Eeva Test: The GPS of Time-Lapse

2015 ABB CRB Workshop

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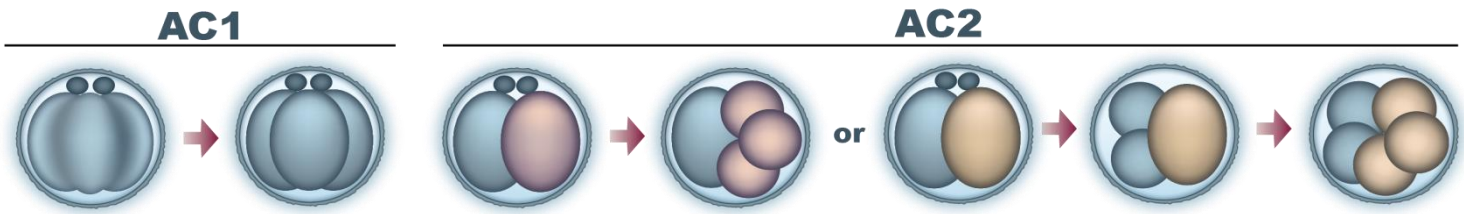
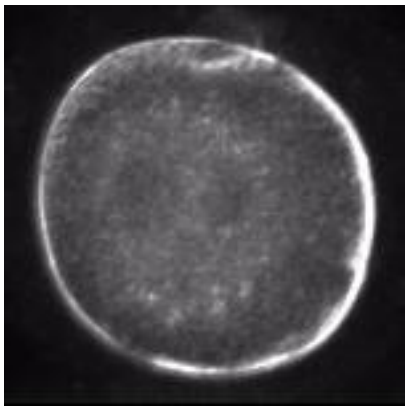
Vice President, Medical & Scientific Affairs, Auxogyn

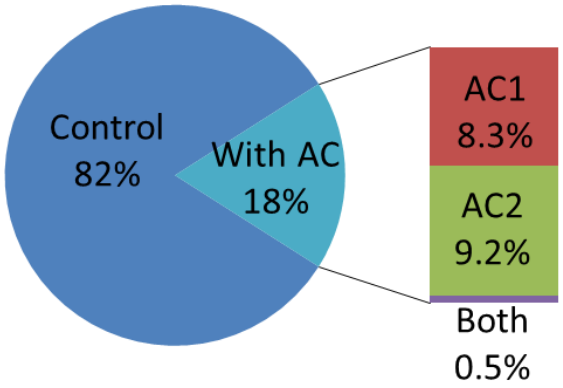
Challenges of Time Lapse

1. Time Lapse = Lots of information
   - ❑ True
   - ❑ False
   - ❑ Don't know
2. Lots of information = useful information
   - ❑ True
   - ❑ False
   - ❑ Don't know
3. Do you know what information Time Lapse gives to you?
   - ❑ Yes
   - ❑ No
   - ❑ Maybe

Abnormal Cleavage







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

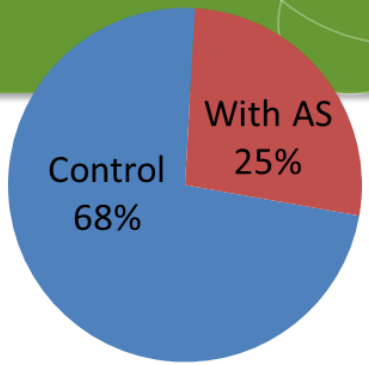
- AC1 and AC2 embryos are often selected for Day 3 transfer (28.6%)
- AC embryos are often good quality (46.9% 6-10 cells, ≤10% frag)
- Morphology is unable to detect AC embryos
- Implantation Rate: 3.7%

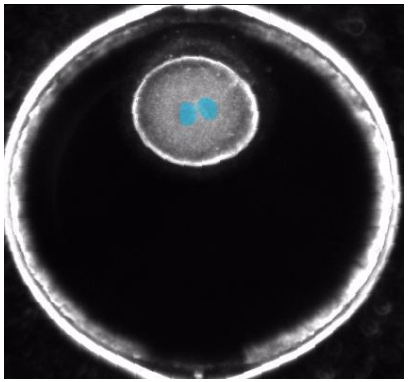
Athayde Wirka , et al., Atypical embryo phenotypes identified by time-lapse microscopy: high prevalence and association with embryo development, *Fertility & Sterility.* 101(6):1637-48, (2014)

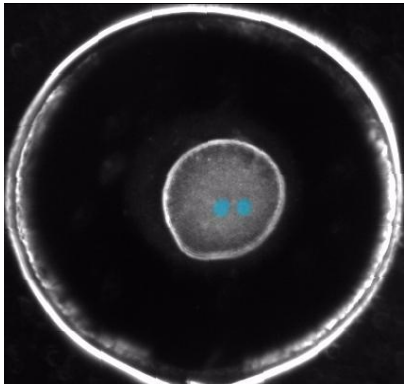
Abnormal Syngamy

Normal Syngamy

Abnormal Syngamy (AS)





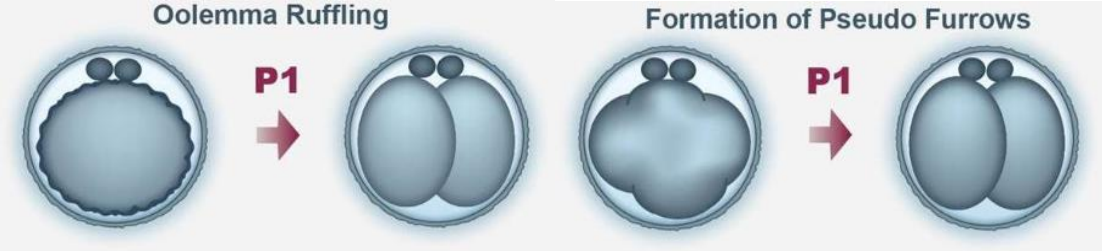


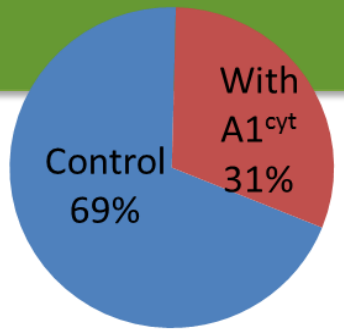
	Blast Rate	Impl Rate
Control (n=443)	45%	18%
With AS (n=163)	22%	0%
p-value	<0.0001	0.08

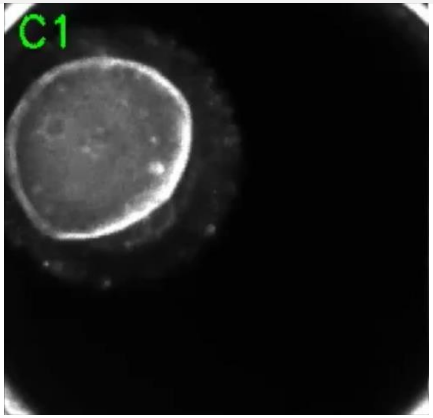
- AS is associated with poorer developmental potential
- Many AS embryos have good morphology on Day 3 and Day 5 and are selected for transfer or freezing
- AS may be related to centrosomes from abnormal sperm

Athayde Wirka , et al., Atypical embryo phenotypes identified by time-lapse microscopy: high prevalence and association with embryo development, *Fertility & Sterility.* 101(6):1637-48, (2014)

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 [1]
- Combining A1^{cyt} phenotype and P1 timing may more finely discriminate embryos for de-selection

Athayde Wirka , et al., Atypical embryo phenotypes identified by time-lapse microscopy: high prevalence and association with embryo development, *Fertility & Sterility.* 101(6):1637-48, (2014). [1] Wong et al. *Nature Biotechnology* (2010)

