



ART LABORATORY AUTOMATION

ART Laboratory: past, present and future

Montse Boada



Hospital Universitario Dexeus
Barcelona

DISCLOSURES



NO - Participation in any of the industrial companies mentioned in this lecture

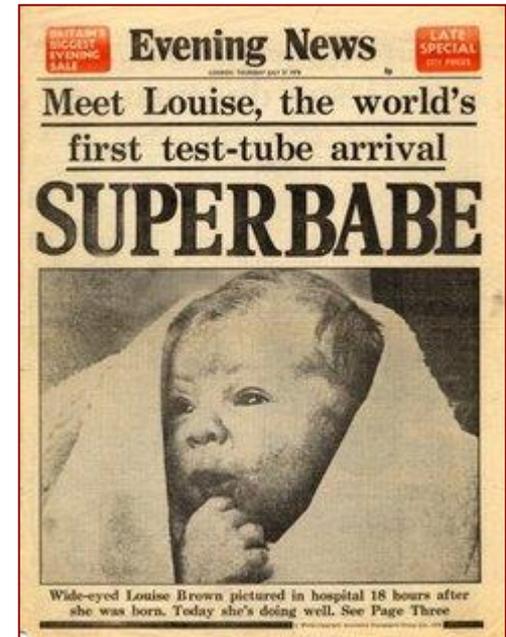
✓ - We have received research support from some of these companies

Steptoe PC & Edwards RG.



Birth after the reimplantation of a human embryo

Lancet 1978; ii: 366.



40 years ago...

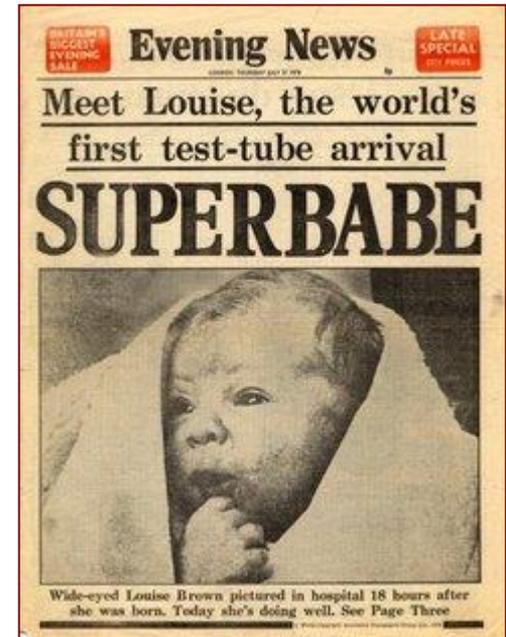


Steptoe PC & Edwards RG.



Birth after the reimplantation of a human embryo

Lancet 1978; ii: 366.

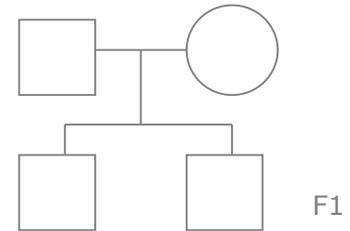


The 2010 Nobel Prize of Physiology or Medicine

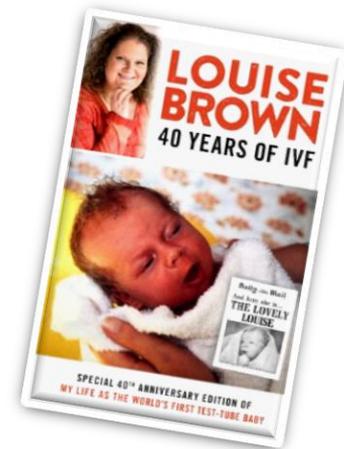
Louise Brown



2006 and 2013



2018

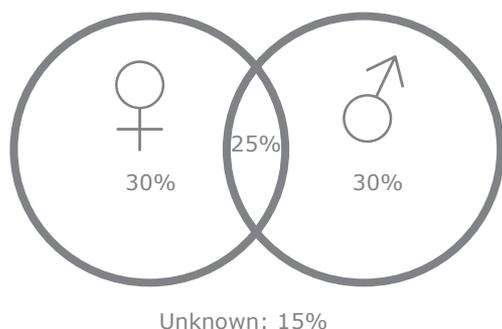


ART INDICATIONS



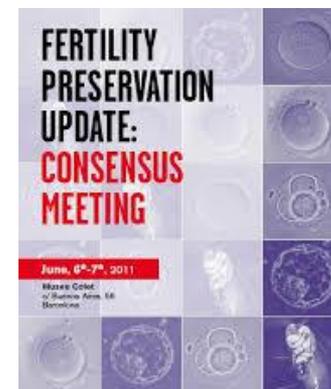
2) Tubal factor:

