Here's Looking at You, Kid: Time Lapse in the Clinical Embryology Laboratory

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Disclosures

Speaker, Auxogyn Symposium, ASRM, 2012

Moderator, Auxogyn Symposium, ASRM, 2013

Participant, MERGE Study sponsored by Auxogyn, Inc. 2014-2015.

Speaker, Product Theater, Auxogyn/Fertility Authority PCRS, 2015

Selected Landmarks
TLM and Human Embryo Selection

Payne *et al.*, 1997 → Pribenszky *et al.*, 2010 →
← Wong *et al.*, 2010 ← Meseguer *et al.*, 2011 →
Hashimoto *et al.*, 2012 → Dal Canto *et al.*, 2012 →
← *Hlinka et al.*, 2012 ← Meseguer *et al.*, 2012 →
Chen *et al.*, 2013 → Conaghan *et al.*, 2013 →
← Kirkegaard *et al.*, 2013 ← Wirka *et al.*, 2014 →
Rubio *et al.*, 2014 → VerMilyea *et al.*, 2014 →
← Kirkegaard *et al.*, 2015 ← Rienzi *et al.*, 2015

Pribenszky *et al.*, Reprod. Biomed. Online 21:533-536, 2010.

- **Used PrimoVision system, a compact digital inverted microscope housed in standard incubator**

Automated time-lapse monitoring in the regular incubator - components

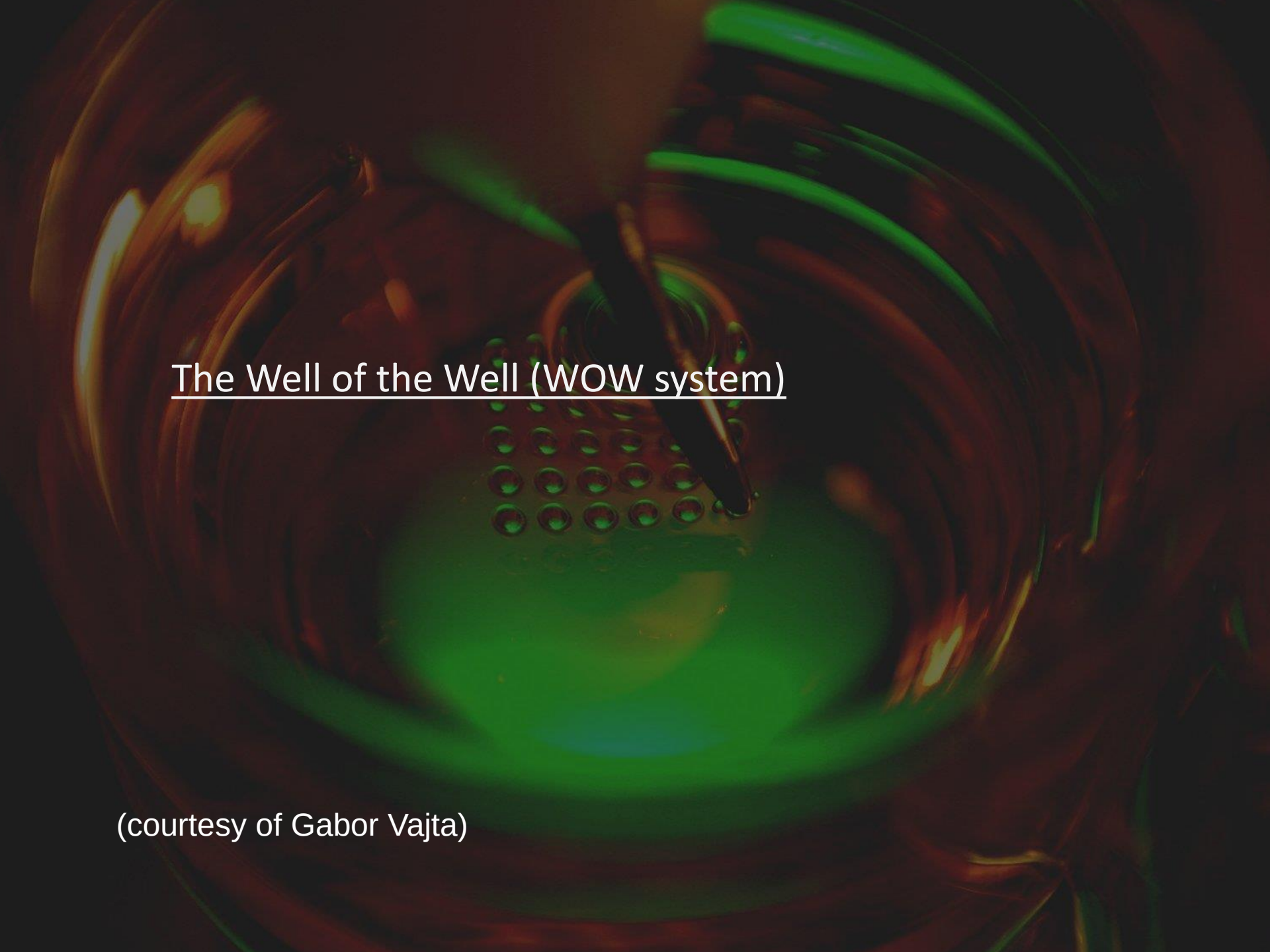
1. The Primo Vision system
    1. Microscope
    2. Embryo culture dish
    3. Controlling unit
    4. Software

Vitrolife

Pribenszky *et al.*, Reprod. Biomed. Online 21:533-536, 2010.

- **Used PrimoVision system, a compact digital inverted microscope housed in standard incubator**

- **5 zygotes imaged simultaneously using well of well dish, introduced to ART by Gabor Vajta**



(courtesy of Gabor Vajta)

Pribenszky *et al.*, Reprod. Biomed. Online 21:533-536, 2010.

- **Used PrimoVision system, a compact digital inverted microscope housed in standard incubator**

- **5 zygotes imaged simultaneously using well of well dish, introduced to ART by Gabor Vajta**

- **Single blastocyst selected for transfer –**
  Criteria: no fragmentation, rapid division to 2 and 3 cells, "synchronized cleavage" to 4 cell.
- **Term delivery, healthy male.**

Non-invasive imaging of human embryos before embryonic genome activation predicts development to the blastocyst stage. Wong *et al.* , 2010.

Kinetic data

100 out of 242 thawed human zygotes imaged until blastocyst formation (day 5,6).

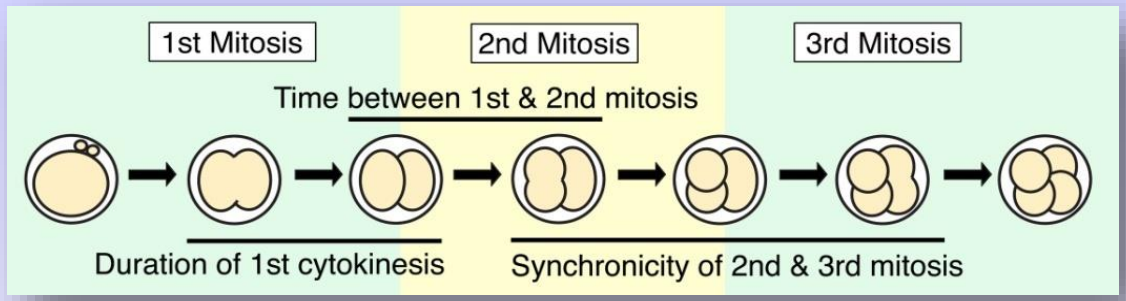
Events predicting blastocyst formation:

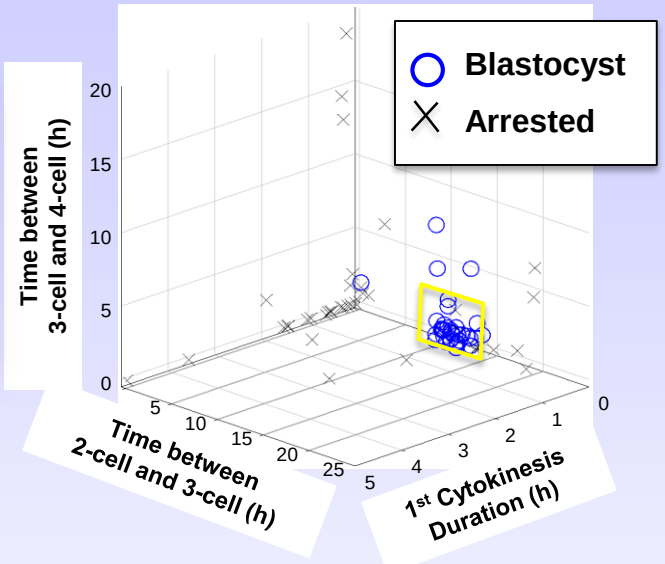
1. **duration of first cytokinesis (14.3±6 min.)**
2. **time between 1st and 2nd mitosis (11.1±2.2 h)**
3. **time between 2nd and 3rd mitosis (1.0±1.6 h)**

Conclusion:

Events predicting blastocyst formation occur prior to embryonic genome activation.

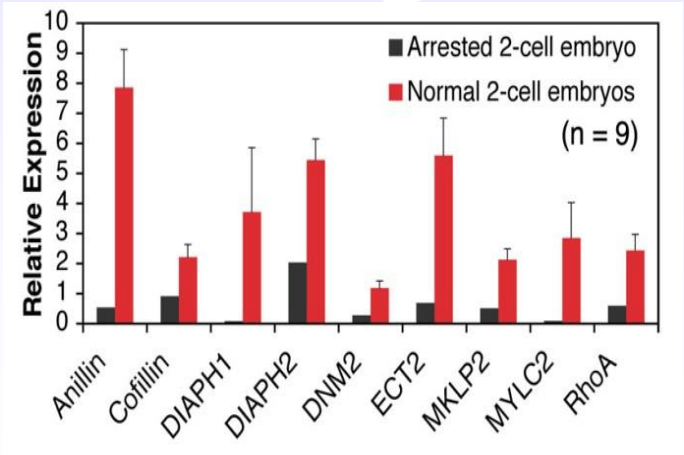
Basic research discovery of time-lapse markers



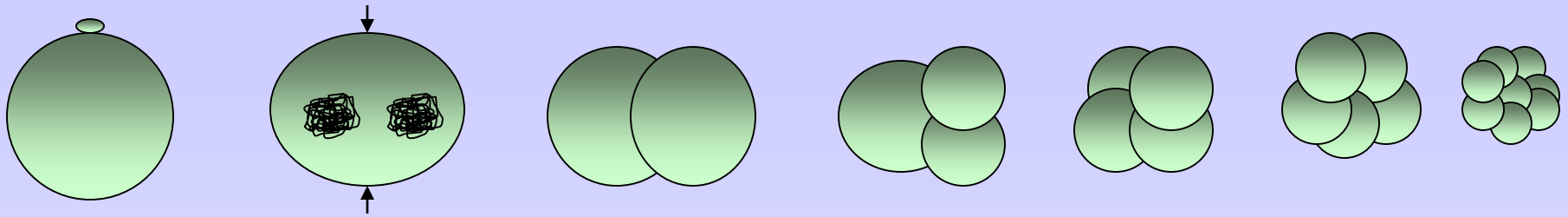


Cell division time-intervals ("P1, P2, P3") predict successful development to the blastocyst stage

- Distinct timing window [1]
- Reflect underlying molecular health [1]
- Later correlated to implantation and blastocyst quality [2-4]
- Most recently examined for aneuploidy [5]



[1] Wong et al. *Nature Biotechnology* (2010), [2] Meseguer et al. *Human Reprod* (2011), [3] Hashimoto et al. *Fertility & Sterility* (2012), [4] Cruz et al. *RBM Online* (2012), [5] Chavez et al. *Nature Communications* (2012)



Wong *et al.*, 2010 (endpoint: blastocyst formation)

14.3 ± 6 min.

