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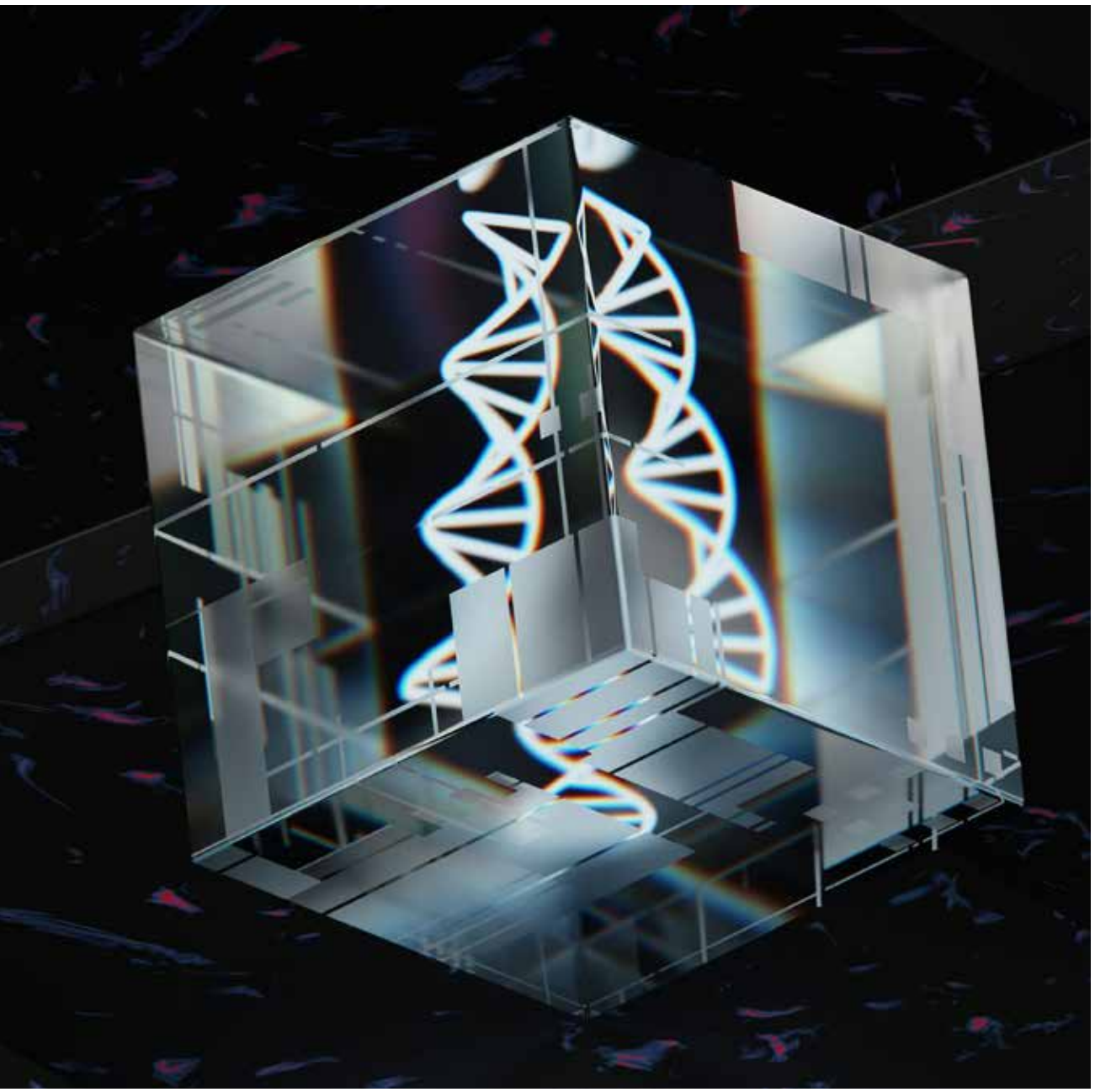
RESEARCH BRIEF

From Algorithms to Embryos

How AI is Changing Assisted Reproduction

Al Malecha



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Introduction

IMAGINE you are experiencing infertility. By the clinical definition, this would mean that despite trying for twelve months, you are still unable to achieve a pregnancy. You have bought the parenting books, prepared space in your home and your life, and dreamt of starting a family, but month after month, the pregnancy tests continue to come back negative. Many of you reading this document need not imagine this scenario—by World Health Organization estimates, 17.5 percent of the world's adult population experiences infertility.[1] Or perhaps, imagine you are LGBTQ+ and you require some form of reproductive technology to conceive or carry a pregnancy. Or finally, imagine that you or your partner carries a genetic mutation that could lead to a serious medical condition. You may choose to pursue in vitro fertilization (IVF) and undergo preimplantation genetic testing (PGT) to prevent passing on a life-threatening disease. These scenarios are only a few of the many possible reasons individuals turn to assisted reproductive technology (ART).

ART is not new—the first IVF baby was born in 1978. However, improvements to laboratory technique and advances in understanding of human physiology have made IVF more successful and more widespread. Along with developments in technology, the high cost of IVF has increased pressure among patients and doctors to select specific embryos based on the likelihood they will result in a live birth. While embryo-selection procedures traditionally utilize laboratory methods, the rise of machine learning (ML) and artificial intelligence (AI) in other sectors has more recently crossed over into fertility medicine. Within the last ten years, a handful of companies have developed products that claim to use big data and image analysis to select the best possible embryo for implantation. Some of these companies have even claimed that their technologies, based on images alone, will be able to conduct preimplantation genetic testing.

While these technologies could have a massive impact on the lives of those living with infertility and those who use ART, they often rely on poorly understood black box algorithms and are not subject to sufficient regulatory oversight to prevent harm from occurring to not only those who use them, but society at large. This brief examines the ethical and moral challenges presented by the introduction of AI into the world of ART. Furthermore, this white paper underscores the need for a framework in the United States that ensures the ethical guidance and implementation of AI-assisted reproductive technologies.

The Use of AI in IVF

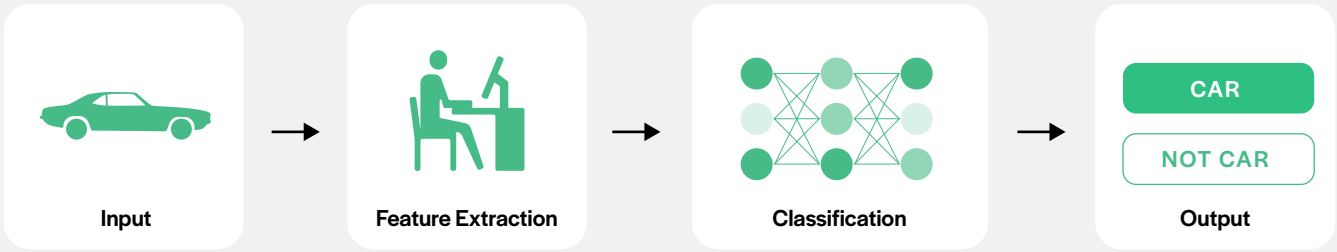
IVF SUCCESS RATES have improved significantly since the first IVF baby was born in 1978. However, since 2010, success rates have declined in the United States and peer countries.[2] There are multiple possible explanations for this decline, with some researchers attributing it to an increase in average maternal age or poor-prognosis patients,[3] and others attributing the decline to an increase in adjunct treatments for which evidence is lacking.[4] Simultaneously, in the last ten years, the enthusiasm for AI has grown significantly, and many believe in the potential of AI to improve birth rates from IVF and solve other fertility challenges without the need for invasive treatments or further medical intervention. New AI-enabled technologies claim to utilize *images alone* to select the embryo most likely to result in a live birth, and some companies claim to go further, stating that their image-based algorithms can conduct a type of preimplantation genetic testing without the need for biopsies. Selecting the embryo most likely to result in live birth is of great importance to patients—the average cost of an IVF cycle in the United States was $12,400 in 2020. In most patients, only one embryo will be implanted per cycle, meaning that patients may require multiple cycles to have a successful pregnancy.[5] Doctors and patients may therefore feel pressure to have a successful first attempt at IVF, and incorporate AI-enabled technologies, as an additional "screening" step.[6] However, as with all AI-enabled technologies, these algorithms are subject to algorithmic bias and are poorly understood. While AI in fertility medicine may possess enormous potential, the lack of regulatory framework to guide ethical advances creates risks to patient health, finances, and equity.

What is AI and How is it Used in ART?

