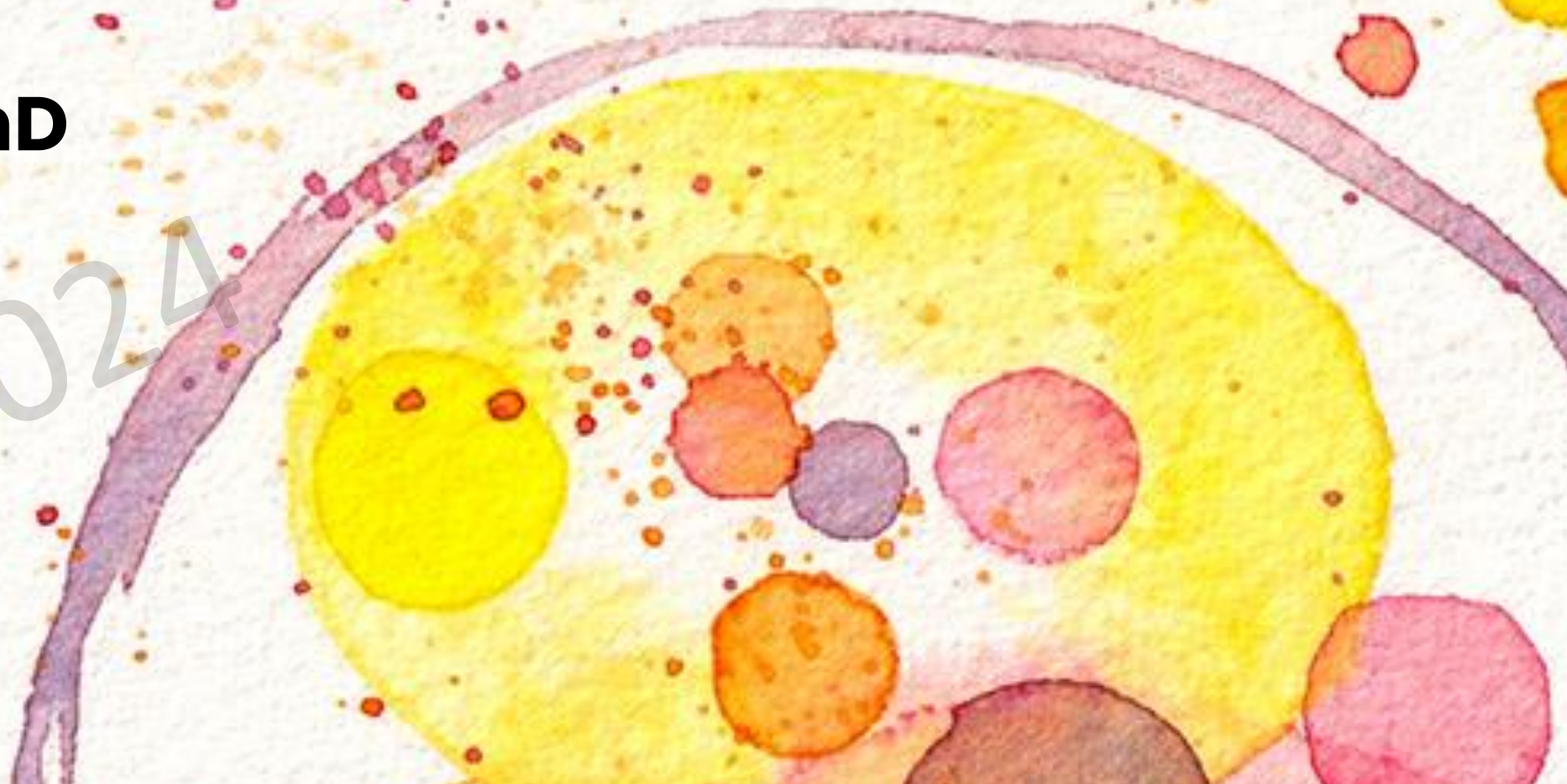
Preimplantation Genetic Testing for Polygenic Disease Risk (PGT-P)

Diego Marin, PhD

Deputy Director
Genomic Prediction

Associate Professor
Rutgers University



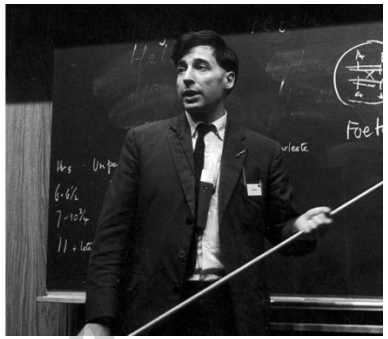
Conflict of Interest

Full-time employee at Genomic Prediction, a PGT provider

IVF pioneers predicting PGT-P

"It **should be possible** to diagnose accurately almost any gene defect that is characterized at the DNA level…for example, diagnosis of **genetic predisposition to heart disease or cancers**"
Reproductive Medicine Review
1993;2:51-61

IVF pioneers predicting PGT-P



"Many of the major human traits are highly **polygenic**, and a large number of genes may possibly be **analysed in embryos in the near future**"

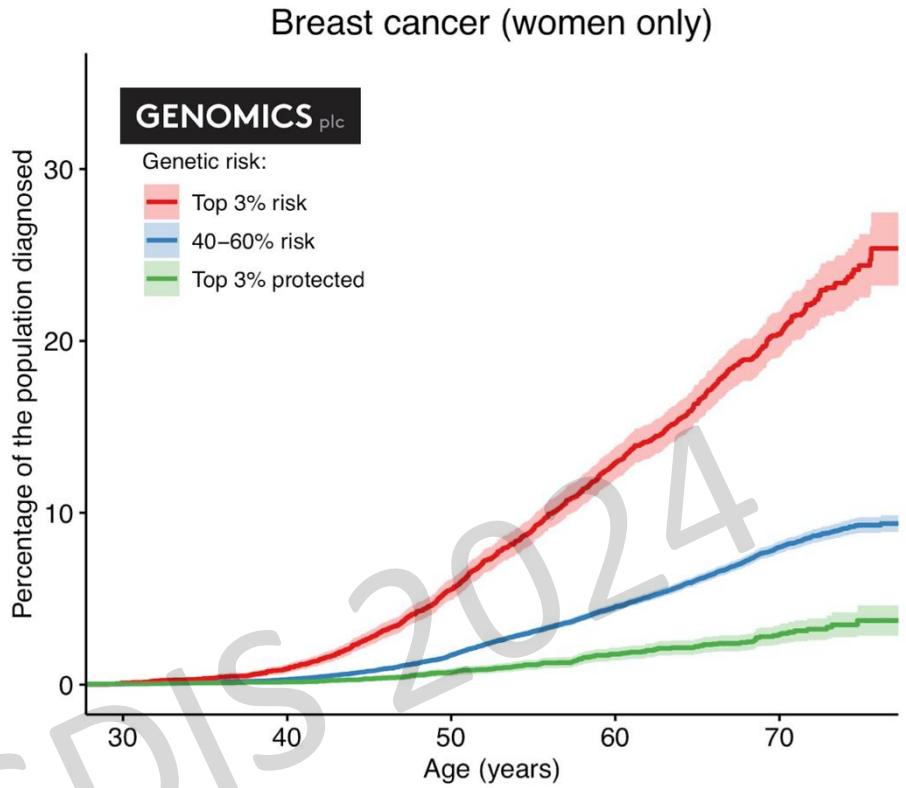
Human Reproduction
1996;3:463-464.