11.1 ± 2.2 hrs.

1.0 ± 1.6 hrs.

The use of morphokinetics as a predictor of embryo implantation. Meseguer *et al.*, 2011.

Patients:

285 couples, first cycle with ICSI

Conditions:

Imaging in "Embryoscope", using trigas with image capture every 15' in 5 focal planes over a 64 hour period post ICSI

courtesy of Fertilitech

The use of morphokinetics as a predictor of embryo implantation. Meseguer *et al.*, 2011.

Findings:

Events significantly correlated with implantation:

1. **time of division to 5 cells post ICSI (48.8 - 56.6 h)**
2. **time between division to 2 cells and 3 cells (≤ 11.9 h)**
3. **time between division to 3 cells and 4 cells (≤ 0.76 h)**

Events largely precluding implantation:

1. **multinucleation at 4 cell stage**
2. **uneven blastomere size at 2 cell stage**
3. **abrupt cell division to 3 or more cells.**

Morphology versus Morphokinetics

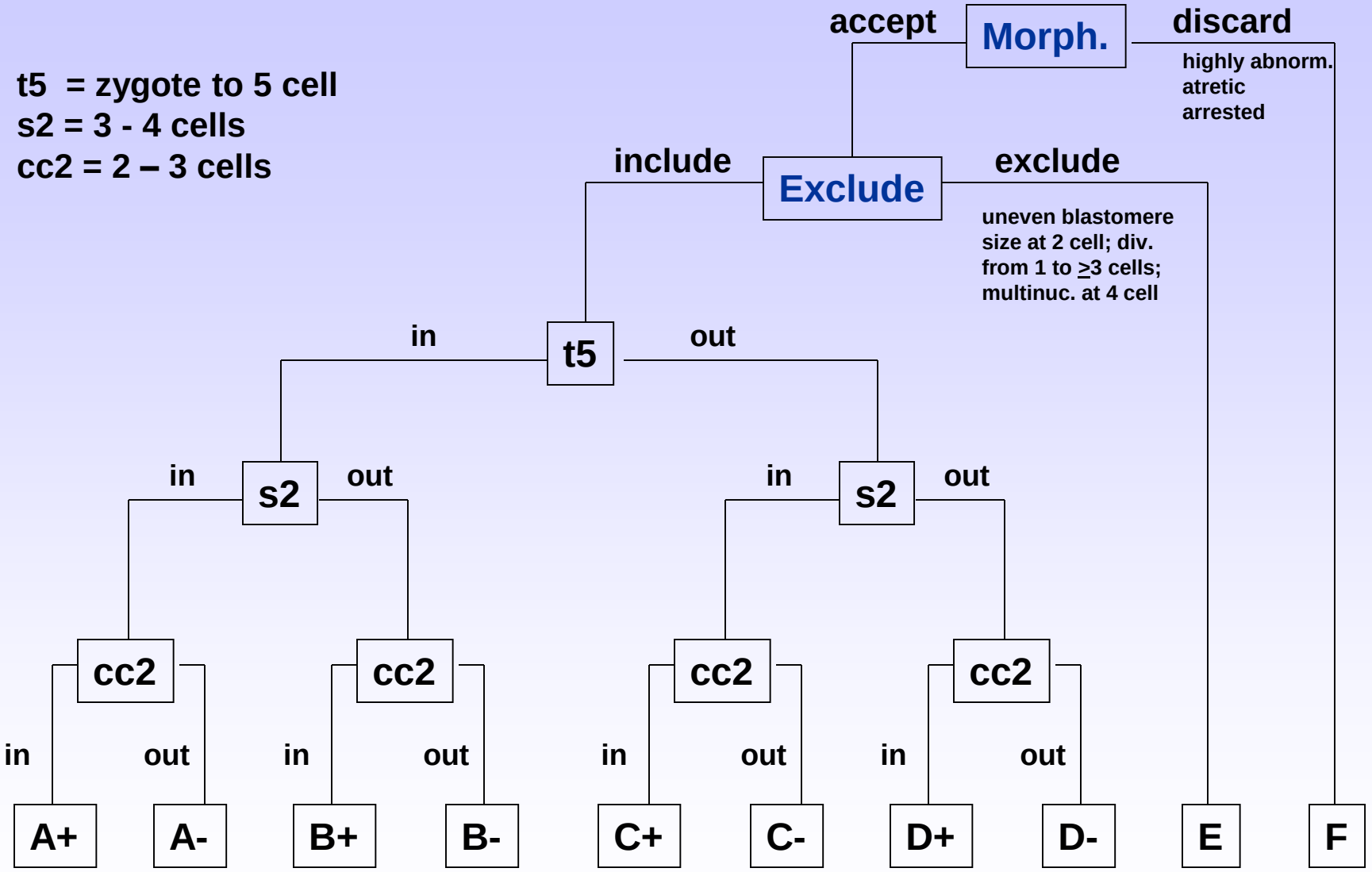
Morphological Assessment of Embryos

All embryos were scored on day 2 (44-48h) and day 3 (64-72h) post ICSI for:

- **cellularity (number of blastomeres)**
- **symmetry/granularity of blastomeres**
- **type and degree of fragmentation**
- **multinucleation**
- **degree of compaction**

Five morphological categories defined via criteria of Alikani *et al.*, 2000, with "1" being the best.

Hierarchical Classification Tree



redrawn from Meseguer et al., 2011

Morphokinetic Hierarchy and Implantation

Meseguer *et al.*, 2011

Category	imp/total (%)	Category	implantation (%)
A+	19/29 (66)	A	52
A-	9/25 (36)		
B+	7/24 (29)	B	27
B-	2/25 (24)		
C+	8/32 (25)	C	19
C-	2/21 (10)		
D+	1/10 (10)	D	14
D-	5/33 (15)		
E	4/48 (8)	E	8

Comparison Between Time-Lapse Categories and Morphological Categories

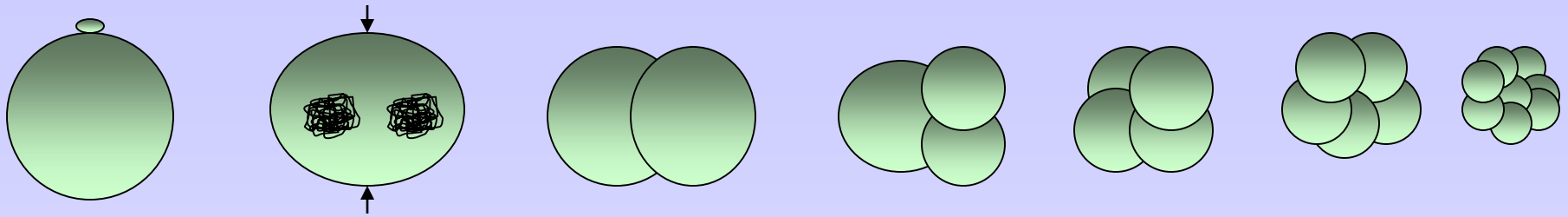
Meseguer *et al.*, 2011

Implantation (%)			
Time-lapse	Imp rate	Morphology	Imp rate
A (n=54)	52	1 (n=35)	43
B	27	2	32
C	19	3	21
D	14	4	13
E	8	5	20

Logistic regression analysis:

morphology, AUC = 0.64

time-lapse, AUC = 0.72



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Meseguer *et al.*, 2011 (endpoint: implantation)

ICSI to 5-cell, 48.8 - 56.6 hrs.

≤ 11 hrs.

≤ 0.76 hrs.

What about blastocyst quality?

Selection of high-potential embryos – microwells and time-lapse imaging.

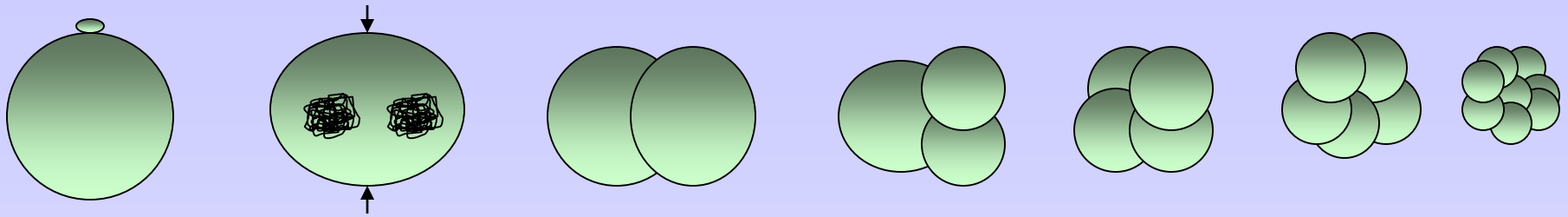
Hashimoto *et al.* Fertil Steril 97:332-337, 2012.

- **80 cryopreserved human zygotes grown in individual PDMS wells**

- **Imaged for 5 days @ 10' intervals in Nikon Biostation CT or Sanyo MCOK-5M imaging incubator**

Endpoint: Quality of blastocysts

Significant predictors: time of 3 to 4 cells (0.7 h)
5 to 8 cells (5.7 h)



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Hashimoto *et al.*, 2012 (endpoint: high versus low scoring blastocysts)

0.7 hrs.

