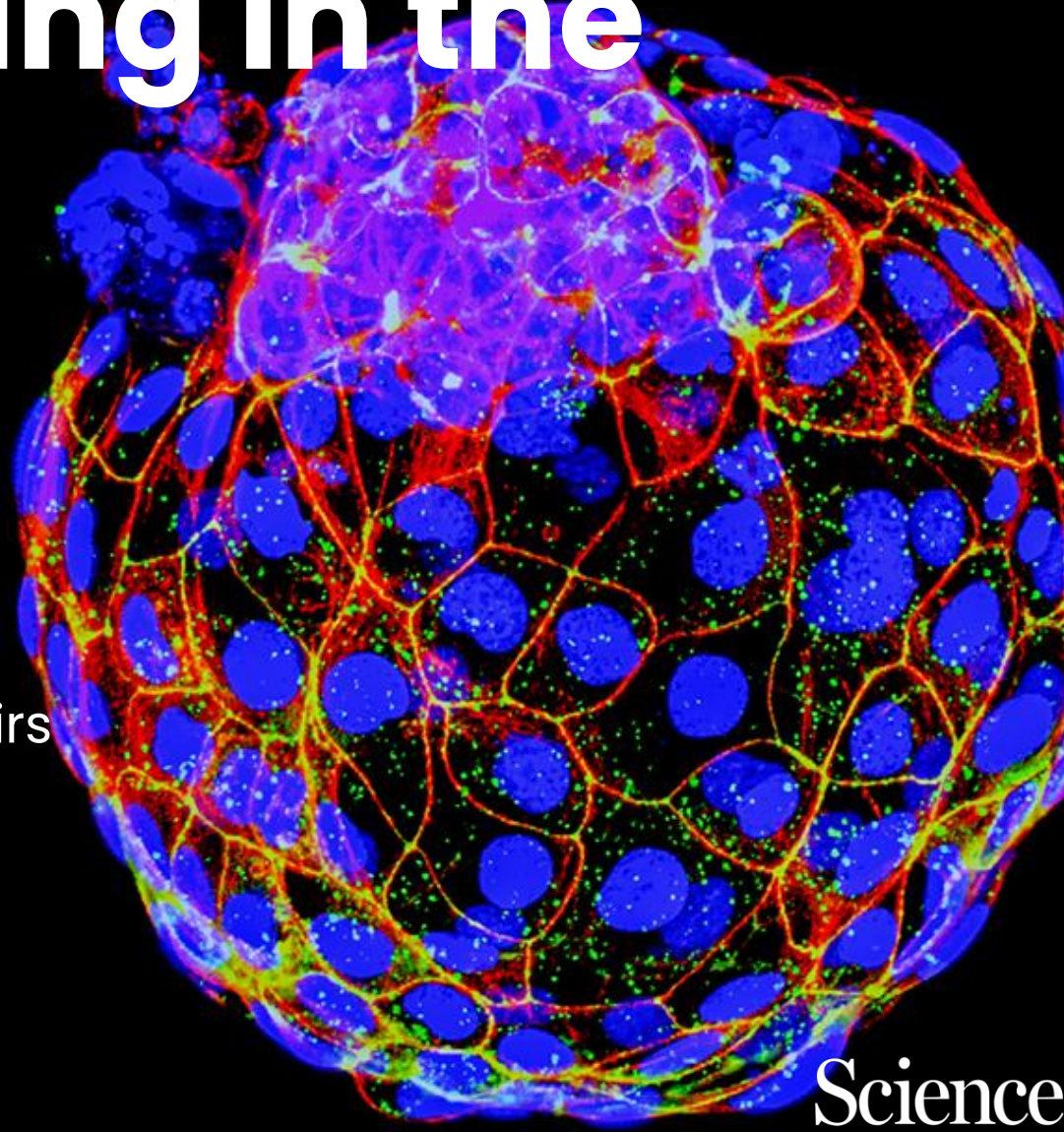
Polygenic Risk Scoring in the Human Embryo

Diego Marin, PhD, HCLD(ABB)

