ChatPGT

Using Artificial Intelligence-Guided Feedback in an Attempt to Improve Embryologists' Selection of Euploid Embryos

Giles A Palmer[1,2,3] Alejandro Chavez-Badiola[2,4] Roberto Valencia Murillo[4] Simon C Harvey[5] Adolfo Flores Saiffe Farias[4,6] Gerardo Mendizabal-Ruiz[4,6] Omar Paredes[2,6]

Darren K Griffin[7,8]

1.International IVF Initiative, New York, New York, USA

2.IVF2.0 Ltd, London, UK

3.Institute of Life, IASO Hospital Athens, Greece

4. Conceivable Life Sciences, New York, New York, USA

5. Faculty of Engineering and Science, University of Greenwich, UK.

6.Biodigital Innovation Lab, Translational Bioengineering Department, CUCEI, Universidad de Guadalajara, Mexico

7. School of Natural Sciences, University of Kent, Canterbury, Kent, CT2 7NJ, UK

8. Animal Genomics and Bioresource Research Unit (AGB Research Unit), Faculty of Science, Kasetsart University, Chatuchak, Bangkok 10900, Thailand

Overview

- Background, Timelapse and AI
- Embryo morphology and chromosome abnormality
- ERICA, hypotheses and methodology
- Outcome measures and results
- Discussion
  - Clinical embryology is relatively unique
  - Confounding factors
  - Integration into clinic
  - Will embryologists like it?
  - Trust!
  - Other Factors
- Conclusions and Acknowledgments

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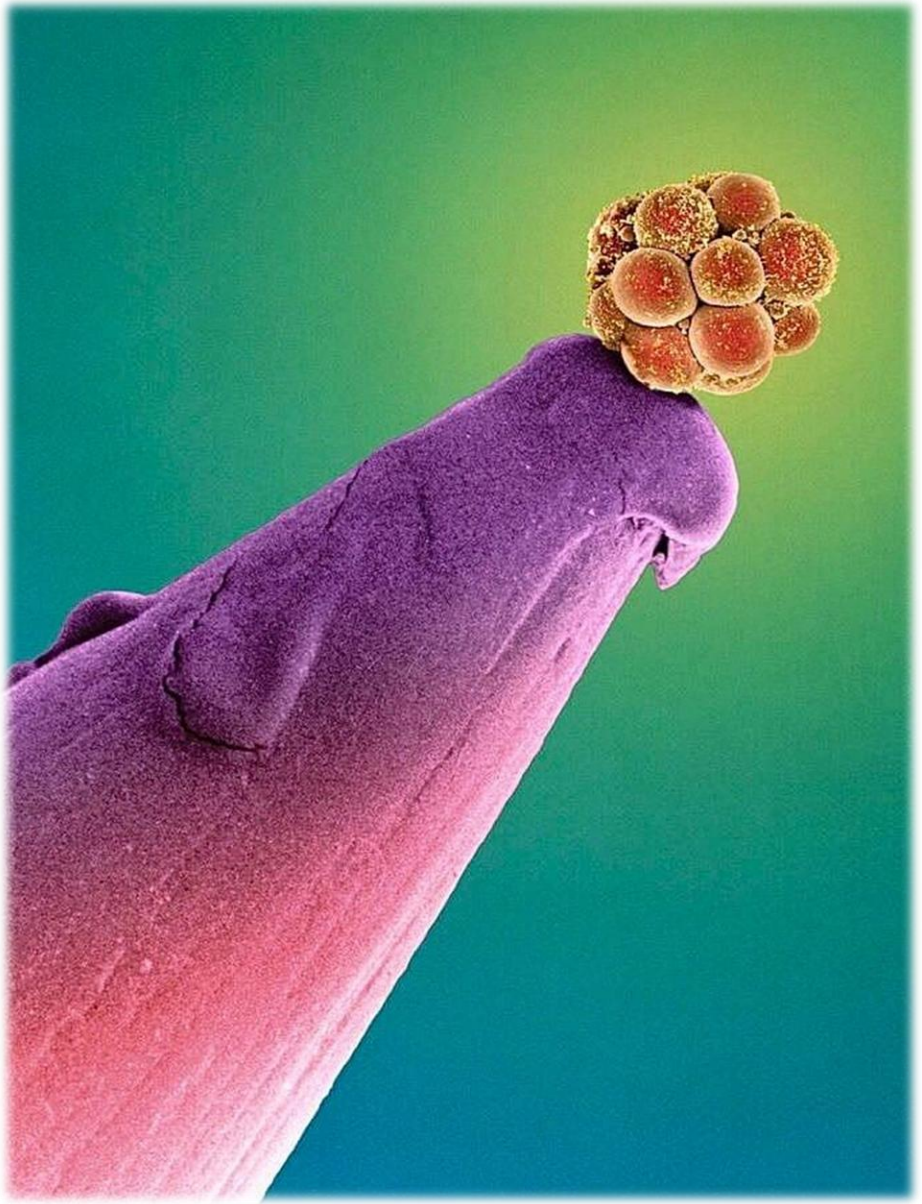
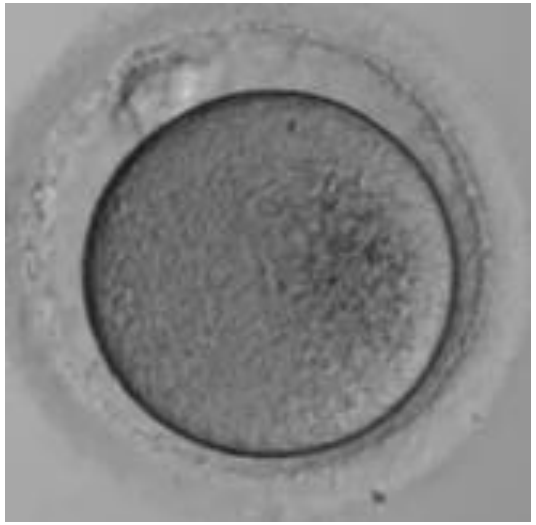
Background

- IVF has undergone many innovations
  - PGT-A
  - Culture media and equipment
    - Time Lapse
  - Vitrification
- Other aspects remain remarkably unchanged
  - Embryologist's subjective judgment for embryo selection
  - Different classification systems proposed over the years
    - Usually include: number of cells, division rates, equality of blastomere size, levels of fragmentation
    - Since blast transfer: hatching status, blastulation rate, assessment of ICM and TE
  - No uniform consensus on how to grade blastocysts
- "Gardner" system with high quality embryos considered for transfer
- Fate of poor-quality embryos depend on
  - Local SOPS
  - Single embryo transfer policies (sET)
- Low chances of survival and likelihood of aneuploidy
  - Most commonly cited reasons for not transferring low scoring embryos
  - Although such embryos can lead to viable offspring



