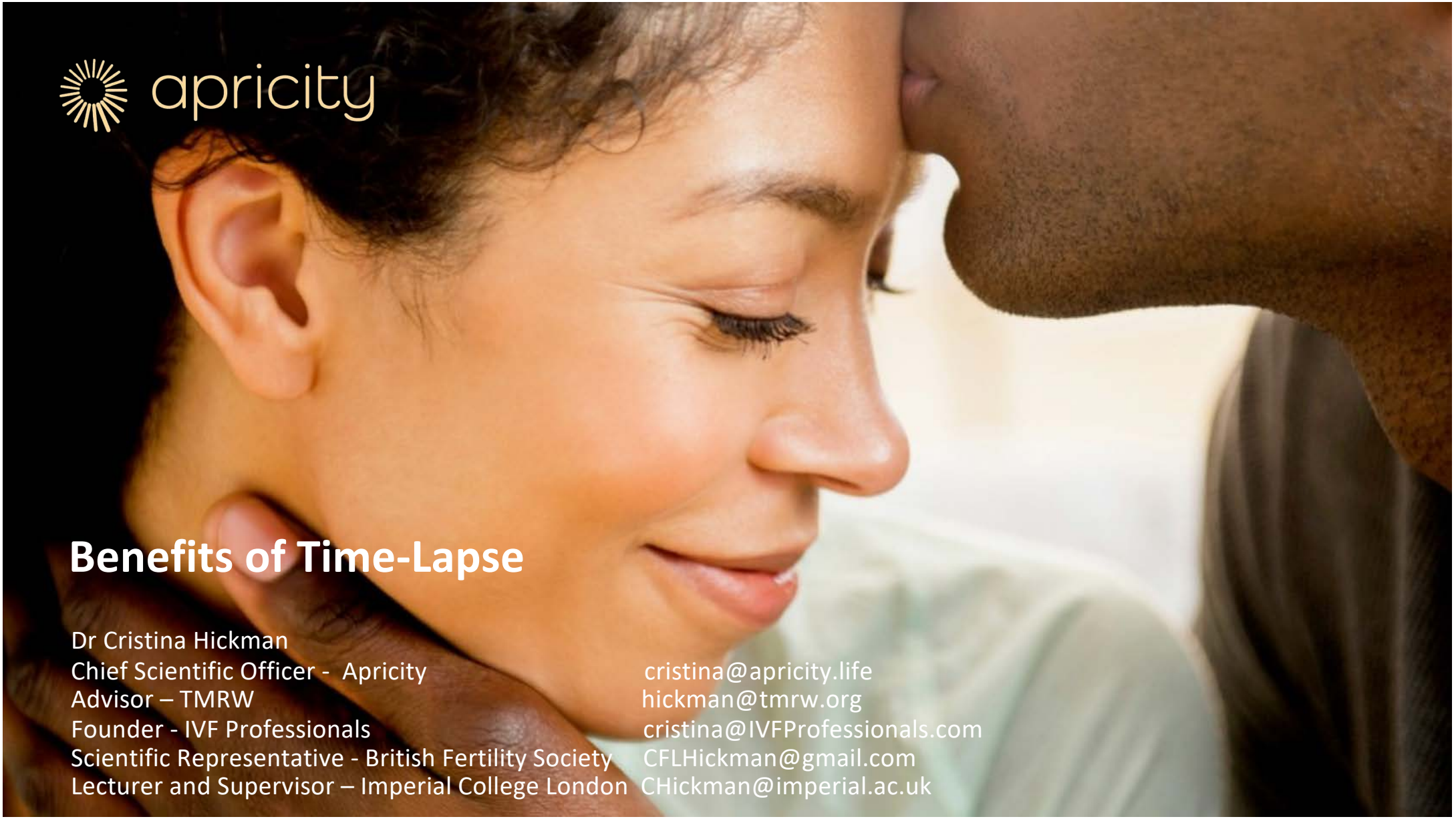


Benefits of Time-Lapse

Dr Cristina Hickman
Chief Scientific Officer - Apricity — cristina@apricity.life
Advisor – TMRW — hickman@tmrw.org
Founder - IVF Professionals — cristina@IVFProfessionals.com
Scientific Representative - British Fertility Society — CFLHickman@gmail.com
Lecturer and Supervisor – Imperial College London — CHickman@imperial.ac.uk

The evolution of Time-Lapse at Boston Place

First Clinic London
100% Time-Lapse

2013

First Clinic Worldwide designed around Time-Lapse

First Clinic UK
100% EmbryoScope

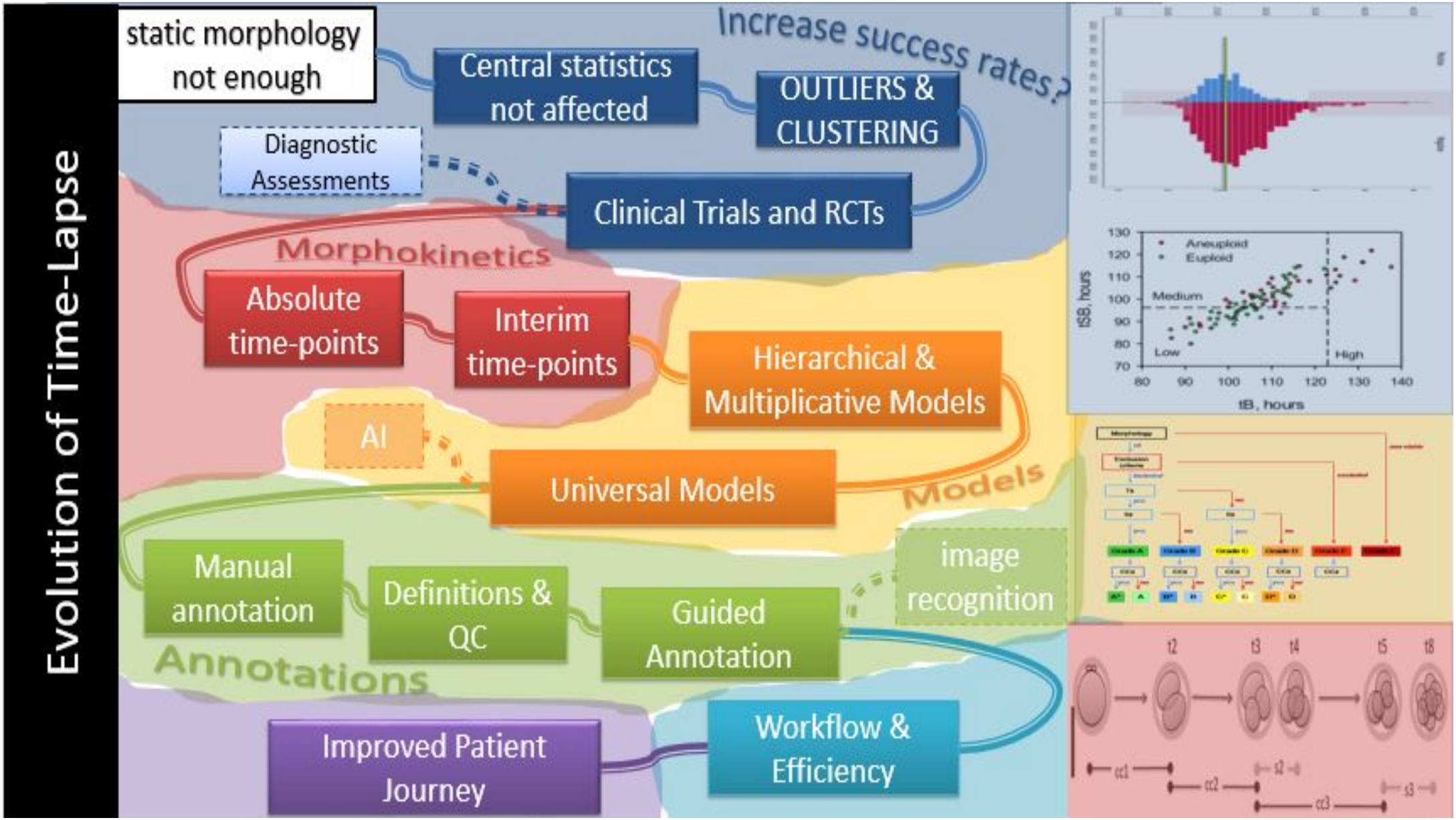
2014

First GERI Pregnancy UK

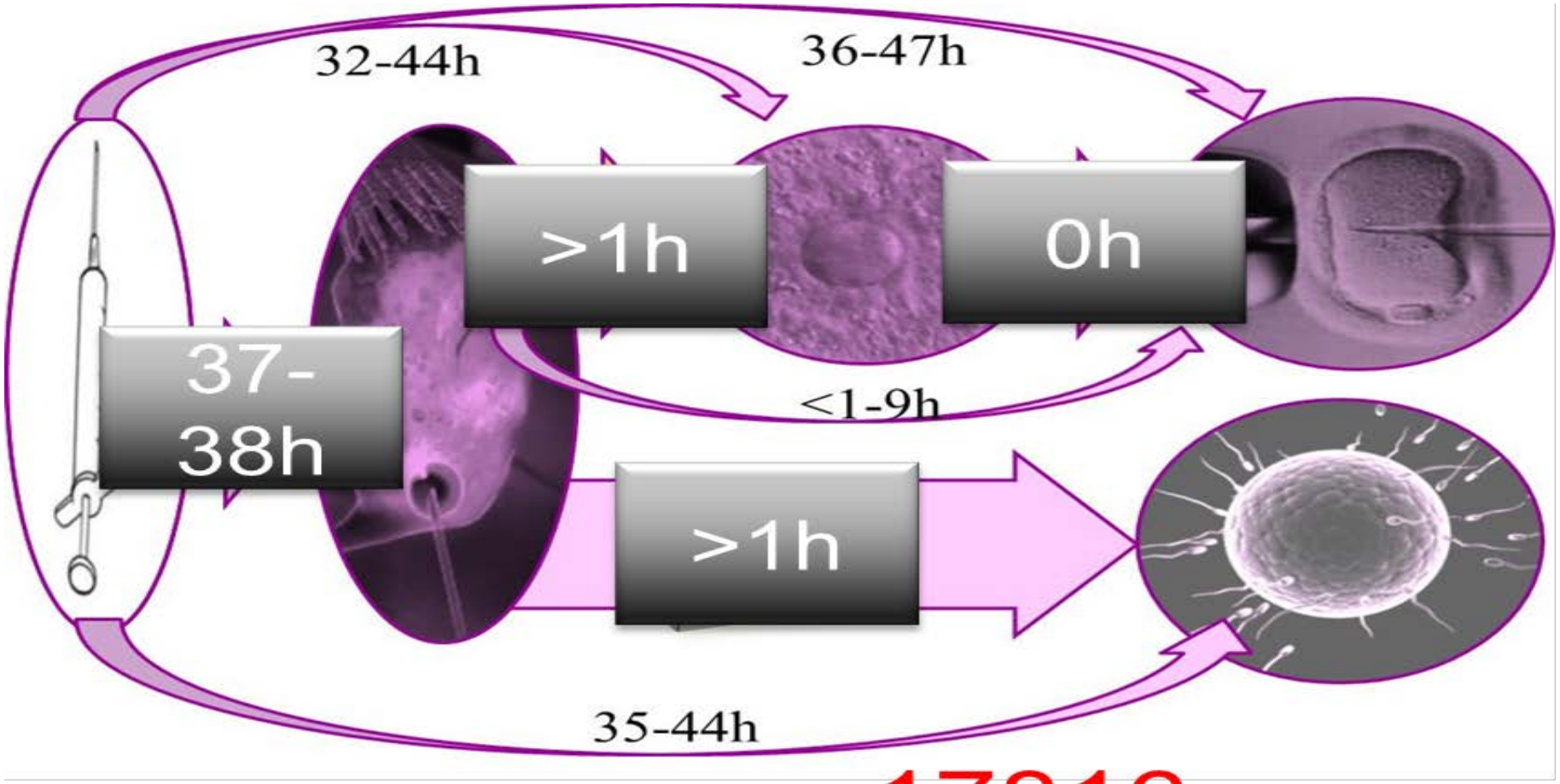
2016

First World EmbryoScope+ (post validation)

October 2016


Evolution of Time-Lapse
static morphology not enough
Central statistics not affected
Increase success rates?
OUTLIERS & CLUSTERING
Diagnostic Assessments
Clinical Trials and RCTs
Morphokinetics
Absolute time-points
Interim time-points
Hierarchical & Multiplicative Models
AI
Universal Models
Models
Manual annotation
Definitions & QC
Guided Annotation
image recognition
Annotations
Improved Patient Journey
Workflow & Efficiency
Aneuploid
Euploid
Medium
Low
High
tSB, hours
tB, hours

