Embryologists: What Were We? What Are We? What Will We Be?

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Disclosures

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Member, Serono Technologies Advisory Board

Editorial Board, J. Assisted Reproduction and Genetics

Board Member, Pacific Coast Reproductive Society

What was he?

Sir Robert Geoffrey Edwards, Ph.D., research scientist

What were his qualities?

- immense investigative talent

- collegiality

- originality

- tremendous vision

Patience, persistence, perseverance

Table 1 Some of challenges that had to be overcome before the first successful live birth following IVF and embryo transfer was achieved.

Challenge
Technical aspects of follicle aspiration (‘new suction gadget’)
Ovulation induction
Timing of laparoscopy
Ovarian stimulation
Cycle monitoring
Oocyte culture
Sperm preparation
Insemination procedure: medium, timing
Culture for embryo cleavage: medium, assessment
Technical aspects of embryo transfer, including route of transfer, medium and timing
Luteal support

From Elder and Johnson, Reproductive BioMedicine and Society, 2015:1:19-33

Patience, Persistence and Perseverance

1969 – 1978	
Patients	282
Potential LOR cycles	495
Proceeding to LOR	457/495
Outcome recorded	436/495
Eggs recovered in	388/436
Inseminations recorded	331/388
Embryos recorded in	167/331 (minimum)
Embryo transfers attempted	112/167
Pregnancies	11 biochem./pre-clinical
Live births	2