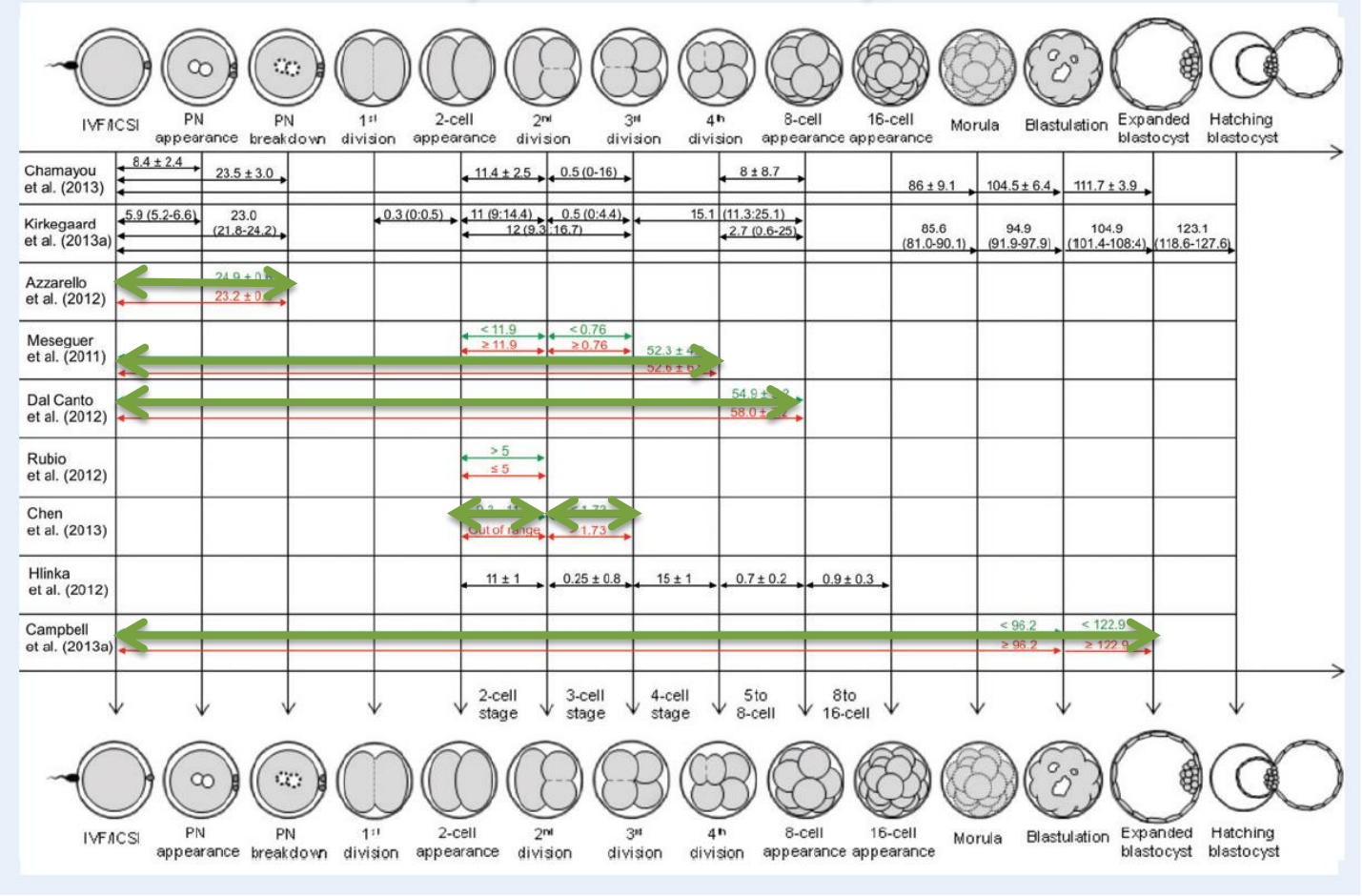
Biological Parameters

Time-lapse observations:

- Abnormal cleavage
- Reverse cleavage
- Multinucleation
- Fragmentation dynamics
- Blastocyst collapsing and re-expansion
- …

Time-lapse markers

Reviewed by Kaser and Racowsky, HRU 2014



More Challenges of Time Lapse

1. Do you know what “algorithm” means and what “statistical modeling” is?
   - ❑ Yes
   - ❑ No
   - ❑ Don’t know

2. How much time do you have to grade embryos and prepare for embryo transfer for each case, on an average basis?
   - ❑ 15 minutes
   - ❑ 30 minutes
   - ❑ Unlimited time

Time-lapse parameters: Just watching is NOT enough

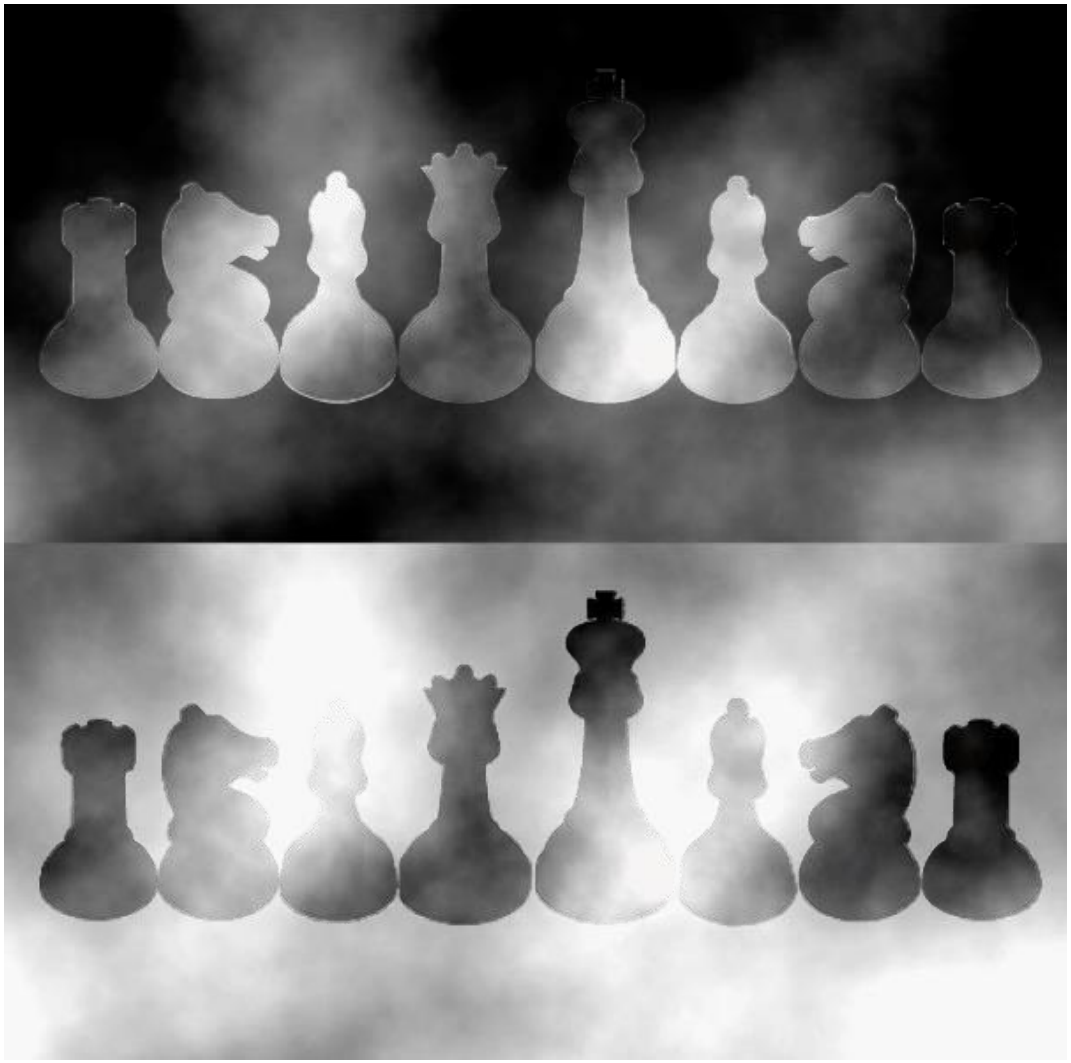
Two Examples:

1. We need to watch and *see*
2. We need to *see beyond* what human vision allows

Example 1: We need to watch and ***see***

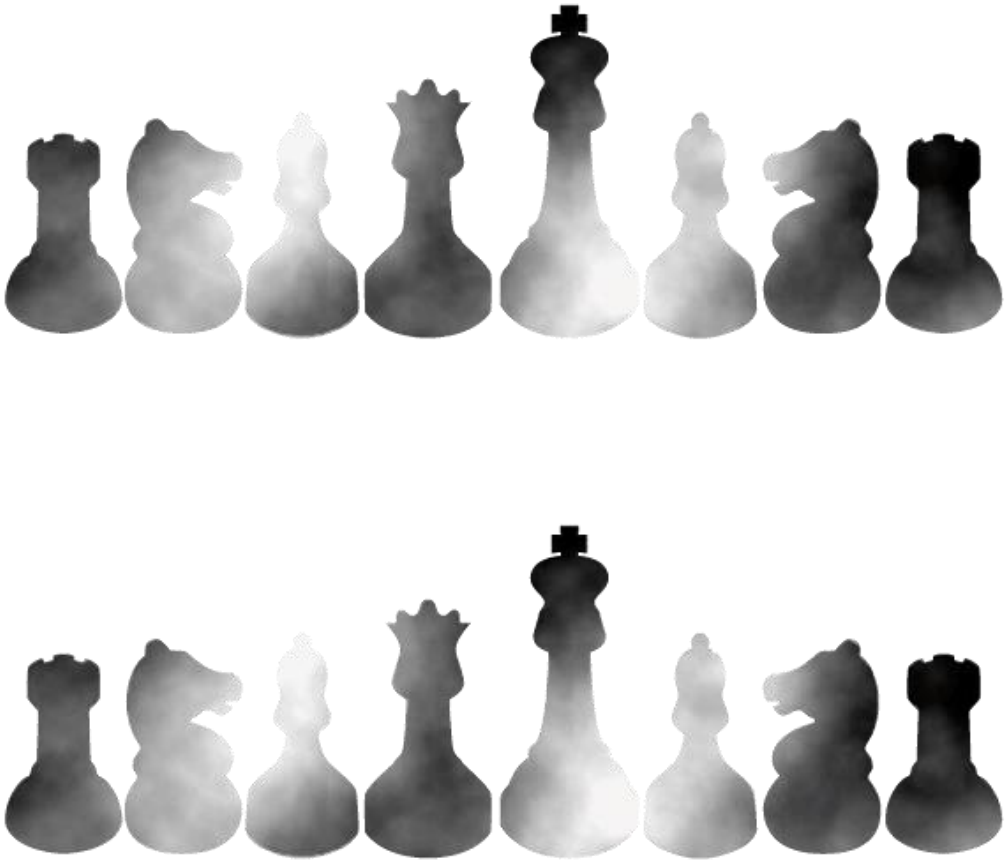
Chabris & Simons, Harvard University/University of Illinois, Urbana-Champaign, 1999

