The Genie Is Out of the Bottle for Polygenic Screening of Embryos: Where To From Here?

March 10, 2023 at 12pm ET/9am PT

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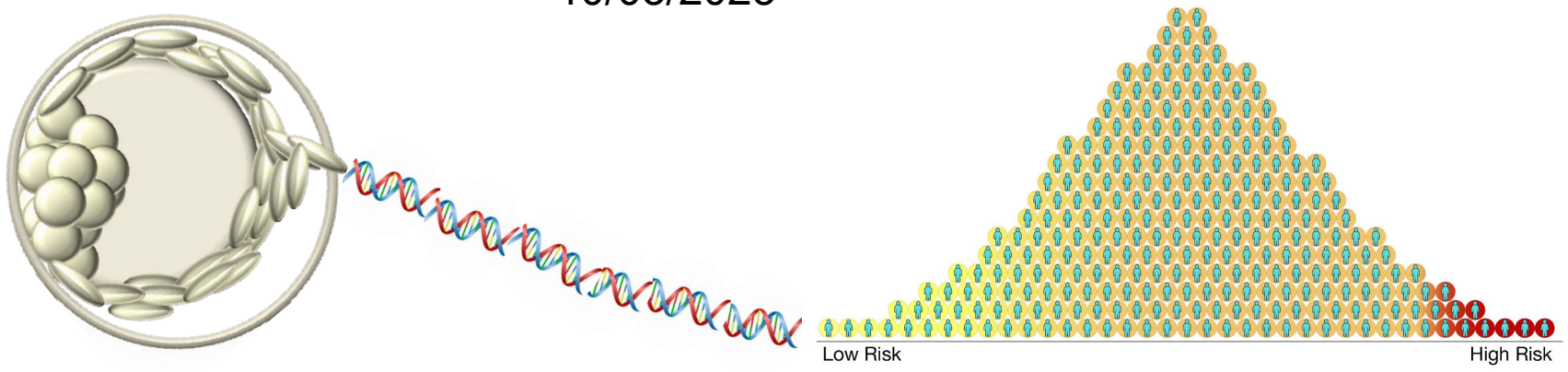
The use of Polygenic (Risk) Scores in PGT (PGT-P)

Francesca Forzano
10/03/2023



Disclosures:

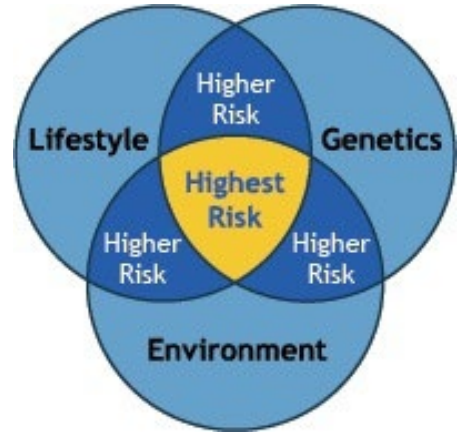
I have No Conflict of Interests to disclose

The context:
PGT = Preimplantation Genetic Testing = population are embryos

The tool:
Polygenic risk scores (PRS)

What are PRSs?

Integration of **common genetic variants** which are more frequent in **adults affected** with a given **common disease/trait**



Common complex disorders =

environmental factors +/x

lifestyle choices +/x

genetic predisposition

About PRS: https://www.genome.gov/Health/Genomics-and-Medicine/Polygenic-risk-scores

What are PRSs?

Hundreds to thousands of variants are tested and combined for each disease considered – and still capture only part of genetic component