"Artificial intelligence" is often used as a blanket term to refer to anything that involves a computer emulating human thought through the identification of patterns and decision making that improves overtime. The majority of what is referred to as "AI" is in the form of chatbots or generated art by machine learning, a subset of AI that allows computers to learn from previous processes without being explicitly programmed to do so. Machine learning requires a dataset and a machine learning model, with which the computer can find patterns and make predictions.[7] Supervised machine learning allows a human programmer to label data, change the model, change the parameters, and select ideal results. On the contrary, unsupervised machine learning allows the algorithm itself to look for patterns that might be overlooked by a human. A particular class of machine learning algorithms called neural networks are modeled after the human brain, such that labeled data moves through nodes, creates an output, and sends the output to other "neurons." A deep learning (DL) network is a neural network with many layers. In an image-recognition deep learning network, each layer may be trained to detect a certain element, such as features of a face, while another element would be trained to determine whether the features are aligned in a way that suggests a face is present in the image. More layers in a deep learning network increase the capacity of the network to complete complex tasks.

How machine learning and deep learning neural networks work

Machine Learning



Deep Learning

Machine learning and deep learning have been utilized in the last fifteen years to perform the task of embryo selection and improve upon the existing technologies of time-lapse imaging (TLI) and preimplantation genetic testing.[8] While promising, these AI-enabled tools have been critiqued by certain researchers for their validity and effectiveness due to the insufficient number of well-designed, peer-reviewed randomized control trials on these technologies' impact on live birth rates. With the incorporation of AI into numerous other health technologies, both time-lapse imaging and preimplantation genetic testing stand out as areas of significant potential for improving live birth rates from IVF.

Time-lapse Imaging

The use of time-lapse imaging in IVF is hardly novel—as early as 1929, scientists used time-lapse imaging to visualize embryonic development, albeit in hamster embryos. The first time-lapse imaging of human embryos occurred in 1981.[9] After the development of the Gardner Score grading scale in 2000,[10] it became standard practice in fertility medicine to observe embryos and score them at various periods from hours after insemination to day 5 (blastocyst stage).

Time-lapse imaging gained traction as an effective way to evaluate embryo morphology because the underlying technology is relatively basic. The most simple versions of time-lapse imaging require only a phase contrast microscope, a digital camera, software, and an incubator.[11] Generally, an embryologist will "score" an embryo at the blastocyst stage (day 5) based on the appearance of the blastocyst cavity, the inner cell mass, and the quality of the cells that surround the embryo, called the trophectoderm grade.[12] From these three scores, the embryologist

Timeline of IVF

The history of IVF is complex—unlike many scientific developments to treat or cure a disease, infertility was not always regarded as a medical issue. Early interest in IVF stemmed from the eugenics movement's desire to "improve the human race" through selective genetics. Thus, when IVF research began moving into humans in the early seventies, governments and funding sources were understandably apprehensive about the pursuit of science with implications that were not too far removed from the "science" of the Nazis 30 years prior. After the first live birth from IVF and wider recognition of infertility as a disease, the technology was gradually accepted, with different countries and entities choosing to regulate the technology in their own ways. Yet even as developments to IVF through the 80s and 90s optimized embryo quality and increased the likelihood of a live birth, regulators limited access to these technologies due to a variety of concerns from religious beliefs and conservatism to worries about the eugenic nature underlying these technologies. In the 21st century, preimplantation genetic testing and AI-based imaging technologies have been met with similar criticisms.

1878

First record of attempts to inseminate mammalian eggs in vitro.

1930s to 1940s

Implantation of rabbit eggs into rabbit recipient.

1951

Austin and Chang experiments found that the spermatozoa of some mammalian species needed to "reside for some time within the female reproductive tract before acquiring the capacity to penetrate eggs," a term Austin coined as "capacitation."

1950s to 1960s

Austin and Chang's work on capacitation revitalized the interest in the fertilization of mammalian eggs, and numerous other researchers throughout the 1950s and 1960s began similar experiments on hamsters, mice, rats, and sheep.

1965

Robert Edwards, the scientist who facilitated the first human IVF birth, published a paper in The Lancet stating that treatment for infertility was one aspect of IVF's potential, and emphasized how IVF could be used to study genetic diseases. He is met with criticism from the scientific community.*

1971

Edwards and his research partner Patrick Steptoe apply for, and are rejected by the UK Medical Research Council (MRC) to perform IVF experiments in humans.

1971

Edwards along with David Sharpe of the National Law Center in Washington D.C. published a 1971 Nature paper entitled "Social Values and Research in Human Embryology." In this paper, Edwards and Sharpe critiqued the stance of the MRC in the UK and society at large across the world—

> [T]he scientist's freedom to inquire is not immutable; society might again force scientists to consult institutions that were not developed for judging the motives of humanitarian biologists and physicians . . . Probably the worst consequence imaginable to scientists working in a political democracy would be the pre-emption by the state of a branch of science such as human embryology.

This paper also highlighted the conflict between ground-breaking science and the law: "few scientists have any lawmaking experience, and hence their judgments will be those of citizens giving their personal social views. Neither do the lawyers have much of an advantage in creating good social policies toward scientific achievements."

1972 to 1973

Edwards and Steptoe proceed in their experiments with funding from the Ford Foundation** as well as a private donor

1974

Edwards and Steptoe again seek funding, the MRC states that they would not fund research in the field unless they were provided with "satisfactory evidence that there would be no increased risk of abnormal offspring."

1975

UK policy changes to allow ova to be obtained from women so long as they had granted consent, had "defined medical reasons" for transfer, and had no "no legal or ethical objections to the transfer of in vitro fertilized ova to the uterus.

1978

Louise Brown, the first live birth from IVF, was born, sparking interest in IVF from the UK's MRC.

1980s

Scientists begin to stimulate ovaries with human menopausal gonadotropin prior to egg retrieval to increase oocyte yield.

1990s

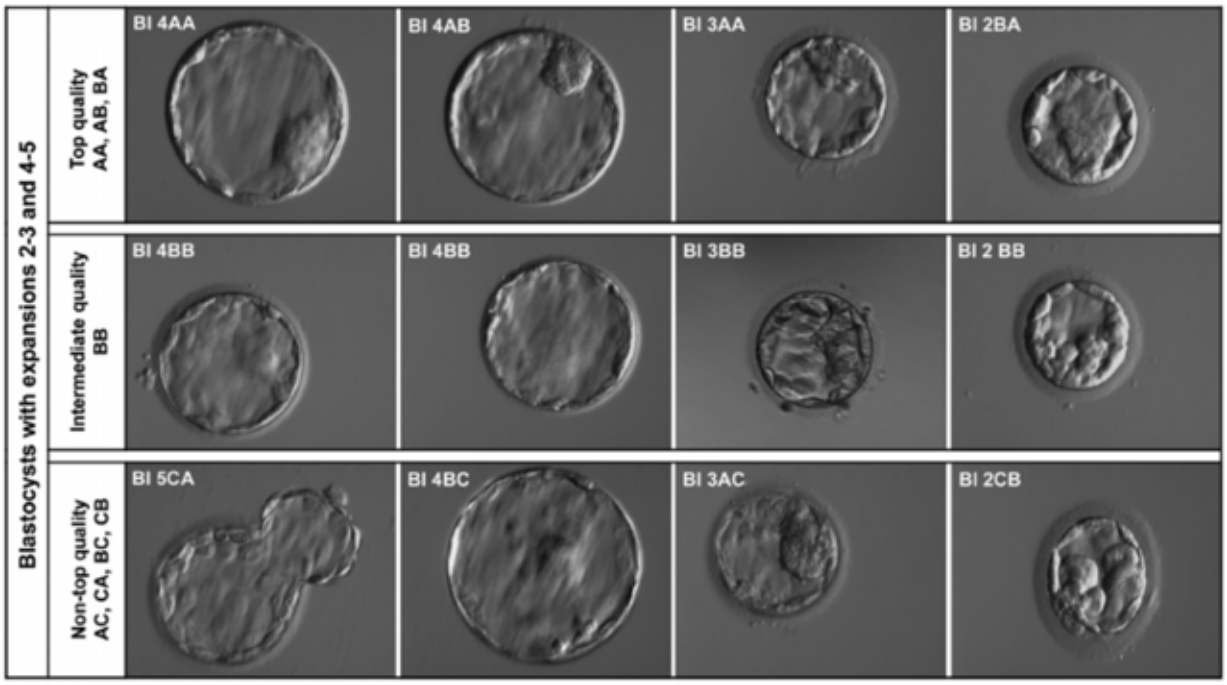
Scientists use Intracytoplasmic sperm injection (ICSI) to treat a common cause of male infertility. ICSI involves injecting sperm directly into an egg, and is used when sperm count or quality is low.

*The general perception of research into infertility was incredibly negative at this time, owing in part to the Nuremburg Code and the lack of research in obstetrics and gynecology more broadly. "It would be wrong to place a major emphasis on techniques for augmenting fertility in infertile patients when we desperately need methods for limiting fertility in the normal population." Martin H. Johnson et al., Why the Medical Research Council refused Robert Edwards and Patrick Steptoe support for research on human conception in 1971, 25 HUM REPROD 2157 (2010).

