ALPHA IVF
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AI for Embryo Morphology Selection

PGDIS 2024

DATO DR. COLIN LEE

MEDICAL DIRECTOR
CONSULTANT O&G AND FERTILITY SPECIALIST

www.alphafertilitycentre.com
www.alphaivfgroup.com

01 DISCLOSURES

- Alpha IVF & Women's Specialists (KL, Malaysia) – Founder
- Alpha IVF & Women's Specialists (Singapore) – Founder
- Genesis IVF & Women's Specialist Centre (Penang, Malaysia) – Founder
- Alhaya Fertility Centre (KL, Malaysia) - Founder
- Presegen (Australia) – Clinical and Scientific Advisory Board Member
- Vitrolife (Sweden) – Scientific collaborator
- Embryonics (Israel) – Scientific collaborator
- Fairtility (Israel) – Scientific collaborator
- Embryoaid (Poland) – Scientific collaborator
- Kai Health (South Korea) – Scientific collaborator

02 EVOLUTION OF ART

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1959	1st IVF (rabbit) (Prof. Min Chueh Chang)
1970s	1st IVF pregnancies in humans
1980s	First clinics; microinjection; cryopreservation; genomics
1990s	culture system
2000s	Time-lapse; omics
2010s	Cloud; networking; automation
2020s	Telehealth; AI; IoT; robotics; regenerative medicine

03 DEFINITION OF AI

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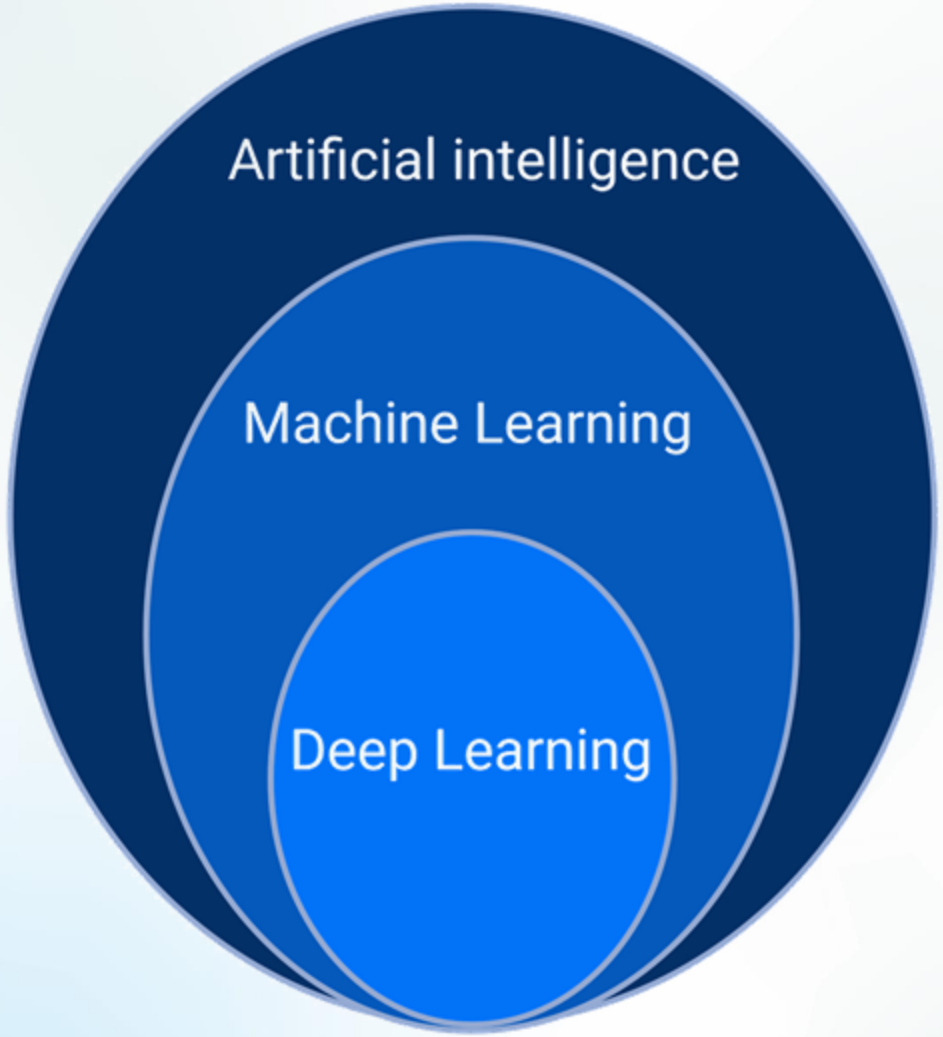
- AI – a technique that enables us to leverage computers and machines to imitate and mimic the problem solving and decision making capabilities of humans