Deputy Laboratory Director
Head of Global Business Development & Scientific Affairs
Genomic Prediction

Adjunct Professor
Department of Human Genetics
Rutgers University



Science

Disclosure

Full-time employee at Genomic Prediction, a PGT service provider (including “PGT-P”)

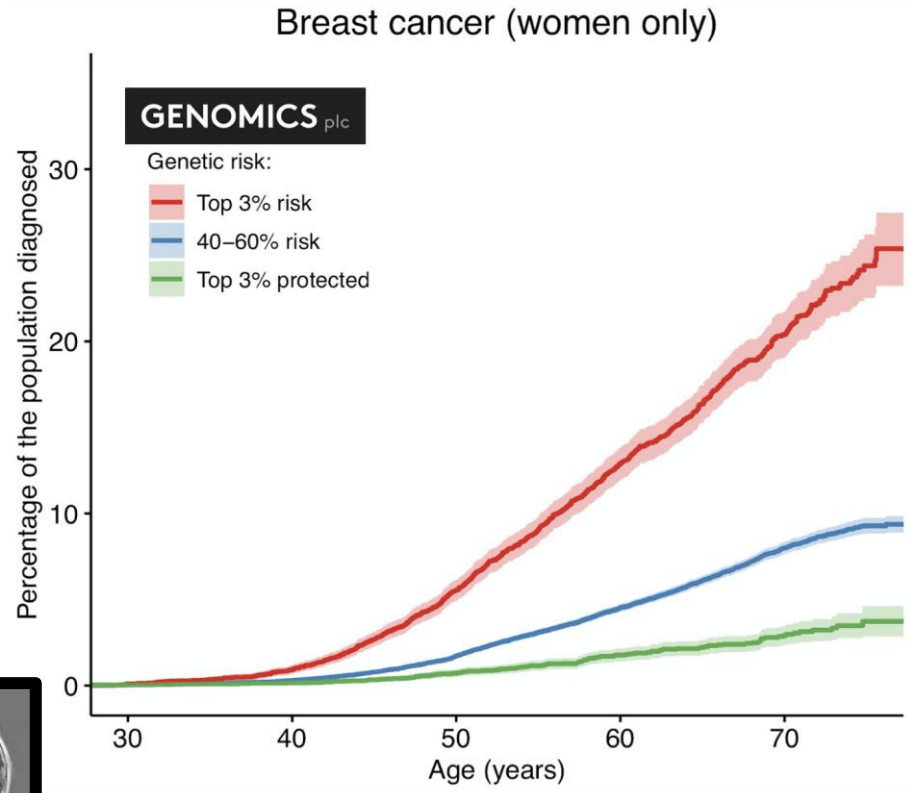
PRS in PGT

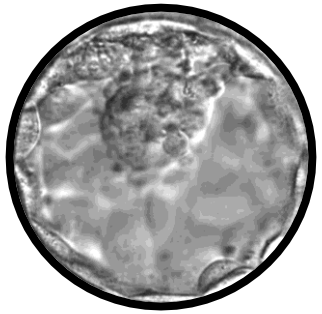
Concept and Clinical Utility

Challenges

Future Applications

Polygenic Risk Scores





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99.7% Genotyping Accuracy

Treff et al. **EJMG** 2019

The Economist Bhattacharya 2018, and the **UK BioBank**

Example of a “PGT-P” Report

Euploid embryos

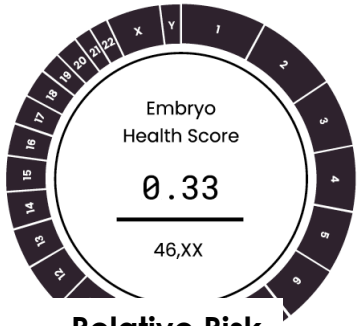
#	PGT-A	Sex
7	46,XX	female
9	46,XX	female
3	46,XY	male
10	46,XY	male
4	46,XX	female
1	46,XY	male
8	46,XX	female
11	46,XX	female
6	46,XX	female
5	46,XY	male