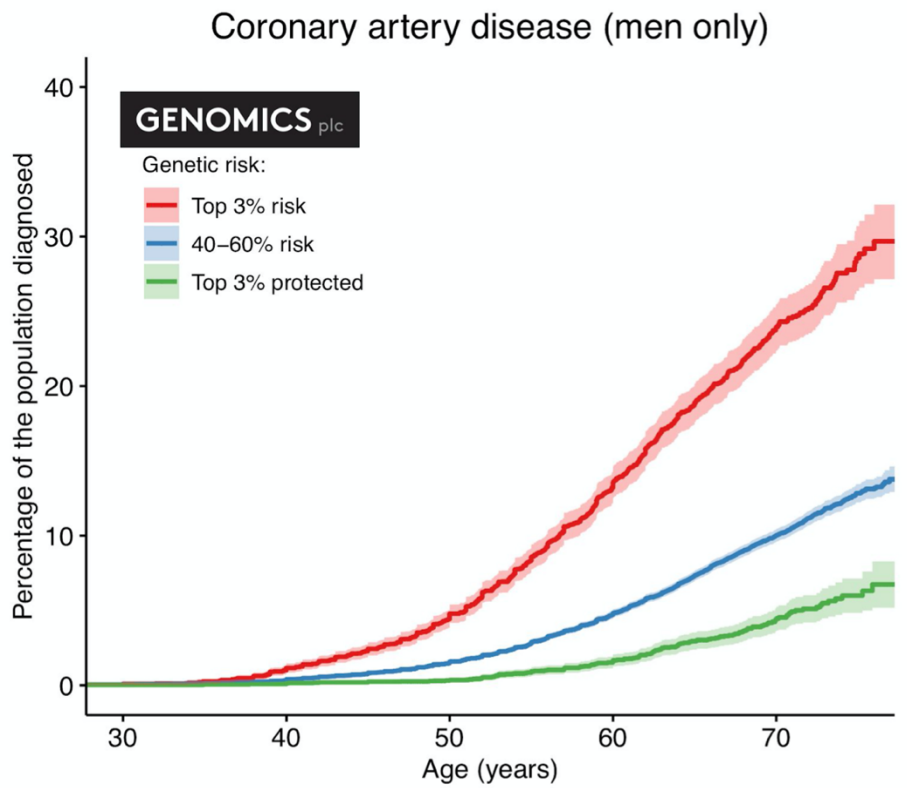
IVF pioneers predicting PGT-P

"**In the near future**, it may be possible to assess an individual's genetic **predisposition for cardiovascular disease, all types of cancer and infectious disease**"

Human Reproduction
2000;15 Suppl5:111-6.

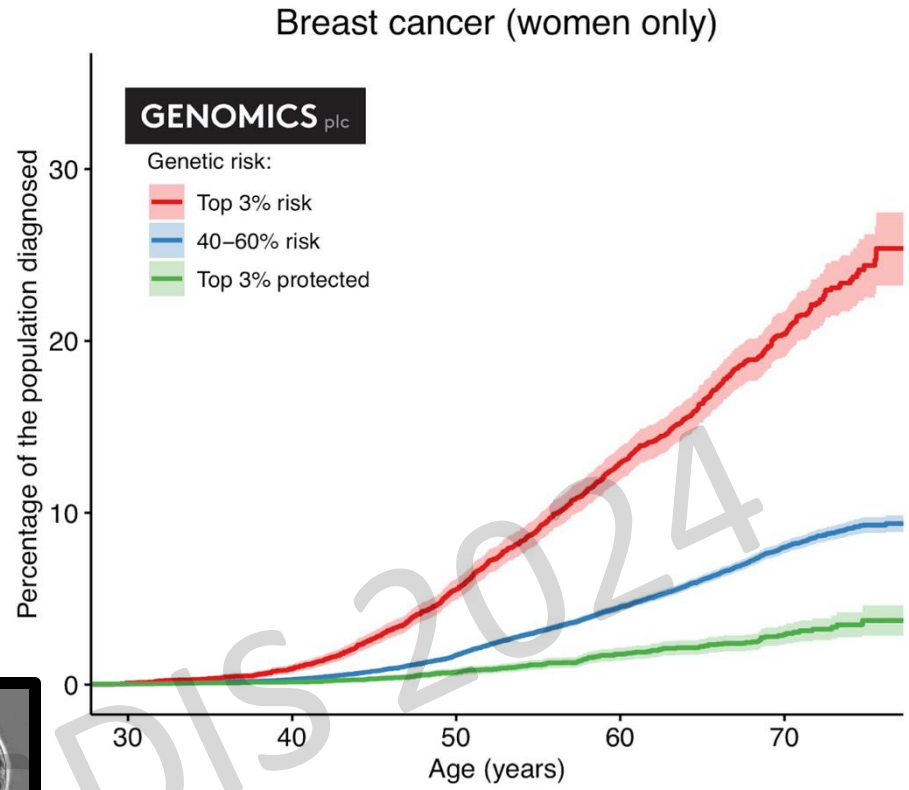
Polygenic Risk Scores

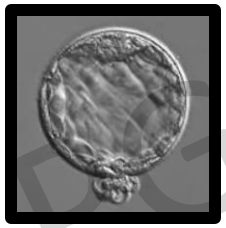


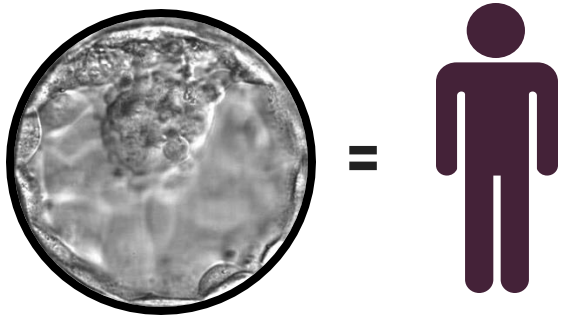


www.genomicsplc.com, **The Economist** Bhattacharya 2018, and the **UK BioBank**

Polygenic Risk Scores







99.7% Genotyping Accuracy

Treff et al. **EJMG** 2019

www.genomicsplc.com, **The Economist** Bhattacharya 2018, and the **UK BioBank**

NIH Study Funded

Polygenic Embryo Screening: Towards Informed Decision-Making

Project Number	Contact PI/Project Leader	Awardee Organization
5R01HG011711-03	LENCZ, TODD Other PIs	FEINSTEIN INSTITUTE FOR MEDICAL RESEARCH

Project Funding Information for 2023

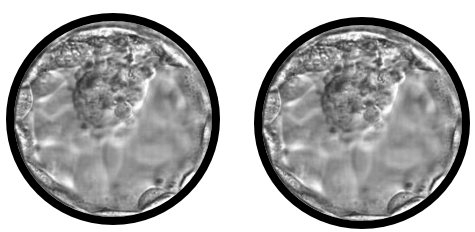
Total Funding	Direct Costs	Indirect Costs
$722,906	$602,948	$119,958

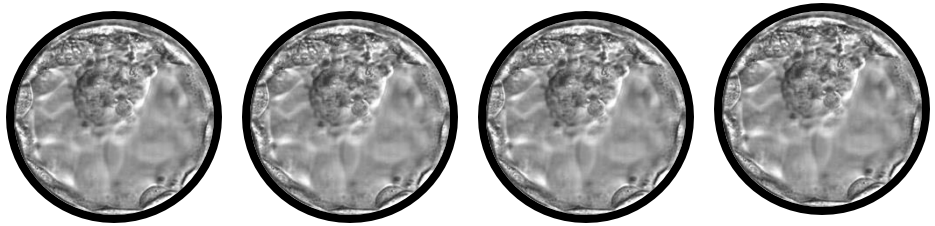
Year	Funding IC	FY Total Cost by IC
2023	National Human Genome Research Institute	$722,906

www.polygenicembryo.org

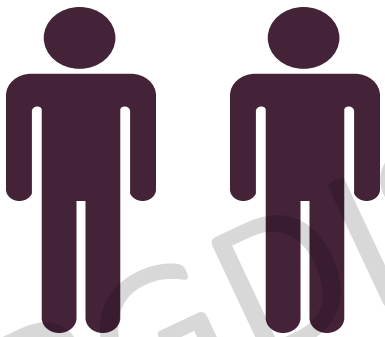
How do we know PGT-P works?