**This was perhaps an unsurprising funding source given Edwards' connections with prominent eugenicists. The Ford Foundation had funded a significant amount of eugenics research in the early 20th century, and despite the foundation's critiques of Henry Ford's "descent into anti-Semitism," many of the core eugenic beliefs of the foundation remained throughout the 1970s.

FIGURE 1

Blastocyst grading scale assignments from Gardner Score criteria[13]



will assign a score to each embryo, and select the highest scored embryo for transfer.[14] This relatively simple task of blastocyst selection is the precursor to semiautomated systems and AI-based systems. These more advanced systems use large datasets of digital images to provide quantitative parameters for the ideal size of the blastocyst cavity, ideal size of the inner cell mass, and the ideal number of trophectoderm cells so a clinician may make the best decision about which embryo to choose.[15] Using quantitative parameters reduces the subjectivity inherent in selecting the best embryos based on appearance alone.

In 2011, Marcos Meseguer and his colleagues at the Universidad de Valencia in Spain developed a process to select the best possible embryo with an algorithm that utilized image processing in tandem with time-lapse imaging to predict embryo implantation.[16] The 247-embryo study found correlations between the timing of embryo cleavages, the duration of cell cycles, and aberrant behavior with the embryo's likelihood to implant.[17] From this data, Meseguer created a multivariable model to classify embryos according to their probability of implantation.[18] This process resulted in the first fully automated system to assess various parameters and select the best candidate embryos based on not only their appearance at the blastocyst stage, but also the development of the embryo over time and other biomarkers that may impact embryo quality.[19] As image processing has advanced in other realms, researchers have sought to apply machine learning/deep learning models to embryo evaluation. While machine learning and deep learning are often used interchangeably with AI, they are instead subsets of AI that rely on algorithms to learn and recognize patterns in data.[20]

In IVF, machine learning models rely on segmentation and classification algorithms that utilize training data to analyze the texture and light levels of each pixel of a microscope image and classify each

pixel as a part of the blastocyst.[21] Once each part of the blastocyst is classified by the algorithm, the best embryos can be selected based on statistical analysis of each blastocyst. Similarly, deep learning models can be used for embryo evaluation. Rather than learn, identify, and classify sequentially, deep learning models learn and classify through an automated system, and can incorporate non-image data into their algorithm.[22] In 2019, a team at Weill Cornell Medicine partnered with the Universidad de Valencia's team and created an algorithm from 10,378 embryos that was able to predict with 70 percent accuracy whether an embryo would be aneuploid, or have an abnormal number of chromosomes that can lead to conditions such as Down Syndrome.[23] Yet while deep learning models may be more objective than human or machine learning models at predicting biomarkers in an embryo, they often require larger datasets and higher resolution images. Studies on deep learning applications in embryo scoring have demonstrated that, despite their increased accuracy, deep learning models can "overfit" data during training, resulting in lower consistency.[24]

Preimplantation Genetic Testing

Like time-lapse imaging, the prospect of preimplantation genetic testing predates IVF in humans. In 1965, Robert Edwards, the scientist who facilitated the first human IVF birth, published a somewhat controversial paper in *The Lancet*, stating that treatment for infertility was only one aspect of IVF's potential. Edwards believed that preimplantation genetic testing could prevent disease and saw early IVF technology as a precursor for the study of genetic diseases, sex linked disorders, and chromosomal abnormalities.[25] IVF would therefore further "positive eugenics"—the idea that favorable traits could be selected to reduce disease.[26] During the years of his early IVF experiments, Edwards was a trustee on the Council of the Eugenics Society in Britain,[27] and Edwards saw IVF as the necessary first step in reducing disease through the manual selection of certain traits. Undoubtedly, some of the criticism toward Edwards' and Patrick Steptoe's work was rooted in concern about Edwards' admitted eugenic beliefs, having only been a few decades removed from World War II. While those in the sixties and seventies were skeptical of Edwards' far-fetched ideas, the hesitancy toward IVF and genetic testing shifted as IVF became a viable way to conceive, and developments to IVF technology allowed parents to select the embryos with the highest likelihood of resulting in a pregnancy.

Nearly sixty years later, there are four types of preimplantation genetic testing. The first, PGT-M, tests to ensure that a parent carrying a genetic mutation that only impacts a single gene does not pass it on to the embryo.[28] The second, PGT-A, is used to look for aneuploidy, wherein an embryo has an abnormal number of chromosomes.[29] The third, PGT-SR, screens for chromosomal rearrangements like translocations and chromosome inversions.[30] The fourth, and the most recently developed, PGT-P, tests for polygenic disease risk, testing the entire genome to estimate the likelihood of diseases like diabetes, depression, or quantitative traits like height.[31]

PGT-M was first conducted in the 1990s via polymerase chain reaction-based methods, and shortly after, via screening cleavage-stage embryos by fluorescence in situ hybridization to visualize chromosomal rearrangements.[32] PGT-M now consists of taking a biopsy from the trophectoderm of a day 5 blastocyst and analyzing the genome through a sequencing-based approach.[33] From the gene sequence, clinicians are able to identify whether an embryo contains a specific gene defect that leads to diseases like cystic fibrosis, Marfan syndrome, and sickle cell anemia.

PGT-A is used to detect when too many or too few chromosomes are present in the embryo, a factor that is thought to cause nearly half of first-trimester miscarriages.[34] While PGT-A is not always recommended in IVF, it is recommended to patients over the age thirty-five or those who have had recurrent pregnancy loss.[35] As AI-based image analysis technology has evolved, several techniques purport to achieve the same goal as PGT-A—identification of aneuploid embryos—based solely on the algorithm's

classification of a still image or the time-lapse imaging of an embryo.

PGT-P is a similar process to both PGT-M and PGT-A but it involves both the biopsy of a day 5 blastocyst and saliva from both biological parents to screen embryos for polygenic traits—characteristics that are controlled by multiple genes.[36] Companies like Orchid and Genomic Prediction that offer PGT-P claim that these technologies can not only predict certain health markers at birth but can also predict the lifetime likelihood incidence of diseases like cancer and Alzheimer's, allowing them to "score" embryos by their predicted disease states and traits.[37] However, PGT-P has questionable analytic and clinical validity, as an embryo's score is based off the genetics of the original study population of those who have lived long lives in specific environments.[38] As environments and life conditions differ, it is hard to predict whether these original study participants have much in common with the genetics of a given embryo. Even beyond concerns about PGT-P's efficacy, there are concerning social implications of scoring embryos based on the likelihood of possessing certain traits. For example, many of the diseases screened for in PGT-P are more likely to occur in males, which would give female embryos a default "better" score.[39] Using PGT-P to select for sex or favorable traits while selecting against disease and disability harkens back to IVF's eugenic origins and the thought that "controlled" reproduction could eliminate undesirable traits from the gene pool. Furthermore, as IVF patients in the United States are disproportionately white or Asian and upper-middle class, the use of PGT-P is likely concentrated in these communities.[40] If PGT-P becomes more common, this could result in disability and disease becoming even more concentrated in low-income and minority communities that already lack necessary health-care resources and infrastructure.[41] While AI-enabled PGT-P scoring does not yet exist, it will likely be developed as AI becomes more prevalent in fertility medicine. Without proper regulation, AI algorithms will only amplify existing biases in embryo selection, leading to large-scale social implications.

Current Policy and Regulation

PART OF THE CHALLENGE of regulating AI in fertility medicine is that this field is already complex due to a patchwork of regulations that simultaneously over-regulate embryo research and underregulate fertility treatments. Adding AI-based technologies to the fertility space only creates another level of difficulty. This section outlines the relevant restrictions and regulations for AI-enabled fertility technologies in the United States.

Embryo Research Regulation in the United States

Research involving human embryos in the United States has historically been stifled by political conservatives. Shortly after the passage of *Roe v. Wade* in 1973, Congress made federal funding for human embryo research illegal, to prevent "encouraging women to have abortions so as to provide materials for research,"[42] and the Department of Health, Education, and Welfare (later the Department of Health and Human Services) placed a moratorium on research on living embryos.[43] While this moratorium expired in 1975, federal funding continued to be prohibited for embryo research for nearly twenty years.[44] In 1993, President Clinton finally lifted the ban on federal funding for research on human embryos, but this ultimately did not change the state of funding for IVF research, because the National Institutes of Health (NIH) still withheld funding for infertility treatment due to the likelihood of congressional opposition.[45] The NIH's concern about congressional opposition was valid—the Dickey-Wicker Amendment was passed in 1995, continuing the ban on federal funding for human embryo research.[46] In the early days of George W. Bush's presidency, stem cell lines that had been created before August 9, 2001, were approved for research, and in 2009, President Obama repealed Bush's stem cell policy to reverse these limitations and allowed for research to occur on new stem cell lines.[47] However, federal funding for embryo research (and therefore, a significant portion of fertility research) is still prohibited in the United States.[48]