- Selective Hysterosalpingogram
- Surgery:** microsurgery: after fallopscopy:
 - Salpingolysis, salpingostomy, excision & reanastom. (success from 10-40%)
 - Uterine distortion or anomalies: - Myomectomy for fibroids
 - Metroplasy in certain cases
- I.V.F programme



ESHRE PGD Consortium data collection XIV–XV: cycles from January 2011 to December 2012 with pregnancy follow-up to October 2013

M De Rycke, V Goossens, G Kokkali, M Meijer-Hoogeveen, E Coonen, C Moutou
 Human Reproduction, Volume 32, Issue 10, 1 October 2017, Pages 1974–1994,



Oocyte cryopreservation for age-related fertility loss†

ESHRE Task Force on Ethics and Law, including, W. Dondorp^{1*}, G. de Wert¹, G. Pennings², F. Shenfield³, P. Devroey⁴, B. Tarlatzis⁵, P. Barri⁴, and K. Diedrich⁷

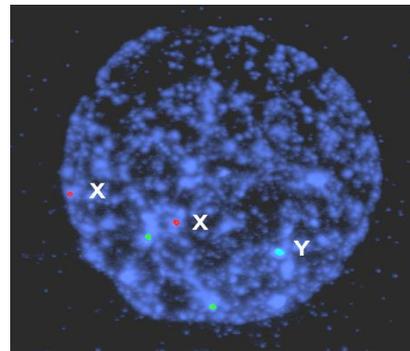
ART INDICATIONS



Hum Reprod. 1987 May;2(4):321-3.

Pregnancy after the replacement of a frozen-thawed embryo with less than 50% intact blastomeres.

Veiga A, Calderon G, Barri PN, Coroleu B.



Nature. 1990 Apr 19;344(6268):768-70.

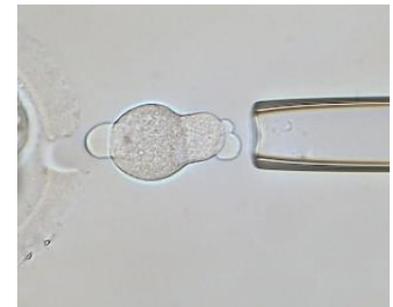
Pregnancies from biopsied human preimplantation embryos sexed by Y-specific DNA amplification.

Handyside AH¹, Kontogianni EH, Hardy K, Winston RM.

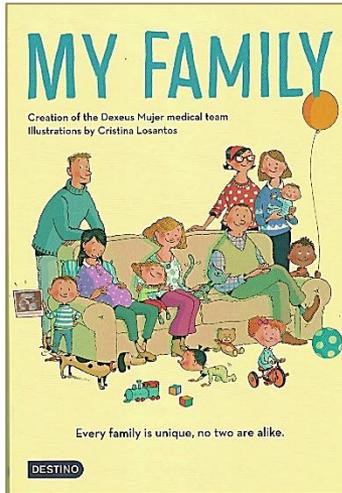
Hum Reprod. 1994 Nov;9(11):2156-9.

Twin pregnancy after preimplantation diagnosis for sex selection.

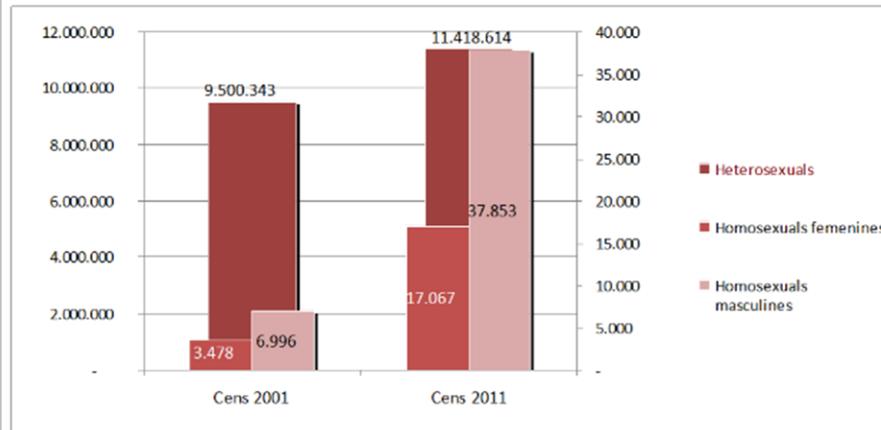
Veiga A¹, Santaló J, Vidal F, Calderón G, Giménez C, Boada M, Egozcue J, Barri PN.



