

Cryo-management & Safety

Achilleas Papatheodorou

PhD, M.Med.Sci., ESHRE Senior Embryologist

Embryolab Lab Director

Embryolab Academy Board Member

Conflict of Interest:

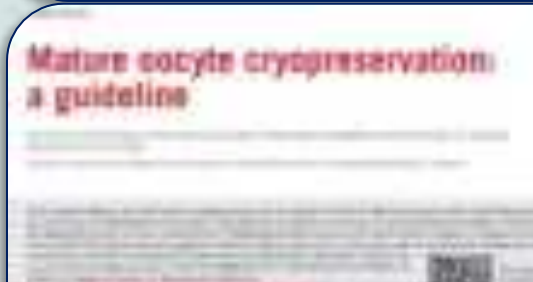
None

Vitrification



Kuwayama M. Highly efficient vitrification for cryopreservation of human oocytes and embryos: the Cryotop method. Theriogenology. 2007

Vitrification soon Transformed Our Routine Practices ...

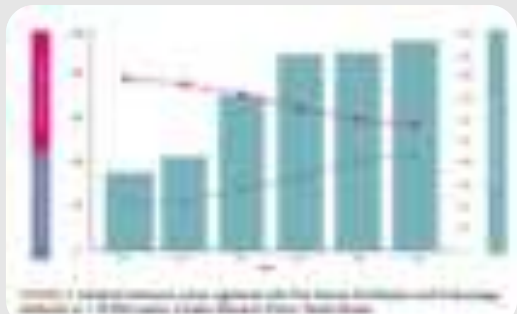
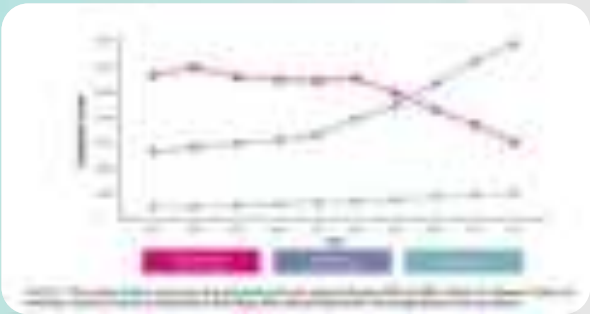
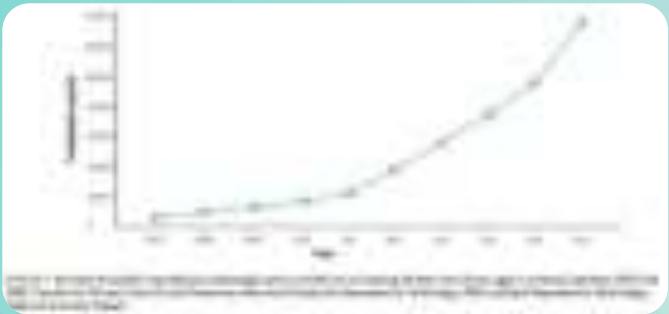


Elective Freeze All Strategies



- High Responders – OHSS
- Low Responders – Embryo Banking
- All patients ?

Embryo Vitrification



Embryo cryopreservation and utilization in the United States from 2004–2013

Mindy S. Christianson, M.D.,^a Judy E. Stern, Ph.D.,^b Fangbai Sun, M.P.H.,^c Heping Zhang, Ph.D.,^d Aaron K. Styer, M.D.,^e Wendy Vittek, M.D.,^f and Alex J. Polotsky, M.D.^g

^aDivision of Reproductive Endocrinology, Johns Hopkins University School of Medicine, Baltimore, Maryland; ^bObstetrics and Gynecology, Dartmouth-Hitchcock, Lebanon, New Hampshire; ^cCollaborative Center for Statistics in Science, Yale School of Public Health, New Haven, Connecticut; ^dColorado Center for Reproductive Medicine (CCRM) Fertility Clinic, Boston, Massachusetts; ^eUniversity of Rochester School of Medicine and Dentistry, Rochester, New York; and ^fObstetrics and Gynecology, University of Colorado Denver, Denver, Colorado

Objective: To evaluate the quantity and use of embryos cryopreserved at assisted reproductive technology (ART) clinics in the United States from 2004 through 2013 and to characterize trends in ART cycles in which all embryos were cryopreserved.

Design: Retrospective analysis.

Setting: Not applicable.

Patients(s): Registry data from the Society for Assisted Reproductive Technology.

Intervention(s): Historical cohort of U.S. ART cycles reported to the Society for Assisted Reproductive Technology Clinical Outcomes Reporting System between 2004 and 2013.

Main Outcome Measure(s): Number of embryos cryopreserved and factors associated with having cryopreserved embryos.

Result(s): The percentage of fresh cycles in which all embryos were frozen increased dramatically each year after 2010: 15.6% (2010), 19.9% (2011), 30.7% (2012), and 42.7% (2013). During 10 years, 1,994,548 embryos were cryopreserved and 717,145 embryos were transferred. In freeze-only cycles from 2004 to 2013, there was a significant increase in the percentage of women with diminished ovarian reserve (19.9% to 34.1%) and in those who used preimplantation genetic testing (1.2% to 6.9%). During the 10-year period, there were 244,576 fresh cycles with embryo transfer and at least one embryo cryopreserved. Overall, 52.9% ($n = 154,543$) did not undergo a subsequent frozen embryo transfer, 29.5% ($n = 40,462$) were left with no frozen embryos, 50.4% ($n = 68,875$) had one embryo, and 20.0% ($n = 27,396$) had \geq six. Factors associated with having excess embryos included donor oocyte cycles and increased antimiterlin hormone levels.

