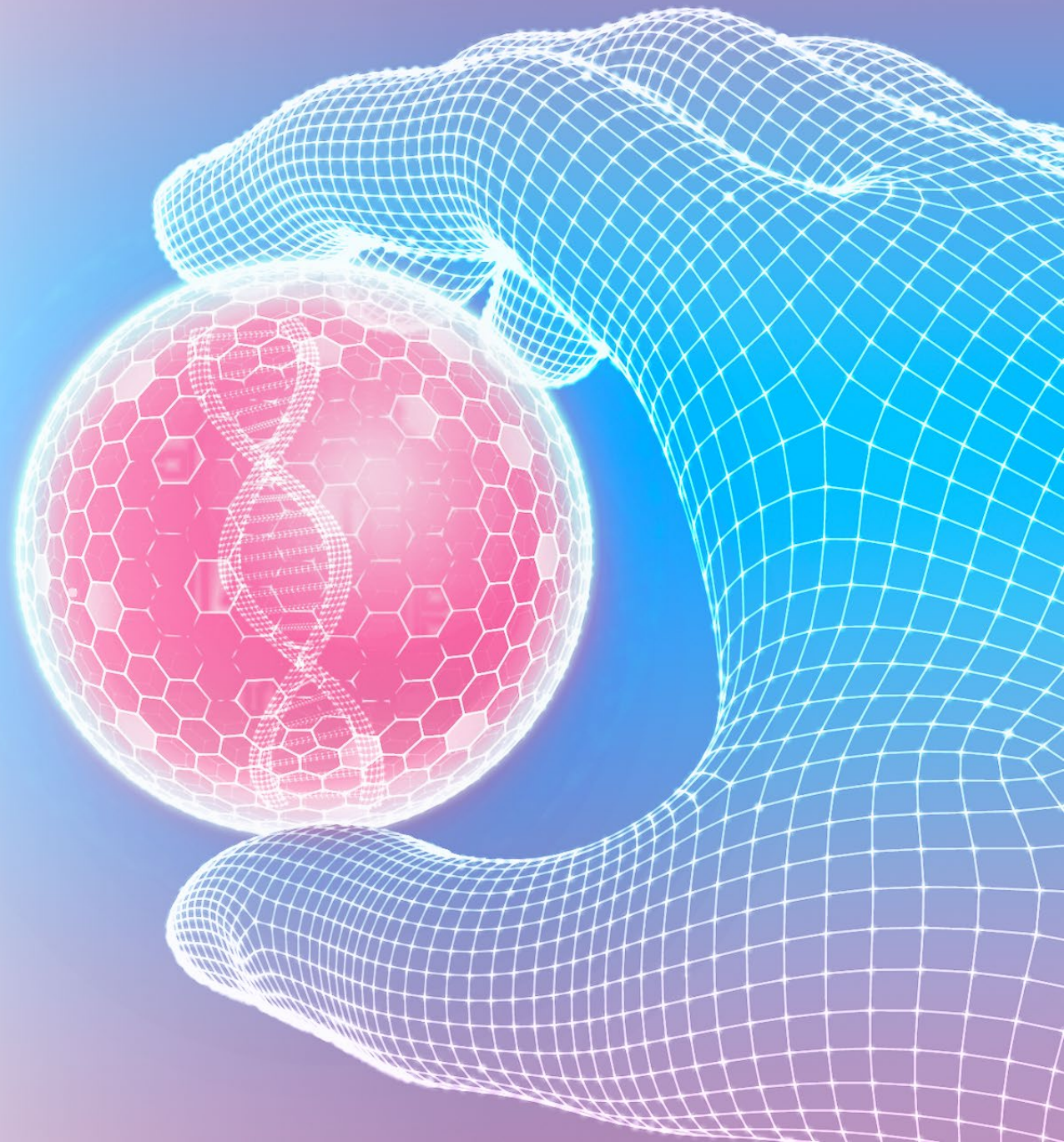
# Preimplantation genetic testing with whole-genome sequencing (PGT-WGS)

## *Panacea* - GenomeScreen™

Nick Murphy PhD, GenEmbryomics
nick@genembryomics.com

**PGDIS, Kuala Lumpur, Malaysia, 2024**



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# Affiliations and Disclosures

- Managing Director @ GenEmbryomics Limited
- Adjunct Research Fellow @ Dept. Drug Delivery Disposition & Dynamics, Monash Institute of Pharmaceutical Sciences, Monash University

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# Background

- PhD@Monash University – HLA haplotype phasing
- Melbourne IVF – PGT
- Monash IVF – PGT
- Genetic Techologies Ltd. – Senior Dev. Scientist
- GenEmbryomics Limited

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# PGT-WGS

- PGT background and genetic screening
- Rare diseases and mutations detectable by testing platforms
- GenEmbryomics & PGT–WGS with *Panacea*-GenomeScreen™
  - Process overview
  - Validation
  - Gene selection, case processing, variant curation, reporting, counselling, limitations,
- Acknowledgements

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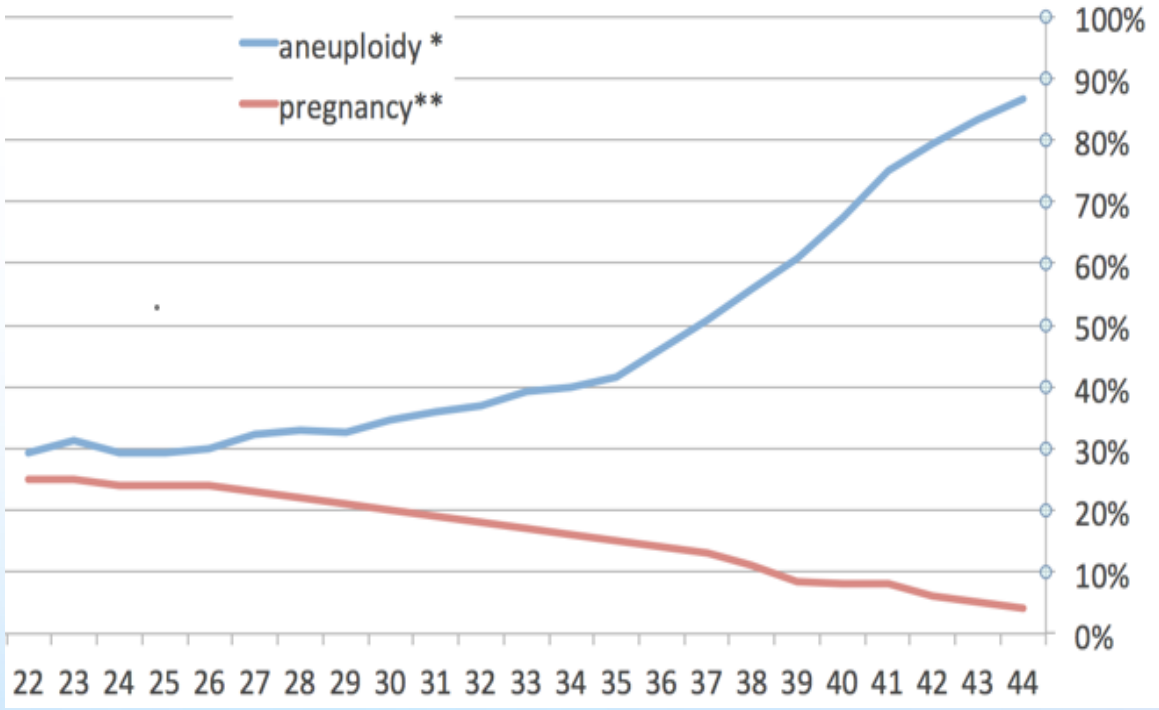
# Delayed reproduction = infertility by aneuploidy

- Selecting euploid embryos for transfer should improve ongoing pregnancy rates per transfer (Munné, *et al*. 1993)