ART INDICATIONS



Tipus de parelles: 99.5% heterossexuals, les homossexuals s'han multiplicat per 5 els últims 10 anys. Les homossexuals masculines són més del doble que les femenines



INE, 2011

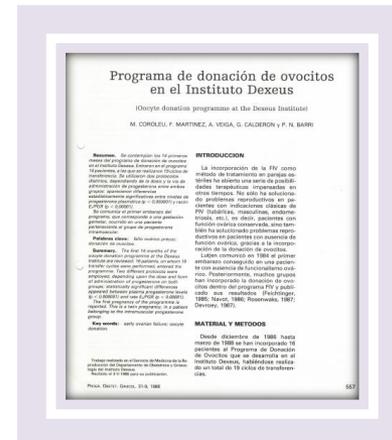
ART INDICATIONS



Nature 1984 Jan 12;18:307(5947):174-5.

The establishment and maintenance of pregnancy using in vitro fertilization and embryo donation in a patient with primary ovarian failure.

Lutjen P, Trounson A, Leeton J, Findlay J, Wood C, Renou P.



CLINICAL PROCEDURES



Image courtesy of Merck



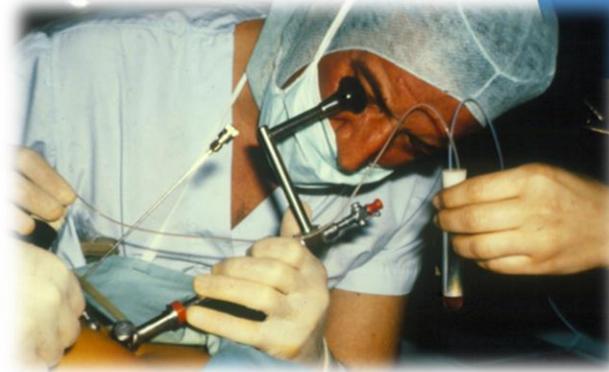
Ovarian stimulation and luteal phase support: Purified urinary products
Intramuscular injections
Single bolus dose of hCG

...

CLINICAL PROCEDURES



Oocyte retrieval, under general anaesthesia in operating theatres

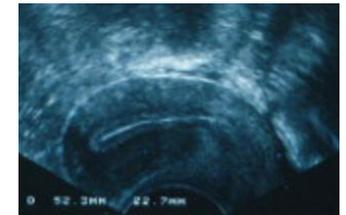


Embryo transfers without ultrasound guidance and the patient in a supine position

Human Reproduction vol.15 no.3 pp.616-620, 2000

Embryo transfer under ultrasound guidance improves pregnancy rates after in-vitro fertilization

B.Coroleu¹, O.Carreras, A.Veiga, A.Martell, F.Martinez, I.Belil, L.Hereter and P.N.Barri

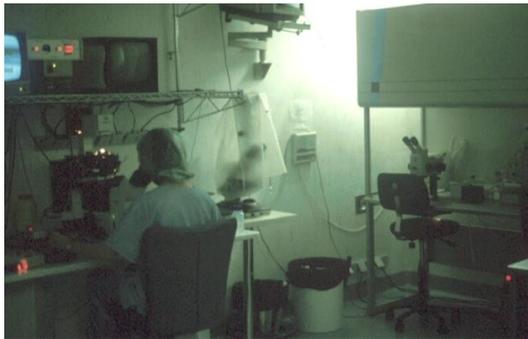


Multiple pregnancies

ART Laboratories



ART Laboratories



ART Laboratory: past, present and future

*“**Embryology laboratories** have become **epicenters** of assisted reproductive technology as the practice of IVF has moved to blastocyst transfers and the utilization of trophectoderm biopsy for PGT.”*

Dean E. Morbeck 2015

*“The results of ART procedures are **especially influenced by the laboratory staff’s skills** to handle **high-tech** equipment and their **accuracy**, persistence and patience in performing micromanipulations on gametes and embryos.”*

Kovacic et al, 2015

ART Laboratory: past, present and future



“There are well over 200 other variables (culture media) that may influence the results in an IVF cycle”

In: Human Embryo Culture media Comparisons. Pool et al 2012

More than 200 factors!