To circumvent the ban on federal funding for research involving embryos, states have opted to fund research on their own. Proposition 71, passed in California in 2004, created the California Institute for Regenerative Medicine (CIRM) and authorized $3 billion in stem cell research for institutions and companies in the state.[49] In 2020, California voters passed Proposition 14, which continued to fund grants for CIRM.[50] While the majority of the funding for CIRM was directed toward stem cell research, inevitably, some of this was directed toward research on embryos, and thus, has been used to fund research on ART. After California, other states followed suit to fund embryonic stem cell research: Massachusetts, Connecticut, Maryland, New Jersey, and Missouri.[51]

Current Regulation of IVF in the United States

There is no direct regulation of IVF by the US federal government. Rather, drugs, biological products, medical devices, and clinical laboratories

Comparative regulation of embryo research and AI medical devices

Country	Regulation of Embryo Research/IVF	Regulation of AI in Medical Devices
China	Ministry of Health oversees all facilities authorized to conduct ART treatment. strict regulations regarding who is eligible for ART—those with "mental disease" or "serious genetic disease" are not permitted to utilize ART services per the Maternal and Infant Healthcare Law of 1994. Couples are required to undergo a premarital medical examination to detect serious disease. If one person in a couple is found to have a "genetic disease of a serious nature," the couple must commit to "long-term contraceptive measures" or sterilization operations before marriage. IVF is prohibited for unmarried women.	China is one of the first jurisdictions to act to regulate AI technologies, with most of China's AI regulations implemented within the last year. Per these regulations, algorithms would need to be submitted to the Cyberspace Administration of China with a filing containing the type of support provided by the algorithm, the areas/products it would be used in, a security assessment, and ethical review. The Draft Ethical Review Measure was introduced in April 2023, and this would specifically implicate research and development of AI technologies, especially those in "ethically sensitive" sectors. This would require that algorithm developers submit an annual work report to an ethical review committee, and that follow-up of the high-risk science and technology activities would occur at least twice each year. It is not yet clear whether this would apply to all AI algorithms or whether it will just apply to a select set, and the recommendations will likely change when the measure is finalized.
Australia and NZ	Reproductve Technology Accrediation Committee regulates clinic operations and utilizes an auditing process.	In 2020 New Zealand's Minister of Statistics launched the "Algorithm charter for Aotearoa New Zealand" to increase confidence and visibility for government algorithms used by the public. Signatories to the charter included the Ministry of Health, the Ministry for Women, and the Department of Justice. Each signatory is required to assess algorithm decisions using a risk matrix that quantifies the likelihood of an unintended adverse outcome against the relative level of impact. Each algorithm is regularly peer reviewed to assess for unintended consequences, and for each algorithm, a public point of contact must be listed with a channel to challenge or appeal decisions informed by algorithms.

Country	Regulation of Embryo Research/IVF	Regulation of AI in Medical Devices
United Kingdom	Human Fertilisation and Embryology Authority: tasked with inspecting clinics every two years, guidance for consent, storage, facilities and personnel. Specific policies for how PGT-M can be used for certain diseases and limits on how many embryos can be transferred to a patient. The HFEA also facilitates access to IVF through the NHS.	In March 2023, the UK's Department for Science, Innovation & Technology introduced a white paper titled "A pro-innovation approach to AI regulation." Unlike the EU, the UK does not seek to create an overarching new regulator for AI, but rather will implement AI regulation into existing sectors, while developing a central monitoring, evaluation, and risk assessment function. A 2022 partnership between the NHS and other regulators outlined the desired approach to AI as a Medical Device.
European Union	Within the EU, 32 countries have national registries of ART regulation—in 26 of these countries, registration of ART facilities is mandatory. Each country has different regulatory bodies for how IVF may be conducted and in which instances it is covered by national healthcare programs.	The proposed EU AI Act of 2021 classifies AI algorithms into different categories based on their risk levels. High risk AI systems, Class III, are defined as those "intended to be used as a safety component of a product, or is itself a product," wherein "the safety component is the AI system or the AI system itself as a product." To qualify as high risk, the systems must "pose a risk of harm to the health and safety, or a risk of adverse impact on fundamental rights" and also be intended for use in an enumerated category. Biometric data is further protected as it relates to the "physical, physiological or behavioural characteristics of a natural person."* The EU's General Data Protection Regulation (GDPR) additionally prevents "fully automated' decision making.

*For those devices that purport to conduct preimplantation genetic testing, various potential disease states of an embryo would be implicated in this data. From this information, it would be theoretically possible to extrapolate the disease or disease carrier status of the parent, thus also implicating the biometric identification of a natural person (even if the embryo itself does not merit this protection).

are regulated individually.[52] Drugs and medical devices are subject to standard US Food and Drug Administration (FDA) review processes, and clinical laboratories are subject to the Clinical Laboratory Improvements Amendments Act (CLIA). CLIA, passed in 1988, requires that all US laboratories that "provide information for the diagnosis, prevention, or treatment of any disease or impairment of, or the assessment of the health of, human beings," be issued a certificate by the Secretary of Health and Human Services.[53] Receipt of the certificate is contingent on personnel qualifications, quality of reagents and materials, calibration of devices, and methodologies for examinations and other procedures.[54] Noncompliant laboratories can be subject to an injunction, criminal sanctions, fines up to $10,000 per violation, and even civil suits if "continuation of the activity would constitute a significant hazard to the public health."[55]

Only one statute has been passed by Congress that deals specifically with ART—the Fertility Clinic Success Rate and Certification Act (FCSRCA) of 1992 mandates that fertility clinics report success rates for various procedures to the Centers for Disease Control and Prevention (CDC).[56] Since 1997, the CDC has published reports of each clinic, and as of 2020, there were 326,468 ART cycles from 449 reporting clinics.[57] The most recent National Summary Report from 2019 shows that forty-one clinics did not report data to the CDC, in violation of the statute.[58] The only repercussion for failure to report appears to be the publication of a clinic/doctor's name in the report,[59] and unlike the CLIA, the FCSRCA does not allow the US Department of Health and Human Services (HHS) to sanction or revoke the license of clinics with low success rates.[60]

Beyond the FCSRCA, the American Society for Reproductive Medicine (ASRM) and their fertility affiliate, the Society for Assisted Reproductive Technology (SART), have attempted to regulate clinics.[61] SART is, unlike most other medical organizations, a voluntary advertising committee whose goal is to maintain the standards for ART and encourage transparency and reliability in clinic advertising. In 2018, 86 percent of IVF clinics in the United States were members of SART.[62] Despite criticisms that suggest SART's self-regulation model may be ineffective, a study of SART's methods showed that of forty-four clinics found to have at least one violation in 2019, thirty-four had resolved the violations by 2020.[63] The majority of violations were related to improper maintenance of consistent and transparent supplemental data on clinic websites.[64]

Beyond the regulation of clinics, there is minimal regulation of the procedures themselves. While the number of embryos created per patient will vary, there is no restriction on how many may be created, or what may be done with embryos after they are produced. A 2018 study estimated that in women ages 35–37, 38–40, 41–42, and over 42 years, a clinician would need to collect 5, 7, 10, and 20 oocytes, respectively, to ensure that at least one embryo with the correct number of chromosomes develops.[65] However, clinics may retrieve as many oocytes as they wish, which can negatively impact the patient's health as well as contribute to the large number of unused embryos in storage.[66] Furthermore, while the ASRM recommends single-embryo transfer in all cases where a euploid embryo is transferred, clinics are not restricted by any federal guidelines should they wish to transfer multiple embryos at once, increasing a patient's likelihood of adverse events.[67] The lack of regulation extends beyond direct harm to patients—as preimplantation genetic testing becomes more popular, more clinics have opened up their services to allow patients to select for sex and cosmetic purposes.[68]

Current Regulation of AI in Medical Devices in the United States

In the United States, there is no single regulatory framework to guide the development of AI in the health sciences, much less so for AI in fertility medicine. As such, algorithms are not evaluated for bias as part of the approval process, nor are they adequately supervised as they are updated.

Availability of AI-Enabled fertility products

Company	Product	Where Available	Year Formed	First Available	Current Status	Purpose
Auxogyn	Eeva	Australia, EU, UK	2008	2012	After being sold in the EU in 2012, Canada in 2013, and the US in 2015, Auxogyn merged with fertility benefits company Fertility Authority and Auxogyn stopped marketing the Eeva product. The technology underlying the Eeva test was sold to Genea Biomedx for use in its Geri+ benchtop incubator.	Embryo selection at the blastocyst stage to improve viability/live birth rates.
Harrison.ai/ Virtus Health/ Vitrolife	iDA Score	Australia, EU, UK	2018	2021	Harrison.ai's algorithm was acquired by Virtus Health, who licensed it to IVF technology firm Vitrolife. The algorithm was incorporated into the iDA Score program which is part of Vitrolife's Embryoscope line of time-lapse data collection devices and is available individually.	Embryo selection at the blastocyst stage to improve viability/live birth rates.
Presagen	Life Whis-perer	Australia, Canada, Europe (EEA), US, UK, Japan, India, UAE, Hong Kong, Israel, Malaysia, Thai-land, Vietnam, Singapore, New Zealand, Turkey, Trinidad and Tobago, Guyana	2016	2018	LifeWhisperer Genetics was made available in the United States in October 2023. There are two versions of the LifeWhisperer product: LifeWhisperer Viability, which observes mor-phological features of embryos to determine which are the best candidates for transfer, and LifeWhisperer Genetics, which could be used to detect genetic abnormalities from photos of the embryo alone, forgoing the need for invasive testing like PGD or PGT. LifeWhisperer is in the form of an app, and does not require a time-lapse imaging system to function, instead requiring only a photo of the embryo on day five.	Replace traditional PGT with a pho-to-based test for identifying aneuploidy.

