

Systemic Reviews

Regulatory and Artificial Intelligence (AI) Advances and Impact on Global Access to OBGYN and IVF/ Third Party Reproductive Care

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The European Society of Human Reproduction and Embryology held its annual international meeting in Copenhagen, Denmark June 25 th – 28 th , 2023. NAPGO enlisted IVF & Life Sciences expert and journalist Lisa Ditkowsky to attend the Scientific Programme and report on the latest leading-edge developments in the REI space. Strong themes of artificial intelligence, third- party reproduction, government regulatory effects, and increased access to care permeated this exciting international conference.

What happens in North America when certain science, medicine and technology is not regulated, or is scarcely regulated, is that most entrepreneurs rush to innovate and say they are at the forefront of whatever the next big thing is. Whereas, in the European Union, the trend is to collaborate and put social welfare and results before publicity.

Nowhere is this stark contrast more apparent than with Artificial Intelligence and Third-Party Reproduction and the differences in the IVF and Life Sciences fields. In the EU and neighboring countries, we see large IVF clinics groups, such as IVIRMA Global (now KKR Private Equity owned) collaborating on AI work across the human embryology field, with their vast laboratory networks and partner hospitals and academic institutions across the world. In the USA and Canada, the tendency to put the cart before the horse is best evidenced in the media machine and press releases touting “smart money” funding rounds.

For almost 5 years, TMRW Life Sciences has promised the world fully robotic and automated IVF labs. The company originally debuted a movie-trailer quality teaser (2019) of what it set out to do. Few realized that TMRW was always the USA marketing arm of Brooks Life Sciences (now Azenta Life Sciences) attempts to create a fully automated robot to retrieve gametes from cryotanks via robots and RFID, therefore eliminating the human element. TMRW even put out press releases in Mandarin and other languages touting its fully robotic laboratory customers (would-be-robotic-IVF-clinic customers) throughout the United States. However, years later, and after many false promises, massive layoffs, and a just-appointed third CEO, TMRW Life Sciences does reportedly have software that is being used in IVF labs. The latest round of press releases again touts “50 fully automated labs,” while this is sheer impossibility and we still do not know what “fully automated” even means.

Since we are in the infancy of AI-meets-human-reproduction – and both are scarcely regulated globally - the “fully automated” and “AI-implemented” spectrums are as

open to interpretation and continual defining as the autism and dementia spectrums.

We can contrast the elusiveness of “fully automated robotic IVF labs” with Argentine billionaire Martin Varsavsky’s company Overture, with lead scientist, Santiago Munné; Overture is willing to show the world video evidence of their team’s first USA trials of robotic ICSI (Intracytoplasmic Sperm Injection), when the sperm is literally injected into the egg, and both the promise that the robotic technology holds, as well as the work it still needs to surpass manual ICSI.

The USA’s Cornell University has recently launched a number of Centers for AI and AI groups, and is assembling the USA and partners’ thought leaders and self-appointed thought leaders in the AI space.

The main difference with AI in the EU, China, Japan, Israel and throughout the Middle East is that the trials and innovation pre-date the press releases and lauded funding rounds, to the point that these countries many even have new medically relevant technologies to sell before they tell the world everything about them and their plans.

ARTIFICIAL INTELLIGENCE, HUMAN REPRODUCTION, AND THE TECHNOLOGICAL DIVIDE

IVF is only 46 years young, if judged by the first live human birth resulting from an embryo transfer into a traditional surrogate (the genetic mother). Louise Brown (45) was born in 1978 in England due to the medical success at Bourn Hall stewarded by Dr. Bob Edwards and Dr. Patrick Steptoe. Then, in 1981, Elizabeth Carr (41) was the first IVF baby born in the United States of America in Virginia, USA, under the guidance of Dr. Howard Jones and Dr. Georgeanna Jones.

In 2023, the IVF field is looking to apply work from much older industries than the nascent Assisted Reproduc-

tive Technologies field to optimize the still young field and make producing live births around the world more efficient and treatment outcomes more predictable. The difference in the EU and partner countries, versus the USA and partner countries, is that the EU is unapologetic about looking to outside industries for help in optimizing human reproduction. Whereas USA leaders tend toward secrecy or misleading about who their partners are. Ultimately, those IVF leaders who do not embrace a collaborative approach to moving IVF and ART into the future are going to be left behind and end up buying and licensing new technologies from the countries who are surging ahead with teamwork.

The world is experiencing a demographic decline, exacerbated by pandemic and politics, and the situation is dire. While embryology and ART are certainly miraculous fields, the medicine and science is by no means affordable, easily accessible, or optimized and efficient to most of the world. The access to care bell curve is steep due to cost and spotty public health and insurance coverages. It is often cited in the USA that at least 90 percent of infertile intended parents cannot access care. So, it is incumbent upon those advancing artificial intelligence and high-tech solutions to human reproductive care, to simultaneously solve affordability and access to care problems as they innovate.

In June 2023, the global think tank, International IVF Initiative (i3, www.IVFMeeting.com), hosted an online webinar on AI. An HCLD (High Complexity Lab Director) and embryologist, Christine Allen, told global leaders in science and medicine that to find answers to automating labs with AI, we need to look to computer engineering, biomedical engineering, robotics, software developments, etc. She astutely noted that if her peers only look within the narrow confines of healthcare and human reproduction, they will not find answers to solve problems with AI.