Behr and Wang, 2004; Pool et al., 2002, 2005, 2012

Correct operation of ART laboratory:

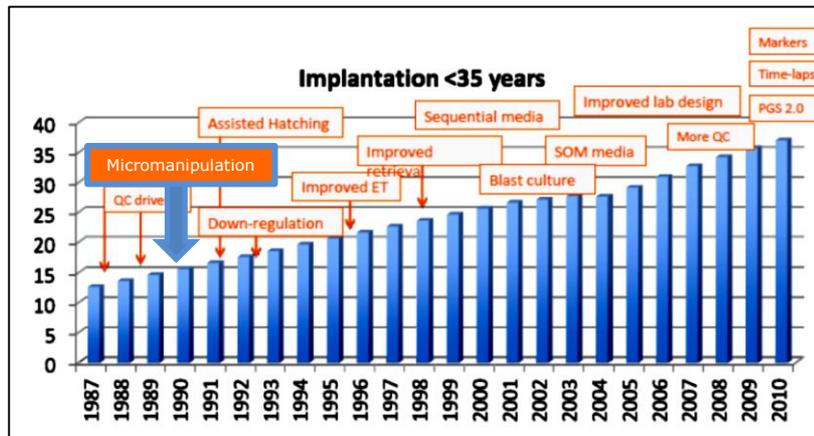
- Environmental conditions
- Gamete and embryo manipulation
- In vitro culture conditions
- Embryo selection ...



ART Laboratory: past, present and future



TECHNOLOGICAL ADVANCES:



J Cohen, ALPHA 2012

ART LABORATORIES:

- Equipment
- Procedures
- Lab construction
- Witnessing
- Quality Management System

IVF PROGRAMME I.U.DEXEUS



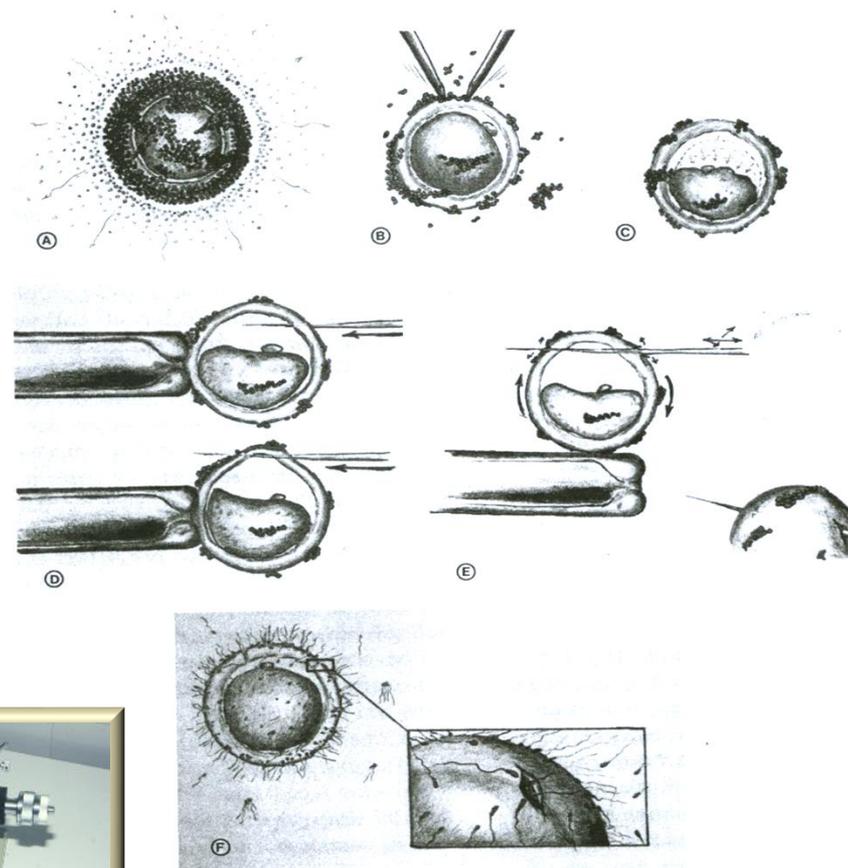


- 12.07.1984
First IVF birth in Spain
- 21.07.1987
First birth in Spain with frozen-thawed embryos
- 24.11.1988
First birth in Spain after egg donation
- 18.12.1990
First birth in Spain after PZD
- 15.03.1994
First birth in Spain after PGD (Haemophilia)
- 24.08.1994
First birth in Spain after ICSI
- 28.07.2006
First birth in Spain with IVM