From Elder and Johnson, Reproductive BioMedicine and Society, 2015:1:19-33

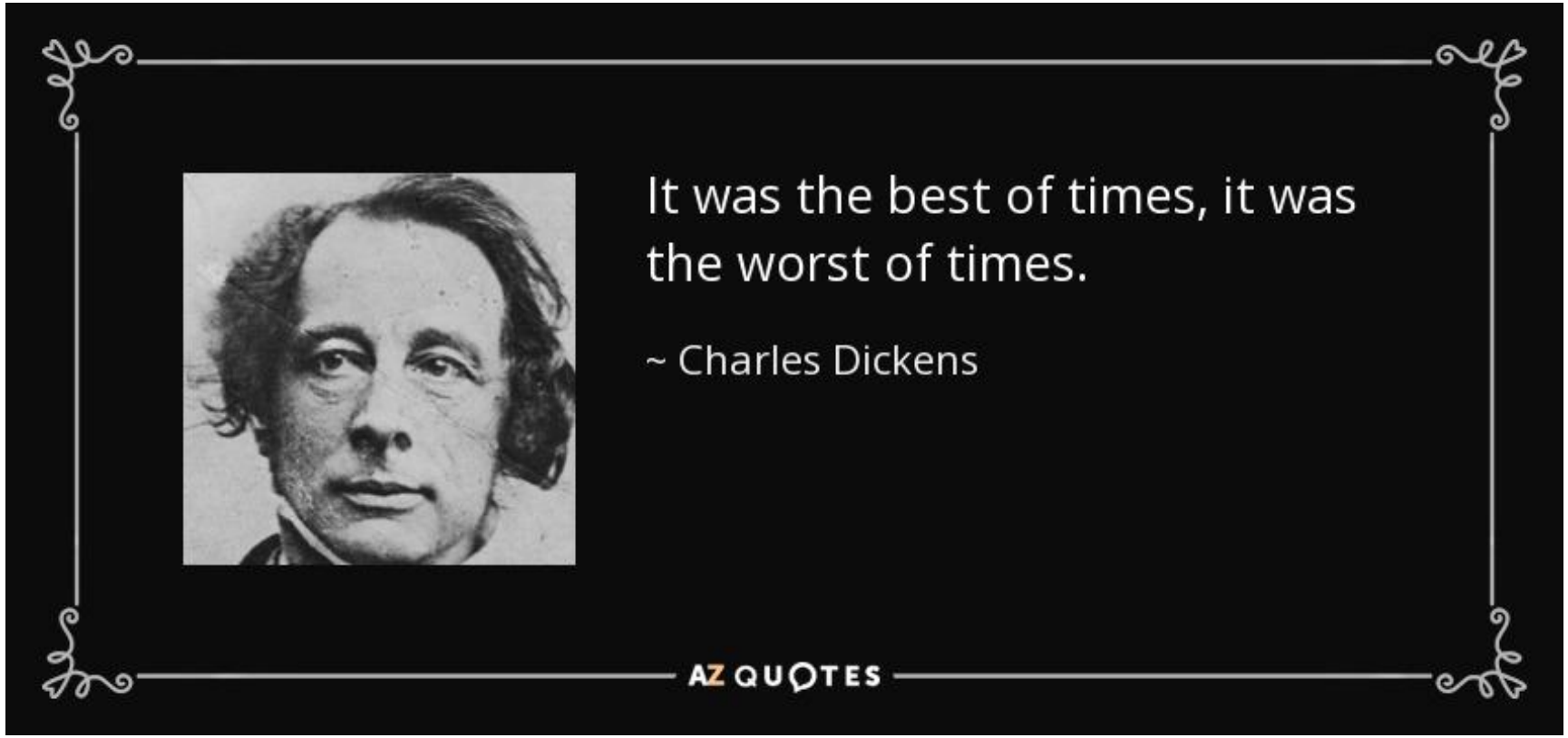
Patient L666/P264

Cycle type:	**natural**
Embryo transfer number:	**81**
Laparoscopic ovum retrieval	**10 November 1977**
Embryo transfer:	**12 November, 11:50 p.m.**
Embryo stage:	**8-cell**
Culture medium 1:	**Earle's BSS with 7.5% human serum**
Culture medium 2:	**Ham's F-10 with 15% human serum**

What were we?

We were fundamentally research scientists with backgrounds in animal science, cell biology, developmental biology, medical technology, basic and applied reproductive biology.

Also:



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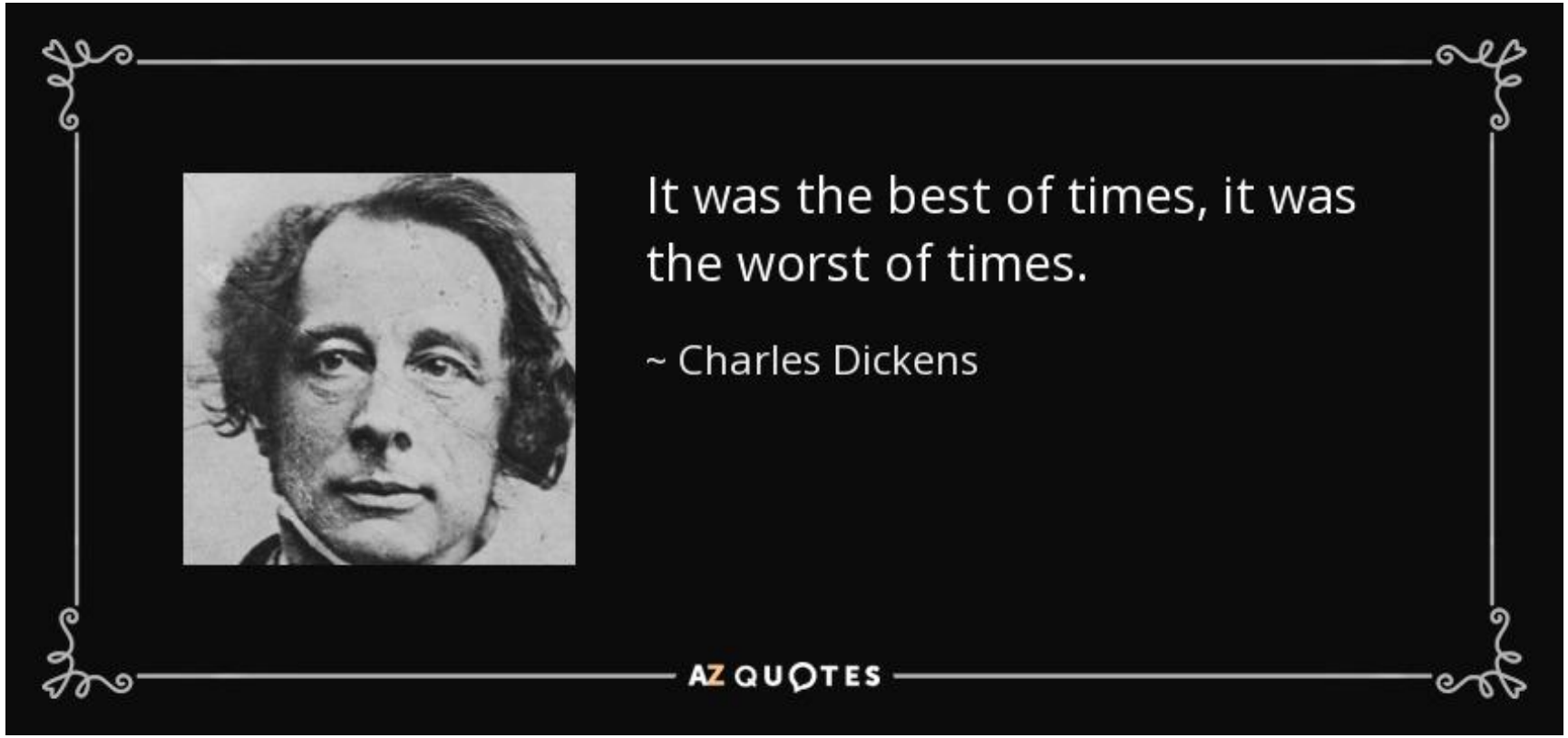