In Copenhagen June 25 – June 28, 2023, it was good to see that the 39th Annual ESHRE (European Society of Human Reproduction and Embryology) Annual meeting AI sessions brought in experts from outside of human reproduction and healthcare to speak. Even the American speakers mostly mentioned AI, regardless of the topic of their talks, to leave it on record that AI is front of mind. Dr. Marcelle Cedars from UCSF turned her “Future of ART” talk into a list of definitions of AI, no doubt to let USA’s global partners to know that ASRM is contemplating AI.

EUROPEAN REGULATION OF THIRD-PARTY REPRODUCTION AND ACCESS TO EQUAL HUMAN REPRODUCTIVE CARE

Two of the most globally relevant human reproduction care topics likely to remain in sharp focus now into 2024-2025 are: Regulation of Third-Party Reproduction and regulation of AI, as both impact global access to human reproductive care.

ESHRE is an unparalleled global forum for cutting-edge science, medicine and academic thought leadership, and 2023 in Copenhagen, Denmark closely mirrored 2018 in Barcelona, Spain. A key development was that the Expo was even more robust and commercial in 2023, with a probable

record number of startups, spinoffs and merged entities exhibiting their medical and scientific products and services.

Sunday, June 25th, 2023’s ESHRE Pre-conference Scientific Programme workshops lived up to their worthwhile reputation with almost two-dozen well-attended selections. For the purpose of worldwide medical press reporting, I elected to split the day between the two most relevant to finding ways to improve global access to human reproductive care. One workshop focused on European regulation of Third-Party Reproduction. The other workshop highlighted progress with employing AI for consistency and predictability of medical outcomes in IVF.

Janne Rothmar Herrmann, PhD, LL.M, LL.B, is a professor at University of Copenhagen focusing on legal regulation of health technology and healthcare. Professor Herrmann spoke on framing the rights of potential parents (known as “IPs” or intended parents in the United States). One of Herrmann’s ways of framing the discussion was in terms of original population control versus everyone’s right to have a family. She framed European Union rights to have a family in terms of the margin of appreciation. Margin of appreciation is a legal doctrine for balancing the rights of the EU member states with individual rights and requires being cognizant of differences in individual EU states.

The European Convention on Human Rights went into effect on September 3, 1953, forming the basis of the margin of appreciation. Herrmann said that it is difficult to develop a uniform statute of human rights across Europe, so lowest common denominator is often used. However, there is a wider margin when ethical or moral, which is reduced if Court identifies a consensus towards the recognition of certain rights. Its use by the Court is not always consistent in human reproductive issues.

The European Court must balance the member states, and Herrmann cited a gray area between knowing the human gamete donor and total prohibition (donor anonymity). The USA stands at a similar crossroads, and bioethicists cannot deny the reality that promises of “donor anonymity” are untrue, because DNA testing is leading to citizens finding their previously unknown genetic relatives every single day worldwide (mothers, fathers, brothers, sisters, cousins, etc.). For six years, we have witnessed bioethicists feign novelty with the same cartoon of a “DNA Tidal Wave” washing ashore. Yet, anonymous donor gametes (eggs, sperm, embryos) ping-ponging across the globe, often zigzagging from city to city to obscure sourcing, is the reality in an industry where the profit margins are through the roof, and the more anonymous eggs available, the bigger the profit margins.

Herrmann cited competing legal cases in the EU and said that there are likely to be continuing human rights issues and Third-Party Reproduction legal cases. The Court must balance the member states, but the Courts have not always applied the margin of appreciation consistently. Herrmann advised that Fertility treatment techniques fall within the sensitive area of regulation where states are given a wide margin of appreciation. However, the margin of appreciation might be narrowing, because a child’s rights always take precedence. Professor Herrmann notes that all the le-

gal cases on Surrogacy are on the effects of Surrogacy performed abroad. Gestational Surrogacy is when a non-genetically linked woman carries an embryo / fetus for the intended parent / parents and is compensated for use of her womb. In the United States, commercial surrogacy is legal, as it is in Russia and Ukraine. Though, USA is virtually the only country in the world that allows both single women and men, as well as gay couples, to both hire gestational surrogates and commercially compensate them with profit / income vs. only reasonable compensation for time and expenses.

Denmark implemented legislation to control population growth in the 1950s by preventing certain groups from procreating. This included sending mentally ill people and others targeted to specific islands and instituting forced sterilization and gender separation measures. Additionally, Denmark was responsible for putting IUDs in young women in Denmark as a form of birth control.

The motivation behind this population control is said to have been the rising population in Greenland, a Danish territory, along with a perceived stagnation in the standard of living. However, these actions raised concerns about human rights violations and one's fundamental right to procreate and have a family. The population control measures ceased in 1991, when Denmark ended forced sterilization.

In a U.S. human reproduction forum, human reproductive rights would likely never be framed in terms of population control (or eugenics) versus autonomy and individual freedoms. This is likely because as soon as forced sterilizations propelled by *Buck v. Bell* (1927) waned in the mid 1960s and 1970s in the USA, abortions rose for decades.

In May of 2022, one month before *Roe V. Wade* was overturned by the United States Supreme Court, USA Today media tried to make a case that more than a hundred other countries allow abortions -

"More than 100 other countries, states and territories allow for abortions in specific instances like "to save a woman's life."

Belize, Britain, Fiji, India, Japan and Rwanda are among countries that allow abortions for a range of social and economic reasons as well." (USA TODAY)

But, what the media does not say is that most of the ethical world would indeed save a mother's life, and that Japan allows abortion up until 22 weeks with spousal consent if the woman has a spouse, and only to protect the mother's health, or in case of rape.

