How Can We Improve Outcome (Embryology)
Ovarian Club – December 2018
Hong Kong
Simon Fishel
CARE Fertility Group
Conflict of Interest

Minor Shareholding CARE Fertility Group
The need to bring about change

- 1991 – Ave Success 14.1%
- 2013 – Ave Success 26.5%
- (Top Clinics: 33%; 50% <35)
Why strive for new technologies

Two Simple Truths
The search for the viable embryo

- Live Birth
- Miscarriage
- Aneuploidy

- >80%
- ~7%
- ~10%

CARE fertility
We’re not yet good enough & too inconsistent!

**UK National Data**

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### UK National Data

<table>
<thead>
<tr>
<th>Clinic Name</th>
<th>Nat Ave</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;35 All Ages</td>
<td>33.4%</td>
</tr>
<tr>
<td>All Ages</td>
<td>24.5%</td>
</tr>
</tbody>
</table>

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### Nat Ave US CDC SART

<table>
<thead>
<tr>
<th>Clinic Name</th>
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<tr>
<td>&lt;35 All Ages</td>
<td>39.6%</td>
</tr>
<tr>
<td>All Ages</td>
<td>25.5%</td>
</tr>
</tbody>
</table>

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### Nat Ave UK National Data

<table>
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<th>Clinic Name</th>
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</tr>
</tbody>
</table>
Biomarkers of embryo viability: the search for the “holy grail” of embryo selection

Zev Rosenwaks, M.D.

“search for a marker of embryo quality with the goal of selecting the single best embryo for transfer continues to be the major challenge facing our field”

“although one cannot ignore the fact that uterine receptivity is in part responsible for implantation efficiency, it is generally agreed that embryonic factors are mainly culpable for implantation failure.”

Why Does Failure Happen - embryos, endometrium, ♀ physiology!
Embryo ploidy assessment

PGT-A (PGS)
US CDC –SART data 2014 - Embryo ‘Success’

# Embryos Transferred  139,832
# babies born from those embryos  35,631

12%; ≈16,780

[Bar chart showing the percentage of non-PGS and PGS embryos in different age groups]
# PGT-A: Overview of RCTs – Meta Analyses

(ET is embryo powered not patient powered)

<table>
<thead>
<tr>
<th>Study</th>
<th>Meta analysis</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dahdouh et al. 2015</td>
<td>IR and OPR and LB</td>
<td>↑ clinical IR &amp; sustained IR on OS</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Reduction in miscarriage</td>
</tr>
<tr>
<td>Chen et al. 2018 PloS One</td>
<td>IR and OPR and LB</td>
<td>↑ clinical IR &amp; sustained IR on OS</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Reduction in miscarriage</td>
</tr>
<tr>
<td>Natsuaki &amp; Dimler. 2018 World J Pediatr</td>
<td>IR and OPR</td>
<td>↑ clinical IR &amp; sustained IR on OS</td>
</tr>
</tbody>
</table>

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*Source: CARE Fertility*
# PGT-A: Overview of RCT’s (embryo power, not patient)

<table>
<thead>
<tr>
<th>Study</th>
<th>Methodology</th>
<th>Collected</th>
<th>Single/multi-center</th>
<th>Sample</th>
<th>Sample size</th>
<th>Key findings</th>
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</thead>
<tbody>
<tr>
<td>Forman et al. 2013</td>
<td>rtPCR</td>
<td>2011-2012</td>
<td>Single</td>
<td>Blastocyst</td>
<td>175</td>
<td>↑ sustained IR, ↓ MR, ↓ MP</td>
</tr>
<tr>
<td>Scott et al. 2013</td>
<td>qPCR</td>
<td>2009-2012</td>
<td>Single</td>
<td>Blastocyst</td>
<td>155</td>
<td>↑ sustained IR, ↑ DR</td>
</tr>
<tr>
<td>Rubio et al. 2017</td>
<td>aCGH</td>
<td>2012-2014</td>
<td>Multi</td>
<td>Day 3</td>
<td>205</td>
<td>↑ delivery and LB/Transfer and /Pt, ↓ MR, 50% less time to achieve preg</td>
</tr>
<tr>
<td>Chang et al. 2016</td>
<td>Retrospective</td>
<td>2011-2012</td>
<td>Multi</td>
<td>Blastocyst</td>
<td>106,902</td>
<td>↓ Odds of miscarriage women 35+, ↑ odds CP LB MP women 37+</td>
</tr>
<tr>
<td>Verpoest et al, 2018</td>
<td>aCGH</td>
<td>2012-2016</td>
<td>Multi</td>
<td>1st + 2nd PB</td>
<td>396</td>
<td>↓ MP, ↓ MR</td>
</tr>
<tr>
<td>STAR</td>
<td>NGS</td>
<td>2014-2016</td>
<td>Multi</td>
<td>Blastocyst</td>
<td>662</td>
<td>↑ OPR for 35-40</td>
</tr>
</tbody>
</table>
Blastocyst biopsy with comprehensive chromosome screening and fresh embryo transfer significantly increases in vitro fertilization implantation and delivery rates: a randomized controlled trial