- ML - a computer program that learns a given task over time through experience and improves itself to achieve better performance; helps you build AI-driven applications

- DL – is a machine learning that utilizes deep-convolutional neural network (CNN) to extract, process and predict information by learning from image recognition



04 CURRENT APPLICATIONS OF AI IN ART

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Embryo Development & Selecion	Sperm & Oocyte	Lab Data Management
• Blastulation prediction • Embryo grading • Embryo selection • Prediction of euploid	• MII analysis • Fertilization prediction • Blastulation prediction • Semen analysis • Real-time sperm selection during ICSI	• Data management/ structuring • KPI tools

05 SELECTION OF EMBRYOS

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- Gardner's grading - well correlated with IR & LBR
  - well correlated with ploidy status
  - grading by embryologist non consistent inter & intra
- Scoring systems – Kidscore/IDAScore/LWV/LWG/CHLOE
- Chromosome status using PGT on trophectoderm cells
  - ✓ concordance (98.54% TE euploid: ICM euploid; 97.9% TE aneuploid: ICM aneuploid, Kim et al, 2022)
  - ✓ based on cut-off threshold (20%-25%)
  - ✓ Mosaicism
  - ✓ "self-correction"

06 KEY CHALLENGES IN EMBRYO GRADING

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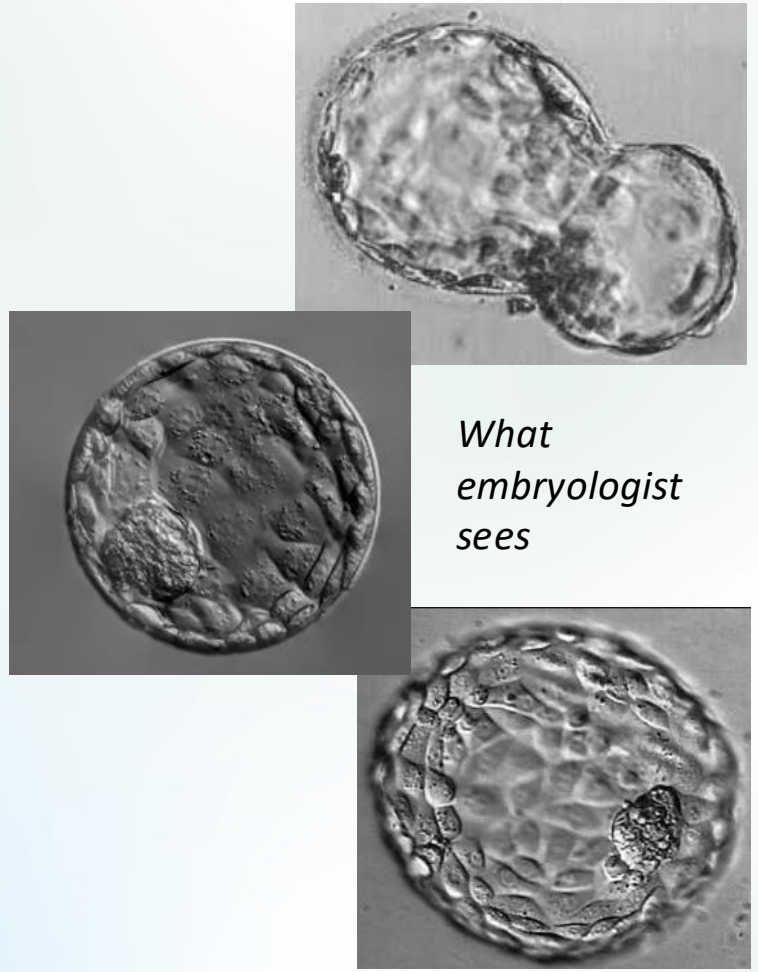
- high level of subjectivity
- intra- and inter-operator variability that exists

AI = automated and unbiased



What embryologist sees

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07 SUBJECTIVITY VS OBJECTIVITY

DOES AI HELP IN IMPROVING EMBRYO SELECTION?

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P-955 3:30 PM Wednesday, October 21, 2020

SHOULD THERE BE AN "AI" IN TEAM?: EMBRYOLOGISTS IMPROVE SELECTION OF HIGH IMPLANTATION POTENTIAL EMBRYOS WITH THE AID OF AN ARTIFICIAL INTELLIGENCE ALGORITHM.