- MICROINSEMINATION

PZD

SUZI



Malter HE & Cohen J, 1989



• MICROMANIPULATION

ICSI – Intracytoplasmic Sperm Injection

1992 Palermo. Lancet 340:17-18

REPRODUCTION
ANNIVERSARY REVIEW

Development of ICSI

C L O'Neill, S Chow, Z Rosenwaks and G D Palermo

The Ronald O. Perleman and Claudia Cohen Center for Reproductive Medicine, Weill Cornell Medicine, New York, New York, USA

Correspondence should be addressed to G D Palermo; Email: gdpalerm@med.cornell.edu

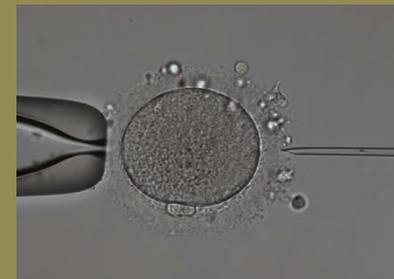
This paper is part of an Anniversary Issue celebrating 40 years of in vitro fertilization. The Guest Editor for this section was Professor Lord Robert Winston.

Human Reproduction vol.10 no.11 pp.2835-2838 1995

Intracytoplasmic sperm injection versus conventional in-vitro fertilization: first results

G. Calderón¹, I. Belil, B. Aran, A. Veiga, Y. Gil, M. Boada, F. Martinez, N. Parera, B. Coroleu, J. Penella and P.N. Barri

Reproductive Medicine Service, Department of Obstetrics and Gynecology, Instituto Universitario Dexeus, Paseo Bonanova 69, Barcelona 08017, Spain



- MICROMANIPULATION



At present, ICSI remains the preferred insemination protocol, with some centers using it in >90% of their insemination cycles.

It is possible that ICSI will be perceived by future generations as the evolution of standard in vitro insemination.

THE STORY OF ICSI

G. Palermo, C. O'Neill, S. Chow, Z. Rosenwaks

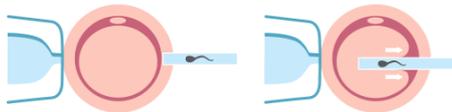
In: FORTY YEARS OF IVF

Fertility & Sterility, July 2018

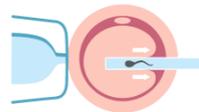
• MICROMANIPULATION

PIEZO-ICSI

PIEZO-ICSI



Without deforming the oocyte, the injection pipette penetrates the zona pellucida.

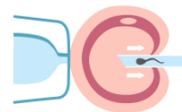


Perforate the plasma membrane with a simple footswitch control to activate the PMM driver.

Conventional-ICSI



The oocytes are deformed with a sharp pipette in the attempt to penetrate the zona pellucida.



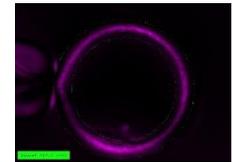
The timing of plasma membrane perforation is difficult to predict, damaging the oocyte is a distinct possibility.

J Assist Reprod Genet (2015) 32:1827–1833
DOI 10.1007/s10815-015-0597-9

TECHNOLOGICAL INNOVATIONS

Clinical efficiency of Piezo-ICSI using micropipettes with a wall thickness of 0.625 μm

Kenichiro Hiraoka¹ · Seiji Kitamura²



IMSI

Don't Let Them Zoom Off!

Zoom in – without losing the specimen from view and make your selection.

- Evaluate sperm morphology with a magnification of up to 50,000x
- Perform both IMSI and ICSI on one single system

Discover the perfect in detail – 4kbit up to your laptop. Details not optical quality.

www.leica-microsystems.com

Living up to Life

POLARIZED LIGHT

IX3-ICSI/IMSI Inverted Microscope
ICSI/IMSI Platform

Additionally, a new automated solution is available, providing single button touch control for the ICSI/ polarization/ IMSI workflow