Source: Cooper Genomics (N > 100,000 PGT cycles), CDC

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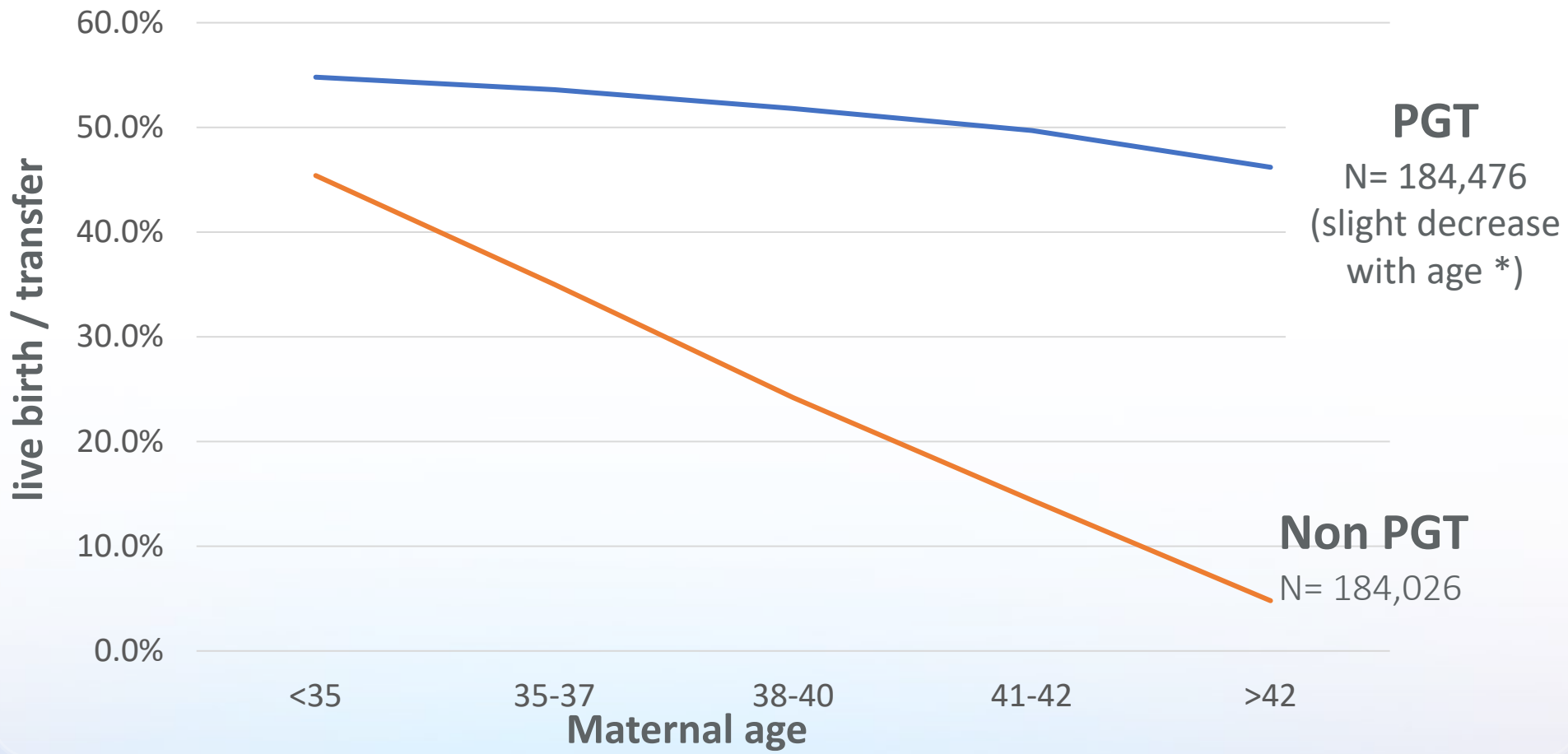
# PGT reduces the maternal age effect on LBR

SART:




Harton, Munné et al. (2013) Fertil Steril., SART 2021

several meta-analysis i.e. Vitagliano et al. (2023) Fertil Steril. report a significant but small trend towards declining OPR with age after PGT-A

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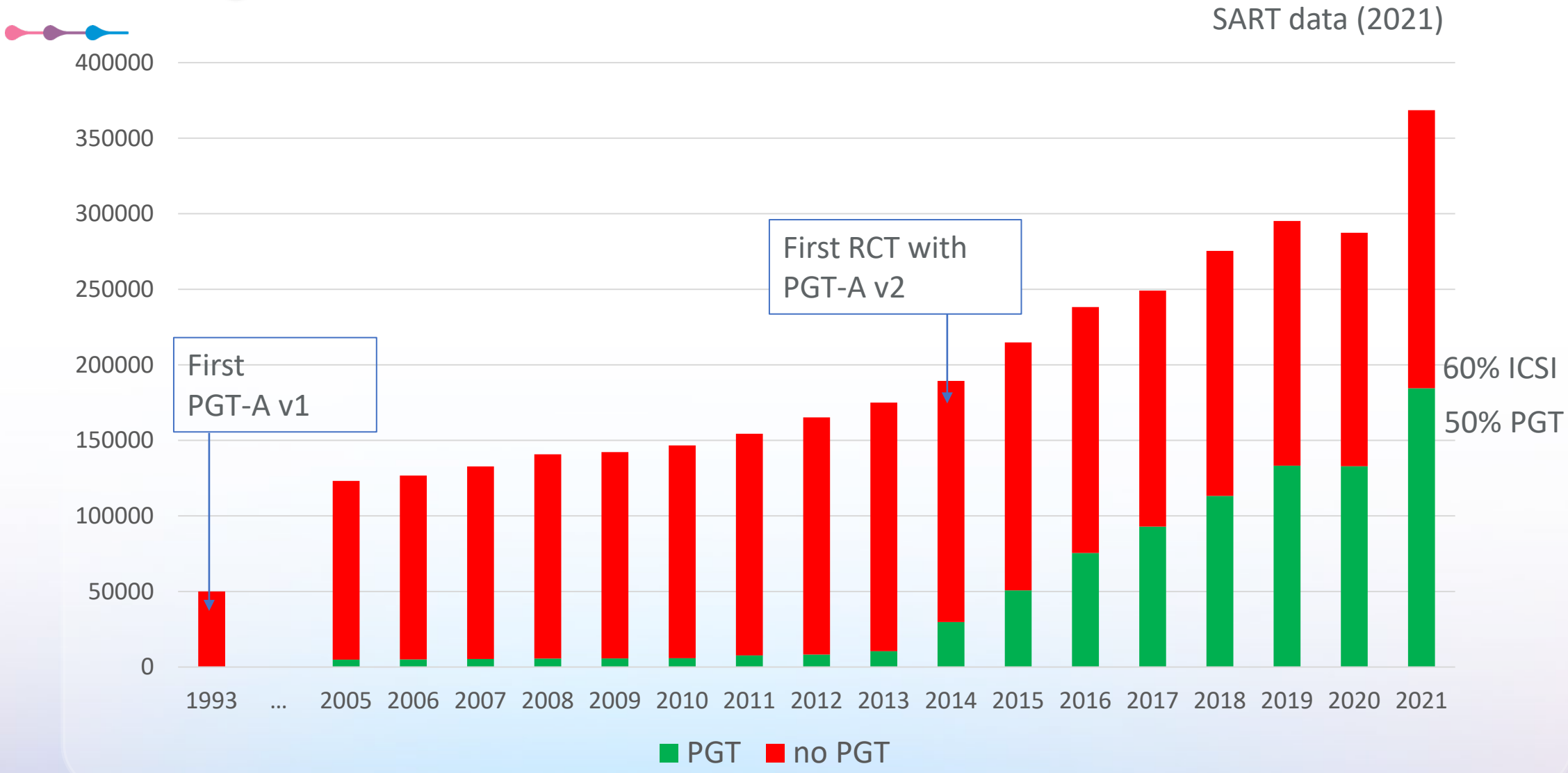
# PGT usage: USA

