ELSI Friday Forum Summary: The Genie Is Out of the Bottle for Polygenic Screening of Embryos

Event Overview

The Center for ELSI Resources and Analysis (CERA) hosted its March 2023 ELSI Friday Forum titled "The Genie Is Out of the Bottle for Polygenic Screening of Embryos: Where To From Here?" on March 10, 2023. The forum explored the emerging practice of using polygenic risk scores to screen embryos during in vitro fertilization (IVF) procedures. The event featured presentations by Francesca Forzano, MD, FRCP, consultant clinical geneticist at Guy's and St. Thomas NHS Foundation Trust and honorary senior lecturer at King's College London, and Gabriel Lázaro-Muñoz, PhD, JD, an expert in neuroscience, law, and bioethics studying the implications of emerging biomedical technologies. The session was moderated by Anna Lewis, DPhil, an ELSI scholar with background in the genetics industry, and was facilitated by Maya Sabatello, LLB, PhD.

The forum aimed to address the scientific, ethical, and societal implications of polygenic embryo screening technology, which has already entered clinical practice despite limited evidence of its validity and utility. As noted by Dr. Lewis in her introduction, in 2020, the first baby selected using preimplantation genetic testing for polygenic disorders was born, and the technology is now available in approximately 30% of fertility clinics throughout the United States.

Context and Background

Dr. Lewis provided important context for the discussion, noting that IVF resulted in over 73,000 births (2% of all infants) in the US in 2018, with rates as high as 5.1% in Massachusetts. She explained that while testing embryos for chromosomal abnormalities (aneuploidy) and single-gene disorders has become common practice, the newer trend of screening for polygenic conditions represents a significant expansion of genetic selection capabilities.

The moderator highlighted that tests like LifeView, offered by Genomic Prediction, are now available in 140 clinics throughout the US. These tests integrate various forms of genetic testing and claim to help select embryos with lower risks for common conditions like heart disease, diabetes, and cancers. Some companies have even developed a "polygenic health index" that aggregates scores across multiple conditions.

Dr. Lewis also referenced a public opinion survey that found 43% of the public would use polygenic screening technology if it were safe, free, and already being used by 10% of other parents—with higher percentages among younger and more educated respondents.

Key Insights from Dr. Francesca Forzano: The European Perspective

Dr. Forzano presented the European Society of Human Genetics' (ESHG) position on polygenic risk scores in preimplantation genetic testing (PGT). She explained that polygenic risk scores (PRS) are collections of many common genetic variants (sometimes hundreds of thousands or millions) that have been associated with particular common traits or conditions in adults.

Key points from Dr. Forzano's presentation included:

1. **Nature of polygenic risk scores**: PRS represent only a proportion of the causal factors for complex conditions, with environmental factors and lifestyle choices also playing significant roles. The scores provide relative risk information, often with modest absolute risk modifications.
2. **Construction of scores**: PRS are "constructed" rather than "discovered," based on specific research questions, and different PRS for the same condition can yield varying risk estimates.
3. **Limitations of PRS in embryo screening**:
   - PRS were developed and validated in adult populations, not embryos
   - Limited genetic diversity within individual families
   - Small number of embryos (typically 2-5) available for selection
   - Mitotic mutations developing in embryos are not detected
   - All embryos will have some degree of risk for different conditions
4. **Scientific consensus**: Multiple scientific societies have issued statements against the use of PRS in preimplantation genetic testing, including the European Society of Human Reproduction and Embryology, the American College of Medical Genetics and Genomics, and the International Society of Psychiatric Genetics.
5. **Equity concerns**: PRS have been primarily developed using data from individuals of European descent, raising significant issues of equity and applicability across diverse populations.

Dr. Forzano concluded that polygenic embryo screening is "not currently considered appropriate for clinical practice" due to lack of validation, evidence of clinical utility, and guidelines for best practice. She emphasized the need for broader societal discussion about what interventions should be offered in preimplantation genetic testing, prenatal diagnosis, and trait selection.

Key Insights from Dr. Gabriel Lázaro-Muñoz: IVF Patient and Provider Perspectives

Dr. Lázaro-Muñoz presented findings from interviews with 27 reproductive endocrinologists and infertility specialists and 26 IVF patients in the United States. His research, funded by the National Human Genome Research Institute and conducted in collaboration with colleagues including Todd Lencz, Shai Carmi, and Stacy Pereira, provided insights into stakeholder perspectives on polygenic embryo screening.