OLYMPUS

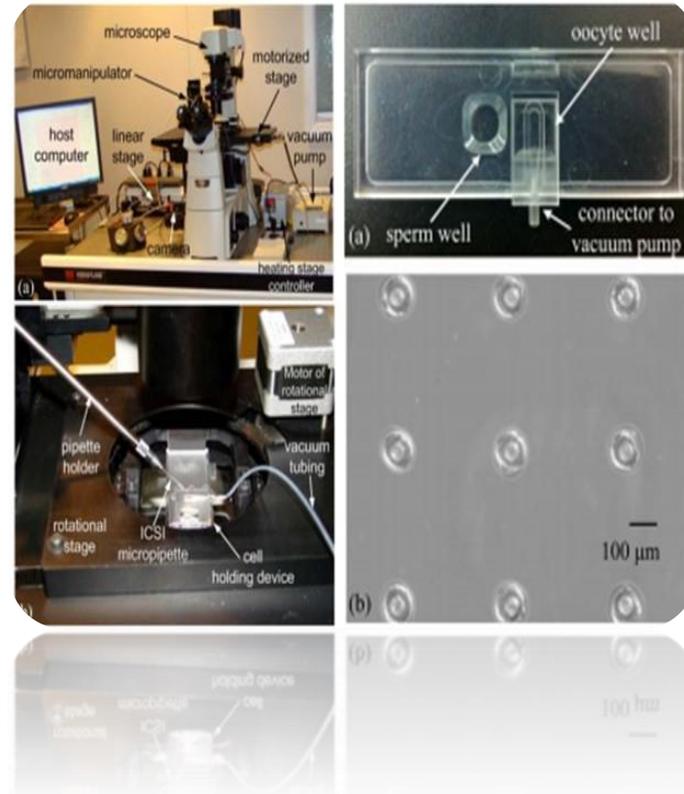
- MICROMANIPULATION

Is this true? Is it a real option?

When it will be available?

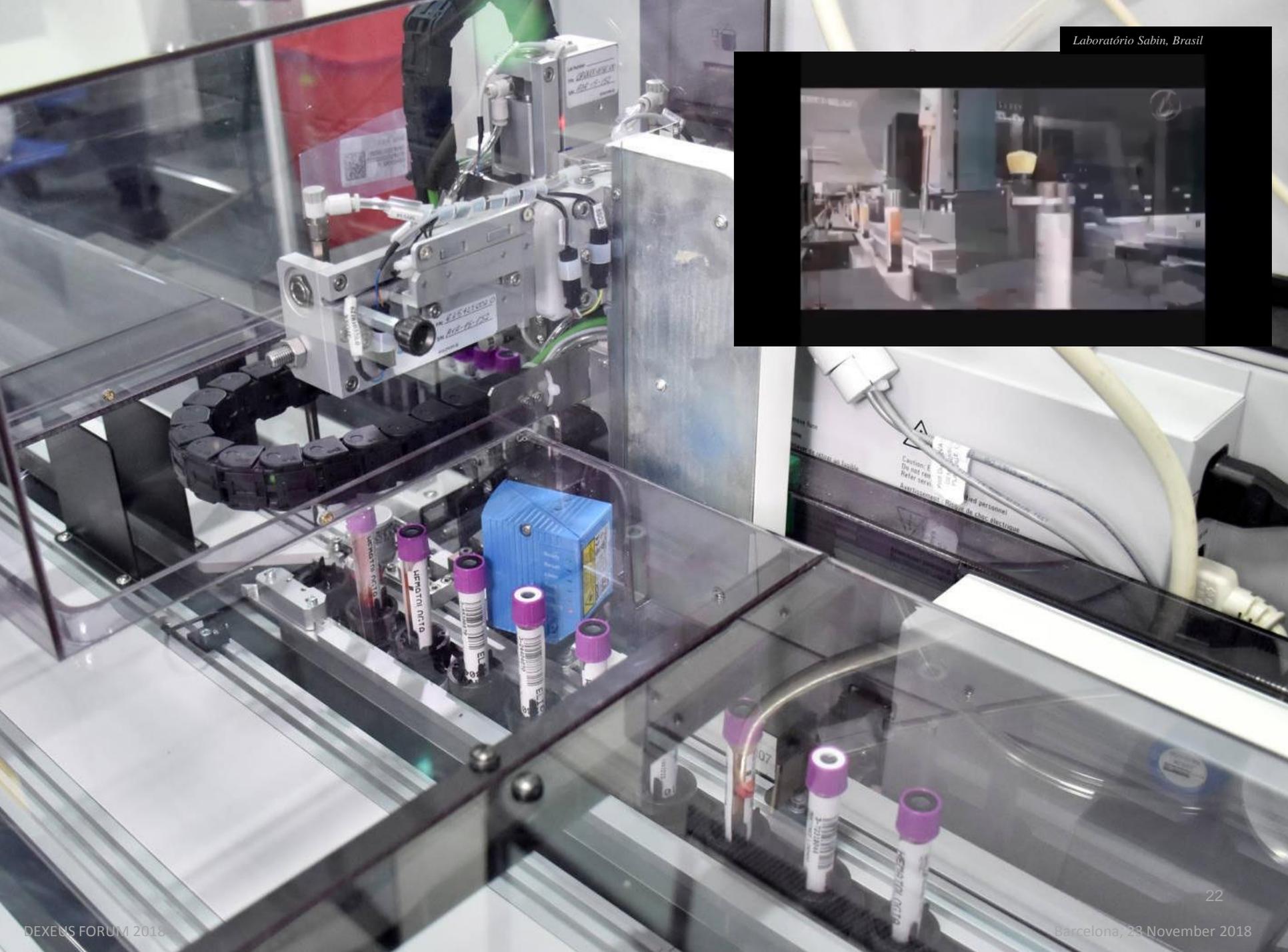
- Suitable for all cases?
- It will really improve results?
 - Fertilization rate
 - Damaged oocytes