Aneuploid embryos

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

Embryo #4

Euploid Female



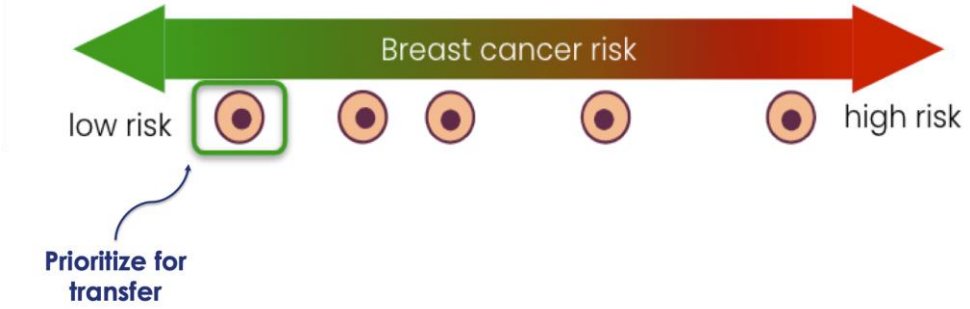
Absolute Risk

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**

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

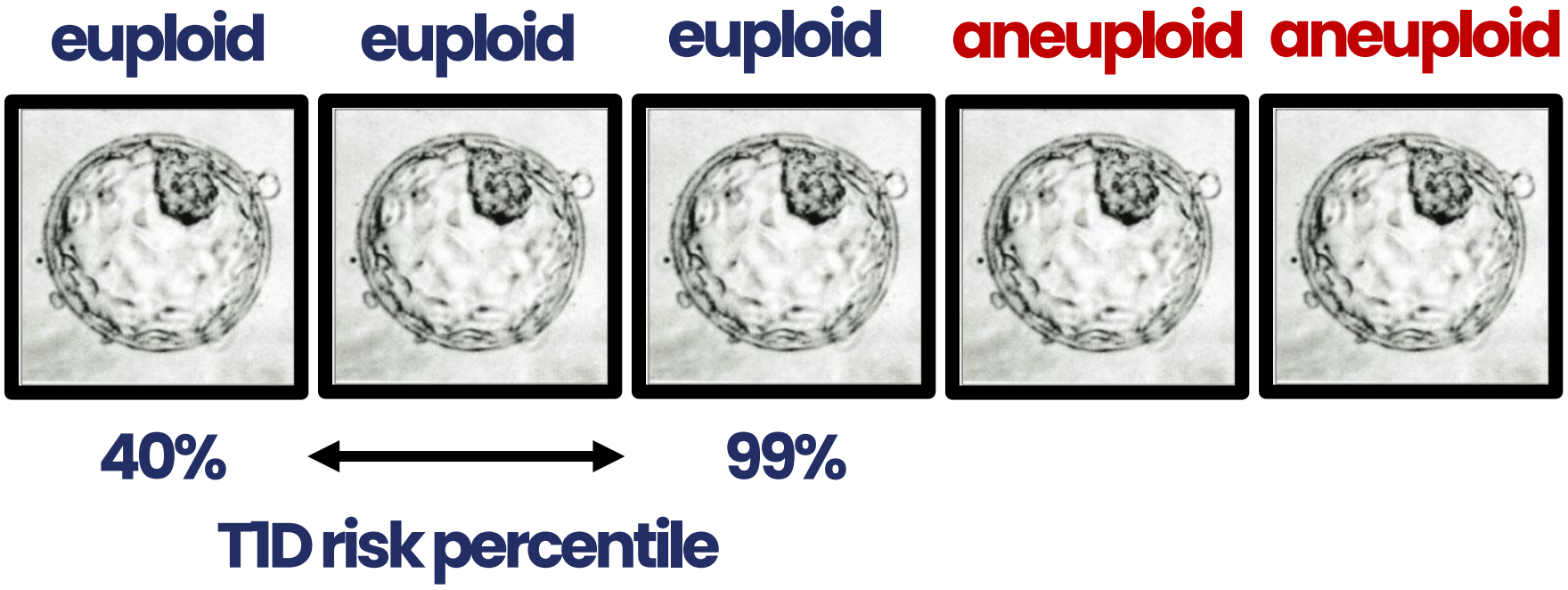
Fertility treatment and childhood type 1 diabetes mellitus: a nationwide cohort study of 565,116 live births