Block randomization was used for each randomization such that 5 out of every 10 patients would be designated as study patients and the other 5 as controls. Important so that each age group was represented in approximately equal proportions for the study and the control groups.

www.clinicaltrials.gov with ID designation NCT01219283
Scott et al 2013 – Class 1 Evidence

Delivery Rate/ITT Stat. Sig ↑ (P=0.03)

Outcome per treatment cycle. Delivery rates are statistically significantly increased in treatment cycles in which embryos undergo comprehensive chromosome screening (P=.03). The initial chemical and clinical pregnancy rates were not different.

STAR Trial - Illumina

ASRM - 2107

Sig ↑ in LB if ♂ >35 years

50.8% in the PGS arm vs 37.2% in the control arm

36.5%
PGT-A (PGS)

ALL EMBRYOS

30%
70%

EUPLOID S

30%
70%
Alternative embryo assessment

Non-Invasive

Metabolomics
Cell-Free DNA
Biomechanics and developmental potential of oocytes and embryos

Fertil Steril 2017;
Jonathan Kort, M.D. and Barry Behr, Ph.D.

Biomechanical Properties:
Viscoelasticity of oolemma and blastocyst

Associations between biophysical properties - biomechanics - and embryo viability
Optical coherence microscopy as a novel, non-invasive method for the 4D live imaging of early mammalian embryos

Karol Karnowski², Anna Ajduk², Bartosz Wieloch³, Szymon Tamborski³, Krzysztof Krawiec³, Maciej Wojtkowski¹,⁴ & Maciej Szkulmowski⁵,⁶

Measures internal motion of cytoplasm and high resolution intracellular time lapse imaging

Prospects for non-invasive cell count in real time
Assessment of embryo morphology and developmental dynamics by time-lapse microscopy: is there a relation to implantation and ploidy?

Nikica Zaninovic, Ph.D., a Mohamad Irani, M.D., b and Marcos Meseguer, Ph.D. b

- great potential for enhancing embryo selection
- enhance conventional morphological assessments
- detects several morphological phenomena that are often missed with static observations using conventional incubators
- morphokinetic parameters can aid in differentiating between euploid and aneuploid embryos

“A compelling body of evidence has shown that TLM, especially when combined with standard morphological assessment, can improve embryo selection”
TLI – computing morphokinetics

\[ VP = t_1 - t_{PNf} \]
\[ CC1 = t_2 - t_{2PB} \]
\[ CC2 = t_4 - t_2 \]
\[ CC3 = t_8 - t_4 \]
\[ CC4 = t_{16} - t_8 \]
\[ S2 = t_4 - t_3 \]
\[ S3 = t_8 - t_5 \]

Compaction = \[ t_M - t_{SC} \]
Blastulation = \[ t_{HN} - t_{SB} \]
Collapse = \[ t_{BCend(n)} - t_{BCi(n)} \]
TLI – computing morphokinetics: ‘CAREmaps’

