Screening IVF embryos with polygenic risk scores: Pros and cons

Shai Carmi

Public Health

The Hebrew University of Jerusalem

scarmilab.org

@ShaiCarmi

British Fertility Society

January 2023

בית הספר לבריאות הציבור ורפואה קהילתית
של האוניברסיטה העברית והדסה ע"ש בראון
Braun School of Public Health and Community Medicine
Hebrew University-Hadassah

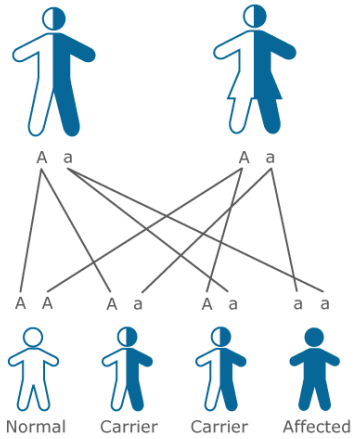
הפקולטה לרפואה
FACULTY OF MEDICINE
האוניברסיטה העברית בירושלים
THE HEBREW UNIVERSITY OF JERUSALEM

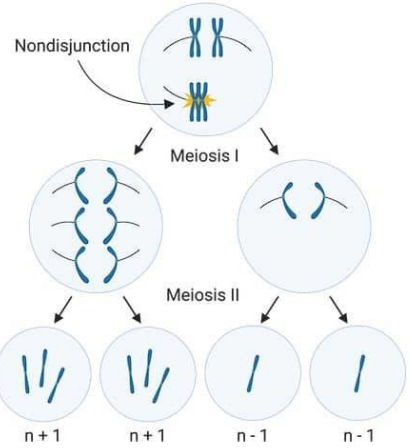
Outline

- **What is preimplantation genetic testing with polygenic scores (PGT-P)?**
- Can PGT-P reduce disease risk?
- Can PGT-P cause harm?

Preimplantation genetic testing (PGT)

- Current focus:
  - Severe, monogenic pathogenic variants
  - Aneuploidy and structural variants
- Technology:
  - STR markers around variant
  - Shallow whole-genome sequencing
- New methods:
  - Deep(er) **whole-genome** sequencing/genotyping
  - Universal PGT
- **Should we look beyond monogenic diseases?**





Handyside et al, J Med Genet, 2010; Natesan et al, Genet Med, 2014; Kumar et al, Genome Med, 2015; Xu et al, Clin Chem, 2015; Yan et al, PNAS, 2015; Zamani-Esteki, AJHG, 2015; Backenroth et al, Genet Med, 2019, 2021; Masset et al, Hum Reprod, 2019; Treff et al, EJMG, 2019; Murphy et al, Sci Rep, 2020; Masset et al, Nucleic Acids Res, 2022; Kumar et al Nat Med, 2022; De Witte et al, Hum Reprod, 2022; Xia et al, 2022; Xie et al, Hum Reprod, 2022

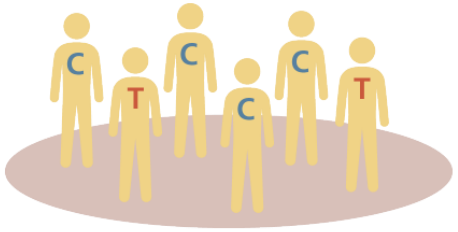
Polygenic ("complex") diseases

- Examples: heart attack, stroke, hypertension, cancers, diabetes, Crohn's disease, asthma, Alzheimer's disease, schizophrenia, depression

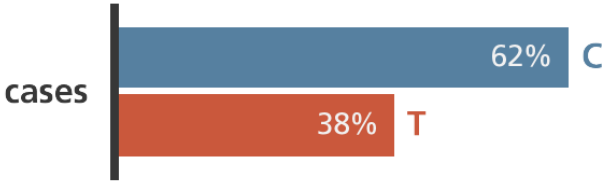
- Study design: GWAS
- Recent studies: 500k-1M individuals

- Hundreds of strong associations per phenotype
- Summary data publicly available

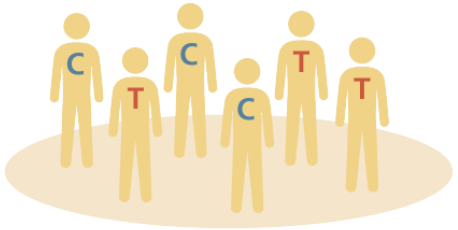
Genome-wide association study (GWAS)