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,†]

Example Case with a Child Affected with T1D



Challenges of PRS in the Preimplantation Embryo

“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

Social and Racial Disparities

PGT-P Panel: Caucasian

Patient (or egg donor) self-reported ancestry: Caucasian(Non-Hispanic)
Partner (or sperm donor) self-reported ancestry: Caucasian(Non-Hispanic)

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	-

PGT-P panel: Hispanic/Native American

Patient (or egg donor) self-reported ancestry: Caucasian(Hispanic)
Partner (or sperm donor) self-reported ancestry: Caucasian(Hispanic)

Euploid embryos

#	PGT-A	Sex	Embryo Health Score
6	46,XY	male	2.21
3	46,XX	female	1.74
7	46,XY	male	-0.08
9	46,XX	female	-1.47

Aneuploid embryos

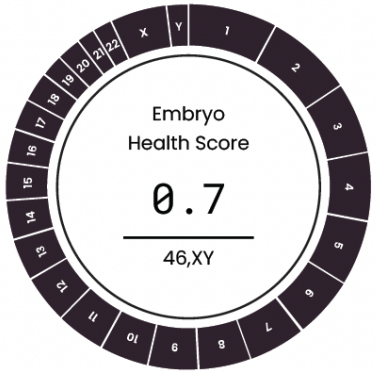
#	PGT-A	Sex	Embryo Health Score
4	45,XX,-22	female	-
5	45,XX,+13	female	-

PGT-P Panel: Caucasian

Patient (or egg donor) self-reported ancestry: Caucasian(Non-Hispanic)
Partner (or sperm donor) self-reported ancestry: Caucasian(Non-Hispanic)

Embryo #3

Euploid Male



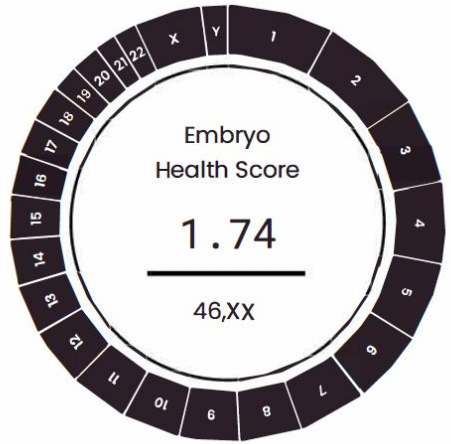
	Risk	Avg Risk	Ratio	Risk Percentile
Type 1 Diabetes	0.57%	0.70%	0.82x	42
Type 2 Diabetes	13.86%	30.57%	0.45x	1
Testicular Cancer	0.54%	0.52%	1.03x	64
Prostate Cancer	14.37%	14.27%	1.01x	57
Basal Cell Carcinoma	26.43%	26.00%	1.02x	56
Malignant Melanoma	2.57%	2.60%	0.99x	52
Heart Attack	11.26%	14.90%	0.76x	16
Atrial Fibrillation	41.43%	29.70%	1.4x	88
Coronary Artery Disease	35.61%	43.30%	0.82x	23
Inflammatory Bowel Disease	1.73%	1.44%	1.2x	72
Asthma	8.02%	5.00%	1.6x	90
Schizophrenia	1.00%	1.31%	0.76x	45

PGT-P panel: Hispanic/Native American

Patient (or egg donor) self-reported ancestry: Caucasian(Hispanic)
Partner (or sperm donor) self-reported ancestry: Caucasian(Hispanic)

Embryo #3

Euploid Female



	Risk	Avg Risk	Ratio	Risk Percentile
Type 2 Diabetes	26.70%	46.19%	0.58x	11
Asthma	4.54%	5.00%	0.91x	44

Social and Racial Disparities

“The first “PGT-P” baby was born in 2020… how do you know this technology works if she is just 5?”