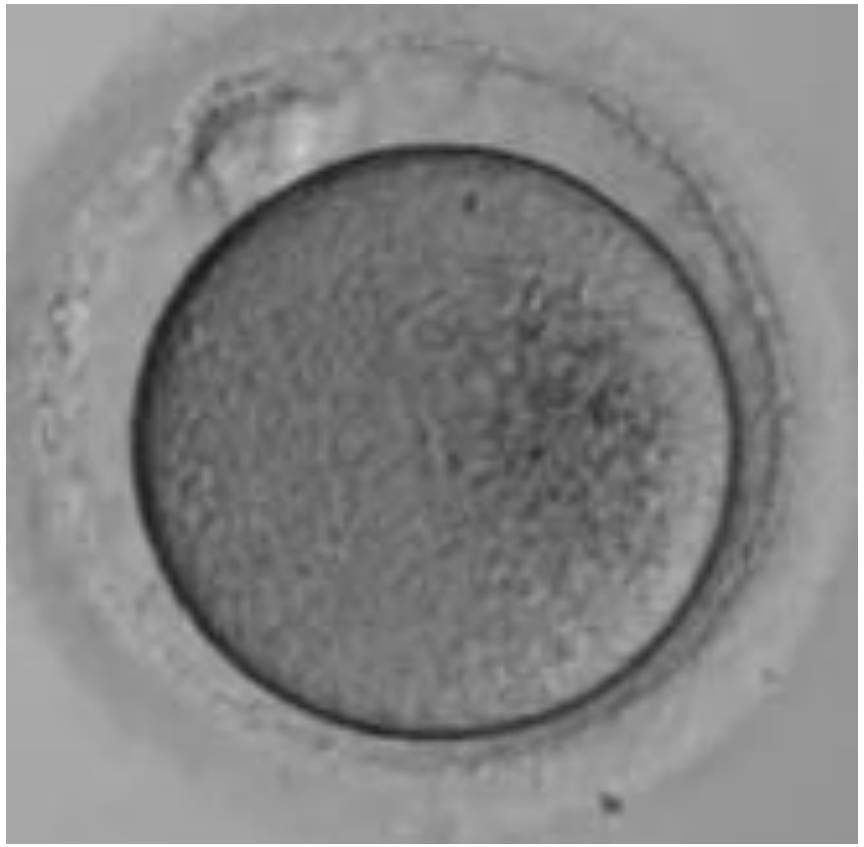
Timelapse Imaging (TLI) and Monitoring



- With digitalization
  - Transforms humble microscope into an advanced analytical tool
  - Elevating its role from mere observation to active data analysis.
- Can output either static or video images
- Gives embryologists opportunity to observe more aspects of development
- Benefits of TLI in terms of improving IVF outcomes are however not certain
- Many investigations established
  - TLI + morphokinetic embryo selection algorithms can result in improved clinical outcomes
  - Pribenszky et al's. (2017) meta-analysis
    - TLI associated with improved ongoing clinical pregnancy rates, early pregnancy loss and live birth rates
    - Morphokinetic-based algorithms could provide objective hierarchical embryo quality ranking
    - Better discriminating power than visual inspection by an embryologist

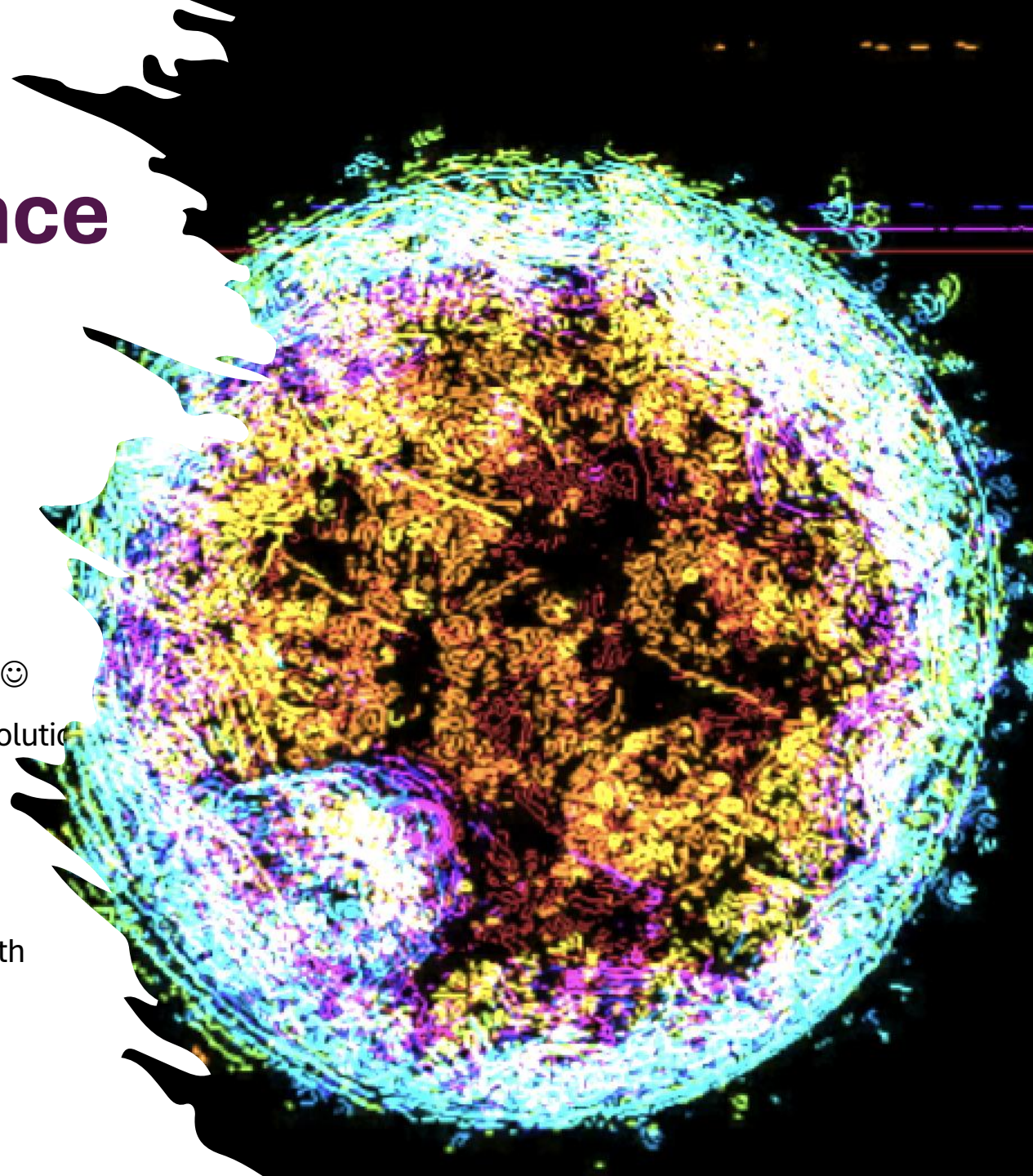
Pros and Cons of TLI

- Must be assessed on clinic-by-clinic basis
- Debate surrounding TLI no sign of abating
- Recent controversy whether AI enhanced or not
  - Often subject to significant hype
- Some notable real-world truths
  - AI's markedly faster than embryologists
  - Manual assessments can be fluctuating
  - The Hawthorne effect
    - Embryologists can perform better than usual as a result of being part of a study