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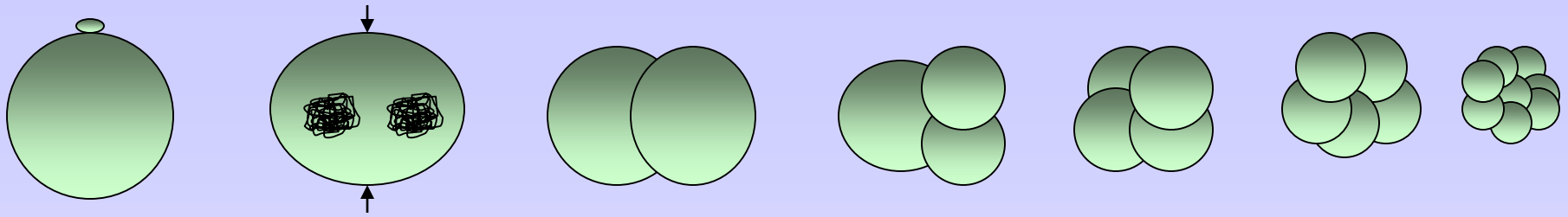

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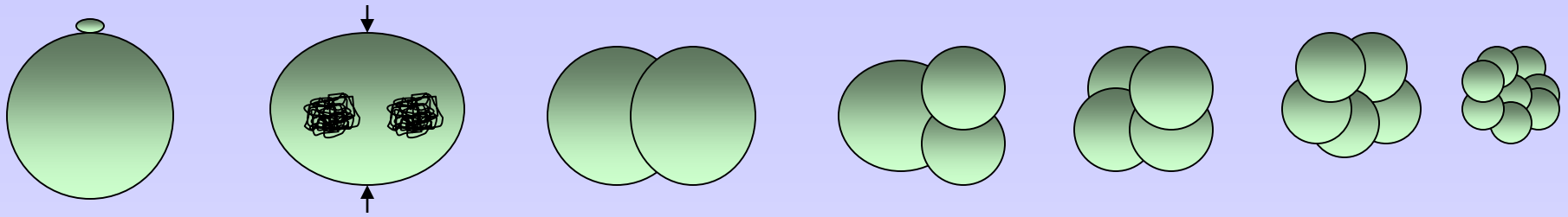

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5.7 hrs.

Morphokinetics: predicting development to blastocyst, expansion and implantation

Dal Canto *et al.*, Reprod. Biomed. Online 25:474-480, 2012.

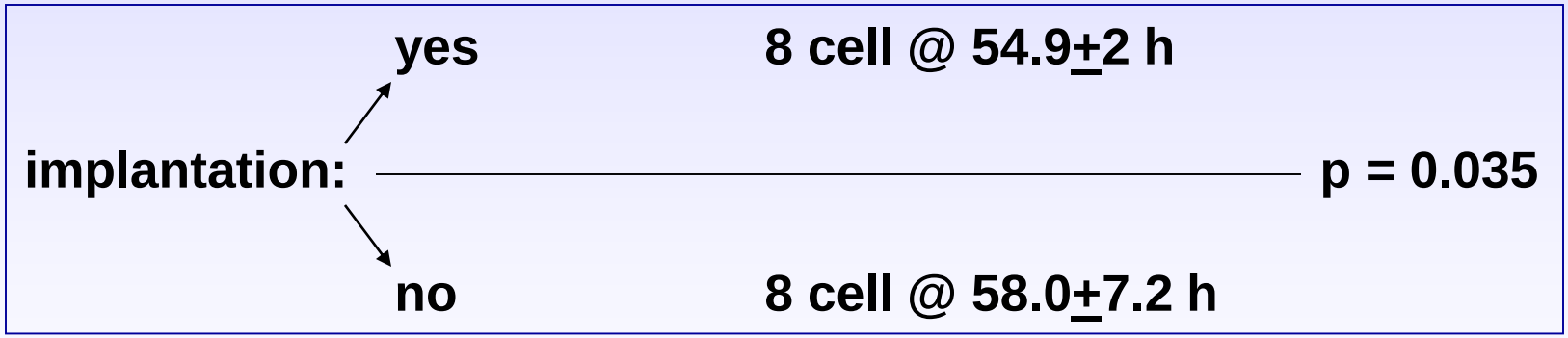
459 zygotes scored from 2 cell to 8 cell with Embryoscope, 20'.

	7 cells		p value
	56.5±8.1	58.8±10.4	0.03
	8 cells		
	61.0±9.4	65.2±13.0	0.0008
	↑	↑	
	Embryos that formed blastocysts	Embryos that arrested after 8 cell stage	

Morphokinetics: predicting development to blastocyst, expansion and implantation

Dal Canto *et al.*, Reprod. Biomed. Online 25:474-480, 2012.

Embryos reaching the blastocyst stage without blastocoel expansion on day 5 associated with progressive cleavage delay



Conclusion: **Conventional static observations on day 2 (42-44 h) and day 3 (66-68 h) are inappropriate for accurate evaluation**

Can time-lapse monitoring (TMS) improve reproductive outcome over standard incubation (SI) in a multicenter trial?

Meseguer *et al.,* Fertil Steril 98:1481-1489, 2012

- **10 centers throughout Spain**
- **All ICSI**
- **1,390 TMS cycles vs. 5915 SI cycles**
- **TMS with Embryoscope, 5 images, 15'**
- **both systems, 5% CO2 in air**
- **TMS utilized hierarchical classification**

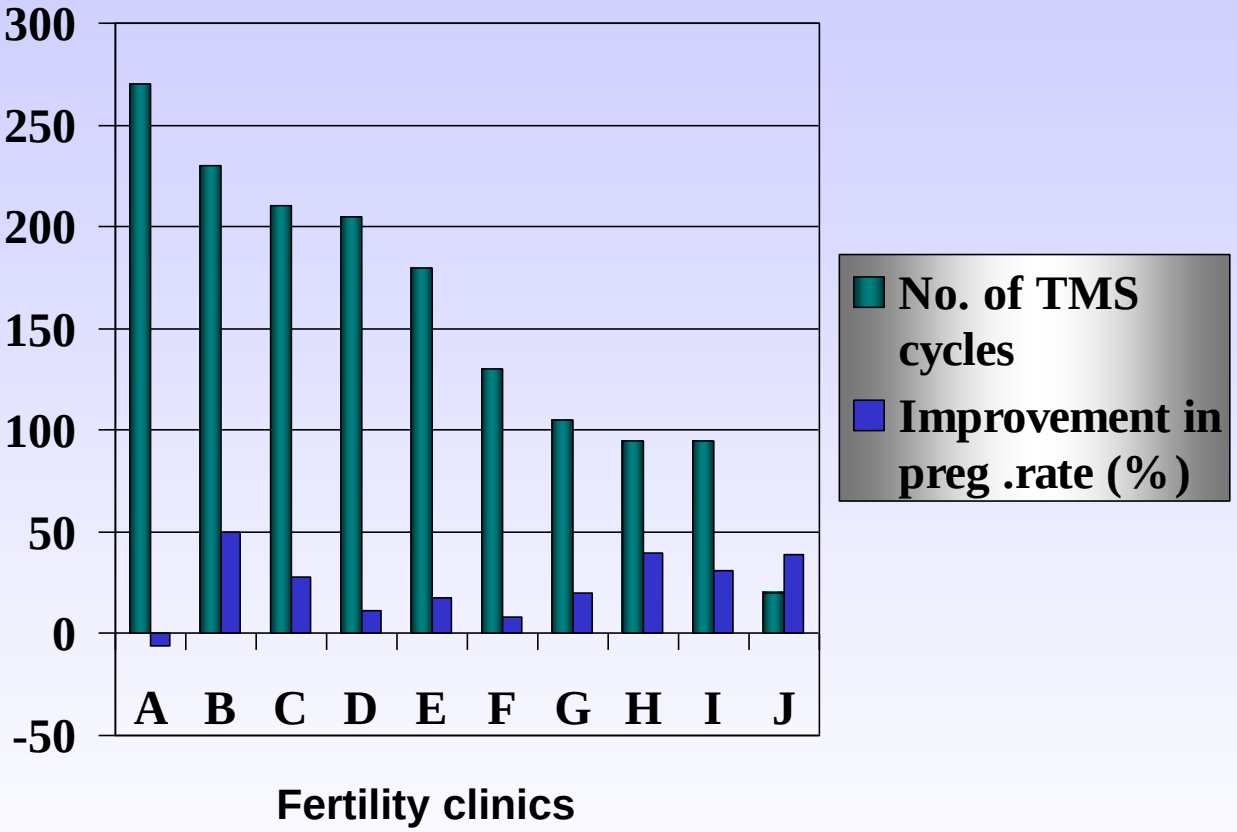
Can time-lapse monitoring (TMS) improve reproductive outcome over standard incubation (SI) in a multicenter trial?

Meseguer *et al.,* Fertil Steril 98:1481-1489, 2012

Logistic regression model, incubation method as covariate:

- **type of incubation**
- **type of cycle (autologous, donor)**
- **day of transfer (d3, d5)**
- **oocyte source (fresh, vitrified)**
- **no. mature oocytes injected**
- **patient age, autologous cycles**
- **no. prior treatments**
- **no. embryos transferred**
- **stimulation protocol**
- **female etiology**
- **clinic where cycle was performed**

Multicenter trial – Meseguer *et al.*, 2012



Avg. improvement = 20% (weighted for no. of TMS cycles)

Multicenter trial – Meseguer *et al.*, 2012

Conclusions:

- **Use of TMS can improve clinical pregnancy rate by an estimated relative 20% [OR 1.201; p = 0.0043]**
- **Use of TMS includes less handling of embryos thus reducing the risk of loss or contamination**
- **TMS offers strictly controlled environment and stable incubation conditions**

Is there a universal algorithm for assessing embryonic viability?

Con:

- **Fertilization method (ICSI v IVF) determines kinetics if insemination time is the starting point.** Cruz *et al.*, 2013.

- **Dose of rFSH and [E2] on day of hCG affect embryo kinetics.** Munoz *et al.*, 2012.

- **Culture technology (medium, pH, O2, etc.)?**

  Ciray *et al.*, 2012 – medium, yes
  Basile *et al.*, 2013 – medium, no

Is there a universal algorithm for assessing embryonic viability?