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# Increased congenital abnormalities in ART

- Babies conceived through ART have more congenital abnormalities than naturally conceived babies.
- This could be the result of higher parental age of IVF patients, or underlying mutations causing infertility
- Therefore if we are going to perform PGT, more reason to analyze also for de novo mutations

The Fetal Medicine Foundation

**Congenital anomalies**
**ART vs natural**

| Meta-analyses | Articles | ART infants | Pooled estimate (95% CI) |
|---|---|---|---|
| Wen *et al* (2012) | 46 | 124,468 | 1.37 (1.26, 1.48) |
| Hansen *et al* (2013) | 45 | 92,671 | 1.32 (1.24, 1.42) |
| Zhao *et al* (2018) | 46 | | 1.40 (1.31, 1.49) |
| Hoosnan *et al* (2017) | 30 | | 1.99 (1.87, 2.11) |
| - Cardiac defects | | | 1.43 (1.27, 1.62) |
| - CNS defects | | | 1.36 (1.10, 1.70) |
| - Urogenital defects | | | 1.58 (1.28, 1.94) |
| - Musculoskeletal | | | 1.35 (1.12, 1.64) |
| - Chromosomal | | | 1.14 (0.90, 1.44) |
| Giorgione *et al* (2018) | 8 | 25,856 CHD | 1.45 (1.20, 1.76) |
| Zhao *et al* (2019) | 46 | 112,913 | 1.43 (1.31, 3.52) |

**ARTs increase risk of birth defects by about 40%**

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# The likelihood of having a rare genetic disease

**1 in 14 people have a rare genetic disorder**

Calculated based on prevalence estimates and number of disorders in each category

Prevalence of rare disorders

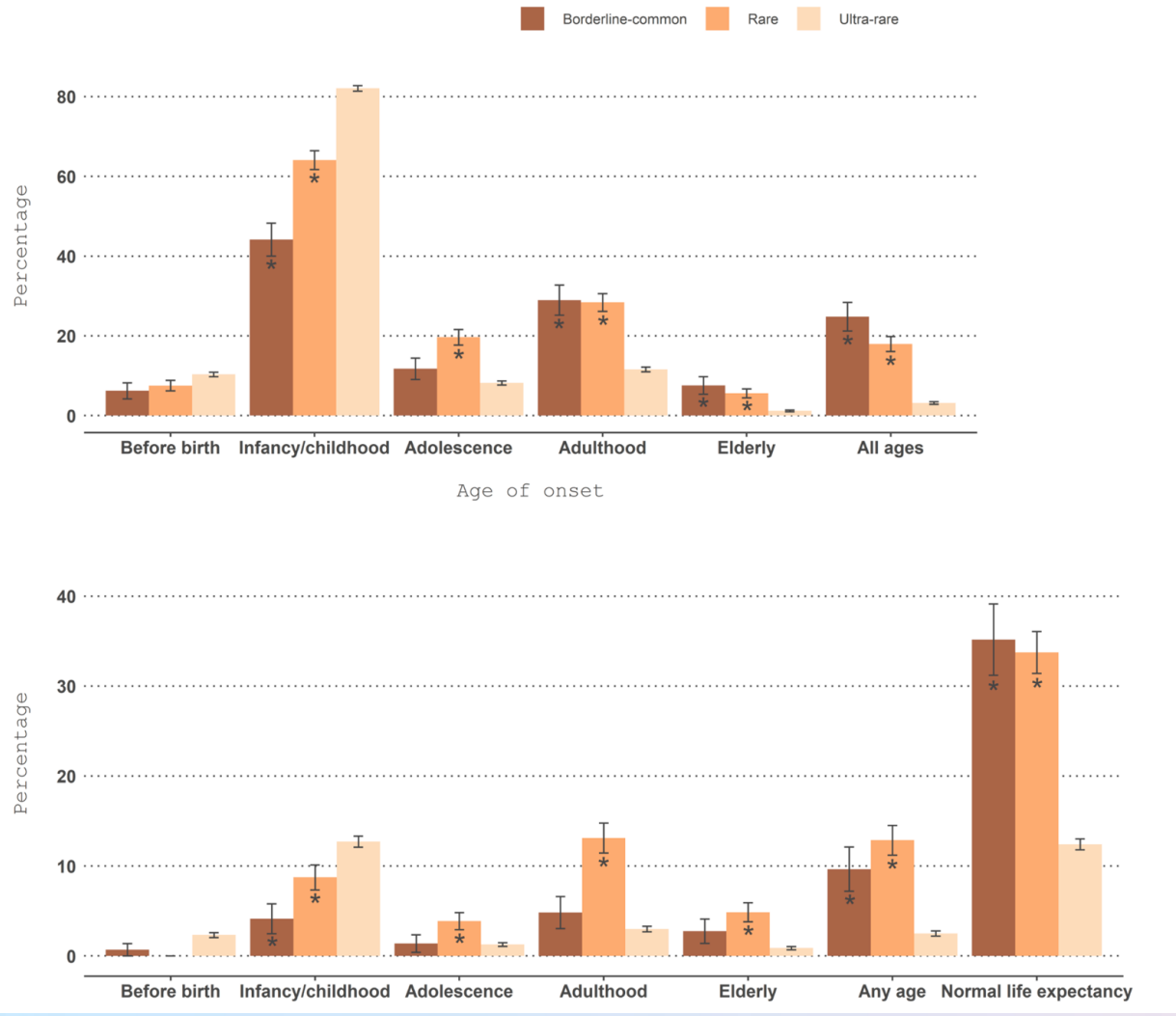
- 6.53% are expected to have a borderline-common disorder
- 0.34% are expected to have a rare disorder
- 0.30% are expected to have an ultra-rare disorder

Of all rare disorder patients in a population:

- 91.2% would have a borderline-common disorder
- 4.7% would have a rare disorder
- 4.2% would have an ultra-rare disorder

Ultra-rare disorders are the most numerous, comprising 84.2% of all rare disorders

Affect 0.30% of the population due to low prevalence




Frederiksen *et al.* (2022).

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# Rare Disease

- There are ~20,000 protein coding-genes
- 10,000 genetic diseases have been identified of which >7000 are rare[1]
- PGT-M has been performed for >1,500 genetic diseases
- The genetic basis of rare diseases can be diagnosed by whole exome sequencing[2]:
  - 32% (158/500) patients with these rare diseases had primary findings 195 pathogenic variants identified
  - Most were autosomal dominant (61.6%), followed by autosomal recessive (25.6%) and X-linked (12.8%)
  - 50% discovery yield in consanguineous patients

(1) Boycott *et al*. 2013; (2) Quaio *et al*. (2020)

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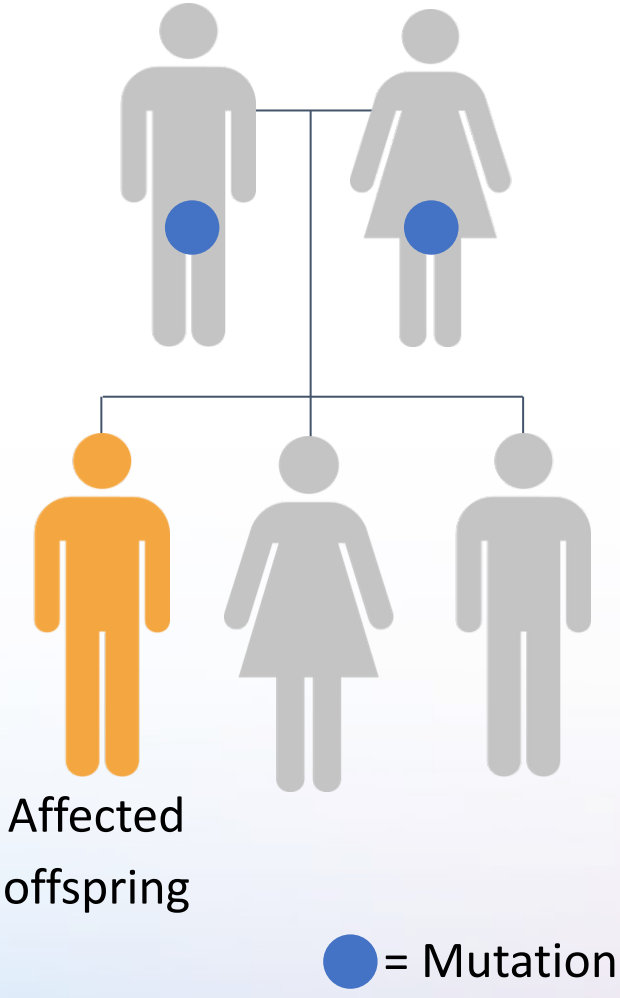
# *De novo* mutations (DNV)