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]

scientific reports

OPEN

Sibling variation in polygenic traits and DNA recombination mapping with UK Biobank and IVF family data

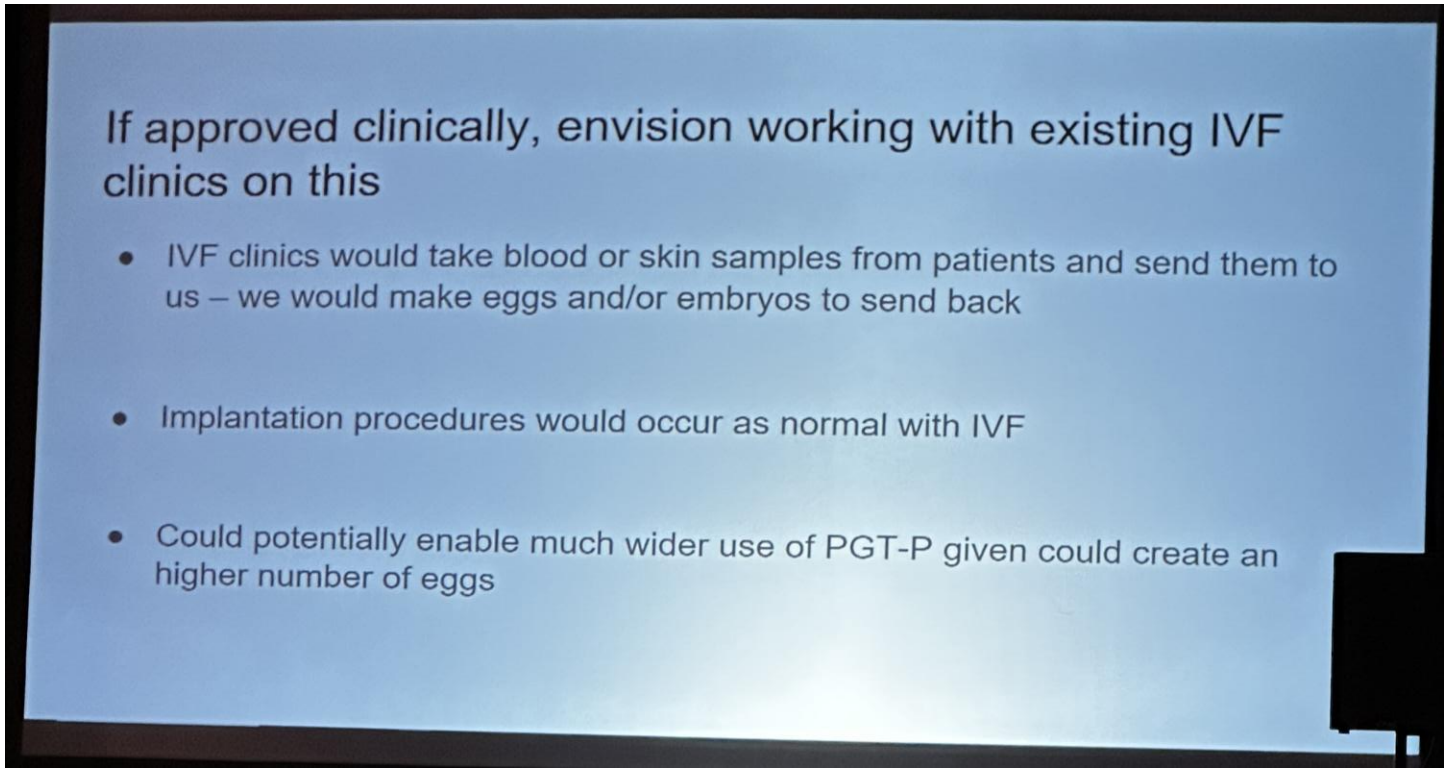
Louis Lello[1,2]✉, Maximus Hsu[1], Erik Widen[1,2] & Timothy G. Raben[2]

Future Applications

CONCEPTION

Turning stem cells into human eggs

https://conception.bio/



Pablo Hurtado, Co-founder & CSO. *PCRS 2025*

¡Gracias!

diego@genomicprediction.com

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