Eeva Test: The GPS of Time-Lapse

2015 ABB CRB Workshop

Shehua Shen, MD, ELD (ABB)
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
• 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%

Abnormal Syngamy

- 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

Abnormal First Cytokinesis (A1$^{\text{c yt}}$)

- A1$^{\text{c yt}}$ phenotype is associated with poorer developmental potential
- Previously research has correlated 1$^{\text{st}}$ cytokinesis timing (P1) to developmental competence [1]
- Combining A1$^{\text{c yt}}$ phenotype and P1 timing may more finely discriminate embryos for de-selection

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<thead>
<tr>
<th></th>
<th>Blast Rate</th>
<th>Impl Rate</th>
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<tbody>
<tr>
<td>Control (n=443)</td>
<td>45%</td>
<td>17%</td>
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<tr>
<td>With A1$^{\text{c yt}}$ (n=196)</td>
<td>22%</td>
<td>6%</td>
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</tbody>
</table>

p-value $<$0.0001

Biological Parameters

Time-lapse markers
Reviewed by Kaser and Racowsky, HRU 2014

Time-lapse observations:

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

The Eeva Test is *prognostic* for embryo selection.

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

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

Connie C. Wong, Kevin E. Loewke, Nancy I. Bossert, Barry Behr, Christopher J. De Jonge, Thomas M. Baer, and Renee A. Reijo Pera.
Inside the Eeva System...

- Identify Cell Divisions
- Calculate Timing Intervals
- Classify Embryos

HIGH

- P2: 10 hrs. 10 min
- P3: 10 min

LOW

- P2: 14 hrs. 15 min
- P3: 10 min
Day 3 Demo 1: 38 year old with 6 embryos

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<thead>
<tr>
<th>Well</th>
<th>D3 cell number</th>
<th>D3 symmetry</th>
<th>D3 fragmentation (%)</th>
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Desired SET
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**Outcome:** Clinical pregnancy (singleton)
Day 3 Demo 4: 26 year old with 11 embryos

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**Outcome:** Clinical pregnancy (twins)
Scientific foundation of the Eeva Test

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

Recently examined for aneuploidy

Correlate to implantation & blastocyst quality

Reflect underlying molecular health

Provide distinct timing windows

Predict successful development to blastocyst

Summary of Early Predictive Time-Lapse Markers

Chen et al. Fertility & Sterility, (2013)

* 5-8 cell stage: 40 ± 10 m; 8 cell stage: 23 ± 1 h; 9-16 cell stage: 55 ± 15 h
** dynamic assessment of fragmentation was also included in the study
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

Atypical embryo phenotypes identified by time-lapse microscopy; high prevalence and association with embryo development
http://www.fertstert.org/article/S0015-0295(14)00051-7/abstract

Improving embryo selection using computer-automated time-lapse imaging plus day 3 morphology: results from a prospective multicenter trial
http://www.fertstert.org/article/S0015-0295(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

The use of innovative, intelligent software and non-invasive embryo imaging to predict blastocyst formation by day 3
H. Marzban, J. Conaghan, K. Kari, R. Gregoria, C. Kingsland, T. Teja
Awarded the “Fosse Paper” for Clinical Achievement

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

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

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

Research to Advance Science

Computer-automated time-lapse analysis test results correlate to clinical pregnancy and embryo implantation: a prospective, blinded, multicenter 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
Place dish onto Eeva Scope
Analysis Begins
Day 3 Imaging Complete

Eeva Result Generated

Patient: KLAIN, GIA
DOB: 1976-03-01
ID: 0123456789

Healthcare Professional: HENRY LEE MD

Export Results Report
Export Patient Report
Export Videos
**Review Eeva Test Results adjunctively to morphology**

<table>
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<tr>
<th>Well</th>
<th>P3 Normal Range: 0hrs 0min – 1hrs 44min</th>
<th>P3 Normal Range: 9hrs 20min – 11hrs 28min</th>
<th>Eeva Result</th>
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<tr>
<td>A1</td>
<td>05h 15m</td>
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<td>B1</td>
<td>02h 5m</td>
<td>02h 35m</td>
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<td>C1</td>
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First Clinically Validated Model
Consistent Test results within and across clinics

Generalizable Prediction Model

Test with Independent Data Set

denovo clearance

Multi-center (5 US clinics)

- 160 patients
- 1825 embryos

STANFORD HOSPITAL & CLINICS
Reproductive Science Center
Pacific Fertility Center®
Fertility Physicians of Northern California
HRC Fertility
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

<table>
<thead>
<tr>
<th>Eeva System</th>
<th>Other Time Lapse Systems</th>
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<tbody>
<tr>
<td>FDA De Novo Clearance</td>
<td>510(k) Clearance</td>
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<tr>
<td>Assisted Reproduction Embryo Image Assessment System</td>
<td>Assisted Reproduction Accessories</td>
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</table>
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 eSET 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

Time-lapse markers
Reviewed by Kaser and Racowsky, HRU 2014

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**

Automation reduces the need for manual measurements

**Statistical Modeling**

Computer vision detects surrogate image markers

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

Wirka et al. Fertil Steril 2014

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

Kady Atta-Oued Wirka, M.S., Aliya A. Loh, Ph.D., Joe Conaghan, Ph.D., Kristen Issani, Ph.D., Marina Gushchina, M.D., Ph.D., Barry Lehr, Ph.D., Vashali Sunaj, M.S., Lin Tan, Ph.D., and Shehala Tham, M.D.*

*Sanoviv, Menlo Park, CA; Pacific Fertility Center, San Francisco; Reproductive Science Center of the Bay Area, San Ramon; Fellowship, Physicians of Northern California, Palo Alto Medical Foundation, San Jose; and St. Francis and Marin County Medical Centers, Palo Alto, CA.
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

Eeva Today (April 2015)
- 8 countries
- >45 clinics
- >4,000 patients tested
- >22,000 embryos imaged
- >35 publications
Select with Confidence