Sibling Studies





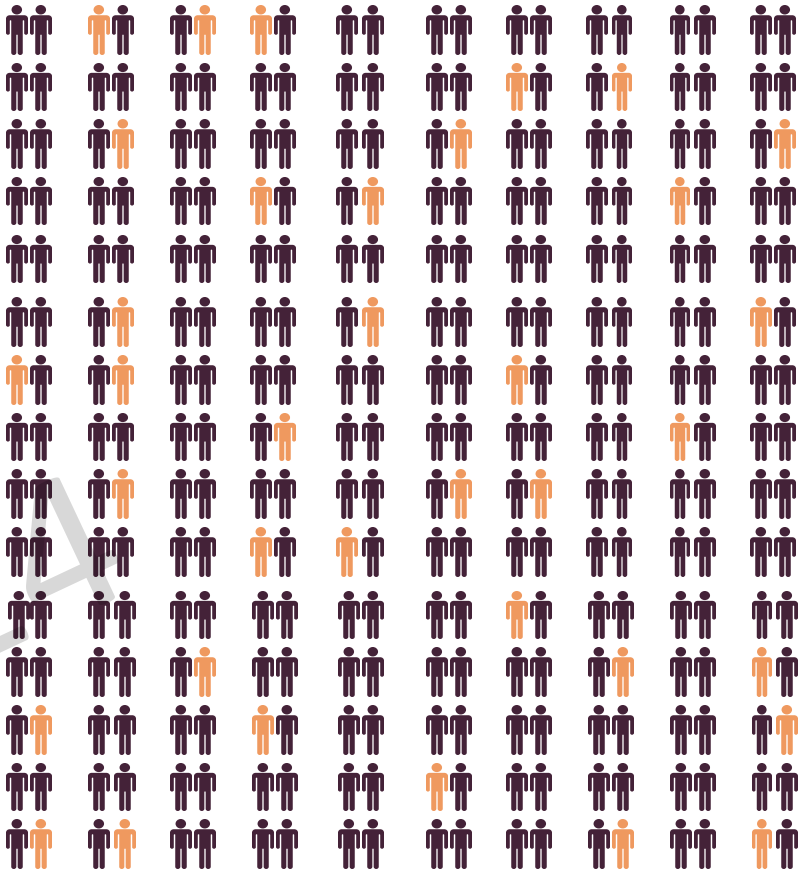
Factors in the *environment*



Validation

affected

unaffected



*11,883 sibling pairs

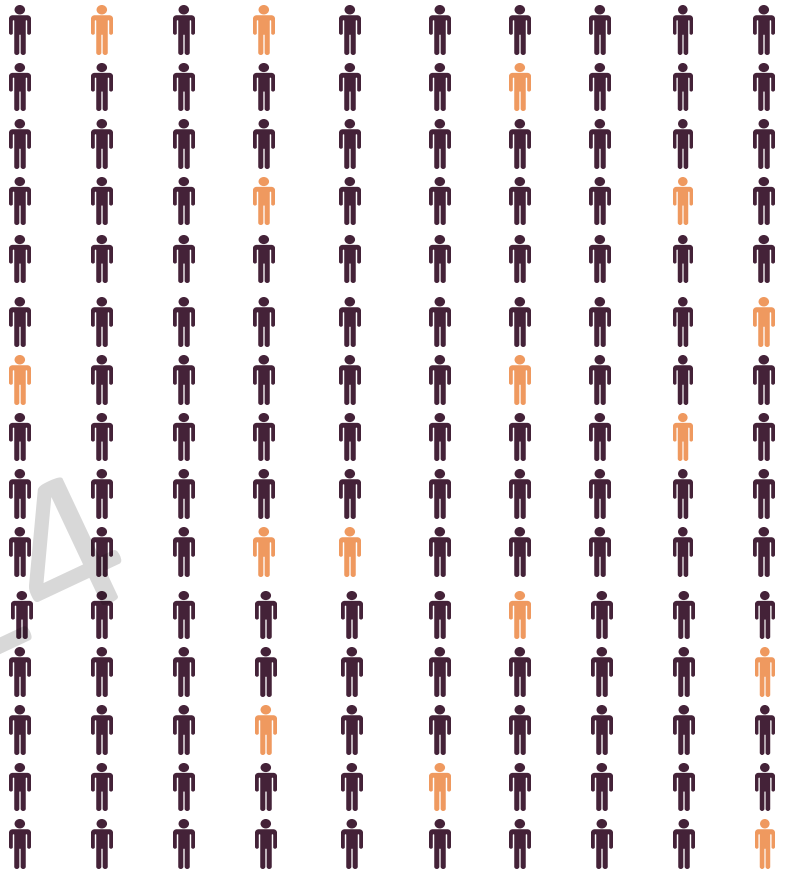
prevalence

11%

Validation

affected

unaffected



Random Selection

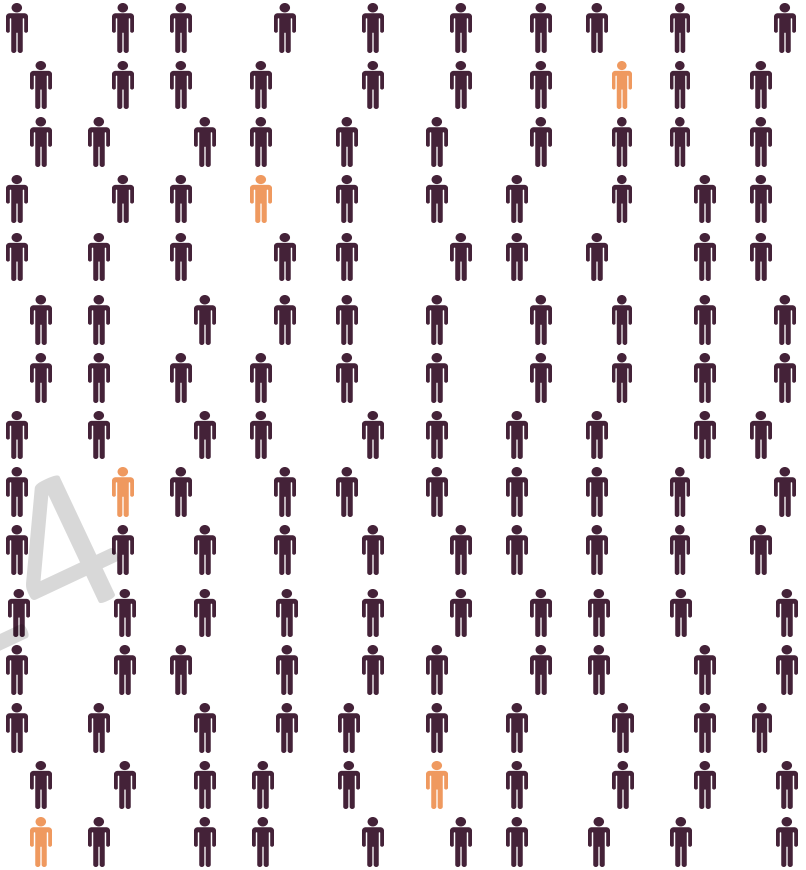
prevalence

11%

Validation

affected

unaffected



Genetic Selection

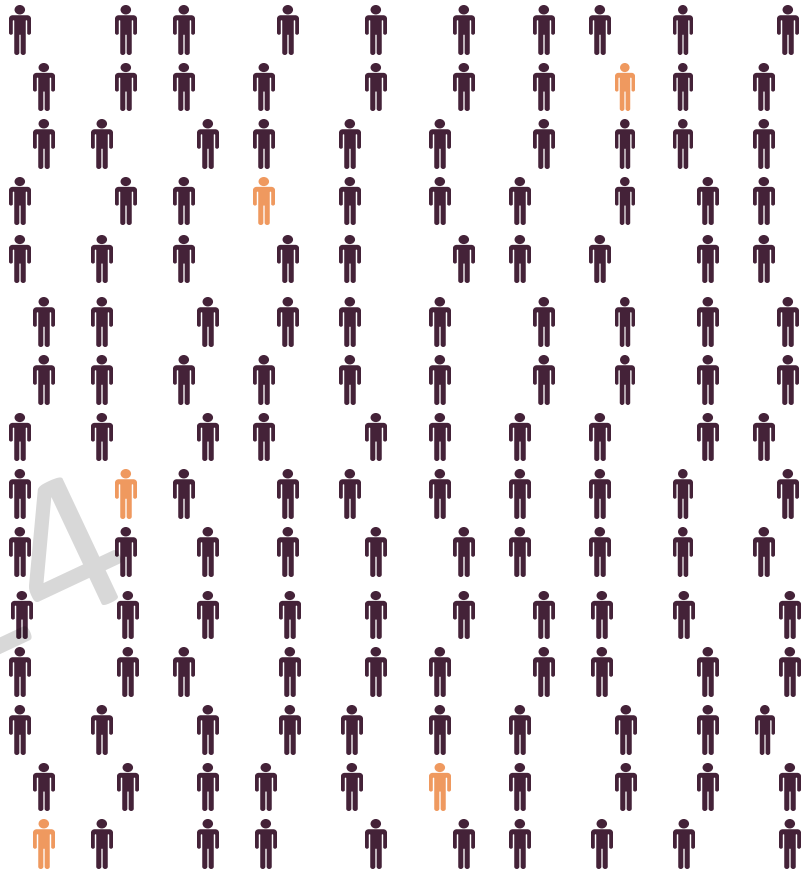
prevalence

3%