Key findings from the provider interviews included:

1. **Provider reluctance**: Only 3 out of 27 clinicians said they would tell patients about polygenic embryo screening, with 12 explicitly opposing it due to scientific limitations. Most said they would discuss it only if patients specifically asked.
2. **Concerns about accuracy**: Most clinicians expressed concerns about the test's accuracy and scientific validity.

From the IVF patient interviews, Dr. Lázaro-Muñoz reported:

1. **Interest in screening for various conditions**: Before discussing polygenic embryo screening specifically, many patients expressed interest in screening for neurological and psychiatric conditions, along with physical health conditions.
2. **Intended use of screening information**: 16 patients said they would use genetic information to select or exclude embryos, while others mentioned prioritizing embryos or using the information to prepare for potential health issues in their future children.
3. **Trait selection**: When asked about screening for traits like intelligence, height, or eye color, 12 patients said they would be interested, while 12 said they would not, and 2 were uncertain. All patients who expressed interest in trait selection mentioned intelligence as a desired trait.
4. **Interest after explanation**: After being shown embryo report cards and receiving an explanation of polygenic embryo screening, 18 out of 26 patients said they would want to use this technology, 4 said no, and 4 were uncertain.

Dr. Lázaro-Muñoz noted the contrast between clinicians (who were generally reluctant to offer polygenic screening) and patients (who showed considerable interest after being informed about the technology).

Q&A Session Highlights

The Q&A session explored several key issues:

Line-drawing in trait selection

Dr. Lewis asked Dr. Forzano about the ESHG's call for societal debate on acceptable trait selection and how this relates to disability rights critiques. Dr. Forzano acknowledged this as a complex issue that requires extensive discussion and is relevant not only to polygenic screening but also to prenatal testing and gene editing. She noted that different societies have different values and options available regarding reproductive choices, and that tensions often arise when conditions considered medical problems by some are viewed as part of identity by others.

Comparison with embryo editing

When asked about similarities between polygenic screening and embryo editing debates, Dr. Lázaro-Muñoz expressed concern that polygenic embryo screening has received less attention and research despite conceptual similarities. He emphasized the need for greater focus on this technology.

Patient education and ethics

Both speakers emphasized the importance of education for prospective parents. Dr. Lázaro-Muñoz stressed the need to ensure parents can make decisions aligned with their values and interests, with proper understanding of the technology's capabilities and limitations. Dr. Forzano highlighted equity concerns, noting that different populations would not have equal access to effective polygenic screening due to ancestry-based limitations in current scores.

Gatekeeping role of physicians

Dr. Lázaro-Muñoz discussed the minimal regulation of genetic screening in US fertility clinics, noting that physicians serve as gatekeepers. He predicted that market forces might eventually lead initially reluctant clinicians to offer polygenic screening as patients seek these services elsewhere. Dr. Forzano added that in the absence of regulatory frameworks, clinicians typically look to best practice guidelines from scientific societies, though these recommendations have not been widely followed in the US context.

Key Themes and Takeaways

Several important themes emerged throughout the forum:

1. **Scientific concerns**: Both speakers emphasized limitations in the current state of polygenic risk score science, particularly regarding validation, predictive accuracy, and applicability across diverse populations.
2. **Tension between autonomy and responsibility**: The discussion highlighted ongoing tensions between respecting reproductive autonomy of prospective parents and societal responsibilities to prevent eugenics or discrimination.
3. **Commercial vs. clinical perspectives**: Speakers noted the blurred boundaries between clinical care and commercial interests, particularly in the less regulated US fertility market.
4. **Need for broader engagement**: Both speakers called for wider societal discussion about appropriate uses of genetic selection technologies, going beyond scientific and medical communities to include diverse public perspectives.
5. **Regulatory differences**: The contrast between European and US approaches to regulating reproductive technologies was evident, with European scientific societies taking stronger positions against premature clinical implementation.

The forum did not reach definitive conclusions on where boundaries should be drawn in embryo selection, but rather emphasized the need for continued research, public engagement, and thoughtful consideration of both individual and societal implications of these rapidly advancing technologies.