Best because -

Simple sperm prep (swim-up or wash).

Insemination only (no ICSI).

Day 2 embryo transfers.

No extended culture.

No hatching, no biopsy.

No embryo oocyte or freezing.

No SART or FDA!

(Note – best for the embryologist, not necessarily the patient.)

Worst because-

Laparoscopic egg retrievals – OR

No commercial media or supplements
- unproven formulae, water quality, chemical sources, serum collection, heat inactivation, filtration

Washing, autoclaving, gas sterilization & off gassing

No ICSI – miniPercoll gradients or sperm donor

Tubal transfers – GIFT, ZIFT, TET

Good embryos discarded

Our discipline evolves:

Ultrasound-guided retrievals and transfer
Commercial media and supplements
Embryo-specific culture platforms
ICSI
Embryo cryopreservation; equilibrium cooling and vitrification
Day 3 embryo transfers
Day 5 embryo transfers
Assisted hatching; acid Tyrode's and laser
Day 3/Day 5 embryo biopsy
FISH cell prep/biopsy tubing
Oocyte vitrification and warming
Surgical sperm retrieval; MESA, PESA, TESE, microTESE
IVM

Comprehensive evaluation of contemporary assisted reproduction technology laboratory operations to determine staffing levels that promote patient safety and quality care

Mina Alikani, Ph.D., HCLD
Kathryn Go, Ph.D., HCLD
Caroline McCaffery, Ph.D., HCLD
David McCulloh, Ph.D., HCLD

Fertility and Sterility 102:1350-1356, 2014.