Validation

affected

unaffected



Genetic Selection

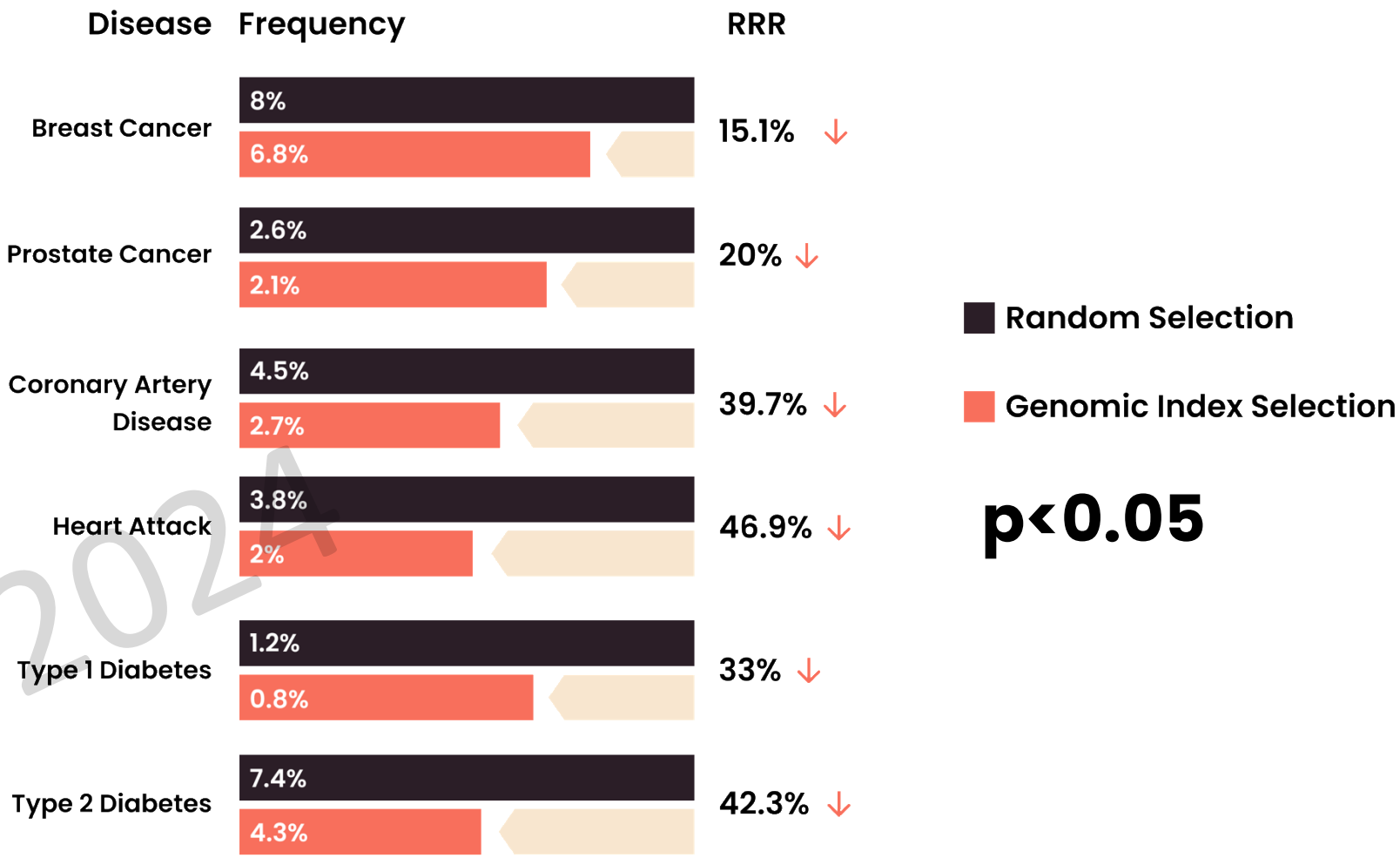
prevalence

11% → 3%

relative risk reduction

↓73%

Relative Risk Reduction (n=11,883)



Treff et al. ***Genes***. 2020

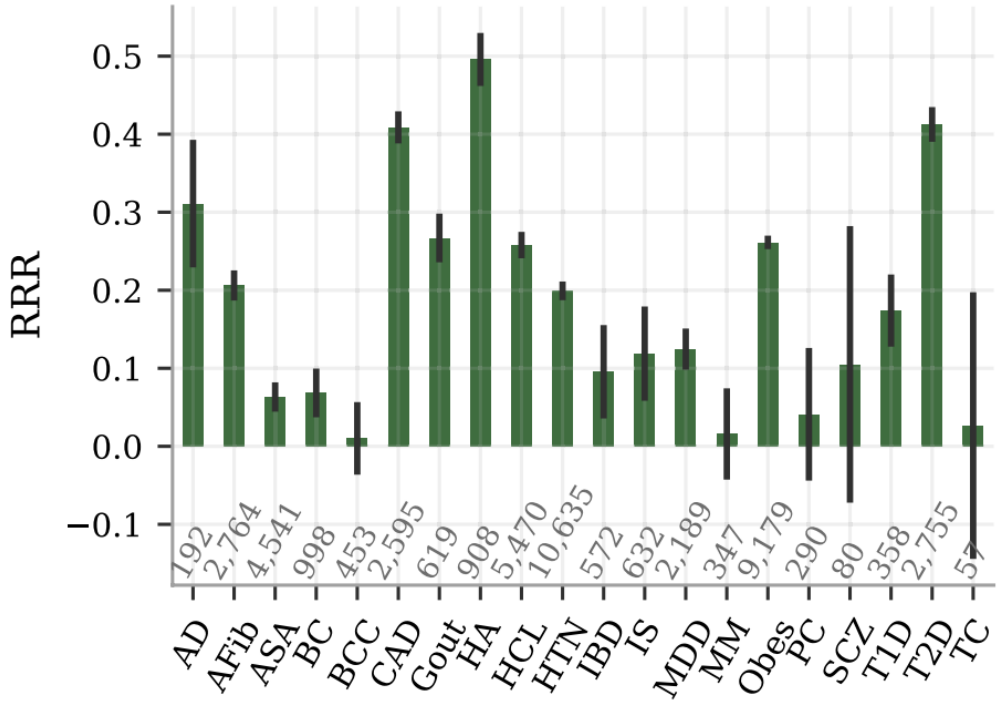
Pleiotropy?

scientific reports

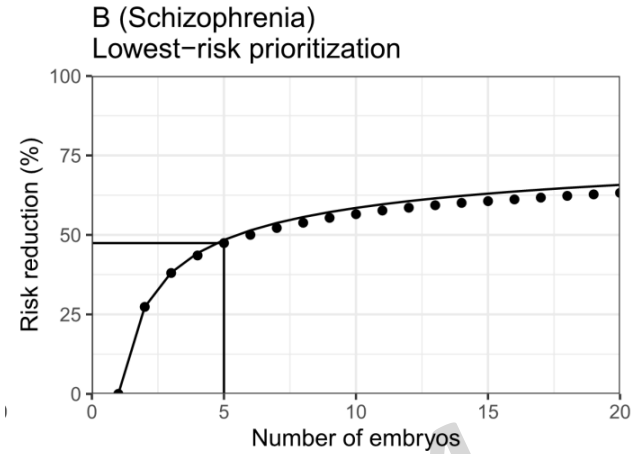
OPEN

Polygenic Health Index, General Health, and Pleiotropy: Sibling Analysis and Disease Risk Reduction