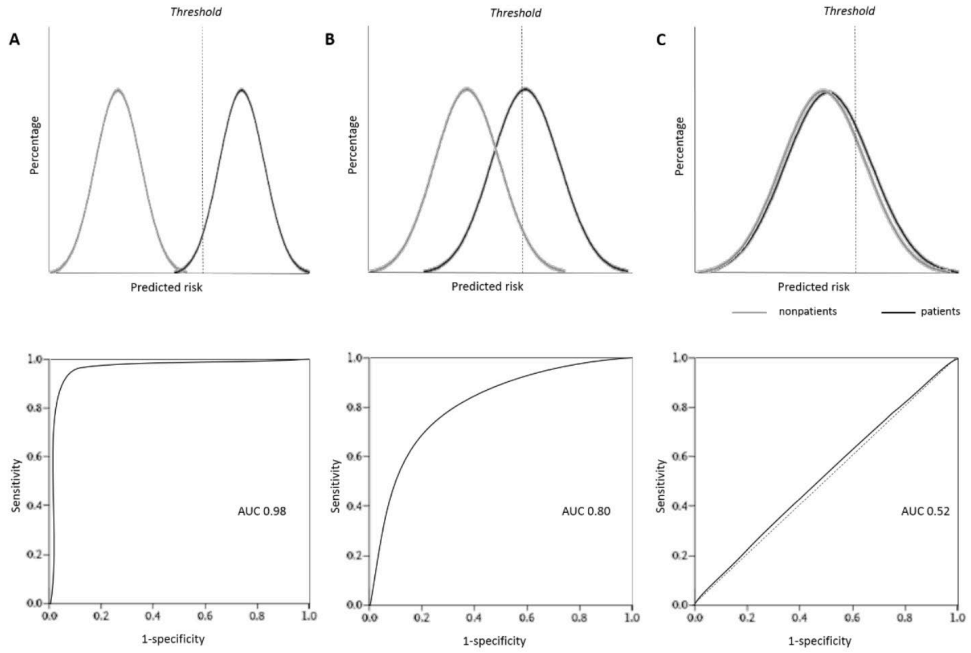
Variants can be inside or outside genes (known or unknown)

Association = we do not know what these variants do

Currently in research domain / pilots

Prediction Research
An introduction
A. Cecile J.W. Janssens, MA, MSc, PhD
Forike K. Martens, MSc
Version 2.1 (May 2018)

Figure 6 Risk distributions and the area under the ROC curve (AUC)



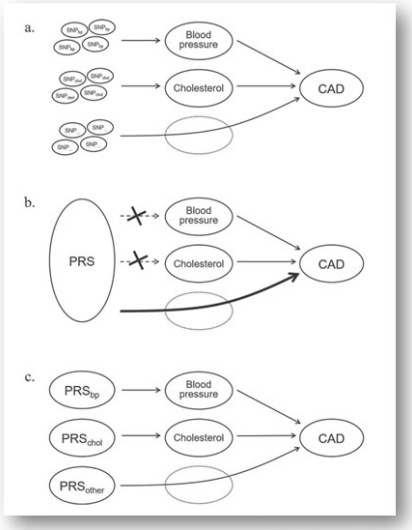
PRS does not 'exist', it's constructed.

Is PRS independent from clinical risk factors?

Many studies find that PRS is unrelated to clinical risk factors;

identifies high-risk individuals that cannot be identified by clinical risk factors

Makes little sense
PRS is independent factor because it is designed so



Prediction Research
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NEW YORK — Polygenic risk scores for the same disease can provide different risk estimates for the same person, an issue that could affect their use in the clinic.

Assessing agreement between different polygenic risk scores in the UK Biobank

Lei Clifton[1✉], Jennifer A. Collister[1], Xiaonan Liu[1], Thomas J. Littlejohns[1] & David J. Hunter[1,2]

scientific reports

Limits of PRSs

They provide **relative** risk, **not absolute** risk, which is often only slightly modified

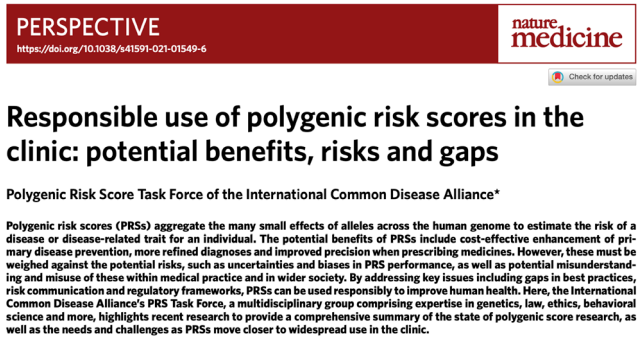
Pleiotropy: one variant might have multiple and opposite associations