The FDA has two broad categories that AI in ART could fall into: Software in a Medical Device (SiMD) and Software as a Medical Device (SaMD). SiMD, as the name implies, is any software that helps to run a medical device. SaMD is a bit more complex, defined by the International Medical Device Regulators Forum as "software intended to be used for one or more medical purposes that perform these purposes without being part of a hardware medical device."[69] Some SaMD have already been approved by the FDA: an image analysis software designed to detect wrist fractures,[70] another to detect potential strokes and alert a patient's doctor,[71] and another for use in Apple Watches that monitors heart rhythm to estimate atrial fibrillation burden.[72] Per the FDA's own website, 521 devices that are AI/machine learning enabled have been approved by the FDA, with the majority of these devices intended for use in either radiology or cardiology.[73]

All medical devices are categorized into a class by their intended use, their indications for use, and the risk they pose to the user.[74] A device's respective class dictates the type of premarketing submission and application required for FDA clearance.[75] Class I devices are those that pose the lowest risk, Class II devices are considered moderate to high risk, and Class III devices pose the highest risk.[76] The majority of medical devices are considered Class II devices—before a manufacturer can market a medical device in the United States, it must notify the FDA of its intent to market a device per Section 510(k) of the Food, Drug, and Cosmetic Act.[77] Once the manufacturer has notified the FDA, the FDA will determine if the device is "substantially equivalent" to a device that is already on the market, and thus, whether the proposed device is as safe and as effective as what is already available.[78] For Class II devices, the 510(k) pathway is notably faster than a de novo classification request, which is the required pathway for devices that do not have a legally marketed predicate.[79] For Class III devices, premarket approval is required.[80]

As it pertains to devices that use AI, the International Medical Device Regulators Forum guidelines suggest that the risk classification be changed as a manufacturer makes changes to SaMD. If the risk level of a device changes, this could accordingly change the device's class and the requirements for market approval.[81] Most SaMD are Class II devices, but could be classified as Class III devices if they "support or sustain human life, are of substantial importance in preventing impairment of human health, or which present a potential, unreasonable risk of illness or injury."[82] The risk classification framework does not align well with how machine learning/deep learning algorithms work—part of what makes these algorithms so compelling is their ability to adapt internally as a dataset grows or changes. These algorithms, often called black box algorithms, change themselves without the user's knowledge of *how* they are changing. Current options for embryo selection via AI only claim to replace PGT-A and therefore should only detect aneuploidy, or when there is an atypical number of chromosomes. Yet, as more data is added to the dataset, the algorithm might "learn" of other factors that improve live birth rates and select for those traits without the user having explicit knowledge. Since the risk classification framework only accounts for the risk to the patient, these changes might not necessarily result in a change of device class. Similarly, while manufacturers would theoretically be required to submit a new 510(k) or de novo request for these changes, current guidelines do not adequately define at what point a change would need to be resubmitted.

In 2017, the FDA announced a Digital Health Innovation Action Plan geared toward resolving problems that relate to the faster iteration inherent in software-based technologies.[83] Shortly after, in 2019, the FDA created a pilot framework called the Software Precertification Pilot Program (SPPP) that allows the developer of a software program to be evaluated before reviewing devices individually. The FDA hoped that this program would permit qualified developers to undergo a streamlined review process and make changes to the products without having to go through the traditional review pathways.[84] However, in a 2022 report summarizing the SPPP, the FDA recognized that only nine devices were ultimately eligible for the pilot, and that it was difficult to "harmonize" information across pilot participants to create a consistent methodology in the current statutory and regulatory environment.[85]

A 2021 proposal from the FDA addressed how to resolve these issues in the context of AI and machine learning.[86] One aspect of the proposal involved a Predetermined Change Control Plan (PCCP) to "provide reasonable assurance of safety and effectiveness and would include review of the SaMD's performance, the manufacturer's plan for modifications, and the ability of the manufacturer to manage and control resultant risks of the modifications."[87] Despite the FDA's attempts to reckon with the conflict between technological improvement and patient safety, an SaMD developer who seeks to make an improvement to an authorized device is still required to submit a 510(k) for any change that is made with the intent to impact the safety and effectiveness of the device, any change that may have unintended consequences, or any change that differs from the initial risk-based assessment of the device. "The majority of the currently FDA-approved AI algorithms have proceeded through 510(k) premarket notification or de novo pathway approval, but it is unclear how many of these algorithms have been resubmitted via 510(k)s for each change made to improve the functionality or performance of their devices.[88]

Concerns about Ethical Abuses

THE PHENOMENON where policies in one country are influenced by existing policies in other countries is called policy diffusion and is a well-documented feature of modern global politics.[89] As such, the United Kingdom, as the first country to create ART-specific policies, has had a significant role in influencing how ART policy evolved in other countries.[90] Similarly, privacy policy around the world is heavily influenced by the European Union's 1995 Data Protection Directive and the 2016 General Data Protection Regulation.[91] While there are many mechanisms by which policy diffusion occurs, the outcome is the same: the first countries to act guide the direction of policy elsewhere. At present, the United States lacks both substantial federal policies to govern ethical embryo research and regulate AI technologies in medical devices. Failure to act *quickly* may mean that the United States cannot be a leader in developing policy that considers the sensitive ethical, moral, and scientific problems of AI in fertility medicine. Failure to act *at all* may mean that generations of Americans will use and be impacted by technology that may, at best, be ineffective, and at worst, may harken back to the era of "positive eugenics" that influenced IVF's initial discovery.

Failure to act *quickly* will mean that the United States cannot be a leader in developing policy that considers the sensitive ethical, moral, and scientific problems of AI in fertility medicine.

Widespread Adoption of Ineffective Technology

Adoption of machine learning/deep learning embryo-selection technologies has progressed quickly, without concrete evidence of their efficacy. In 2021, the global fertility services market was $17.45 billion, and by 2029, it is expected to grow to $31.59 billion.[92] Numerous factors belie this projected growth: an increase in maternal age over time (associated with increased difficulty to conceive), increased access to IVF technology, new technologies entering the market, and an increase in large companies providing fertility benefits to their employees.[93] There is a significant market incentive for companies to purchase fertility benefit plans for their employees to recruit and retain excellent talent. Per a 2022 McKinsey report, 32 percent of surveyed employers offer "family-building benefits," and 48 percent of surveyed employers are interested in offering family-building benefits.[94] Of the surveyed employers, 77 percent believed that offering family-building benefits would result in a return on investment.[95]

The drive to adopt more adjunct technologies in fertility medicine has also risen with the acquisition of fertility clinics by private equity firms. A study of private equity purchasing of fertility clinics in Australia and New Zealand since 2006 found "consolidation and industrialization" of the IVF field, with only three companies controlling 80 percent of IVF

cycles across the two countries.[96] In the same period, both Australia and New Zealand saw declining live birth rates from IVF as well as increasing cycle costs—leading some to believe that the adoption of new technologies by these clinics is "driven largely by profit targets," rather than efficacy.[97] Both time-lapse imaging and preimplantation genetic testing are among the adjunct treatments commonly offered by fertility clinics.

A 2017 study reviewed six time-lapse imaging algorithms and measured each on the likelihood that it would result in embryos with a fetal heartbeat. None of the algorithms presented a "clinically relevant means" to aid in embryo selection, due to the "heterogeneity in the origin and culture of the embryos used for the development of [the algorithms]."[98]

an algorithm learning from itself could ultimately deduce that a certain genetic trait is not favorable and select against this trait without consent or knowledge from the parents, without ever assessing the underlying genetic material.