cases (n=1,000)
people with heart disease



SNP: single nucleotide polymorphism



controls (n=1,000)
people without heart disease

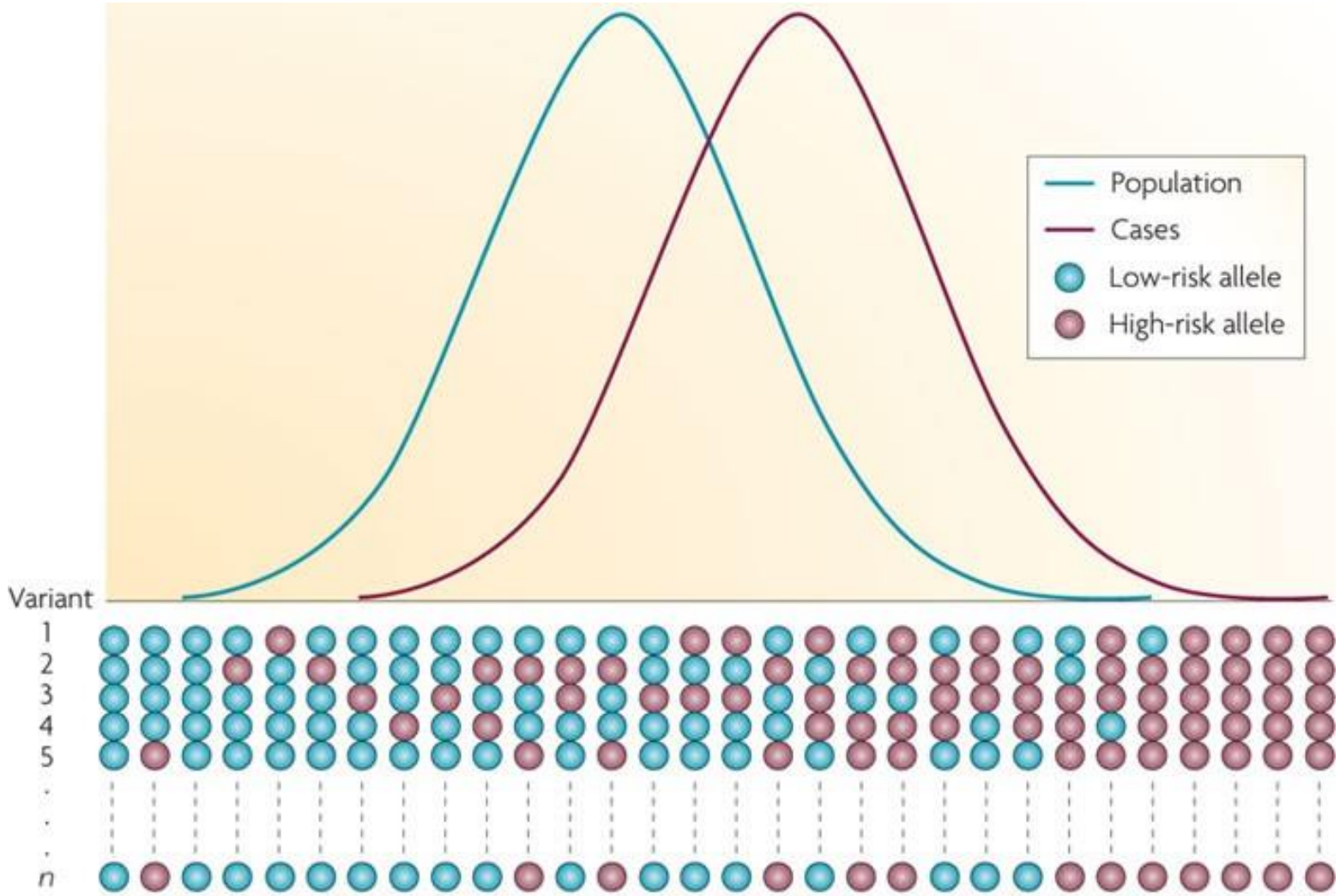
Polygenic risk scores

- $PRS = \hat{\beta}_1 g_1 + \cdots + \hat{\beta}_M g_M$

- M: number of SNPs
- g_i: number of risk alleles (0,1,2)
- $\hat{\beta}_i$: effect size (log-odds-ratio)

- **Can IVF embryos be ranked based on their PRS?**

Fletcher and Houlston, Nat Rev Cancer, 2010



Polygenic embryo screening, or PGT-P

- Current provider: Genomic Prediction/LifeView (USA)
  - Sells in Argentina, Brazil, Mexico, New Zealand, Taiwan, and Thailand

- Diseases screened:
  - Cancers (basal cell carcinoma, breast, melanoma, prostate, testicular)
  - Cardiovascular (coronary artery disease, heart attack, hypertension, hypercholesterolemia)
  - Diabetes (type1/type2), schizophrenia

- Future providers: ORCHID myome

Outline

- What is preimplantation genetic testing for polygenic scores (PGT-P)?
- **Can PGT-P reduce disease risk?**
- Can PGT-P cause harm?

Can PGT-P reduce disease risk?

- Is there enough variation?
- What risk reduction can be achieved?
- Can risk be reduced for multiple diseases in parallel?
- Are there enough embryos?
- Will it work in non-European populations?
- Will it work for late-onset diseases?
- Other issues