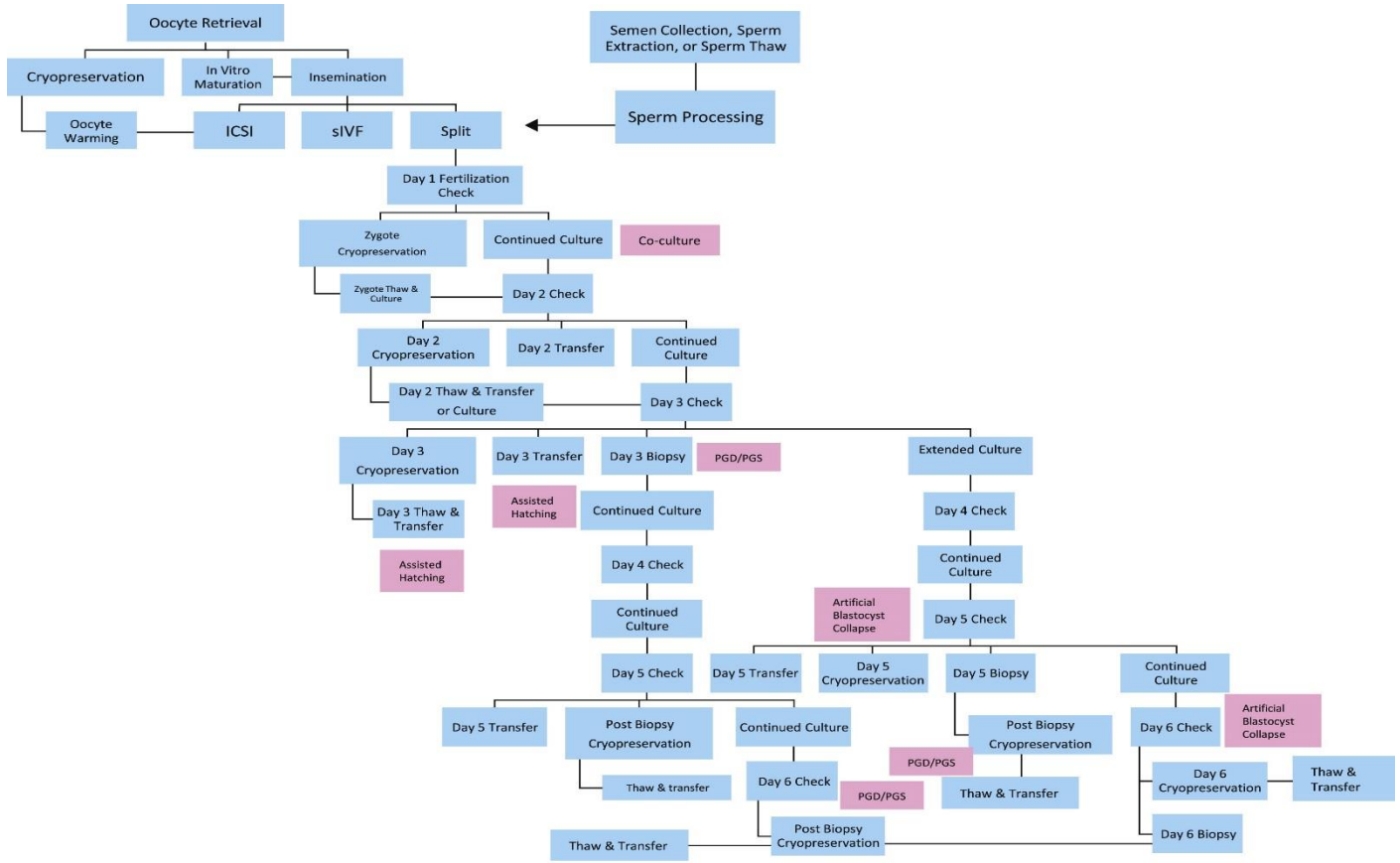


Table 2 A comparison of the estimated number of person hours required for completion of a traditional versus contemporary versus contemporary with PGD/PGS cycles (the latter requiring almost three times as many person hours as the traditional model).

Table 2	IVF traditional		IVF contemporary		IVF/PGS/PGD	
	Procedure time (min)	Witness (min)	Procedure time (min)	Witness (min)	Procedure time (min)	Witness (min)
Preparation all	30	0	60	0	80	0
Oocyte retrieval	60	10	60	10	60	10
Sperm preparation	60	10	60	10	60	10
Insemination/ICSI	20	10	40	20	40	20
Fertilization check	40	10	40	10	40	10
Day 2 check	20	0	20	0	20	0
Day 3						
Check	20	0	20	0	20	0
Transfer	40	10	0	0	0	0
Cryo	40	10	0	0	0	0
Assisted hatching	20	0	20	0	60	0
Extended culture	0	0	40	10	40	10
Day 5						
Check	0	0	20	0	20	0
Transfer	0	0	40	10	0	0
Biopsy	0	0	0	0	80	40
Cryo	0	0	40	20	80	40
Day 6						
Check	0	0	20	0	20	0
Biopsy	0	0	0	0	80	40
Cryo	0	0	40	20	80	40
No. of minutes	350	60	520	110	780	220
No. of hours	5.83	1.00	8.67	1.83	13	3.67
Total time (h)	6.83		10.50		16.67	

A few facts of life regarding the evolution of ART

With the exception of ultrasound applications and the multi-dose injection pen, innovation in ART has been in the laboratory.

Many new procedures require precise timing.

Many procedures require a specific set-up with a preincubation period.

The day still only has 24 hours – we are now protocol-driven, not science-driven.

