126

278/938 29.6%

Human Reproduction, Vol.37, No.12, pp. 2730–2734, 2022

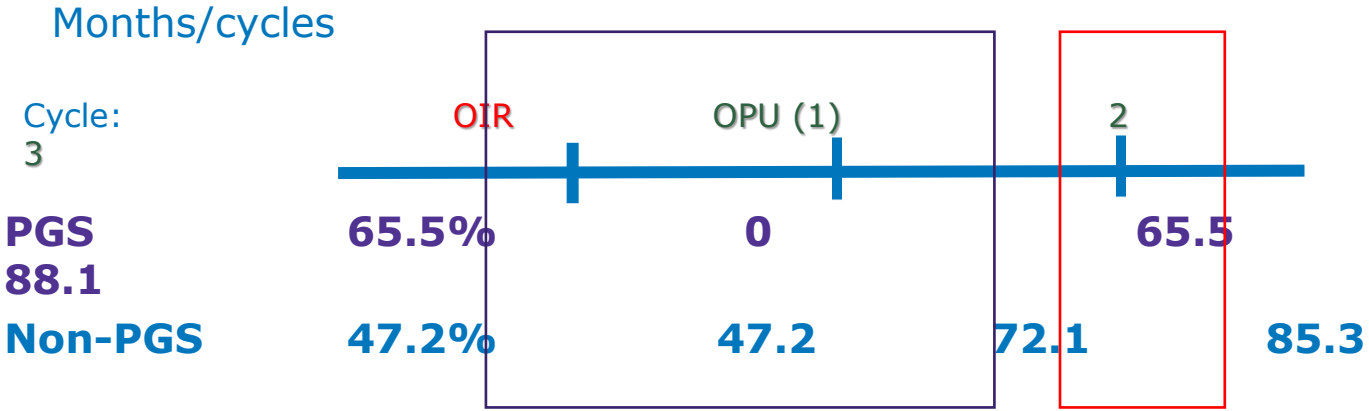
We have reached a dead end for preimplantation genetic testing for aneuploidy

Norbert Gleicher[1,2,3,4], David H. Barad [1], Pasquale Patrizio[5], and Raoul Orvieto [6,7,*]

?

Limited Clinical Indications

TIME TO PREGNANCY



100-65.5=34.5 34.5X0.655=22.6 65.5+22.6=88.1

100-47.2= 52.8 52.8X0.472=24.9 47.2+24.9=72.1 100-72.1=27.9 27.9X0.472=13.1
72.1+13.1=85.2

The use of preimplantation genetic testing for aneuploidy: a committee opinion

(2024)

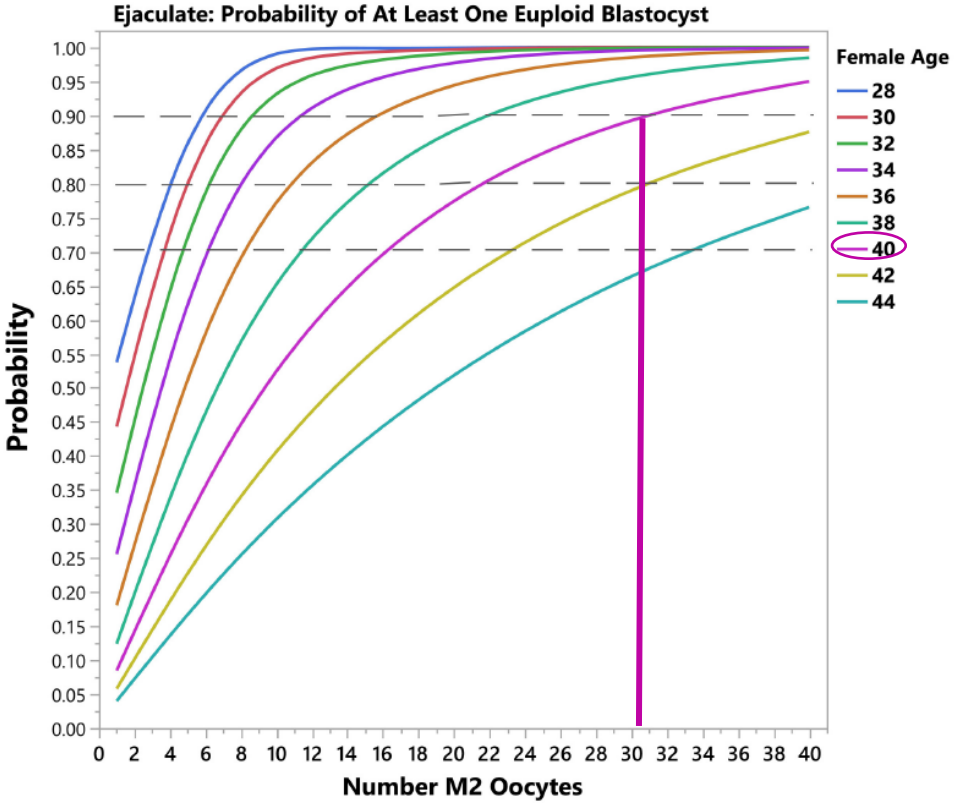
Practice Committee of the American Society for Reproductive Medicine and the Society for Assisted Reproductive Technology