More useful if combined with age, environment and lifestyle choices

Confounding genetic factors – for instance variant unbeknownst with mendelian effect (increase / reduce risk)

Only validated for **European descent**

Different PRSs for same disease might provide different risk estimates



PERSPECTIVE
https://doi.org/10.1038/s41591-021-01549-6

nature medicine

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Responsible use of polygenic risk scores in the clinic: potential benefits, risks and gaps

Polygenic Risk Score Task Force of the International Common Disease Alliance*

Polygenic risk scores (PRSs) aggregate the many small effects of alleles across the human genome to estimate the risk of a disease or disease-related trait for an individual. The potential benefits of PRSs include cost-effective enhancement of primary disease prevention, more refined diagnoses and improved precision when prescribing medicines. However, these must be weighed against the potential risks, such as uncertainties and biases in PRS performance, as well as potential misunderstanding and misuse of these within medical practice and in wider society. By addressing key issues including gaps in best practices, risk communication and regulatory frameworks, PRSs can be used responsibly to improve human health. Here, the International Common Disease Alliance's PRS Task Force, a multidisciplinary group comprising expertise in genetics, law, ethics, behavioral science and more, highlights recent research to provide a comprehensive summary of the state of polygenic score research, as well as the needs and challenges as PRSs move closer to widespread use in the clinic.

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Different PRSs for same disease might provide different risk estimates

CLINICAL UTILITY NOT DEMONSTRATED

Limits of PRSs in embryos

They provide **relative** risk, **not absolute** risk, which is often only slightly changed

Pleiotropy: one variant might have multiple and opposite associations

More useful if combined with environment and lifestyle choices

Confounding genetic factors – for instance variant unbeknownst with mendelian effect (increase / reduce risk)

Only validated for European descent

Different PRSs for same disease might provide different risk estimates

Not validated for children or embryos

In one individual family the diversity is limited

Embryos will develop mitotic mutations, which cannot be detected

All embryos will be at risk for something

Slippery slope towards selection for traits not related to diseases

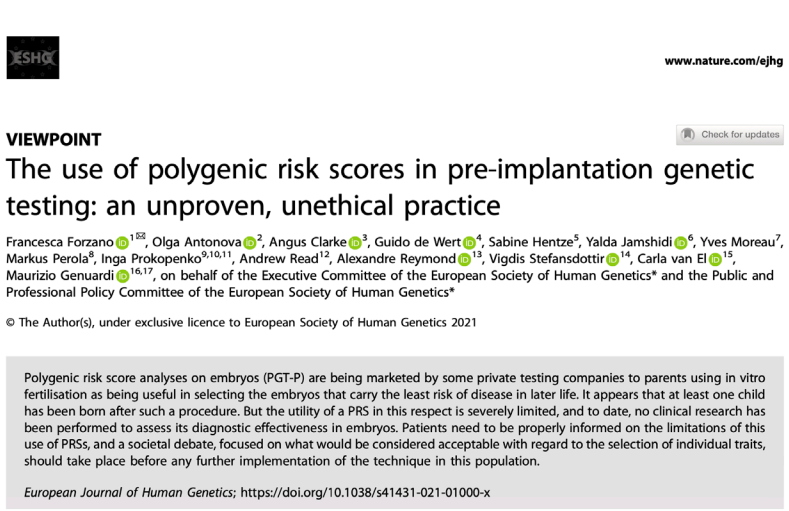
PGT-P = Preimplantation Genetic Testing for Polygenic risk scores (PRS)

Not a validated genetic test – either as diagnostic or screening test

There is no current evidence of clinical utility in the original context (adults)