Well understood, thought to work

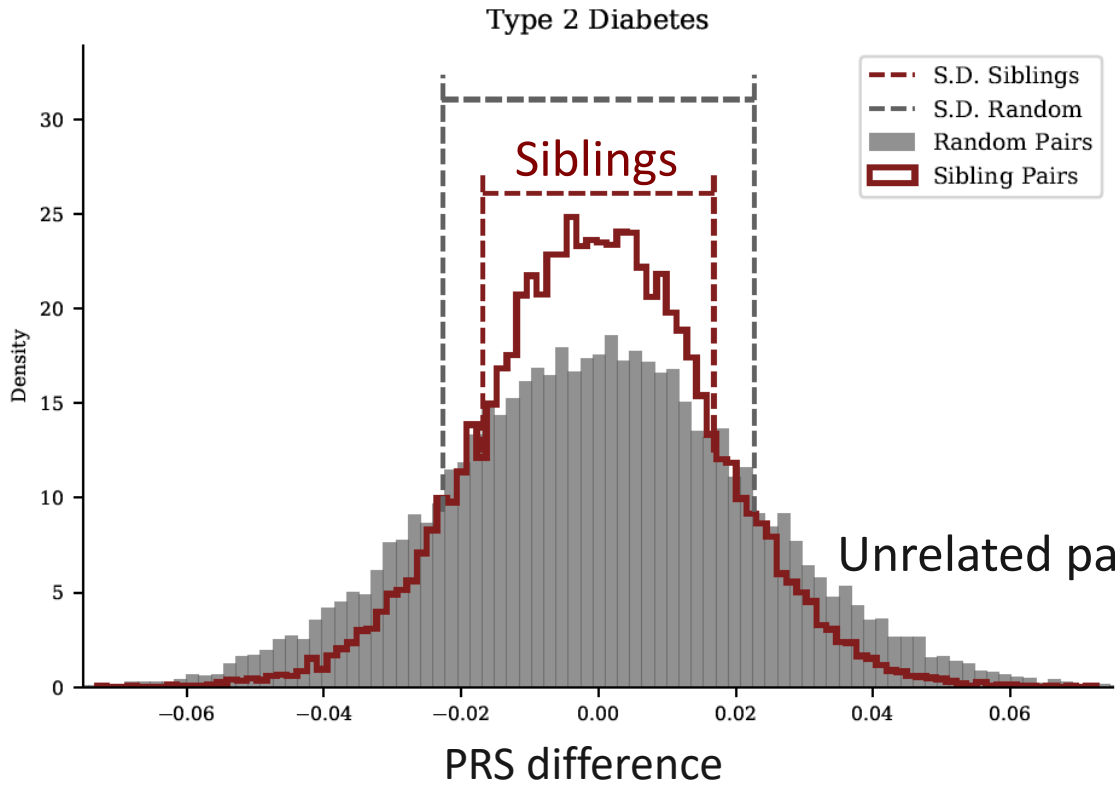
Likely a problem

Unknown impact

Misconception, likely not a problem

Is there enough variation?

- Common myth: “there isn’t enough genetic variation between siblings”
- **Fact:** the variance of the PRS across sibs is **half** the population variance
- Regardless of the parental PRS



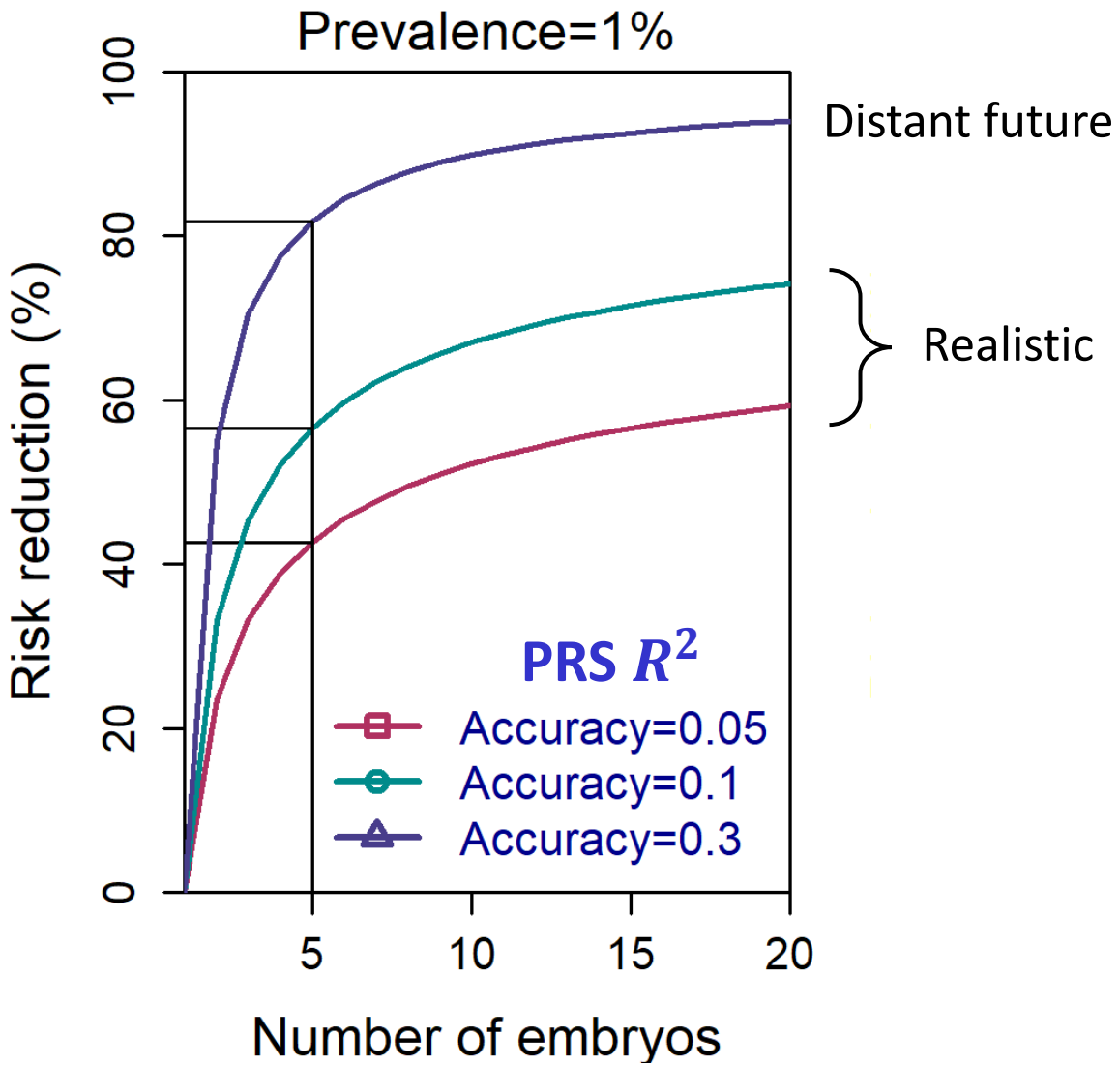
Lello et al, 2022
UK biobank data
21,700 pairs

See also:
Lencz et al, eLife, 2021
Chen et al, 2020

What risk reduction can be achieved?