Conclusion(s): There has been a sharp increase in U.S. ART cycles in which all embryos are frozen and this may result in more embryos in storage. (Fertil Steril Rep® 2020;1:71–7. ©2020 by American Society for Reproductive Medicine.)

Key Words: Embryo cryopreservation, embryo disposition, in vitro fertilization

Discuss: You can discuss this article with its authors and other readers at <https://www.fertsteridialog.com/users/16110-fertility-and-sterility/posts/sfre19-00001>

With the evolution of techniques in human assisted reproductive technology (ART), many more fertilized eggs and early embryos are created than can be safely transferred to a woman's uterus.

To avoid the morbidity of multiple gestation, embryo cryopreservation has developed as a routine practice among U.S. ART clinics (1). Despite the clinical advantages that embryo cryopreservation provides, it also presents new

ethical, legal, and healthcare policy challenges. As a result of the prevalent practice of embryo cryopreservation, in 2003 it was estimated that at least 400,000 cryopreserved embryos were in storage at that time in the United States (1). Couples primarily have five choices regarding disposition of supernumerary embryos: save the embryos for a future embryo transfer cycle, donate embryos for research, thaw and discard, donate their embryos to another intended parent, or continue to store embryos. Evidence suggests, however, that many embryos remain in storage with no specific plan for future use because the majority of patients delay the final disposition decision (1).

Received January 1, 2020; revised May 23, 2020; accepted May 29, 2020. M.S.C. has nothing to disclose. J.E.S. has nothing to disclose. F.S. has nothing to disclose. H.Z. has nothing to disclose. A.K.S. has nothing to disclose. W.V. has nothing to disclose. A.J.P. has nothing to disclose. Supported by the Clinical Research Scientist Training Program, Eunice Kennedy Shriver National Institute of Child Health and Human Development (R01HD075721). Report requests: Mindy S. Christianson, M.D., Johns Hopkins University School of Medicine, Division of Reproductive Endocrinology, 72531 Falls Rd, Suite 280, Baltimore, MD 21285 (E-mail: mchris21@jhmi.edu).

Fertil Steril Rep® Vol. 1, No. 2, September 2020 2666–2681
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<https://doi.org/10.1016/sfre.2020.05.010>

Planned Oocyte Cryopreservation (POC)

Planned oocyte cryopreservation to preserve future reproductive potential: an Ethics Committee opinion

Recommendation of the National Committee for Bioethics
November 2014

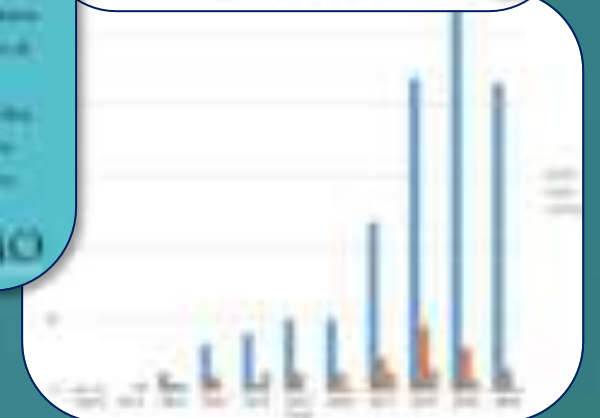
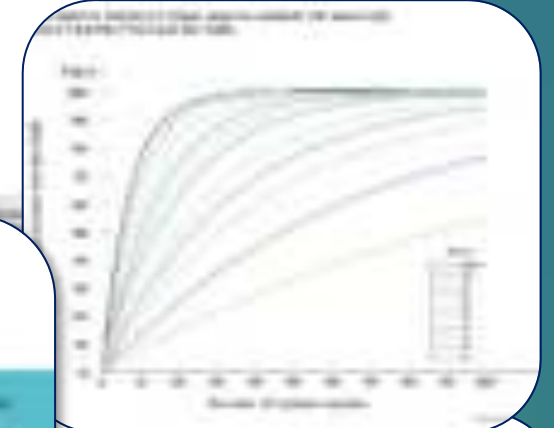


Planned oocyte cryopreservation: the state of the ART

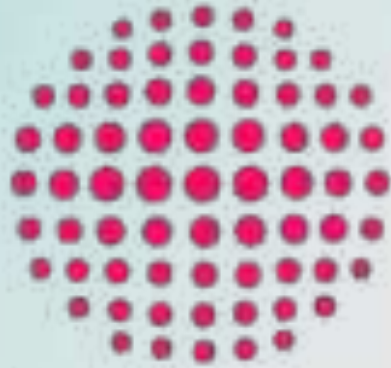
Isabelle Drelich, Université de Bordeaux
Myriam Lecomte, Université de Bordeaux

Planned oocyte cryopreservation (POC) is a reproductive technology that allows women to preserve their fertility for future use. It involves the collection of oocytes, their freezing, and their subsequent thawing and fertilization. This technology is particularly relevant for women who are delaying childbearing or who are facing a high risk of infertility due to medical treatments. The ethical implications of POC are complex, involving issues of autonomy, informed consent, and the potential for commercialization. This document provides an overview of the current state of the art in POC, including the latest research and clinical practice.