$VP = t_1 - t_{PNf}$

$CC1 = t_2 - t_{2PB}$

$CC2 = t_4 - t_2$

$CC3 = t_8 - t_4$

$CC4 = t_{16} - t_8$

$S2 = t_4 - t_3$

$S3 = t_8 - t_5$

$Compaction = t_M - t_{SC}$

$Blastulation = t_{HN} - t_{SB}$

$Collapse = t_{BCend(n)} - t_{BCi(n)}$
TLI – Cleavage anomalies

‘Reverse Cleavage’
<table>
<thead>
<tr>
<th>Patient Name</th>
<th>Embryologist</th>
<th>Pn</th>
<th>2P</th>
<th>3cell</th>
<th>4cell</th>
<th>5cell</th>
<th>6c</th>
<th>7c</th>
<th>8c</th>
<th>9+</th>
<th>st comp cell</th>
<th>CB</th>
<th>CC</th>
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</thead>
<tbody>
<tr>
<td>Abi</td>
<td>2.4</td>
<td>7.6</td>
<td>2</td>
<td>24.</td>
<td>1</td>
<td>26</td>
<td>39.4</td>
<td>39.6</td>
<td>52.</td>
<td>54.</td>
<td>55. 6 6</td>
<td>71.</td>
<td>7</td>
</tr>
<tr>
<td>Cath</td>
<td>2.4</td>
<td>9.4</td>
<td>7</td>
<td>24.</td>
<td>1</td>
<td>26</td>
<td>39.4</td>
<td>39.6</td>
<td>52.</td>
<td>54.</td>
<td>55. 6 6</td>
<td>72.</td>
<td>85.7</td>
</tr>
<tr>
<td>Claire</td>
<td>2.5</td>
<td>6.7</td>
<td>9</td>
<td>23.</td>
<td>2</td>
<td>26</td>
<td>39.4</td>
<td>39.6</td>
<td>52.</td>
<td>54.</td>
<td>55. 6 6 3</td>
<td>71.</td>
<td>7</td>
</tr>
<tr>
<td>Rachel</td>
<td>2.9</td>
<td>7.6</td>
<td>9</td>
<td>14.</td>
<td>3</td>
<td>2</td>
<td>39.4</td>
<td>39.7</td>
<td>52.</td>
<td>54.</td>
<td>55. 6 9 55.1 9</td>
<td>71.</td>
<td>8</td>
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<tr>
<td>Sarah</td>
<td>2.9</td>
<td>9.2</td>
<td>7</td>
<td>10.</td>
<td>23.</td>
<td>26.</td>
<td>39.4</td>
<td>39.7</td>
<td>52.</td>
<td>54.</td>
<td>55. 6 8 7</td>
<td>79.2</td>
<td>94.3</td>
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<tr>
<td>Median</td>
<td>2.5</td>
<td>7.6</td>
<td>2</td>
<td>24.</td>
<td>1</td>
<td>26</td>
<td>39.4</td>
<td>39.6</td>
<td>52.</td>
<td>54.</td>
<td>55. 6 6</td>
<td>71.</td>
<td>76.5</td>
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<tr>
<td>Mean</td>
<td>2.6</td>
<td>8.1</td>
<td>1</td>
<td>24.</td>
<td>2</td>
<td>1</td>
<td>39.4</td>
<td>39.6</td>
<td>52.</td>
<td>54.</td>
<td>55. 6 56.8 56</td>
<td>78.7</td>
<td>93.9</td>
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<tr>
<td>Max</td>
<td>2.9</td>
<td>9.4</td>
<td>6</td>
<td>23.</td>
<td>24.</td>
<td>26.</td>
<td>39.4</td>
<td>39.7</td>
<td>52.</td>
<td>54.</td>
<td>55. 6 8 6 9 7</td>
<td>85.7</td>
<td>94.9</td>
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<tr>
<td>Min</td>
<td>2.4</td>
<td>6.7</td>
<td>7</td>
<td>10.</td>
<td>23.</td>
<td>26.</td>
<td>39.4</td>
<td>39.6</td>
<td>52.</td>
<td>54.</td>
<td>55. 4 6 9 7 7</td>
<td>76.0</td>
<td>92.4</td>
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# QA – Attainment Scores