- Screen for a single disease
- Select the embryo with the lowest PRS

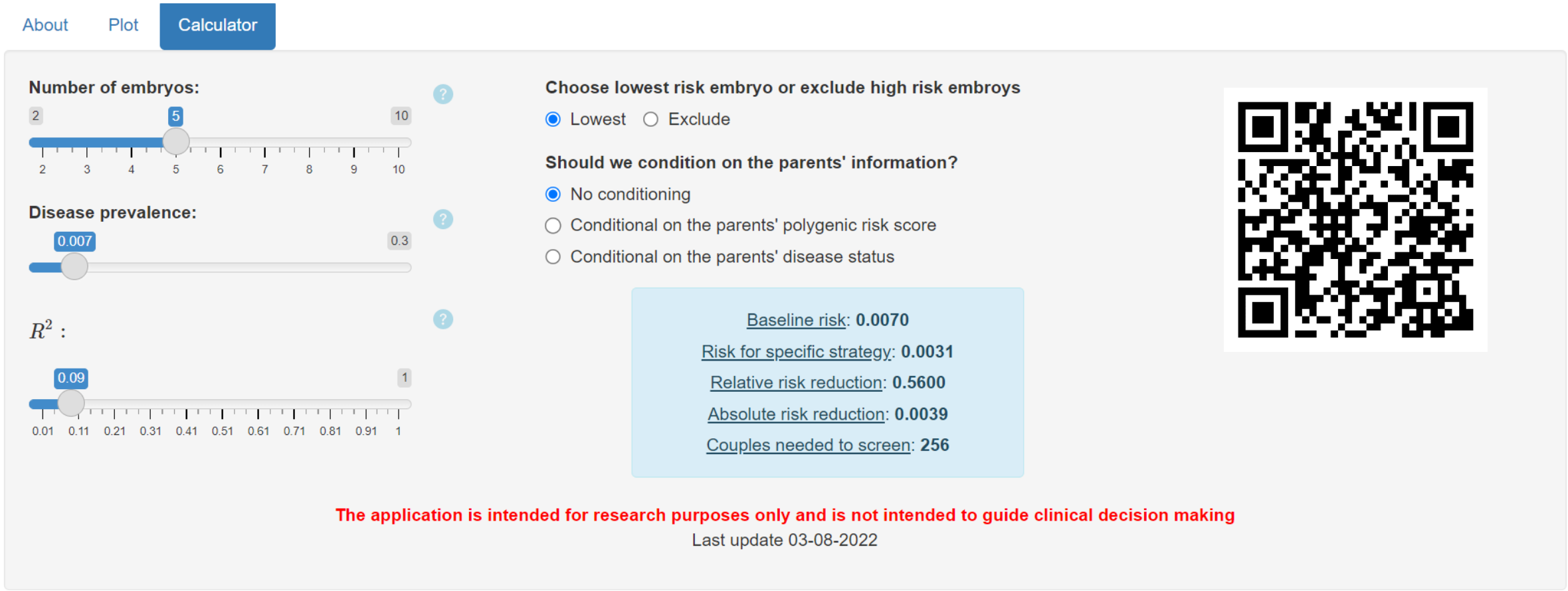
- Substantial risk reductions can be achieved
- Even with just 5 embryos!



Lencz et al, eLife, 2021

Online risk reduction calculator

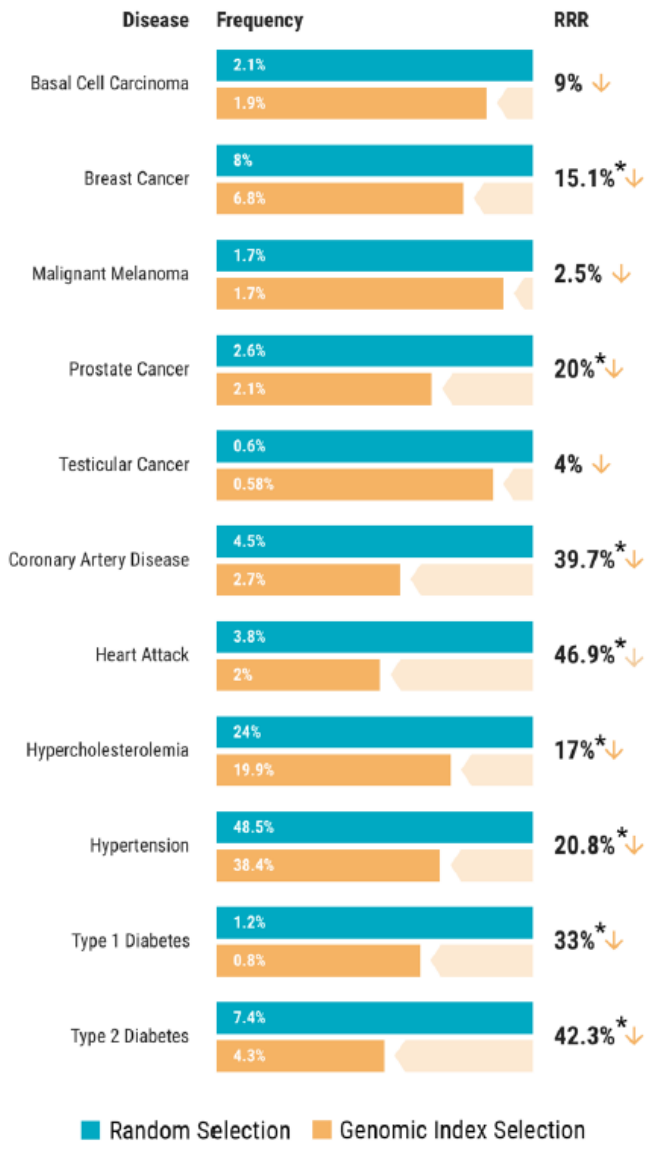
https://pgt-p-outcome-calculator.shinyapps.io/selectioncalc/