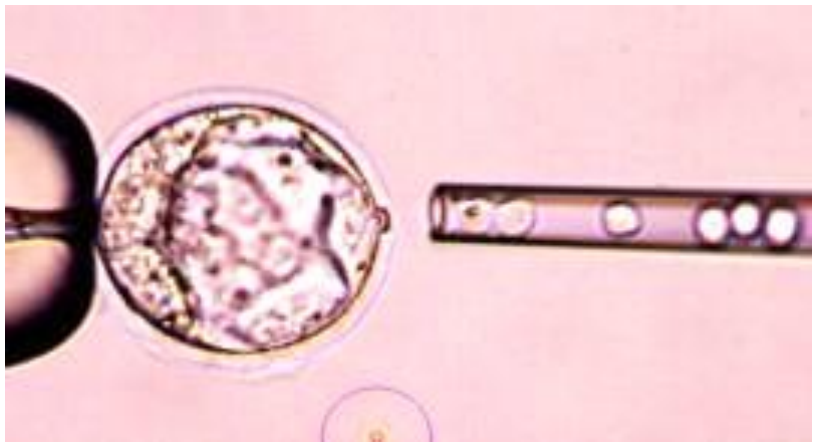


AI – Artificial Intelligence

- Use of AI on static pictures and time-lapse imaging
  - Identify embryos most likely to implant
    - ERICA
    - CareMaps
- AI is reliable and reproducible
  - Within its own defined parameters
- Human embryologists can be subjective, biased and disagree ☺
- AI can learn and analyse complex patterns in much higher resolutio
  - Orders of magnitude more variables
- Non-selection trails
  - Aneuploid embryos rarely result in live births
- Some AI algorithms trained against (an)euploidy as ground truth



AI is Under-Studied for Blastocyst Selection



- How different is blastocyst selection between embryologists and AI?
- How often will the AI choose a different blastocyst?
  - Particularly when embryologists cannot always agree, even among themselves!!!!
- Currently no standards
  - For choosing AI system for embryo evaluation
- Depends on
  - Type and size of the data set
  - Output queries
  - Specific time point for image analysis

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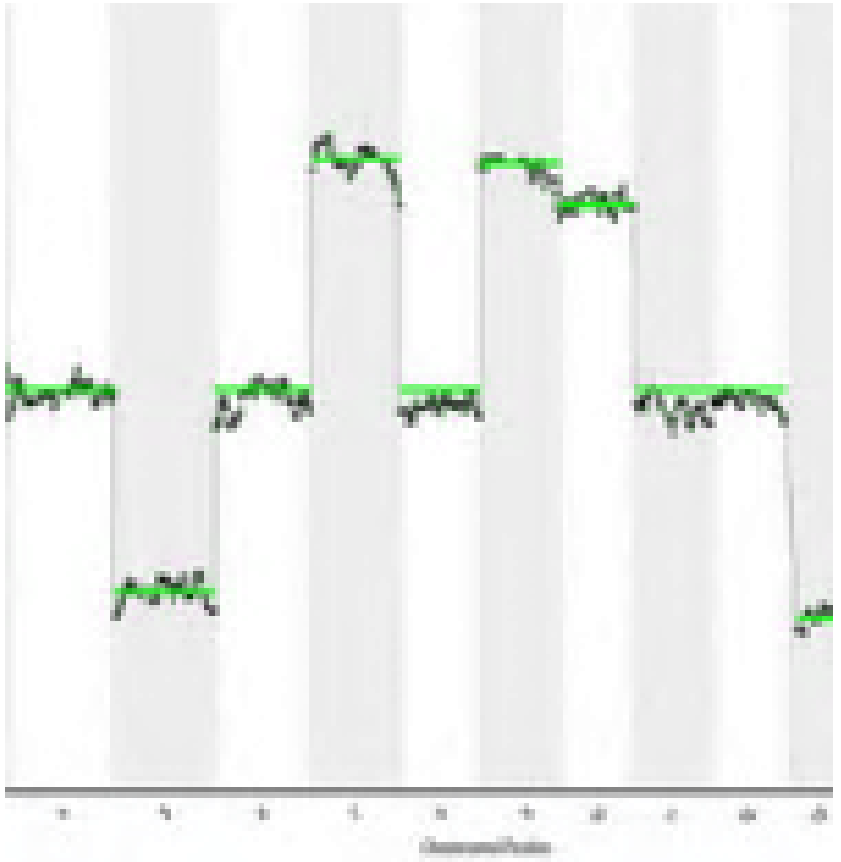
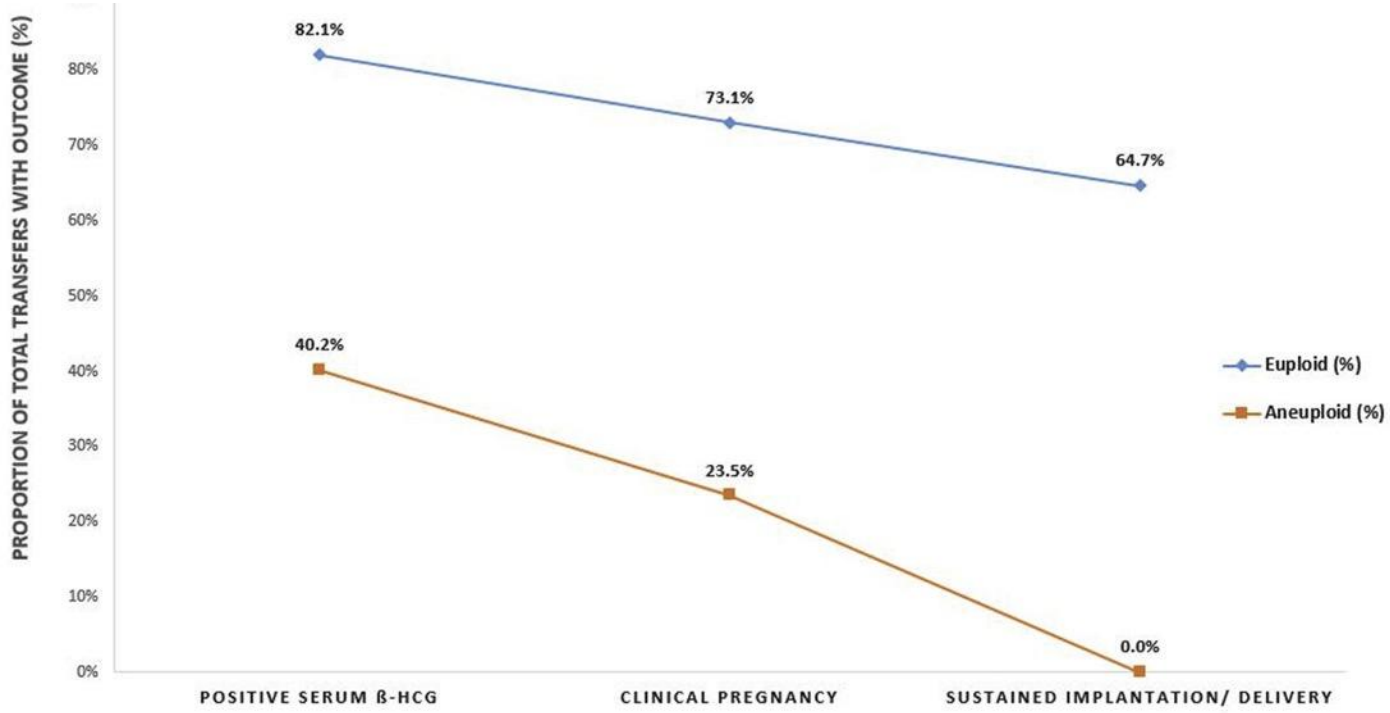
Embryo Morphology vs. Chromosome Abnormality