Pro:

- **Recurring predictive value of similar kinetic measures between unrelated studies**

- **Clinical trials with Eeva**

Clinical validation of embryo culture and selection by morphokinetic analysis: a randomized, controlled trial of the EmbryoScope

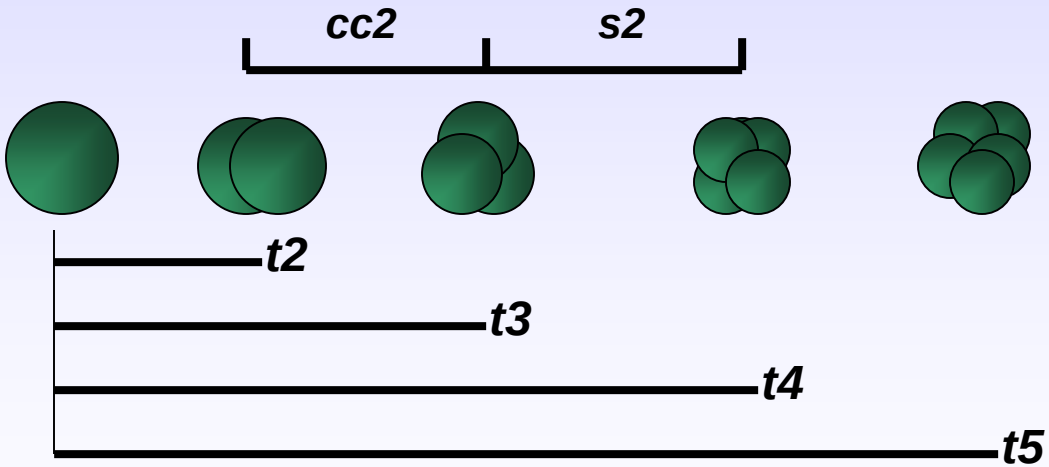
Rubio et al., 2014 Fertil Steril 102:1287-94.

Design: 843 couples, all ICSI (gynecologist/statistician blinded)

Culture: Cook cleavage medium (days 1-3)

Vitrolife CCM (days 3-5); 5.5% CO_2 in air;

Incubation volume – S.I. 50 µl; TMS 25 µl



TMS morphokinetic parameters

Category 1 (best)

Category 5 (worst)

Morphology

Rubio et al., 2014

Embryo Development and Fate

	TMS (n=2638)	Control (n=2427)	*p* value
Fragmentation (%)	7.5 ± 0.1	6.9 ± 9.4	.006
Optimal embryos			
day 3 (%)	46.2	43.1	.010
day 5 (%)	20.9	16.6	.001

Not significantly different:

No. of blastomeres
Symmetry
Blast. rate
Transferred embryos
Cryopreserved embryos

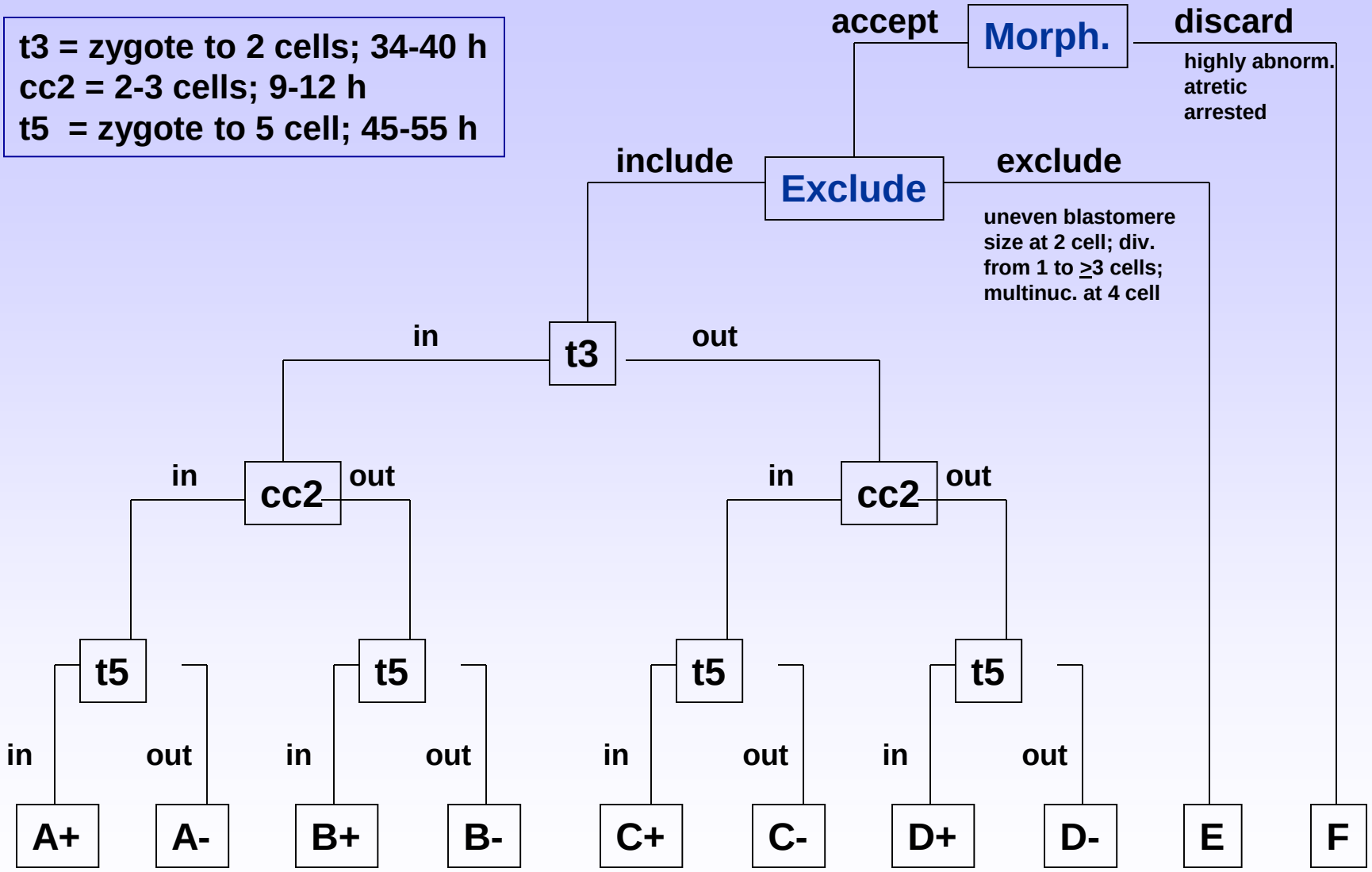
Rubio *et al.*, 2014

Outcome	*TMS*	*Control*	*P value*
Per retrieval (n)	**438**	**405**	
Pregnancy (%)	**61.6**	**56.3**	**.12**
Ongoing preg (%)	**51.4**	**41.7**	**.005**
Per transfer (n)	**415**	**373**	
Pregnancy (%)	**65.3**	**61.1**	**.22**
Ongoing preg (%)	**54.5**	**45.3**	**.01**
All preg cycles	**271**	**228**	
Early preg loss (%)	**16.6**	**25.8**	**.01**
All transferred emb.	**775**	**699**	
implantation rate (%)	**44.9**	**37.1**	**.02**

•***Ongoing pregnancy after 12 wks sig. affected by day of transfer and incubation type (TMS versus S.I.)***

The New Algorithm for Embryo Selection – Multicentric Study

t3 = zygote to 2 cells; 34-40 h
cc2 = 2-3 cells; 9-12 h
t5 = zygote to 5 cell; 45-55 h



Basile et al., Hum Reprod 30:276-283, 2015

*Phase 1, development; n = 765 cycles
Phase 2, test of algorithm; n =885 cycles

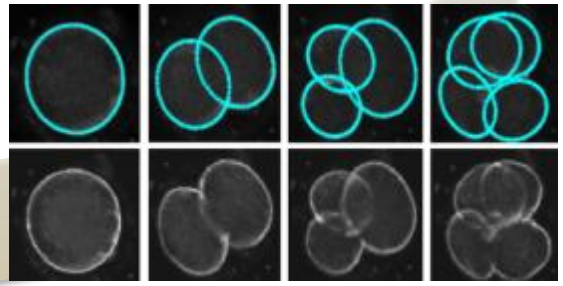
Implantation by Embryo Category – Basile et al., 2015

Category	imp/total (%)	Category	implantation (%)
A+	106/333 (32)	A	32
A-	23/74 (31)		
B+	40/124 (32)	B	28
B-	12/61 (20)		
C+	23/70 (33)	C	26
C-	14/70 (20)		
D+	8/38 (21)	D	20
D-	30/155 (19)		
E	34/197 (17)	E	17

The Eeva Test – How it Works

Multi-well Eeva dish provides individual culture within the same media drop

Eeva System using time lapse imaging and intelligent computer vision software collects data inside a standard incubator



Using a proprietary algorithm, images are automatically analyzed

Eeva Test results deliver consistent and objective information to assist embryo selection

FDA submission pending. Not available for sale in the U.S. CE marked and commercially available in select EU countries.