Similarly, a 2019 review of nine randomized control trials determined that time-lapse imaging did not provide any considerable benefit over conventional morphological assessment (wherein conventional incubation results in a 35 percent chance of a live birth, and the use of time-lapse imaging would result in between a 27 and 40 percent chance).[99] As machine learning/deep learning technology has improved, there is some evidence to suggest that embryo scoring algorithms improve live birth rates, but these results come from smaller, often retrospective studies conducted by the creators of the respective algorithms.[100]

A study reviewing clinic reporting to the CDC found that in 2018, an estimated 30 percent of ART cycles took place at private equity-affiliated practices.[101] The study did not find differences in live birth rates between clinics that were funded by private equity and those that were not, but they did find that patients at private equity-affiliated clinics were more likely to use preimplantation genetic testing.[102] However, due to the limited scope of the data collected by the CDC, the authors were unable to conclude whether the higher use of preimplantation genetic testing in private equity-affiliated clinics was due to a confounding variable such as difference in patient population or marketing.[103] Without crucial data stemming from the mandatory rather than the optional surveillance of fertility clinics, there is no way to determine whether private equity-affiliated clinics are taking advantage of patients in a challenging situation and overutilizing tests that may not be necessary under the guise of being "responsible" about their fertility decisions.

Part of the challenge in evaluating the influence of private equity in fertility is due to the fact that the CDC does not differentiate between PGT-M and PGT-A in its clinic questionnaire.[104] This is relevant in evaluating the efficacy of a treatment, as while there are often medically indicated reasons for a patient to choose PGT-M, such as a family history of illness, PGT-A is used to check the number of chromosomes.. If a patient is under 40, PGT-A is of generally limited utility, as embryos identified as "abnormal" by PGT-A have nevertheless resulted in healthy live births, and PGT-A is often much more costly than IVF alone.[105] There is currently no available data to suggest whether algorithms used with preimplantation genetic testing are more effective than their biopsy-based counterparts, and while some evidence exists for the effectiveness of certain time-lapse imaging algorithms, this needs to be confirmed with better controls and blinded studies. If these technologies were approved in the United States before this necessary testing and validation occurs, clinics driven by the need for short-term profit will likely market them to patients at their own expense, regardless of the nonexistent or insufficient evidence of their effectiveness.

Lack of Transparency and Eugenics

Some may question why there is fear of the potential of a resurgence of eugenics enabled by advanced fertility technologies when ART provides many with the ability and choice to have biological offspring. From this perspective, ART is thought to empower those who have historically been the target of eugenics, such as queer or disabled individuals. However, because some forms of ART give people the ability to select for or against certain traits, new fertility technologies should be introduced with caution.

This is not to say that all genetic testing necessarily implicates eugenics concerns. Many future parents who use PGT-M are doing so due to the desire to prevent life-threatening illness or significant disease. Two people of Ashkenazi Jewish heritage may be concerned about the risk of their child having Tay-Sachs disease, or a woman who lost a sibling to cystic fibrosis may hope to avoid passing on the gene to her own children. Similarly, when chromosomal disorders are thought to be the case in over half of first-trimester miscarriages, future parents might choose PGT-A to reduce the likelihood that they miscarry.[106] But if genetic testing involves an algorithm that learns from itself and alters its selection without supervision when making decisions, these scenarios are more concerning: an algorithm learning from itself could ultimately deduce that a certain genetic trait is not favorable and select against this trait without consent or knowledge from the parents, without ever assessing the underlying genetic material.

Positive eugenics urged the selection of desirable traits—in the 1930s, Charles Galton Darwin (grandson of Charles Darwin) characterized positive eugenics as a necessity that would "induce the better endowed to have larger families," as the "absence of natural selection" resulting from better health care and conditions "inevitably leads to degeneration."[107] In 1939, Darwin emphasized that it was not necessary to fully understand all of the technicalities of human genetics in order to nevertheless "accomplish" something—the goal was not to "construct men with the certainty and accuracy with which an engineer can construct a bridge," but to leverage the probability that two intelligent individuals would likely produce intelligent children.[108] Aggressive proponents of AI advocate a similar desire to charge ahead, even without a concrete understanding of how it works or may work in certain contexts.[109] While this could have disastrous and unpredictable consequences in other domains, to leave this underregulated or unregulated when it implicates eugenics demonstrates a lack of regard for the value of a disabled individual's life.

People in the disability rights community have been the first to sound the alarm on the potential harm caused by some forms of genetic testing. To some people with disabilities, the very field of genetic counseling and genetic testing is "inherently directive in a way that is biased against individuals with a disability," as it causes parents to harbor concerns about embryos and their future disease state rather than an embryo's potential.[110] Although only about 2 percent of babies in the United States are born via IVF,[111] PGT-A was used in nearly 30 percent of IVF cycles,[112] indicating that genetic testing is prevalent in those who undergo IVF. While this is still a minority in the United States and even more so globally, the increase in IVF rates over time and the increase in additional testing is the exact type of issue with which the disability rights movement is concerned. The disability rights movement asserts itself as "*the* space from which to think through a host of political, theoretical, and practical issues that are relevant to all."[113] Bioethicist Adrienne Asch, in comparing disability to other drivers of health inequities such as poverty and racial discrimination, said "[p]ublic health is committed to ending such

If we don't understand how an algorithm selects "for" or "against" certain traits based off an embryo's image, it is impossible to know whether it is inadvertently discriminating.

inequities, not to endorsing them, tolerating them, or asking prospective parents to live with them. Yet the current promotion of prenatal testing condones just such an approach to life with disability."[114] While we may hope that advances in science will prevent our future children from suffering, this requires that we overlook the underlying cause of such suffering: our society is fundamentally organized to exclude people with disabilities. This is not to argue that we must ban AI-based preimplantation genetic testing, but rather, that our regulatory framework should require that algorithms are better understood before we allow them to make such important decisions**. If we don't understand how an algorithm selects "for" or "against" certain traits based off an embryo's image, it is impossible to know whether it is inadvertently discriminating.** It is essential that the underlying selection markers are better understood before this technology is made widely available in the United States.

Regulatory, Policy, and Consumer-Driven Solutions

AI-ASSISTED REPRODUCTIVE TECHNOLOGY is inherently complex and implicates a variety of actors: the Department of Health and Human Services, (National Institute of Health, Center for Disease Control and Prevention), the FDA, state agencies, and medical societies. To add to the complexity, while some regulatory frameworks must be adhered to under penalty of law (such as receiving approval for a device before bringing it to market), others are opt in (such as the rules offered by the Society for Assisted Reproductive Technology (SART) and the American Society for Reproductive Medicine (ASRM)). Here, we propose actions to be taken by various entities to prevent the adoption of ineffective technology, protect patients, and ensure the ethical development of novel technologies. As a leader in innovation, the United States must also be a leader in protecting people from potential dangers that arise with new technology.

Preventing the Adoption of Ineffective Technologies and Improving Success Rates

Preventing the adoption of ineffective technologies involves two primary issues: (1) there is no federal oversight of fertility clinics in the United States, and (2) our regulatory frameworks do not ensure that AI-based technologies for embryo selection offer a significant improvement over existing technology, especially given that many of these treatments come at a significant increased cost to the consumer.

Clinic Regulation

The Fertility Clinic Success Rate and Certification Act mandates that fertility clinics report success rates for their various procedures to the CDC.[115] With the adoption of this mandate, clinics have improved their success rates.[116] However, overall improvements to the average success rates of fertility clinics does not address the fact that there are still those clinics whose success rates have remained poor. Although data transparency encourages certain clinics to increase their rates, there is no standardized procedure to assist clinics in improving their success rates, and HHS has no ability to sanction or revoke the license of clinics with low success rates.[117] Similarly, the CDC's ability to regulate is limited to success rate data and does not address other key metrics that would be necessary to understand where certain clinics are lagging behind. Additionally, by only reporting success rates, this incentivizes clinics to implant multiple embryos or increase the dose of fertility drugs.[118]

In creating new benchmarks, HHS can take a page from the regulation of fertility clinics in other countries. If a clinic does not report its data, there should be a penalty that goes beyond having its name published in a CDC report that most patients will never know exists, let alone read. If a clinic has poor outcomes, there should be a path to improvement based on best practices, and the clinic should be given a few years to improve or lose its license. Clinic data should be easily available, and ideally produced quickly so that patients have access to recent information (the most recent report relies on 2019 statistics).

Scholars have called upon the United States to adopt regulations that are common in peer countries, such as the Human Fertilisation and Embryology Act in the United Kingdom, which would require licensing, inspection, and enforcement of certain clinic standards.[119] These standards should include, but are not limited to, a limit on number of embryos created for transfer, single-embryo transfer except for patients over age thirty-five, and mandated disclosure/informed consent requirements about the risks and success rates of certain adjunct treatments.[120]

As a leader in innovation, the United States must also be a leader in protecting people from potential dangers that arise with new technology.

While institutions such as SART, ASRM, and the American College of Obstetricians and Gynecologists have instituted many of these guidelines for their members, this does not protect the most vulnerable patients who may have fewer choices in clinics due to cost or office access. Indeed, most clinics do not adhere to the guidelines established by these entities.[121] But unlike in most of the EU, Australia, New Zealand, and the United Kingdom, in the United States, if a clinic does not adhere to the guidelines, the punishment is simply to revoke its membership. While this is best if implemented on a national level, states could create state-level licensing for clinics, and mandate reporting that goes above and beyond what is voluntarily reported to the CDC. For example, California's Center for Health Care Quality's Licensing and Certification Program is responsible for regulatory oversight of licensed and certified health-care facilities, and with legislation, could be authorized to oversee fertility clinics. Regardless of the mechanism, serious attention must be given to an enforceable mechanism to regulate IVF, especially as new adjunct technologies are introduced with little oversight as to their effectiveness.