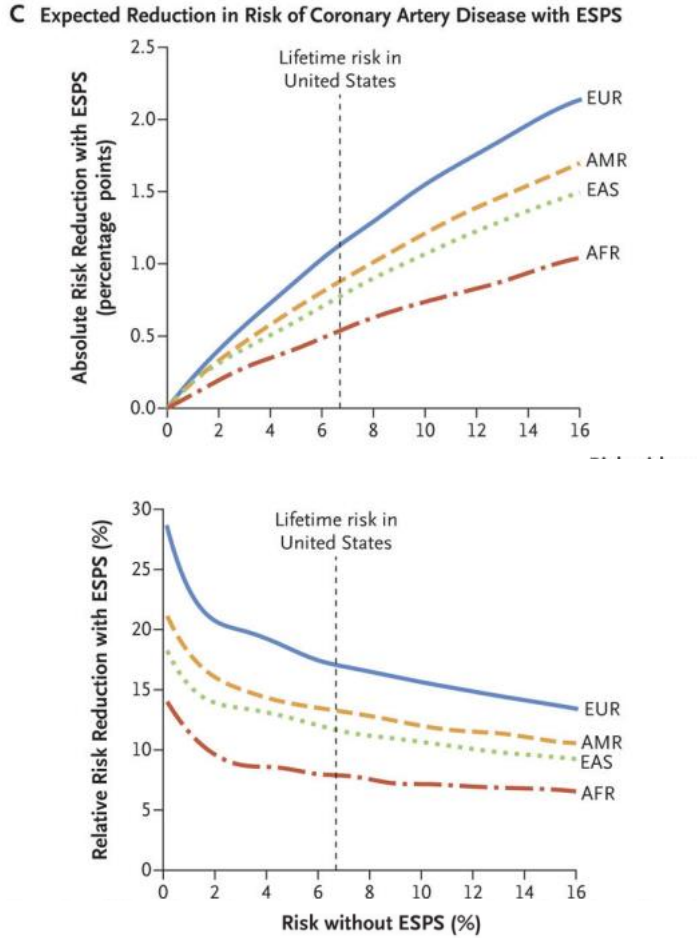
Erik Widen[1,2]✉, Louis Lello[1,2]✉, Timothy G. Raben[1], Laurent C. A. M. Tellier[1,2] & Stephen D. H. Hsu[1,2]



Other research groups have shown benefit



Lencz et al. eLife. 2021



Turley et al. NEJM. 2021

Example

Euploid embryos

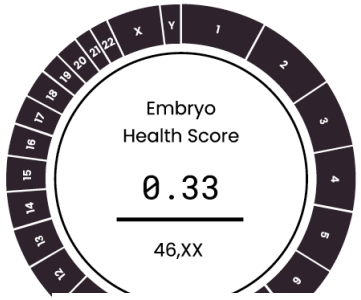
#	PGT-A	Sex	Embryo Health Score
7	46,XX	female	0.77
9	46,XX	female	0.73
3	46,XY	male	0.7
10	46,XY	male	0.69
4	46,XX	female	0.33
1	46,XY	male	0.09
8	46,XX	female	0.08
11	46,XX	female	-0.11
6	46,XX	female	-0.22
5	46,XY	male	-1.19

Aneuploid embryos

#	PGT-A	Sex	Embryo Health Score
2	45,XY,-10	male	-
12	47,XY,+22	male	-

Embryo #4

Euploid Female



	Absolute Risk		Relative Risk	
	Risk	Avg Risk	Ratio	Risk Percentile
Type 1 Diabetes	0.59%	0.70%	0.84x	45
Type 2 Diabetes	19.17%	32.07%	0.6x	5
Breast Cancer	16.34%	10.43%	1.57x	95
Basal Cell Carcinoma	29.65%	27.00%	1.1x	75
Malignant Melanoma	1.86%	2.10%	0.89x	35
Heart Attack	12.11%	15.87%	0.76x	16
Atrial Fibirillation	21.30%	26.70%	0.8x	30
Coronary Artery Disease	23.15%	31.70%	0.73x	17
Inflammatory Bowel Disease	2.34%	1.44%	1.62x	88
Asthma	10.73%	5.00%	2.15x	97
Schizophrenia	0.69%	1.13%	0.61x	33

Clinical Utility of PGT-P

- **Tool to prioritize transfer of euploid embryos**

- ⚠ **PGT-P is not intended to discard embryos** ⚠

- **PGT-P is not intended to select for cosmetic traits** (but it is technically possible ⚠).

- **Patients with family history**

Organized Debates are "All or None"

eshre
SCIENCE MOVING
PEOPLE
MOVING SCIENCE

Session code: 40
Session title: PCC04:Controversies in reproductive genetics - Part 1
Session type: Precongress Course

- ***pcc22-025: PGT for polygenic risk scores: the promise***
- ***pcc22-026: PGT for polygenic risk scores: the limitations and ethical concerns***

New Kids on the Block: Should PGT for Polygenic Disease be Offered to All – or None?

Should preimplantation genetic testing for polygenic disease be offered to all – or none?

Nathan R. Treff, Ph.D.,[a,b] Julian Savulescu, Ph.D.,[c,d,e] Inmaculada de Melo-Martín, Ph.D.,[f] Lee P. Shulman, M.D.,[g,h] and Eve C. Feinberg, M.D.[i]

~1.5% of all IVF couples are already affected with T1D

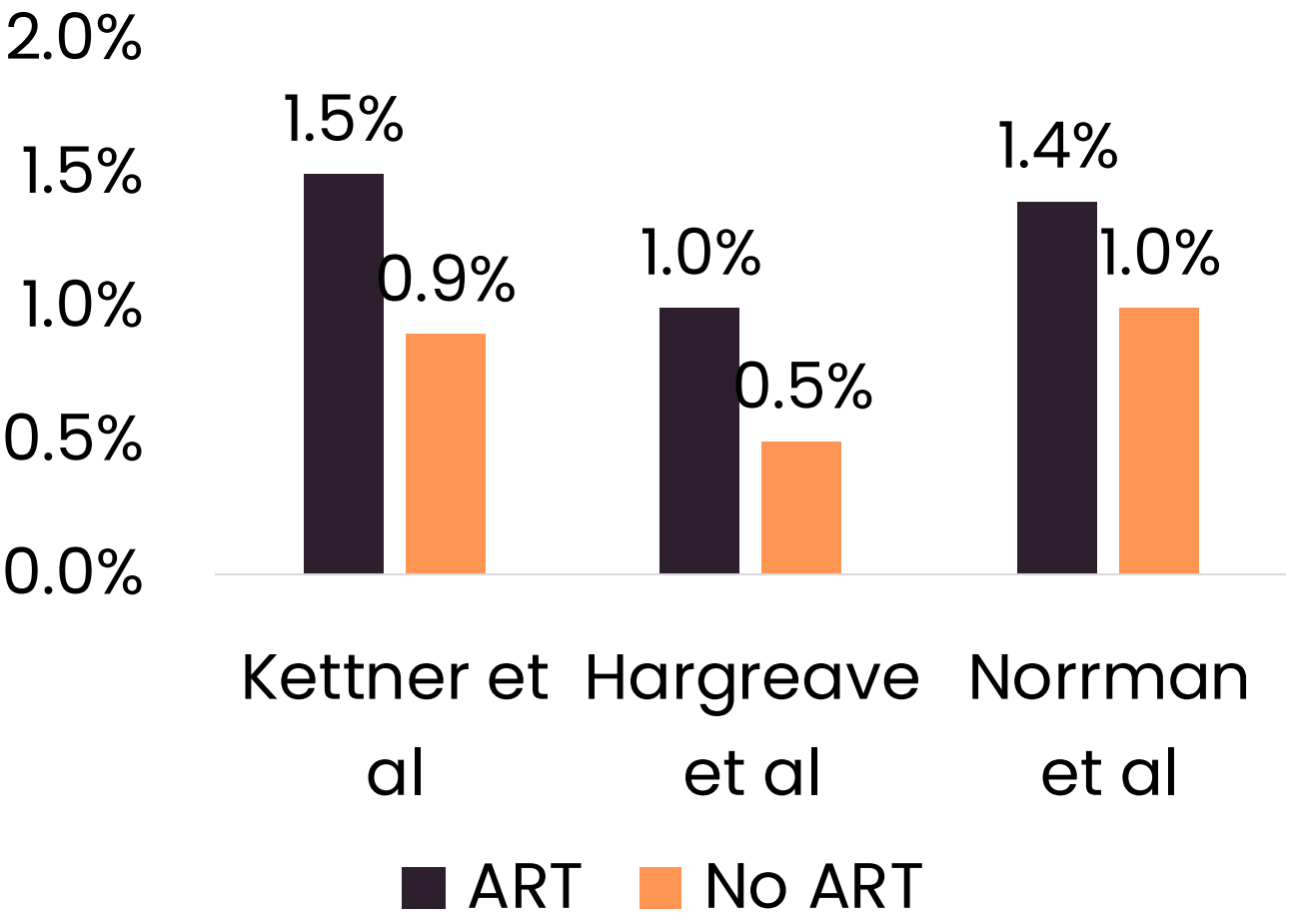
Fertility treatment and childhood type 1 diabetes mellitus: a nationwide cohort study of 565,116 live births