Example 2: We need to see beyond



Barton & Winawer, *Nature* 2005

Example 2: We need to see beyond



Barton & Winawer, *Nature* 2005

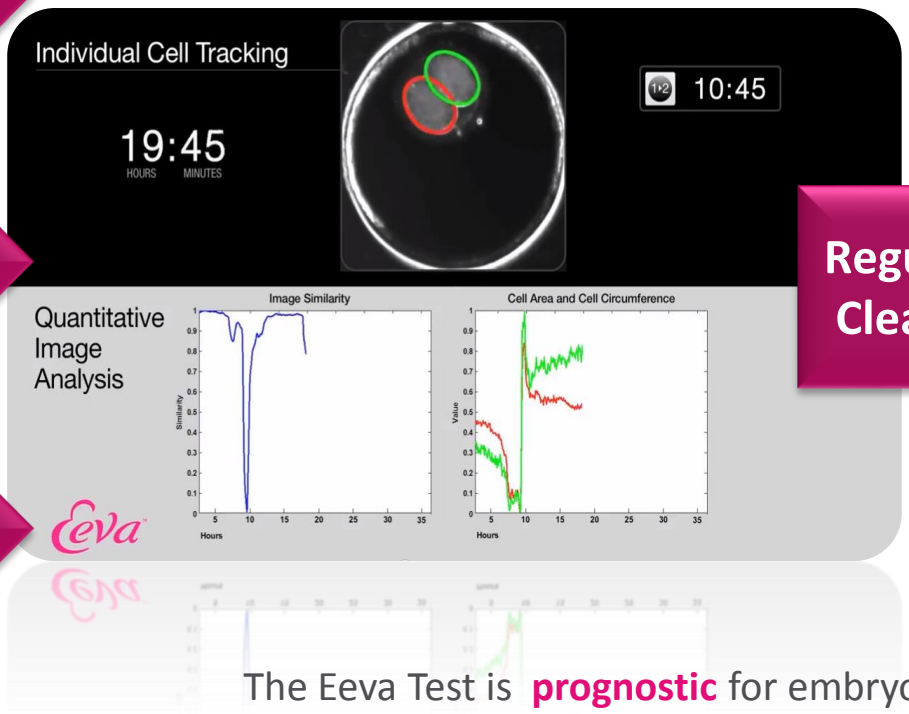
The Eeva Test

Biological Parameters

Statistical Modeling

Automation + Computer Vision

Clinical Validation



Regulatory Clearance

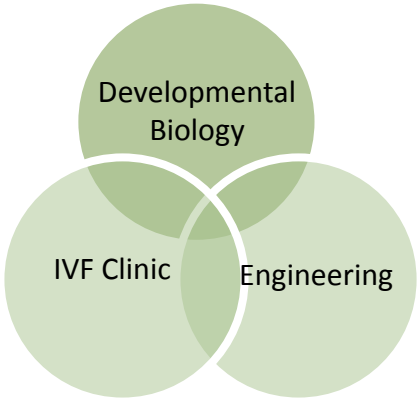
Proven benefit to patients

The Eeva Test is **prognostic** for embryo selection

The Eeva Test provides **objective** information about the developmental potential of embryos

Founded on Science. Dedicated to your Success

STANFORD UNIVERSITY



TIME

Top 10 Medical Breakthroughs of 2010

TOP 10 MEDICAL BREAKTHROUGHS

8. Predicting IVF Success

By Alice Park | Thursday, Dec. 09, 2010

For couples choosing to start a family with in vitro fertilization (IVF), the odds are not always in their favor. The procedure, even under the best circumstances, has a 30% chance of resulting in a live birth on average. So it was welcome news indeed when Stanford University researchers reported on a new method for selecting the strongest embryos, which would most likely result in a pregnancy and live birth.

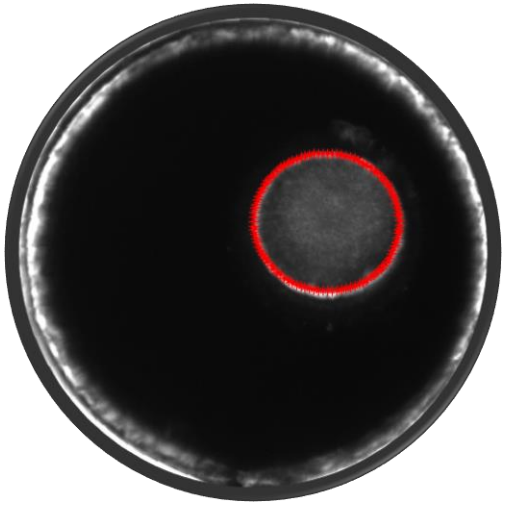
nature biotechnology

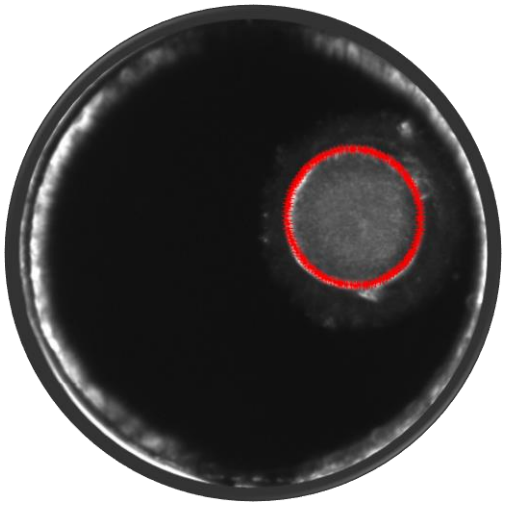
Non-invasive imaging of human embryos before embryonic genome activation predicts development to the blastocyst stage

Connie C Wong[1,2,7], Kevin E Loewke[1–3,6,7], Nancy L Bossert[4], Barry Behr[2], Christopher J De Jonge[4], Thomas M Baer[5] & Renee A Reijo Pera[1,2]

Inside the Eeva System…

Identify Cell Divisions





Calculate Timing Intervals

P2: 10 hrs. 10 min
P3: 10 min

P2: 14 hrs. 15 min
P3: 10 min

Classify Embryos

HIGH

LOW

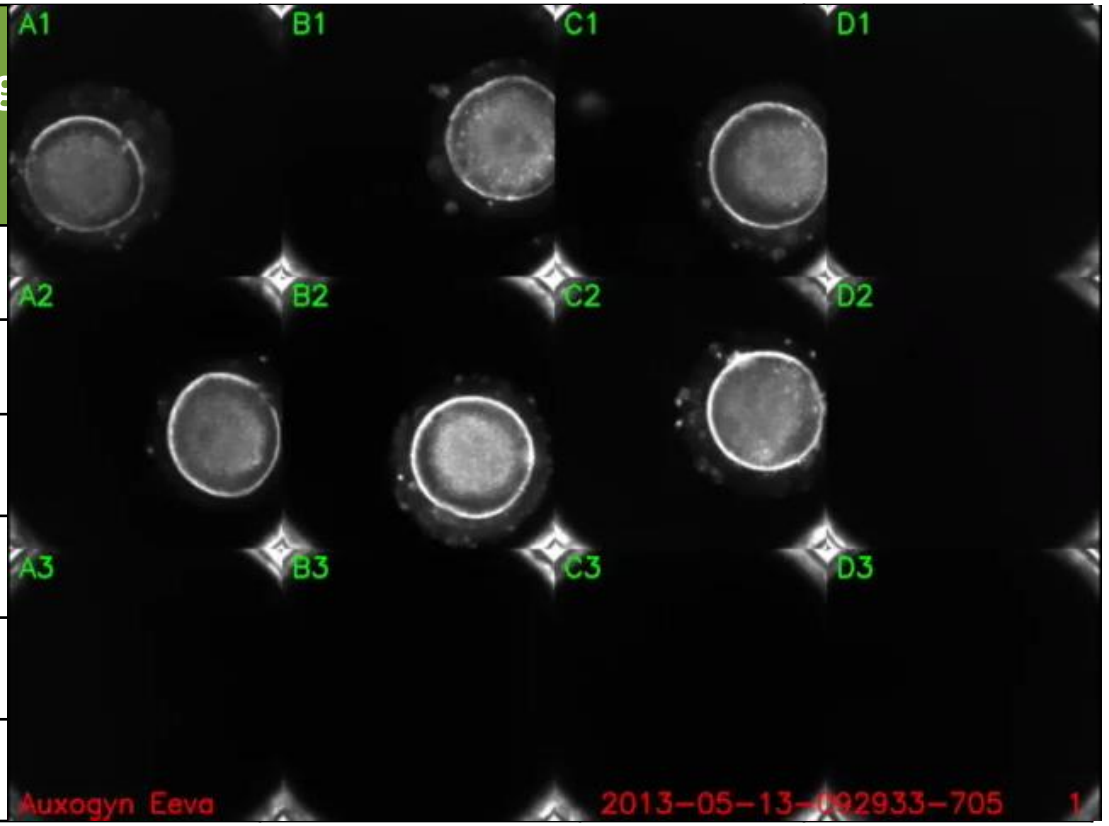
Day 3 Demo 1: 38 year old with 6 embryos

Well	D3 cell number	D3 symmetry	D3 fragmentation (%)			Fate
A1	6	Moderate	1-10			
A2	8	Symmetric	1-10			
B1	6	Moderate	1-10			
B2	6	Moderate	1-10			
C1	8	Symmetric	1-10			
C2	8	Symmetric	1-10			

Desired SET

Day 3 Demo 1: 38 year old with 6 embryos

Well	D3 cell number	D3 symmetry	D3 frag
A1	6	Moderate	
A2	8	Symmetric	
B1	6	Moderate	
B2	6	Moderate	
C1	8	Symmetric	
C2	8	Symmetric	



Desired SET

Day 3 Demo 1: 38 year old with 6 embryos

Well	D3 cell number	D3 symmetry	D3 fragmentation (%)	Eeva Result	Notes	Fate
A1	6	Moderate	1-10	**High**		
A2	8	Symmetric	1-10	**Low**	AC2	
B1	6	Moderate	1-10	**Low**		
B2	6	Moderate	1-10	**Low**		
C1	8	Symmetric	1-10	**High**		**Transferred**
C2	8	Symmetric	1-10	**Low**	AC1	

Outcome: Clinical pregnancy (singleton)