- DNV mutations accumulate in the parents' gametes and are not detectable by carrier screening.
- There are 74 DNV mutations per embryo: 1-2 pathogenic[1-3]
- DNV mutations increase with paternal age[4]. Fathers 45 years old have x3.5 risk of autistic[5,6] and x27 risk of bipolar offspring than 25 years old[7].
- DNV mutations are more detrimental than inherited mutations not exposed to natural selection[11]




*(1) Acuna-Hidalgo et al. (2015) Am J Human Genet 97, 67–74, (2) Kondrashov (2003) Human Mutation 21, 12–27, (3) Acuna-Hidalgo et al. (2016) Genome Biology 17, 241. (4) Kong et al. 2012, Nature, (5): D'Onofrio et al. 2014, JAMA (4) Sanders Nature 2012;485:237–41.(7) Sandin S et al. (2016). Mol Psychiatry. 21:693-700 (8) Lord Lancet 2019;393:747–57, (9) de Ligt N Engl J Med 2012;367:1921–9. (10) Kong et al. 2012, Nature, (11): Veltman Nat Rev Genet 2012;13:565–75.*

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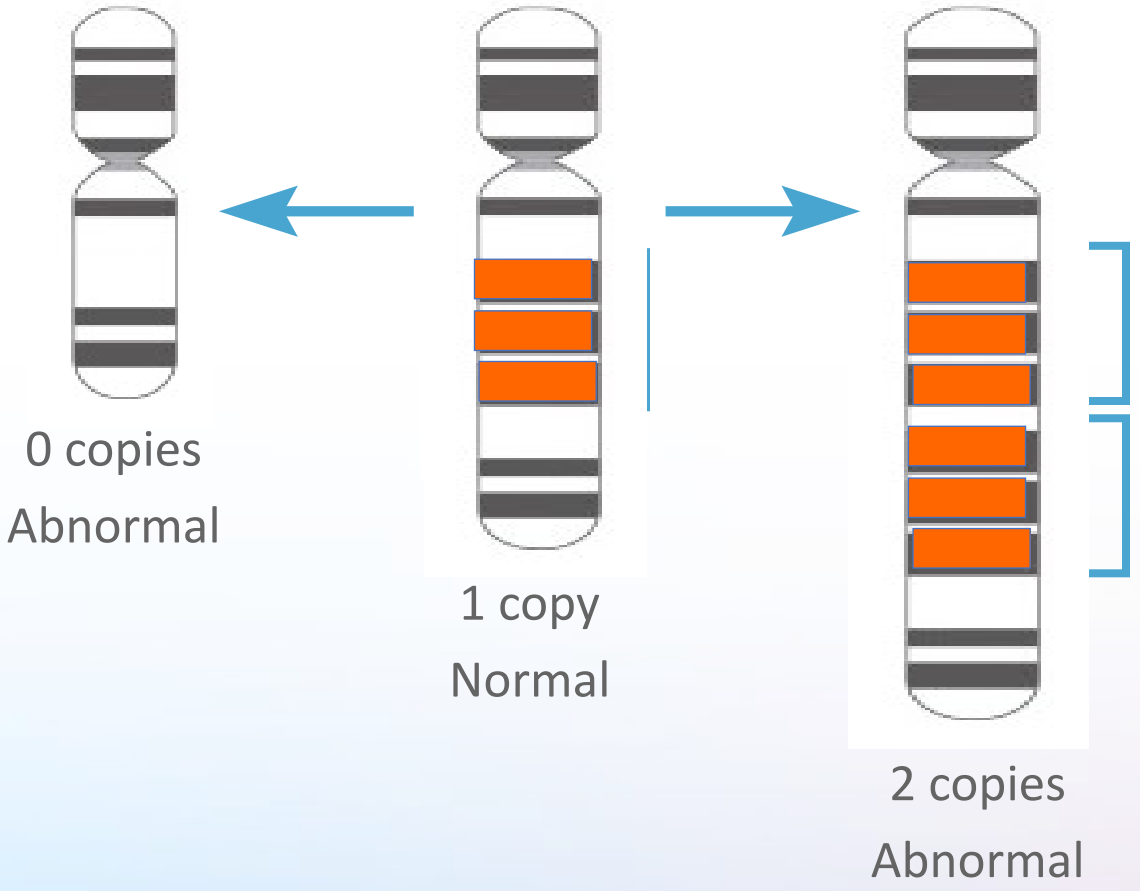
# *De novo* copy number variants (CNV)

- Copy number variants (CNV) are the result of segmental duplications and /or deletions >500bp
- Unlike point mutations, CNVs are extremely unlikely to be amplification or sequencing artifacts
- 1-2% of conceptions carry CNVs that are 100kb to 10Mb, not detectable by low-coverage PGT-A

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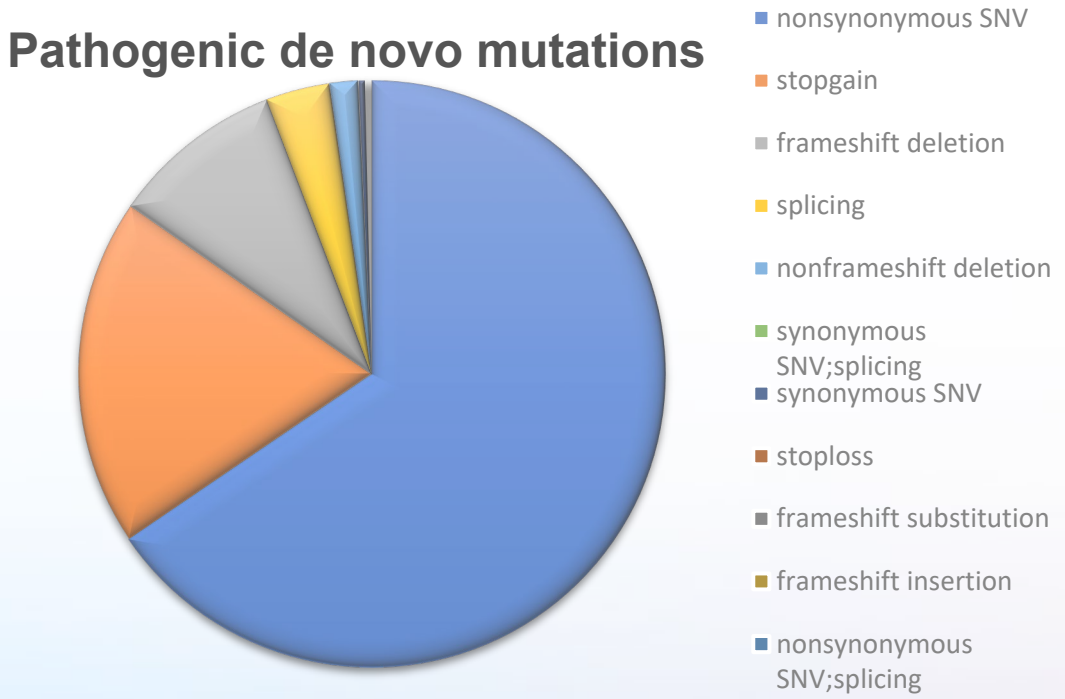
# Rate of pathogenic *de novo* mutations

- 750,000 *de novo* mutations identified (Gene4Denovo)[1]
- 8,500 coding pathogenic SNP de novo mutations in 850 genes catalogued [2]




1. Guihu Zhao *et al*. (2020)
2. *2. Li K et al. (2024)*

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# PGT indications and platform needs

- **PGT-A** PGT for aneuploidy requires only copy number. Usually done through low-coverage sequencing (<0.1X genome coverage). ~10Mb size limit
- **PGT-SR** PGT for structural chromosome abnormalities such as deletions and translocations. Low-coverage sequencing can detect imbalances. **SNP analysis** *needed to differentiate carrier from normal.*
- **PGT-M** PGT for monogenic diseases. Performed by linkage or **SNP analysis**, either by haplotyping or specific detection of the mutation.
- **PGT-P** PGT for polygenic conditions. Requires **SNP analysis**.
- **PGT-WGS** all of the above & more.. Requires **SNP analysis**.