- Increased temperature - O2 tension can affect cytoskeleton organization
  - Spindle damage and subsequent chromosomal errors
- Morphokinetic features altered in aneuploid embryos
  - Time to reach eight cells
  - Time to blastulation
  - Time to achieve expanded blastocyst
- Prognostic potential
  - Degree of fragmentation
  - Multinucleation until the four-cell stage
  - Frequency of embryo contractions
  - Not for early multinucleation (after 4 cell) nor unequal cleavage.
  - Bamford et al 2022





- Euploid diagnosis (5/5 cells normal)
  - 64.7% chance of live birth
  - 8% chance of miscarriage
- Aneuploid Diagnosis (5/5 cells aneuploid)
  - ZERO % chance of live birth (maybe 1%)
  - 23.5% chance of miscarriage
- The literature (post 2020) has 267 uniformly aneuploid diagnoses that were transferred
- **<u>THREE led to live birth (~1%)</u>**
- And they may be misdiagnoses

Tiegs et al Vol. 115, No. 3, March 2021,
Wang et al Prenatal Diagnosis. 2021;41:1709–1717.
Yang et al Nature cell Biology Vol 23 April 2021, 314-321
Barad et al Human Reproduction, Vol.37, No.6, pp. 1194–1206, 2022

The Key Issue

- PGT-A = most objective way to assess for aneuploidy
- But invasive nature, cost and concerns about mosaicism limit widespread use
- TLI morphokinetic evaluation morphology assessment and AI systems
  - Aimed to compare PGT-A outcomes against their findings
  - *Still difficult to find studies presenting AI systems for embryo ranking trained against ploidy status as a ground truth*
- AI models can outperform embryologists in predicting embryo quality and outcomes
  - AI has great potential to enhance reliability of embryo
  - Further research and validation necessary before implementing AI for embryo selection in clinical practice.

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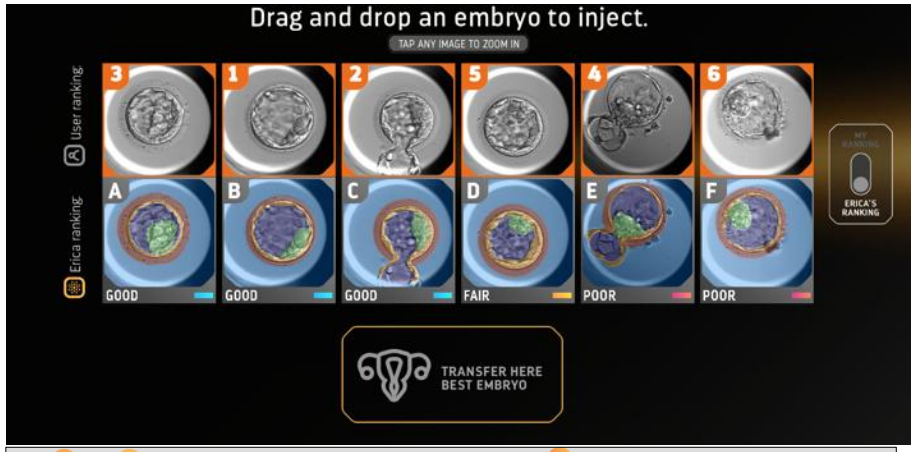
ERICA

- Embryo Ranking Intelligent Classification Algorithm (IVF 2.0 Ltd, UK)
  - Ranks embryos based on ability to predict euploidy and pregnancy test results
  - Uses single static blastocyst image in known outcome data set
  - Following training and validation
    - ERICA more successful than both random selection and experienced embryologists
    - Correctly identifying and ranking embryos with euploidy and highest implantation potential
    - Without the need for time-lapse or embryo biopsy.
  - Relationship between use of ERICA and predicting the chances of spontaneous miscarriage

- This study
  - Used a training tool
    - 19 embryologists (6 junior, 6 intermediate, 7 experienced)
    - Invited to determine ploidy status of embryo images
    - Then presented with an ERICA ranking of the same
  - Then, armed with both pieces of information
    - Asked to make a final judgment on whether an embryo was (an)euploid



ERICA
EMBRYO RANKING INTELLIGENT CLASSIFICATION ASSISTANT

Hypotheses

Embryologists can differentiate euploid from aneuploid embryos significantly better than random

Experienced human judgement, augmented by AI (ERICA) is the superior approach compared to either alone.

ERICA is more effective than, or at least as good as, experienced embryologists for predicting euploidy in human embryos

In Each Exercise

- 5 cases of 2-5 blastocyst images presented
- Limited to only these 5 cases a day
- Minimize operator fatigue
- Opportunity to perform up to 150 cases in total
  - 30 individual days at 5 cases per day
- Had to select the best embryo from the available cohort
  - Even when all embryos were of only fair to medium quality