B
SANYO
O2/CO2 INCUBATOR
Eva
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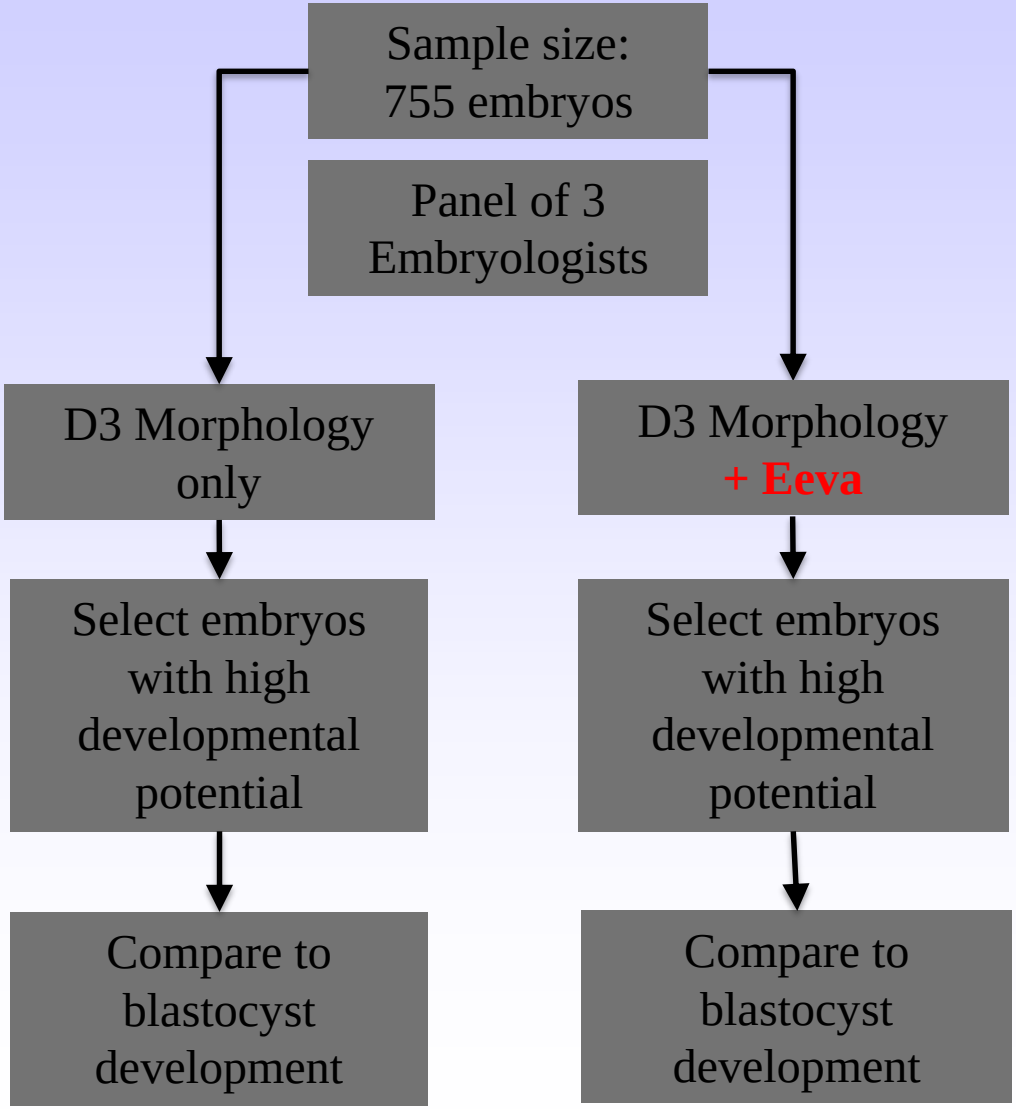
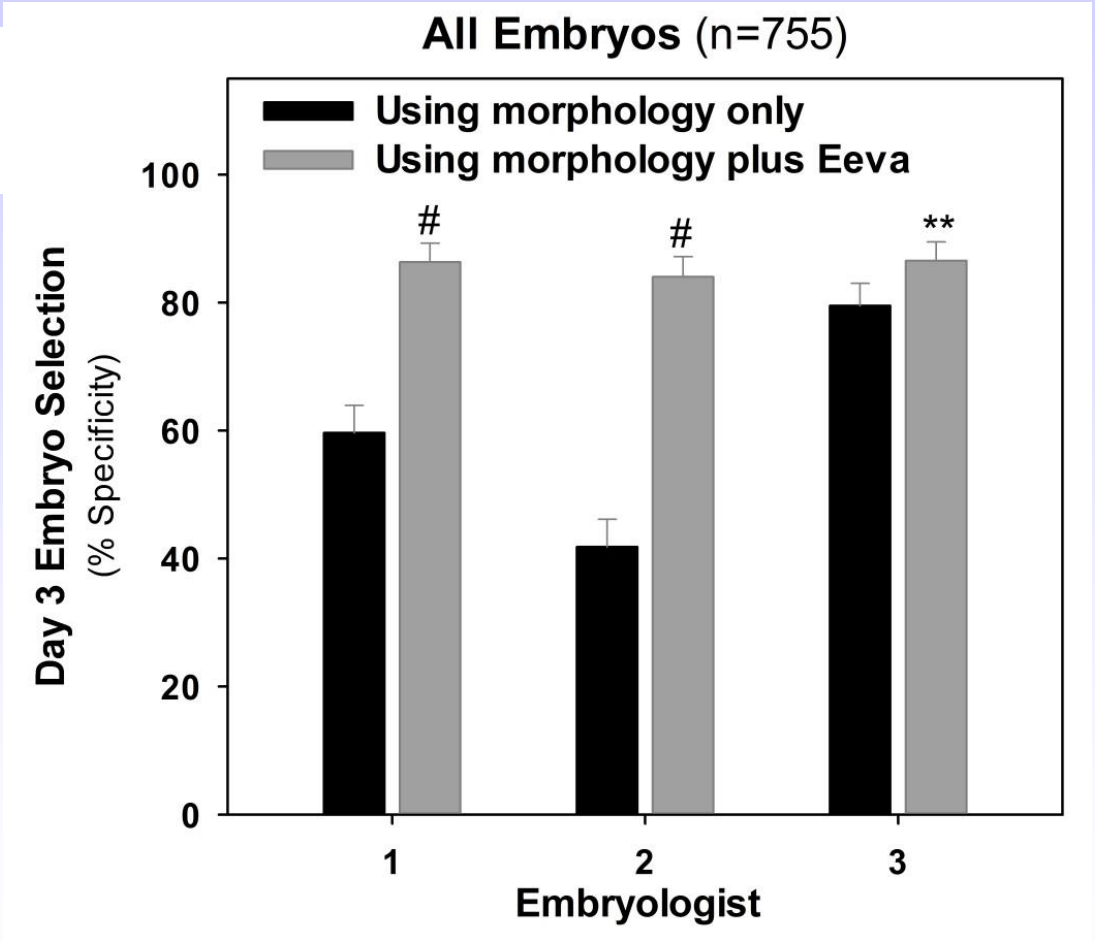
Eeva Adjunct Study



- **Objective:** Compare two methods of selecting the embryos with high developmental potential
- One week wash-out period was given between arms.
- Results were compared to ground truth of blastocyst formation

Conaghan et al. *Fertility & Sterility* (2013)

Eeva Adjunct Study Results

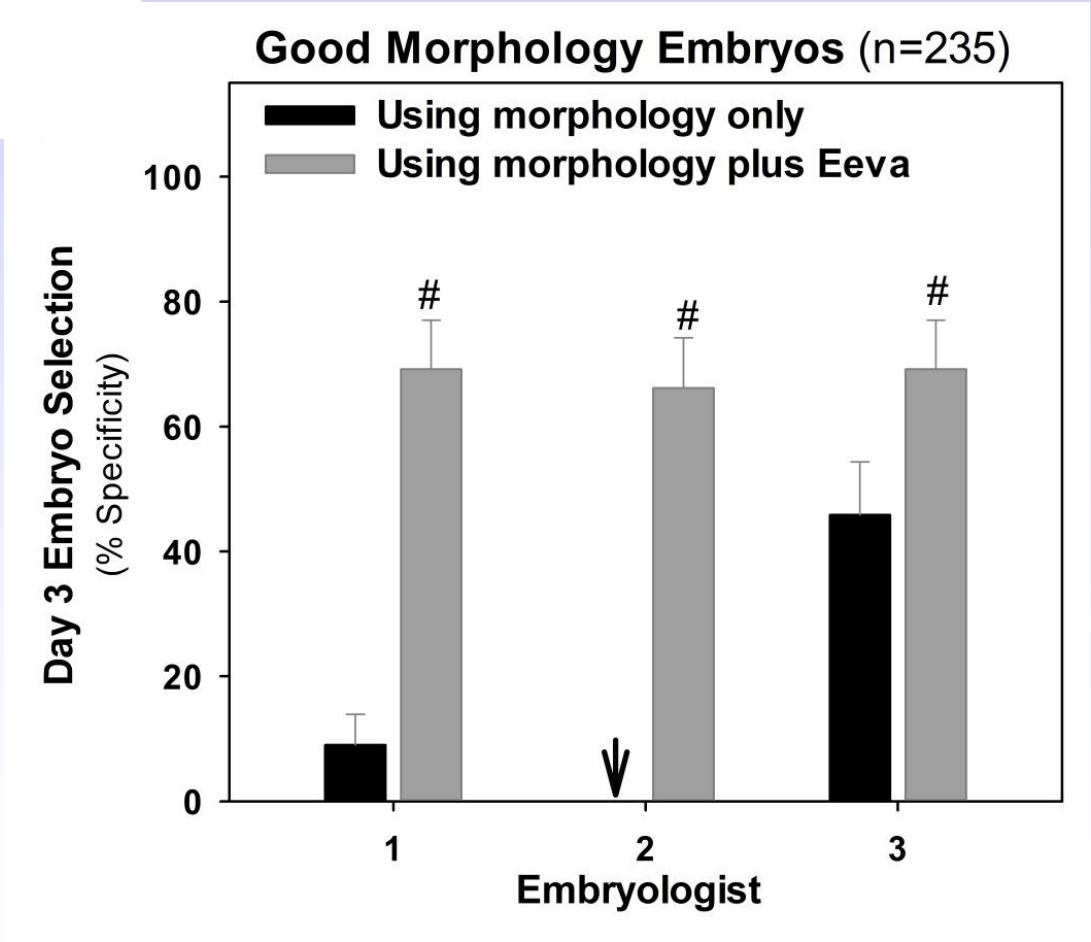


- Specificity – measures false positives
- Significantly improved in 3 out of 3 embryologists
- More consistent embryo assessment using D3 morphology + Eeva information

 # p<0.0001
***p<0.001 relative to Morphology only*

Conaghan et al. *Fertility & Sterility* (2013)