Victoria W. Fitz, MD, MSCR,[1] Manoj Kumar Kanakasabapathy, MS,[2] Prudhvi Thirumalaraju, BS,[2] Leslie B. Ramirez, PhD,[3] Jason E. Swain, PhD, HCLD,[4] Carol Lynn Curchoe, PhD, TS (ABB),[5] Kaitlyn E. James, PhD,[1] Irene Dimitriadis, MD,[1] Irene Souter, MD,[1] Charles L. Bormann, PhD,[1] Hadi Shafiee, PhD.[2] [1]Massachusetts General Hospital, Harvard Medical School, Boston, MA; [2]Brigham and Women's Hospital, Harvard Medical School, Boston, MA; [3]Extend Fertility, New York, NY; [4]CCRM Fertility Network, Lone Tree, CO; [5]San Diego Fertility Center, San Diego, CA.

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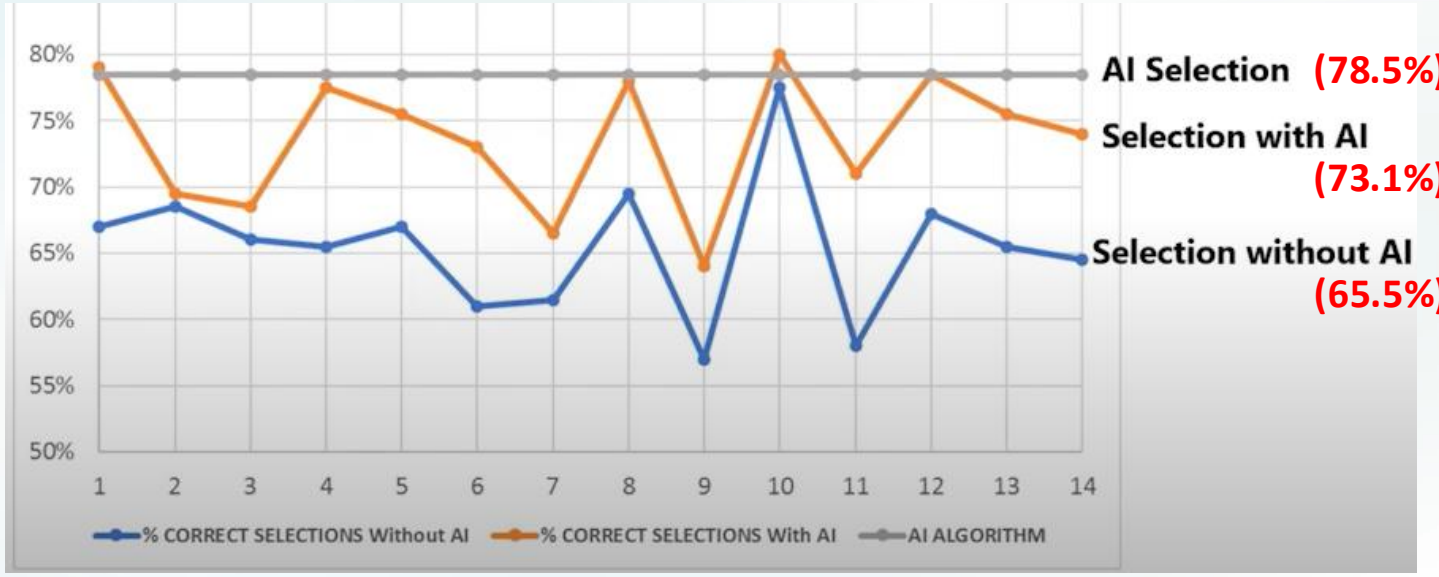


This group challenged their embryologists:

- Select without AI assistance
- Select with AI assistance

Average correct selection without AI = 65.5%
Average correct selection with AI = 73.1%; 8.1% improvement
AI correct selection = 78.5%

CAN AI BE USED TO STANDARDIZE EMBRYO GRADING?

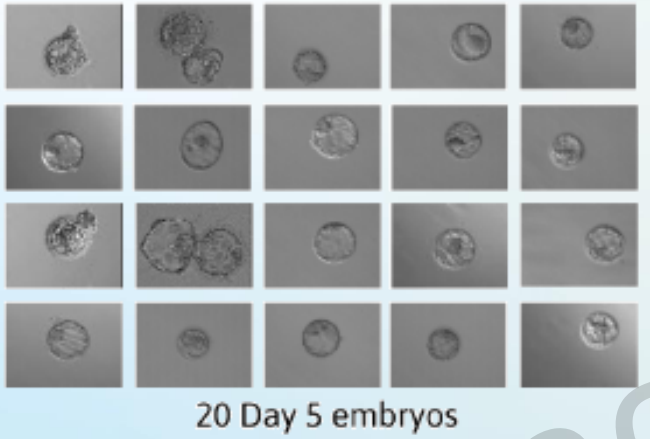
OPEN ACCESS
FERTILITY & REPRODUCTION
Vol. 5, No. 4 (Dec 2023)
© The Author(s)
DOI: 10.1142/S2661318223742406