<table>
<thead>
<tr>
<th>Full name</th>
<th>Alison Campbell</th>
</tr>
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<tbody>
<tr>
<td><strong>Embryology Competencies</strong></td>
<td></td>
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<tr>
<td>Overall Percent:</td>
<td>89%</td>
</tr>
<tr>
<td>Time Allowed:</td>
<td>8:00</td>
</tr>
<tr>
<td>Time Taken:</td>
<td>7:43</td>
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<tr>
<td><strong>Cryopreservation</strong></td>
<td></td>
</tr>
<tr>
<td>Overall Percent:</td>
<td>100%</td>
</tr>
<tr>
<td>Time Allowed:</td>
<td>5:00</td>
</tr>
<tr>
<td>Time Taken:</td>
<td>2:21</td>
</tr>
<tr>
<td><strong>HFEA regulation</strong></td>
<td></td>
</tr>
<tr>
<td>Overall Percent:</td>
<td>42%</td>
</tr>
<tr>
<td>Time Allowed:</td>
<td>10:00</td>
</tr>
<tr>
<td>TimeTaken:</td>
<td>3:41</td>
</tr>
<tr>
<td><strong>Laboratory equipment and QC</strong></td>
<td></td>
</tr>
<tr>
<td>Overall Percent:</td>
<td>78%</td>
</tr>
<tr>
<td>Time Allowed:</td>
<td>6:00</td>
</tr>
<tr>
<td>Time Taken:</td>
<td>3:58</td>
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<tr>
<td><strong>Micromanipulation</strong></td>
<td></td>
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<tr>
<td>Overall Percent:</td>
<td>91%</td>
</tr>
<tr>
<td>Time Allowed:</td>
<td>5:00</td>
</tr>
<tr>
<td>Time Taken:</td>
<td>0:39</td>
</tr>
<tr>
<td><strong>Semenology</strong></td>
<td></td>
</tr>
<tr>
<td>Overall Percent:</td>
<td>71%</td>
</tr>
<tr>
<td>Time Allowed:</td>
<td>15:00</td>
</tr>
<tr>
<td>Time Taken:</td>
<td>6:10</td>
</tr>
</tbody>
</table>
CARE Fertility Group - 1000 Live Births

Live births after embryo selection using morphokinetics versus conventional morphology: a retrospective analysis

Simon Fishel a,*, Alison Campbell a, Sue Montgomery b, Rachel Smith c, Lynne Nice d, Samantha Duffy b, Lucy Jenner e, Kathryn Berrisford e, Louise Kellam e, Rob Smith f, Ivy D’Cruz g, Ashley Beccles a

Live births = 973 deliveries

Mean ♀ Age:
CAREmaps = 36.9
SI = 35.3
Inclusive Confounding Variables

- Embryoscope (y/n)
- Patient age (<38/38+)
- Day of embryo transfer
- No. embryos transferred
- Patient type
- Donor age
- Total previous cycles
- Total no. previous live births
- ICSI (y/n)
- Total no. miscarriages
- Intralipid (y/n)
- Duration of infertility
- Total # ectopic
- BMI
- AMH
- AFC
- Gonadotropin type
- Gonadotropin dosing days
- Gonadotropin total dose
- # Eggs collected
- # M2 eggs
- Ratio M2 eggs to total
- # M2 eggs fertilised
Confounding variables included in the model

- Embryoscope (y/n)
- Patient age (<38/38+)
- Day of embryo transfer
- No. embryos transferred
- Patient type
- Donor age
- Total previous cycles
- Total no. previous live births
- ICSI (y/n)
- Total no. miscarriages
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- Gonadotropin total dose
- # Eggs collected
- # M2 eggs
- Ratio M2 eggs to total
- # M2 eggs fertilised
CARE Fertility Data (Live Birth Outcome Only)

24,000 records of treatment

- **21,379** Standard incubation treatments
- **2,527** Embryoscope treatments
- **14,878** unique patients

**Statistical Analysis:**
* multiple variable logistic regression models were fit to assess the effects of embryo rank on each potential confounder
* Akaike information criterion (AIC) penalty fit for number of parameters and stepwise selection
Live Births (delivery events age <38) - Sig Points

<table>
<thead>
<tr>
<th>Category</th>
<th>TLI</th>
<th>SI</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td># pos Beta</td>
<td>* P&lt;0.0001</td>
<td>* P&lt;0.0001</td>
<td></td>
</tr>
<tr>
<td># with &gt;=1FH</td>
<td>* P&lt;0.0001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Biochem Loss</td>
<td></td>
<td></td>
<td>* P&lt;0.0001</td>
</tr>
<tr>
<td># Implantations</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td># Clin miscarriage</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td># Live Birth Event</td>
<td>* P&lt;0.0001</td>
<td></td>
<td>* P&lt;0.001</td>
</tr>
<tr>
<td>babies/EmbTrd</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Live Births (delivery events)

CAREmaps vs Standard (1,007 Deliveries vs 6,874 Deliveries)

- Overall Single Blast Uplift
- Significance diluted in >37 age group

- * P<0.0001

- Overall: 19%
- Single Blast: 25%
Time-Lapse Imaging Algorithms Rank Human Preimplantation Embryos According to their Probability to Result in a Live Birth.