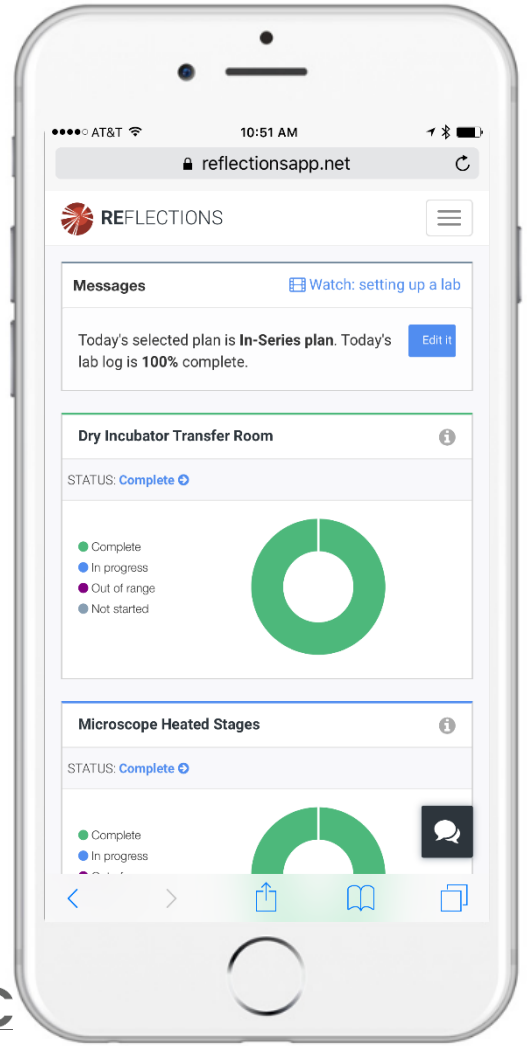
Paperwork, data handling

- **20 – 49.2% of doctor's time on EMR** (any specialty)
- **25 - 50% of embryologist time** (estimated)
- **50 - 85% of HCLD time** (estimated)

A task conducted by Harris Poll, 2014

3 ways of dealing with electronic systems for data handling in IVF

- ignore
- ponder
- embrace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STATUS: Complete
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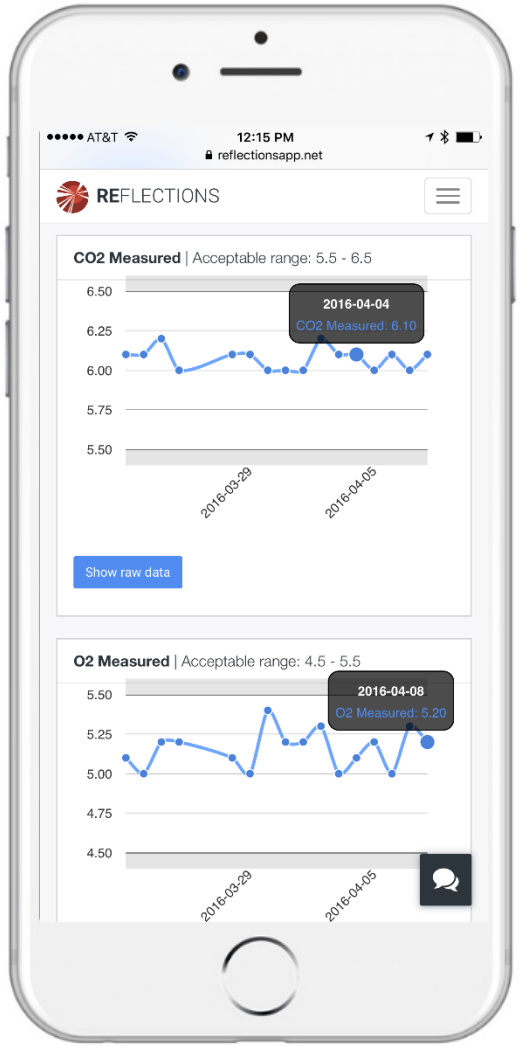
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CO2 Measured: 6.10
2016-03-29
2016-04-05
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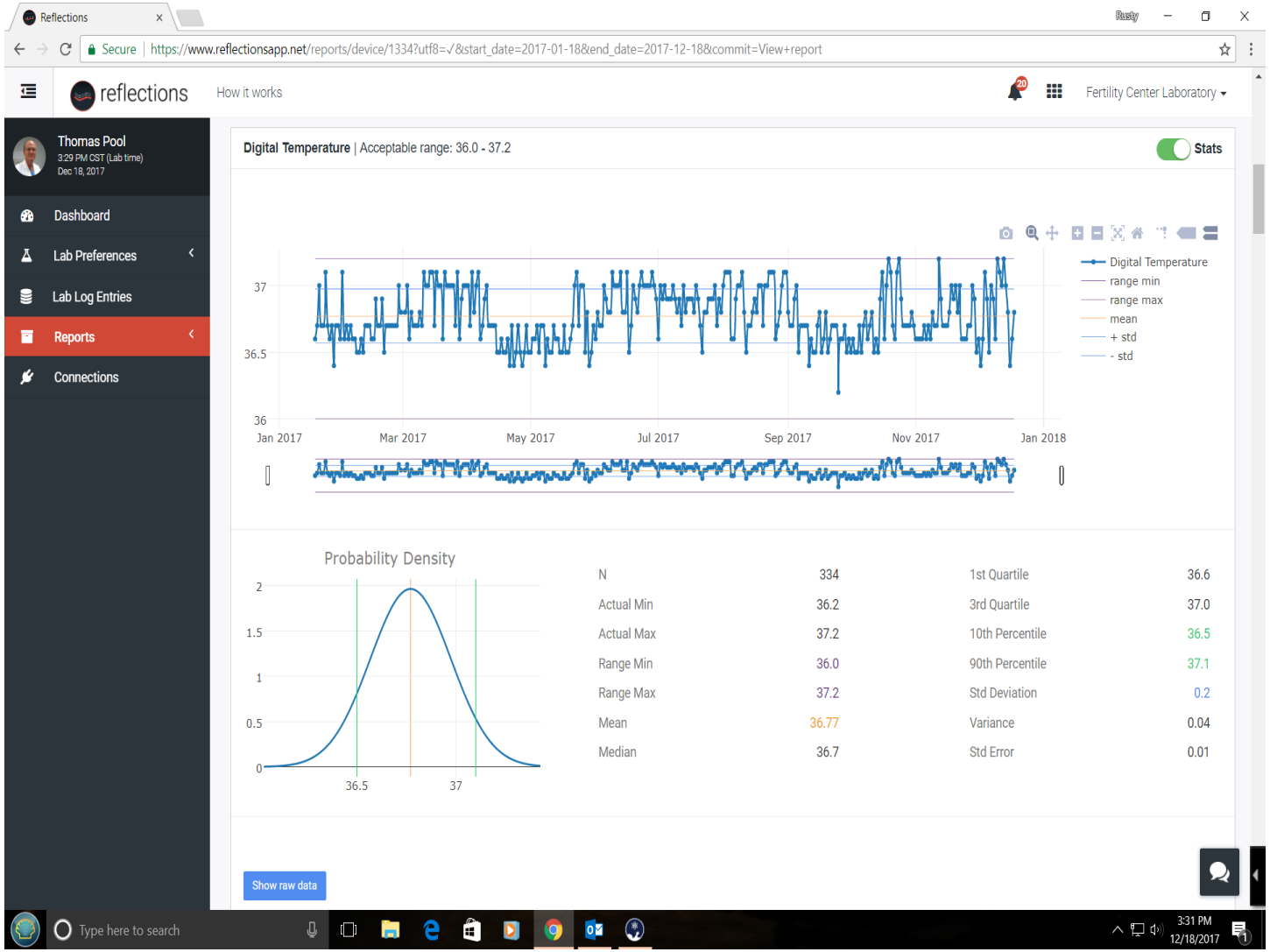
2016-03-29
2016-04-05