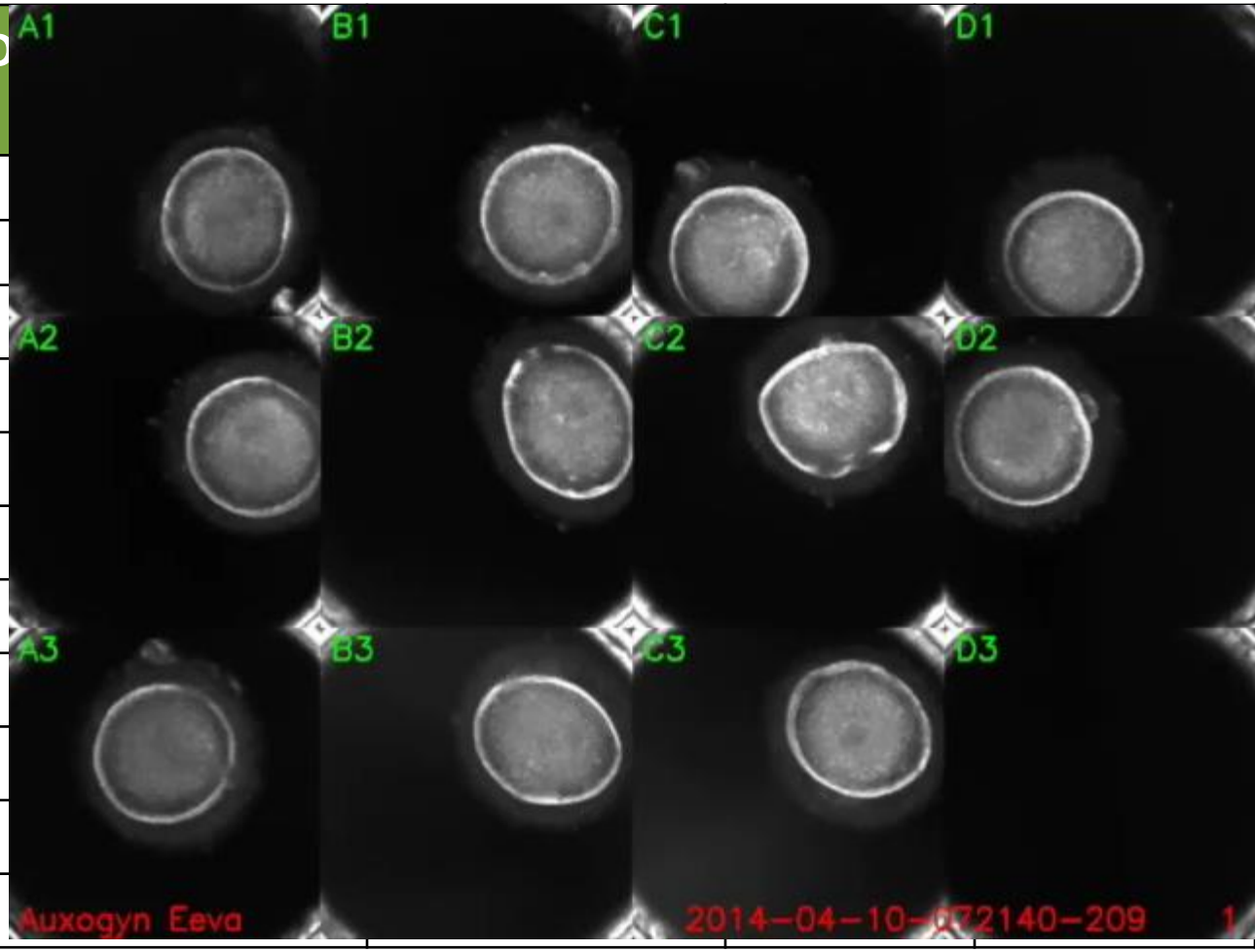
Day 3 Demo 4: 26 year old with 11 embryos

Well	D3 cell number	D3 symmetry	D3 fragmentation (%)			Fate
A1	8	Symmetric	1-10			
A2	8	Symmetric	1-10			
A3	8	Symmetric	1-10			
B1	Morula	Symmetric	1-10			
B2	Morula	Symmetric	1-10			
B3	8	Symmetric	1-10			
C1	8	Symmetric	1-10			
C2	8	Symmetric	1-10			
C3	8	Symmetric	1-10			
D1	8	Symmetric	1-10			
D2	6	Symmetric	1-10			

Desired DET

Day 3 Demo 4: 26 year old with 11 embryos

Well	D3 cell number	D3 symmetry	D
A1	8	Symmetric	
A2	8	Symmetric	
A3	8	Symmetric	
B1	Morula	Symmetric	
B2	Morula	Symmetric	
B3	8	Symmetric	
C1	8	Symmetric	
C2	8	Symmetric	
C3	8	Symmetric	
D1	8	Symmetric	
D2	6	Symmetric	



Day 3 Demo 4: 26 year old with 11 embryos

Well	D3 cell number	D3 symmetry	D3 fragmentation (%)	Eeva Result	Notes	Fate
A1	8	Symmetric	1-10	**High**		**Transferred**
A2	8	Symmetric	1-10	**High**		**Transferred**
A3	8	Symmetric	1-10	**Low**		
B1	Morula	Symmetric	1-10	**Low**		
B2	Morula	Symmetric	1-10	**Low**	RC	
B3	8	Symmetric	1-10	**High**		
C1	8	Symmetric	1-10	**Low**		
C2	8	Symmetric	1-10	**Low**	RC	
C3	8	Symmetric	1-10	**Low**		
D1	8	Symmetric	1-10	**Low**		
D2	6	Symmetric	1-10	**Low**		

Outcome: Clinical pregnancy (twins)

Scientific foundation of the Eeva Test

Cell division time-intervals ("P1, P2, P3")…

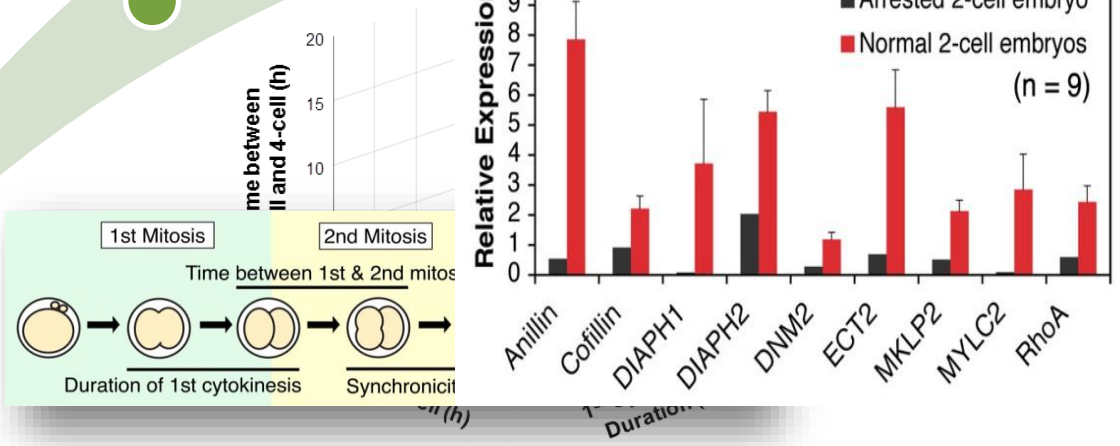
Predict successful development to blastocyst

Provide distinct timing windows[1]

Reflect underlying molecular health[2]

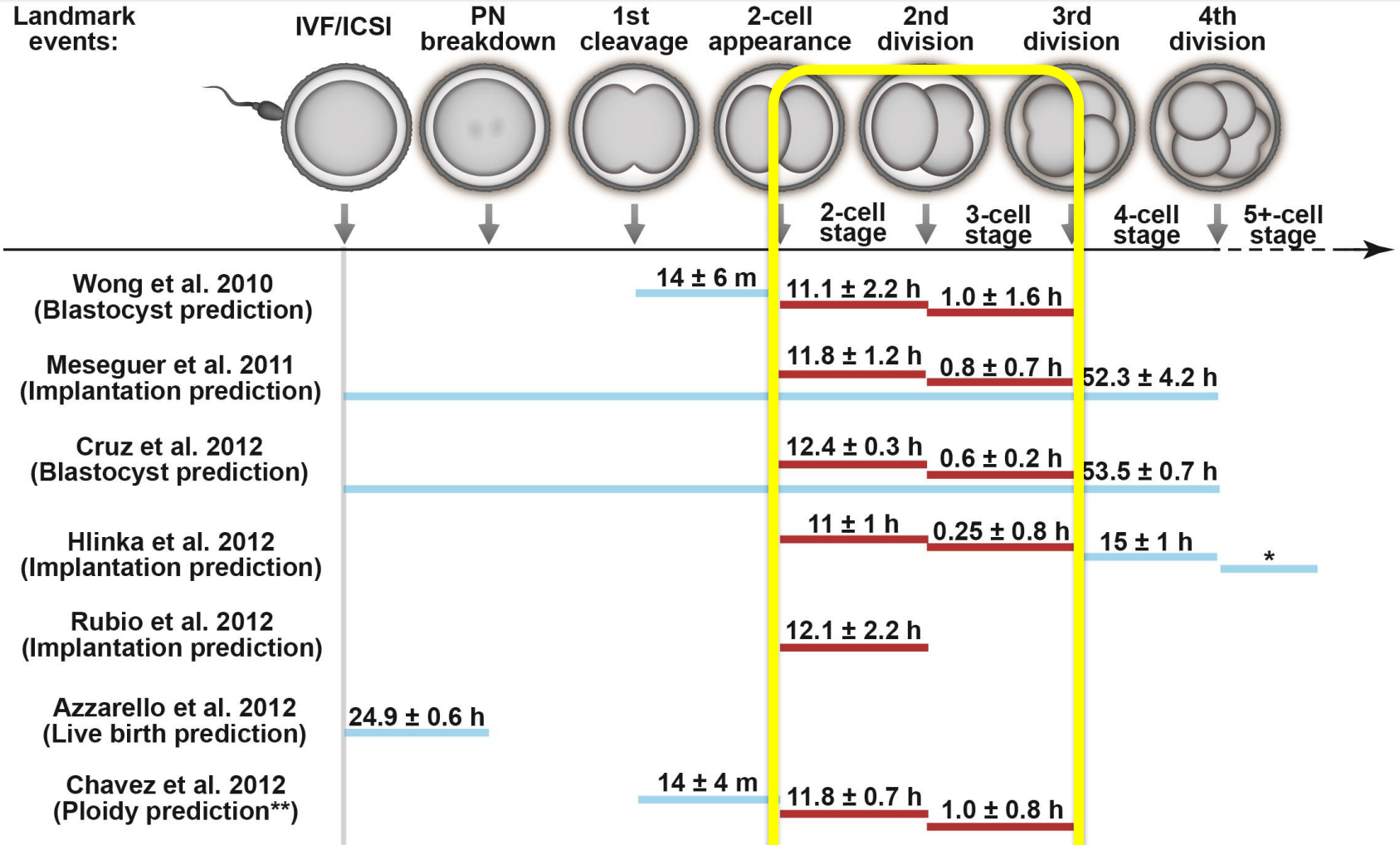
Correlate to implantation & blastocyst quality[2-4]