#92 : An Artificial Intelligence Algorithm Outperforms Highly Variable Embryologist Grading for Predicting the Likelihood of Pregnancy Outcome from Embryo Images

Dr Matthew VerMilyea[2], Dr Jonathan Hall[1,3], Dr Michelle Perugini[1,3], Dr Tuc Nguyen[1], Dr Don Perugini[1], Dr Sonya Diakiw[1]

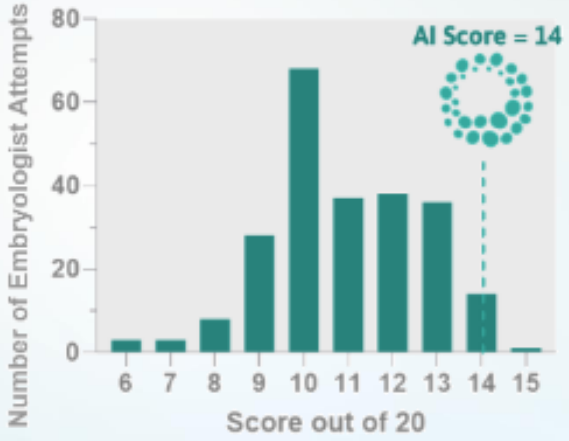
[1]Life Whisperer Diagnostics (a Subsidiary Of Presagen), San Francisco Bay Area, United States, [2]Ovation Fertility, Austin, United States, [3]The University of Adelaide, Adelaide, Australia

To evaluate whether an AI algorithm can standardize and improve embryo evaluation during IVF



20 Day 5 embryos

158 Embryologists
vs
Artificial Intelligence



- AI correctly predicted 14 images (70% accuracy)
- 6% (14/236 attempts) of embryologists also correctly predicted 14 images
- Only 1 embryologist correctly predicted 15 images in 1 attempt (1/236 attempts) (75% accuracy)
- Remaining 94% of embryologists correctly predicted 6-13 images (221/236 attempts) (30-65% accuracies)

Demonstrates the inherent variability and lack of objectivity
AI has great potential to standardize embryo assessment and good training tool for junior embryologist

IS AN AI MODEL AS GOOD AS AN EXPERIENCED EMBRYOLOGIST?

JOURNAL ARTICLE

P-289 Evaluation of AI-based, non-invasive and annotation free EMBRYOAID software with embryologists: time and prediction

P Wygocki, M Siennicki, P Pawlik, H Kompanowski, T Gilewicz. P Sankowski. J Kuśmierczyk-Kubiak, C S S Lee, A Y X Lim, B Stankiewicz . et al

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[6]Invicta- Research and Development Center, Faculty of Electronics- Telecommunications and Informatics- Department of Biomedical Engineering, Sopot, Poland
[7]Invicta- Research and Development Center, Department of Medical Biology and Genetics, Sopot, Poland

Human Reproduction, Volume 38, Issue Supplement_1, June 2023, dead093.647, https://doi.org/10.1093/humrep/dead093.647
Published: 22 June 2023

Properly trained AI models can perform as good as embryologists with respect to accuracy, improving in the same time decisiveness.

150 pairs of Day-5 embryo time-lapses with known outcome

- Pregnancy prediction by AI → **AI** 66.9 (CI 63.1 – 70.7)
- Pregnancy prediction by 10 embryologists (average 10 yrs experience) → **Embryologist** 63.8 (CI 62.6 – 65.0)

08 WHICH CONFOUNDERS AFFECT THE ABILITY OF AI TO PREDICT BLASTULATION BASED ON OOCYTE IMAGES?

Confounders analyzed: sperm quality, oocyte dysmorphism, culture time, images pre or post-ICSI, age

Sample size: 1281 pre-ICSI and post-ICSI oocyte images were analyzed

Primary endpoint: blastulation

Results:

- AI can predict blastulation better using post-ICSI images compared to using pre-ICSI images (AUC 0.66 vs 0.57; $p < 0.001$)
- Sperm quality does not affect AI prediction
- Lower AI scores seen in oocytes with enlarged perivitelline space, dysmorphic oocytes, abnormal Zona pellucida, cytoplasmic abnormalities and dark and enlarged oocytes.

Findings:

Oocyte dysmorphism, pre or post-ICSI image should be controlled for when building AI algorithms to predict blastulation based on oocyte images.