Efficient workflow

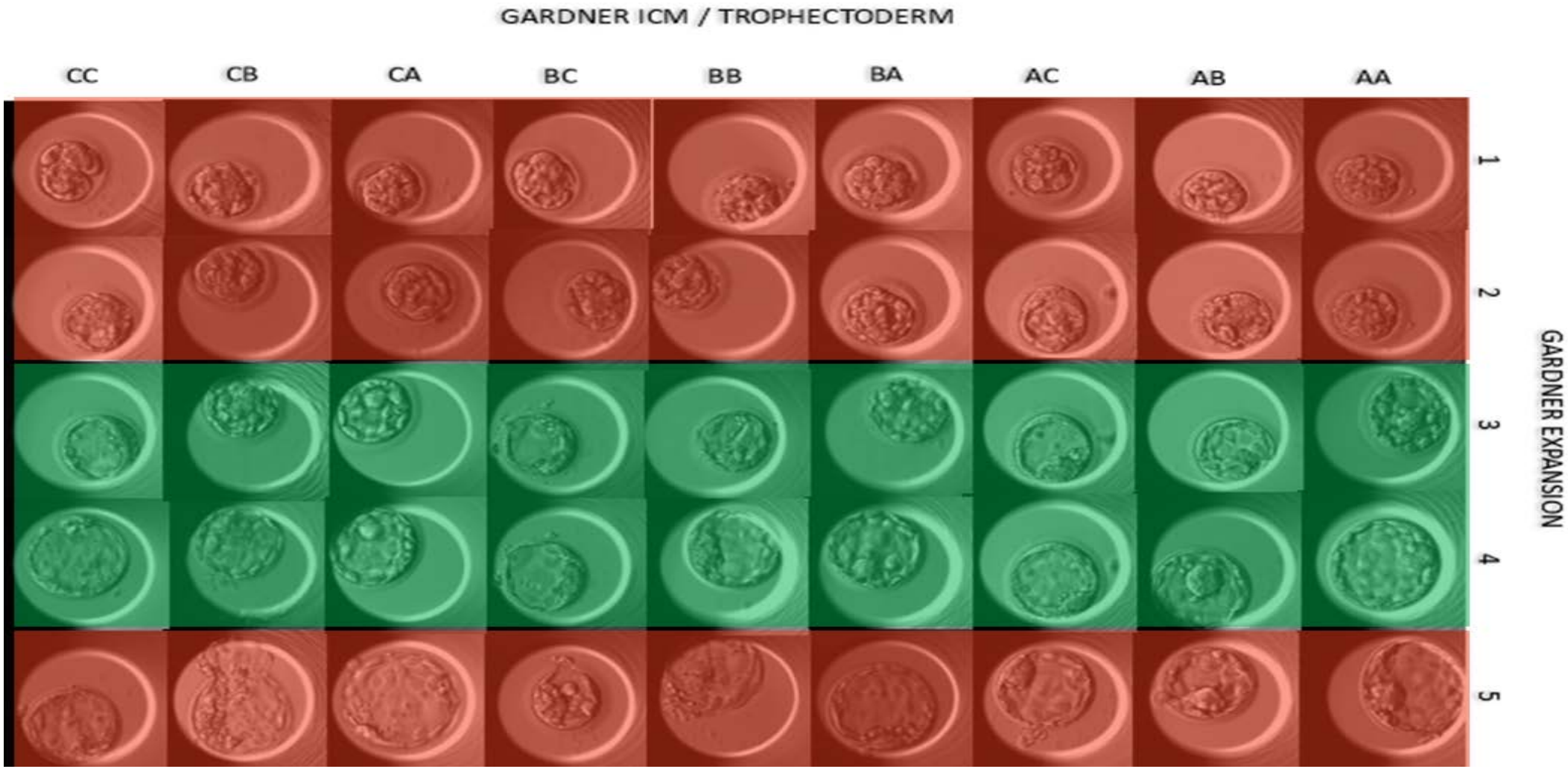


- Retrospective n=17816 fresh cycles
- 4 IVF clinics from 2006 to 2010

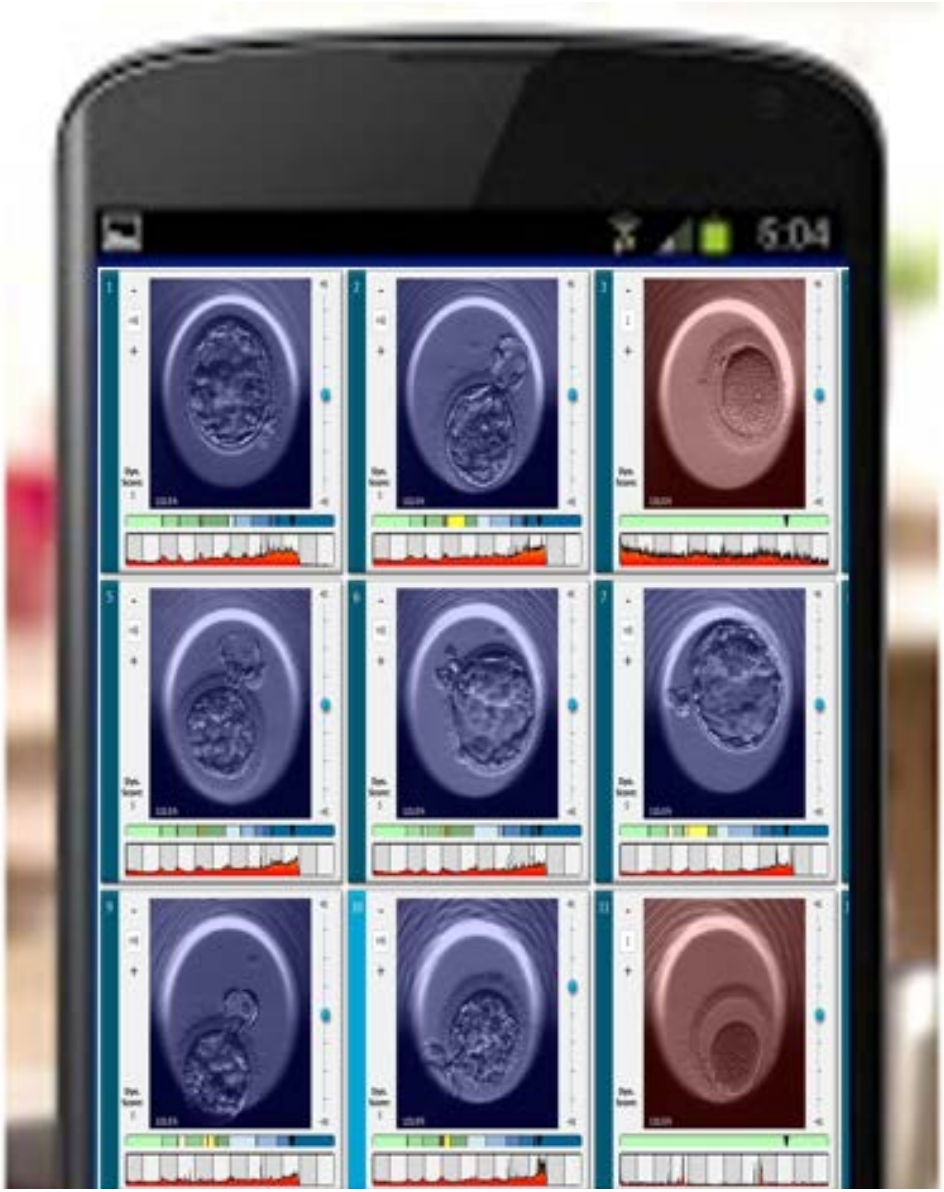
Procedures occur at the best time for the embryo

Day 0	Time flexibility to perform stripping, IVF, ICSI	
Day 1	Time flexibility to perform Day 1 checks	
Day 2-4	Time flexibility of when to check embryos	
	Time flexibility of when to call patients	
Day 5-7	Early ICSI → More Day 5 Blastocysts	
	Time flexibility of when to biopsy	
	Time flexibility of when to freeze	

Time-Lapse as a tool to improve PGS/Vitrification Workflow

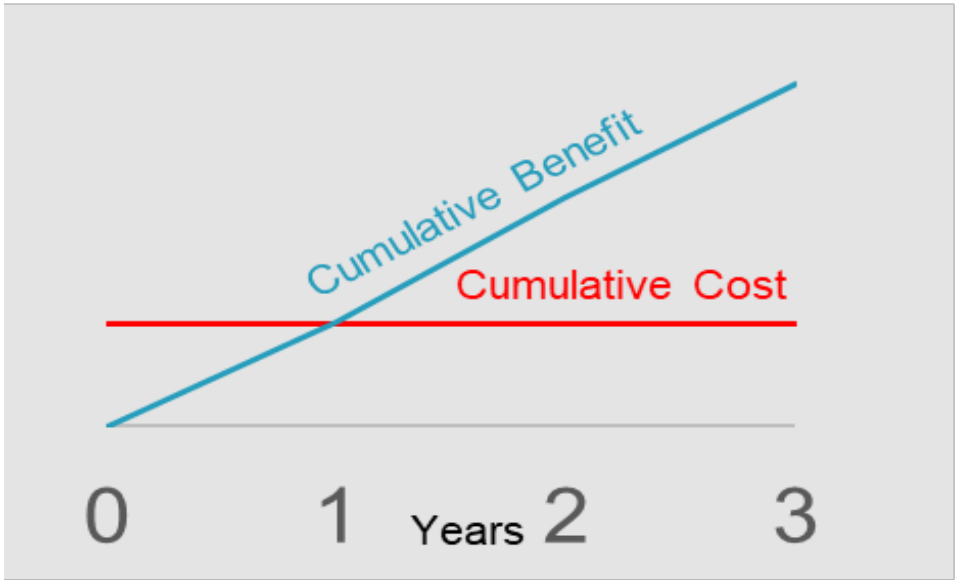


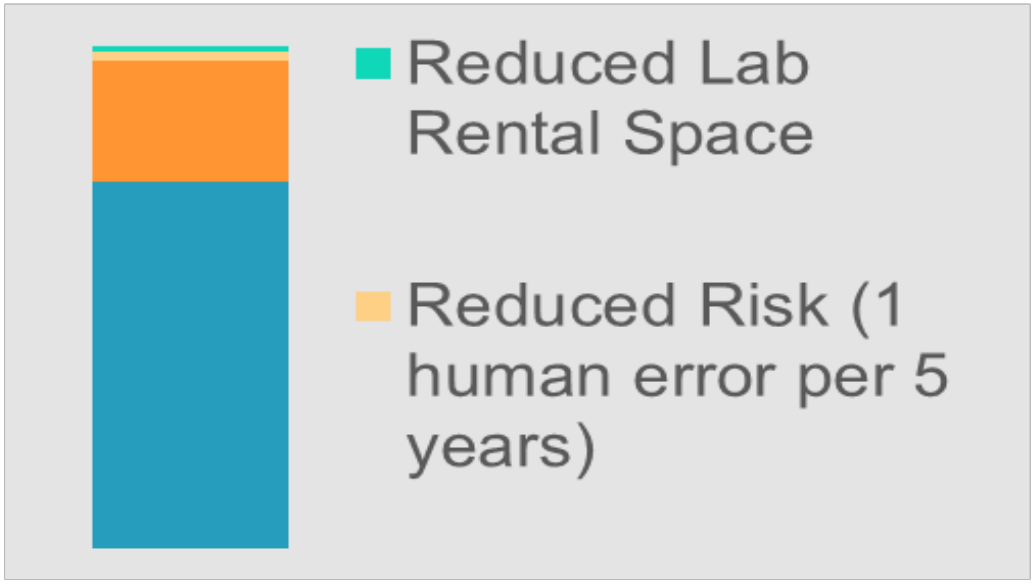
Remote Access



How much does it cost you not to be 100% time-lapse?