IVFOC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reflections
How it works
Fertility Center Laboratory
Thomas Pool
3:29 PM CST (Lab time)
Dec 18, 2017
Dashboard
Lab Preferences
Lab Log Entries
Reports
Connections
Digital Temperature | Acceptable range: 36.0 - 37.2
Stats
Digital Temperature
range min
range max
mean
+ std
- std
37
36.5
36
Jan 2017
Mar 2017
May 2017
Jul 2017
Sep 2017
Nov 2017
Jan 2018
Probability Density
2
1.5
1
0.5
0
36.5
37
N 334
Actual Min 36.2
Actual Max 37.2
Range Min 36.0
Range Max 37.2
Mean 36.77
Median 36.7
1st Quartile 36.6
3rd Quartile 37.0
10th Percentile 36.5
90th Percentile 37.1
Std Deviation 0.2
Variance 0.04
Std Error 0.01
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What will we be?

Automation

1. Metabolomics

Non-invasive metabolomic profiling of day 2 and day 5 embryo culture medium: a prospective randomized trial

Aim: To investigate if NIR spectroscopy system, utilizing on-site instrumentation loaded with previously established algorithms, was able to improve the ongoing single embryo transfer pregnancy rate when added to embryo morphology scoring.

Hardarson *et al., 2012* Hum Reprod 27:89-96.