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# Comprehensive PGT methods

## SNP ARRAYS - GENOTYPING

- Karyomapping [1]
- Haplarithmisis [2]
- High throughput SNP array [13]
- HaploSeq
- APCAD [4]
- Genome prediction PGT-PS [3]
- Haplotype-Aware [5]
- Whole genome prediction [6]

## GENOTYPE BY SEQUENCING

- PGT Complete [12]
- One PGT [7]
- Genotyping by sequencing [8]
- Chen et al. [9]
- HaploPGT [10]
- S-HaploSeek [11]

## SEQUENCING + TARGET SNPs

- PGT-Seq
- OneGene PGT [14]

*(1) Handyside et al. J. Med. Genet. 47, 651–658 (2010); (2) Zamani Esteki, et al. , Am. J. Hum. Genet. 96, 894–912 (2015). (3): Treff et al. (2019) Fronteers Endocrinol (4) Verdyck et al. 2022, (5) Ariad et al. (2021) . (6) Kumar (2022) Nature Medicine 28:513–516, (7) Masset et al. Hum. Reprod. 34, 1608–1619 (2019); (8) Masset et al. (2022) Nucleic Acid Res, (9) Chen et al. (2020) Human Reprod; (10) Xie et al. (2022) Human Reprod 37:2546–59.(11) Backenroth et al. (2023) Nature Scientific Reprots 13:18036 (12) Buldo-Licciardi et al. 2020. ASRM; (13) Treff et al. Eur J Med Genet. 2019;62: 103647. (14) Hornak et al(2024) JARG*

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# Companies offering WGS embryo screening

GEN EMBRYOMICS

>3,200 genes, *de novo* & inherited

Gattaca Genomics

Recently established in Florida, USA

ORCHID

1,400 gene panel of inherited pathogenic diseases & polygenic risk

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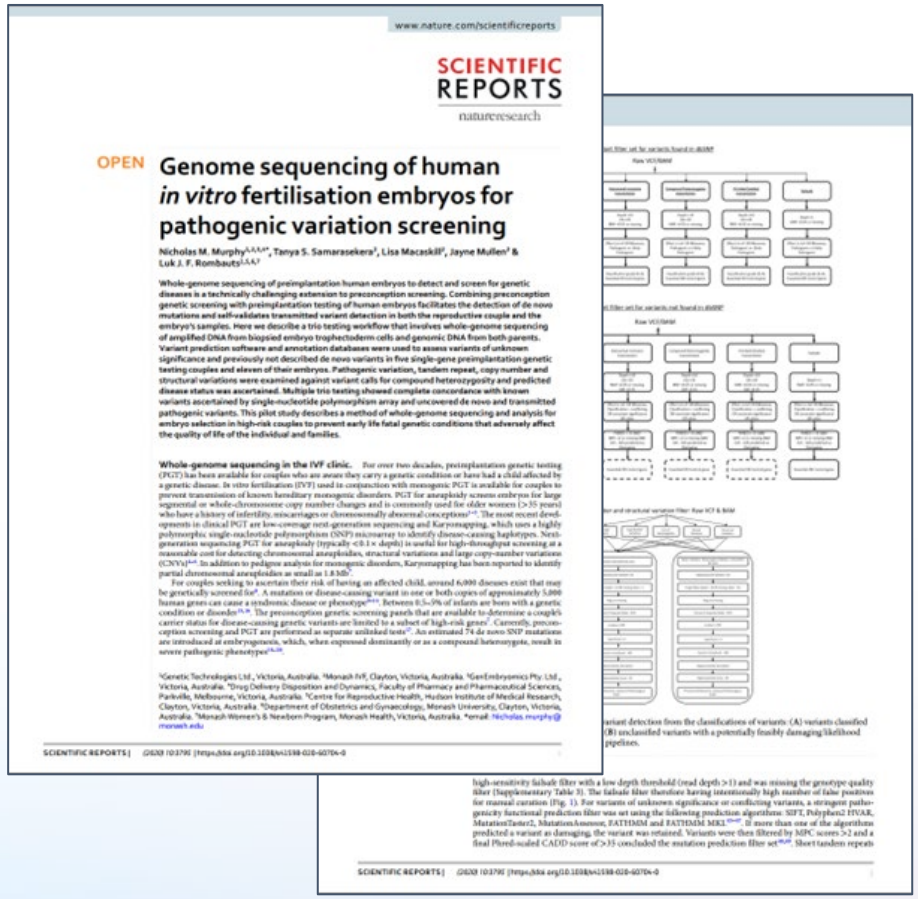
# GenEmbryomics

- Initial R&D performed with Monash IVF
- GenEmbryomics was established in 2019 to further develop the test
- Proof-of-principle published in Scientific Reports (2020)




Murphy *et al*. (2020) Scientific Reports 10:3795

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# PGT-WGS for inherited and *de novo* mutations

**Methods:**

- Amplification by MDA
- Whole genome sequence of parents at x30 and embryos at x50 depth
- Extensive variant filtration to eliminate false-positives
- Variants annotation performed from >50 annotation sources, pathogenicity prediction algorithms, and ACMG guidelines.

**Outcomes:**

- All classes of pathogenic variants detectable:
  - *de novo* mutations
  - Inherited mutations
  - Copy number variants >10kb
  - Carrier trinucleotide repeats (e.g. *FRM1*; fragile X)
- Aneuploidies, translocations, triploidy, mosaicism