So, as of August 2023, the 50 United States interpret and enact abortion laws, with USA still by far the most welcoming place in the world for IVF, Third-Party Reproduction, as well as abortions. Historically a vast majority of abortions are had by low-income minority women in the USA, and it is because of this statistic that the USA and EU have fundamental differences in framing the rights to access IVF and Third-Party Reproduction in terms of children's rights coming first. Whereas in the EU, leading human reproduction, academics and law is more progressive. EU acknowledges its contemporary history of population control measures and individual and children's rights as key frames of reference. Whereas USA still reverts to universal health insurance coverage arguments and framing IVF access in

terms of abortion access, when the two are completely unrelated. Often, USA discussions of access to human reproductive care are politically framed with the preoccupation on freedom to terminate pregnancies, whereas in EU, the focus is on human rights and individual rights, including the unborn children's rights.

To best improve equal access to human reproductive care, an important start could be taking the Five Eyes alliance (Canada, USA, UK, Australia and New Zealand) and adding the EU for purposes of building consensus on LGBTQ and single intended parent access to human reproductive care. Protecting human rights is a Security and Intelligence Global concern. Building global consensus would include all forms of Third-Party Reproduction, including commercial and altruistic gestational surrogacy. Donor anonymity must be condemned and banned universally, and all human donor gametes must be understood by all parties to be Open ID at age 18. This should have happened in 2013, when ASRM (American Society of Reproductive Medicine) lifted the experimental label from egg freezing. 23andMe launched consumer genetic testing in November 2007. Sixteen year later, the IVF field is still kicking the can down the road, with many IVF doctors marking up anonymous donor eggs for profit by astronomical profit margins. This is because in most of the world, young women are barely compensated for human egg donation, if at all, and regulatory is weak.

PROFESSOR GEOFFREY WILLIAMS OF BELGIUM ADVOCATES FOR A UNIFIED AND CONSISTENT FRAMEWORK FOR THIRD-PARTY REPRODUCTION

Professor Geoffrey Willems is from Belgium and teaches at UClovaan. Professor Williams balances the individual's rights to Third-Party Reproduction access with the focus on children's rights and invites discussion of the alternative of "multiple parent families." This would be accomplished through Open ID gamete donation and promoting relationships between IPs (intended parents) and Surrogates.

Willems discussed the glaring difference between the rights of gamete donors (considered "no ones") versus the IPs (the main concern). He noted that even the gestational surrogates have rights to make medical decisions during pregnancy. In Europe, it is generally thought that surrogates have rights as mothers and can decide to keep the child. This is in stark contrast to Surrogacy in the USA, where due to it being a commercial deal and business contract, this thinking would be what most IPs would fear most.

Willems said that 29 countries (of 50) in Europe allow gamete donation and that the main issue is "Should the donor conceived child have a right to know the donor?" Nine states maintain that donors should remain anonymous (Eastern Europe), fifteen States in Western Europe want transparency, and 5 states, including Belgium, are mixed. However, EU shows a strong trend towards transparency.

As for Surrogacy, Willems noted a shy trend towards intention, with the surrogate downplayed as “not a mother, but a significant third party.” Willems pointed out that though the 2021 Verona Principles are non-binding, he is already seeing impact in the UK and Ireland.

International Social Service, founded in 1924 in Geneva, Switzerland, published the February 2021 Verona Principles. Following are some highlights that demonstrate EU’s progressive and children’s best interests’ approach to regulating Third-Party Reproduction.

Although global consensus on surrogacy has not yet been reached, the rights of children born through surrogacy need to be addressed urgently. And The Verona Principles are inspired by and grounded in the provisions of the Convention on the Rights of the Child, its Second Optional Protocol on the sale of children, child prostitution and child pornography and other relevant international human rights instruments. Given that surrogacy is not explicitly addressed in these instruments but raises significant children’s rights issues, guidance is needed to ensure the proper protection of the rights of the child in the context of surrogacy. Continued work of these Principles was recommended by the United Nations Special Rapporteur on the Sale and Sexual Exploitation of Children (UN Doc. A/HRC/37/60) ...Compliance with the procedures and safeguards set out in these Principles requires that regulation of surrogacy in any form excludes violations of the human rights of children such as discrimination, statelessness, abuse and lack of access to origins... The Verona Principles are based on the premise that, where surrogacy occurs, it creates and severs relationships. There should be openness in these relationships and where appropriate, they should be valued and sustained... Particular attention should be paid to rights relating to birth registration and identity (including but not limited to name, nationality and family relations).

The Verona Principles are steeped in the common sense that if an EU member state is going to allow gestational surrogacy, the state needs to have the ability to effectively regulate surrogacy and ensure compliance with the 30-page Verona Principles. The Verona Principles goes on to dictate that -

The above must be interpreted consistently with other principles, inter alia, best interests of the child, human dignity, the prevention and prohibition of the sale of children and trafficking in children, protection of identity and access to origins....1) In order to safeguard the child’s rights at birth, States permitting surrogacy should ensure regulatory requirements and standards are in place to ensure that: whenever human reproductive material is used other than from the intending parent(s), there is screening of transmissible disease(s) and/or genetic disorders and notification of results to the surrogate mother and intending parent(s).

Principle 9 is “Consent of persons providing human reproductive material” and Principle 11 is: “Protection of identity and access to origins.” So, Willems’ summary of EU leanings on all matters Third-Party Reproduction is in synch with the Verona Principles, in protecting all parties, with special emphasis on Donors, Donor-conceived children, Surrogates and children born to Gestational Surrogacy.