REMO



Donor Oocyte Banking





Additional Contributory Factors

Improved Culture Systems

Increasing use of SET

1 embryo per carrier system

More than >10 MII for POC

Two-three oocytes per carrier system

Prolonged storage

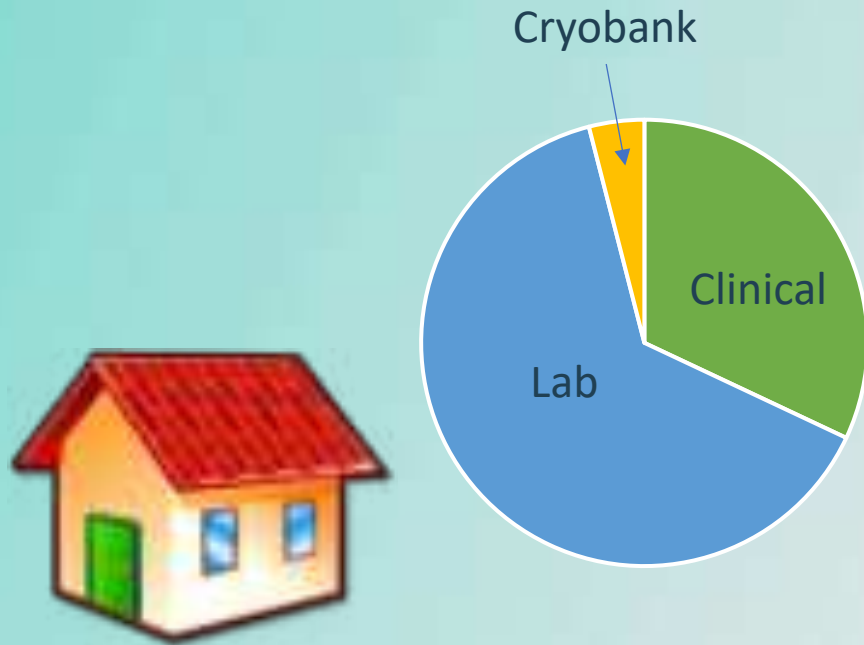
Mosaic embryos

Abnormal Embryos & Bioethical dilemmas

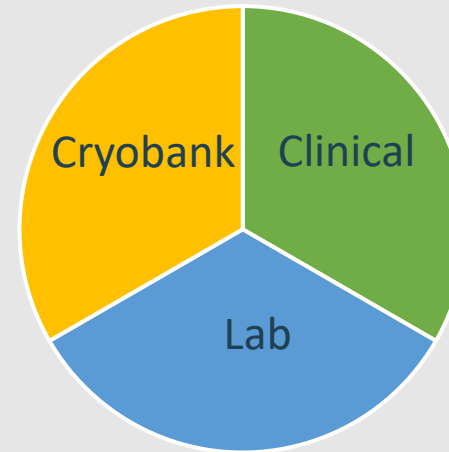
Unused and unclaimed Embryos/Oocytes

Advancements in PGT

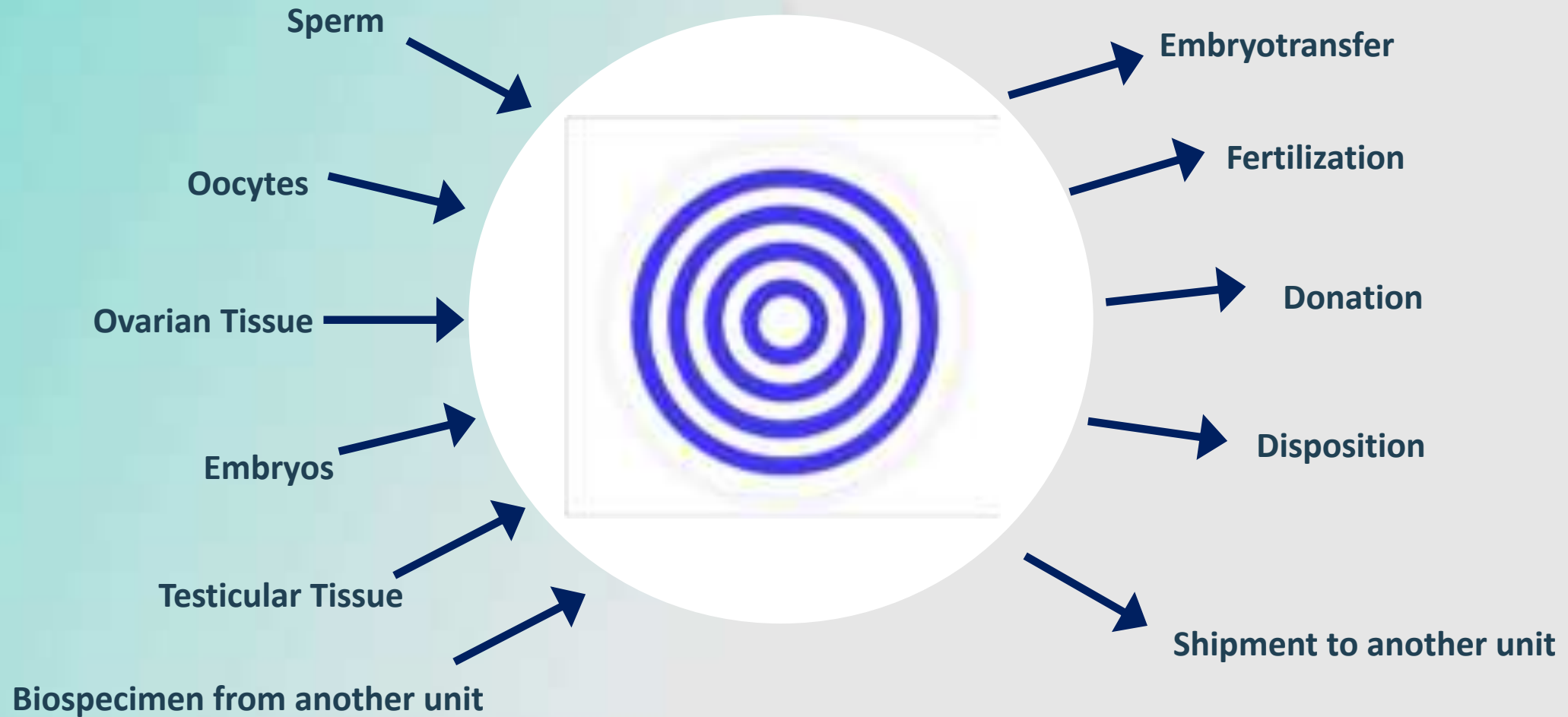
Cryobanks in 2000



Cryobanks in 2025



CRYOBANKS in Next Gen ART Units





Cryostorage of reproductive tissues in the in vitro fertilization laboratory: a committee opinion

Committee on the Ethical and Legal Aspects of Human Reproductive Medicine
National Academies of Sciences, Engineering, and Medicine
National Academies Press
2019



Quality Systems

- ✓ **Mandatory** (Legal requirement, Professional guideline)