Simon Fishela, Alison Campbella, Sue Montgomeryb, Rachel Smithc, Lynne Niced, Samantha Duffyb, Lucy Jennere, Kathryn Berrisford, Louise Kellame, Rob Smithf, Fiona Foadg, Ashley Becclesa
Hierarchical selection of embryos:

<table>
<thead>
<tr>
<th></th>
<th>% LBR</th>
<th>Miscarriage (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>51.7</td>
<td>24.0</td>
</tr>
<tr>
<td>B</td>
<td>35.0</td>
<td>32.5</td>
</tr>
<tr>
<td>C</td>
<td>31.2</td>
<td>32.6</td>
</tr>
<tr>
<td>D</td>
<td>13.8</td>
<td>35.3</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Group</th>
<th>Description</th>
<th>Miscarriage (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>tSB or relSBIVF ≤ 93.1 h</td>
<td>47.7%</td>
</tr>
<tr>
<td>B</td>
<td>tSB or relSBIVF &gt;93.1 h dB ≤ 12.5 h</td>
<td>47.7%</td>
</tr>
<tr>
<td>C</td>
<td>tSB or relSBIVF &gt;93.1 h dB &gt;12.5 h</td>
<td>47.7%</td>
</tr>
<tr>
<td>D</td>
<td>Unable to be annotated</td>
<td>47.7%</td>
</tr>
</tbody>
</table>

Single Blast Transfer

P < 0.001
Ranked embryo LB outcome.

Strong evidence of an effect of embryo rank on the odds of live births.

- D << A (OR = 0.3046; P<0.010)
- D << B (OR = 0.428; P<0.01)
- B < A  (OR = 0.7114; P<0.01)
- C < A  (OR = 0.6501; P< 0.01)
- B > C  (OR = 1.09; P<0.01)
- C >> D (OR=2.135; p<0.01)

A has a 233% chance of LB compared to D
CAREmaps vs morphology:

Grade 2:2 highest LB!
CAREmaps Morphokinetics v Morphology

1373 Blast SET cycles
679 (50%) Live Births

Live Births (%) v MK Grade

Live Births (%) v Morphology

Grade

A
B
C
D

Morphology

1:1
1:2
2:1
2:2
2:3
3:3
CAREmaps Morphokinetics v Morphology

Strong evidence of the superiority of the embryo rank model compared with the transfer grade model (p<0.0001)

Bootstrap, Generalised ROC Curves (excluding covariates) - Standard patients

- Embryo Rank (AUC = 64.32%)
- Transfer Grade (AUC = 55.52%)
Mitochondrial DNA quantity as a biomarker for blastocyst implantation potential

Dagan Wells, Ph.D.

- chromosomal status is the most definitive for embryonic potential.
- this is only one factor amongst many of relevance to embryo viability, as evidenced by the fact that even the transfer of a chromosomally normal embryo cannot guarantee a pregnancy.

...embryo - and not just the embryo!
Endometrial Biomarkers & Endometrial Receptivity Assay (ERA)

Discovery of biomarkers of endometrial receptivity through a minimally invasive approach: a validation study with implications for assisted reproduction

Chan et al 2013
Perinatal outcomes after natural conception versus in vitro fertilization (IVF) in gestational surrogates: a model to evaluate IVF treatment versus maternal effects

- Several adverse outcomes:
  - lower gestational age at delivery
  - higher rate of preterm delivery
  - lower birth weight
  - increase in adverse maternal outcome
    - including gestational diabetes
    - hypertension

“assisted reproductive procedures may affect embryo quality and that its negative impact cannot be overcome even with a proven healthy uterine environment”

Iatrogenic
Or
Genetic-Physiology
Specific Patient Populations?
Annexin A5 (ANXA5) M2 Haplotype (Stratification/PBM)

ANXA5 M2 haplotype is 4 base pair mutation in the ANXA5 gene causing a reduction in Annexin 5 - normally present in high concentration on the apical surface of syncytiotrophoblasts.

It’s presence indicates risk $\Rightarrow$ hypercoagulation & and thrombotic risk.

Studies demonstrating association with pregnancy outcome complications & benefit of anti thrombotic therapy

- $n = 29$

Reviews of Annexin A5

Annexin A5 gene variants
Initially found through systematic sequence analysis of the ANXA5 gene in 70 patients in Northern German origin with RPL (>2 foetal losses), non-carriers of PTm and/or FVL mutations.