The Federal Trade Commission (FTC) can play a role in ensuring that clinics are not putting profits over the patient's benefit, especially given that it is the current trend in private equity to recommend adjunct treatments that are not always clinically validated and increase cost.[122] This has been demonstrated in Australia and New Zealand, where private equity-owned clinics contributed to decreasing IVF live birth rates,[123] and in the United States, where private equity clinics were more likely to use PGT.[124] The FTC has recently filed antitrust lawsuits against the private equity firm Welsh Carson for the acquisition of numerous anesthesia clinics in a given geographic area.[125] If a number of fertility clinics in one area are acquired by a private equity firm, this reduces the patient's ability to compare and contrast testing options, understand what is medically necessary, and make an informed decision. While this does not directly relate to the regulation of AI in fertility medicine, as the fertility industry booms, it is essential to recognize the role that other regulatory agencies may have in indirectly preventing patients from unnecessary or harmful treatment.

Creation of Policies that Allow for Software to be Updated Without Requiring Companies to Undergo Rereview

The FDA's current approach to regulating AI in SaMD and SiMD technologies will be ineffective as more AI-based medical devices enter the market. The current framework does not allow for algorithms that learn and adapt as new data is added, and new regulations should be passed that address the desire to advance technology while protecting patients. The current pathway that would require a device to be resubmitted as a 510(k) each time the algorithm makes "significant" changes is insufficiently clear to ensure that there is continued oversight, and disincentivizes manufacturers from submitting changes to the FDA, as it requires a significant amount of work and time without necessarily providing any material benefit.

At a minimum, the FDA should adopt policies that explicitly require AI medical devices to show a clinical association between the output of the device and a

given condition, with reliable, accurate, and precise output data that achieve the intended purpose of the device.[126] As part of this policy, the FDA should adopt an algorithm change protocol that balances the desire to iterate quickly with the need for effective and safe devices. Any update would need to have a demonstrated clinical benefit over a previous version or seek to fix a "bug" or other error such that the data produced is more reliable and accurate. This policy change would allow for continued oversight and surveillance without requiring that the device is completely resubmitted via the 510(k) pathway, striking a balance between innovation and protection of patients.

The FDA itself acknowledged this priority in the final report for the SPPP, advocating for legislation that would allow for "ongoing visibility into Key Performance Indicators (KPIs), Real-World Performance (RWP) metrics, and other data that are transparent and objective, enabling timely and targeted actions to resolve issues, creating opportunities to prevent adverse events, and increasing regulatory compliance."[127] While legislation that would allow for postmarket and continuous review in SaMD has not been introduced, it should be introduced as quickly as possible to allow for sufficient oversight over AI-based technologies.

The FDA issued a draft guidance document on April 3, 2023, called the "Marketing Submission Recommendations for a Predetermined Change Control Plan for Artificial Intelligence/Machine Learning (AI/ML)-Enabled Device Software Functions" (PCCP).[128] A PCCP would be included in the initial submission of an authorization for a device and would demonstrate how a manufacturer would change its device over time. This would remove the future necessity for a 510(k), premarket supplement, or de novo plan to be submitted when changes are made to a machine learning-enabled device.[129] A PCCP would consist of a description of modifications, modification protocol, and an impact assessment to support the changes made.[130] Modifications that would fall within the scope of a PCCP include modifications to quantitative performance measures, to device inputs, and for use within a specific subpopulation.[131] The PCCP guidance demonstrates how an image analysis software could be updated to better serve its purpose, and would require transparency to users and real-world monitoring plans with each modification. While a final version of the guidance has not been published, it is a promising step in the right direction by the FDA for improved surveillance of machine learning-enabled medical devices. Existing legislation elsewhere does not solve this problem, and therefore, the United States can benefit from a first-mover advantage in this area.

Yet as we wait for finalized recommendations by the FDA, consumers and industry should advocate for increased transparency about AI-based medical technologies. In a 2020 memo on AI in EU medical device legislation, the nonprofit trade group COCIR advocated for AI "to be made transparent to the point of becoming actionable to the user."[132] Its suggestion to manufacturers was to make clear to both regulators and users the following: how the AI learns over time, the boundaries of an AI-based change, what caused the change, how the performance and safety is assured with adaptation, how quality control of new data is conducted, what triggered the change to the algorithm, the confidence levels during a given time frame, and whether the user can reject an algorithm change or roll back to a previous version. By making this information available to patients, this would resolve some of the information asymmetry inherent in AI technologies and allow embryologists to feel more confident in the selection of certain technologies for their clinics. Similarly, consumers who feel that they have a better understanding of how an AI device works might feel more inclined to use it. In a 2022 Pew Research Center report, 47 percent of those who had heard about how AI-based pain management programs worked were likely to want the treatment in their own care, versus only 27 percent who had heard nothing about it.[133] Knowing that a patient is more likely to want a treatment if they understand the underlying process, it could incentivize companies to make decisions about their algorithms more transparent.

Preventing Ethical Abuses

As AI-enabled reproductive technologies continue to develop in the coming years, the United States must develop policies to prevent ethical abuses and guide groundbreaking research. Because conservative policies severely limit the use of federal funds for embryo research, the federal government has not created ethical guidelines for IVF research. This has created a patchwork regulatory environment in the United States, with guidelines adhered to only by researchers who opt-in to certain societies, and with no real penalty for those who fail to meet certain standards. A cohesive federal regulatory framework for embryo research is needed in the United States to prevent ethical abuses and legitimize the products of American research for a global audience. While the United States similarly lacks a cohesive framework to guide AI research, it can be one of the first countries to create guidelines for the ethical use of AI in medicine. Such guidelines could serve as an exemplar for AI-enabled medical devices on a global scale and could play a part in shaping research even beyond the United States' borders.

Improving US Embryo Research

As the world's largest funder of health research, the NIH is a critical entity in ensuring that research is directed toward and conducted in a way that upholds ethical standards.[134] Yet, as a result of the Dickey-Wicker Amendment, the NIH is not permitted to fund human embryo research (with the exception of some stem cell research that was allowed following President Obama's 2009 executive order).[135] The lack of funding has not necessarily hindered the progress of innovation in the field, but the lack of a clear NIH policy has resulted in ambiguity for researchers who wish to work with embryo models to improve IVF—there is no federal guideline for how IVF research should be conducted.[136] Without explicit direction as to how research should move forward, the United States risks "bad actors taking advantage and conducting questionable work."[137] In light of the NIH's lack of clear guidelines, the National Academies of Sciences, Engineering, and Medicine (NASEM) and the International Society for Stem Cell Research (ISSCR) have developed ethical guidelines that are used in the United States.[138]

In 2005, the NASEM recommended that institutions conducting stem cell research create embryonic stem cell research oversight (ESCRO) committees. As a result, many ESCROs were created at large universities and hospitals, and some ultimately became required by state law.[139] However, unlike institutional review boards (IRBs), which are federally required to maintain a "robust set of protections for research subjects,"[140] ESCROs are not subject to any federal regulations. Although NIH has created an intramural ESCRO that guides all embryo research conducted on NIH campuses,[141] it is restricted to existing stem cell lines and prohibits research that involves derivation of embryos.[142] This, therefore, leaves many ESCROs to model themselves after one another and after the guidelines established by the NASEM and ISSCR.

The ISSCR is an independent nonprofit that seeks to support stem cell research and facilitate informed regulatory decision making.[143] The ISSCR created three categories of human embryo research that should be subject to review. Category 1A and 1B involve research that is either exempt from review by specialized oversight or only requires reporting to a given agency. Category 2 requires a specialized oversight process, and Category 3A and 3B involve unsafe, uncompelling, or unethical practices.[144] The use of AI for embryo selection is not explicitly addressed in the ISSCR categorization; however, transferring human embryos that have undergone mitochondrial replacement techniques falls under Category 2.[145] As AI-based embryo-selection techniques would not involve any manipulation of an embryo's genetics, but similarly addresses the desire of parents to prevent serious disease, it would likely fall under this same category. Research that falls under Category 2 requires a "compelling scientific rationale" and should utilize the "minimum number of embryos necessary to achieve the scientific objective."[146] The ISSCR's guidelines are not particularly strict but, nevertheless, provide guidance as to how patients are recruited, how data is collected and monitored, and

which types of interventions should be subjected to specialized review processes.[147]

The Dickey-Wicker Amendment clearly limits the NIH's ability to oversee embryo research, as NIH funding is contingent on compliance with the terms and conditions of NIH grants.[148] Without NIH grants in play, the NIH has no ability to penalize or put a halt to research that is either unethical or not scientifically sound. However, the NIH still has significant influence over researchers' actions, as researchers in both the public and private sectors may nevertheless follow NIH guidelines in the hopes that future work could receive federal funding. The NIH serves an important role in setting norms and general guidelines for research funded by state agencies and private actors. Nothing about the Dickey Wicker Amendment prohibits the NIH from setting and maintaining guidelines for scientifically rigorous and ethical research on human embryos. Thus, at a minimum, the NIH should adopt guidelines like that of the ISSCR and should provide guidance as to how ESCROs should be formed.