Eeva Adjunct Study Results

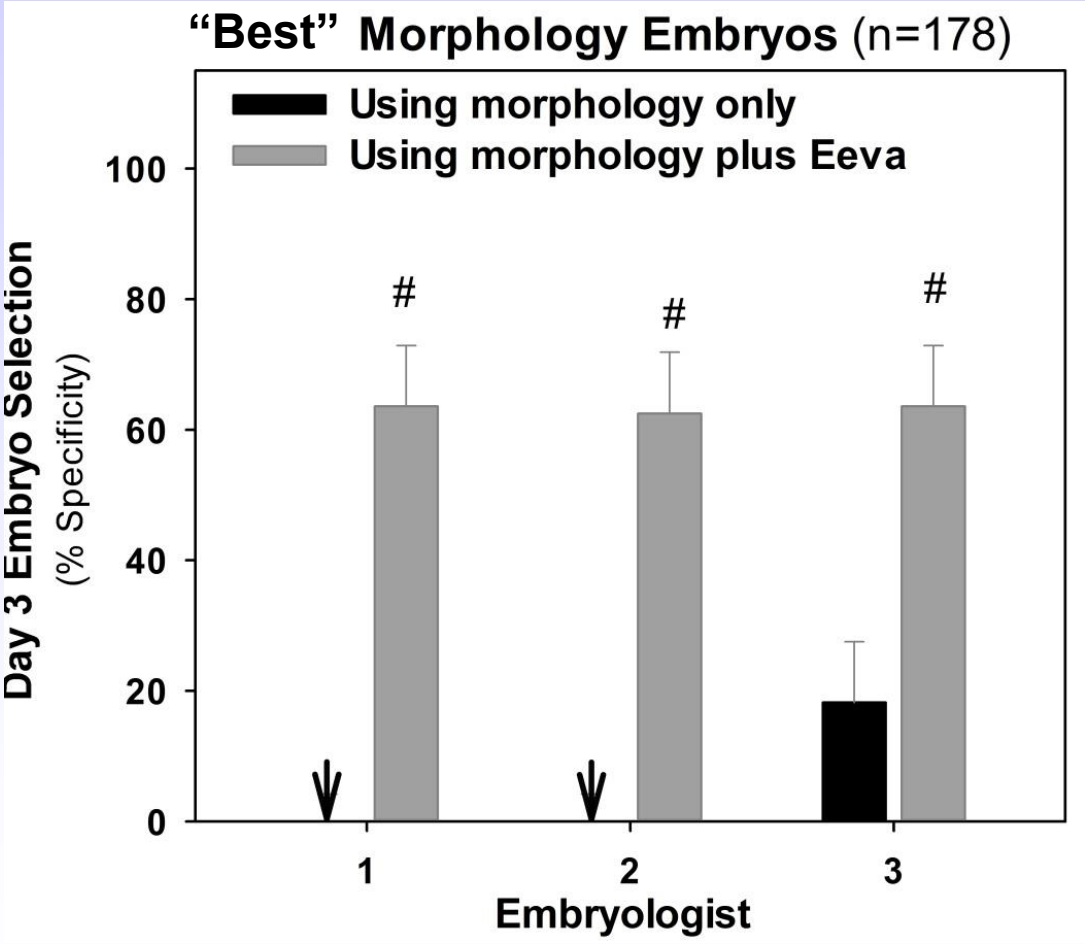


- "Good" morphology:
  - 6-cell and above,
  - <10% fragmentation
  - Perfect symmetry
- Eeva helps discriminate which "good-looking" embryos have high probability to arrest

Conaghan et al. *Fertility & Sterility* (2013)

 # p<0.0001 relative to Morphology only

Eeva Adjunct Study Results



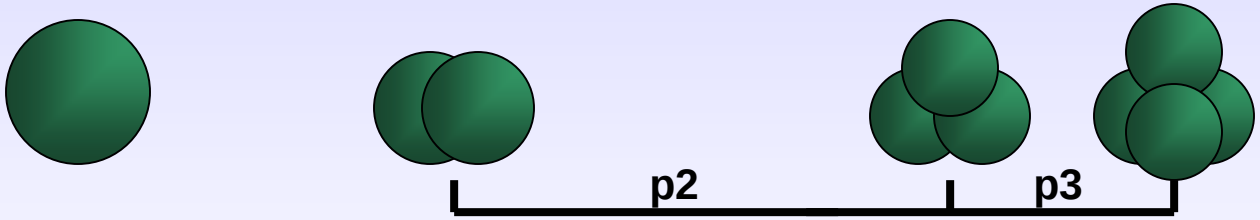
- "Best" morphology:
  - 7-8 cells
  - <10% fragmentation
  - Perfect symmetry
- Eeva helps discriminate which "best-looking" embryos have high probability to arrest

Conaghan et al. *Fertility & Sterility* (2013)

 # p<0.0001 relative to Morphology only

Computer-automated time-lapse analysis results correlate with embryo implantation and clinical pregnancy: A blinded, multi-centre study VerMilyea *et al.*, 2014 Reprod BioMed Online 29:729-36.

Study design: multi-center, non-selection of Eeva scores 205 patients; 6 clinics; Eeva was scored but blinded for transfers, day of ET not stated (assume d5).



Eeva	*p2*	*p3*
High	9.33 – 11.47 h	0 – 1.73 h
Medium	9.33 – 12.65 h	0 – 4 h

VerMilyea *et al.*, 2014

Correlation of Eeva Score and Implantation

	Eeva score			
	High	***Medium***	***Low***	***P-value***
Implant. rate	***41/111***		***50/220***	
(%)	***37***		***23***	***.003***
Implant. rate	***41/111***	***29/83***	***21/137***	
(%)	***37***	***35***	***15***	
	37	***35***		***NS***
	37		***15***	***.0001***
		35	***15***	***.0004***

VerMilyea *et al.*, 2014

Correlation of Eeva Score and Clinical Pregnancy

Transferred	Patients	No. emb trans.	Preg rate
At least:			
one high	105	1.8 ± 0.8	51% (54/105)
Only low	100	1.8± 0.7	39% (39/100)

At least one Eeva high versus only Eeva low, p=0.04

VerMilyea *et al.*, 2014

Correlation of Eeva Score and Clinical Pregnancy

Transferred	Patients	No. emb trans.	Preg rate
At least:			
one high	105	1.8 ± 0.8	51% (54/105)
one medium	53	1.8 ± 0.7	43% (23/53)
Only low	47	1.8 ± 0.8	34% (16/46)

At least one Eeva high versus only Eeva low, p=0.02

Patient Enrolled In MERGE Trial

MERGE Study	Prospective (selection study), multi-center, single arm
Purpose	To record and evaluate the use of traditional morphology grading combined with Eeva in IVF treatment.
# of clinics	11 clinics in US
Total patients enrolled	533 patients consented and enrolled
Patient population	All comers
Protocol	Embryo selection for fresh transfer is using Eeva Results adjunctive to traditional morphology grading.
Results	213 Day 3 fresh ET 234 Day 5 fresh ET 69 cases no fresh ET

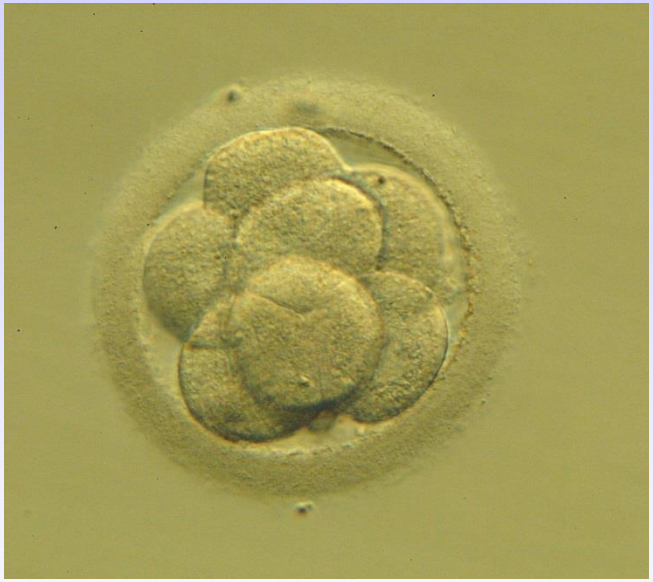
MERGE stands for MulticEnter ReGistry with Eeva

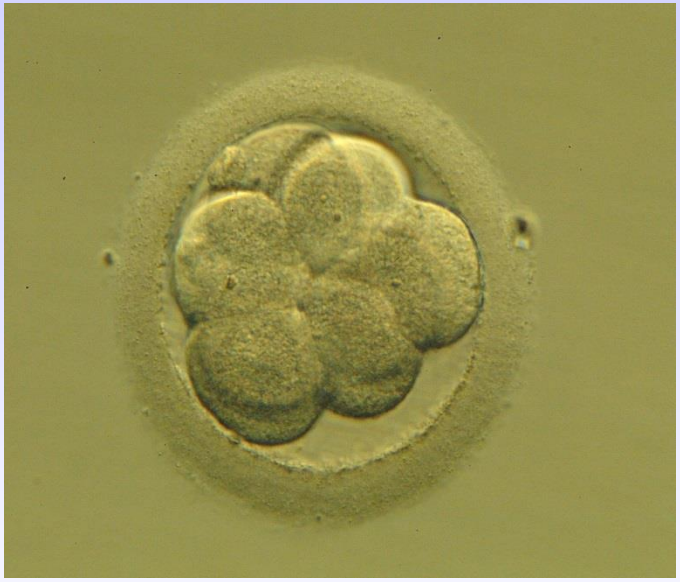
Fertility Center of San Antonio
2014

Day 3 transfers (no PGS, no donor oocytes):

Age range: 25-45
Clinical pregnancy rate: 138/248 (55.6%)
Implantation rate: 197/505 (39%)

Age < 35
Clinical pregnancy rate: 75/117 (64.1%)
Implantation rate: 115/217 (53%)





Merge- San Antonio

MERGE Interim Analysis

	Day 3 Practice (3 sites)	Day 5 Practice Overall	Day 3 ET San Antonio
# Patients	106	234	42
Age	32.3 ± 4.1	34.0 ± 4.7	32.5 ± 4.5
# 2PN	8.5 ± 4.0	10.5 ± 5.6	8.7 ± 4.3
# Embryos transferred	2.0 ± 0.5	1.5 ± 0.5	2.0 ± 0.3
Positive hCG	70 (66%)	158(68%)	32 (76%)
Clinical Pregnancy	63 (60%)	134 (57%)	28 (67%)
Implantation Rate	80/215 (37%)	146/349 (42%)	37/83 (44%)
Multiple Rate	22/63 (35%)	24/134 (19%)	12/28 (43%)

Fertility Center of San Antonio
Effect of Eeva in MERGE Study

Embryos transferred	n	+hCG	FHR	Ongoing
Only Eeva "low"	22	14 (63.6%)	11 (50%)	11 (50%)
Only Eeva "high"	11	9 (81.8)	11 (81.8)	8 (72.7)
At least 1 "high"	22	20 (90.9)	18 (81.82)	16 (72.7)

Eeva and Cryopreservation

Eeva	Trans.	Cryo.	Total
Low	58 (17%)	33 (11.8%)	338
High	31 (37%)	25 (47.2%)	84

Time-lapse Analysis and Aneuploidy

- **Is there are relationship between morphokinetics and embryo aneuploidy?**

- **Is it possible to develop an algorithm, based upon different kinetic behaviors, that distinguishes euploid from aneuploid embryos?**

Potentially:

Campbell *et al.*, 2013a
Campbell *et al.*, 2013b
Campbell *et al.*, 2014
Basile *et al.*, 2014