JOURNAL ARTICLE

P-310 Bringing Transparency to Oocyte Assessment: the importance of including confounders when building Artificial Intelligence (AI) based support tools to quantify oocyte viability

FREE

A.Y.X. Lim[1], A. Zepeda[2], C. Hickman[2], B. Kantor[3]

[1]Alpha IVF & Women's Specialists, IVF Laboratory, Petaling Jaya, Malaysia
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Human Reproduction, Volume 38, Issue Supplement_1, June 2023, dead093.668, https://doi.org/10.1093/humrep/dead093.668

Published: 22 June 2023

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Abstract

Study question

Which confounders (sperm quality, oocyte dysmorphism, culture time, images pre or post-ICSI, age) affect the ability of AI to predict blastulation based on oocyte images?

Summary answer

Sperm quality, oocyte dysmorphism, pre or post-ICSI image should be controlled for when building AI algorithms to predict blastulation based on oocyte images.

What is known already

Previous studies reporting on the use of AI to predict blastulation based on oocyte images have: (i) not accounted for confounders affecting blastulation (i.e. sperm quality, culture time), and (ii) used post-ICSI images; without assessing whether the ICSI procedure affects the oocyte image as assessed by AI. Therefore, there is a risk of mislabeling viable oocytes as non-viable due to external factors, which could cause uncontrolled bias and failure to generalize when used in clinical practice. The objective was to assess how these confounders affect efficacy of prediction of blastulation from oocyte images by an AI-based oocyte assessment tool: CHLOE-OQ(Fairtility).

Study design, size, duration

Cohort study. Images of 1281 oocytes (February to June 2022) were taken pre and post ICSI using the Embryoscope, and the embryos cultured until day 7. Oocyte donor source and age, oocyte dysmorphias and sperm quality were

09 CAN AI PREDICT EMBRYO PLOIDY? (EXPLAINABLE AI)

A pioneering study from IVI combines 5 modules of embryo image analysis using AI to detect aneuploidy

Objective: to develop an AI model for PGT triage & preferential transfer

Study design:

- Single-center study
- Retrospective dataset
- Ground truth labels – 2,502 time-lapse images up to 144 hpi with know ploidy status
- 70% dataset for model training, 15% for validation, 15% for accuracy testing
- 5 modules were studied and used in the AI model for ploidy prediction

JOURNAL ARTICLE

O-073 Artificial intelligence (AI) based triage for preimplantation genetic testing (PGT); an AI model that detects novel features in the embryo associated with ploidy

M Meseguer Escriva, R Maor, L Bori, M Shapiro, A Pellicer, D Seidman, A Mercader, D Gilboa

Human Reproduction, Volume 37, Issue Supplement_1, July 2022, deac104.087, https://doi.org/10.1093/humrep/deac104.087
Published: 30 June 2022

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Abstract

Study question

Can an AI based triage system noninvasively detect aneuploidy in preimplantation embryos in a precise and valid manner?

Summary answer

Using a feature extraction approach to identify features in time-lapse images, an AI model was validated and found to noninvasively detect ploidy with unprecedented accuracy.

What is known already

Invasive PGT with trophectoderm biopsy is the gold standard for evaluating the genetic integrity of an embryo prior to transfer. Even so, its utility and diagnostic accuracy is debated due to concern of structural damage, sampling bias and viability after vitrification-warming. Though several noninvasive methods for evaluating ploidy have been developed, their main limitations lay in their accuracy. This study reports on the ongoing validation of an AI model that relies on feature extraction and thresholding techniques to distinguish between aneuploid and euploid embryos; the model is intended to be used in clinical settings for PGT triage and preferential transfer.

Study design, size, duration

In this single-center study, we used a retrospective dataset consisting of time-lapse images from 2,502 preimplantation embryos with known ploidy status to

Morphokinetic Parameters

Detect abnormal morphokinetic patterns to predict aneuploidy

(52% accuracy)

+

Embryo Morphology

Previously validated A-C embryo grading classification algorithm

(68% accuracy)

+

Cell Activity

Differential cell division activity and compaction

(73% accuracy)

Mitochondrial Activity

AI-based classification of mitochondrial DNA content

(77% accuracy)

+

Warping/Shrinkage

Blastocoelic contractions of more than 8 micron in diameter

(56% accuracy)