Non-invasive metabolomic profiling of day 2 and day 5 embryo culture medium: a prospective randomized trial

Estimated from power analysis: 768 patients
(384 per arm; 80% power to detect 10% in PR at .05 level

Population		NIR	Control		p value
ITT		n=164		n=163	
	Day 2	31.0% (27)	26.5% (22)		0.63
	Day 5	39.0% (30)	45.0% (36)		0.55
PP		n=152		n=160	
	Day 2	33.3% (27)	27.2% (22)		0.49
	Day5	39.4% (28)	45.6% (36)		0.55

Study terminated early by Data Safety Monitoring Board

Hardarson *et al., 2012* Hum Reprod 27:89-96.

Automation

1. Metabolomics
2. Microfluidics

Automation

1. Metabolomics
2. Microfluidics
3. Morphokinetics

Automation

Precision Medicine

What is the future?

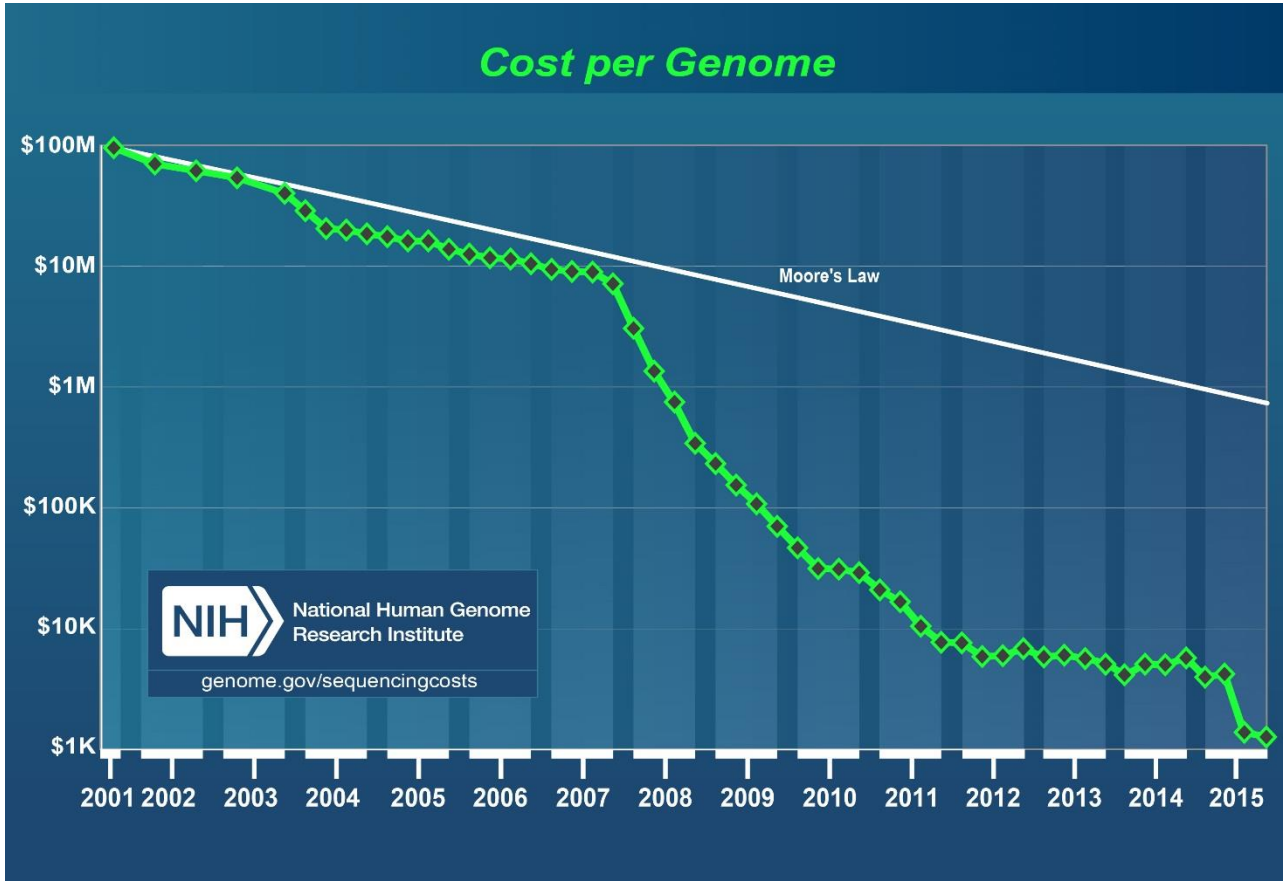
Precision/personalized medicine

GENOMICS
Our genes can suggest what diseases we *might* be predisposed to, but it's an incomplete picture of human health.