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)

Summary of Early Predictive Time-Lapse Markers



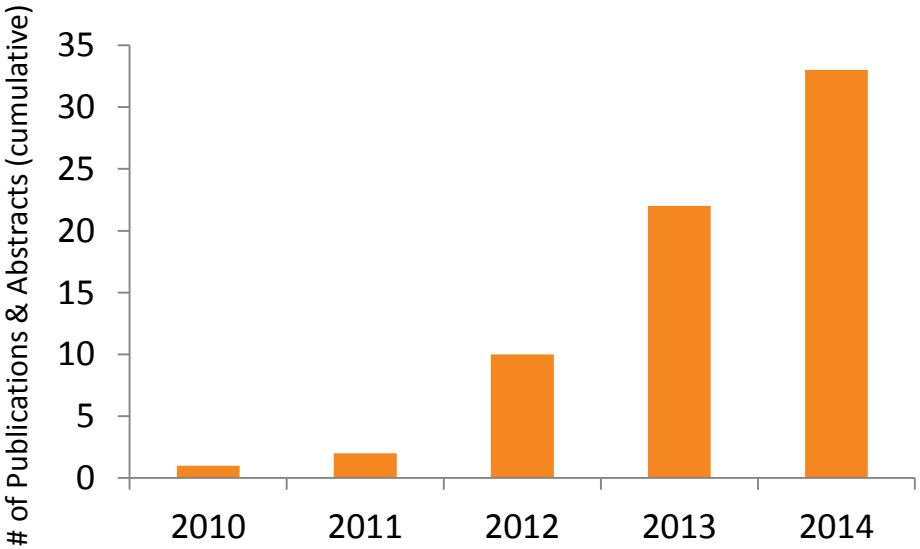
* 5-8 cell stage: 40 ± 10 m; 8 cell stage: 23 ± 1 h; 9-16 cell stage: 55 ± 15 m

** dynamic assessment of fragmentation was also included in the study

Chen et al. *Fertility & Sterility,* (2013)

Ongoing Effort to Continue Scientific Discovery

- Publications and abstracts continue to increase
- Impact of Eeva Test on clinical pregnancy and implantation is under study



Publications

Clinical Validation and Research

Using the Eeva™ Test adjunctively to traditional day 3 morphology is informative for consistent embryo assessment within a panel of embryologists with diverse experience

M.P. Diamond, V. Suraj, E.J. Behnke, X.Yang, M.J.Angle, J.C. Lambe Steinmiller, R. Watterson, K. Athayde Wirka, A.A. Chen, S. Shen, *Journal of Assisted Reproduction and Genetics*, 2014

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

K. Athayde Wirka, A.A. Chen, J. Conaghan, K. Ivani, M. Gvakharia, B. Behr, V. Suraj, L. Tan, S. Shen, *Fertility and Sterility*, 2014.
http://www.fertstert.org/article/S0015-0282(14)00203-9/abstract

Improving embryo selection using computer-automated time-lapse imaging plus day 3 morphology: results from a prospective multi-center trial

J. Conaghan, A.A. Chen, S.P. Willman, K.Ivani, P.E. Chenette, R.Boostanfar, V.L.Baker, G.D. Adamson, M.E. Abusief, M.Gvakharia, K.E. Loewke, S. Shen, *Fertility & Sterility*, 100(2): 412-9, 2013.
http://www.fertstert.org/article/S0015-0282(13)00517-7/abstract

Automated time-lapse analysis in adjunctive use with morphology is highly informative in allowing diverse embryologists to select embryos with high developmental potential

M.P. Diamond, L. Tan, J. Conaghan, K. Ivani, A. Le, A.A. Chen, S. Shen, V. Suraj, European Society of Human Reproduction and Embryology (ESHRE) Annual Meeting 2014, Jun 29-Jul 2, 2014, Munich, Germany

The use of innovative, intelligent software and non-invasive embryo imaging to predict blastocyst formation by day 3

H. Marsden, J. Conaghan, K. Ivani, R. Gregoire, C. Kingsland, S. Troup
British Fertility Society/ Association of Clinical Embryologists (BFS/ACE) Annual Meeting 2013, Jan 3-5, 2013, Liverpool, UK
Awarded the "Prize Paper" for Clinical Achievement

Improved embryo selection accuracy using cell division characteristics defined by time-lapse and automated image analysis

A.A. Chen, K. Ivani, J. Conaghan, M. Gvakharia, A. Le, S. Shen
American Society for Reproductive Medicine (ASRM) Annual Meeting 2012, October 20-24, 2012, San Diego, California, *Fertility & Sterility* Vol.98(3):S17.

Prediction of embryo viability using validated cell division time intervals measured by time-lapse imaging

A.A. Chen, K.E. Loewke, S.P. Willman, P.E. Chenette, R. Boostanfar, S. Shen
American Society for Reproductive Medicine (ASRM) Annual Meeting 2012, October 20-24, 2012, San Diego, California, *Fertility & Sterility* Vol.98(3):S31.

Early cell cycle durations detected by time-lapse imaging predicts embryo developmental potential

S. Shen, A.A. Chen, S.P. Willman, P.E. Chenette, R. Boostanfar, V.L. Baker, M. Abusief, V. Suraj, K. Wirka, K. Loewke
European Society of Human Reproduction and Embryology (ESHRE) Annual Meeting 2012, July 1-4, 2012, Istanbul, Turkey, *Human Reproduction* Vol.27(2):ii22.

Research to Advance Science

Computer-automated time-lapse analysis test results correlate to clinical pregnancy and embryo implantation: a prospective, blinded, multi-center study