Laura Ozer Kettner, M.D.,[a] Niels Bjerregaard Matthiesen, Ph.D.,[a] Cecilia Høst Ramlau-Hansen, Ph.D.,[b] Ulrik Schiøler Kesmodel, Ph.D.,[c] Bjørn Bay, Ph.D.,[d] and Tine Brink Henriksen, Ph.D.[a]

Type 1 diabetes in children born after assisted reproductive technology: a register-based national cohort study

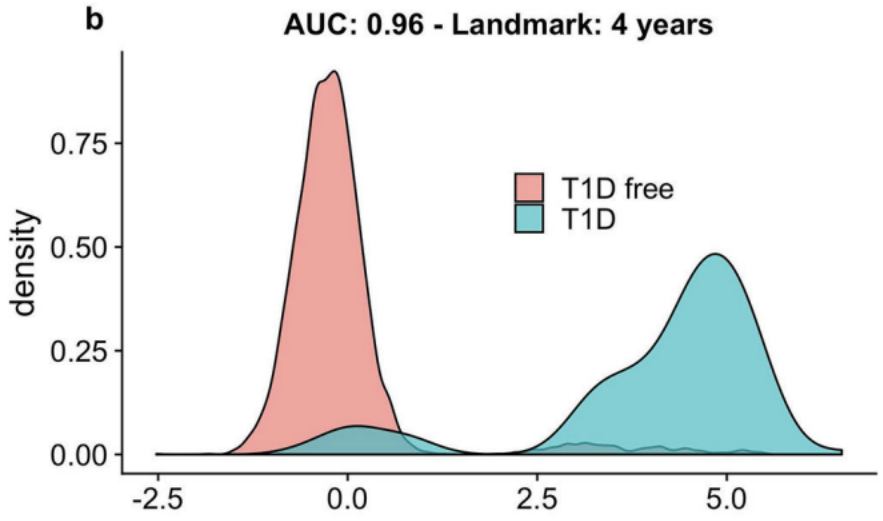
E. Norrman[1,*], M. Petzold[2], T.D. Clausen[3], A-K. Henningsen[4], S. Opdahl[5], A. Pinborg[4], A. Rosengren[6], C. Bergh[7,†], and U-B. Wennerholm[1,†]

Significantly higher in ART patients



Example: Type 1 Diabetes (T1D)

- More than 1 in 100 IVF couples are affected with T1D (1,2)
- Children of affected parents have 3 to 20 times the risk (3)
- Polygenic risk scores are highly predictive (4)
- 45 to 72% risk reduction with PGT-P (5)



Liability?

Argument: It is unethical not to inform IVF patients with T1D about the option for PGT-P

1. Kettner et al. Fertility and Sterility, (2016) 106(7), 1751-1756.
2. Norrman et al. Human Reproduction, (2020) 35(1), 221-231.
3. Redondo et al. Pediatric Diabetes, (2018) 19(3):346-353.
4. Farrat et al. Nat Med. (2020) 26(8): 1247–1255
5. Treff et al. Genes (2020) 12;11(6):648

Current Challenges of PGT-P

Social and Racial Disparities

CanPath
Canadian Partnership for Tomorrow's Health

Availability of polygenic risk scoring across diverse populations

PRABARNA GANGULY, PH.D. | JUNE 16, 2021 | PRESS CONTACT

nature genetics

Technical Report https://doi.org/10.1038/s41588-023-01583-9

BridgePRS leverages shared genetic effects across ancestries to increase polygenic risk score portability

Received: 18 January 2022

Accepted: 20 October 2023

Clive J. Hoggart[1], Shing Wan Choi[1,2], Judit García-González[1], Tade Souaiaia[3], Michael Preuss[4] & Paul F. O'Reilly[1]

nature genetics

Article https://doi.org/10.1038/s41588-024-01704-y

Leveraging functional genomic annotations and genome coverage to improve polygenic prediction of complex traits within and between ancestries

Received: 1 October 2022

Accepted: 5 March 2024

Published online: 30 April 2024

Check for updates

Zhili Zheng[1,2,3], Shouye Liu[1], Julia Sidorenko[1], Ying Wang[1], Tian Lin[1], Loic Yengo[1], Patrick Turley[4,5], Alireza Ani[6,7], Rujia Wang[6], Ilja M. Nolte[6], Harold Snieder[6], LifeLines Cohort Study*, Jian Yang[8,9], Naomi R. Wray[1,10], Michael E. Goddard[11,12], Peter M. Visscher[1,13] & Jian Zeng[1]

nature medicine

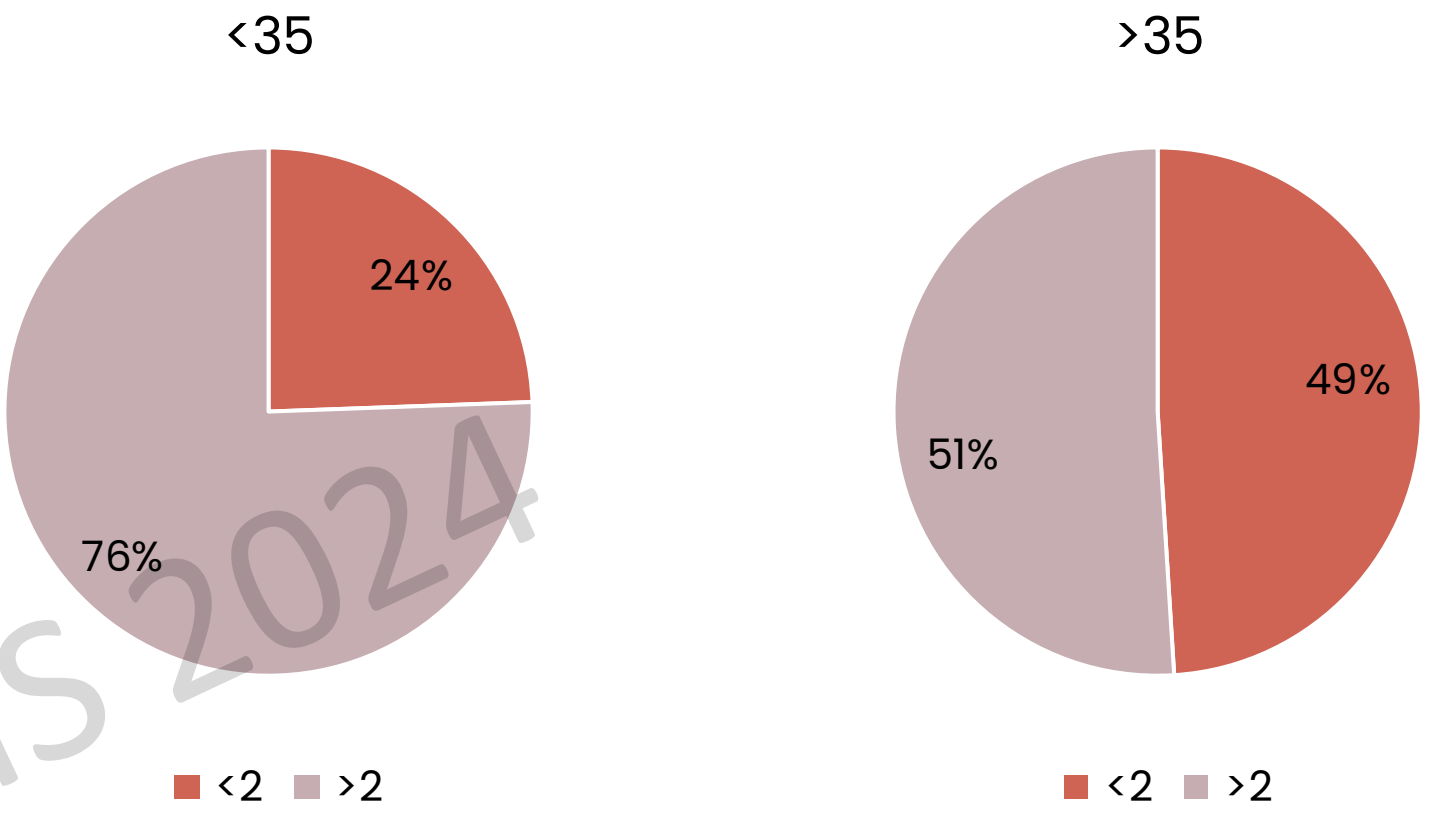
Article https://doi.org/10.1038/s41591-024-02796-z