- ✓ **Voluntary** (Good practice)



*..It is in the interest of **competent laboratories** that **OUR** competence is verified through a process of inspection and compared against appropriate standards as a confirmation of **OUR** good standing..*





“In an IVF lab, frozen sperm, oocytes or embryos **are absolutely priceless** and quite rightly patients who consent to storage, they expect the **best possible condition**.

It is therefore imperative that patients and other users of the services such as oncologists, gynecologists and general practitioners are reassured that **quality systems are in place** to look after their samples for the entire storage period, which, of course may be many years”.

Tomlison M., HR, 2005



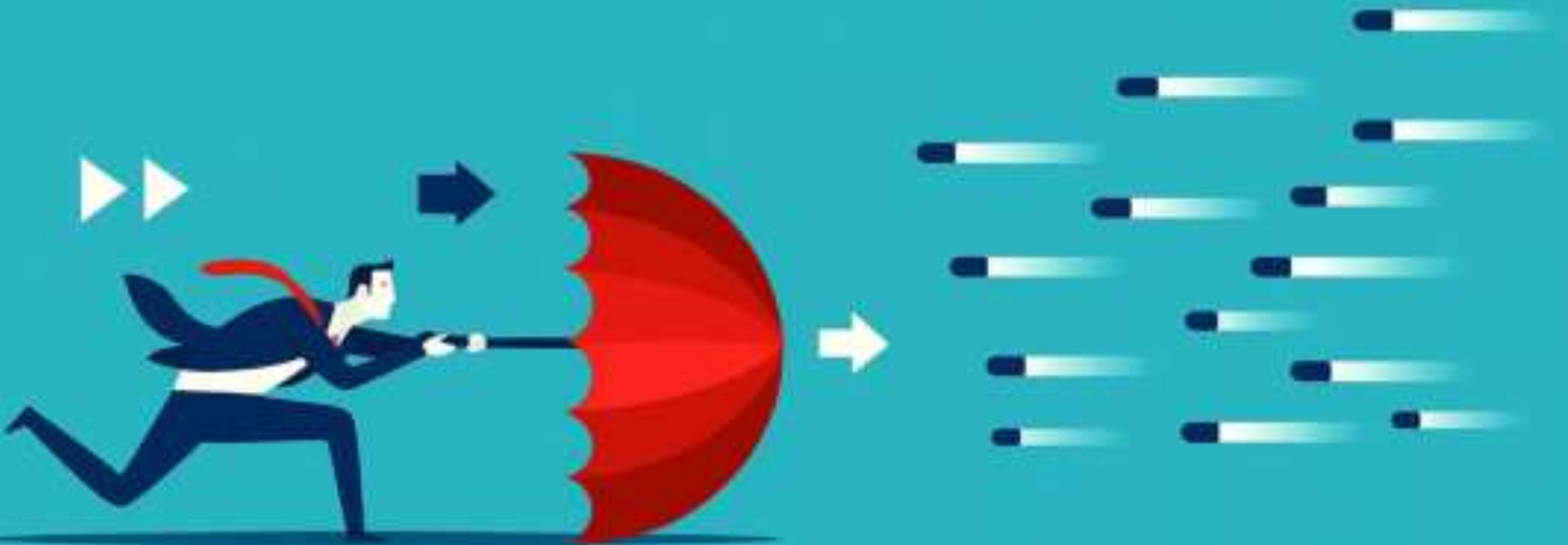
Risk Management makes THE difference

System not
prepared when an
unforeseen event
occurs!
System crashes!