There are no guidelines or recommendations for best practice

There have never been research protocols on embryos



www.nature.com/ejhg

VIEWPOINT

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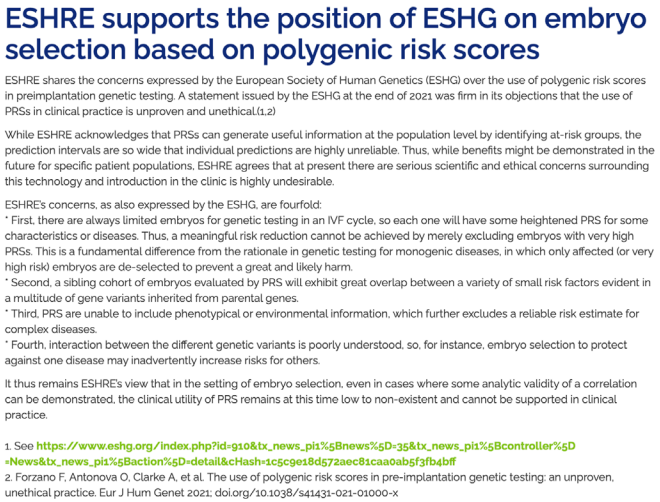
The use of polygenic risk scores in pre-implantation genetic testing: an unproven, unethical practice

Francesca Forzano[1✉], Olga Antonova[2], Angus Clarke[3], Guido de Wert[4], Sabine Hentze[5], Yalda Jamshidi[6], Yves Moreau[7], Markus Perola[8], Inga Prokopenko[9,10,11], Andrew Read[12], Alexandre Reymond[13], Vigdis Stefansdottir[14], Carla van El[15], Maurizio Genuardi[16,17], on behalf of the Executive Committee of the European Society of Human Genetics* and the Public and Professional Policy Committee of the European Society of Human Genetics*

Polygenic risk score analyses on embryos (PGT-P) are being marketed by some private testing companies to parents using in vitro fertilisation as being useful in selecting the embryos that carry the least risk of disease in later life. It appears that at least one child has been born after such a procedure. But the utility of a PRS in this respect is severely limited, and to date, no clinical research has been performed to assess its diagnostic effectiveness in embryos. Patients need to be properly informed on the limitations of this use of PRSs, and a societal debate, focused on what would be considered acceptable with regard to the selection of individual traits, should take place before any further implementation of the technique in this population.

European Journal of Human Genetics; https://doi.org/10.1038/s41431-021-01000-x



ESHRE supports the position of ESHG on embryo selection based on polygenic risk scores

ESHRE shares the concerns expressed by the European Society of Human Genetics (ESHG) over the use of polygenic risk scores in preimplantation genetic testing. A statement issued by the ESHG at the end of 2021 was firm in its objections that the use of PRSs in clinical practice is unproven and unethical.(1,2)

While ESHRE acknowledges that PRSs can generate useful information at the population level by identifying at-risk groups, the prediction intervals are so wide that individual predictions are highly unreliable. Thus, while benefits might be demonstrated in the future for specific patient populations, ESHRE agrees that at present there are serious scientific and ethical concerns surrounding this technology and introduction in the clinic is highly undesirable.

ESHRE's concerns, as also expressed by the ESHG, are fourfold:

* First, there are always limited embryos for genetic testing in an IVF cycle, so each one will have some heightened PRS for some characteristics or diseases. Thus, a meaningful risk reduction cannot be achieved by merely excluding embryos with very high PRSs. This is a fundamental difference from the rationale in genetic testing for monogenic diseases, in which only affected (or very high risk) embryos are de-selected to prevent a great and likely harm.
* Second, a sibling cohort of embryos evaluated by PRS will exhibit great overlap between a variety of small risk factors evident in a multitude of gene variants inherited from parental genes.
* Third, PRS are unable to include phenotypical or environmental information, which further excludes a reliable risk estimate for complex diseases.
* Fourth, interaction between the different genetic variants is poorly understood, so, for instance, embryo selection to protect against one disease may inadvertently increase risks for others.

It thus remains ESHRE's view that in the setting of embryo selection, even in cases where some analytic validity of a correlation can be demonstrated, the clinical utility of PRS remains at this time low to non-existent and cannot be supported in clinical practice.