IVF2.0

CYCLE INFO: PATIENT AGE more 42 Euploids: 1

CHOSE AND DRAG THE BEST EMBRYO

TAP ANY IMAGE TO ZOOM IN

BEST

CYCLE INFO: PATIENT AGE more 42 Euploids: 1

CHOSE AND DRAG THE POOREST EMBRYO

TAP ANY IMAGE TO ZOOM IN




POOREST

CYCLE INFO: PATIENT AGE more 42 Euploids: 1

CHOSE AND DRAG THE BEST EMBRYO

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TAP ANY IMAGE TO ZOOM IN

POOREST

CYCLE INFO: PATIENT AGE more 42 Euploids: 1

RANK WITH ERICA

RESTART

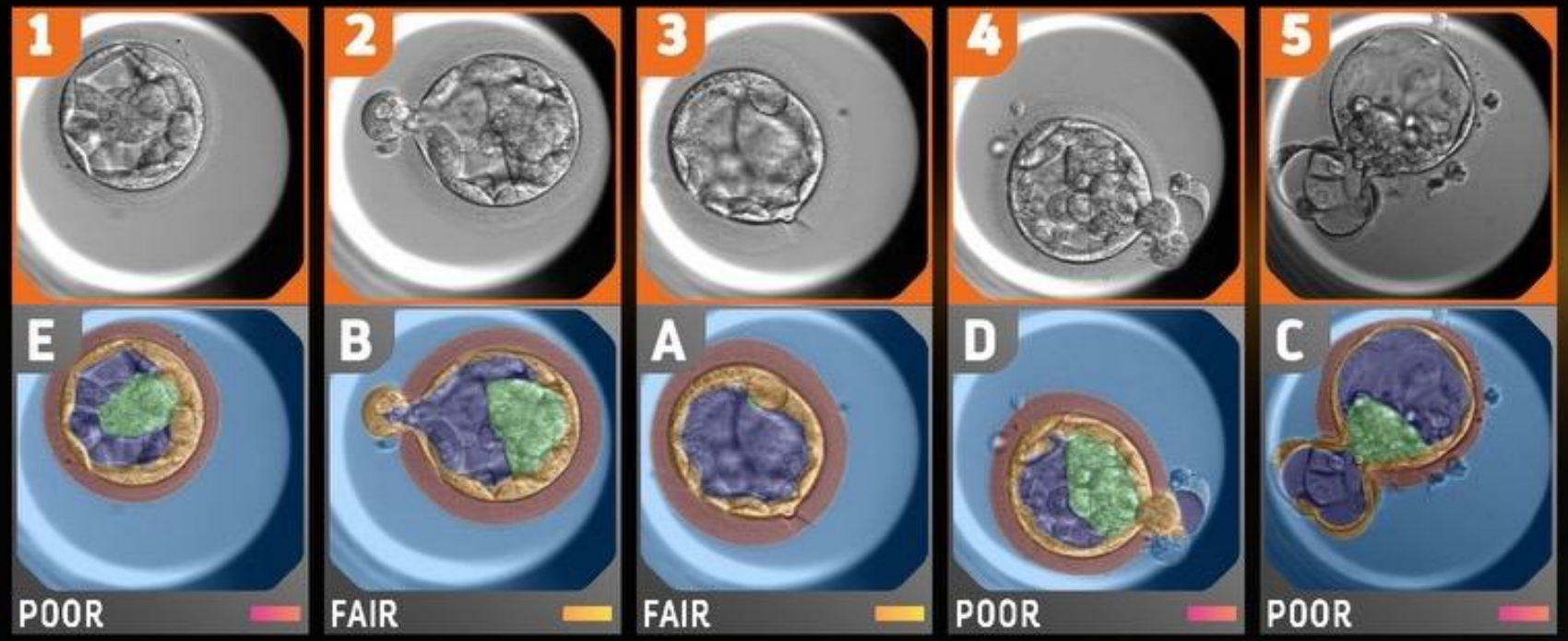
CYCLE INFO: PATIENT AGE more 42 Euploids: 1

Drag and drop an embryo to transfer.

TAP ANY IMAGE TO ZOOM IN

User ranking:

Erica ranking:



MY RANKING

ERICA'S RANKING

TRANSFER HERE
BEST EMBRYO

Well done!
The transferred embryo is euploid.

Back to main menu

67% of the players selected this embryo as first option

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Outcome Measures

1

Mean number of attempts to select a euploid embryo by the user alone

- Without ERICA's assistance

2

Proportion of euploid embryos selected at the first try alone

- Without ERICA's assistance

3

Rate of opinion change

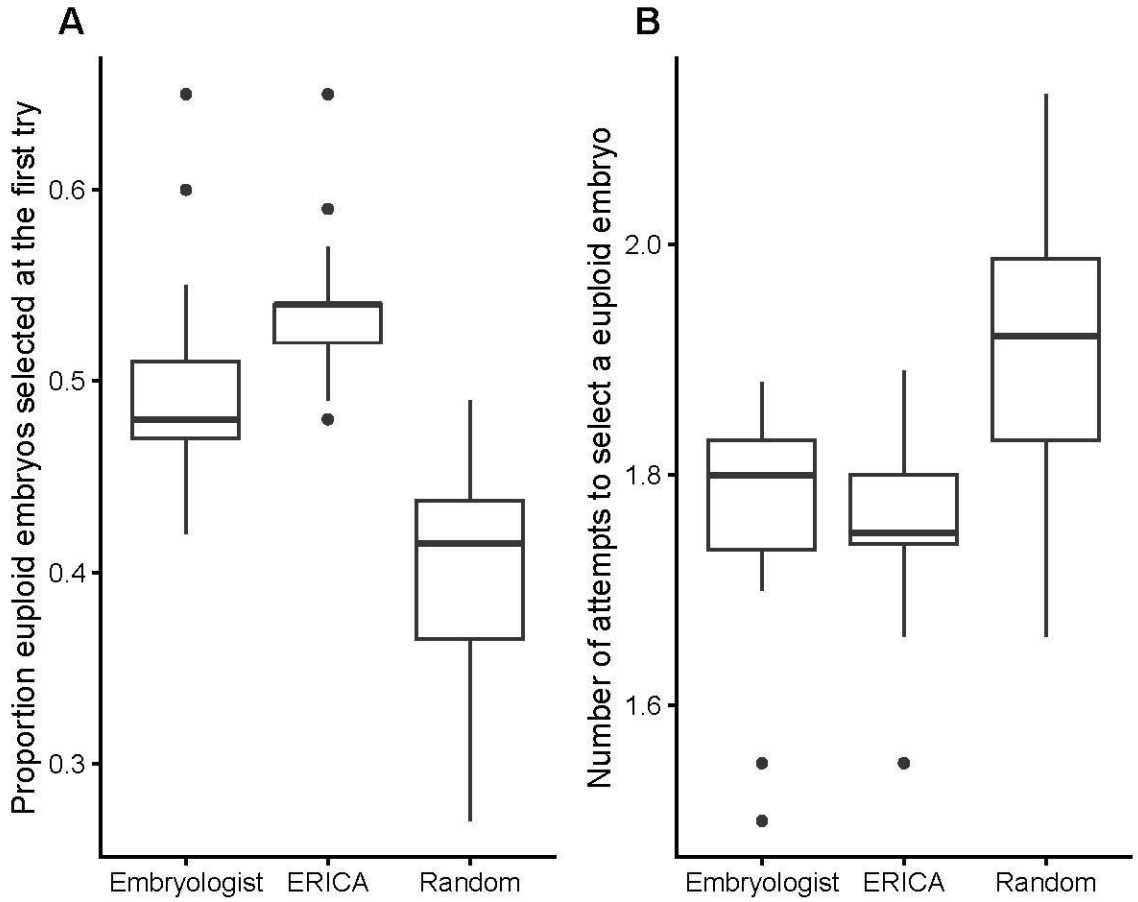
- Proportion of cycles where, following ERICA assessment, embryologist transferred embryo that they did not originally select on first choice
- For the better
- For the worse