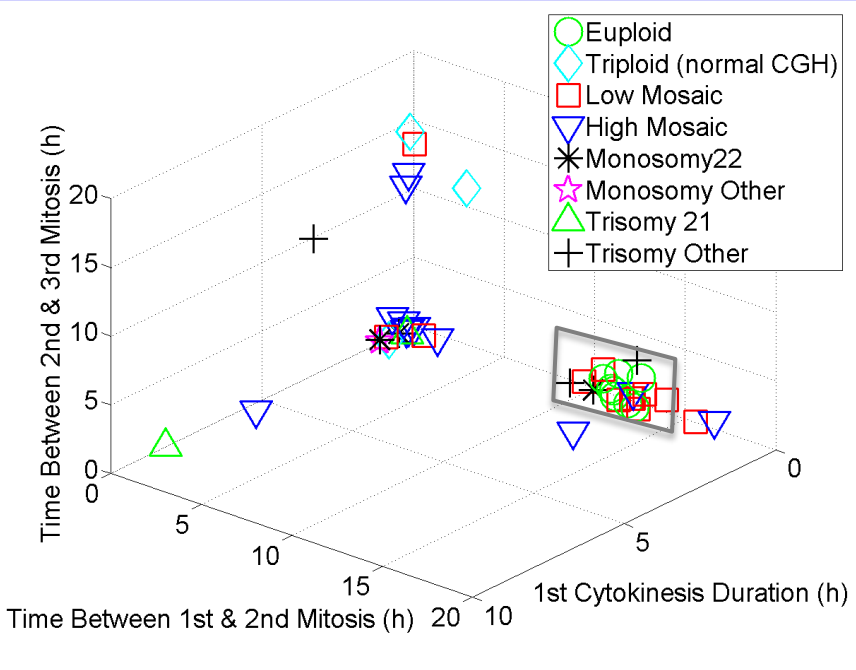
Premature:

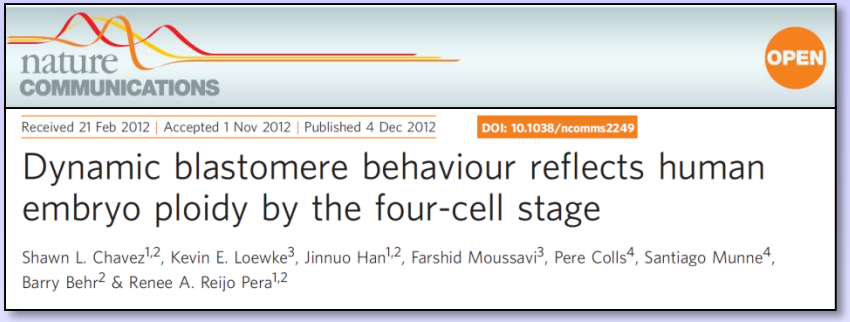
Ottolini *et al.*, 2014

No:

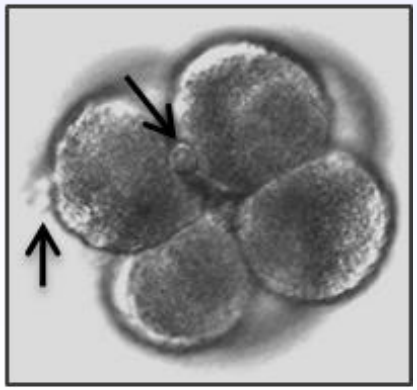
Rienzi *et al.*, 2015

Cell Division Timing & Cleavage-Stage Aneuploidy

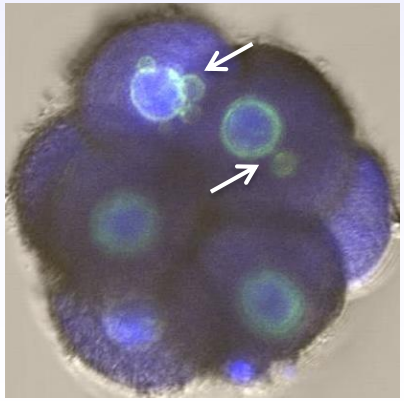




- Time-lapse imaging to 4-cells and chromosomal analysis by aCGH
- Molecular analysis of chromosome localization suggested sequestration in fragments
- Dynamic assessment of fragmentation via cell tracking algorithms



Fragments



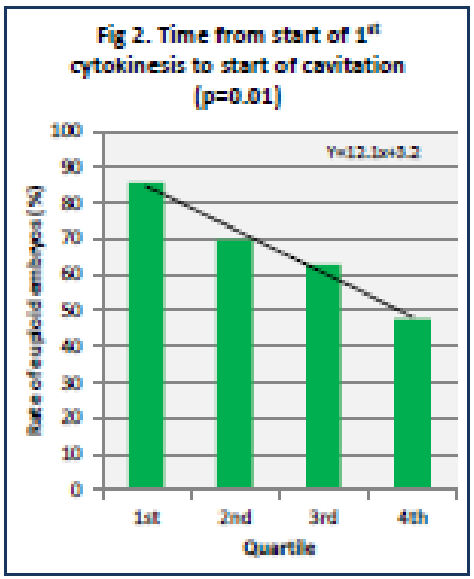
Lamin B-1 / DAPI

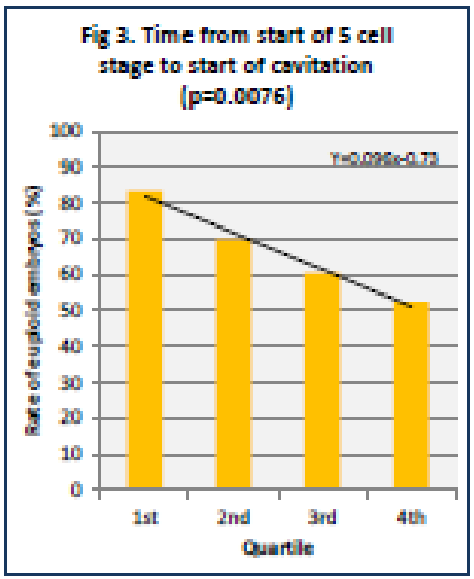
Chavez et al. *Nature Communications* (2012)

Time to Cavitation and Blastocyst Aneuploidy

EARLY TIMES TO CAVITATION ARE ASSOCIATED WITH A REDUCED PREVALENCE OF ANEUPLOIDY IN EMBRYOS CULTURED TO THE BLASTOCYST STAGE: A PROSPECTIVE BLINDED MORPHOKINETIC STUDY

Kathleen H. Hong, MD[1,2], Eric J. Forman, MD[1,2], Andrew Prodoehl, BA[1],
Kathleen M. Upham, BS[1], Nathan R. Treff, PhD[1,2], Richard T. Scott, Jr., MD, HCLD[1,2]
[1]Reproductive Medicine Associates of New Jersey, [2]Rutgers-Robert Wood Johnson Medical School





tCav = time from start of 1st cytokinesis to start of cavitation

T5cell to Cav = time from start of 5 cell to start of cavitation

1. **Patterns of temporal development through the cleavage stage do not predict blastocyst stage aneuploidy**

2. **Two new late stage parameters were correlated with blastocyst aneuploidy risk**

Hong et al. *ASRM 2013, Boston, MA*
Scientific Program Third Prize Poster

No evidence of association between blastocyst aneuploidy and morphokinetic assessment in a selected population of poor-prognosis patients: a longitudinal cohort study Rienzi *et al.* 2015 RBMO 30:57-66.

Study design: longitudinal cohort, 138 patients, 455 blastocysts

Patients: maternal age >36 (n=102); >2 failed IVF (n=16); >2 SAB (n=20) alone or in combination.

Imaging: EmbryoScope post ICSI; 7 focal planes every 7'

PGS: trophectoderm biopsy of all expanded blastocysts at 120 – 160 hours (5-10 cells); CCS via qPCR

Rienzi *et al.* 2015 RBMO 30:57-66.

Parameter	Median Euploid (n=186)	Aneuploid (n=269)	OR
Syngamy	24.06	24.11	0.016
T2	26.61	26.63	0.01
T3	37.48	37.74	0.02
T4	38.62	39.17	0.01
T5	51.15	51.83	0.01
T8	59.83	58.46	0.00
CC1	2.50	2.50	-0.055
CC2	11.5	11.64	0.037
S2	0.75	0.75	-0.009
S3	5.91	6.01	-0.003
CC3	13.95	13.66	0.011
CC3/CC2	1.20	1.20	0.025
T5 - T2	25.19	25.27	0.012
Initation of:			
compaction	90.35	91.07	0.004
blastulation	103.77	102.52	-0.004
Complet. blast	117.05	117.32	0.012

**No significant difference for any parameter.

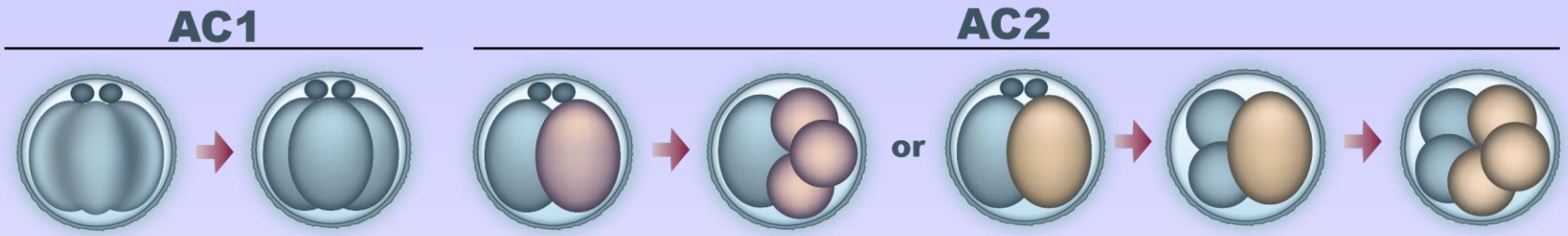
Time-lapse Analysis and Embryo De-selection

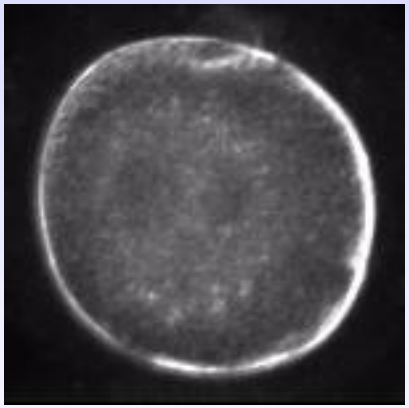
Atypical embryo phenotypes identified by time-lapse microscopy: high prevalence and association with embryo development