New clinic in London would save money within 1 year



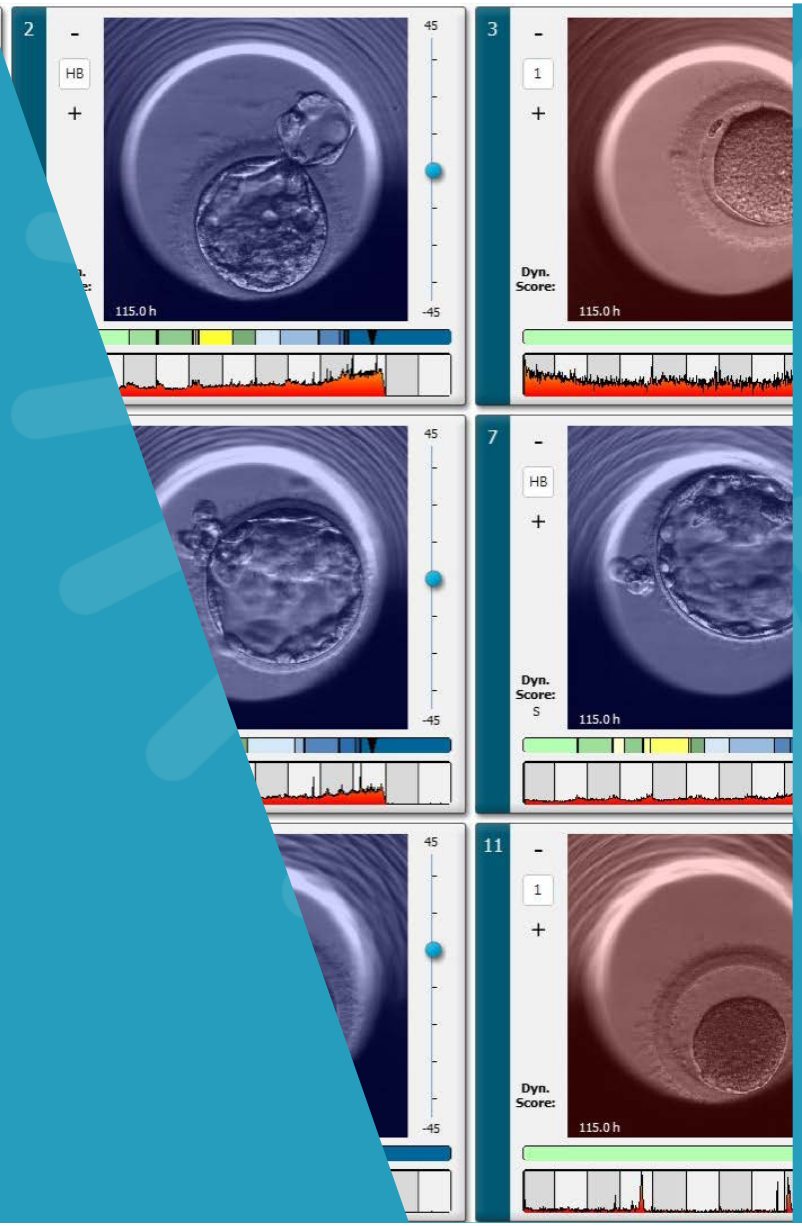


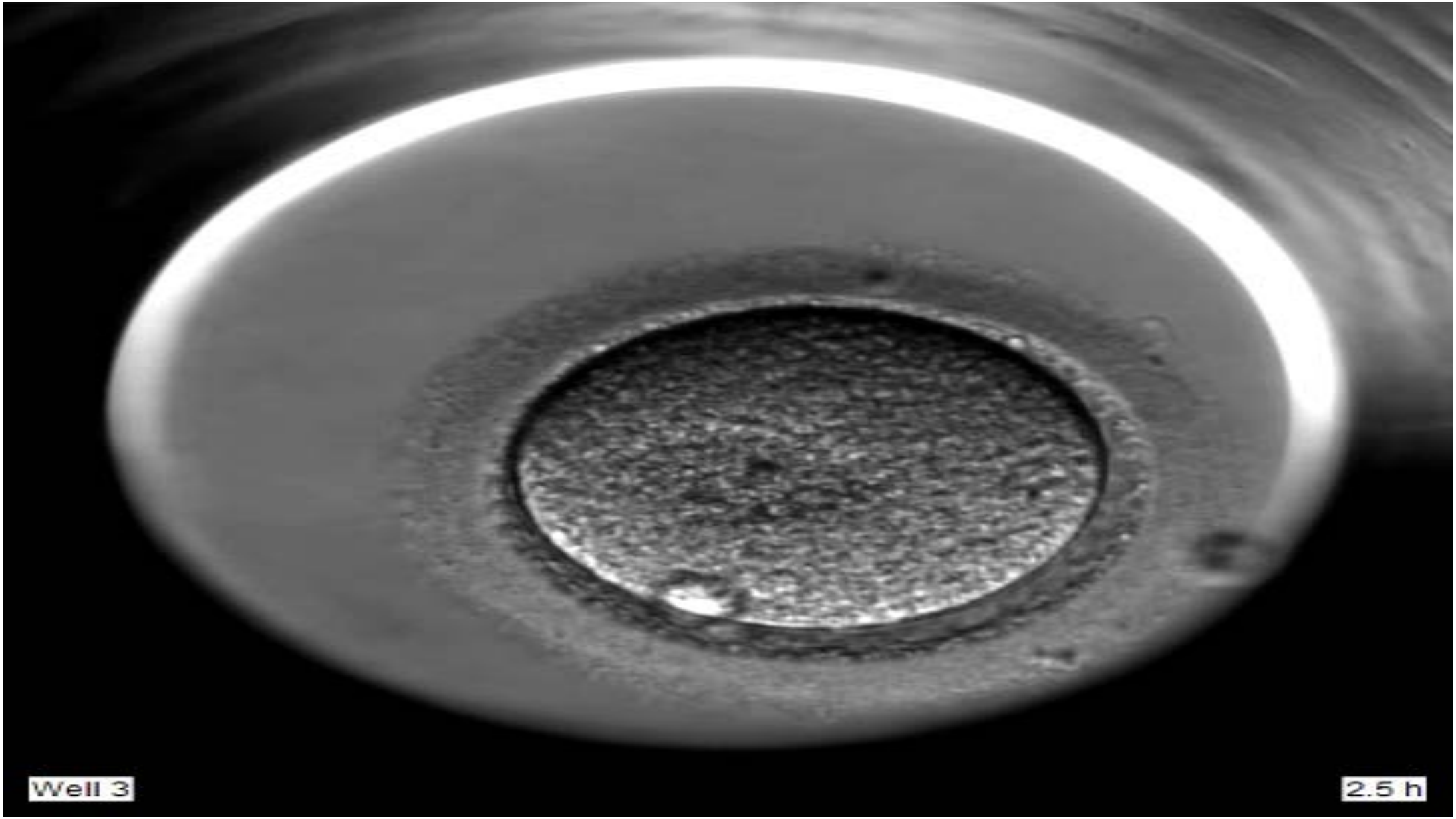
Not included: *savings in consumables, increased patient referrals, 6% patients not requiring FERCS, other intangible benefits (i.e. reduced recruitment costs, staff morale, increased patient satisfaction)*

Depends on:

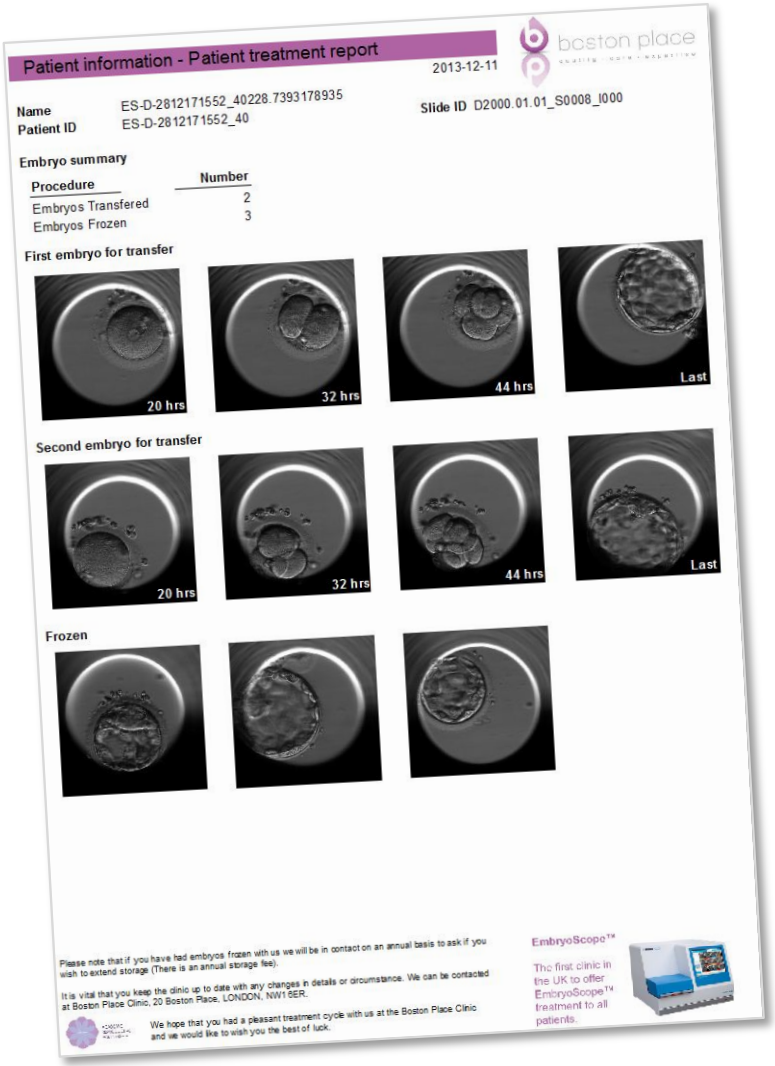
Country? Tax? Staff costs? Expertise availability? How many cycles? Current practice and current performance?

Enhanced Patient Journey




Well 3
2.5 h

Involve your patients



Patient information - Patient treatment report

2013-12-11

boston place
quality · care · expertise

Name ES-D-2812171552_40228.7393178935
Patient ID ES-D-2812171552_40

Slide ID D2000.01.01_S0008_I000

Embryo summary

Procedure	Number
Embryos Transfered	2
Embryos Frozen	3

First embryo for transfer

20 hrs | 32 hrs | 44 hrs | Last

Second embryo for transfer

20 hrs | 32 hrs | 44 hrs | Last

Frozen

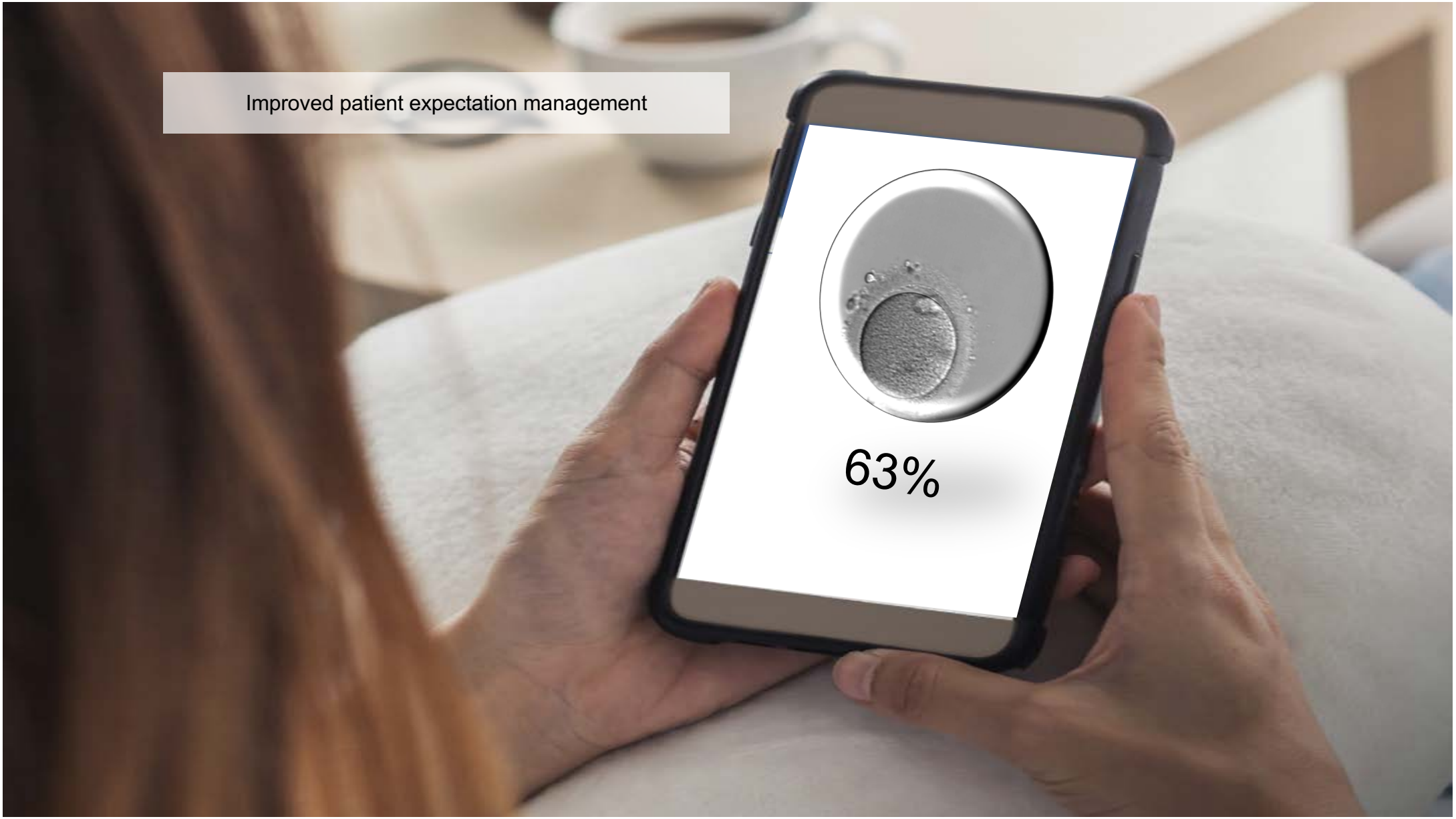
Please note that if you have had embryos frozen with us we will be in contact on an annual basis to ask if you wish to extend storage (There is an annual storage fee).

It is vital that you keep the clinic up to date with any changes in details or circumstance. We can be contacted at Boston Place Clinic, 20 Boston Place, LONDON, NW1 6ER.

We hope that you had a pleasant treatment cycle with us at the Boston Place Clinic and we would like to wish you the best of luck.

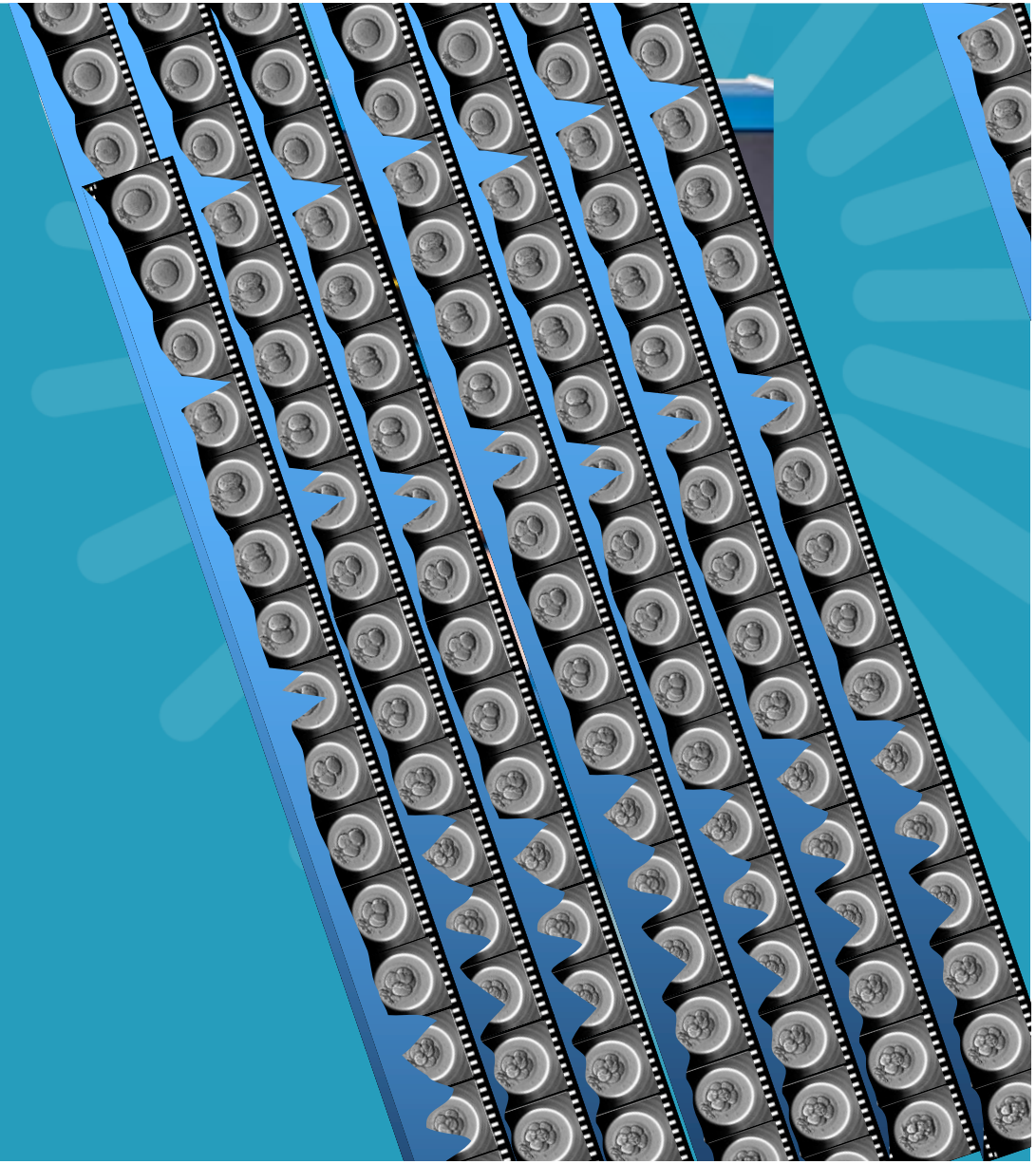
EmbryoScope™

The first clinic in the UK to offer EmbryoScope™ treatment to all patients.