- Refer to Auxogyn.com for complete list of publications/abstracts

http://www.auxogyn.com/clinical-innovation/reproductive-science-publications/

How the Eeva System Works

Introducing the **Eeva™ System**

Simple & Easy to Use

Designed to fit into your lab workflow

Load embryos into Eeva Dish

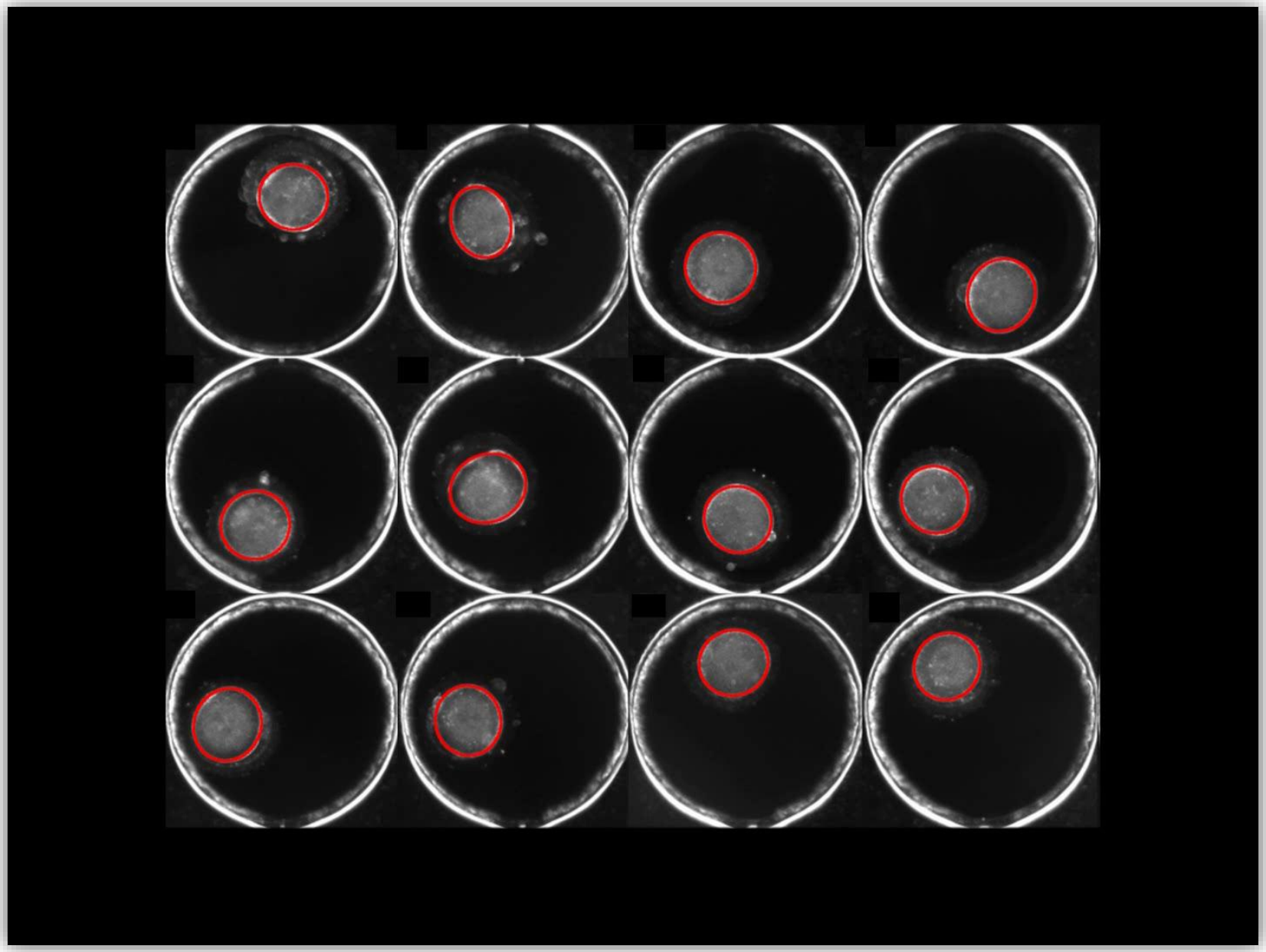

A
B
C
D
1
2
3
Eva™


auxogyn
Eeva
Eeva™
JANE
ABC123
Place dis... onto Eeva Scope

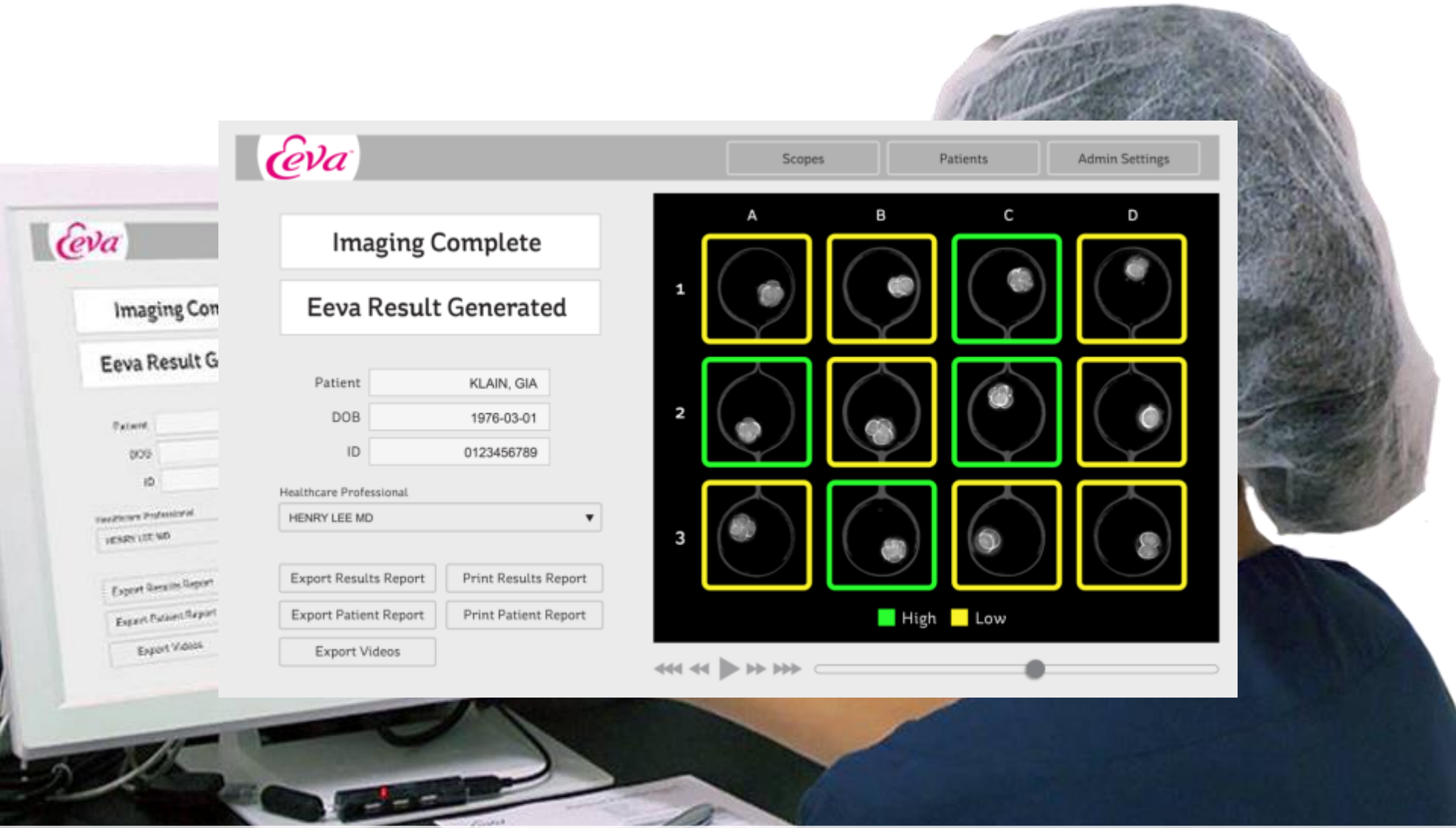
Confirm Alignment


36.9
5.8
Scope 1
Press Here To Start
Scope 2
Scope 3
Press Here To Start
Scope 4
Press Here To Start

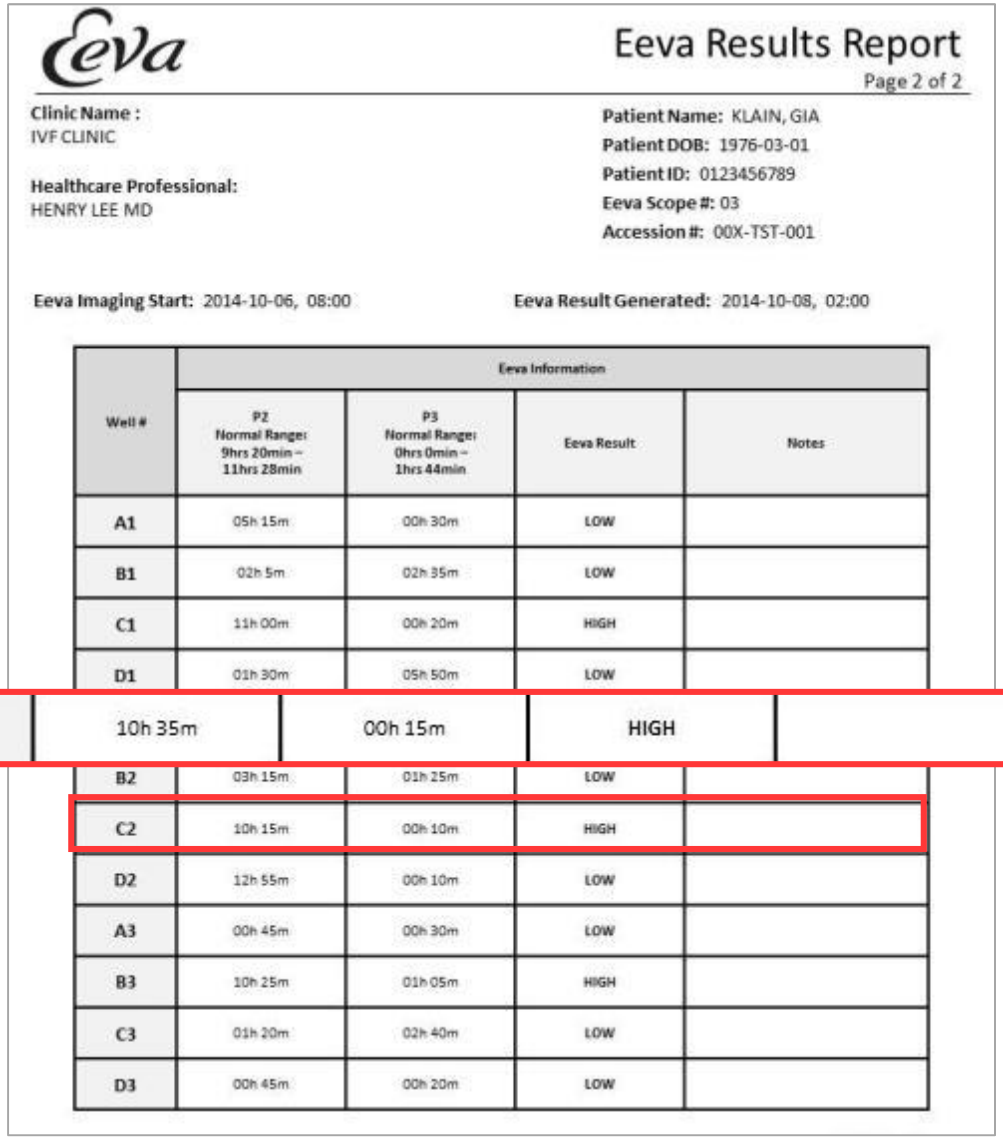
Analysis Begins



Day 1 & Day 2 Imaging



Day 3 Imaging Complete



Eeva Results Report

Page 2 of 2

Clinic Name :
IVF CLINIC

Healthcare Professional:
HENRY LEE MD

Patient Name: KLAIN, GIA
Patient DOB: 1976-03-01
Patient ID: 0123456789
Eeva Scope #: 03
Accession #: 00X-TST-001

Eeva Imaging Start: 2014-10-06, 08:00

Eeva Result Generated: 2014-10-08, 02:00

Well #	Eeva Information			
	P2 Normal Range: 9hrs 20min – 11hrs 28min	P3 Normal Range: 0hrs 0min – 1hrs 44min	Eeva Result	Notes
A1	05h 15m	00h 30m	LOW	
B1	02h 5m	02h 35m	LOW	
C1	11h 00m	00h 20m	HIGH	
D1	01h 30m	05h 50m	LOW	
A2	10h 35m	00h 15m	HIGH	
B2	03h 15m	01h 25m	LOW	
C2	10h 15m	00h 10m	HIGH	
D2	12h 55m	00h 10m	LOW	
A3	00h 45m	00h 30m	LOW	
B3	10h 25m	01h 05m	HIGH	
C3	01h 20m	02h 40m	LOW	
D3	00h 45m	00h 20m	LOW	

Review Eeva Test Results adjunctively to morphology


Eeva
Imaging Complete
Eeva Result Generated
A
B
C
D
1
2
High
Low
Select with Confidence

First Clinically Validated Model

Consistent Test results within and across clinics

Generalizable Prediction Model → Test with Independent Data Set

Multi-center (5 US clinics)

- STANFORD HOSPITAL & CLINICS — Stanford University Medical Center
- Reproductive Science Center — Experience Never Mattered More
- Pacific Fertility Center® — The ART of Conception
- Fertility Physicians of Northern California
- HRC Fertility — huntington reproductive center medical group

- 160 patients
- 1825 embryos

CE

FDA

de novo clearance

eva™

FDA Clearance

Power to Predict required a Unique Path to Market

- The Eeva™ System was cleared through the FDA de novo process in June 2014
  - Pathway for innovative, low to moderate risk devices
  - More rigorous requirements
  - First device of its kind with prognostic assessment

Eeva System	Other Time Lapse Systems
FDA De Novo Clearance	510(k) Clearance
Assisted Reproduction **Embryo Image Assessment** System	Assisted Reproduction **Accessories**

Which patients benefit from the Eeva Test….