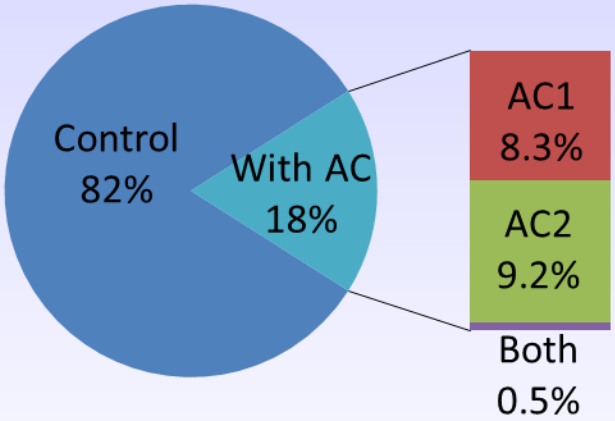
Kelly Athayde Wirka, M.S.,[a] Alice A. Chen, Ph.D.,[a] Joe Conaghan, Ph.D.,[b] Kristen Ivani, Ph.D.,[c] Marina Gvakharia, M.D., Ph.D.,[d] Barry Behr, Ph.D.,[e] Vaishali Suraj, M.S.,[a] Lei Tan, Ph.D.,[a] and Shehua Shen, M.D.[a]

[a] Auxogyn, Menlo Park; [b] Pacific Fertility Center, San Francisco; [c] Reproductive Science Center of the Bay Area, San Ramon; [d] Fertility Physicians of Northern California, Palo Alto Medical Foundation, San Jose; and [e] Stanford Fertility and Reproductive Medicine Center, Palo Alto, California

Abnormal Cleavage







	Blast Rate	Impl Rate
Control (n=524)	43%	18%
With AC (n=115)	12%	4%
p-value	<0.0001	0.05

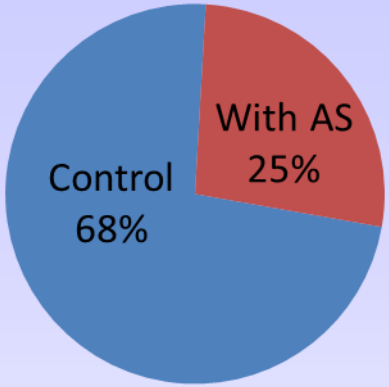
- **AC1 and AC2 embryos are often selected for Day 3 transfer (28.6%)**
- **AC embryos are often good quality (46.9% 6-10 cells, ≤10% frag)**
- **Morphology is unable to detect AC embryos**
- **Implantation Rate: 3.7%**

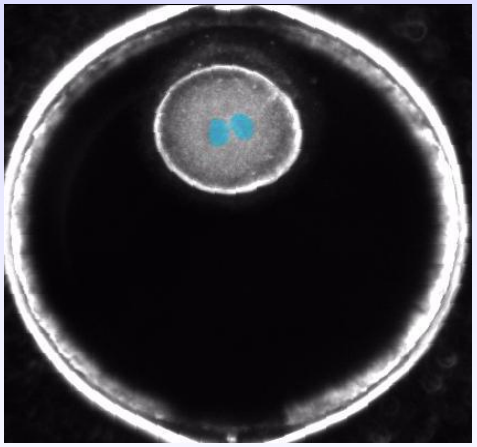
Athayde Wirka et al. *Fertil & Steril,* In Press

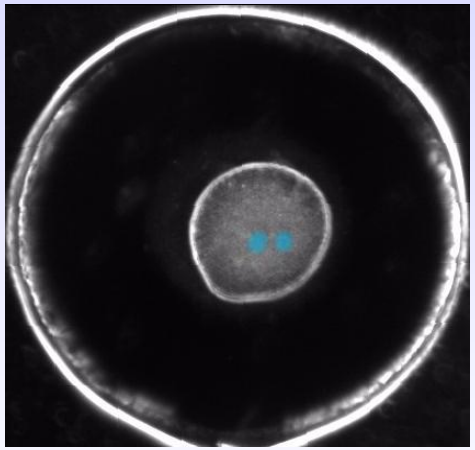
Abnormal Syngamy

Normal

Abnormal Syngamy





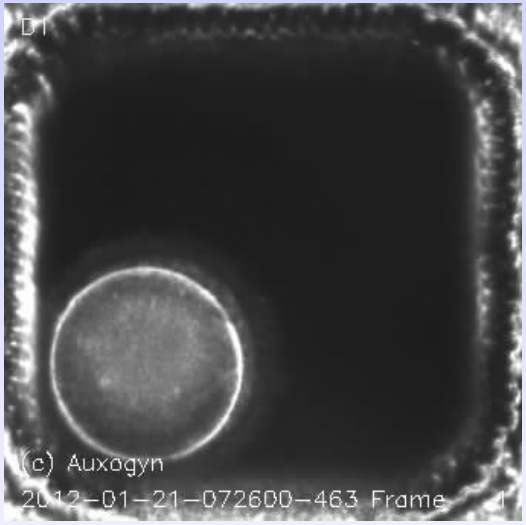


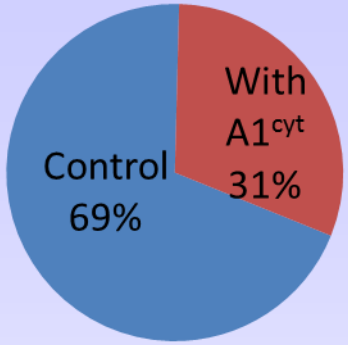
	Blast Rate	Impl Rate
Control (n=443)	45%	18%
With AS (n=163)	22%	0%
p-value	<0.0001	0.08

- **AS is associated with poorer developmental potential**
- **Many AS embryos have good morphology on Day 3 and Day 5 and are selected for transfer or freezing**
- **AS may be related to centrosomes from abnormal sperm**

Athayde Wirka et al. *Fertil & Steril*, In Press

Abnormal First Cytokinesis (A1^{cyt})





	Blast Rate	Impl Rate
Control (n=443)	45%	17%
With A1^{cyt} (n=196)	22%	6%
p-value	<0.0001	0.1

- **A1^{cyt} phenotype is associated with poorer developmental potential**
- **Previously research has correlated 1st cytokinesis timing (P1) to developmental competence**
- **Combining A1^{cyt} phenotype and P1 timing may more finely discriminate embryos for de-selection**

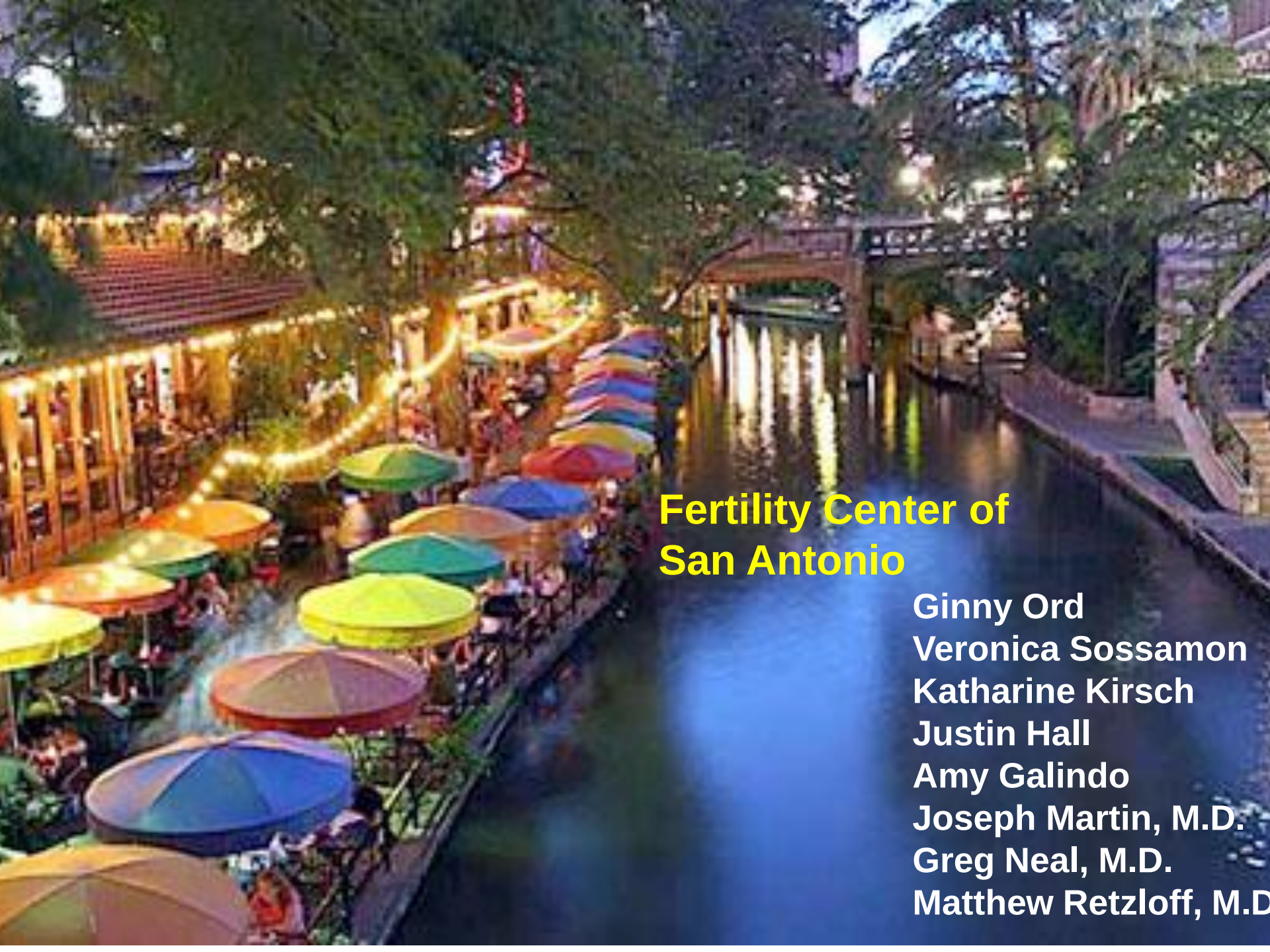
Athayde Wirka et al. *Fertil & Steril*, In Press

Conclusions

Time-lapse analysis, coupled with morphology, significantly improved implantation and clinical pregnancy in multi-center trials using two time lapse systems and algorithms.

Embryo kinetic behavior is affected by aneuploidy but does not appear to be sufficient to define ploidy status at the individual embryo level.

Time-lapse analysis provides a unique opportunity to de-select embryos that show abnormalities of cleavage, syngamy and/or cytokinesis compared to static evaluation.



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