To Date: * >4,500 patients of * Different ethnicities and various obstetric complications have been genotyped
Associated risk in Anxa5 M2 Haplotype carriers is 2.4-4.0 for the various thrombophilia-related phenotypes
Annexin-V M2 characteristics

- Defect conveyed **embryonally**
- Risk is **independent** of maternal / paternal transmission
- **Distinct** from other thrombotic disorders
- Spectrum of pathologies as the lesion is in the placenta
CARE: Incidence in our IVF population

- Male 26%
- Female 24%
- Both partners carriers ~10%
- Couples 44%
- Couples w. unexplained infertility 37%
- Co-exists w. male and female infertility patients (27%)
- Co exists w. PCOS (35%)

Rbmonline 29; 80–87: 2014
Multicentre study of the clinical relevance of screening IVF patients for carrier status of the annexin A5 M2 haplotype

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M2 Haplotype positive – treatment results


Precision Medicine in Assisted Conception: A Multicenter Observational Treatment Cohort Study of the Annexin A5 M2 Haplotype as a Biomarker for Antithrombotic Treatment to Improve Pregnancy Outcome

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Particle Imaging Velocimetry (PIV)

Ca$_2^+$-sensitive fluorescent dye FuraRed,
dramatic periodic increases and decreases in velocity of the cytoplasmic movements

‘Speed Peaks’
Measurements of PF Ooplasm Contractions

Following sperm entry into the ooplasm:

- Contractions of the actomyosin cytoskeleton
- Triggered by $\text{Ca}^{2+}$ oscillations
- Analysis of the cytoplasmic movements predict developmental potential of the zygote

Earliest and fastest, non-invasive way to predict the viability of eggs fertilized *in vitro*
Calculating ‘Speed Peak’ Amplitude and Frequency

Image 1 → Interrogation region 1 → Cross-correlation coefficient distribution → Displacement vector

Image 2 → Interrogation region 2

- Cross-correlating image sub-regions between sequential pairs of images
- Each image was divided into square interrogation
- Cross-correlation coefficient distribution was calculated within a larger region in the next image in the sequence.
- Displacement vector calculated over the time between images.
- Possible to accurately measure sub-pixel movements from displacement of the pattern of contrast of an area of pixels is being measured over many pixels.
Stages PF in relation to ‘Speed Peaks’

Mean cytoplasmic speed in a representative unfertilized egg

Mean cytoplasmic speed in a representative \textit{in vivo} fertilized zygote during Stages 1 – 3
DIC images with vector patterns representative for unfertilized eggs (MII) and for zygotes in Stage 1-3.

Length of the vectors and colour of the background indicate speed of the local cytoplasmic movement.
Robotics
Lab on a chip
In Vivo Fertilisation and Cleavage

Anevivo Device

- Fully permeable silicone tube allowing bidirectional exchange between the embryo and the maternal uterine cavity
- 360 microperforations, 40 μm in diameter
- Inner diameter 0.43mm; outer diameter 0.75 mm
CARE strategy to maximising LBR

- CARE TLI for all patients ♀ age <38 = 19-25% ↑ Live Birth
- ♀ age >35 ⇒ PGT-A
- ♀ age >35: PGT-A and CAREmaps NOT mutually exclusive
- Personalised Genetics - AnnexinV M2 Haplotype
  - Further validated biomarkers
“Can’t you just take one of mine?”
Thank you for listening
CARE Fertility Group of Clinics

Thank you for listening.
CARE Fertility Group Data

♀ Age >35
n = 565

STAR
50.8% in the PGS arm vs 37.2% in the control arm

\[ X^2 = 23.0615, \ P=0.00002 \]
Altmäe et al, 2017
Meta-signature of human endometrial receptivity: a meta-analysis and validation study of transcriptomic biomarkers

- Identified a meta-signature of endometrial receptivity composed of 57 genes
- But their molecular mechanisms in uterine physiology and pathophysiology remain to be investigated
- Importance of immune responses, the complement cascade pathway and the involvement of exosomes in mid-secretory endometrial functions, and could serve as promising biomarkers of endometrial receptivity and achieving a pregnancy
Silber et al 2017 – Natural Cycle – 14,000
<35 Fecundity 25% - months
Age 41 = 14 months

Add-ons by Pasquale