=

5 modules integration achieve 90% accuracy

10 CAN SINGLE-IMAGE-BASED AI PREDICTS PLOIDY?

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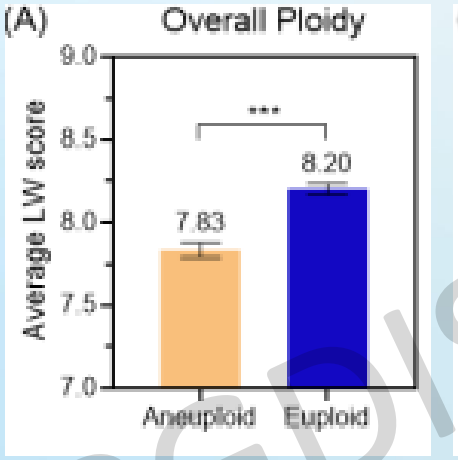
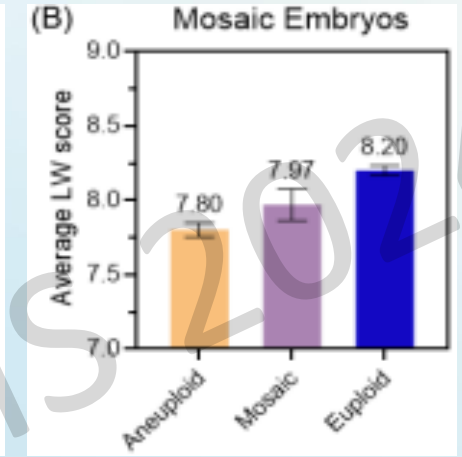
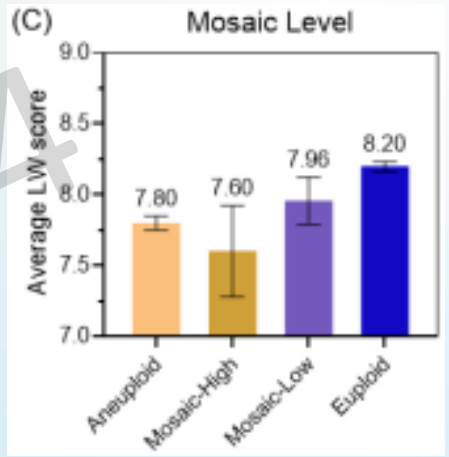
- Retrospective dataset; 5,469 day 5 blastocyst image with known ploidy & AI scores
- Consist of
  - 3,251 (59.4%) euploid
  - 1,815 (33.2%) aneuploid
  - 403 (7.4%) mosaic
- Evaluate the correlation between AI score and euploid, mosaic and aneuploid embryos



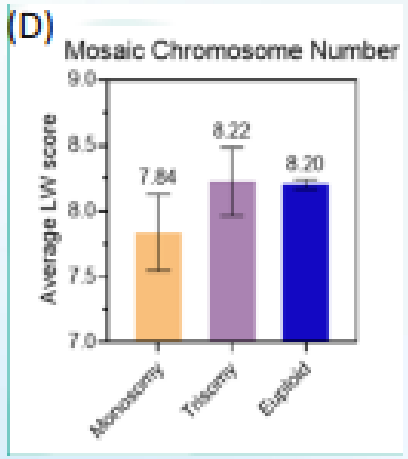
Average AI score for eu significantly higher than aneu



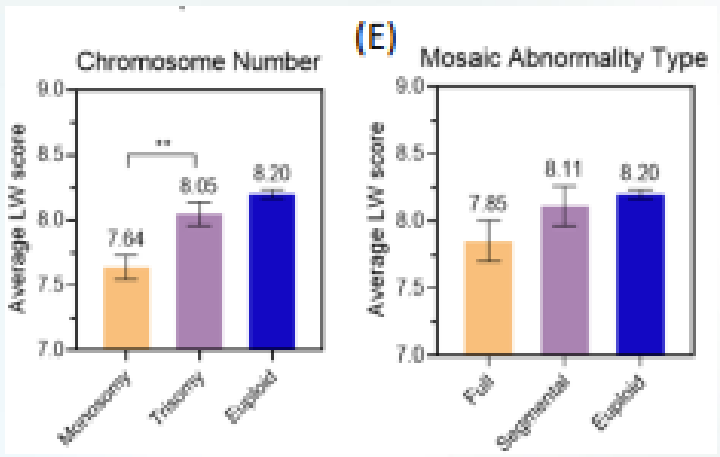
Significant linear increase in AI score from aneu>mos>eu



High mos embryos has lower AI average score than low mos embryos



Trisomic changes has higher AI average scores than monosomic changes



Segmental changes has higher AI average scores than full gain or low

VerMilyea et al, Hum Reprod 2021

11 SINGLE IMAGE OR TIME-LAPSE IMAGE SEQUENCES

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P-08 (Abstract No.273) ASPIRE 2023

COMPARATIVE ANALYSIS OF PREGNANCY PREDICTIVE POTENTIAL USING THE DEEP LEARNING BLASTOCYST SCORING MODEL CALCULATED FROM THE SINGLE FOCUS BLASTOCYST IMAGE AND TIME-LAPSE IMAGE SEQUENCES