While the Eeva Test can be used for any patient, here are some situations where its value is maximized:

The Eeva Test is:

1. Best used when **embryo selection** is needed: patients who may have multiple good quality embryos on the day of embryo transfer (e.g. good responders, donor eggs, etc.)
2. A tool to permit the embryologist to select with confidence when an e**SET** is planned.
3. **Prognostic** not diagnostic. It has limited use in poor responders and patients with poor embryo quality.
4. In all patients, the Eeva Test must be used as an **adjunct to morphology**, not as a substitute for a trained embryologist.

The future of the Eeva Test

Biological Parameters Are Only the Start

Biological Parameters

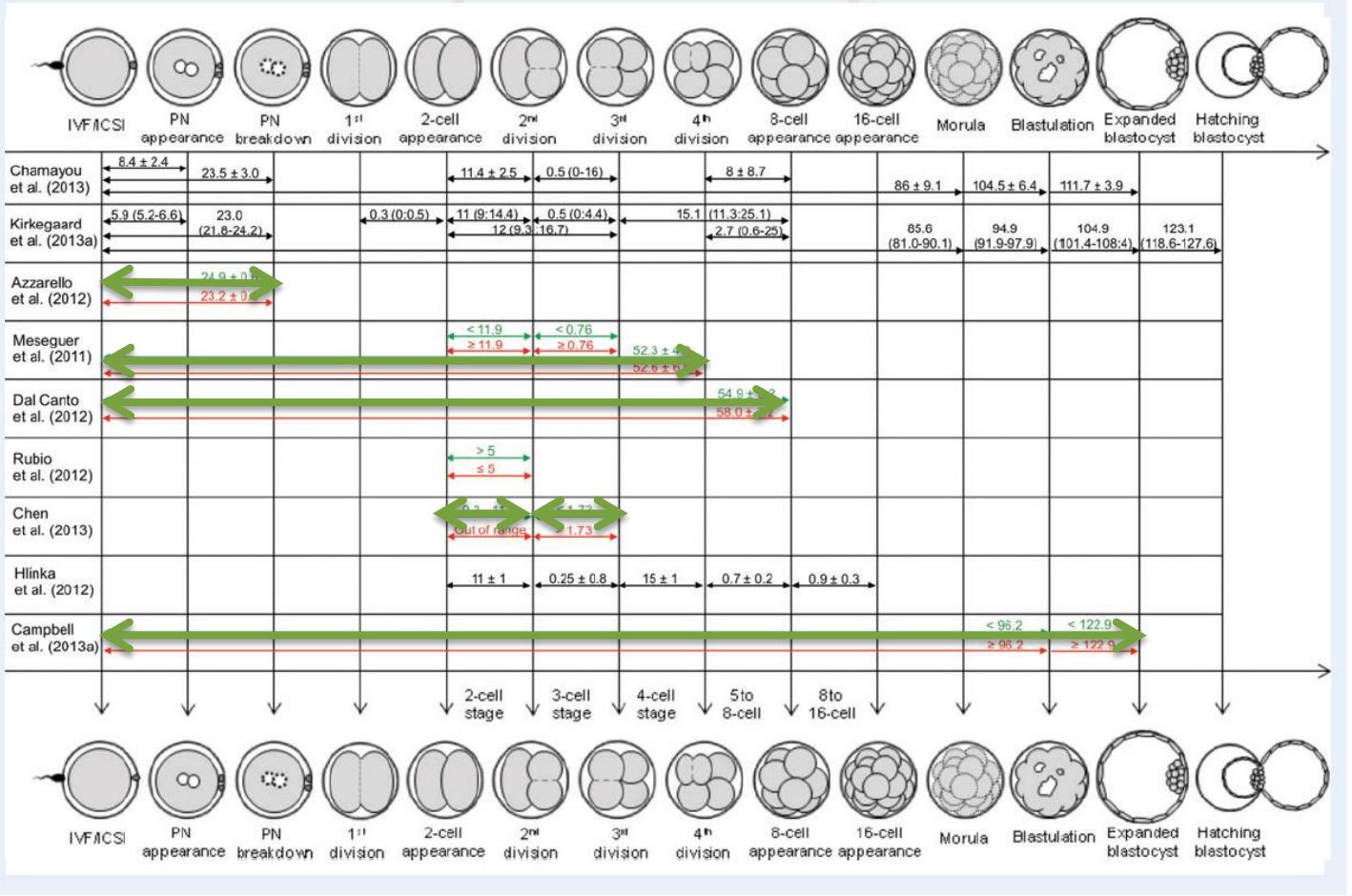
Statistical Modeling

Automation + Computer Vision

Clinical Validation

Time-lapse markers

Reviewed by Kaser and Racowsky, HRU 2014



Statistical Modeling for Multiple Parameters

Biological Parameters

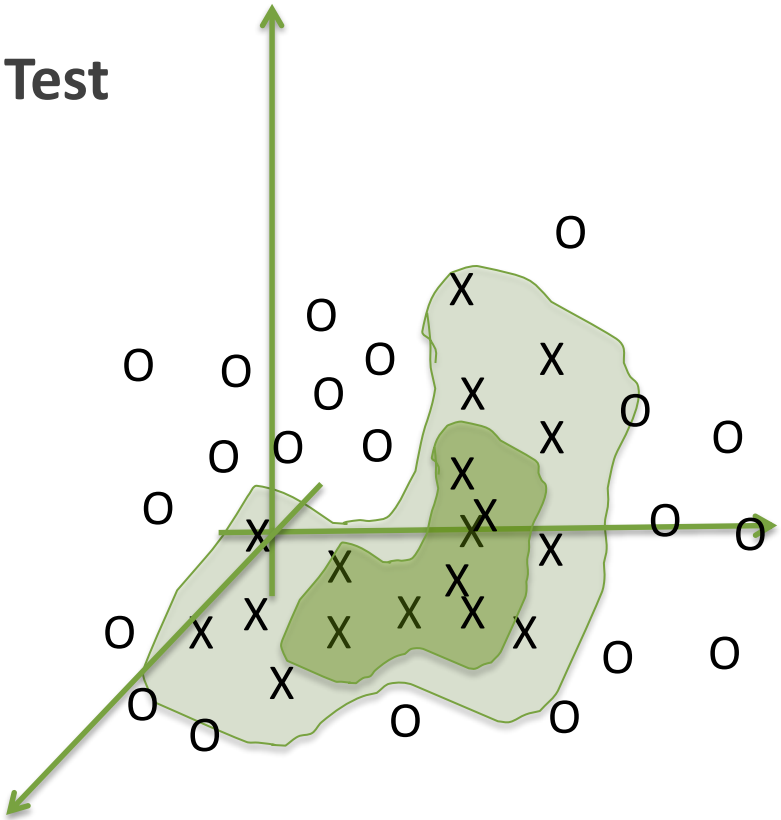
Statistical Modeling

Automation + Computer Vision

Clinical Validation

The future of the Eeva Test will be…

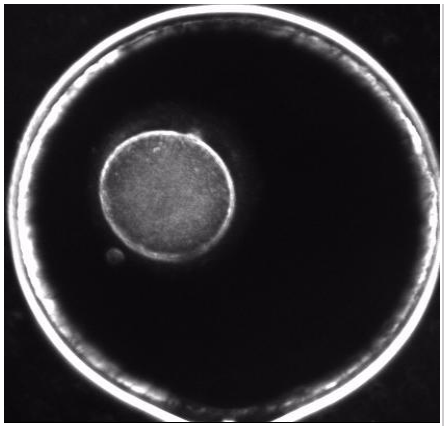
- Multiple biological parameters
- Multi-dimensional prediction space
- Novel surrogate image features extracted from videos

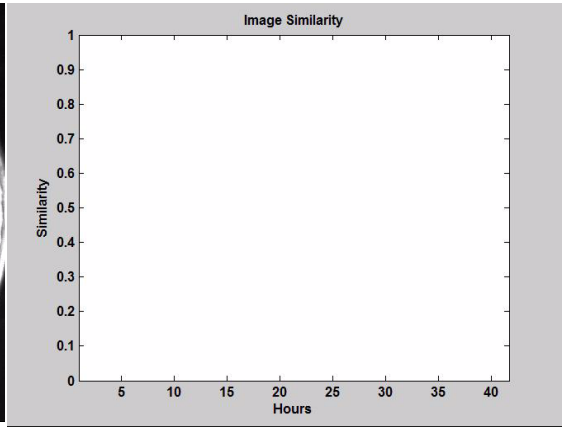


Benefits of Automation + Computer Vision

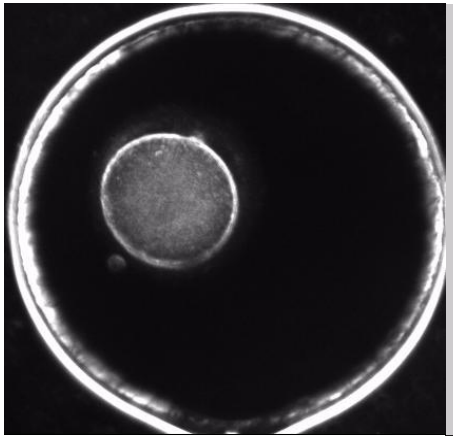
- Biological Parameters
- Statistical Modeling
- **Automation + Computer Vision**
- Clinical Validation

