Polygenic risk scores give inaccurate and highly inconsistent results in embryo selection, researchers find

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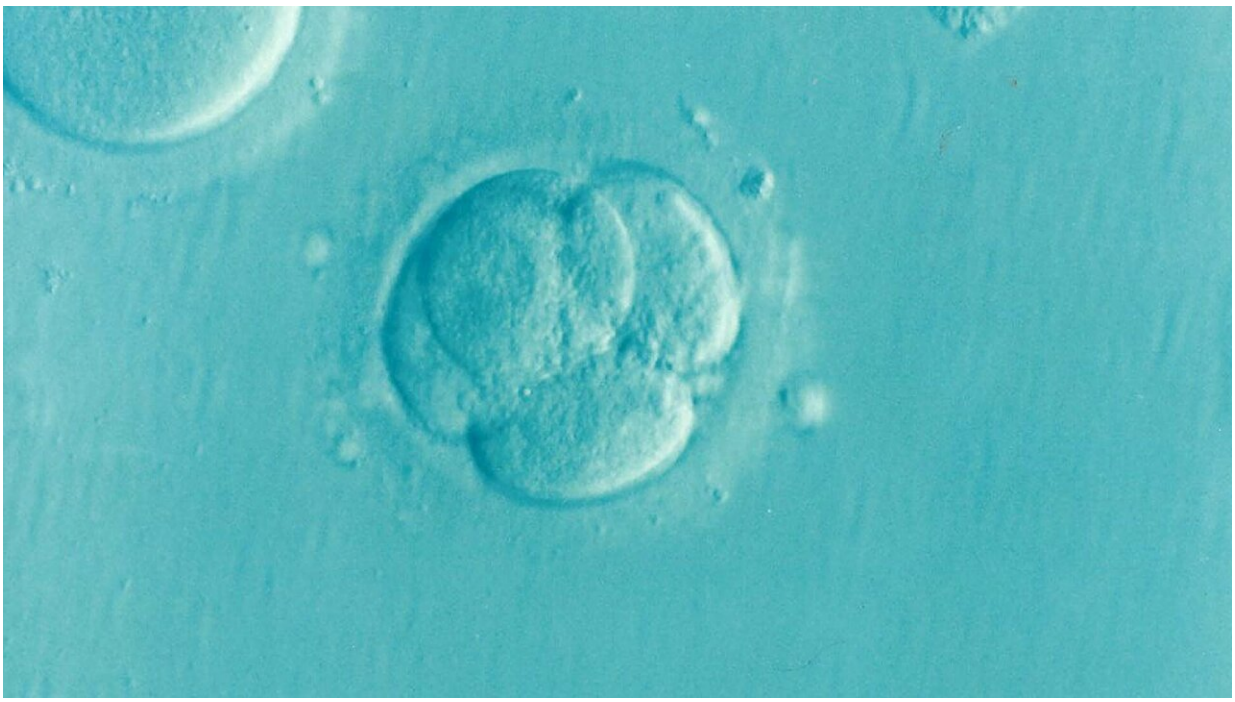

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Polygenic risk scores (PRSs) are estimates of an individual's susceptibility to a specific complex trait obtained by aggregating the effects of dozens, thousands, and potentially millions of genetic variants associated with that specific trait into a single figure. Some private

companies now market PRS embryo screening to prospective parents through the use of in vitro fertilization and pre-implantation genetic testing.

While PRS has great potential for prediction in live-born (mostly adult) individuals, its accuracy is still far from perfect. And this is even truer for its use in the selection of pre-implantation embryos (PGT-P), say the Japanese scientists who have discovered just how inaccurate and inconsistent the outcomes can be. Their results were presented at the annual conference of the European Society of Human Genetics.

Using large-scale computational simulations and data from BioBank Japan, Dr. Shinichi Namba, from the Department of Genome Informatics, Graduate School of Medicine, University of Tokyo, Japan, and colleagues, constructed PRSs for PGT-P to predict adult height, as well as the risk for type 2 diabetes (T2D).

They selected randomly 500 males and 500 females from whom they simulated couples. From each of these couples they simulated 10 embryos, and then applied the six most widely-used PRS methods to predict height and diabetes data for these embryos.

When they evaluated the 'best' embryos, i.e. those predicted to be the tallest and those with the least diabetes risk selected by each method, they were surprised to find that there was little or no concordance between them.

"We had not been expecting such a lack of robustness. No combination of two PRS methods selected the same embryo over half the time. The lowest-ranked embryo ranked using one method could be the top-ranked in another. Even worse, simply repeating the same method produced a different embryo rating each time, and this pattern was the same when screening for both height and T2D.

"There is no single state of the art method, and individual researchers use the one they prefer, but our results were so conclusive that we can say confidently that PRS scores in embryos are basically worthless at present," says Dr. Namba. "There is little point in following up this research until the technology improves."

Many conditions are caused by a combination of genetics and environment, and PRSs are only able to capture parts of any of the relevant genetic component, which is itself likely to be highly complex and difficult to analyze.

Using PRS screenings in order to select a 'suitable' embryo means that many embryos would have to be discarded, perhaps unnecessarily, and this would be unethical. In the context of fertility treatment there are usually very few embryos to choose from to begin with, so it is important that the choice of one over another be based on sound evidence.

"While pre-implantation testing for conditions with a single genetic cause is evidence-based, this is not the case for PRSs. I believe that companies selling this service to prospective parents should clearly state its limitations and acknowledge the inaccurate and inconsistent nature of the results," says Dr. Namba.

"And while we understand the desire to have a healthy baby, should we ever arrive at a stage where the accuracy of this technology is much improved it should not be made widely available without a society-wide debate taking place."

Professor Alexandre Reymond, from the Center for Integrative Genomics, University of Lausanne, Lausanne, Switzerland, and chair of the conference, said, "These results align perfectly with the ESHG recommendation regarding the use of polygenic risk scores in pre-implantation genetic testing, i.e. that it is at the moment both unproven

and unethical."

More information: Abstract no. C02.4 Pre-implantation genetic testing by polygenic risk scores selects different embryos across score construction methods with randomness

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