Selection, optimization and validation of ten chronic disease polygenic risk scores for clinical implementation in diverse US populations

Received: 25 May 2023

A list of authors and their affiliations appears at the end of the paper

Not enough euploid embryos to choose from…



Unpublished Data

PGT-P is Too Complicated for Patients…

Mosaicism

Using outcome data from one thousand mosaic embryo transfers to formulate an embryo ranking system for clinical use

Manuel Viotti, Ph.D.,[a,b] Andrea R. Victor, M.S.,[a] Frank L. Barnes, Ph.D.,[a,b] Christo G. Zouves, M.D.,[a,b] Andria G. Besser, M.S.,[c] James A. Grifo, M.D., Ph.D.,[c] En-Hui Cheng, Ph.D.,[d] Maw-Sheng Lee, M.D., Ph.D.,[d,e] Jose A. Horcajadas, Ph.D.,[f] Laura Corti, M.Sc.,[g] Francesco Fiorentino, Ph.D.,[h] Francesca Spinella, Ph.D.,[h] Maria Giulia Minasi, M.Sc.,[i,j] Ermanno Greco, M.D.,[i,j] and Santiago Munné, Ph.D.[k]

PGT-M example

Euploid Embryos

#	Cycle Number	Grade *	PGT-A	CFTR: c.350G>A	CFTR: 5T	CFTR: c.2491G>T	CFTR: Interpretation	BRCA1: Deletion of exons 1-2	BRCA1: Interpretation	Sex
1	23472	6AA	46,XY	Negative	Heterozygous-Positive	Heterozygous-Positive	Compound Heterozygous	Negative	Negative	male
2	23472	6AA	46,XY	Heterozygous-Positive	Heterozygous-Positive	Negative	Compound Heterozygous	Heterozygous-Positive	Heterozygous Positive	male
3	23472	6AA	46,XY	Negative	Heterozygous-Positive	Heterozygous-Positive	Compound Heterozygous	Negative	Negative	male
4	23472	5AB	46,XY	Heterozygous-Positive	Negative	Heterozygous-Positive	Compound Heterozygous	Negative	Negative	male
5	23472	4AB	46,XY	Heterozygous-Positive	Heterozygous-Positive	Negative	Compound Heterozygous	Heterozygous-Positive	Heterozygous Positive	male
6	23472	4AA	46,XY	Heterozygous-Positive	Negative	Heterozygous-Positive	Compound Heterozygous	Negative	Negative	male
8	23472	3BA	46,XY	Negative	Homozygous-Positive	Negative	Homozygous Positive	Heterozygous-Positive	Heterozygous Positive	male
9	23472	5BB	46,XX	Heterozygous-Positive	Heterozygous-Positive	Negative	Compound Heterozygous	Heterozygous-Positive	Heterozygous ositived	female
10	23472	3BC	46,XX	Negative	Heterozygous-Positive	Heterozygous-Positive	Compound Heterozygous	Heterozygous-Positive	Heterozygous Positive	female
11	23472	3AB	46,XX	Heterozygous-Positive	Heterozygous-Positive	Negative	Compound Heterozygous	Negative	Negative	female
12	23472	6AB	46,XX	Negative	Homozygous-Positive	Negative	Homozygous Positive	Negative	Negative	female
14	23472	3BC	46,XX	Heterozygous-Positive	Heterozygous-Positive	Negative	Compound Heterozygous	Heterozygous-Positive	Heterozygous Positive	female

Aneuploid Embryos

#	Cycle Number	Grade *	PGT-A	CFTR: c.350G>A	CFTR: 5T	CFTR: c.2491G>T	CFTR: Interpretation	BRCA1: Deletion of exons 1-2	BRCA1: Interpretation	Sex
7	23472	4AA	47,XX,+14	Heterozygous-Positive	Heterozygous-Positive	Negative	Compound Heterozygous	Heterozygous-Positive	Heterozygous Positive	female
13	23472	6BC	44,XY,-15,-20	Negative	Homozygous-Positive	Negative	Homozygous Positive	Negative	Negative	male
15	23472	6CB	45,XX,-22	Heterozygous-Positive	Heterozygous-Positive	Negative	Compound Heterozygous	Heterozygous-Positive	Heterozygous Positive	female

What Do Patients and the Public Think?

Public Opinion is POSITIVE

POLICY FORUM

HUMAN GENETICS

Public views on polygenic screening of embryos

Understanding moral acceptability and willingness to use is crucial for informing policy

By Michelle N. Meyer[1,2], Tammy Tan[3], Daniel J. Benjamin[3,4,5], David Laibson[3,6], Patrick Turley[3,7,8]

For decades, people have used genetic information to exercise control over the kinds of children they will have. These technologies have largely targeted chromosomal and monogenic disorders and traits; but most human phenotypes are highly polygenic (and influenced by the environment). One technology that targets the entire genome—preimplantation genetic testing for polygenic risk (PGT-P)—uses polygenic indexes (PGIs) to predict the expected value of the phenotype(s) that would arise for each embryo if successfully transferred; parents can use these predictions to select an embryo for in vitro fertilization (IVF). Seeing gaps in evidence and analysis relevant for potential policy discussions around PGT-P, we conducted a survey of public attitudes. Our data suggest that it would be unwise to assume that use of PGT-P—even for controversial traits—will be limited to idiosyncratic individuals, or that it has little potential to cause or contribute to society-wide changes and inequities.

Historically, technologies to enable control over offspring have included carrier screening, ultrasound, preimplantation genetic diagnosis, amniocentesis, chorionic villus sampling, noninvasive prenatal screening, and selective abortion. Using them, people have selected against diseases such as Huntington's, Down syndrome and other trisomies, and alleles [such as pathogenic breast cancer gene (*BRCA*) variants] that increase an individual's lifetime risk of certain diseases. They have also selected for biological sex and conditions such as deafness. In contrast to those, a PGI—also called a polygenic risk score—is based on the estimated associations (calculated from a large-scale genetic study) between common genetic variants and a particular phenotype. This gene-based index can then be used to make phenotypic predictions—not only to avoid serious disease but also to try to select for phenotypes such as greater cognitive ability or educational attainment.

Another technology that targets the entire genome and could, in principle, vastly expand our ability to select for or against any heritable phenotype is germline genome editing (hereafter "gene editing")—for instance, with clustered regularly interspaced short palindromic repeats (CRISPR). This might someday be used to try to influence offspring characteristics by making thousands of DNA edits (or more) to a gamete or embryo.

> "...public views should influence policy-making but alone do not determine appropriate policy."