Improved patient expectation management
63%

Improved patient expectation management
<1%

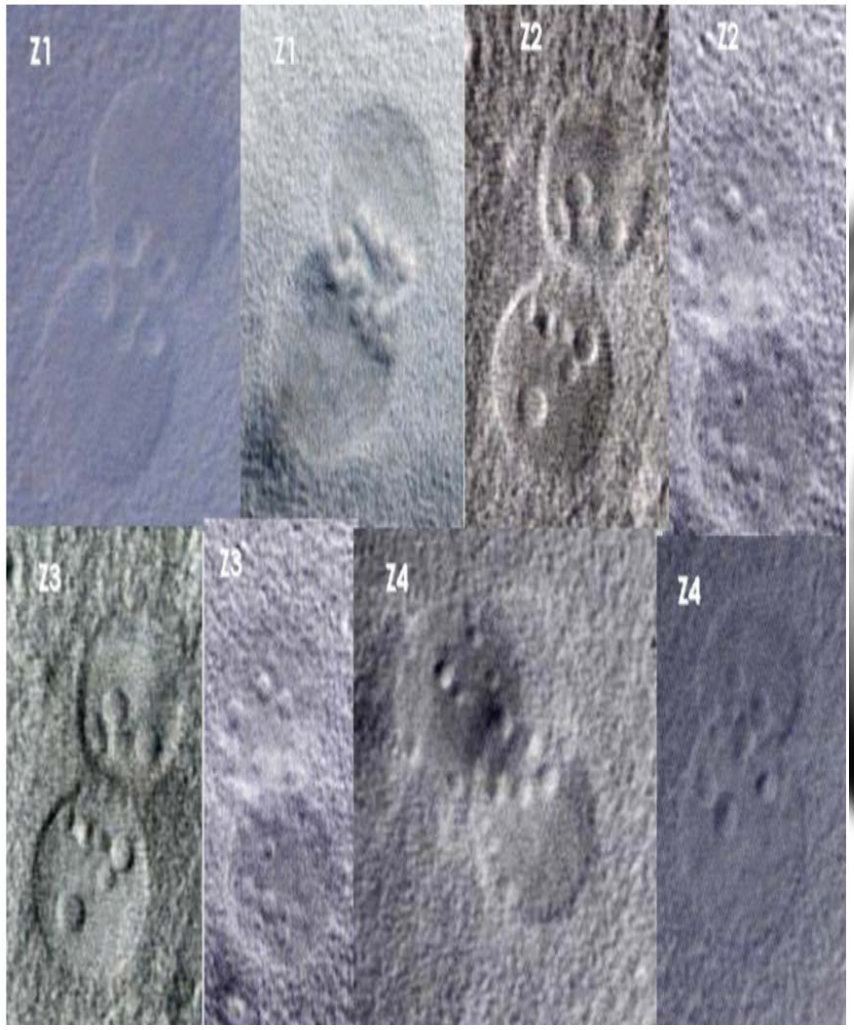
Increased precision in monitoring embryo progression