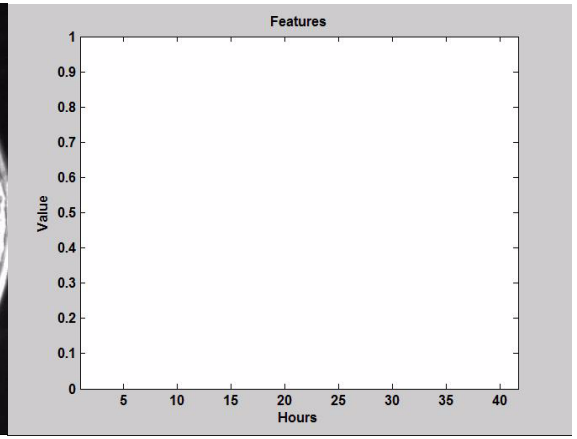
Automation reduces the need for manual measurements



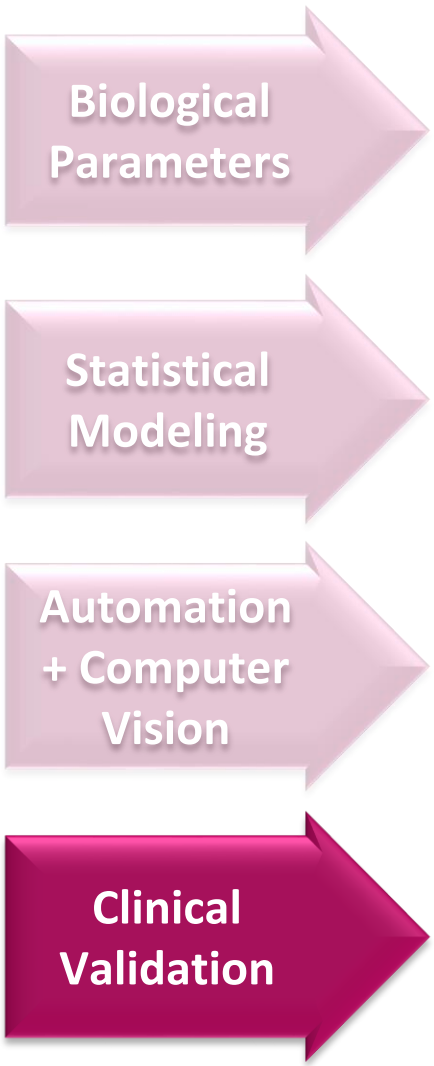


Computer vision detects surrogate image markers





Clinical Validation

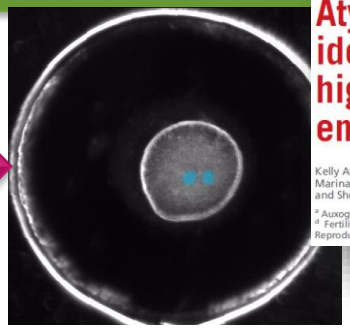


Data Requirements for Developing a Predictive Model:

1. Prospectively collected
2. Multi-clinic and diverse, for generalizable and consistent results
3. Separate training & test datasets

Ongoing Development of the Eeva Test

Biological Parameters



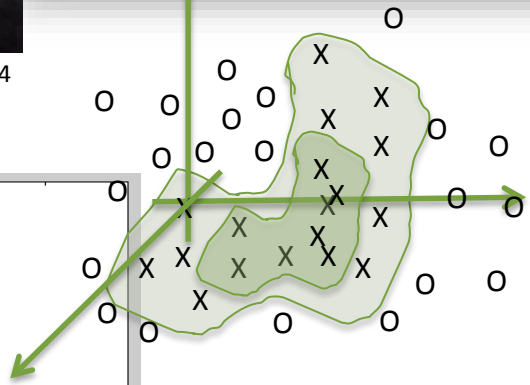
Atypical embryo phenotypes identified by time-lapse microscopy: high prevalence and association with embryo development

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]

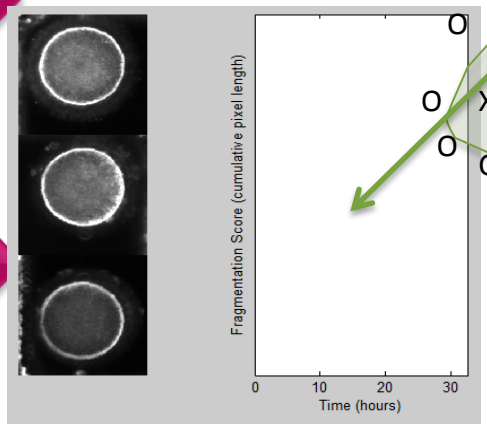
[a] Auxogyn, Menlo Park; [b] Pacific Fertility Center, San Francisco; [c] Reproductive Science Center of the Bay Area, San Ramon; [d] Fertility Physicians of Northern California, Palo Alto Medical Foundation, San Jose; and [e] Stanford Fertility and Reproductive Medicine Center, Palo Alto, California

Wirka et al. *Fertil Steril* 2014

Statistical Modeling



Automation + Computer Vision



Clinical Validation

An Analogy for Eeva

MAPS

GPS

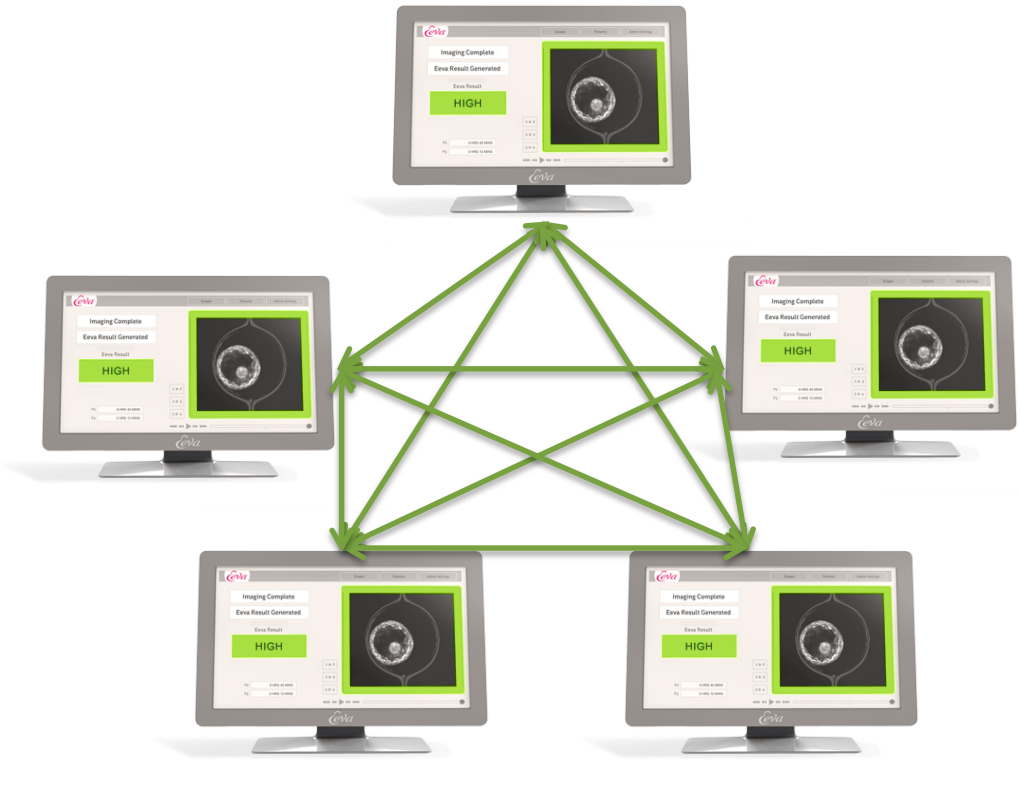
NETWORK

Time -Lapse

Eeva

?

The Future : The Eeva Network



- Users in the network provide information in real-time
- Users receive real-time data analysis within their clinic and compared to all clinics
- Selection algorithms will be continuously updated to optimize results
- Better outcomes for members of the network

Path to Clinics and Patients

auxogyn

First Eeva clinical study

CE

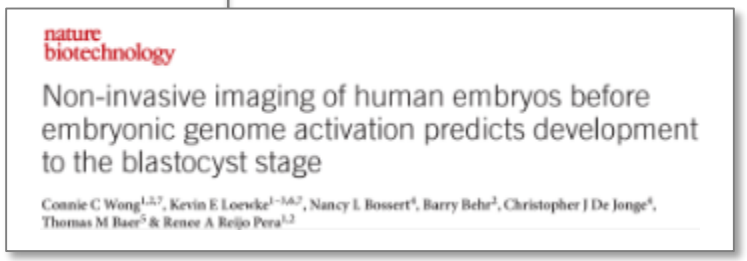
MERCK SERONO

FDA

fertility AUTHORITY

Merger

2010 | 2011 | 2012 | 2013 | 2014 | 2015


nature biotechnology

Non-invasive imaging of human embryos before embryonic genome activation predicts development to the blastocyst stage

Connie C Wong[1,2,7], Kevin E Loewke[1–3,7], Nancy L Bossert[4], Barry Behr[2], Christopher J De Jonge[4], Thomas M Baer[5] & Renee A Reijo Pera[1,2]

Eeva Today (April 2015)

- 8 countries
- >45 clinics
- >4,000 patients tested
- >22,000 embryos imaged
- >35 publications

Eva™

Select with Confidence

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