1. See https://www.eshg.org/index.php?id=910&tx_news_pi1%5Bnews%5D=35&tx_news_pi1%5Bcontroller%5D=News&tx_news_pi1%5Baction%5D=detail&cHash=1c5c9e18d572aec81caa0ab5f3fb4bff
2. Forzano F, Antonova O, Clarke A, et al. The use of polygenic risk scores in pre-implantation genetic testing: an unproven, unethical practice. Eur J Hum Genet 2021; doi.org/10.1038/s41431-021-01000-x

Genetics inMedicine

www.nature.com/gim

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ACMG STATEMENT

Direct-to-consumer prenatal testing for multigenic or polygenic disorders: a position statement of the American College of Medical Genetics and Genomics (ACMG)

ACMG Board of Directors[1]*

Genetics in Medicine (2021) 23:2027–2028; https://doi.org/10.1038/s41436-021-01247-1

ISPG INTERNATIONAL SOCIETY OF PSYCHIATRIC GENETICS

ADVISORY ON THE USE OF POLYGENIC RISK SCORES TO SCREEN EMBROS FOR ADULT MENTAL HEALTH CONDITIONS.

Approved by the ISPG Board May, 2021

Authored By ISPG Ethics Committee: Chair Lea Davis, *Co-Chair* Maya Sabatello, *Head Writer* Todd Lencz, and *Contributors*: Jehannine Austin, Anna Docherty, Laura Bierut, Gabriel Lazaro-Munoz, Consuelo Walss-Bass, Laura Huckins, Holly Peay, Roseann Peterson, Takahiro Soda, David Crepaz-Keay, David Curtis, Franziska Degenhardt, Manuel Mattheisen, Marcella Rietschel, Bettina Meiser

Moving innovation to practice: an Ethics Committee opinion

The Ethics Committee of the American Society for Reproductive Medicine

American Society for Reproductive Medicine, Birmingham, Alabama

The introduction of new strategies, tests, and procedures into clinical practice raises challenging ethical issues involving evaluation of evidence, balancing benefits and harms, supporting patient autonomy, avoiding conflict of interest, and promoting advances in health-care. The purpose of this document is to assist reproductive health practitioners as they introduce new interventions into the clinical care that they provide to patients. This document replaces the previously published document of the same name, last published in 2016. (Fertil Steril® 2021;116:331-6. ©2021 by American Society for Reproductive Medicine.)

El resumen está disponible en Español al final del artículo.

Discuss: You can discuss this article with its authors and other readers at https://www.fertstertdialog.com/posts/32770

KEY POINTS

- Innovation is a fundamental element in improving health-care.
- Clinical research is an essential step in developing new interventions, whether by prospective research or by well-designed assessment of outcomes.

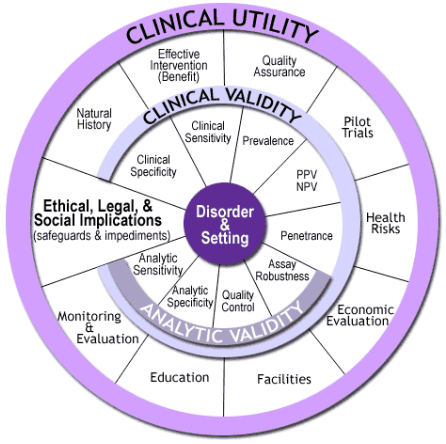
- Evidence of safety and effectiveness is necessary before dissemination of new interventions into clinical practice.

- Practices adopting new interventions should carefully consider the generalizability of research data, the learning curve for technical competence, and informed consent. Ongoing data collection is critical for complete understanding of the benefits, harms, and optimal application of a new intervention.

PGT-P

Tool not currently considered appropriate

But what is our clinical question?



ACCE Model Process for Evaluating Genetic Tests

Visual Storytelling in ELSI Research

April 14, 2023 at 12pm ET/9am PT

Elizabeth Gross Cohn, PhD, RN, FAAN
City University of New York, Columbia University

Gary Ashwal, MA
Booster Shot Media

Moderated by
Sara Ackerman, PhD, MPH
University of California - San Francisco

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