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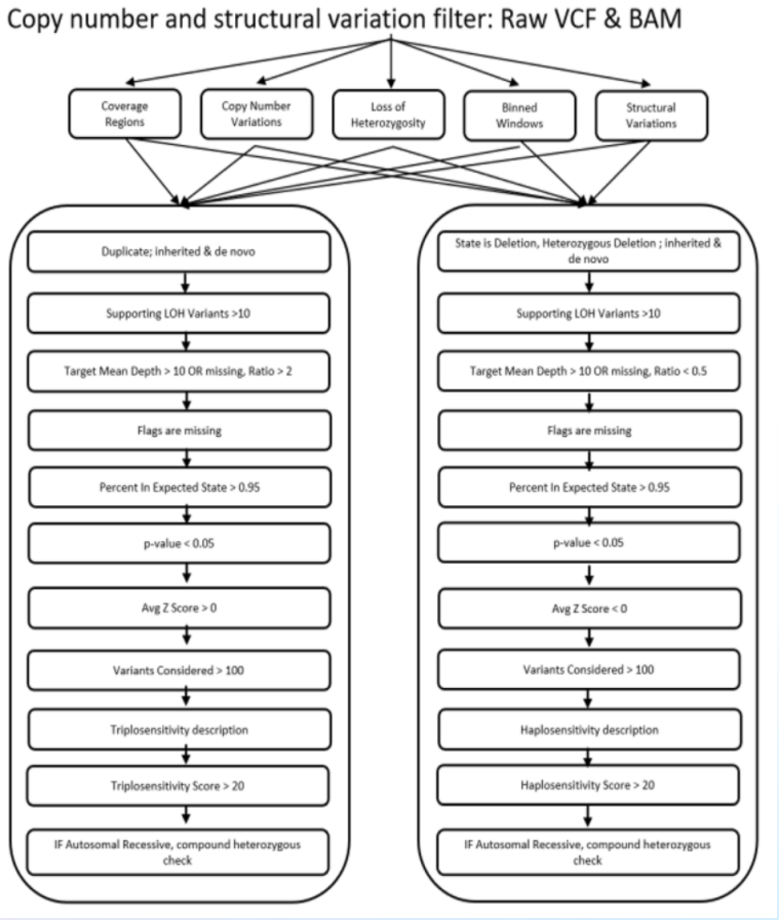
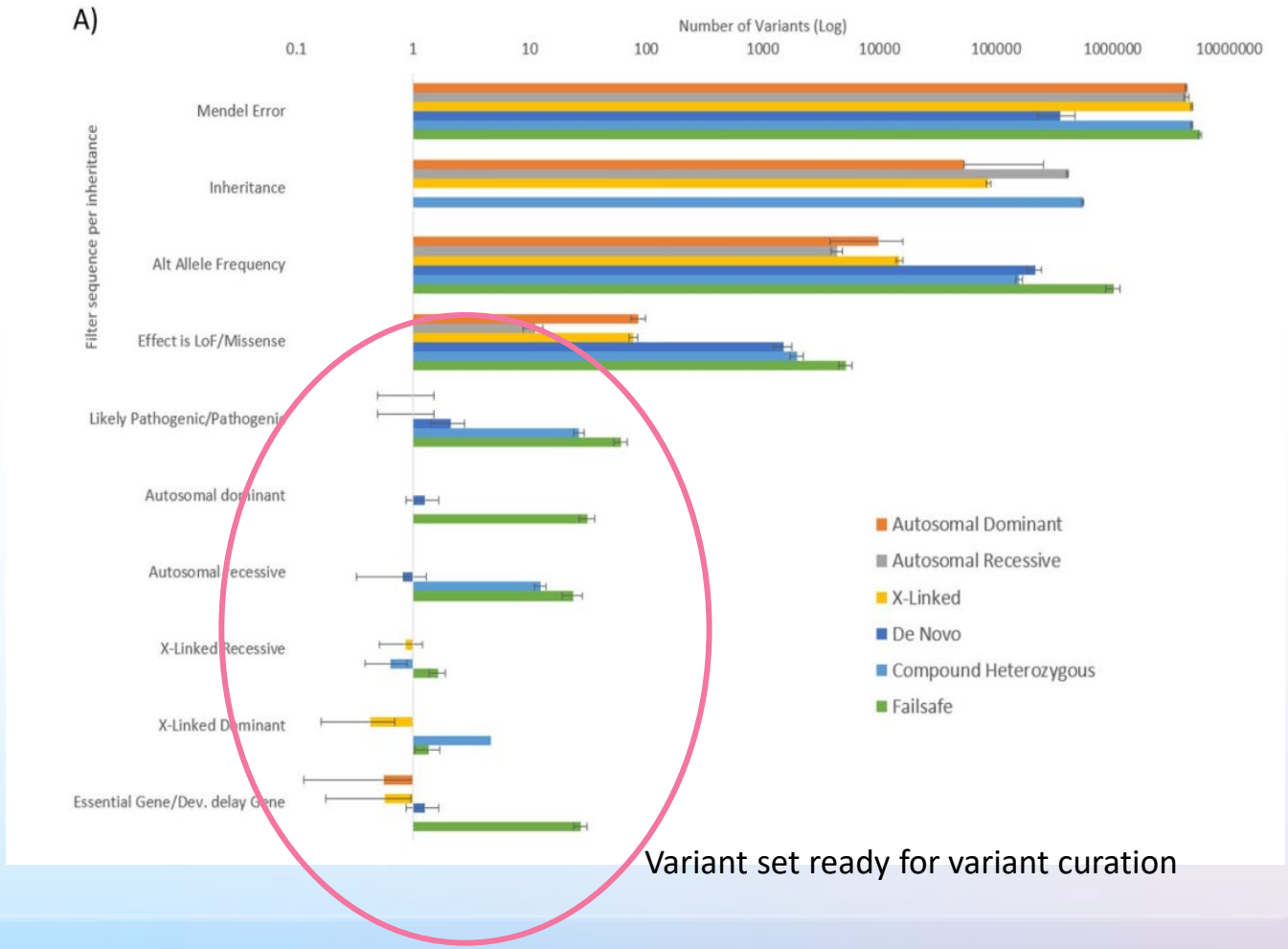
# Variant annotation




Variant set ready for variant curation

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# Benchmarking

- Genome in a Bottle v.3.3.2 NA12878 (HG001) NA12877, NA12879, parents NA12891, NA12892 etc
- Flow sorted GIAB cell lines
- Compared genomic DNA to amplified DNA (using RepliG)
- Assessed using hap.py / VCFEval [1]

1. Conrad Nat Genet. (2011)

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# Clinical validation study

- Whole Genome Sequencing on IVF Embryos and Individual Patients
- Collaboration with Memorial Sisli Hospital, Prof. Semra Kahraman, M.D & Murat Cetinkaya, M.D., PhD
- Aim is to stratify impact of paternal age on *de novo* mutation rates in IVF embryos & clinically validate test performance
- ~80 embryos, biopsies, mother and parents both receiving 30X or higher sequencing
- TE Biopsy (~6 cells) vs Remaining embryo tissue (hundreds of cells)
- Amplified with MDA
- TE Biopsy (Query) vs Remaining embryo tissue (Truth), evaluated via hap.py
- *De novo* mutation rate, concordance, mosaicism

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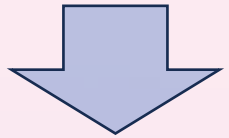
# Rate of observed pathogenic *de novo* mutations

- Detection of de novo mutations pre-annotation:
  - 5-cells model biopsies (NA12878 cell line): 3,632 DNVs
- Detection of de novo mutations post-annotation:
  - Average of 1.17 pathogenic DNVs per biopsy
- Further criteria:
  - Confirmatory testing for gDNV for reporting
- De novo mutations after annotation are confirmed by spent culture media.

**>3000 DNVs**
**Pre-annotation**



**1.2 DNVs**
**After annotation**

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# Where's the line?

- What needs to be established to screen an embryo:
  - Classification guidelines
    - Evidence – the strength and quality of data,
    - Severity– phenotype impact on quality of life, morbidity, mortality, interventions
    - Confidence - penetrance and expressivity
  - Context - Patient Preferences and Values
  - Risk and Recommendation

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# Gene selection

- Pathogenic/ Likely Pathogenic
  - >90% certainty of being disease-causing
- Reviewed status
- >1 lab submitting, no conflicts
- Penetrance High to complete (i.e., 80-100% of individuals having the variant(s) will develop the disease/disorder)
- Simple (monogenic) mode of inheritance:
  - i.e. Autosomal dominant (for PGT-M cases), Autosomal recessive, X-linked, Mitochondrial
  - Exclude genes with digenic, complex, or polygenic inheritance patterns
- Age of onset
- Lack of interventions
- Severe phenotype?