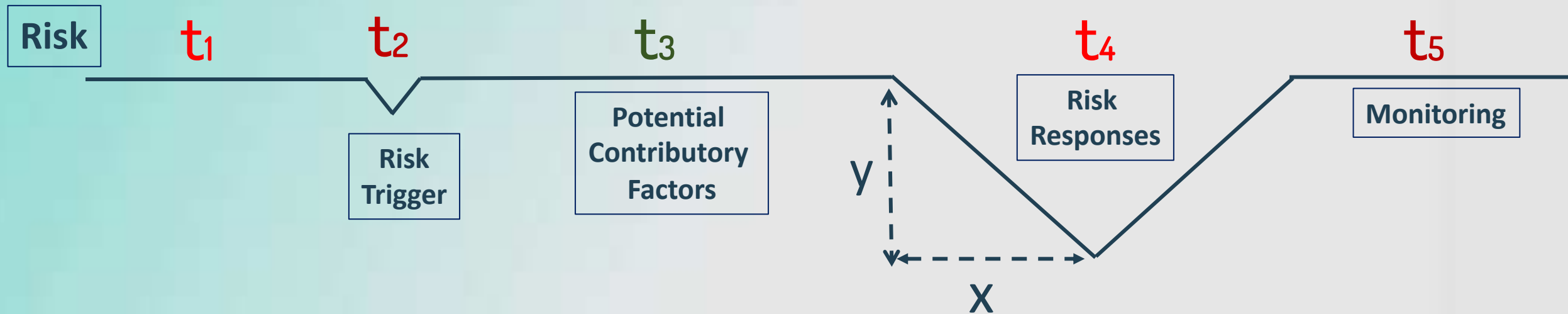


All the risks are
actively assessed,
managed,
prevented
corrected and
eliminated

Cryobank: A Risk Averse System with ZERO Tolerance to Errors!!



The Anatomy of Each Cryo-Risk



Cryobanks in Next Gen ART Units: The Operational Axes

Equipment & Maintenance

Techniques, Procedures & SOPs

Sample Safety & Traceability

Personnel & Training

Personnel Safety

Sample Transportation

Emergency plan

Litigation

Data Safety

Lessons learned

Management of unused embryos

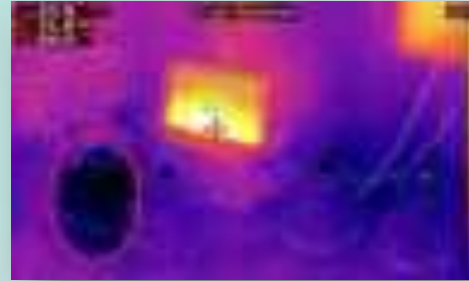
Human factor

1. Equipment & Maintenance

Dewars



Alarm Systems



Monitoring Systems



Equipment

1. Your **Decisions** will determine
the Profile of your Cryobank

Type of Dewars
Storage Conditions
Carrier System
Storage Location
Monitoring System
Alarm systems

2. Each Decision brings Different Risks
into your Cryobank!

3. Risks you need to Address and mitigate



Storage Capacity

- Larger Tanks
- Re-design Extend Cryo-room
- Increase LN2 Supply
- Increase and minimum storage LN2 quantity
- Central installation and LN2
- LN2 production system
- External storage for long term samples



Maintenance

- Daily /Periodic/Continuous Monitoring- QC
- Alarm systems
- Refiling of LN2 procedure
- Visual inspection of the Dewars
- Cleaning Protocols (dewars, cannisters, goblets etc)
- Dewar Validation Protocols
- Replacement of old or a Malfunctioning Dewar
- Cleaning/Validations of a new Dewar
- Emergency plan in case of a tank failure
- Measures Sample Contamination

Techniques, Procedures & SOPs



- Consent forms
- Carrier systems-consumables
- Cryopreservation media
- Cryopreservation protocols
- Labeling system
- Infectious samples
- Samples received from other units
- Resources
- Administration
- Training
- SOPs

- Storage vessels
- LN₂ monitor system
- LN₂ supply system
- Alarms
- Traceability
- Storage of infectious samples
- Vessel maintenance
- Replacement- Cleaning
- Storage duration
- Training
- SOPs

- Thawing protocols
- Thawing media
- Consumables
- Consent form
- Samples shipped to other units
- KPIs
- Culture post thaw
- Discard samples
- Training
- SOPs

Techniques, Procedures & SOPs

Safe and High Performing Processes!



Processes must be :

Optimized

Standardized

Monitored



Sample Safety & Traceability During Storage

Human Reproductive Cell Cryopreservation, Storage, Handling, and Transport: Risks and Risk Management

Shira Wilson, PhD, MEd¹ | Ludovica Ferraguti, PhD²

¹New York University, New York, New York
²Embryolab, Madrid, Spain

¹Embryolab, Madrid, Spain
²Embryolab, Madrid, Spain

www.embryolab.com

Abstract

Millions of human oocytes and embryos are stored in thousands of facilities across the globe. This presents a unique risk to the cryopreservation of human reproductive cells and embryos. The results of studies assessing pregnancy and neonatal outcomes following storage of human reproductive cells and embryos are presented.

Keywords

human reproductive cells, cryopreservation, storage, handling, transport, risks, risk management

- ✓ Prolonged Storage
- ✓ Storage conditions & Temperature Fluctuations
- ✓ Unintended warming:
 - *Human error*
 - *Equipment Failure*

Sample Safety & Lessons Learned

Lawsuit frequency and claims basis over lost, damaged, and destroyed frozen embryos over a 10-year period

Source: Embryolab, Inc. © 2017. All rights reserved.
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Journal Pre-proof

Journal Pre-proof

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Management of Unused and Unclaimed Embryos/Oocytes

Embryo cryopreservation and utilization in the United States from 2004–2013

- Educate patients
- Informed Consent Forms
- Clear Disposition Options
- Regular contact with the patient
- Good billing practices
- Recruitment of a 3rd party service



Personnel Safety

Oxygen monitoring with Alarm

Forced ventilation

Training of staff

Nitrogen is odorless, colorless, and tasteless and may produce asphyxia

1 Liter LN₂ produce
700 liters Nitrogen gas

Emergency Plan



Development of an emergency plan for in vitro fertilization programs: a committee opinion