Can risk be reduced for multiple diseases in parallel?

- LifeView ranks embryos on a genetic health score
  - Based on 11 diseases
- Thought experiment:
  - Take 12k UK biobank sib pairs
  - Select the sib with the higher health score
  - Or a random sib
  - Find if selected sib was affected
  - Record risk reduction
- Risk reduction achieved for all diseases simultaneously!
- Promising results also for 20 diseases (Widen et al, Sci Rep, 2022)

Treff et al, Genes, 2020

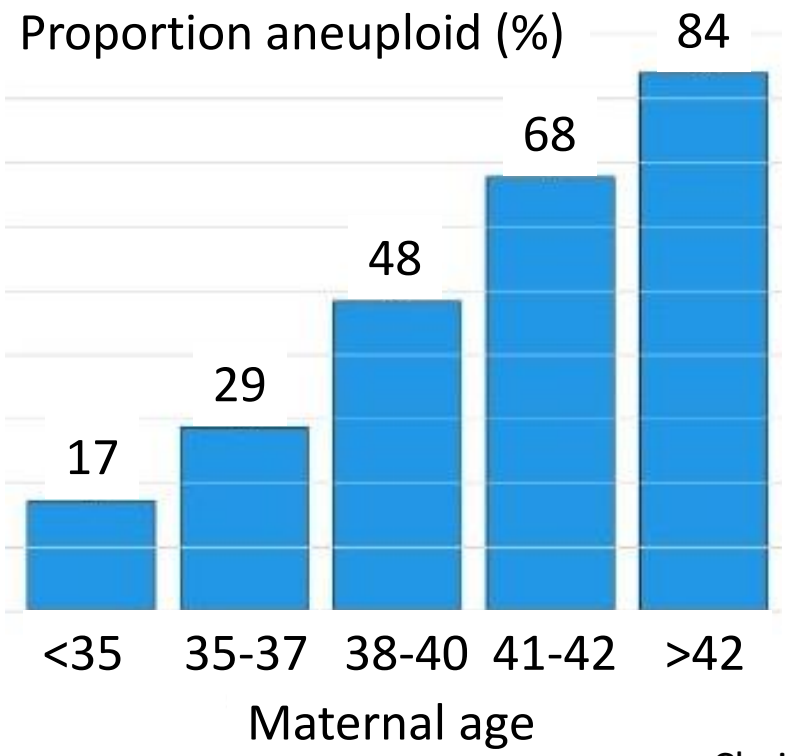


Are there enough embryos?

- The n embryos in our model must have the potential to **be born**

- With advanced maternal age, the number of births is $n \lesssim 1$

- For young fertile couples, $n \approx 5$ can be achieved but is optimistic
- $n \approx 2 - 3$ more typical
- Goldman et al, Hum Reprod, 2017; Kaing et al, Fertil Steril, 2017



Chaim Jalas

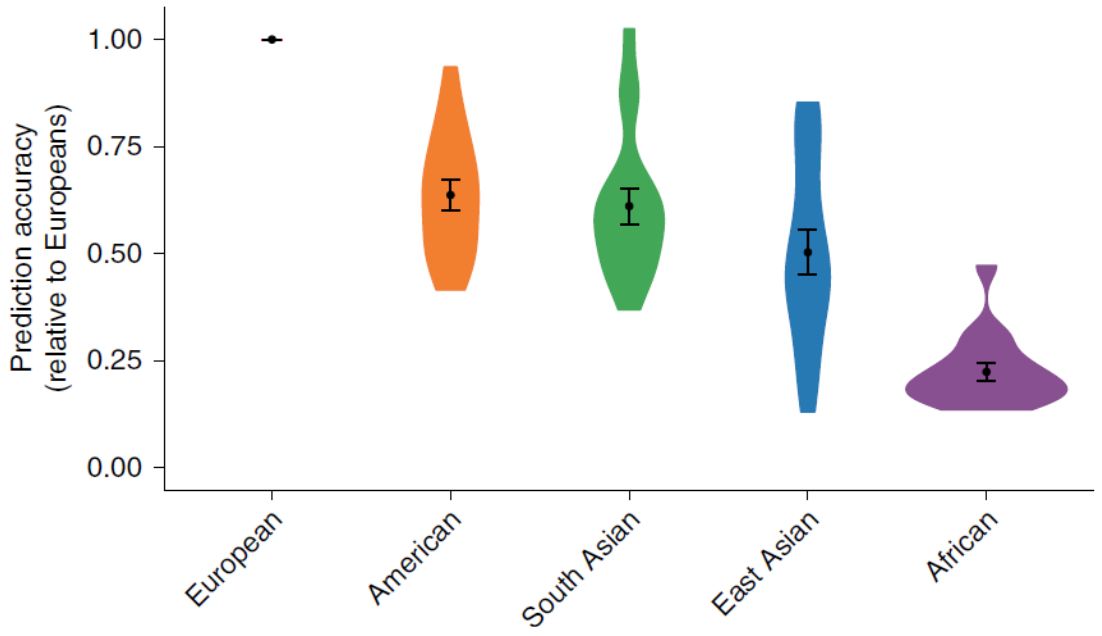
Will it work in non-European populations?