Results

- 20 to 150 simulated IVF cycles
  - Assess performance in identifying euploid embryos

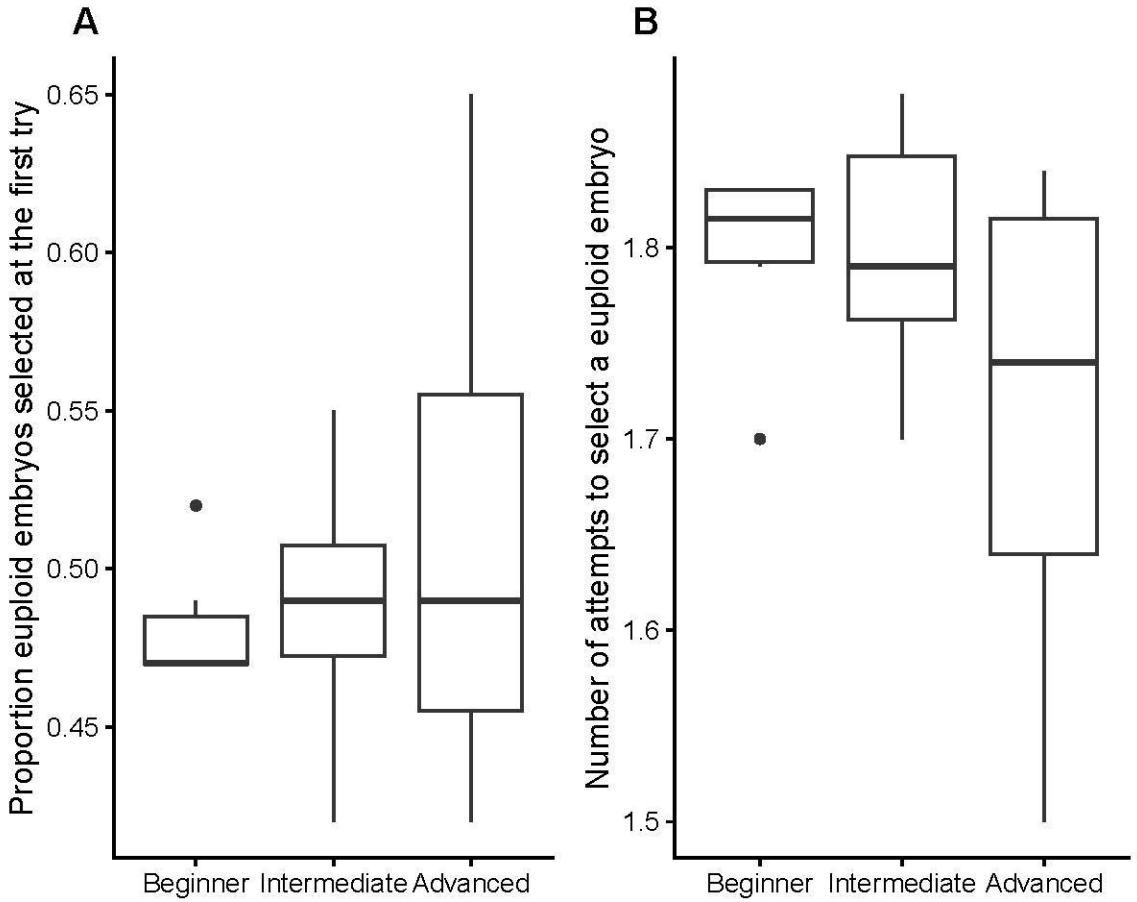
- Embryologists and ERICA identify aneuploidy significantly better than random
- ERICA chose a euploid embryo on the first attempt better than embryologists
- Embryologists' judgement augmented by ERICA not a superior approach compared to either alone

Embryologists and ERICA Perform Better than Random



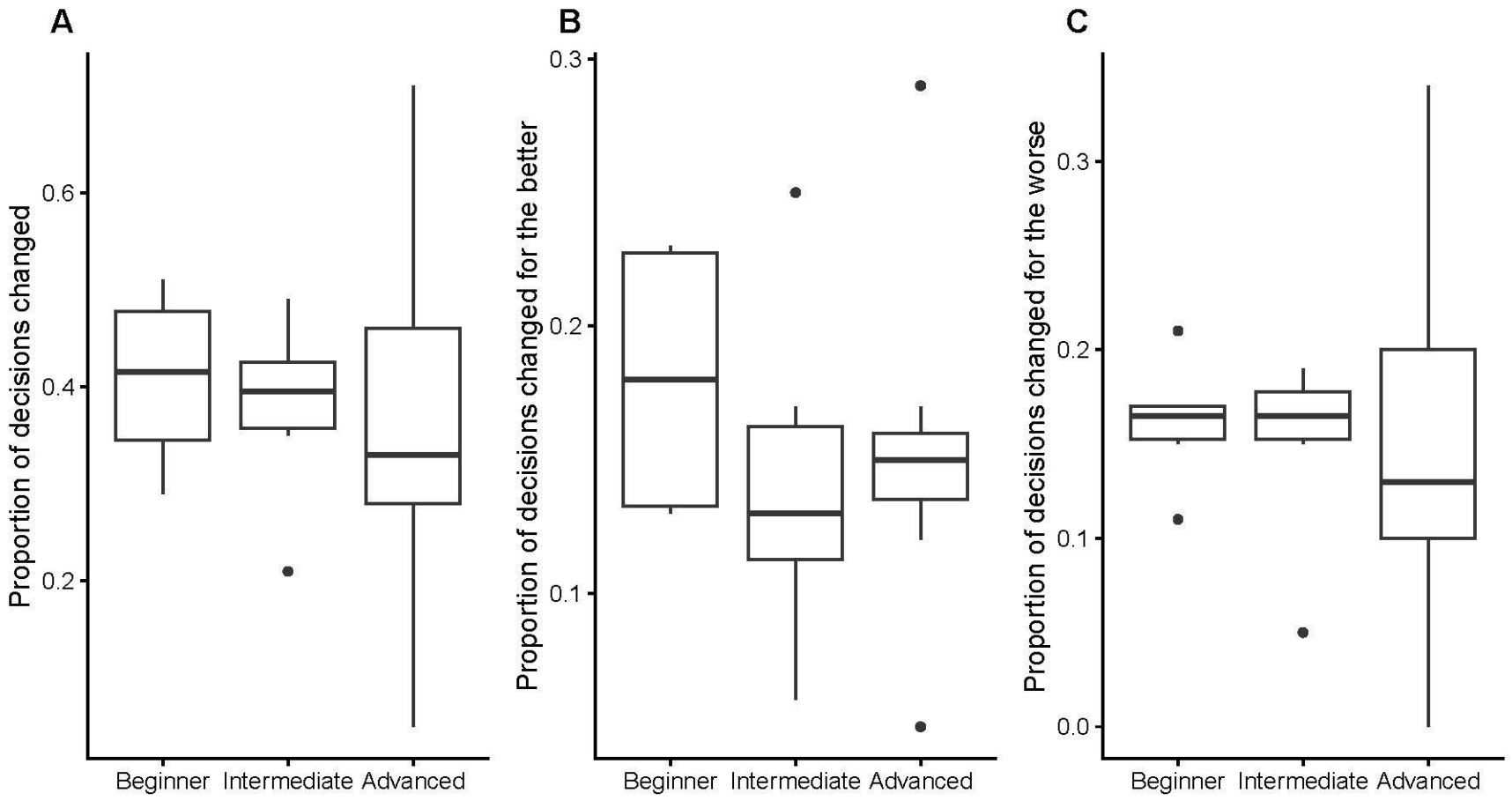
A) Proportion of euploid embryos selected at first try
B) Number of attempts to select a euploid embryo