Willems concluded that a stronger approach relying absolutely on transparency and intention may possibly be more satisfying and concurs with the EU member states advocating adoption of adherence to the Verona Principles. Such principles would even place the EU considerably ahead of the USA and Canada in protecting all the parties to a Third-Party Reproduction arrangement. Therefore, the Verona Principles can also be looked to as a Global solution to building uniformity and consensus, and therefore equal access to care, in IVF and Third-Party Reproduction.

Tullia Penna, studying Medical Law and Bioethics in Human Reproduction at Università degli Studi di Torino, said that although a societal metamorphosis is occurring with gestational Surrogacy growing, EU has no legal competence on family law, and specifically on Surrogacy law. However, the EU does have jurisdiction on Cross-border reproductive care (CBRC), despite the lack of consensus and evasion of the law the regularly occurs.

Penna informed that in Italy, people cannot be prosecuted for using Surrogacy, unless it is illegal in the country where they used Surrogacy. She echoed all the previous speakers by saying that the children’s rights are always considered.

In Belgium, Penna said, what is not expressly prohibited is allowed. According to the ECHR (European Court of Human Rights), “denial of a child’s nationality is detrimental to the rights the child gets.” Penna says that EU has great division on human rights and ethics and does not even have a consensus on Altruistic Surrogacy.

In May of 2022, European Parliament came out with a resolution condemning surrogacy as exploitation of women considering the Ukraine War. There are upwards of 2500 tracked Surrogacy births out of Ukraine each year, which is believed to be 25 percent of the world Surrogacy market. In March 2023, the Italian government ordered Italian mayors to stop registering birth certificates of children born via international Surrogacy.

On June 19, 2023, the Italian government presented a bill to make Surrogacy a universal crime. On July 26th, 2023, Italy’s Parliament approved the bill, and if it passes the Senate vote, it becomes law. Penna pointed out that universal crimes are almost exclusively for war and that “a European regulation is really needed in these times.” She believes there should be a common consensus before ambivalence can be addressed and before the law can be changed.

Penna said that, according to Chambers, et al, a 2021 study, 62 percent of all egg donation cycles per year are through Europe (80K cycles). Sperm donation is done in 41 countries and egg donation in 38 countries. Though she cited wide variability amongst countries regarding if donor’s identity should be open or anonymous and who can access it. Penna pointed to a multi-country 2022 study called “From Scarcity to Sisterhood: The Framing of Egg Donation on Fertility Clinic Websites in the UK, Belgium and Spain.”

Penna stated, “Gamete donation has become entangled with AI systems for matching / selection of donors, expanded carrier screening, egg vitrification, mitochondrial

donation, intermediaries, direct-to-consumer genetic testing.”

This tied in with the ESHRE opening ceremonies EuMAR by ESHRE (European monitoring of Medically Assisted Reproduction) which is planning a registry of 1 million IVF cycles from 1500 IVF clinics throughout Europe. More than a quarter million Europeans have taken advantage of free fertility assessment and counselling throughout Europe over the last 12 years.

In ASRM immediate past president, Dr. Marcelle Cedars’ talk “The Future of IVF,” she discussed the room for variability in IVF and the increasing amounts of data available. The UCSF Health director of the Center for Reproductive Health said, “Big data is really what you need for AI” and “We don’t want confirmation bias in the outcomes (we want pattern recognition).”

The USA ASRM talks drew a large audience that respectfully largely remained for Dr. Cedars’ talk, but not for the whole ASRM session. Dr. Cedars’ talk came across as amended to fit the flow of information at the 39th ESHRE, which was heavy on AI and the latest advances in genetics and science, including the looming reality that EuMAR’s 1M Cycle, 1500 IVF clinic database is going to be “as big as it gets” in terms of “big IVF data” available to crunch.

Cedars did list the complications of going from prototype to mass production, and this is especially true with AI and robotics applied to a still nascent field, where science is continually outpacing society’s ability to integrate the technology and advancements.

Dr. Thierry Suter of Switzerland and Italy said of AI, “Are we lowering cost and increasing access? Are we improving outcome? Is it meaningful?” Dr. Suter practices IVF medicine with Procrea Centro Fertilità in Lugano, Switzerland.

Dr. Francesca Spinella, the Scientific Director of Eurofins Genoma group in Rome, Italy, spoke on continuing to collect clinical data, that mosaic embryos should not be discarded, and that low-grade mosaic embryos are similar to euploid embryos. She said that AI was not yet being used in this process.

Antonio Capalbo, Chief Scientific Officer of Juno Genetics said that multivariate predictive modeling is in the pipeline. Teodora Popa, a PhD researcher in reproductive genetics at UCL in London, spoke of ChatGPT in her talk, as well as Next Generation Sequencing. And Nada Kubikova, Maplethorpe Junior Research Fellow in Biomedical Sciences at University of Oxford, spoke of HDR using an artificial template (detected by sequencing) and time lapse incubation.

UK-based Dr. Christina Hickman is the co-founder and COO of Ovum (Germany) and co-owner of Aria Fertility, the Chief Clinical Officer of Fairtality (Israel), as well as the Chief Scientific Officer and VIP of numerous IVF and Life Sciences companies. Dr. Hickman stated that at current we do not have a rationale for determining oocyte viability. “AI can analyze every pixel in the image and look for patterns that we as embryologists may not be able to identify.” Fairtality, inventors of Chloe for egg quality assessment, sponsored Dr. Hickman for a fascinating talk about “Chloe

oocyte quality insights,” “all performed inside of a time lapse incubator.”