- Polygenic scores are less accurate when moving from Northern Europe to
  - Southern Europe -->
  - The Middle-East -->
  - South Asia -->
  - East Asia -->
  - Africa

- This will reduce gains proportionally

- Scores are getting better
  (e.g., new biobanks in Japan and China)

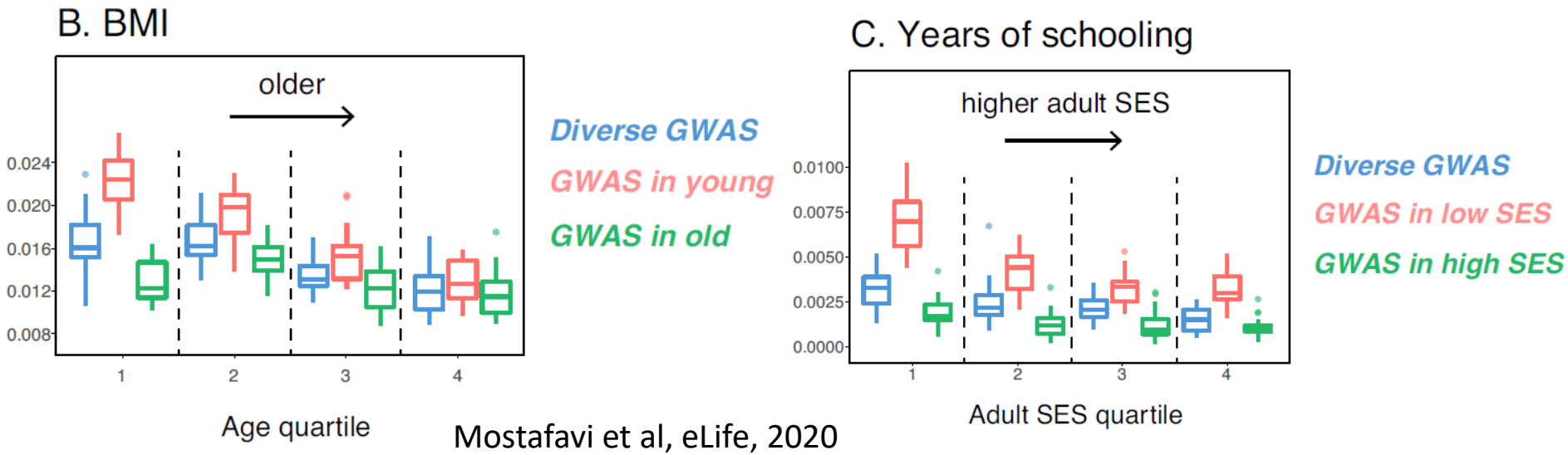
Martin et al, Nat Genet, 2019



Will it work for late-onset diseases?

- Current PRSs were trained on people now in their 60-70s
- Will they be accurate for children born next year?

- No concrete data, but PRS accuracy is likely to be reduced



Mostafavi et al, eLife, 2020

Other issues

- Will it only work for some parents (healthy, low PRS)? 
- Are polygenic scores accurate within the family? 
- Will it work with single cell(s) biopsy? 
- Maybe only exclude high-risk embryos? 
- Can PGT-P be validated?  

Outline

- What is preimplantation genetic testing for polygenic scores (PGT-P)?
- Can PGT-P reduce disease risk?
- **Can PGT-P cause harm?**

Can PGT-P cause harm?

- Decreasing live birth rates
- Harm of IVF/biopsy
- Choice overload
- Ethical and social concerns
- Other issues

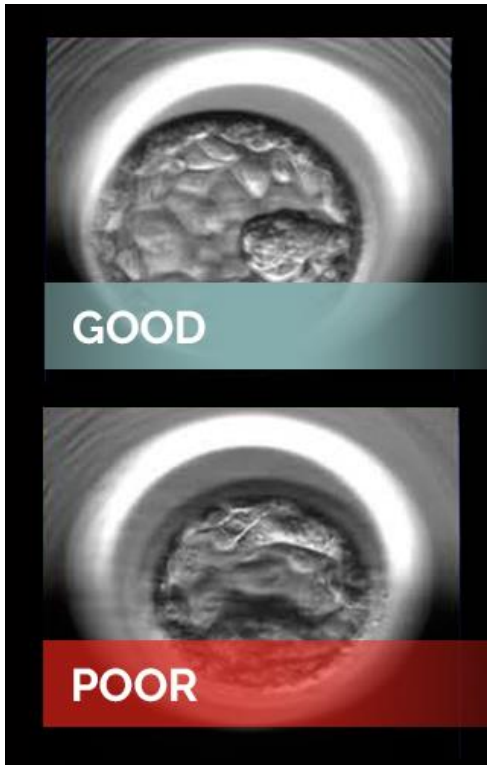
Decreasing live birth rates

?