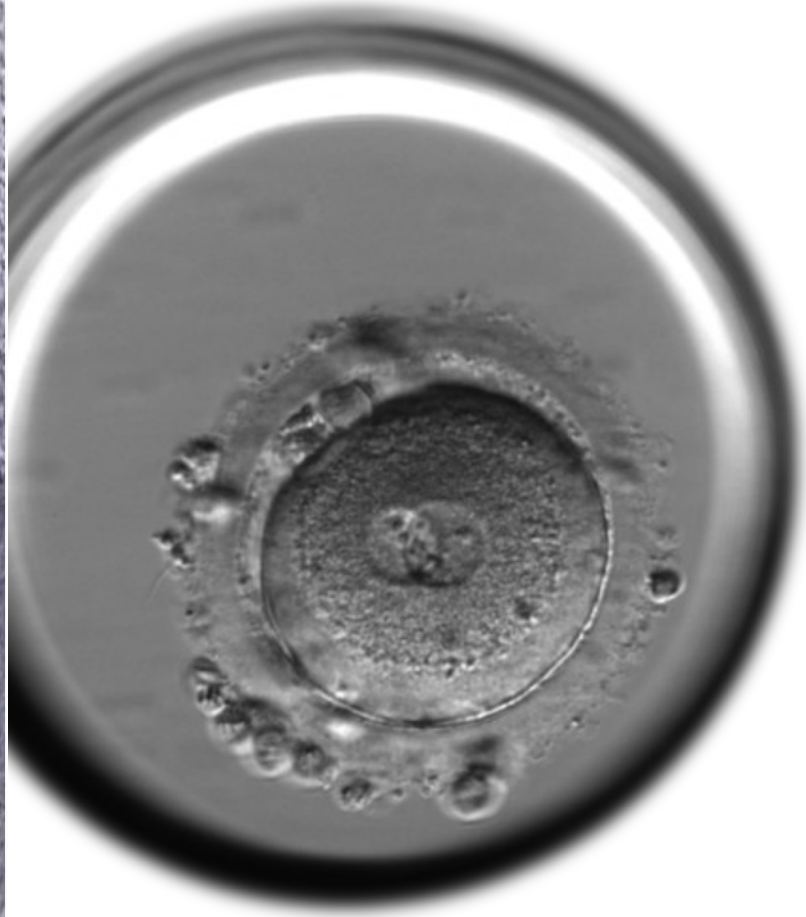


Morphology

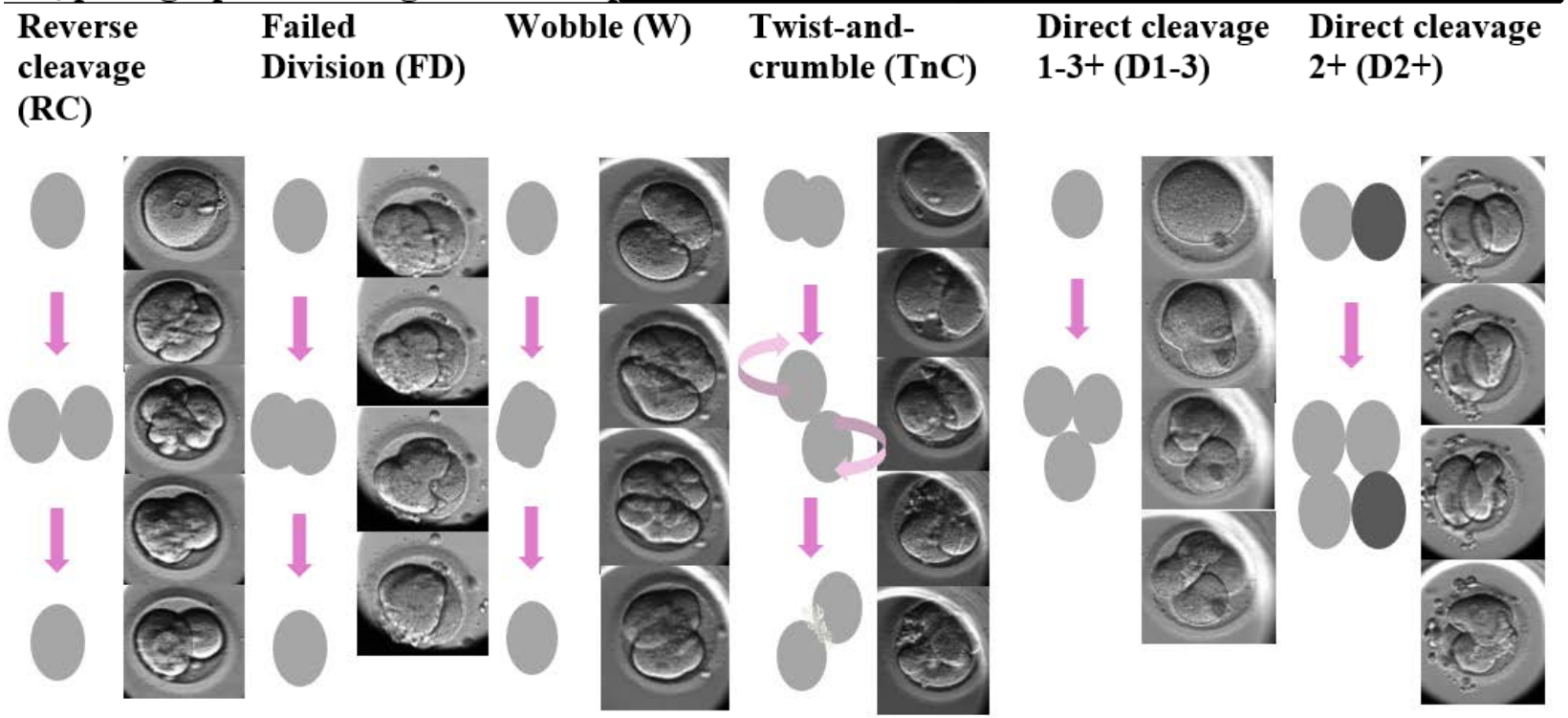
DAY 1

Time-Lapse





Cleavage Patterns

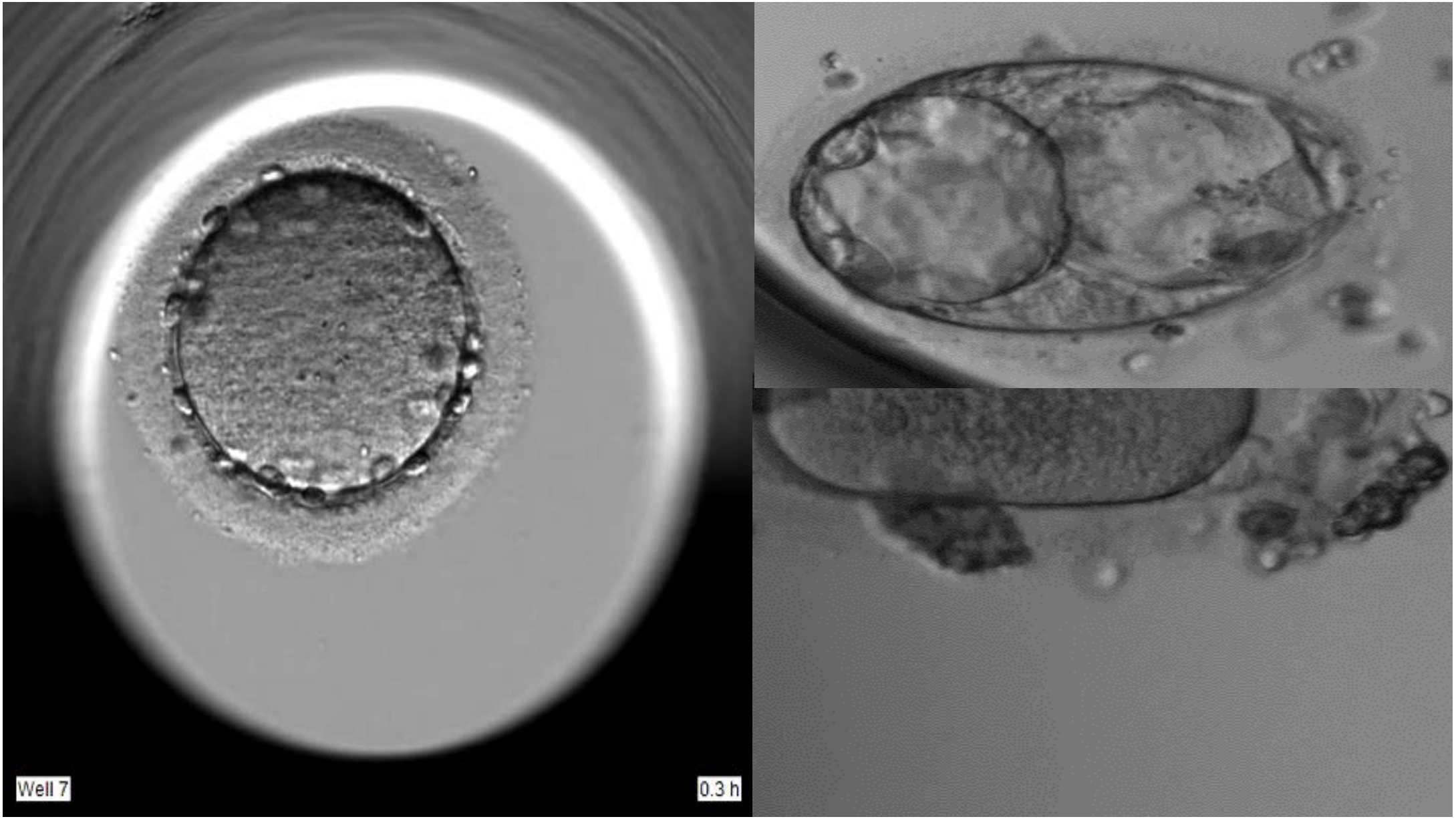


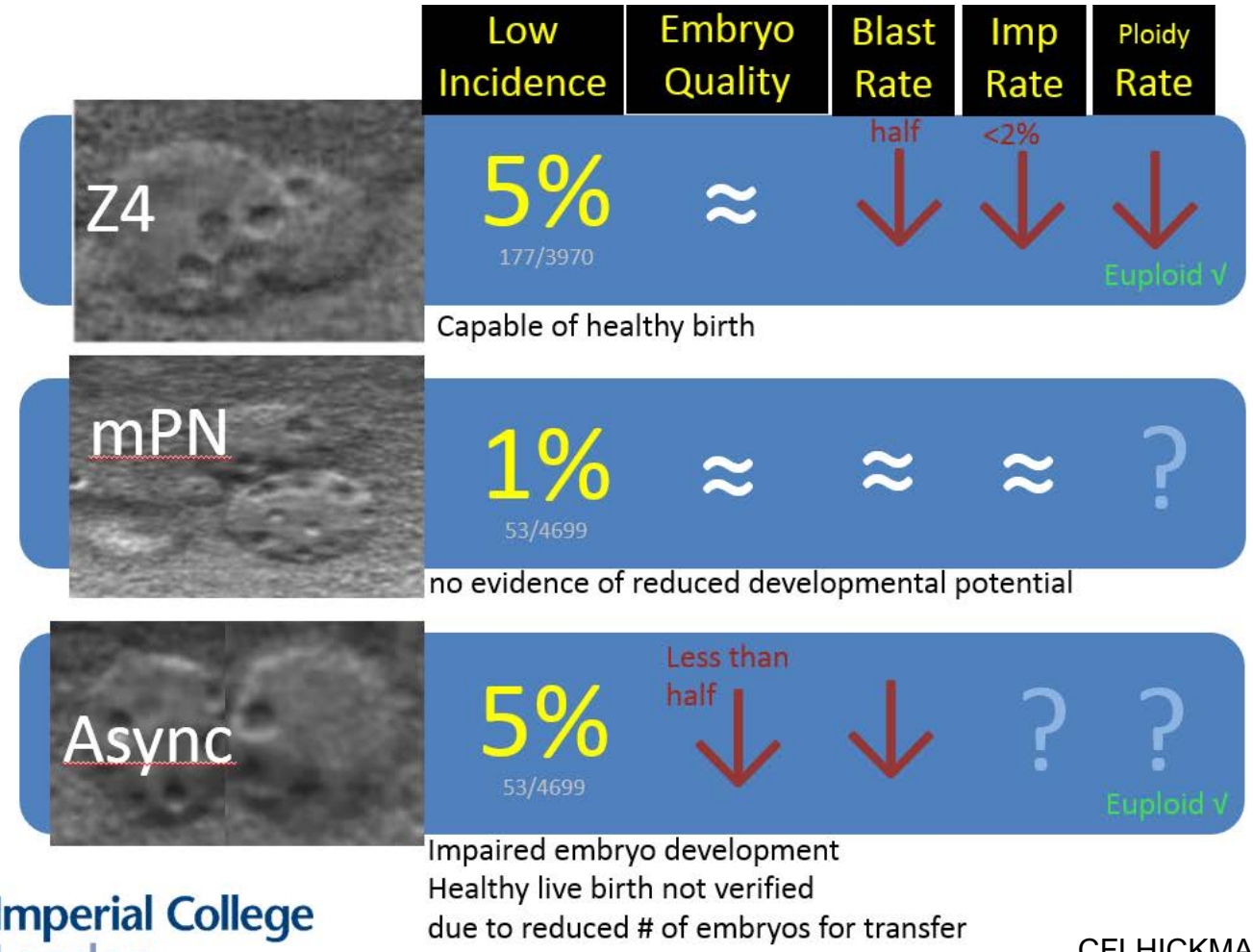
Extruded Material

Multi nucleation

Perivitelline threads

Other morphological features

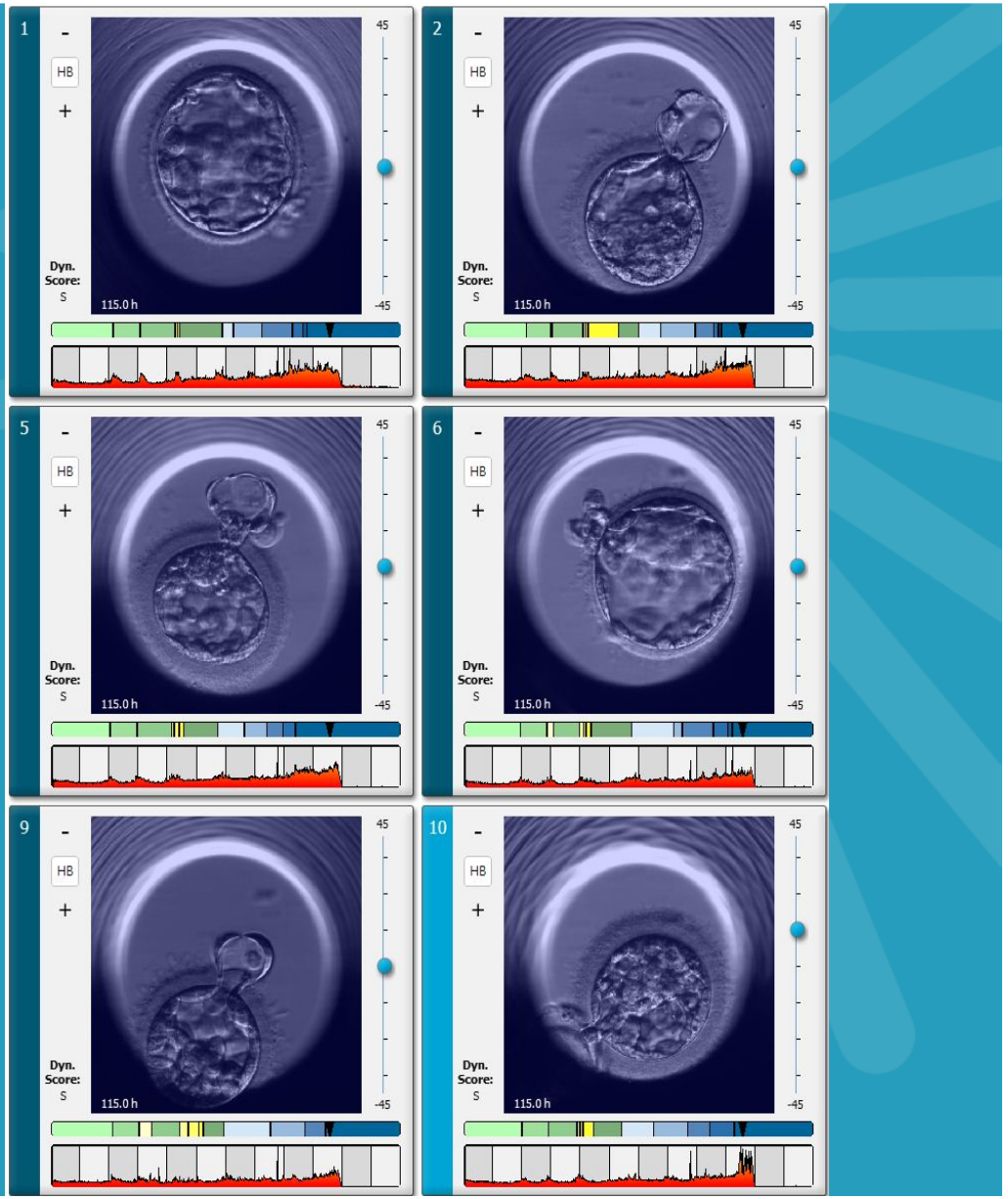

Well 7
0.3 h



Imperial College London

CFLHICKMAN@GMAIL.COM

Increased efficacy in embryo selection



ORIGINAL ARTICLES: ASSISTED REPRODUCTION

Clinical validation of embryo culture and selection by morphokinetic analysis: a randomized, controlled trial of the EmbryoScope

Irene Rubio, Ph.D.,[a] Arancha Galán, Ph.D.,[a] Zaloa Larreategui, Ph.D.,[b] Fernando Ayerdi, Ph.D.,[b] Jose Bellver, M.D.,[a] Javier Herrero, Ph.D.,[a] and Marcos Meseguer, Ph.D.[a]

[a] Instituto Universitario IVI Valencia, University of Valencia, Valencia; and [b] IVI Bilbao, Bilbao, Spain

Outcome results per intention to treat, per cycle, per transfers and per embryo transferred.

Outcome	TMS group	Control group	RR	*P* value
All cycles with oocyte retrieval	438	405		
Pregnancy (% of all treated cycles)	61.6 (56.9–66.0)	56.3 (51.4–61.0)	1.09 (0.98–1.23)	.12
Ongoing pregnancy (% of all treated cycles)	51.4 (46.7–56.0)	41.7 (37.0–46.6)	1.23 (1.06–1.43)	.005
All transfers	415	373		
Pregnancy (% of all transfers)	65.3 (60.6–69.7)	61.1 (56.1–65.9)	1.07 (0.95–1.19)	.22
Ongoing pregnancy (% of all transfers)	54.5 (49.6–59.2)	45.3 (40.3–50.4)	1.20 (1.04–1.39)	.01
All pregnant cycles	271	228		
Early pregnancy loss (% of all pregnancies)	16.6 (12.6–21.4)	25.8 (20.6–31.9)	0.64 (0.45–0.91)	.01
All transferred embryos	775	699		
Implantation rate (% of all transferred embryos)	44.9 (41.4–48.4)	37.1 (33.6–40.7)	1.43 (1.05–1.39)	.02

Note: Results shown as proportion with 95% confidence limits in brackets, relative risk (RR) with 95% confidence limits in brackets and the corresponding *P* value (Fisher's exact test). Total number of cycles are also presented in brackets.

Rubio. Clinical validation of EmbryoScope. Fertil Steril 2014.

+9.2% p=0.01

Does the addition of time-lapse morphokinetics in the selection of embryos for transfer improve pregnancy rates? A randomized controlled trial

Linnea R. Goodman, M.D., Jeffrey Goldberg, M.D., Tommaso Falcone, M.D., Cynthia Austin, M.D., and Nina Desai, Ph.D., H.C.L.D.

Department of Reproductive Endocrinology and Infertility, Cleveland Clinic, Beachwood, Ohio

Outcome results in cycles with selection, stratified by day of transfer and age.

Clinical outcome	TLM	CS	*P* value
All transfers (day 3 and 5)	n = 119	n = 116	
CPR	81/119 (68.1%)	73/116 (62.9%)	.41
IR	122/239 (51.0%)	108/221 (48.2%)	.21
All transfers, <40 y old	n = 110	n = 110	
CPR	79/110 (71.8%)	72/110 (65.5%)	.10
IR	119/211 (56.4%)	99/205 (48.3%)	.31
Blastocyst transfers	n = 91	n = 89	
CPR	67/91 (73.6%)	61/91 (67.0%)	.33
IR	96/173 (55.5%)	83/162 (51.2%)	.44
Pregnancy outcomes	n = 81	n = 73	.23
Viable singleton pregnancy	48 (59.3%)	48 (65.8%)	
Viable twin pregnancy	29 (35.8%)	21 (28.8%)	
Viable triplet pregnancy	2 (2.5%)	1 (1.4%)	

through viewing of time-lapse video footage. In the TLM group, patients with the plan for blastocyst transfer had their top-quality embryos determined by morphology and then the morphokinetic score was used to preferentially rank the best embryos for transfer. Positive and negative features were as-

+5.2% NS

- Negative points: cc2 <5 hours (−1), presence of multinucleation (−0.5), presence of irregular division (−0.5).
- Positive points: t5 45.8–57.0 HPI (+1), s2 0.0–0.1 hours (+1), s3 1.4–7.0 hours (+1), tSB <100 HPI (+1).

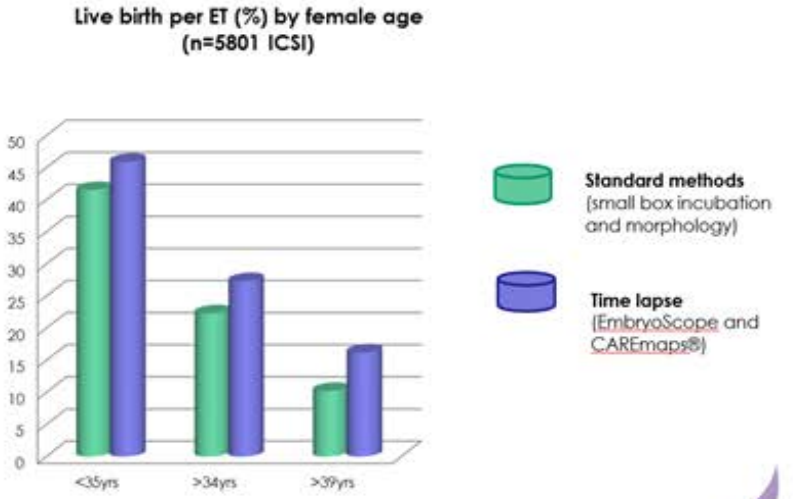
EmbryoScope improves live birth rate

Are culture conditions improved over conventional culture due to uninterruption?

Time lapse improves chances of live birth.

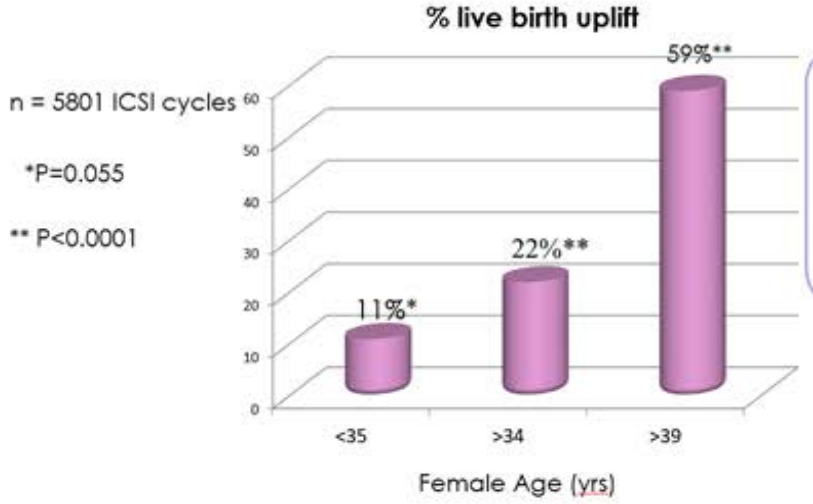
CARE data >1000 Live Births (1/5/11-28/2/14)

In house retrospective analysis



CAREfertility

Use of EmbryoScope and selection models is increasingly effective with advancing maternal age



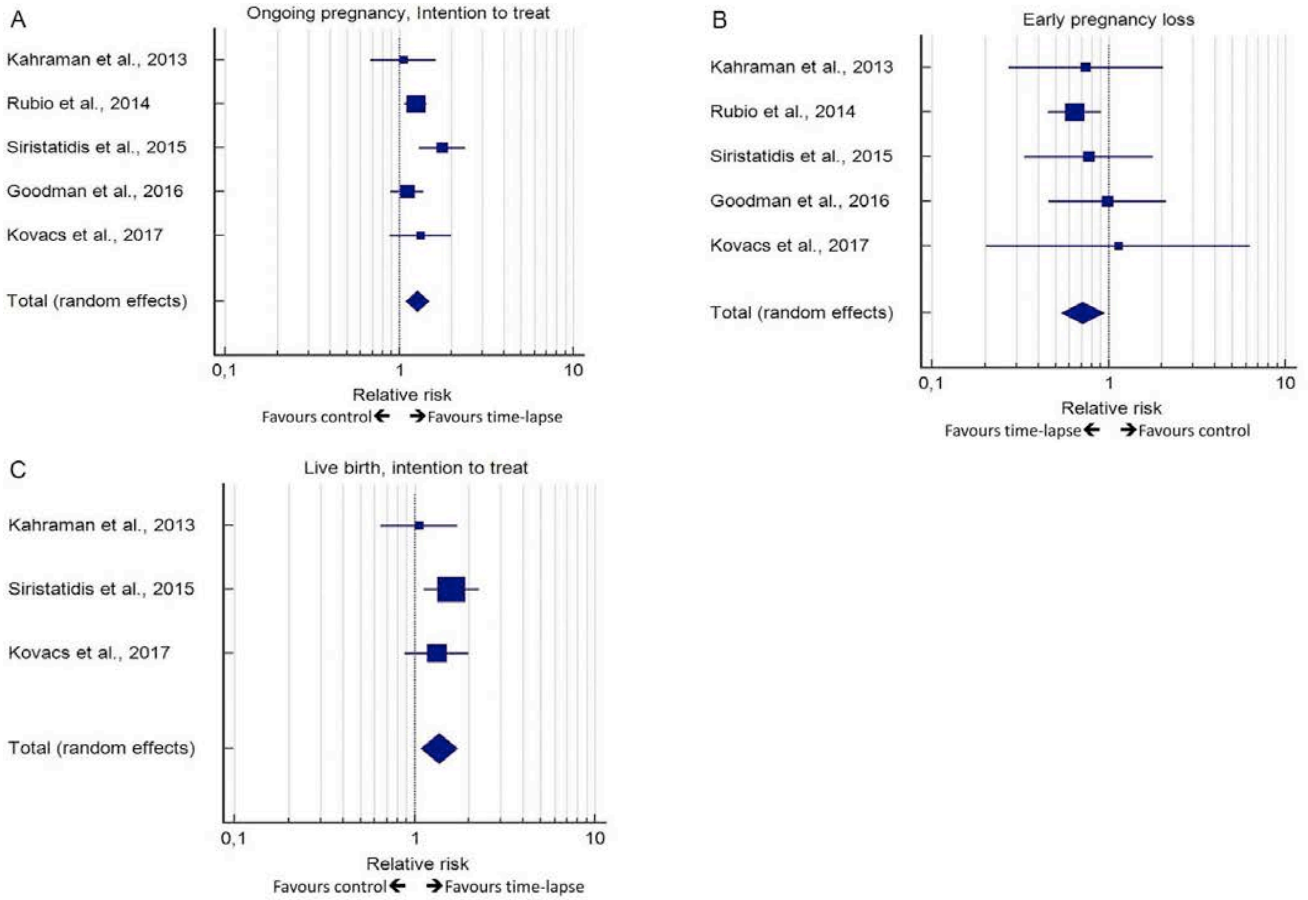
Why?