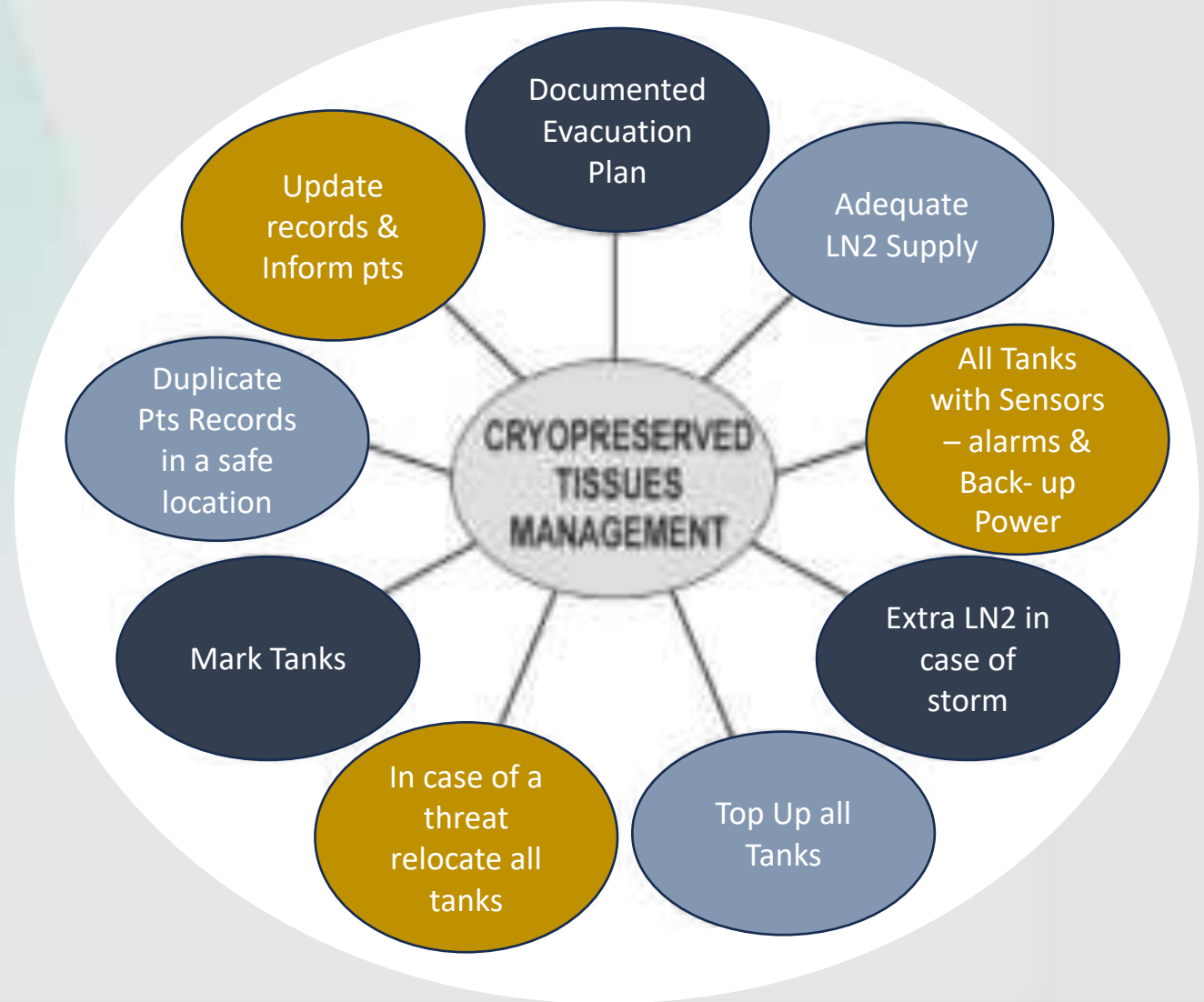
Printed (approved) at the American Society for Reproductive Medicine, 114 Society for Human Reproduction Building, and the Society of Reproductive Medicine and Gynecology.
Approved by the American Society for Reproductive Medicine, American Society

Disaster preparedness in assisted reproductive technology

Received 15 November 2005; accepted 15 November 2005; first published online 15 November 2005

© 2005 Blackwell Publishing Ltd, *Journal of Internal Medicine* 258: 105–112

Emergency Plan - When Disaster Strikes



Sample Transportation

Human Reproductive Cell Cryopreservation, Storage, Handling, and Transport: Risks and Risk Management