PHENOTYPE
A snapshot of the current state of health that can be used to prevent, diagnose and treat disease or improve health.

LIFESTYLE/ENVIRONMENT
External factors like diet, exercise, medications, microbiota and even where we live influence our metabolic state.

Human Genome Project: $3 billion and 10 years



Reproductive BioMedicine Online (2013) 27, 611–623

www.sciencedirect.com
www.rbmonline.com

SYMPOSIUM: FUTURES IN REPRODUCTION
REVIEW

Personalized reproductive medicine on the brink: progress, opportunities and challenges ahead

Piraye Yurttas Beim *, Michael Elashoff, Tina T Hu-Seliger

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* Corresponding author. *E-mail address:* p.beim@celmatix.com (PY Beim).

Dr Piraye Yurttas Beim is a Founder, Director and the Chief Executive Officer of Celmatix, a biotechnology company that, in partnership with fertility clinics throughout the USA, is harnessing the power of clinical data and genomics to help optimize and support medical decisions around fertility. Dr Beim performed her doctoral work on mouse maternal effect genes at Cornell University, Weill Medical College/Sloan Kettering Institute in New York City and her post-doctoral work in the field of mammalian preimplantation embryology at the Gurdon Institute of the University of Cambridge in the UK.

Beim *et al.*, RBMO 27:611-623, 2013.

Personalized Reproductive Medicine

With declining costs of high-throughput DNA sequencing, exome sequencing and whole-genome sequencing should become the primary approach for genetic biomarker discovery.

With sufficient depths of coverage (sequencing reads/genomic site), these approaches are *not reliant on known markers segregating in the population*, but instead enable the identification of rare (<1% frequency in the population) or even *private alleles (unique to the individual or immediate relatives).*

Beim *et al.*, RBMO 27:611-623, 2013.

Personalized Reproductive Medicine

The success in identifying the causal variant(s) of a disease largely depends on the underlying genetic architecture of that disease.

Rare alleles have been shown to confer susceptibility to several complex traits (for example, autism).

It will be important to understand how such rare and private mutations contribute to the genetic architecture of infertility.

Is therapeutic intervention a possibility for embryos?

Origin and composition of cell-free DNA in spent medium from human embryo culture during preimplantation development
M Vera-Rodriguez A Diez-Juan J Jimenez-Almazan S Martinez R Navarro V PeinadoA Mercader M Meseguer D Blesa I Moreno D Valbuena C Rubio C Simon
Human Reproduction, https://doi.org/10.1093/humrep/dey028

This is the first study to combine chromosomal analysis of cell-free DNA, SNP sequencing to identify maternal contamination, and whole-blastocyst analysis for detecting mosaicism. Our results provide a better understanding of the origin of cell-free DNA in spent culture media, offering an important step toward developing future non-invasive karyotyping that must rely on the specific identification of DNA released from human embryos.

Perspect Med Educ. 2013 Nov; 2(5-6): 335–339.
Published online 2013 Mar 15. doi: 10.1007/s40037-013-0047-2
PMCID: PMC3824759

Persistent reservations against the premedical and medical curriculum

Vinay Prasad

The case against organic chemistry, physics, calculus (premed), biochemistry, molecular biology, (prolonged, i.e. 20 weeks of) anatomy, neuroscience, embryology, and even histology has been made repeatedly in the medical education literature.

Despite the many arguments from practicing physicians that this subject matter is not used daily in clinical medicine…these courses continue to be mandated.

Regardless of what we add to medical education, we must cut subjects that are not used by the vast majority of graduating physicians.

Forbes/CMO Network Jan 23,2012
Avi Dan, Contributor

Kodak –

Founded in 1888 by George Eastman.

In 1975, developed the first digital camera.

In 1976, held 85% of camera sales and 90% of film sales in the U.S.; by 1998 had 170,000 employees

January 19, 2012, filed for Chapter 11 bankruptcy.

Keys to future success as an embryologist

Never lose sight of the fact that you are a scientist. Methods will change – the fundamental science will not.

Growth in ART has been in the laboratory. This will not change but there is no room for complacency.

Automation is not an enemy of the embryologist.

The more one embraces genetics and big data, the better.

As to corporate IVF, the setting will not matter if you do the above.