Robotic ICSI



Zhe Lu, Member, IEEE, Xuping Zhang, Member, IEEE, Clement Leung, Navid Esfandiari, Robert F. Casper, and Yu Sun*





ART Laboratory: past, present and future

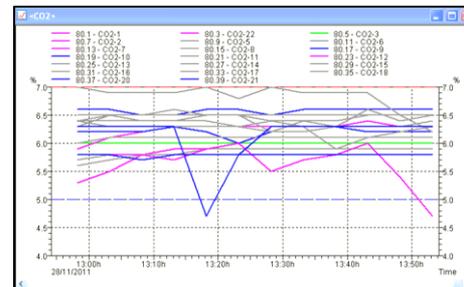
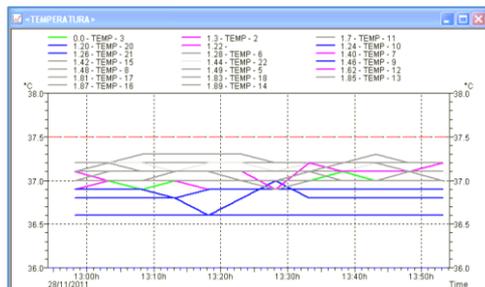
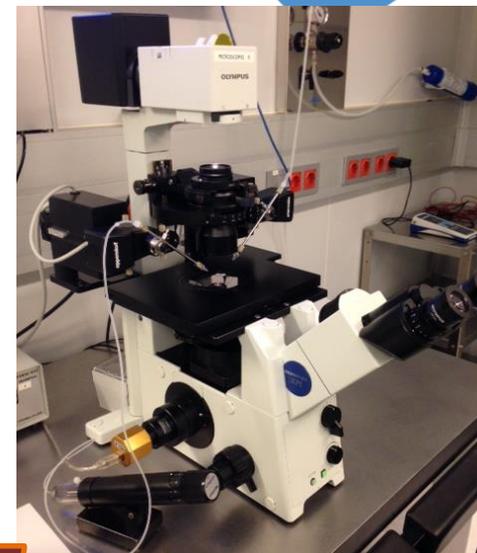
- EMBRYO CULTURE AND SELECTION



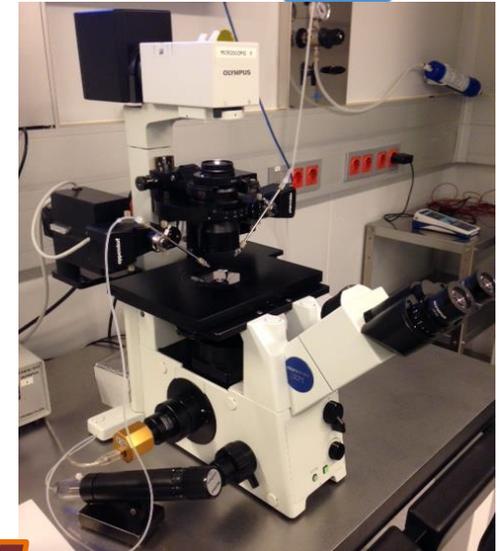
ART Laboratories



• EMBRYO CULTURE AND SELECTION



• EMBRYO CULTURE AND SELECTION



Key Benefits Time-lapse Integrated Incubators:

- 1- Undisturbed culture in a stable environment. Improvement culture conditions
- 2- Constant surveillance of all embryos. More information

ART Laboratories



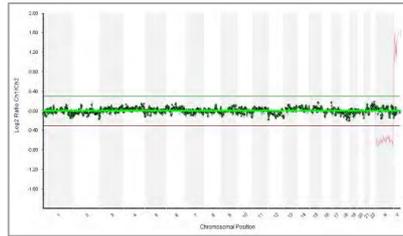
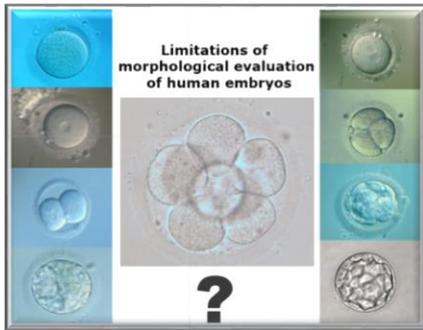
morphological assessment
is enough?