- More active deselection
- Older patient embryos less resilient to stresses of standard culture?

CAREfertility

Slides reproduced with permission from Alison Campbell

Time-lapse improves clinical outcome? 5RCTs



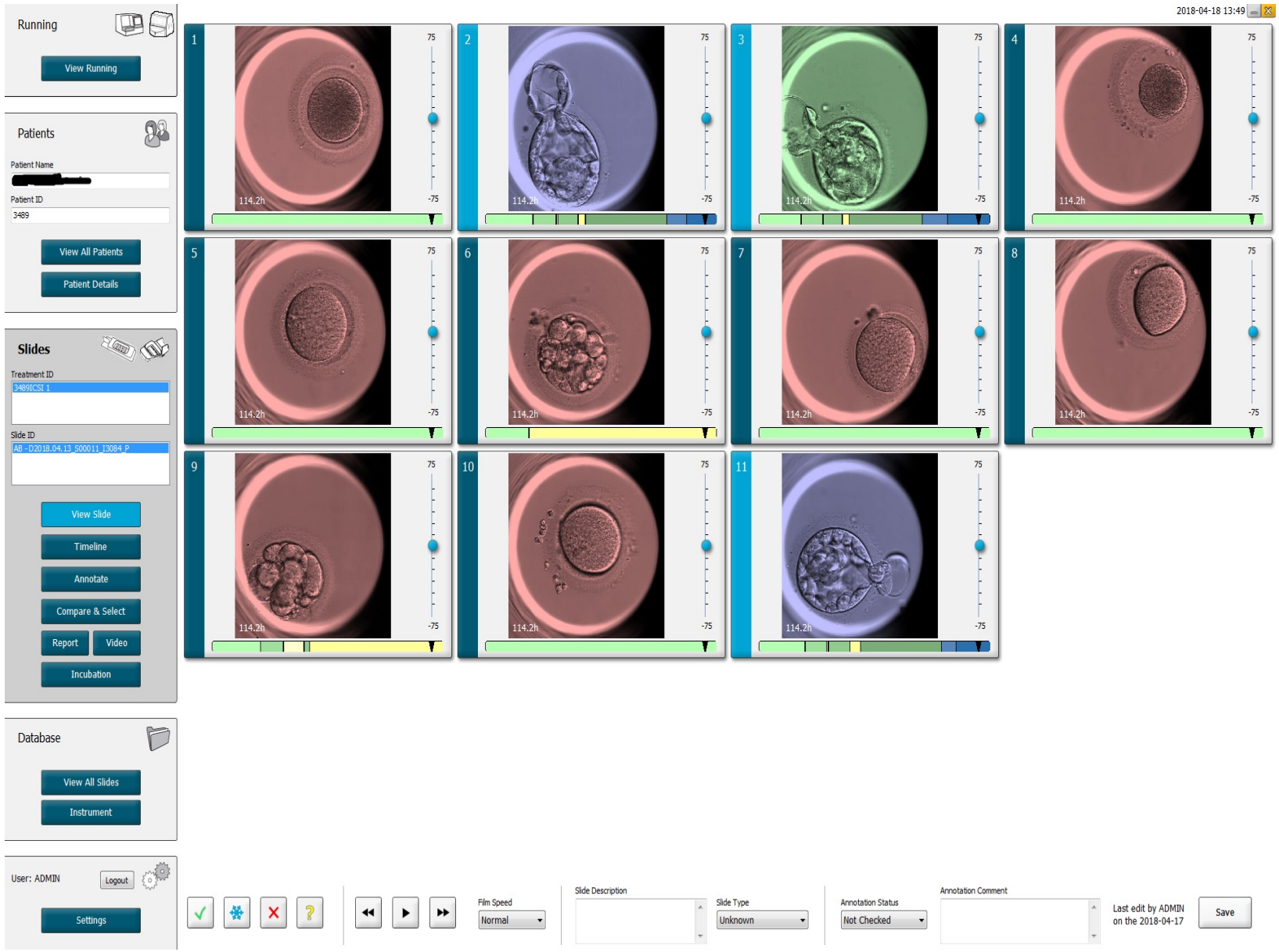
Reproductive BioMedicine Online DOI: (10.1016/j.rbmo.2017.06.022)

Cochrane Library

Cochrane Database of Systematic Reviews

Time-lapse systems for embryo incubation and assessment in assisted reproduction (Review)

Armstrong S, Bhide P, Jordan V, Pacey A, Marjoribanks J, Farquhar C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Patients
Patient Name
Patient ID
3489
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Patient Details
Slides
Treatment ID
3489ICSI 1
Slide ID
AB - D2018.04.13_S00011_I3084_P
View Slide
Timeline
Annotate
Compare & Select
Report
Video
Incubation
Database
View All Slides
Instrument
User: ADMIN
Logout
Settings
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2
3
4
5
6
7
8
9
10
11
75
-75
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Film Speed
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Slide Type
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Annotation Status
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Annotation Comment
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on the 2018-04-17
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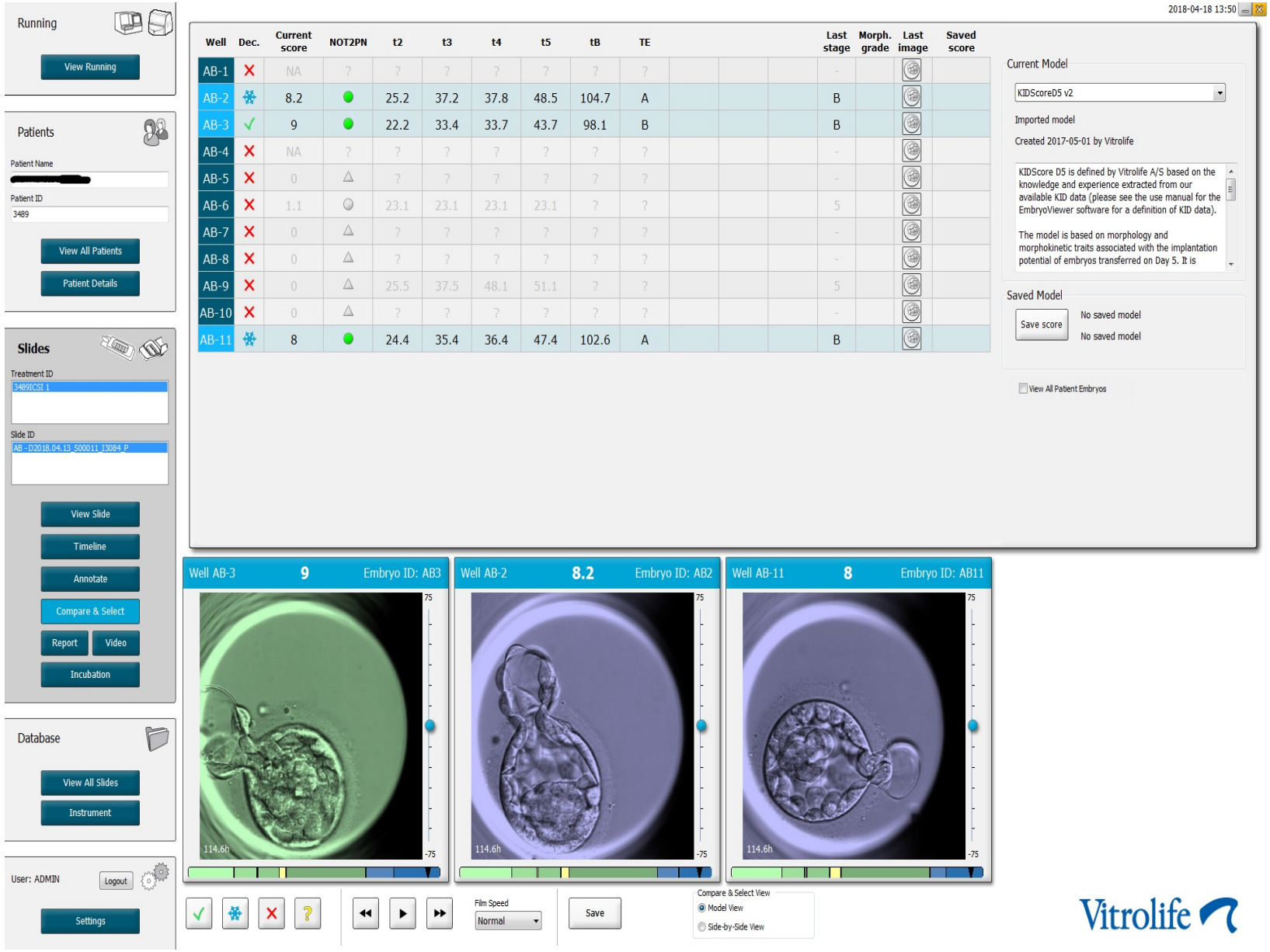
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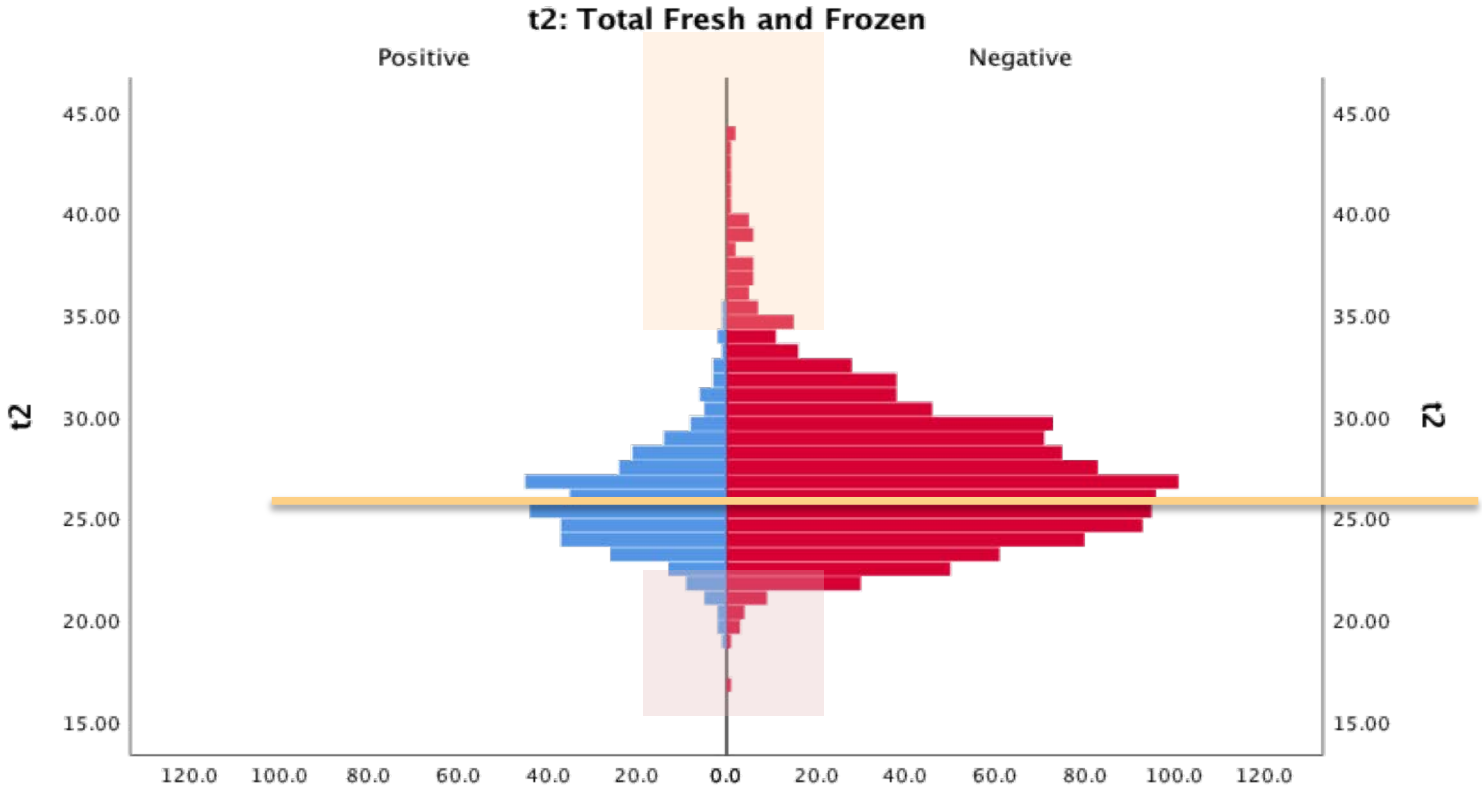
View Slide
Timeline
Annotate
Compare & Select
Report
Video
Incubation
Database
View All Slides
Instrument
User: ADMIN
Logout
Settings
2018-04-18 13:50
Well Dec. Current score NOT2PN t2 t3 t4 t5 tB TE Last stage Morph. grade Last image Saved score
AB-1 NA B
AB-2 8.2 25.2 37.2 37.8 48.5 104.7 A B
AB-3 9 22.2 33.4 33.7 43.7 98.1 B B
AB-4 NA B
AB-5 0 B
AB-6 1.1 23.1 23.1 23.1 23.1 5
AB-7 0 B
AB-8 0 B
AB-9 0 25.5 37.5 48.1 51.1 5
AB-10 0 B
AB-11 8 24.4 35.4 36.4 47.4 102.6 A B
Current Model
KIDScoreD5 v2
Imported model
Created 2017-05-01 by Vitrolife
KIDScore D5 is defined by Vitrolife A/S based on the knowledge and experience extracted from our available KID data (please see the use manual for the EmbryoViewer software for a definition of KID data).
The model is based on morphology and morphokinetic traits associated with the implantation potential of embryos transferred on Day 5. It is
Saved Model
Save score
No saved model
No saved model
View All Patient Embryos
Well AB-3 9 Embryo ID: AB3
Well AB-2 8.2 Embryo ID: AB2
Well AB-11 8 Embryo ID: AB11
75
-75
114.6h
Film Speed
Normal
Save
Compare & Select View
Model View
Side-by-Side View
Vitrolife