Mina Alkass, PhD, HCDD¹ | Lodoico Parmegiani, PhD²

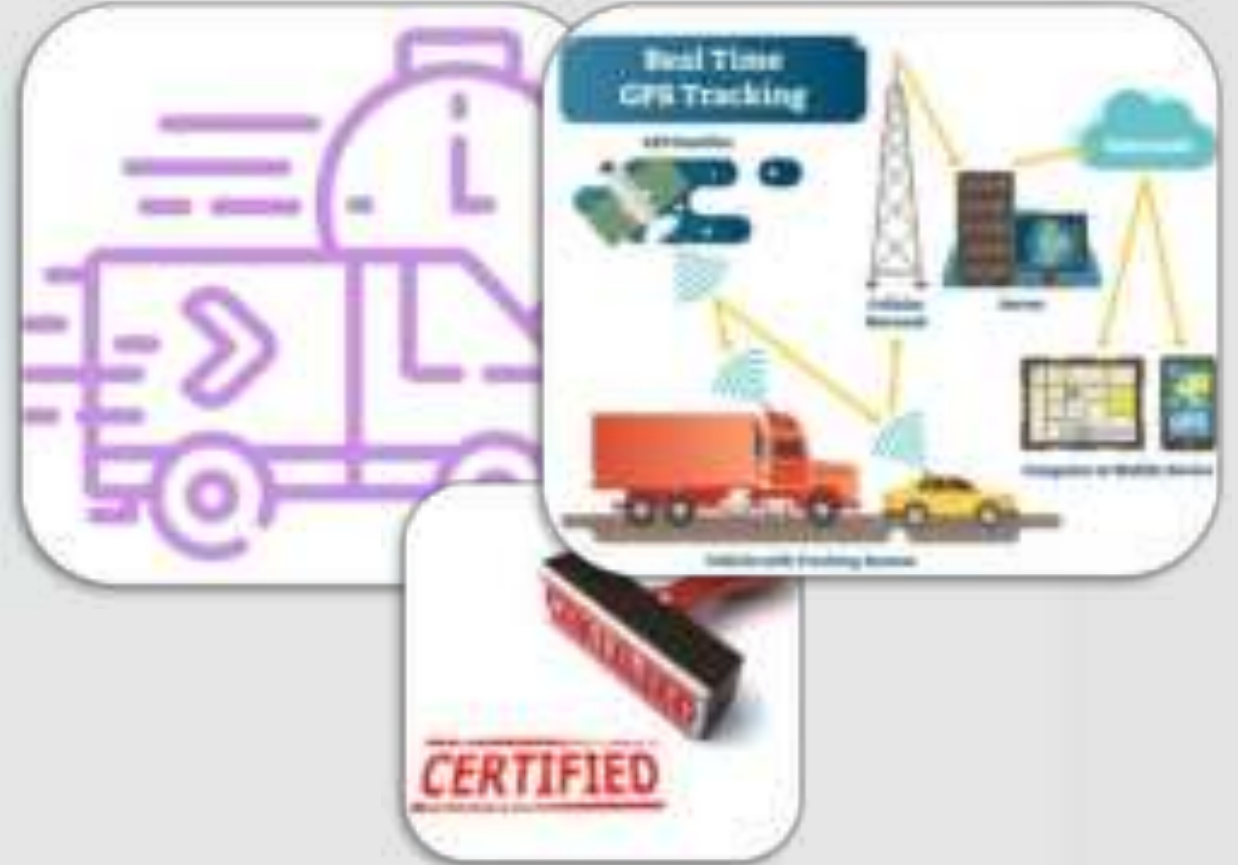


Sample Transportation

Storage, transport, and disposition of gametes and embryos: legal issues and practical considerations

HA A. Wright, BA, BBA, CD

LegalCounseling.com, Walnut Creek, CA, USA



Data Safety



HACK BRIEF: HACKERS ARE HOLDING AN LA HOSPITAL'S COMPUTERS HOSTAGE



AUTHOR: BRIAN BARRETT.
SECURITY DATE OF PUBLICATION: 02.16.16.
TIME OF PUBLICATION: 5:26 PM

- ✓ Role/user based access
- ✓ Fire walls
- ✓ Internet Filter
- ✓ No USB policy
- ✓ Antivirus programs
- ✓ AntiSpyware and AntiMalware
- ✓ Monitored Network Attached Storage (NAS)
- ✓ Several daily back ups
- ✓ Several Back up Servers

Law-Regulations-Guidelines



Personnel Training

Cryobiology Principles

Procedures

Logbook

Audits and DOPs

External Quality Assessment

- ✓ Cryo protocols
- ✓ Labelling
- ✓ Positioning
- ✓ Emergency plans
- ✓ Safe use of LN2
- ✓ LN2 Monitoring
- ✓ Tank Validation
- ✓ Sample Transportation
- ✓ Administration
- ✓ Cryo sample disposition
- ✓ Patient Counselling



Staffing in Next-Gen Cryobanks

Health Affairs. 2014;33(10):1700-1704. doi: 10.1371/journal.pone.0141140.
Epub 2014 Oct 15.

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

Wong JH, et al. *Health Affairs*. 2014;33(10):1700-1704.
doi:10.1371/journal.pone.0141140.

Recalculating the staff required to run a modern assisted reproductive technology laboratory

E. Veiga^{1,2}, C. Olmos^{1,2}, J. Sills^{1,2}, A. Pineda^{1,2}, E. Fuster^{1,2}, and R. Ortiz^{1,2}

FERTILITY & REPRODUCTION

Guidelines for Best Practice for Staffing of ART Laboratories and Professional Development of IVF Scientists

By Robert H. ...

Best practice for embryology staffing in IVF licensed assisted reproduction centers: guidance from Association of Reproductive & Obstetrical Scientists

Robert H. ...

Cryobank Adverse Events



**Damaged frozen embryos:
do you have a compensation
claim?**



Hayley Lewis
Associate / Medical negligence

[Read the blog post](#)

ALABAMA'S SUPREME COURT RULED FROZEN EMBRYOS ARE CHILDREN. IT COULD HAVE CHILLING EFFECTS ON IVF, CRITICS SAY



"If the policy outcomes mandated under this decision stand, the consequences will be profound. Modern fertility care will be unavailable to the people of Alabama, needlessly blocking them from building the families they want... Clinics will be forced to choose between providing sub-optimal patient care or shutting their doors."