However—with the notable exception of three Chinese children whose C-C chemokine receptor type 5 (*CCR5*) genes were illicitly edited while they were embryos in a misguided attempt to provide them with AIDS resistance (*1*, *2*)—gene editing has not been used. Indeed, it is not permitted in some 70 countries (*1*), and experts have called for a global moratorium (*2*).

PGT-P, by contrast, is already offered by at least one US company whose embryo screening business operates in several countries and US states (*3*). Yet it has received far less academic, policy, and regulatory analysis than gene editing, leading to calls for urgent research about public attitudes towards PGT-P (*4*). Recent surveys have measured acceptance of gene editing (*5*, *6*), intentions to use gene editing (*7*), and views about whether certain forms of embryo selection should be legally permitted (*8*). Someone's view about whether the law should prohibit a technology may be distinct from their view of whether the technology is morally acceptable, and both may be distinct from whether they themselves would use the technology. To our knowledge, this paper is the first to measure PGT-P use intentions—and the effects of social norming on these intentions.

ACCEPTABILITY AND WILLINGNESS

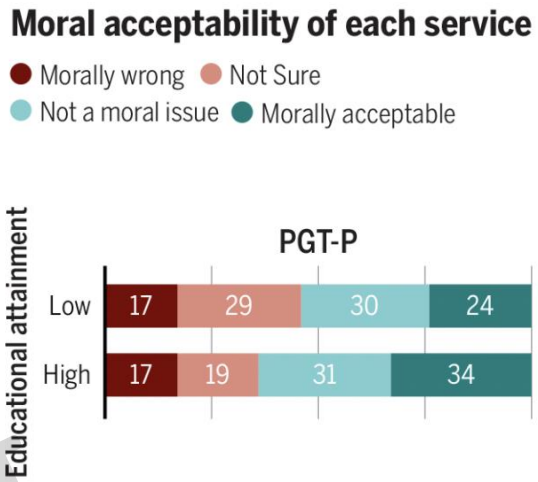
In January 2022, we conducted a preregistered, nationally representative US survey-based experiment on the attitudes of 6823 people towards three services: PGT-P, gene editing, and—as a nongenetic benchmark for attitudes toward interventions targeted at college admissions—courses to prepare for the SAT test (effective *N* after applying weights, 3805; see table S1 for sample characteristics). We randomized participants to answer two questions, in randomized order, about one of these three services. One question asked whether the respondent views the service as morally acceptable, morally wrong, or not a moral issue; participants could also indicate whether they were unsure. For this question, both PGT-P and gene editing were described as being potentially used for "medical and nonmedical traits."

The other question measured willingness to use each service by asking participants how likely it was—on a scale from 0 to 100%—that they would use the service to increase the odds that their offspring will attend a top-100 college by selecting for genetic variants, or enrolling their child in courses, associated with higher educational attainment. We asked participants to assume that each service was free. We also asked them to assume a realistic effect size: We told them that about 3% of high school seniors attend a top-100 ranked college, and that each service would raise their likelihood of having such a child by two percentage points (from 3 to 5%). In the cases of gene editing and PGT-P, we asked them to assume that they were already using IVF and that the add-on service was safe. Finally, we further randomized participants within each "service condition" to be told that it was used on average by either "1 out of every 10" or "9 out of every 10" similarly situated people (for the PGT-P and gene editing arms, "people currently having babies"; for the SAT prep arm, "people who currently have high-school–age children").

[1]Department of Bioethics and Decision Sciences, Geisinger Health System, Danville, PA 17822, USA. [2]Geisinger Commonwealth School of Medicine, Scranton, PA 18510, USA. [3]National Bureau of Economic Research, Cambridge, MA 02138, USA. [4]Anderson School of Management, University of California Los Angeles, Los Angeles, CA 90095, USA. [5]David Geffen School of Medicine, University of California Los Angeles, Los Angeles, CA 90095, USA. [6]Department of Economics, Harvard University, Cambridge, MA 02138, USA. [7]Center for Economic and Social Research, University of Southern California, Los Angeles, CA 90089, USA. [8]Department of Economics, University of Southern California, Los Angeles, CA 90089, USA.
Email: michellenmeyer@gmail.com

Public Opinion is POSITIVE

Meyer et al. Science. 2023



83% think PGT-P is not unethical

Patient Perspectives are POSITIVE

Embryo Health Study (EHS)

ClinicalTrials.gov ID NCT04528498

Over 50% of fully informed patients elect to add PGT-P

Eccles et al. ASRM. 2022

What Do “Experts” Think?

Social Science & Medicine
Volume 343, February 2024, 116599

"Are we not going too far?": Socio-ethical considerations of preimplantation genetic testing using polygenic risk scores according to healthcare professionals

Maria Siermann [a b], Ophelia Valcke [a], Joris Robert Vermeesch [c], Taneli Raivio [b], Olga Tšuiko [c d], Pascal Borry [a]

VIEWPOINT OPEN
Check for updates

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*

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)

Article | Published: 20 March 2023

Limitations, concerns and potential: attitudes of healthcare professionals toward preimplantation genetic testing using polygenic risk scores

Maria Siermann, Ophelia Valcke, Joris Robert Vermeesch, Taneli Raivio, Olga Tšuiko & Pascal Borry

European Journal of Human Genetics **31**, 1133–1138 (2023) | Cite this article

Patient interest in and clinician reservations on polygenic embryo screening: a qualitative study of stakeholder perspectives

Genetics | Published: 12 March 2024
(2024) Cite this article

D. Barlevy, I. Cenolli, T. Campbell, R. Furrer, M. Mukherjee, K. Kostick-Quenet, S. Carmi, T. Lencz, G. Lázaro-Muñoz & S. Pereira

Most Opinions are NEGATIVE

Use of preimplantation genetic testing for monogenic defects (PGT-M) for adult-onset conditions: an Ethics Committee opinion

Ethics Committee of the American Society for Reproductive Medicine
American Society for Reproductive Medicine, Birmingham, Alabama

"The Committee further concludes that reproductive liberty arguments ethically allow for PGT-M for adult-onset conditions of lesser severity or penetrance."

Should preimplantation genetic testing for polygenic disease be offered to all – or none?

Nathan R. Treff, Ph.D.,[a,b] Julian Savulescu, Ph.D.,[c,d,e] Inmaculada de Melo-Martín, Ph.D.,[f] Lee P. Shulman, M.D.,[g,h] and Eve C. Feinberg, M.D.[i]

"Respect for procreative autonomy requires allowing couples or single parents to make their own decisions about PGT-P for disease"
-Savulescu

Genetics in Medicine (2024) 26, 101052

ELSEVIER

Genetics in Medicine
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www.journals.elsevier.com/genetics-in-medicine

ACMG STATEMENT

Clinical utility of polygenic risk scores for embryo selection: A points to consider statement of the American College of Medical Genetics and Genomics (ACMG)

Theresa A. Grebe[1,2], George Khushf[3], John M. Greally[4], Patrick Turley[5,6], Nastaran Foyouzi[7], Sara Rabin-Havt[8], Benjamin E. Berkman[9], Kathleen Pope[10,11], Matteo Vatta[12], Shagun Kaur[1,2]; on behalf of the ACMG Social, Ethical, and Legal Issues Committee[13]

Correspondence on Clinical Utility of Polygenic Risk Scores for Embryo Selection: A Points to Consider Statement of the American College of Medical Genetics and Genomics by Grebe et al.

Erik Widen, Louis Lello, Jennifer Eccles, Diego Marin, and Nathan R. Treff

Genomic Prediction Inc., 671 US Highway One, North Brunswick, NJ. 08902
erik@genomicprediction.com

Widen et al. ***In Press***

Some other PGT-P misconceptions

- PGT-P is **NOT** a direct-to-consumer test
- PGT-P is performed on patients already doing IVF and PGT-A
- Demand for longitudinal studies spanning as long as 60-70 years?

PGT-P Conclusions

- Polygenic Risk Scoring is becoming a routine component in many fields of medicine
- Accumulating evidence from evaluating adult siblings demonstrate significant risk reductions (utility)
- IVF patients already affected with diseases that can be tested by PGT-P should be informed of options

Thank you!

diego@genomicprediction.com