- **Favorable prognosis patients** - It was concluded that there **was insufficient good-quality evidence** of a difference in cumulative live-birth rate, live-birth rate after the first embryo transfer, or miscarriage rate with and without PGT-A.
- **Advanced maternal age** - PGT-A **may have a beneficial role** in patients of advanced maternal age, especially those with **good ovarian reserve.**
- **Use of donor oocytes** - Overall, the totality of evidence **argues against** the routine use of PGT-A in donor egg cycles.
- **Advanced paternal age** - The available evidence suggests that routine PGT-A testing **should not be performed** for APA.
- **Elective single-embryo transfer** -There was **no significant difference** between groups.
- **Recurrent pregnancy loss** -To date, definitive evidence of the benefit of PGT-A in this patient population **is lacking.**
- **PGT-A with PGT-M** -**Further studies** on the use of PGT-A in the setting of PGT-M **are needed** in this population, and the counseling **needs to be individualized**.
- **Male factor infertility** - The evidence is **insufficient** to make recommendation for

A Novel Predictive Model to Estimate the Number of Mature Oocytes Required for Obtaining at Least One Euploid Blastocyst for Transfer in Couples Undergoing *in vitro* Fertilization/Intracytoplasmic Sperm Injection: The ART Calculator

Sandro C. Esteves[1], José F. Carvalho[2], Fabiola C. Bento[1] and Jonathan Santos[1,3] on behalf of The POSEIDON Group*

Front. Endocrinol. 10:99. (2019)



ESHRE good practice recommendations on recurrent implantation failure†

2023

ESHRE Working Group on Recurrent Implantation Failure, D. Cimadomo [1], M.J. de los Santos [2], G. Griesinger [3,4], G. Lainas [5], N. Le Clef [6], D.J. McLernon [7], D. Montjean [8], B. Toth[9], N. Vermeulen [6], and N. Macklon [10,*]

women who might be expected to have a 60 % chance of implantation

	Maternal age	Implantation rate / pregnancy rate[1]	Cumulative likelihood of implantation for each embryo transfer (embryos of unknown euploidy)						RIF THRESHOLD of >60%
			FIRST ET (n=1)	SECOND ET (n=2)	THIRD ET (n=3)	FOURTH ET (n=4)	FIFTH ET (n=5)	SIXTH ET (n=6)	
Embryos of unknown euploidy	<35	31,5	31,5	53,1	67,9	78,0	84,9	89,7	Intervene after 3 ETs
	35-39	25,9	25,9	45,1	59,3	69,9	77,7	83,4	Intervene after 4 ETs
	≥40	15	15,0	27,8	38,6	47,8	55,6	62,3	Intervene after 6 ETs
Euploid embryos	<35	68,4	68,4	90,0	96,8	99,0	99,7	99,9	Intervene after 2 ETs
	35-40	64,1	64,1	87,1	95,4	98,3	99,4	99,8	Intervene after 2 ETs
	>40	58,0	58,0	82,4	92,6	96,9	98,7	99,5	Intervene after 2 ETs

Figure 2. Applying the recommended definition of RIF in clinical practice: an example. [1]For embryos of unknown euploidy, pregnancy rates per embryo transfer (ET) for patients using their own oocytes were used from the European IVF Monitoring Programme data (Wyns C *et al.*, 2021); for euploid embryos, pregnancy rates were used from published data (Reig *et al.*, 2020). For the sake of simplicity and because of a lack of positive hCG incidence data in the existing studies/registries, implantation and pregnancy

The use of preimplantation genetic testing for aneuploidy: a committee opinion

(2024)

Practice Committee of the American Society for Reproductive Medicine and the Society for Assisted Reproductive Technology

The use of preimplantation genetic testing for aneuploidy (PGT-A) in the United States has been increasing steadily. Moreover, the underlying technology used for 24-chromosome analysis continues to evolve rapidly. The value of PGT-A as a routine screening test for all patients undergoing in vitro fertilization has not been demonstrated. Although some earlier single-center studies reported higher live-birth rates after PGT-A in favorable-prognosis patients, recent multicenter, randomized control trials in women with available blastocysts concluded that the overall pregnancy outcomes via frozen embryo transfer were similar between PGT-A and conventional in vitro fertilization. The value of PGT-A to lower the risk of clinical miscarriage is also unclear, although these studies have important limitations. This document replaces the document of the same name, last published in 2018. (Fertil Steril® 2024;■:

The use of preimplantation genetic testing for aneuploidy: a committee opinion

Reply of the authors: the use of preimplantation genetic testing for aneuploidy: a committee opinion

On behalf of the American Society for Reproductive Medicine (ASRM) Practice Committee, we would like to thank Dr. Orvieto for his insightful comments in response to the recently published ASRM committee opinion on the use of preimplantation genetic testing for aneuploidy (PGT-A). We agree with the important limitations you point out in the studies referenced in the committee opinion.

We agree that it is troubling that the use of PGT-A in the United States is increasing, despite the lack of evidence to support this practice. We have attempted to present the existing data in a nonbiased manner and have incorporated input from experts, epidemiologists, and ASRM members. We

Constable Law, Justice Law Collaborative, and Berger Montague Announce Class Action Lawsuits Against Genetic Testing Companies For Misleading Consumers About PGT-A Testing During IVF Treatment

Wednesday, 16 October 2024 09:45 AM


THANK YOU