-ASRM President Dr. Paula Amato, MD

ESHRE statement

March 2024

ESHRE condemns the recent Alabama supreme court ruling





The Future Of Cryostorage



SCIENTIFIC JOURNAL ARTICLE

Deep technology for the optimization of cryostorage

Authors: J. Doe¹, G. Smith²

Journal: Cryobiology, Volume 123, Number 4, April 2021, Pages 123-130

Abstract:
Cryopreservation is a critical technology for the storage of biological samples. This paper discusses the challenges of cryopreservation and the role of deep learning in optimizing the process. The authors present a novel deep learning model that can predict the optimal cryopreservation conditions for a given sample. The model is trained on a large dataset of cryopreservation experiments and is able to generalize to new samples. The results show that the model can significantly reduce the time and cost of cryopreservation while maintaining the viability of the samples.

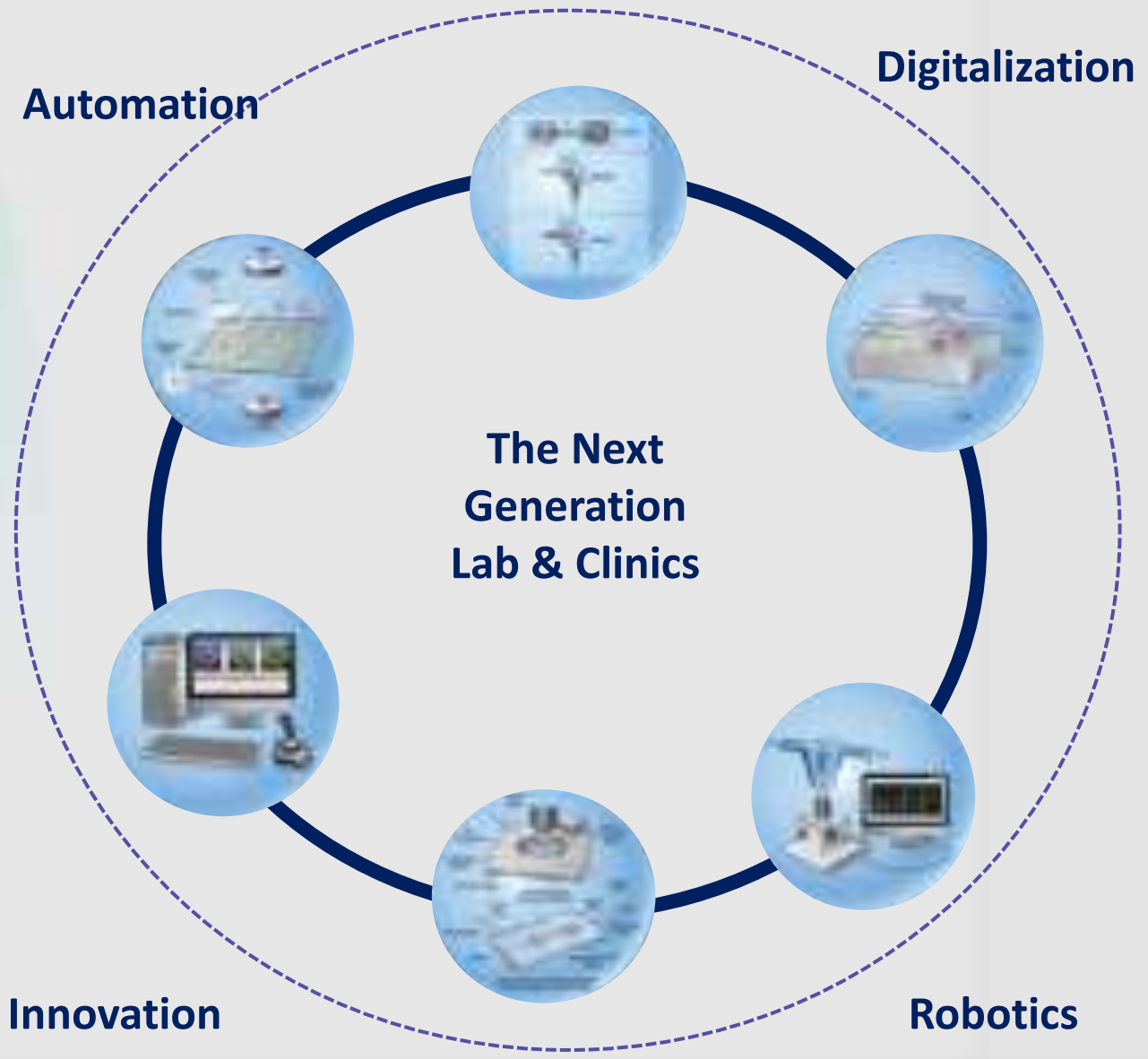
SCIENTIFIC JOURNAL ARTICLE

Automation in ART: Paving the Way for the Future of Infertility Treatment

Authors: A. Brown¹, B. Green², C. White³

Journal: Fertility and Sterility, Volume 115, Number 3, March 2021, Pages 456-465

Abstract:
Automation is a key technology for the future of assisted reproductive technology (ART). This paper discusses the challenges of automation in ART and the role of artificial intelligence (AI) in overcoming these challenges. The authors present a novel AI-based system that can automate the process of IVF. The system is trained on a large dataset of IVF procedures and is able to perform the tasks with high accuracy and efficiency. The results show that the system can significantly reduce the time and cost of IVF while improving the success rate.



AI - Automation - Robotics



Cryobanks & The Human Factor



- Vision
- Mission
- Commitment
- Leadership
- Improvement Opportunities
- Effective Inter and intra department communication
- Process Monitoring
- Process improvement
- Data & Issue Reporting



The role - position - recognition of Clinical Embryologists



Thank you for your attention!