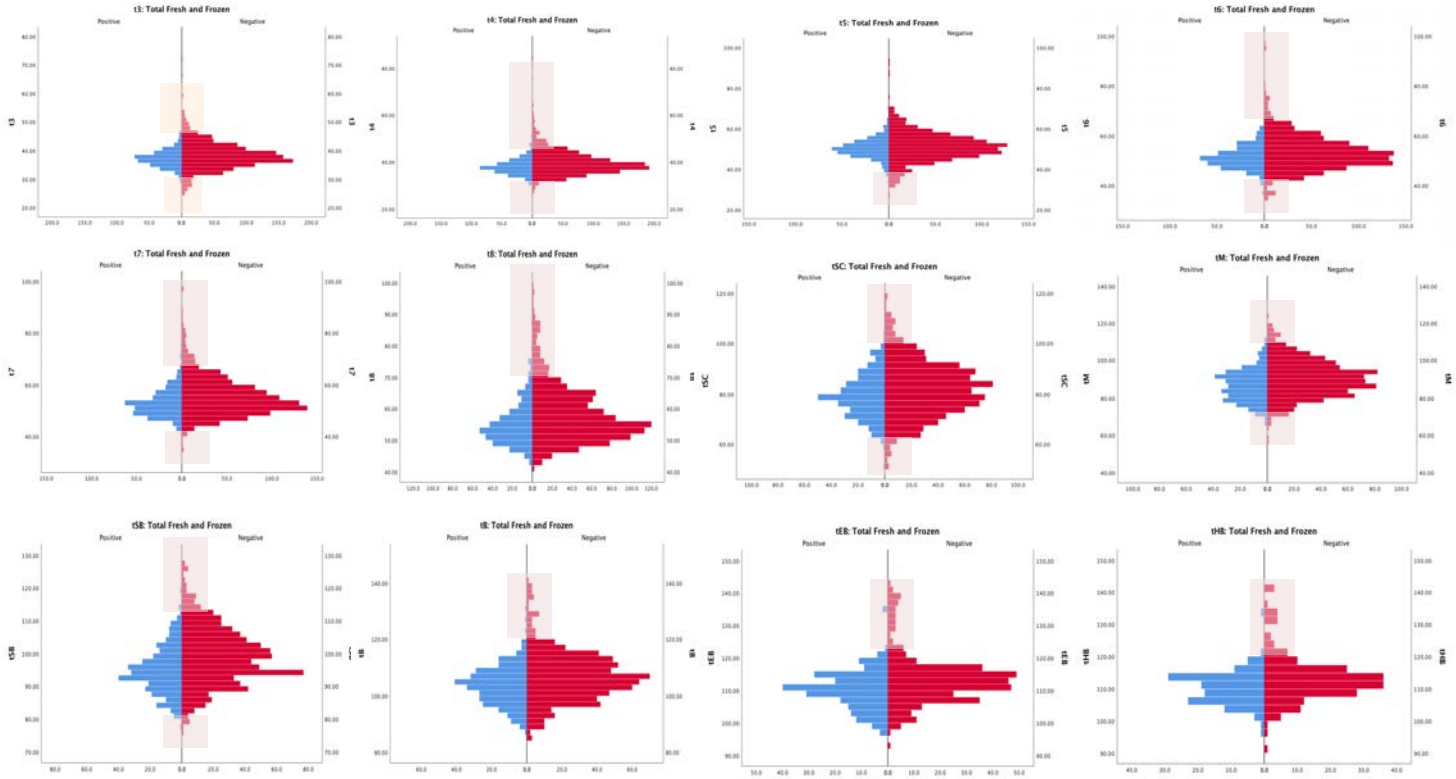
Central statistics not affected: OUTLIERS

Clinically Relevant Time-Lapse identifiable Features not possible to identify with static observation