- Embryos are ranked by morphology to maximize the probability of a live birth

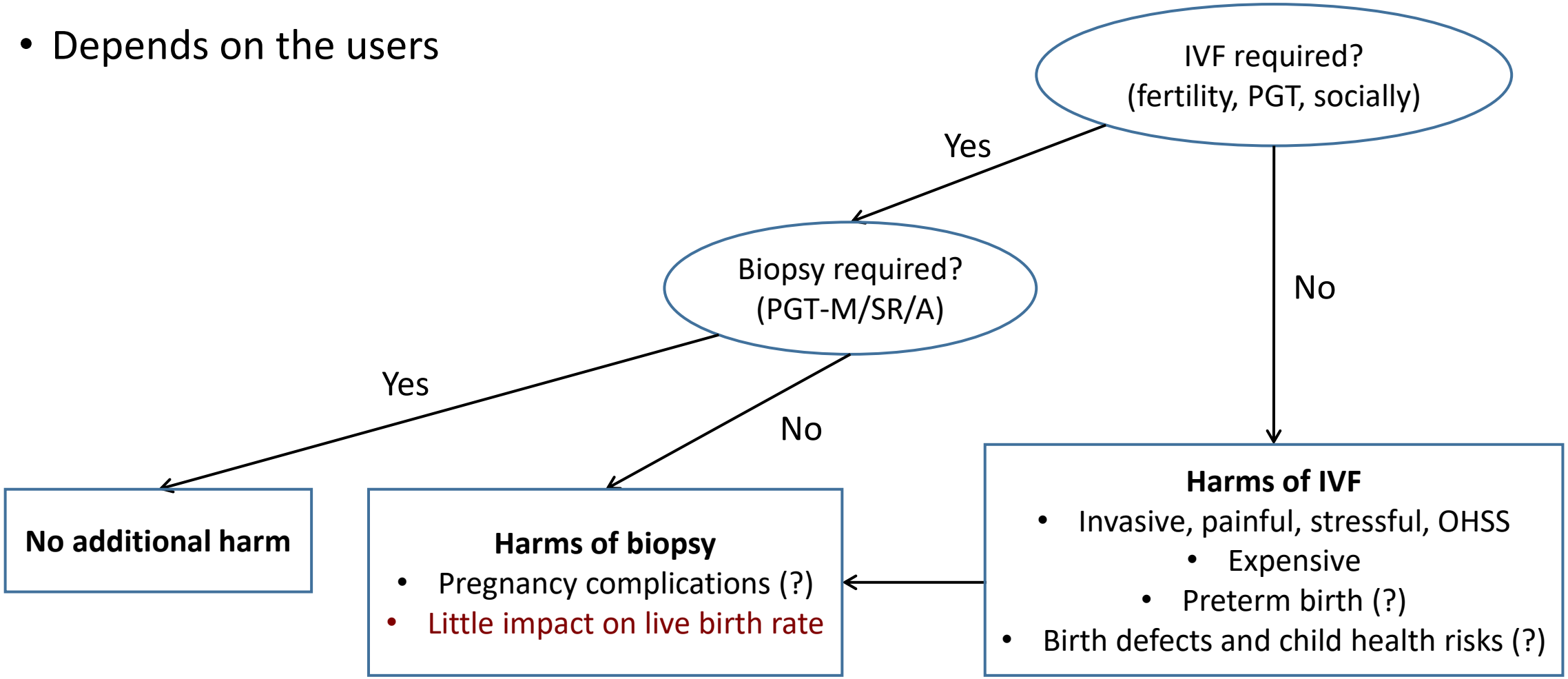
- The embryo with the most desired PRS may have lower chances of live birth

- No data on:
  - Correlation of ranks by morphology and by PRS
  - The impact of PGT-P on live birth rate



Harm of IVF/biopsy

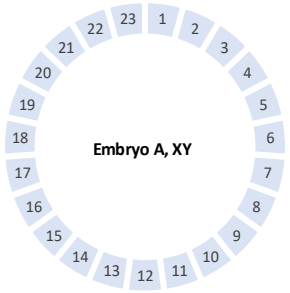
- Depends on the users

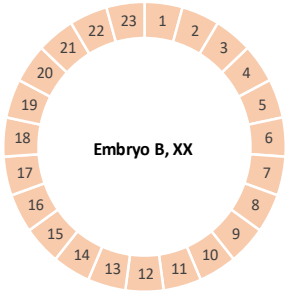


Choice overload

How to prioritize embryos with different risk profiles?

Average risk?
Risk ratio?
Risk percentile?