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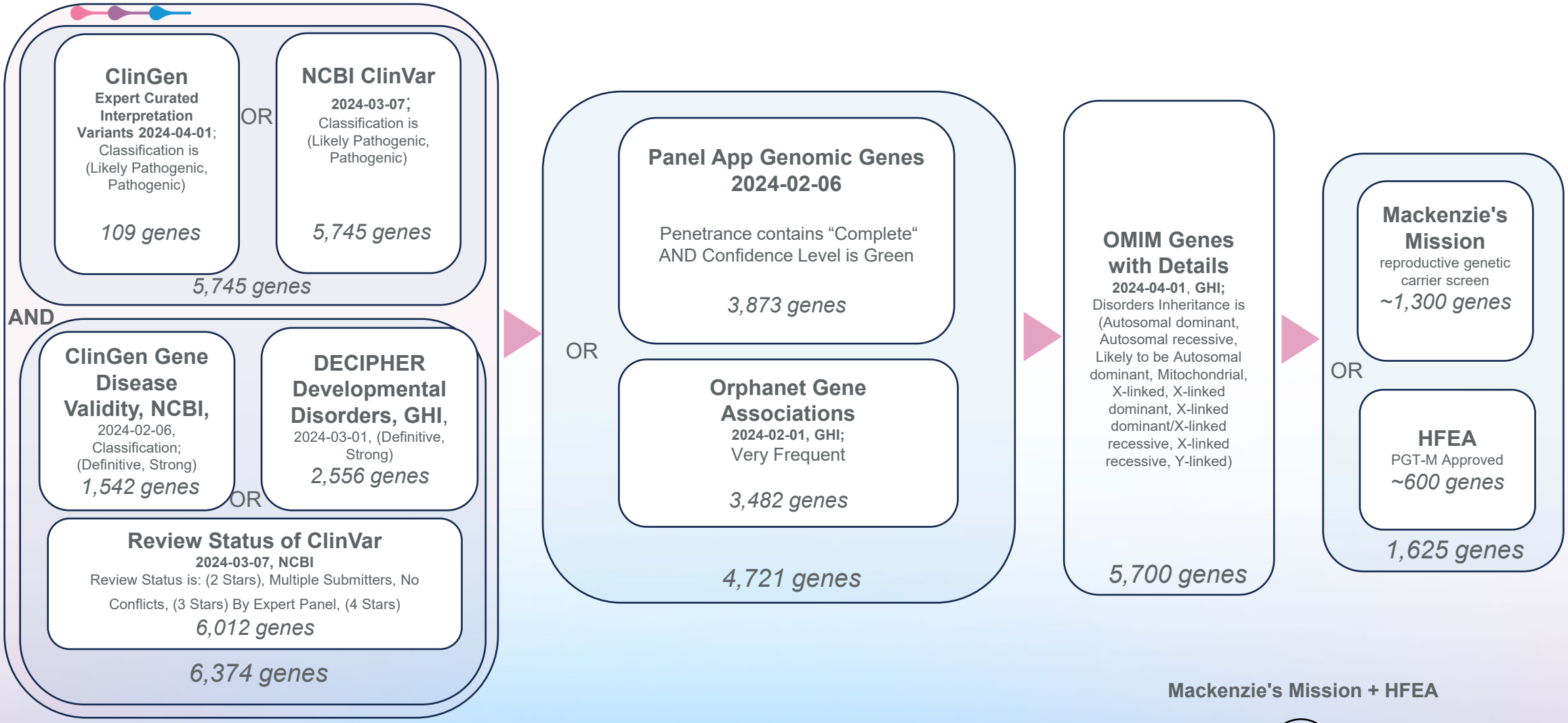
# Gene selection




**3,586 genes** → **3,366 genes** → **3,090 genes**

**Mackenzie's Mission + HFEA**

**>3,200 genes**
**for variant curation**

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# Process of *Panacea*-GenomeScreen™

**Patients seek IVF treatment**

**IVF Provider requests test**

Embryo biopsy & parent DNA Samples are collected and sent to partnering lab

**Sequencing partner**

Amplification and/or sequencing provided by third party

**GenomeScreen clinical report**

Receives data from sequencing lab, processes data & reports

**Clients receive results**

Patients receive embryo report from IVF clinic for consultation with a genetic counsellor.

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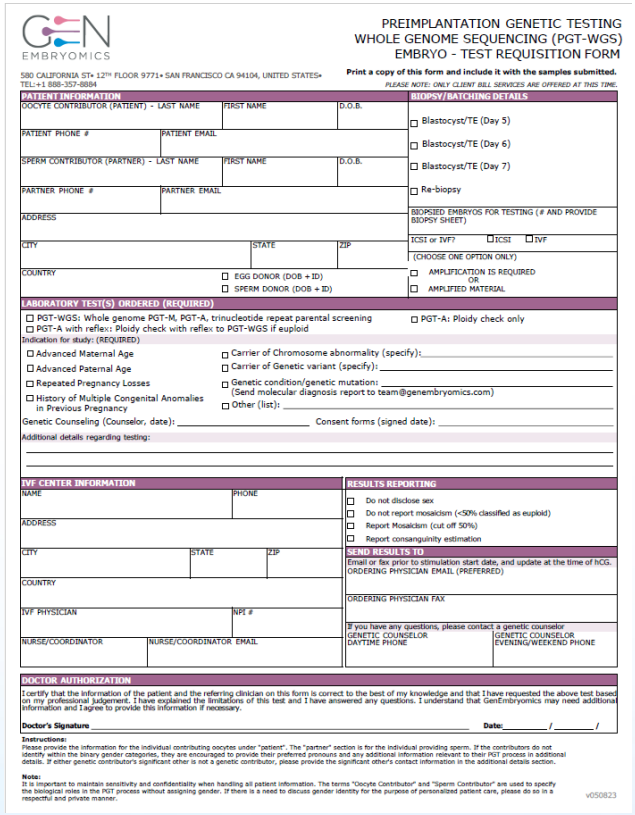
# Case registration

- Patient Registration
- ICSI or IVF embryos
- Ethnicity
- Any medical diagnosis
- Karyotypes recommended
- Informed Consent
- Genetic counselling



GEN EMBRYOMICS

580 CALIFORNIA ST• 12TH FLOOR 9771• SAN FRANCISCO CA 94104, UNITED STATES•
TEL:+1 888-357-8884

PREIMPLANTATION GENETIC TESTING
WHOLE GENOME SEQUENCING (PGT-WGS)
EMBRYO - TEST REQUISITION FORM

**Print a copy of this form and include it with the samples submitted.**
*PLEASE NOTE: ONLY CLIENT BILL SERVICES ARE OFFERED AT THIS TIME.*

**PATIENT INFORMATION**

OOCYTE CONTRIBUTOR (PATIENT) - LAST NAME | FIRST NAME | D.O.B.
PATIENT PHONE # | PATIENT EMAIL
SPERM CONTRIBUTOR (PARTNER) - LAST NAME | FIRST NAME | D.O.B.
PARTNER PHONE # | PARTNER EMAIL
ADDRESS
CITY | STATE | ZIP
COUNTRY
☐ EGG DONOR (DOB + ID)
☐ SPERM DONOR (DOB + ID)

**BIOPSY/BATCHING DETAILS**

☐ Blastocyst/TE (Day 5)
☐ Blastocyst/TE (Day 6)
☐ Blastocyst/TE (Day 7)
☐ Re-biopsy
BIOPSIED EMBRYOS FOR TESTING (# AND PROVIDE BIOPSY SHEET)
ICSI or IVF? ☐ ICSI ☐ IVF
(CHOOSE ONE OPTION ONLY)
☐ AMPLIFICATION IS REQUIRED
OR
☐ AMPLIFIED MATERIAL

**LABORATORY TEST(S) ORDERED (REQUIRED)**

☐ PGT-WGS: Whole genome PGT-M, PGT-A, trinucleotide repeat parental screening
☐ PGT-A with reflex: Ploidy check with reflex to PGT-WGS if euploid
☐ PGT-A: Ploidy check only

Indication for study: (REQUIRED)

☐ Advanced Maternal Age
☐ Advanced Paternal Age
☐ Repeated Pregnancy Losses
☐ History of Multiple Congenital Anomalies in Previous Pregnancy
☐ Carrier of Chromosome abnormality (specify):
☐ Carrier of Genetic variant (specify):
☐ Genetic condition/genetic mutation:
(Send molecular diagnosis report to team@genembryomics.com)
☐ Other (list):