To give a glimpse into the geographic scope of the race to develop mass-adopted AI technologies in IVF, Fairtality, an Israeli company, partnered with Esco Medical and its time-lapse incubator technology, a Singapore company. Scientists, embryologist and lab director Hickman is in London, UK, with USA partners in common with Esco Medical. They aim to be able to “score eggs” before performing ICSI.

When asked about AI predicting embryo quality / grading, Dr. Hickman said, “We were saving that for the next conference.” She added, “The further we get away from the egg, the more confounders we introduce.” Dr. Hickman ended emphatically with, “But, yes, that’s the goal, to get to live birth.”

When Rohi Hourvitz, the CEO and co-founder of Israeli’s Fertilai spoke, a doctor pointed out that Hourvitz was not a physician or scientist and asked if he wanted to replace physicians and steal their work. Hourvitz said, “No, we are not going to replace physicians. AI is just an extra statistical analysis that you can use.” He suggested the goal is to get the physicians more good embryos. Hourvitz is a young computer programmer and electrical engineer, and has developed an AI app, which he is gaining ground in implementing in IVF clinics for use with patients / intended parents.

When asked how his AI solutions are reducing IVF costs and improving access to IVF for infertility patients, Hourvitz says that Fertilai can lower the amount of tests, lower the number of IVF cycles necessary, optimize medication, and improve the clinical pregnancy rates.

Lorin Cohen, President of Canada’s Xytex Corporation, says, “If AI is explained appropriately, more intended parents (IPs) are going to be more receptive to understanding.”

ARTIFICIAL INTELLIGENCE IN ART – DESCRIBED AS “A PRACTICAL COURSE FOR IVF PRACTITIONERS”

Vlad Stirbu from Finland spoke on “Certifying Artificial Intelligence.” Once Stirbu, his colleague, and another pre-conference workshop presenter, spoke of their impressive backgrounds outside of the human reproduction field, this resonated with what Dr. Christine Allen, PhD and HCLD had said weeks earlier on the International IVF Initiative webinar. Dr. Allen said that the answers to implementing AI to improve global access to IVF care are going to come from talent outside of IVF and Life Sciences.

Stirbu describes himself as a technical guy who works with machine learning systems, including those used in industrial and medical settings, as well as having expertise in quantum computers and the software required for them. Having worked for Nokia, and on remote EKG monitoring, Stirbu noted that this was his first opportunity to speak at a medical conference. This suggests the newness of AI in healthcare in general, but especially the human reproduction field’s desire to embrace AI early.

Stirbu went on to discuss the challenges of certifying medical devices and the regulatory landscape surrounding

them. The EU's AI Act, fully adopted by the European Parliament in June 2023, is mentioned as a hot topic, with discussion around whether regulation hinders innovation. Stirbu highlighted past regulations such as the General Product Safety Act (2001), Medical Device Directive (2007), and Medical Device Regulation (2017). Stanford University came out on July 21, 2023, and analyzed the EU AI Act and told the USA and USA partners and lawmakers to familiarize themselves with the EU AI Act. Stirbu noted at ESHRE in June 2023, that "Media vs. Reality" is a hot topic, and as if on cue, USA headlines were dominated in July 2023 with themes of AI use across Media platforms.

Stirbu also touched on the concept of AI and its historical development, describing it as computer systems capable of performing tasks that typically require human intelligence. The importance of design control, safety, and effectiveness in medical software and devices is emphasized, along with the different stages of AI development and the involvement of data engineers and data scientists.

The concept of technical debt in machine learning systems was mentioned, with various aspects such as ML code (machine learning), configuration, automation, data collection, testing, debugging, and model analysis highlighted. Stirbu referenced a 2015 9-page academic paper by Sculley et al, the point being the "Hidden Technical Debt in Machine Learning Systems" and that Machine Learning Code is the smallest part of successful deep learning and AI.

In addition to technical debt, Stirbu touched upon the challenges and considerations surrounding the development of AI in medical products. Data preparation, including data assessment and management, was one of the key aspects mentioned. The quality and reliability of the data used to train AI models are crucial for accurate and unbiased predictions.

Data preparation is a crucial step in AI development for medical products. It involves a meticulous assessment and management of data, ensuring its accuracy and relevance. Data cards, as proposed by Pushkarna et al. in 2022, can provide a structured approach for organizing and documenting essential information about the data. Additionally, lifecycle management strategies need to be implemented to track data changes over time, according to Stirbu.

During the training phase, monitoring metrics and assessing actual medical benefits are critical. Model cards, as suggested by Mitchell et al. in 2019, can help document pertinent information about the AI model, such as its limitations and intended uses. Per Stirbu, it is imperative to detect data drift and promptly make necessary changes to ensure the reliability and effectiveness of the model, suggesting a dynamic and ever-changing quality-control process. For example, monitoring for data and concept drifts that may occur once the AI is implemented is important.

Deployment of AI models in medical products is discussed as well. The need for capabilities to detect data and concept drifts, continuous quality assurance, and model re-deployment is emphasized. Stirbu mentioned the FDA's requirement for regulatory lock before a product is certified to go to market, indicating the importance of meeting reg-

ulatory standards and ensuring the safety and effectiveness of the product.