Ideally, the HHS and the FDA would propose federal regulations that mandate ESCROs to oversee the embryo research process, much like IRBs oversee human subject research. While the IRB approval process is not perfect and is subject to (warranted) criticism, this would require companies to have taken some minimum steps to ensure safety and ethics before taking products to market.

For de novo medical devices in Class II that involve human subject research, clinical studies must show "reasonable assurance of the safety and effectiveness of the device" during the period of the FDA's premarket notification submission.[149] These clinical studies must be approved by IRBs, which are required to register with HHS's Office for Human Research Protections. Similar IRB regulations still apply during the 510(k) premarket notification period.[150]An IRB's membership, operations, and records are all subject to federal requirements, with the penalty of disqualification should an IRB not comply.[151] Similar regulations should be proposed for ESCROs. While not exhaustive or exclusive, ESCRO membership should consist of scientific and nonscientific members; members of varied genders, ethnicities, and races; more than one member not affiliated with the institution; and a requirement that members with conflicting interests be excluded. Given the sensitive issues of disability and health, ESCROs should also be required to have at least one member who has significant personal experience or academic experience with disability. In proposing the regulations, it should be made explicit that ESCROs do not serve the same role as IRBs. Whereas an IRB's goal is to protect the dignity and health of human subjects, an ESCRO's goal should be to direct future innovation with an eye to minimizing risk and furthering ethical research. This is essential, as while it is important to address the potential eugenic harms of technology that involves human embryos, the language used must not inadvertently create a form of embryonic personhood that creates other challenges for access to reproductive health.

Appropriate AI Frameworks

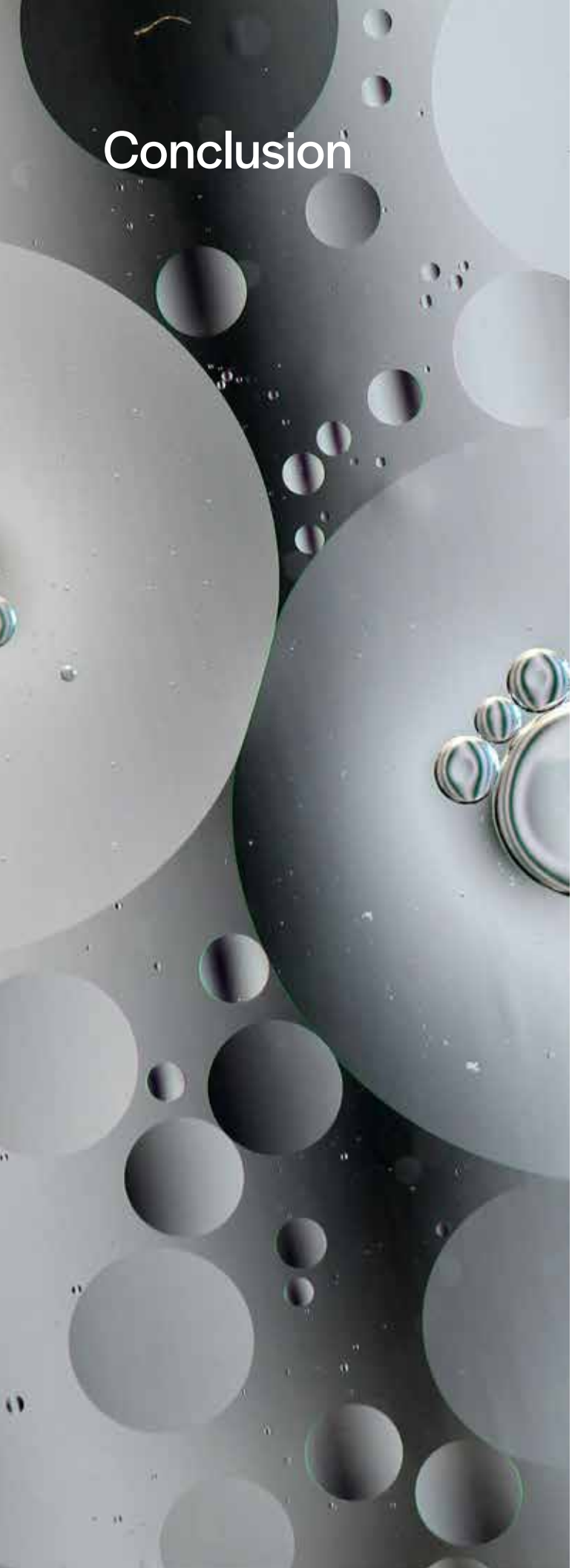
The Biden administration introduced the "Blueprint for an AI Bill of Rights," which recognized that "systems supposed to help with patient care have proven unsafe, ineffective, or biased," and that disparities in AI frameworks should be assessed, mitigated, and monitored.[152] While the framing of AI policy as a privacy and civil rights issue is promising, the proposal has no authority and does not effectively lay out policy for AI medical regulation. Attempts by other countries similarly fall flat, and no country has a comprehensive AI regulation that would adequately address the challenges AI poses in fertility medicine.

The EU Artificial Intelligence Act has been highly anticipated as one of the first major attempts to regulate and understand AI's role in our world. However, the AI Act does not effectively regulate technology, especially as it pertains to AI and medical devices.

The EU relies on the Charter of Fundamental Rights and preexisting legislation on data protection, consumer protection, nondiscrimination, and gender equality in crafting AI policies to reduce bias. However, a critical aspect of AI is that an algorithm's

effectiveness depends on the data used to train it. The EU AI Act does not effectively differentiate between an algorithm and an algorithm's training data. While it defines "training data" as "data used for training an AI system through fitting its learnable parameters, including the weights of a neural network," it fails to describe exactly how a researcher would procure the "non-discriminatory access to health data" to train the algorithm.[153] **This is not a problem of AI or algorithms, but of underlying biases in health data—those that reflect and amplify existing racial biases.** An algorithm might be fair but it will nevertheless reproduce biases if they are present in the dataset. As one group of researchers put it, "[f]or example, is it enough to satisfy the fundamental right of nondiscrimination to build AI systems to ignore variables such as race, or is that right violated if the system nonetheless produces disparate impact on various racial groups? What happens if including race as a variable produces more racially equitable outcomes?"[154]

In some countries in the EU, such as France and Germany, collection of data that indicates race or ethnicity is limited to first- and second-generation immigrant status.[155] **In this case, the United States' hesitancy to approve and regulate AI technologies before the EU could result in datasets that amplify biases inherent to the European method of data collection.** While steps can be taken to reduce bias that would harm future generations, this is a potential oversight in the EU's AI framework. In crafting policy around the ethical challenges presented by AI, the United States should consider the concerns of bioethicists and disability scholars who understand the potential eugenic impact of AI in fertility medicine, and act to create policy that prohibits the use of AI-based technologies unless developers are able to understand and explain how their algorithm selects against certain diseases or traits that are already commonly screened for through traditional preimplantation genetic testing.



Conclusion

DETERMINING HOW TO REGULATE AI is a complicated task—the technology progresses faster than lawmakers can set guidelines, and the potential consequences and ethical implications of AI vary greatly depending on how the technology is used. Moreover, the subject matter implicitly deals with a variety of moral and ethical concerns. Due to these factors, combining AI with ART is an unprecedented regulatory challenge that requires an understanding of how both technologies work and the potential consequences of failure to act.

This brief advocates for the United States to act where possible to regulate AI in fertility medicine and acknowledges that many of the ideal solutions to this problem are unlikely to be achieved due to decades of conservative policies designed to keep the federal government out of embryo research. As such, the FDA is perhaps the key regulator to address the issues posed by AI embryo selection. It can ensure that technologies do not enter the market without sufficient clinical validation of their effectiveness and that transparency and reduction of bias are at the forefront of policies to govern AI-enabled medical devices. The FDA should adopt policies that specifically address the ability of ART to disproportionately impact people with disabilities and lead to eugenics-like policies. However, the FDA need not be the sole actor to review these technologies as they are invented and seek to be introduced to the public. Professional agencies, state governments, and consumers all have a role to play in advocating for safe and effective AI implementation in not only fertility medicine, but in all health-care applications.

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The Othering & Belonging Institute brings together researchers, community stakeholders, and policy-makers to identify and challenge the barriers to an inclusive, just, and sustainable society in order to create transformative change.