?



• EMBRYO CULTURE AND SELECTION



Mol Hum Reprod. 2016 Oct 22;10(10):704-718. Epub 2016 Aug 30.

Assessment of human embryo development using morphological criteria in an era of time-lapse, algorithms and 'OMICS': is looking good still important?

Gardner DK¹, Balaban B².

Cell Res. 2017 Aug 27;6:967-988. doi: 10.1038/cr.2017.82. Epub 2017 Jun 16.

Single-cell multi-omics sequencing of mouse early embryos and embryonic stem cells.

Guo F^{1,2,3,4}, Li L^{1,2}, Li J^{1,2,3,5}, Wu X^{1,2,5}, Hu B^{1,2}, Zhu P^{1,2,5}, Wen L^{1,2}, Tang F^{1,2,3}.

Nat Cell Biol. 2018 Jul 20;7(7):847-858. doi: 10.1038/s41556-018-0123-2. Epub 2018 Jun 18.

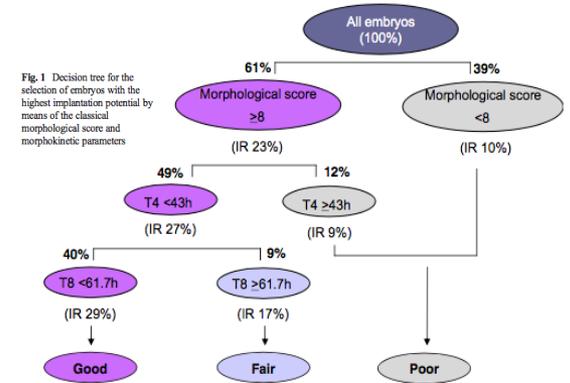
Single-cell multi-omics sequencing of human early embryos.

Li L^{1,2}, Guo F³, Gao Y^{1,2}, Ren Y^{1,4}, Yuan P^{1,4}, Yan L^{1,4,5}, Li R^{1,4}, Lian Y^{1,4}, Li J^{1,2,6,7}, Hu B^{1,2}, Gao J^{1,2}, Wen L^{1,2}, Tang F^{8,9,10}, Qiao J^{11,12,13,14}.

J Assist Reprod Genet (2017) 24:983–990
DOI 10.1007/s10883-017-0015-x
EMBRYO BIOLOGY

Selecting embryos with the highest implantation potential using data mining and decision tree based on classical embryo morphology and morphokinetics

Bontré-Carrasco¹, Gamma Arroyo¹, Yolanda Gil¹, M-José Gómez¹, Ignacio Rodríguez¹, Pedro N. Barri¹, Anna Vega^{1,2}, Montserrat Boada¹



Future ART Laboratories

Full in vitro fertilization laboratory mechanization: toward robotic assisted reproduction?

Marcos Meseguer, Ph.D.,^a Ulrich Kruhne, Ph.D.,^b and Steen Laursen, Ph.D.^c

^aInstituto Valenciano de Infertilidad, Universidad de Valencia, Valencia, Spain; ^bCenter for Process Engineering and Technology, Technical University of Denmark, Lyngby, Denmark; and ^cIVF-SYD, Fredericia, Denmark

Fertility and Sterility® Vol. 97, No. 6, June 2012

Human Reproduction, Vol.27, No.2 pp. 303–313, 2012
Advanced Access publication on December 12, 2011 doi:10.1093/humrep/der414

human reproduction OPINION

When and how should new technology be introduced into the IVF laboratory?

Joyce Harper^{1,*}, M. Cristina Magli², Kersti Lundin³,
Christopher L.R. Barratt⁴, and Daniel Brison⁵



“Every procedure involving application to the human body should be defined as experimental until adequate scientific evidence is provided regarding its safety and efficacy” UCL- Joyce Harper, Barcelona 2014

Experts strongly recommend that new techniques should only be used routinely after randomized control trials have confirmed that the technique is of benefit and all safety issues have been addressed.



40 years of IVF. Congratulations!



Thank you very much for your attention!



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