Experienced Embryologists Performed Marginally Better than Less Experienced (NSS)



A) Proportion of euploid embryos selected at the first try
B) Number of attempts to select a euploid embryo

Change of Decision



Overall

For the better

For the worse

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Discussion

- Results have implications on how embryos are selected
- Impact that AI scoring has on decision-making
- Trust inferred by the automated process

Clinical Embryology is Relatively Unique

- Limited automation, relying heavily on
  - Manual dexterity
  - Teamwork
  - Subjective judgment

- Role of embryologist become more complex recently: Increased
  - Admin. duties
  - Cryopreservation
  - Embryo biopsies

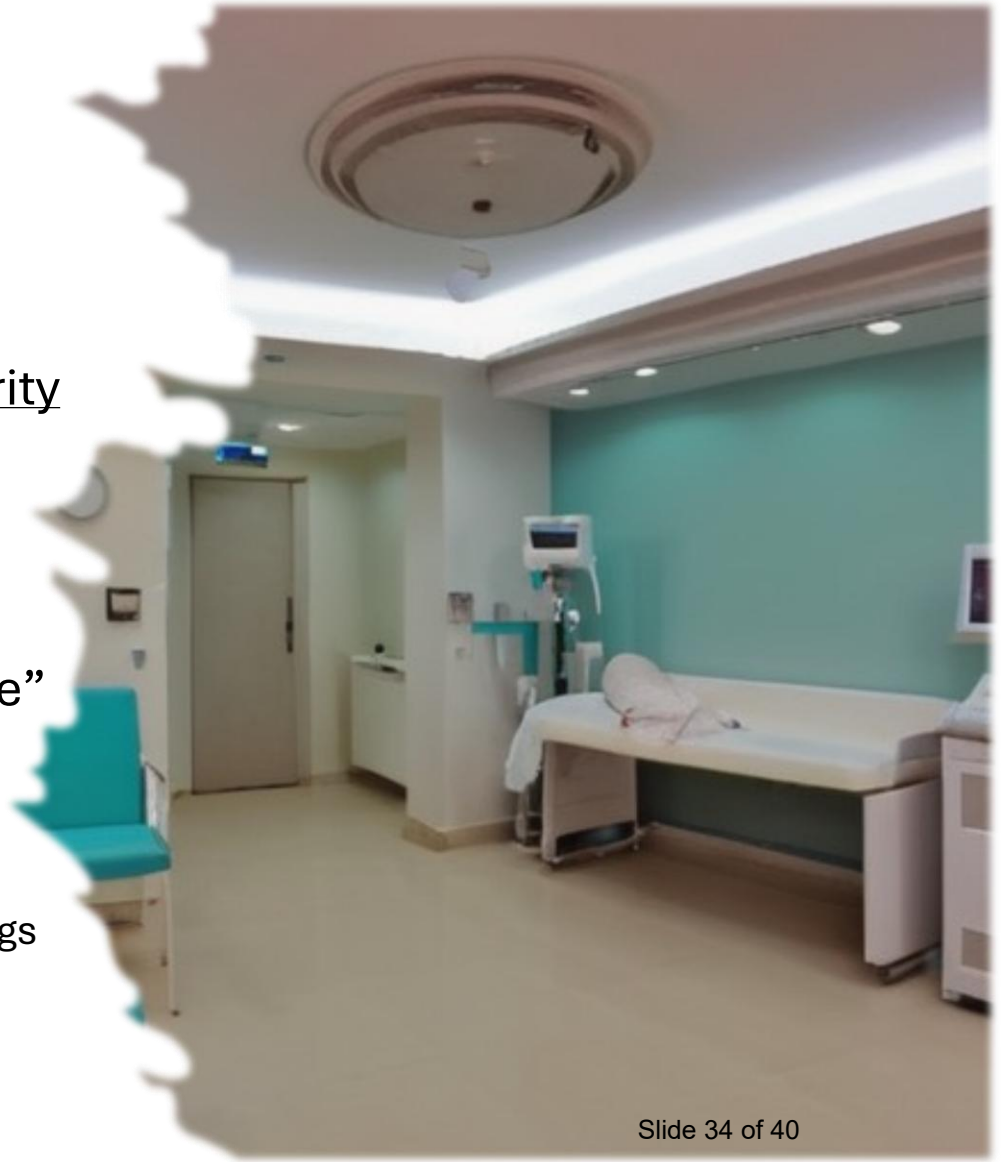
Confounding Factors

- Morphokinetic annotations themselves are initially assigned by humans
  - Thus are subjective
- Most studies performed on retrospective data under experimental settings
- Clinical application of AI still requires prospective investigations
  - Secondary factors -laboratory conditions or other human factors not analyzed
  - Nor included in the models
- Culture conditions and human expertise
  - Important factors that influence embryo development and quality
  - Need to be incorporated into models to achieve a useful and objective prediction
- Predicting implantation solely on embryo quality is an incomplete assessment
  - AI embryo prediction models should focus on ranking embryos within the patient cohort rather than on implantation prediction
  - Inter-centre success rates variation impedes establishment of universal AI models