M. Shioya[1,2], T. Kobayashi[1,2], S. Nakano[1], T. Sugiura[1], M. Kinoshita-Okabe[1], M. Fujita[1], K. Takahashi[1].

[1] Takahashi Women's Clinic, Reproductive Medicine, Chiba, Japan
[2] Department of Reproductive Medicine, Chiba University Graduate School of Medicine, Chiba, Japan

- Life Whisperer (LW, Fujifilm) – AI-based blastocyst evaluation model that uses a single-focus blastocyst image at a single-time point
- iDAScore (iDA, Vitrolife) – AI-based blastocyst evaluation model that uses time-lapse image sequences at multiple-time points

This study analyzes the predictive ability of LW for pregnant blastocyst and compare it to an AI-model using TLM (iDAscore, Vitrolife)

Methods

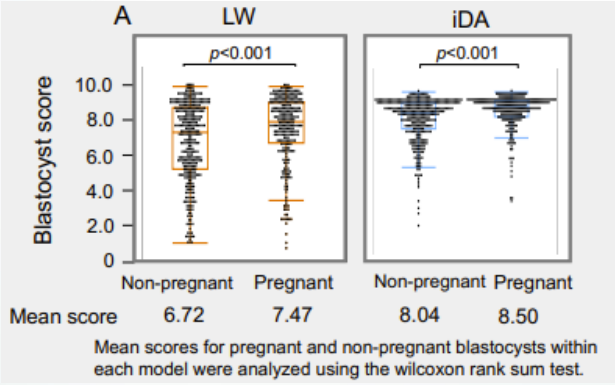
- Retrospective single-center study
- 666 day 5 blastocysts transfer cycles (Jan 2019-Dec 2022)

Score calculation & analysis

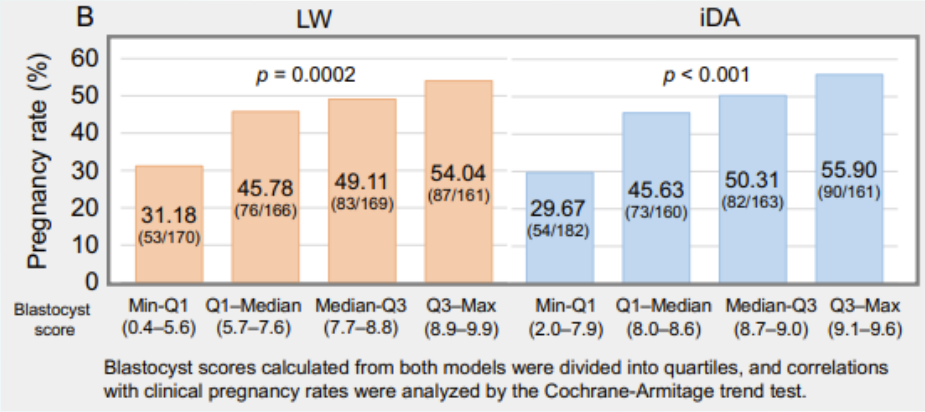
- LW : 1 image taken before vitrification
- iDA : TL images taken at 11 focal points every 10 min post-ICSI (7920 images)

Results

- Mean AI score was higher in pregnant blastocysts for both AI models
- Pregnancy rates increased according to higher scores in both AI models
- Odds for clinical pregnancy increased with higher scores in both models
- AUC 0.60 for LW vs 0.62 for iDA (*p* value = 0.4479)



Mean scores for pregnant and non-pregnant blastocysts within each model were analyzed using the wilcoxon rank sum test.



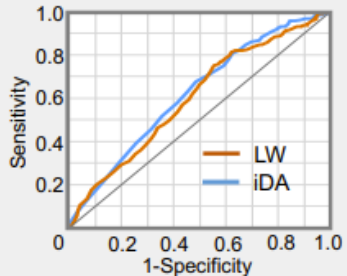
Blastocyst scores calculated from both models were divided into quartiles, and correlations with clinical pregnancy rates were analyzed by the Cochrane-Armitage trend test.

Table 2. Odds ratios of both scores for pregnancy

	aOR	95% CI	*p* value
LW	1.14	1.06–1.24	0.0007
iDA	1.41	1.20–1.66	<0.0001

Adjusted odd ratios (aOR) for clinical pregnancy was calculated by multivariate logistic regression analysis including confounding factors (patient age, BMI, and basal AMH).

Figure 2. Evaluation of the predictive ability for pregnant blastocysts in two AI-models



	AUC	95% CI	*p* value
LW	0.60	0.56–0.64	0.4479
iDA	0.62	0.58–0.66	

To evaluate the predictive ability of the two AI-models for clinical pregnancy, ROC curve analysis was performed and evaluated by area under the curve (AUC).