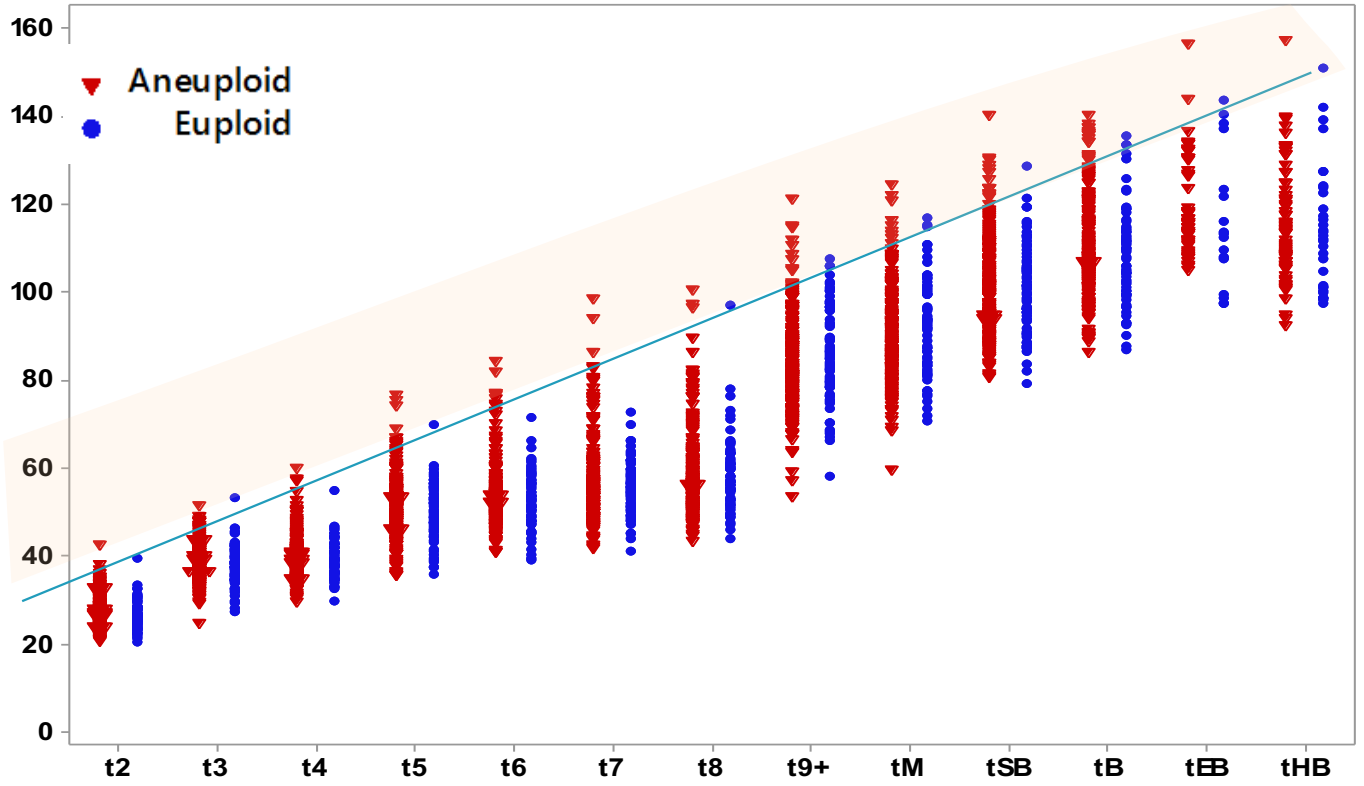
N=1507 KID embryos

Similar patterns throughout morphokinetics Identify and Remove Redundancies



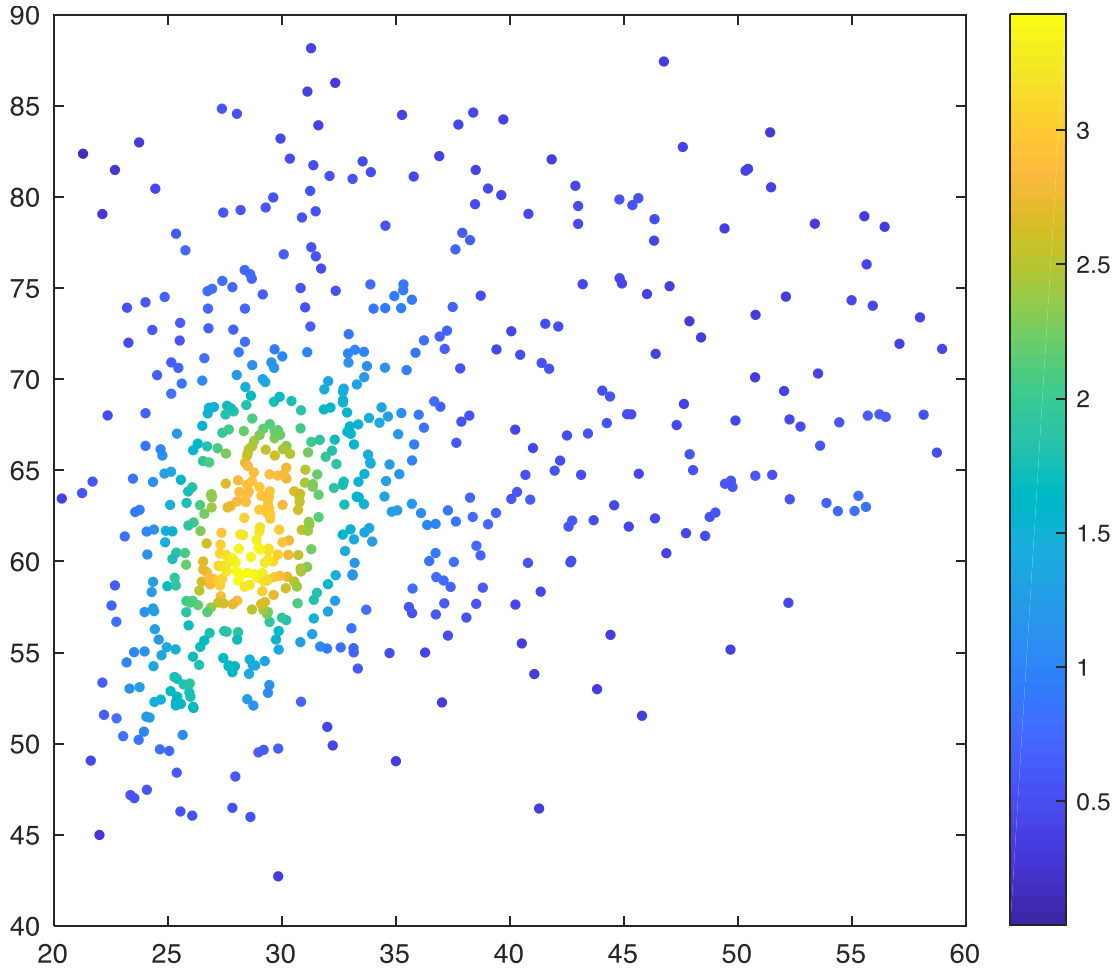
N=1507 KID embryos

Prediction of Aneuploidy

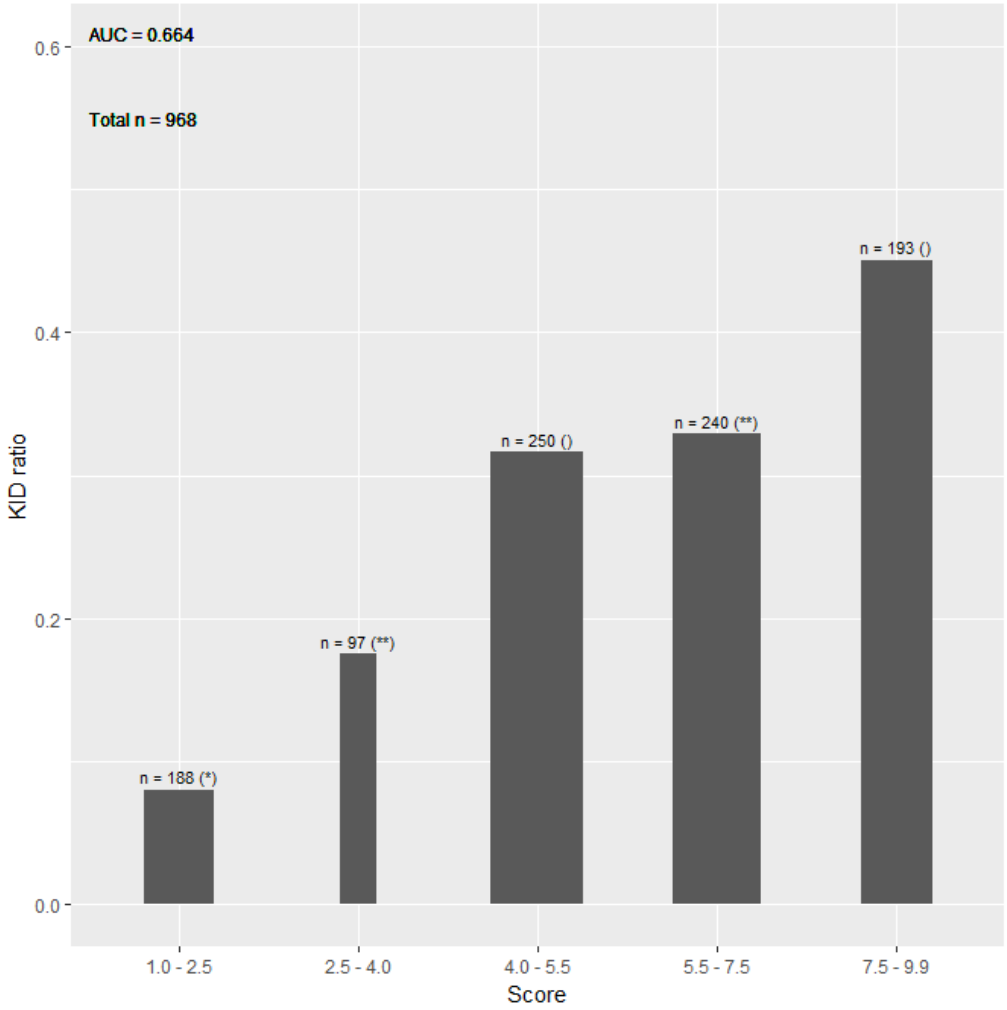


N=535 Known Ploidy Blastocysts

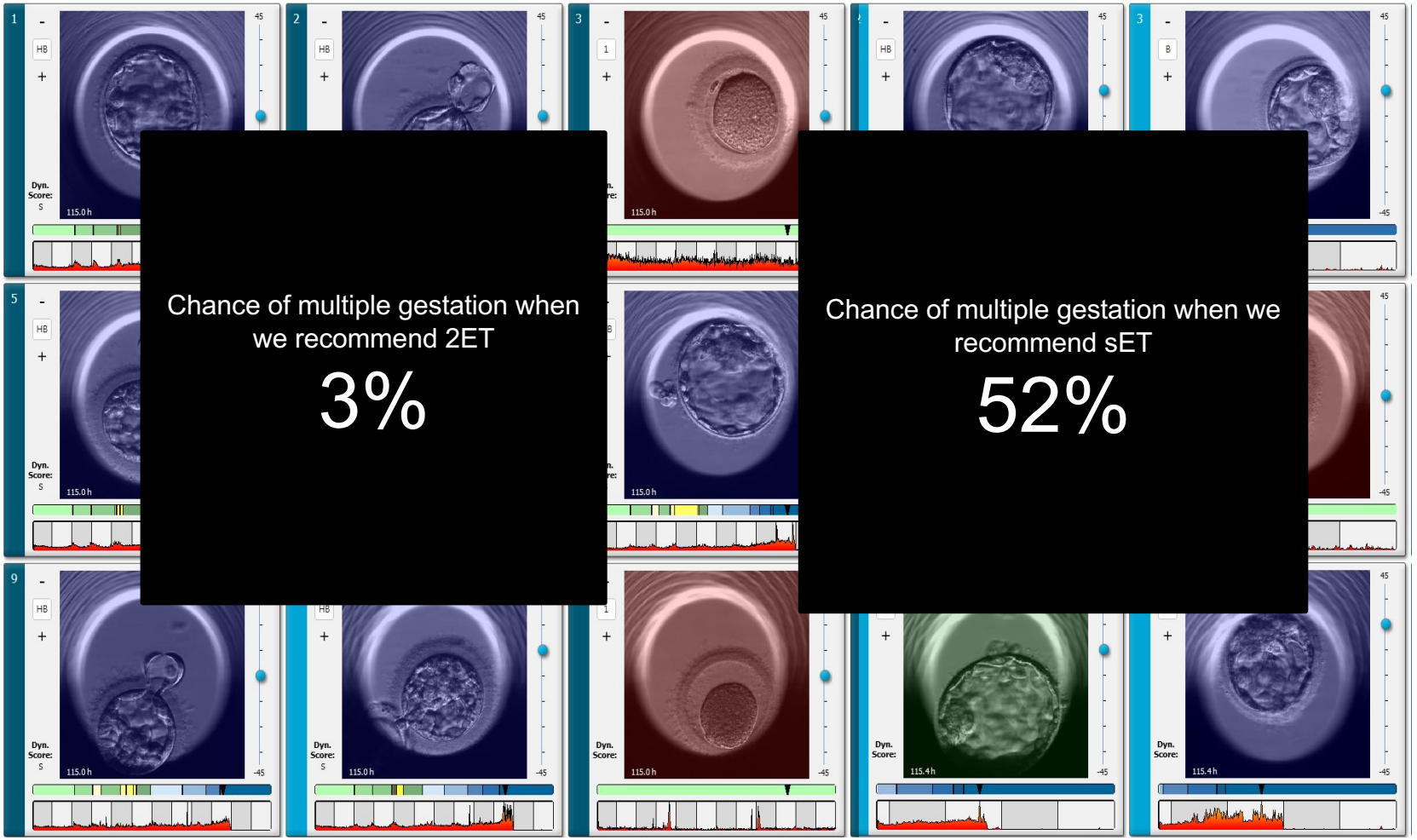
Prediction of Live Birth from Euploid Transfers

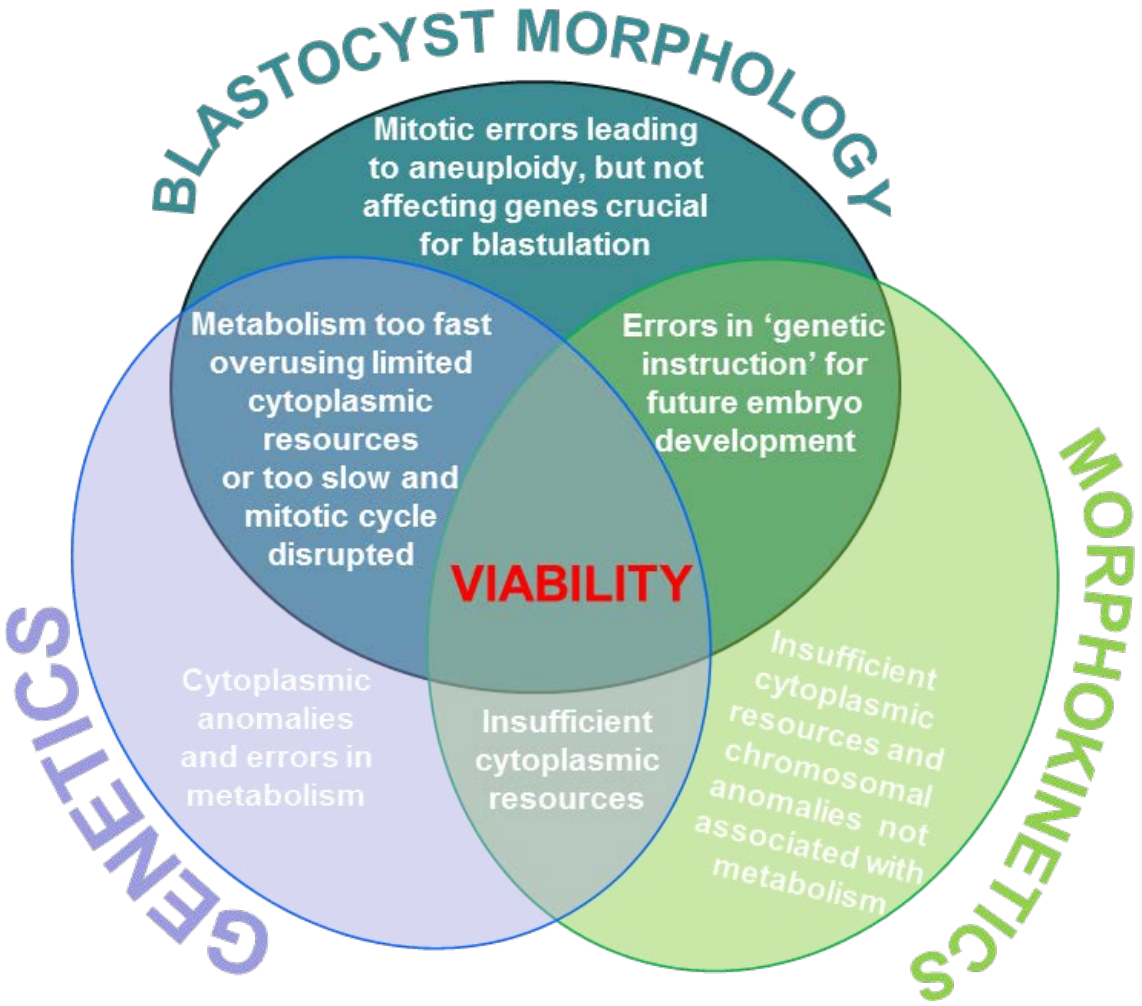


Increase embryo selection efficiency



Improved decision for multiple transfers



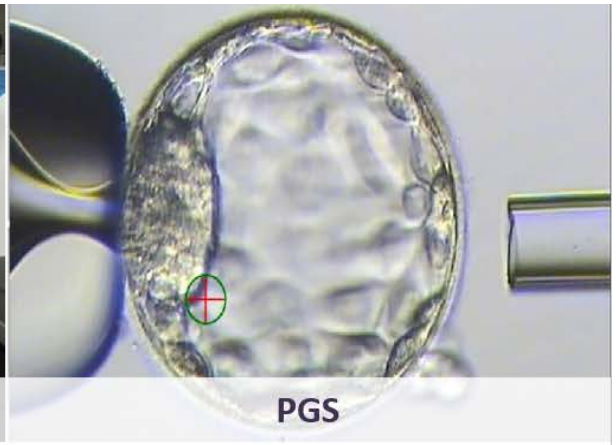

BLASTOCYST MORPHOLOGY
Mitotic errors leading to aneuploidy, but not affecting genes crucial for blastulation
Metabolism too fast overusing limited cytoplasmic resources or too slow and mitotic cycle disrupted
Errors in 'genetic instruction' for future embryo development
VIABILITY
Cytoplasmic anomalies and errors in metabolism
Insufficient cytoplasmic resources
Insufficient cytoplasmic resources and chromosomal anomalies not associated with metabolism
GENETICS
MORPHOKINETICS

Continuous improvement

What makes a good embryo selection method?

Morphology

Time-Lapse



PGS

ACCESSIBLE

Cheapest | Expensive set-up cost-saving over time | Most expensive per patient

NON-INVASIVE

Non-INVASIVE | INVASIVE

CONSISTENT

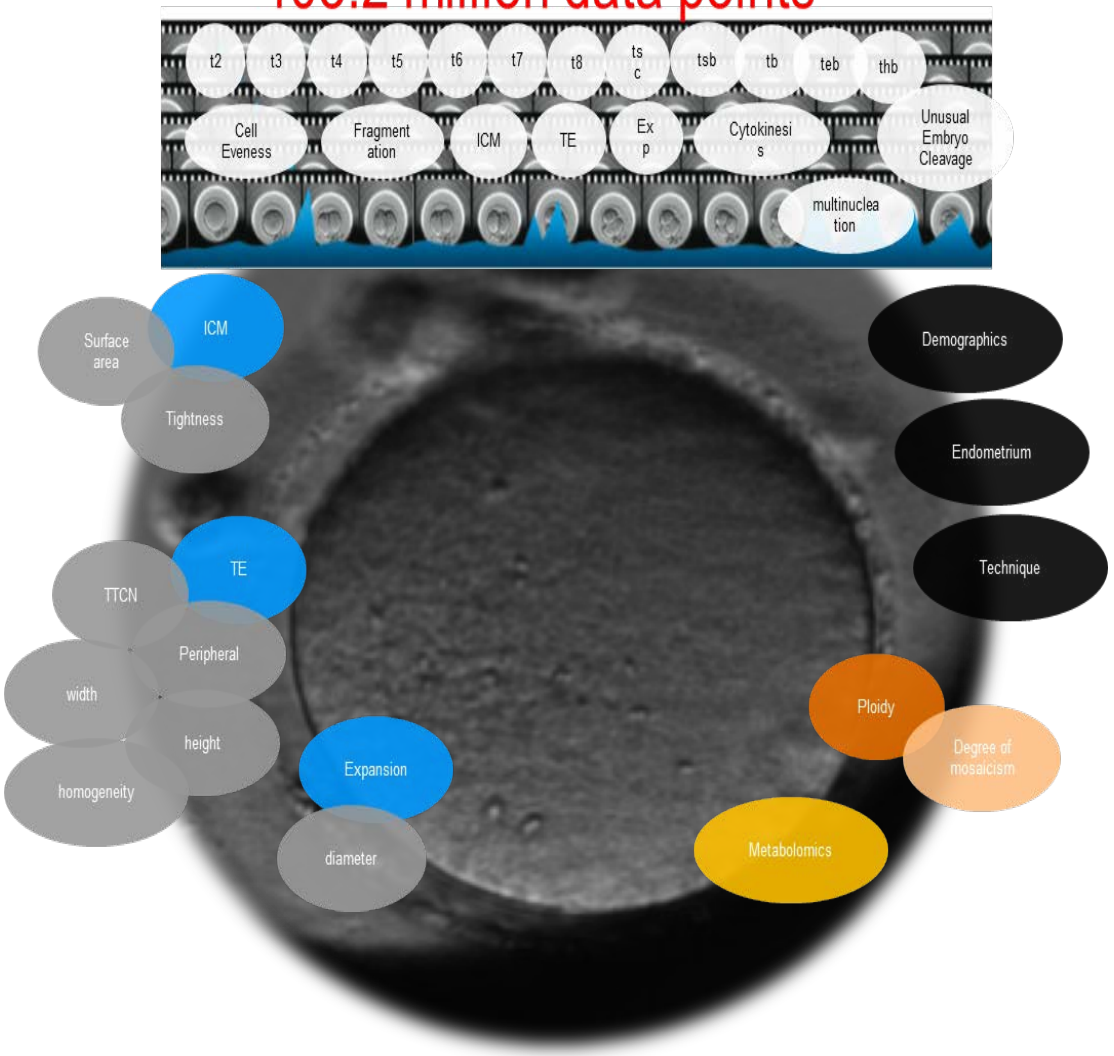
INCONSISTENT
Lowest Inter and intra-operator agreement

Increasing consistency

PREDICTIVE OF OUTCOME

Poor quality evidence of efficacy of prediction

403.2 million data points



AI in Embryo selection

ACCESSIBLE

NON-INVASIVE

CONSISTENT

PREDICTIVE OF OUTCOME

Inexpensive

Non-Invasive

Consistent, Objective, Reproducible

Improves Diagnostic Power

Allows for all the information to be used

additional parameters
not detectable by
optical observation of blastocysts

Imagine what AI with Time-Lapse can bring to Drs and their patients

Making AI Accessible to all IVF clinics…..

To evolve evidence based medicine and invigorate the best type of intelligence:

the one that is not artificial

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