Embryo A	Risk		Avg. Risk	Ratio	Risk Percentile
Type 1 Diabetes	0.4%	High	0.1%	4.0x	98%
Type 2 Diabetes	32%	Normal	35.0%	0.9x	39%
Testicular Cancer	0.49%	Normal	0.4%	1.2x	75%
Prostate Cancer	6.9%	Normal	11.0%	0.6x	9%
Basal Cell Carcinoma	20%	Normal	30.0%	0.7x	14%
Malignant Melanoma	1.8%	Normal	2.0%	0.9x	51%
Heart Attack	28%	Normal	35.0%	0.8x	12%
Atrial Fibrillation	27%	Normal	38.0%	0.7x	2%
Coronary Artery Disease	20%	Normal	30.0%	0.7x	2%
Hypertension	46%	Normal	40.0%	1.2x	69%
High Cholesterol	0.26%	Normal	0.3%	0.9x	43%
Schizophrenia	1.1%	Normal	0.98%	1.1x	67%

Embryo B	Risk		Avg. Risk	Ratio	Risk Percentile
Type 1 Diabetes	0.19%	Normal	0.3%	0.6x	21%
Type 2 Diabetes	47%	Normal	35.0%	1.3x	86%
Breast Cancer	25%	High	12.0%	2.0x	99%
Basal Cell Carcinoma	26%	Normal	30.0%	0.9x	35%
Malignant Melanoma	2.1%	Normal	2.0%	1.0x	73%
Heart Attack	24%	Normal	35.0%	0.7x	1%
Atrial Fibrillation	27%	Normal	38.0%	0.7x	18%
Coronary Artery Disease	19%	Normal	30.0%	0.6x	1%
Hypertension	37%	Normal	40.0%	0.9x	41%
High Cholesterol	0.22%	Normal	0.3%	0.7x	31%
Schizophrenia	1.1%	Normal	0.98%	1.1x	67%

Ranking by overall health: solving choice overload?

Tellier et al, Genes, 2021 (LifeView)

- Weighted average by lifespan (DALYs)
- Still complicated
- Parents may want to screen other diseases

Case report: PGT-P at Genomic Prediction

"Genomic Prediction doesn't offer scores on cognitive function or height. … So the Collinses **downloaded the raw embryo data** from Genomic Prediction and exported it to the website of SelfDecode… They created a spreadsheet with each embryo's scores, **weighting them according to their desired mental health status**."

https://www.bloomberg.com/news/features/2022-05-26/dna-testing-for-embryos-promises-to-predict-genetic-diseases

Additional case reports from Genomic Prediction

"All five remaining embryos were euploid, and two displayed a high risk for breast cancer. **The couple elected to perform another cycle** before proceeding with embryo transfer"
Treff et al, Frontiers in Endocrinology, 2019 (first ever clinical application)

"Klaus Wiemer, lab director at Poma Fertility, … recounted a recent experience in which **a woman opted for a second cycle** of IVF in search of embryos with better risk scores.
"Even though the embryos are genetically normal, **she was just unhappy with the heritable scores** that the embryos got for certain traits."
https://www.genomeweb.com/sequencing/embryo-selection-polygenic-risk-scores-enters-market-clinical-value-remains-unproven (2022)

"Of the eight patient's that learned their PGT-P results six decided to transfer an embryo while **one decided to do another cycle** to produce more embryos. **The final patient decided to take a break from the IVF process** at this time…. neither provided additional comments regarding their decision."
"[These] **Two patients demonstrated high levels of anxiety** with a score of 60 and 67 respectively."
https://rucore.libraries.rutgers.edu/rutgers-lib/67610/ (2022)

Ethical and social concerns

- Eugenics-related problems:
  - Deterioration towards state-based coercion (???)
  - Imposing new social norms, often reflecting market values
  - Promoting genetic essentialism and fatalism
- Having to rank by conditions/traits, particularly mental
- Stigmatization of future disease cases (whether tested as embryos or not)
- Health disparity (costs in time and $$)

- Counter point: an embryo has to be selected anyhow, so “choice over chance”

LifeView™
choice over chance

More reading

- Lazaro-Munoz et al, Genet Med, 2021
- Turley et al, NEJM, 2021
- Munday and Savulescu, J Med Ethics, 2021
- Forzano et al, EJHG, 2021
- Tellier et al, Genes, 2021
- Treff et al, Fetil Steril, 2022
- Nature editorial, 2022 (603/549)
- Polyakov et al, Hum Reprod, 2022
- Lencz et al, Lancet Psychiat, 2022

Other issues

- Increasing the risk of another disease 

- Selecting for European ancestry in embryos of admixed couples ?
- Massive loss of genetic diversity 

- Impact on well-being of children ?

Summary

	Risk reduction	Harm
Pros	• Technologically feasible • Large risk reduction possible for single common diseases • Parallel risk reductions for 10-20 diseases • Risk reductions stable across parents, even with high PRS or affected	• When IVF/biopsy required, low cost, no harm, and must select an embryo anyhow
Cons	• Lower gains for non-Europeans and unclear outcomes in admixed • Must actively select the best-scoring embryo • Not enough embryos for older/infertile couples • May not be relevant in 2070 • Cannot be experimentally validated	• If not required, harms of IVF and biopsy • May decrease live birth rate • Patient confusion and choice overload • Market-imposed social norms • Encouraging genetic essentialism • Potential for stigmatization and increasing health disparity • Psychological impact on children unclear

Acknowledgements

- Todd Lencz, Northwell, NY

- Hebrew University: Daniel Backenroth, Liraz Klausner, Or Zuk
- ELSI: Gabriel Lazaro-Munoz (Harvard), Stacey Pereira (Baylor)
  - Dorit Barlevy, Remy Furrer, Ilona Cenolli, Kristin Kostick-Quenet, Meghna Mukherjee

National Human Genome Research Institute

R01 HG011711

polygenicembryo.org

We’re recruiting!