Genetic embryo screening for health issues and IQ inch closer to reality. Here's a primer on what you can expect

T he world of IVF has introduced a host of ethical quandaries. For now, Alabamians will be spared grappling the latest, genetic design of their future children, as their high court has effectively foreclosed the procedure. The laboratories offering these genetic selection tests are based in NJ and California, and we can expect a host of genetic tourism to ensue.

Once upon a time, if you wanted a tall, handsome, healthy child, you married a tall, goodlooking, healthy spouse. That approach isn't always reliable, since by virtue of genetic laws two tall people still have a respectable chance of having a short, gawky kid, and numerous extrinsic factors, including the environment, impact both height and health. Don't despair. There's a technique, called 'preimplantation testing for Polygenic Disorders' (PGT-P), marketed to give prospective parents a "choice over chance." Does it work? Is it safe? Is it ethical?

Human prenatal genetic testing has been used (or misused) for decades, culminating in the genetic editing of twin girls in 2018 by Chinese embryologist, He Jiankui. Perhaps more benign, but still controversial, is using pre-natal genetic screening to select particular embryos for birthing based on the genetic traits desired. Commercially available in the US, but beyond comprehensive government oversight, use of these technologies is circumscribed only by the few voluntary guidelines produced by medical organizations. Recently, the American College of Medical Genetics and Genomics (ACMG) sounded in.

Post-natal genetic screening was first used and legally mandated, in 1963 to identify babies born with PKU, a devastating metabolic disorder that can be prevented by diet. Adult use of wide-spectrum genetic screening, utilizing Genome-Wide Associations Studies (GWAS), is now commonly available to identify disease *risks* that can be relieved or possibly prevented by lifestyle or environmental changes. For example, assessing for the presence of assessing BRCA 1 and BRACA mutations may lead to earlier detection and more effective treatment. Gene therapy utilizing bespoke drugs or use of modified genes can remedy certain conditions, even in utero. Valid uses for *post*-conception genetic screening abound.

Using genetic screening in the pre-implantation stage is more fraught. In conjunction with IVF (in vitro fertilization), p*re*natal genetic testing (*PGT)* is conventionally employed to *deselect* embryos with Mendelian abnormalities. i.e., those with certain and serious adverse post-birth outcomes, or those which would have difficulty implanting. Using PGT to facilitate genetic editing of the embryo, however, is verboten. Another use of PGT is identifying embryos to generate compatible tissue for transplantation to an already born, but ill, child, called savior siblings. The technique was first effectuated almost a quarter of a century ago, and the practice is controversial, accounting for only 1% of PGT done today.

The issue before us pertains to yet another use:applying the screening techniques chosen by adults for the yet unborn.

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Prophecy v. prediction

Once unabashedly advertised, at least two American laboratories reportedly claimed to identify the healthiest embryo of the IVF litter for selection. (Their current adverts are distinctively toned down from earlier versions). In actuality, the technique does not identify a particular disease to which the embryo will succumb, but rather predicts *risks* of disease. The service provides a cumulative health ranking, called the polygenic risk score (PGS), grading the genetic predisposition for numerous conditions.

> Unlike any other service in the world, LifeView patients also have access to Embryo Health Scores, which have been proven to reduce the risk of common diseases like: diabetes, cancer, and heart disease in your future child…

Because we are looking at overall health, and because the disorders targeted are polygenic, with their expression governed by the synchronized effects of multiple genes and further mediated by environmental stressors, the PGS is far from definitive in its predictive capability. Nevertheless, it might provide some indicia of possibilities, giving parents the advertised "choice over chance."

The prospective parent, in basing their embryo selection on genetic risk indicators, theoretically has the option of configuring a kid with the most brains or brawn or beauty. Although these techniques are not currently on the table, , the possibility has incited ethical outrage.

> Accurate IQ predictors will be possible, if not the next five years, the next 10 years certainly
>
> — Stephen Hsu of Genomic Prediction, a commercial marketer of the PGT technology

> You are not going to stop the modeling in genetics, and you are not going to stop people from accessing it. It's going to get better and better.
>
> — Matthew Rabinowitz, CEO of the prenatal-testing company Natera

The ACMG, advises that the scores may be both inaccurate predictors and require unnecessary and dangerous procedures.Their rationale is medical, which, while informative, doesn't provide the ethical guidance needed should the medical/scientific obstacles be surmounted. Nevertheless, let's take a peek at the effectiveness of the technique before diving deeper.

Inaccuracies are derived from various systemic deficits:

- Probabilistic statistics are based on population data and not predictors of individual likelihoods of disease.

- The data derive from research populations (e.g., white European) which are not transferrable to the racial diversity of the American market.
- Adult experiences on which predictive algorithms are modelled may not translate to embryos.
- Expression of risk are not entirely genetic and are highly influenced by external factors, which cannot be predicted.
- Low PGS are not indicative of no risk, creating a false aura of assurance of safety.
- The testing samples in IVF embryonic biopsies may be too small to provide accurate results.

Risk communication of probabilistic results is fraught with difficulty. Embryo selection based on uncertain statistical information couples uncertainty with uncertainty. How does one address results that, for example, reveal an embryo with a low risk of cancer but a high risk of diabetes?

A Risk-Benefit Analysis:

> [Other] perinatal risks include preeclampsia, abnormal placentation, cesarian section, prematurity, low birth weight and miscarriage. Studies of fetal risks of IVG have identified increased risks of birth defects, as well as imprinting disorders.
> – ACMG

Inextricably wedded to the speculative nature of these predictive tools are the dangers involved in IVF, a necessary precursor to using PGT-P technology. For those needing IVF to address infertility, these risks may be an acceptable tradeoff. For prospective parents wishing to influence trait selection, the required IVF, which involves heavy maternal exposure to hormonal stimulation, is not.

The ethicists sound in

The ACMG invites review and investigation by the ethical and legal communities, acknowledging that their review did not assess these concerns and will be needed. So, what do the ethicists have to say? In terms of specifics, not much.

> Companies promote their services directly to consumers and promise 'advanced embryo screening' for …diverse conditions. There are significant concerns, which render such claims suspect and the introduction of this technology for embryo selection, ethically questionable.
>
> — Alex Polyakov Clinical Associate Professor, Faculty of Medicine, University of Melbourne et. al.

Many bioethicists uniformly oppose the practice. Of note is Julien Savelescu, the author of the doctrine of parental beneficence, who onced claimed that parents are obligated to choose the "best" children. Savelescu has backtracked from this earlier position. Now he limits his advocacy of the technique to parents using IVF for infertility purposes.

The limitations of the current ethical considerations can be seen by rationale offered by the ethicists

which, track the same objections the medical community offers: analytic validity, clinical validity, and clinical utility – all of which will wane once the techniques become more precise and a greater body of data is generated. Appended to this list, in Brutus-like obeisance, without specific anchor, are the traditional bioethical precepts: autonomy,, beneficence and non-maleficence (a fancy way of saying harms and benefits), and social justice concerns.

A specific structural basis to decide what is ethical in this context, however, is missing, a fact lamented and recognized by Ronald J. Wapner, MD, vice chair of research in the Department of Obstetrics and Gynecology and director of Reproductive Genetics at the Columbia University Irving Medical Center.

Perhaps it's time to see what the law has to say.

Source:

Polygenic risk score for embryo selection—not ready for prime time Human Reproduction DOI: 10.1093/humrep/deac159

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