Stirbu said that the FDA is looking at a faster cycle (compared to full regulatory cycle), if a medical product developer needs minor changes in product due to anomalies; Whereas, the European side is a bit more complicated. Topics highlighted included: Cybersecurity, Privacy, Information Security - Connected Systems, Regulations (MDR / FDA Guidelines), GDPR, HIPAA Standards - ISO 27001. ISO / IEC 27011 (the international standard to manage information security) was revised most recently in 2022 and published October 25, 2022.

Regulatory approaches for medical technology and devices are different in the USA with the FDA versus the EU and the CE Mark. Stirbu said that the USA is risk-benefit centered with recognized third parties. The EU is conformance centered. Stirbu noted parallel processes with EU and USA, where commercial companies apply for approval, but the regulatory bodies can only vet that the QA and due diligence procedures were followed, but they cannot vet the actual products themselves. This is because they do not have the required expertise and knowledge. Stirbu did point to clinical trials being important. He concluded that Quality Management Systems covering AI development need to be instituted, along with documented proof of AI alignment, and even without AI, QMS are needed. AI alignment is designing and utilizing AI to augment human capabilities rather than work against human interests. AI should enhance human capabilities, not conflict with or replace humans.

"CAN AI HELP THE INFERTILITY DOCTOR?" - SAMUEL DOS SANTOS-RIBEIRO, IIVIRMA PHYSICIAN, PORTUGAL, IIVIRMA GLOBAL RESEARCH ALLIANCE

Dr. Dos-Santos-Ribeiro is already employing AI in some of his IVF clinics, because in a field with a lot of negative pregnancy tests, they use technologies before they are vetted and approved. Dos Santos posited that with embryology, most happens inside of the lab, so that AI can make it possible to include the physician. He cited computer technology which is predictive of endometrium lining to predict pregnancy and says that AI can be used for patient evaluation and treatment.

Dr. Dos-Santos explained that all patients want to know, "What is the likelihood that I (we) will have a baby?" AI helps to combine numerous variables into probability analysis. He said that if you only use one predictive variable, such as age, this can decrease success chances by 10 percent. He provided an example of an IP being old, having low ovarian reserve, and being obese. Knowing all three of these variables helps with accuracy in probability of pregnancy success rate.

While neither AI, nor using clinical prediction models are new, applying AI and predictive analysis to patient counselling is new, and implementation of this use of AI can likely decrease treatment costs and prevent unneces-

sary treatments. Dos-Santos cited a likely decrease in patient drop out. Currently, he said, “A lot of our patients give up after their first conversation.” Dos-Santos used the example that solely looking at one variable (age) for likelihood of success can decrease pregnancy chances by 10 percent. In the doctor’s example of a patient being old, having low ovarian reserve, and being obese, all three factors would decrease likelihood of success.

“The prediction is only as good as the data that you put in,” said Dos-Santos. So, again, the refrain that integrity and reliability of data is everything in AI. It is clear that in the next couple of years, Global IVF is going to have to come to a consensus on who can be entrusted with the human reproduction and genetic cross-border data mines. The field is still niche but exploding at the same time. The data pools are not big enough without partnership of countries and continents, and this involves politics and regulatory. Such reality is why international laws and regulations are changing rapidly.

The current approaches to ovarian stimulation and triggering in IVF treatments are often based on routine and past cycles. Nomograms, which are predictive models based on patient characteristics, may be available but are rarely used. “We are overtreating some patients if results can be similar,” Dos-Santos said.

To summarize Dos Santos’ closing points:

1) The transition to the “Freeze-All” strategy may involve more aggressive ovarian stimulation, leading to the development of a larger number of follicles. This might necessitate longer stimulation periods before triggering ovulation.

2) AI for Stimulation and Triggering: Artificial Intelligence (AI) is being explored in the context of ovarian stimulation and triggering. The focus might shift from individual follicle size to the total number of developing follicles. AI can help predict the best time to trigger ovulation, which could lead to better outcomes and higher chances of obtaining blastocysts.

3) Benefits of On-Time Matches: Ensuring that the trigger is accurately timed could result in more blastocysts being produced during IVF cycles, improving the overall success rates.

4) AI for Standardization and Training: AI is also being considered for standardizing procedures and training in the field of IVF. It could help streamline workflows, improve consistency, and provide valuable insights for IVF professionals.

5) AI Image Processing for IVF: Dos Santos mentioned that AI image processing is still at an early stage in the context of IVF. AI image processing could have potential applications in analyzing embryo images and other related data to aid in decision-making during IVF cycles.

“CAN AI HELP THE EMBRYOLOGIST?” –

DANILO CIMADOMO. SCIENCE AND RESEARCH
MANAGER, GENERALIFE IVF, ROME, ITALY

Cimadomo started out by quoting Alan Turing on wondering if computers can think. He stated, “blastocyst morphol-

ogy is associated with competence” and “the main goal of AI for embryo assessment is removing its subjectivity.” Cimadomo pointed to his country’s work with the IVI RMA Global Research Alliance and the promise of “homogenizing embryo assessment through AI.” He says that what is “good enough” for clinical use is highly relevant from a clinical perspective. An AI-powered definition of quality uses multiple variables or parameters, and AI crunches the numbers and produces a score.

However, Cimadomo acknowledged that there is still a long way to go in AI improving embryo selection, because the nature of the data affects the efficiency of the models, as does the sample size. Thus, multi-IVF center studies are needed, with the training set of data representing all possible conditions. Cimadomo’s cautionary note against non-invasive PGS through AI is that it should rank embryos, not diagnose embryos.