12 AI Reduces Time-to-Pregnancy for IVF Patients, reducing patient cost

P-92 4:30 PM Saturday, October 17, 2020

EVIDENCE FOR SUPERIOR BLASTOCYST COHORT RANKING USING ARTIFICIAL INTELLIGENCE BASED ON RETROSPECTIVE CLINICAL PREGNANCY RESULTS. Matthew David VerMilyea, PhD,[1] Milad A. Dakka, PhD,[2] Jonathan MM. Hall, PhD,[3] Sonya M. Diakiw, PhD,[2] Tuc Van Nguyen, PhD,[2] Don Perugini, PhD,[2] Kaylen Silverberg, MD,[4] Michelle Perugini, PhD[2] [1]Ovation Fertility, San Antonio, TX; [2]Presagen and Life Whisperer, Adelaide, SA, Australia; [3]Australian Research Council Centre of Excellence for Nanoscale Biophotonics, Adelaide, SA, Australia; [4]Texas Fertility Center, Austin, TX.

13.8%

Reduction in time-to-pregnancy
TTP for AI Ranking = 1.506±0.003
TTP for Embryologist Ranking = 1.746±0.004

Cost savings through fewer IVF cycles

- To evaluate TTP using simulated embryo cohorts
- AI was used to rank embryos in each cohort
- TTP is determined by how many transfers would be needed for successful pregnancy

VerMilyea et al. Fert Stert 2020

13 ALPHA IVF'S EXPERIENCE IN INTRODUCING AI TO OUR PATIENTS

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- Tested out on 32 patients, pregnancy rate 80% (Lim et a, ASPIRE 2022). Patients paid for the usage
- Initially on patients who had ≥ 2 blastocysts
- Currently offered without charge to patient as a standard evaluation to all even to those with single blastocyst. Alpha IVF absorbed the cost

14 IMPLEMENTATION OF AI IN OUR CENTRE

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1

Collaborations (started in 2018);

Anonymised data transfer

2

Validation

VerMilyea et al, 2019; VerMilyea et al, 2020; Lim et al, 2022; Diakiw et al, 2022

3

SEA's first successful live birth following frozen embryo transfer of blastocyst selected using AI

(Lim et al, 2021)

4

Continuous analysis and training to embryologists and clinicians

5

Fine-tuning and development of in-house comprehensive embryo selection system

6

Awareness to patients through health talks, live interactive sessions, seminars etc

15 NON-INVASIVE APPROACH TO PLOIDY PREDICTION

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- PGT-A requires biopsy (invasive procedure)
- PGT-A requires skillful embryologist
- PGT-A very costly
- AI can predict ploidy without the disadvantages of above
- Combined use of viability AI and genetic AI improves selection of embryos leading to clinical pregnancy *(Diakiw et al, 2022)*

16 POSSIBLE INDICATIONS OF AI REGARDING CHROMOSOME STATUS

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- Predicting likelihood of euploidy
- Prioritization/selection of embryos for PGT-A
  - financial/other considerations
  - may only want low score to select for PGTA
  - may only want high scores to select for PGTA
- Mosaic embryos
- Aneuploid embryos

} To predict eventual euploidy

- AI generally not meant to replace PGT-A
  - centres with not so effective freeze-thaw system. Fresh transfer
  - centres with not so effective biopsy expertise
- in patients who has very limited available embryos
- in countries where PGT-A not allowed
- in centres where PGT-A not available

17 COMPREHENSIVE EMBRYO SELECTION SYSTEM

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1. **Standard morphology (Gardner's grading)**
2. **Morphokinetics**
3. **Artificial Intelligence**
4. **PGT-A**

18 R&D

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Our completed R&D

Project	Collaborators	Country
Use of AI to perform embryo viability assessment for embryo selection	- Presegen - 12 IVF Clinics	Malaysia, Australia, USA, New Zealand
Use of AI to predict blastulation, ploidy & implantation	- Fairtility - 6 IVF Clinics	Malaysia, Israel, Spain, UK, Turkey, Italy
Validate AI prediction tool for embryo selection	- MIM - 3 IVF Clinics	Malaysia, Poland, Turkey

Our existing/ on-going R&D

Project	Collaborators
Evaluation of endometrial receptivity using AI – aid clinician in selecting optimal day for embryo transfer or deciding to continue or cancel the cycle	- Presegen
3 Projects on Development and validation of an AI model for embryo selection	- 1st with Vitrolife - 2nd with Embryonics - 3rd with Kai Health

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THANK YOU!