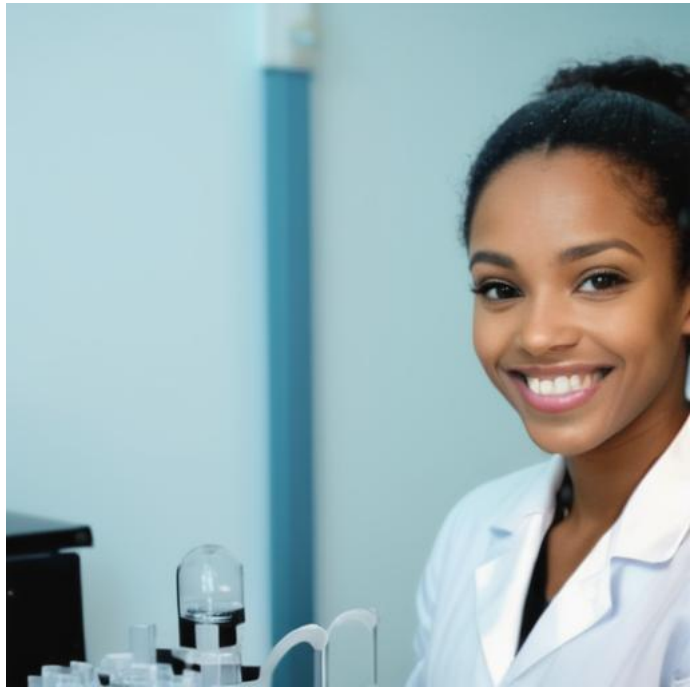
Integration into Clinic

- Lack of RCTS may slow adoption as clinics weigh cost-benefit concerns
- AI's value may lie in efficiency rather than clinical superiority
  - Could drive its integration

- How might AI predictions influence decision-making?
- This research sets out how to quantify this with "game-like" scenario
  - Deduces how AI influences for embryo selection choice
  - Acts as a training exercise
    - Familiarizing operator with the software used in clinical settings
    - Educating embryologists to the dilemma of choice



Will Embryologists Like it?



- Palmer et al., 2024 (international survey)
  - 93.7% of embryologists well-informed about AI in the workplace
  - Recognize its limitations
  - Open to its adoption
- Tools that support decision-making could
  - Provide valuable assistance in daily tasks
  - Most embryologists view the use of AI in the laboratory as inevitable.
  - Express a willingness to incorporate AI in the selection of gametes and embryos
- 59.8% believe AI should be integrated into routine lab procedures
- 73.3% are open to adopting AI technologies in near future
- But only 5.4% of respondents extremely confident in using AI in their roles
  - need for more training and experience

- **Gamification may be a way to increase uptake through familiarity and trust of AI tools**

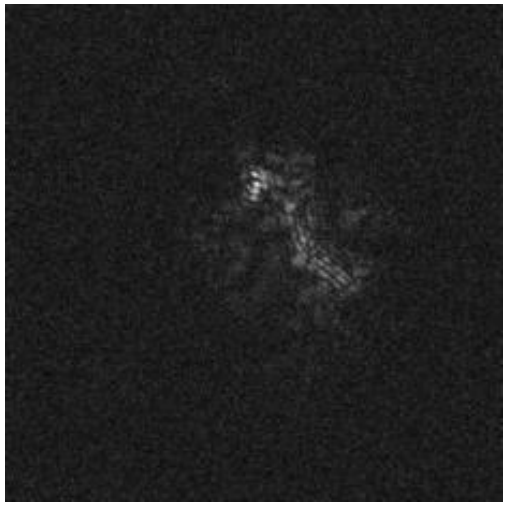
Trust!

- Key factor if AI is to gain widespread adoption in IVF
- Aligns with efforts to "democratize IVF"
- Technology can significantly enhance accessibility and efficiency

- **Lack of trust in AI output balanced with the embryologists' experience introduces challenges and barriers to adoption and implementation**

- Strategies outlined here
  - Enables us manage uncertainty
  - Shaped by human factors
    - User education
    - Biases and perceptions
    - The system's characteristics e.g. ease of use and transparency.
  - Reliability is the key
    - AI's ability to perform tasks predictably and consistently

Other Factors



- Embryo freezing dates
- Maternal age
- Provide valuable insights that could enhance decision-making
  - Especially across multiple cycles
- Future AI models may improve predictions and better reflect clinical complexity
- This study assumes a level playing field between embryologists and AI
  - Embryologists are accustomed to specific imaging formats and contrast lighting techniques
  - May influence ability to assess unfamiliar images
  - Despite efforts to standardize images, differences in formats remaare a confounding factor
- Real-world embryo selection often involves limited choices
  - Reducing decision-making complexity and potentially favouring AI
  - Future model iterations could integrate simpler scenarios to better reflect clinical reality

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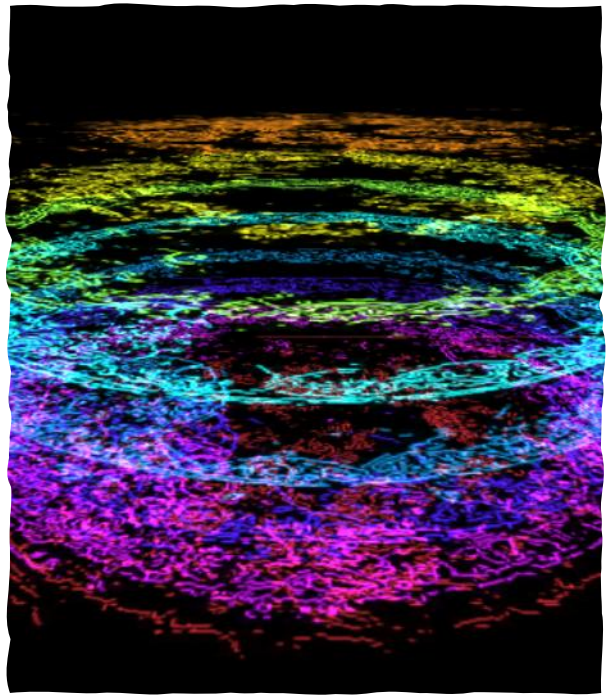

- AI simulation training could play valuable role in embryology
  - Similar to use in other fields like surgery
- Recreating real-life scenarios that can be endlessly repeated and refined can enhance skill development without replacing human expertise
  - Provide a controlled environment for operators to practice and improve their techniques
  - Humans, like AI, will improve performance with greater exposure to more data
  - Essential for achieving optimal performance
  - Emphasis on the need for AI to function as a co-pilot alongside human expertise
- We present a means by which this may be achieved
- Combining ERICA & human intervention has potential to be effective & popular
  - Engendering trust and addressing issues such as fatigue and ethical challenges
- Could cut down on overthinking
- Could encourage strategies for self-reflection

IVF 2.0

Acknowledgments

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International IVF Initiative, New York, New York, USA

IVF2.0 Ltd, London, UK

Institute of Life, IASO Hospital Athens, Greece

Conceivable Life Sciences, New York, New York, USA

Faculty of Engineering and Science, University of Greenwich, UK.

Biodigital Innovation Lab, Translational Bioengineering Department, CUCEI, Universidad de Guadalajara, Mexico

School of Natural Sciences, University of Kent, Canterbury, Kent, CT2 7NJ, UK

Animal Genomics and Bioresource Research Unit (AGB Research Unit), Faculty of Science, Kasetsart University, Chatuchak, Bangkok 10900, Thailand