Additionally, AI can help standardize the moment where it is appropriate to perform an embryo biopsy, but Cimadomo said that AI will never replace the embryologist (i.e. – humans). A summary of where Cimadomo sees AI offering embryology value is 1) AI can effectively automate morphogenetic annotation 2) The Electronic Witnessing System increases Safety 3) Automation of cryo-room management, automatic tank filling 4) Recently we have the first baby born from automatic ICSI 5) Raw timelapse data -useful clinical data

Cimadomo emphasized the significance of data in making AI effective, illustrating this with an example of AI confusing a dog with a wolf. This indicates that without sufficient and accurate data, AI can make mistakes, which are critical to avoid when dealing with delicate processes like embryo selection.

The rapid advancement of AI raises concerns about its validation before implementation. Given the speed at which AI is evolving and the wide dispersion and fragmentation of the data pools, it may be challenging to thoroughly validate its results before using it in practical applications.

Cimadomo is pleased as a scientist to have access to these AI tools in his field of work and expressed a desire for a reliable tool that can rank and select embryos effectively. He highlighted the educational aspect of using AI in embryology and the need for standardization in practice.

The real advantage of AI is seen not in IVF centers doing a large number of IVF cycles per year, Cimadomo noted, but in centers doing a smaller number of cycles but using AI effectively.

Using AI to predict live births requires pre-selecting embryos, which suggests that the AI is used to aid in the selection process, rather than diagnosing embryo conditions.

Cimadomo’s personal prediction was development of a tool to predict live births rather than just analyzing euploid embryos.

THROUGHOUT THE ESHRE 39TH ANNUAL CONFERENCE IN COPENHAGEN, DENMARK, SPEAKERS FROM AROUND THE WORLD WENT OUT OF THEIR WAY TO PAY HOMAGE TO THE HOT TOPIC OF AI IN EMBRYOLOGY AND IVF

During the “ORGANON LLC: Are you ahead of the curve? Freeze is now” session, Dr. Laura Rienzi from Italy, Laboratory Director of the GENERA Centres for Reproductive Medicine, said that the use of AI may move from traditional medicine to precision medicine, but that we need data scientists and need to understand biomarkers. Dr. Juan A. Garcia-Velasco, the CSO of IVIRMA said that AI can help answer - How many oocytes should we expose to sperm? Chair Dr. Angeline Beltsos spoke on managing patient care and a large team / staff, but not without giving a shout out to AI, as the whole Organon panel did. Known throughout the world as “Angie,” Dr. Beltsos was a Medical Director at Fertility Centers of Illinois, before founding VIOS Fertility and merging with Kindbody, as CEO and Medical Director of both clinic groups. Dr. Beltsos is also founder and Executive Chair of MRSi (Midwest Reproductive Symposium International).

Samuel Ojosnegros Martos’ online profile describes him as “Head of Open Innovation Laboratory - Bioengineering in Reproductive Health en Institute for Bioengineering of Catalonia (IBEC).” Ojosnegros (as described in the ESHRE program) opened one of the 39th ESHRE meeting’s closing sessions – “News on Artificial Intelligence (AI).” “Metabolic classification of embryos and oocytes based on hyperspectral imaging and machine learning.”

“The goal of our research is to try to improve embryo selection,” Ojosnegros began. He described studying the “intrinsic signals in the embryo” and said that is all the pixels in the images separated by their color. He likened the pixel analysis to “a metabolic barcode.” They then take the 3D and 4D images (adding temporal data to spatial information) and can use the histogram to determine embryo selection based on hyper spectral structure. Whereas, he said, human graders were “pretty close to random guesses.”

Ojosnegros said that a good morphology embryo does not determine if it is a physiologically good embryo. He stated that there is a lot of information visually which the human eye struggles to determine. He mentioned promise for “oocyte classification based on hyper spectral structure.” Ojosnegros mentions Nuno Costa-Borges of Barcelona’s Embryotools as “very good at embryo culture and with their tools.” Embryotools, since 2011, is known as having the highest quality control standards and for being top laboratory consultants and a leading QC training center. This is an example of AI alignment mentioned earlier in this abstract.

The success rate of improving embryo selection reached in studies is 82.2 percent. Some of Ojosnegros closing thoughts were “Different colors mean different parameters for the algorithms” and “especially if we compare to B&W images from microscopes” and “we do not believe that aneuploidy embryos have a certain metabolic fingerprint.”

Lucía Murria’s social media describes her as a “Predoctoral PhD candidate researcher at IVI RMA GLOBAL.” Murria spoke on “Artificial intelligence algorithms in assisted reproduction: differences in the evaluation of embryos from fresh or vitrified donor oocytes.” She first mentioned “intracellular ice formation” and the sensitivity of oocyte preservation. From her presentation “Embryo scores by AI software depending on the oocyte origin,” Murria noted that fresh embryos received higher scores.

“The embryos that develop from fresh oocytes develop a little bit better than the one coming from frozen oocytes,” noted Murria, citing almost a 2.5 – 4 percent difference. “Embryos from vitrified oocytes have significantly lower scores than that from fresh embryos,” she said. Vitrolife’s EmbryoScope and EmbryoScope+ where the incubators used, with identical warming protocols in the study.

Ioannis Sfontouris spoke on “A model based on artificial intelligence for the non-invasive prediction of embryo aneuploidy.” Sfontouris is Director of Embryology Hygeia IVF Embryogenesis in Greece. “There is a constant need for embryologists across the world to select the best embryo,” he explained. “It is critical that the embryo is euploid to have a high chance of implantation.”

Sfontouris stated that the goal of AI is to have “non-invasive embryo evaluation techniques.” This means the cells and medium are not biopsied or disturbed. He said that AI involves deep learning and mentioned that iDAScore is incorporated into EmbryoScope and correlates with embryo aneuploidy. The Vitrolife website describes iDAScore as follows -

“iDAScore is an AI-based scoring system that provides fully automated analysis of time-lapse sequences. Now you can get an objective ranking based on the likelihood of achieving a fetal heartbeat on days 2, 3 or blastocyst stage of each of a patient’s embryos at once – with just a touch of a button.” (<https://www.vitrolife.com/our-products/idascore-intelligent-data-analysis-for-embryo-evaluation/>).

Three speakers later, Vitrolife’s Danish senior biostatistician Martin Johansen spoke on “Comparing the performance of an artificial intelligence model for predicting embryo implantation between clinics with patient cohorts of different maternal age distributions.” Johansen confirmed “The iDAScore is an AI model intended for ranking embryos within a treatment” Johansen also attested to the validity of the AI technology.

Keiichi Kato of Japan’s Kato Ladies Clinic presented “Does embryo categorization by existing artificial intelligence, morphokinetic, or morphological embryo selection models correlate with blastocyst euploidy rates?” Kato noted, “AI is now a very hot topic in all fields.” He said that AI models have been proposed for predicting ploidy status. Kato said that using the time-lapse system for PGT-A avoids unnecessary genetic tests and costs on deciding which embryo to biopsy for PGT-A.

Tsubasa Takahashi of Kato Ladies Clinic IVF Laboratory spoke on “Association of a deep learning-based scoring system with morphokinetics and morphological alterations in human embryos.”

Takahashi described iDAScore as “a deep learning-based scoring system for blastocyst evaluation” (vs. Gardner score or KIDS Score). He said the “Black Box Issue” is “*Deep learning-based AI shows only the results, not the process of thinking.*” However, his conclusion was that iDAScore correlated with morphokinetic parameters in different embryo stages and that “The trust in deep learning model-based embryo selection may be increased.”

To conclude “News on Artificial Intelligence (AI)”, Dr. Daniel Seidman, Chief Medical Officer and Co-founder of AIVF in Israel spoke. Dr. Seidman presented “Personalized pregnancy odds estimation can be obtained using AI embryo evaluation and individual patient characteristics.” AIVF’s AI platform is EMA™. The AIVF website states that its AI-powered insights improve efficiency and outcomes and gives statistics, and the name seems to merge the words embryo and AI.

Where Dr. Seidman’s talk differed from the previous speakers is that he is a clinician. “As a clinician, I have problems with these AI scores; These AI scores were really made for embryologists,” he said, adding, “All the embryos in a cohort have the same metadata” (BMI, age, etc.).” Dr. Seidman noted that “*Every clinic does things differently, media, timing, etc.*” and “*Every clinic has its own X factor.*”

Dr. Seidman threw in a statement that, “Clinics in America generally have better results than in Europe.” Though, many countries in Europe and many clinic groups and clinics in Europe would take issue with that statement. IVF success rates have great variability by specific IVF clinic and location by country and even within countries. IVF patients need to research and compare success rates, reputation, philosophy, prices and services offered.

AIVF created “reliability curves” with personalized data from USA, Spain and Israel, to improve the performance of the machine learning. “Personalized data improved the performance of the ML,” he said. USA and Spain are two of the largest IVF and donor gamete markets in the world, so it makes sense to use data pools from these world-leading markets.

“We retrain the data for each clinic, recalibration curves,” stated Dr. Seidman. He explained that they need to calibrate the machines for each specific clinic, and metadata and personalized data is important. Dr. Seidman concludes by stating, “If you build a model based on other data,

not only morphokinetics you can greatly improve the prediction.”

CONCLUSION

In the opening ceremonies for the 39th Annual ESHRE Scientific Meeting, 11,533 global attendees were treated to an inspiring and gracious welcome from Professor Dr. Karen Sermon, professor in Genetics and Embryology at the Vrije Universiteit Brussel, Belgium. Dr. Sermon is the Chair of ESHRE. Co-welcoming the IVF world back to Copenhagen, Denmark for the first time since 2005, Professor Dr. Anja Pinborg of University of Copenhagen shared the stage.

The ESHRE hosts showcased the history of Denmark, and hosted ballet dancers, singers and violinists for the opening ceremonies. With in-person turnout similar to 2018 in Barcelona, but with leaps and bounds of academic, clinical and scientific progress made in EU and globally during and since pandemic, we can only believe that the best is yet to come and that ESHRE will be a leading part of our global progress in AI, Third-Party Reproduction, Regulatory and Clinical outcomes.

ESHRE Barcelona 2018 opening ceremonies had performers hanging from the industrial rafters above in giant bubbles and entertaining airborne. The IVF, private equity and entrepreneurship froth was palpable in 2018. A year-and-a-half later, the world began shutting down. In 2019, Vienna was more subdued, 2020 and 2021 were cancelled / virtual. 2022 saw a sweltering partial lockdown, hybrid Milan ESHRE Congress. ESHRE 2023 returned with a vengeance and overflowing with class. The international vibe in Copenhagen was both relaxed and exciting. A sense of the calm after the storm and trying to outpace another storm prevailed. It is an incomparable time in medical and scientific history, especially with human reproduction and genetics. We reach for global equality in access to human reproductive medical care and protecting individuals’ rights and freedoms. Many countries have opportunities to lead in IVF and Life Sciences, and specifically with Genetics, Databases, AI, Big Data, Regulatory and Third-Party Reproduction.

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