Genetic Counseling (Counselor, date): Consent forms (signed date):

Additional details regarding testing:

**IVF CENTER INFORMATION**

NAME | PHONE
ADDRESS
CITY | STATE | ZIP
COUNTRY
IVF PHYSICIAN | NPI #
NURSE/COORDINATOR | NURSE/COORDINATOR EMAIL

**RESULTS REPORTING**

☐ Do not disclose sex
☐ Do not report mosaicism (<50% classified as euploid)
☐ Report Mosaicism (cut off 50%)
☐ Report consanguinity estimation

**SEND RESULTS TO**

Email or fax prior to stimulation start date, and update at the time of hCG.
ORDERING PHYSICIAN EMAIL (PREFERRED)
ORDERING PHYSICIAN FAX

If you have any questions, please contact a genetic counselor
GENETIC COUNSELOR DAYTIME PHONE | GENETIC COUNSELOR EVENING/WEEKEND PHONE

**DOCTOR AUTHORIZATION**

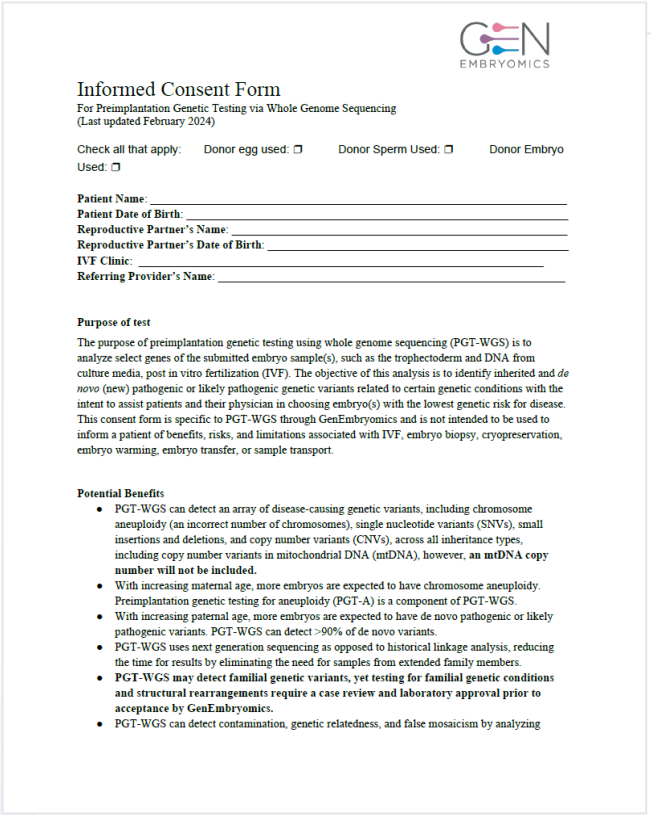
I certify that the information of the patient and the referring clinician on this form is correct to the best of my knowledge and that I have requested the above test based on my professional judgement. I have explained the limitations of this test and I have answered any questions. I understand that GenEmbryomics may need additional information and I agree to provide this information if necessary.

**Doctor's Signature** _____ **Date:** ____/____/____

**Instructions:**
Please provide the information for the individual contributing oocytes under "patient". The "partner" section is for the individual providing sperm. If the contributors do not identify within the binary gender categories, they are encouraged to provide their preferred pronouns and any additional information relevant to their PGT process in additional details. If either genetic contributor's significant other is not a genetic contributor, please provide the significant other's contact information in the additional details section.

**Note:**
It is important to maintain sensitivity and confidentiality when handling all patient information. The terms "Oocyte Contributor" and "Sperm Contributor" are used to specify the biological roles in the PGT process without assigning gender. If there is a need to discuss gender identity for the purpose of personalized patient care, please do so in a respectful and private manner.

v050823



GEN EMBRYOMICS

## Informed Consent Form

For Preimplantation Genetic Testing via Whole Genome Sequencing
(Last updated February 2024)

Check all that apply: Donor egg used: ❒ Donor Sperm Used: ❒ Donor Embryo Used: ❒

**Patient Name**: _____
**Patient Date of Birth**: _____
**Reproductive Partner's Name**: _____
**Reproductive Partner's Date of Birth**: _____
**IVF Clinic**: _____
**Referring Provider's Name**: _____

**Purpose of test**

The purpose of preimplantation genetic testing using whole genome sequencing (PGT-WGS) is to analyze select genes of the submitted embryo sample(s), such as the trophectoderm and DNA from culture media, post in vitro fertilization (IVF). The objective of this analysis is to identify inherited and *de novo* (new) pathogenic or likely pathogenic genetic variants related to certain genetic conditions with the intent to assist patients and their physician in choosing embryo(s) with the lowest genetic risk for disease. This consent form is specific to PGT-WGS through GenEmbryomics and is not intended to be used to inform a patient of benefits, risks, and limitations associated with IVF, embryo biopsy, cryopreservation, embryo warming, embryo transfer, or sample transport.

**Potential Benefits**

- PGT-WGS can detect an array of disease-causing genetic variants, including chromosome aneuploidy (an incorrect number of chromosomes), single nucleotide variants (SNVs), small insertions and deletions, and copy number variants (CNVs), across all inheritance types, including copy number variants in mitochondrial DNA (mtDNA), however, **an mtDNA copy number will not be included.**
- With increasing maternal age, more embryos are expected to have chromosome aneuploidy. Preimplantation genetic testing for aneuploidy (PGT-A) is a component of PGT-WGS.
- With increasing paternal age, more embryos are expected to have de novo pathogenic or likely pathogenic variants. PGT-WGS can detect >90% of de novo variants.
- PGT-WGS uses next generation sequencing as opposed to historical linkage analysis, reducing the time for results by eliminating the need for samples from extended family members.
- **PGT-WGS may detect familial genetic variants, yet testing for familial genetic conditions and structural rearrangements require a case review and laboratory approval prior to acceptance by GenEmbryomics.**
- PGT-WGS can detect contamination, genetic relatedness, and false mosaicism by analyzing

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# DNA Collection

- Each parent, saliva/blood collection for genomic DNA
- TE biopsy (>4 cells recommended) or amplified TE biopsy
  - ICSI & IVF embryos TE biopsy suitable
- Spent culture medium (10uL)

↪ Ship to partnering lab

PROGENESIS
We help you start a healthy family

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# Bioinformatics

- .fastq.gz raw data processed via Dragen (Illumina) pipeline
- Outputs:
  - genome coverage metrics,
  - quality score filtering
- Direct assessment & compound het: SNV & Indel, CNV,
- Individual assessment Ploidy, mosaic, SV, CYP2D4*, HLA*, Repeat expansion

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# Case setup

- Case setup
  - .fastq selection (AWS)
- Pedigree described
- Proband .fastq
- Paternal & maternal .fastq files imported
- >3,200 genes included as standard for *potential* curation

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# Quality control – Relatedness

- Coverage uniformity
- Relatedness, i.e.:
  - Mother to embryo
  - Father to embryo
  - Mother to father
  - Contamination detection
- ROH/LOH

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# Case curation – Auto/AI Prioritisation

- SNVs
- Indels,
- CNV (>1kb),
- (inc. compound hets), Repeat expansion carrier status,
- MT-DNA (5%)

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# Case curation – Individual assessments

## Variant curation

- Individual assessments;
  - Ploidy & mosaics
  - BAF
  - ROH/LOH

SNV variant curation

- Autosomal recessive (AR)
- Compound Het
- *De novo*
- X-Linked

LOH/ROH

- Loss of heteozygosity
- allele dropout and/or no coverage
- TE biopsy cross-checked for haploid/no-coverage in embryo sample
- Avoids loss of recessive conditions

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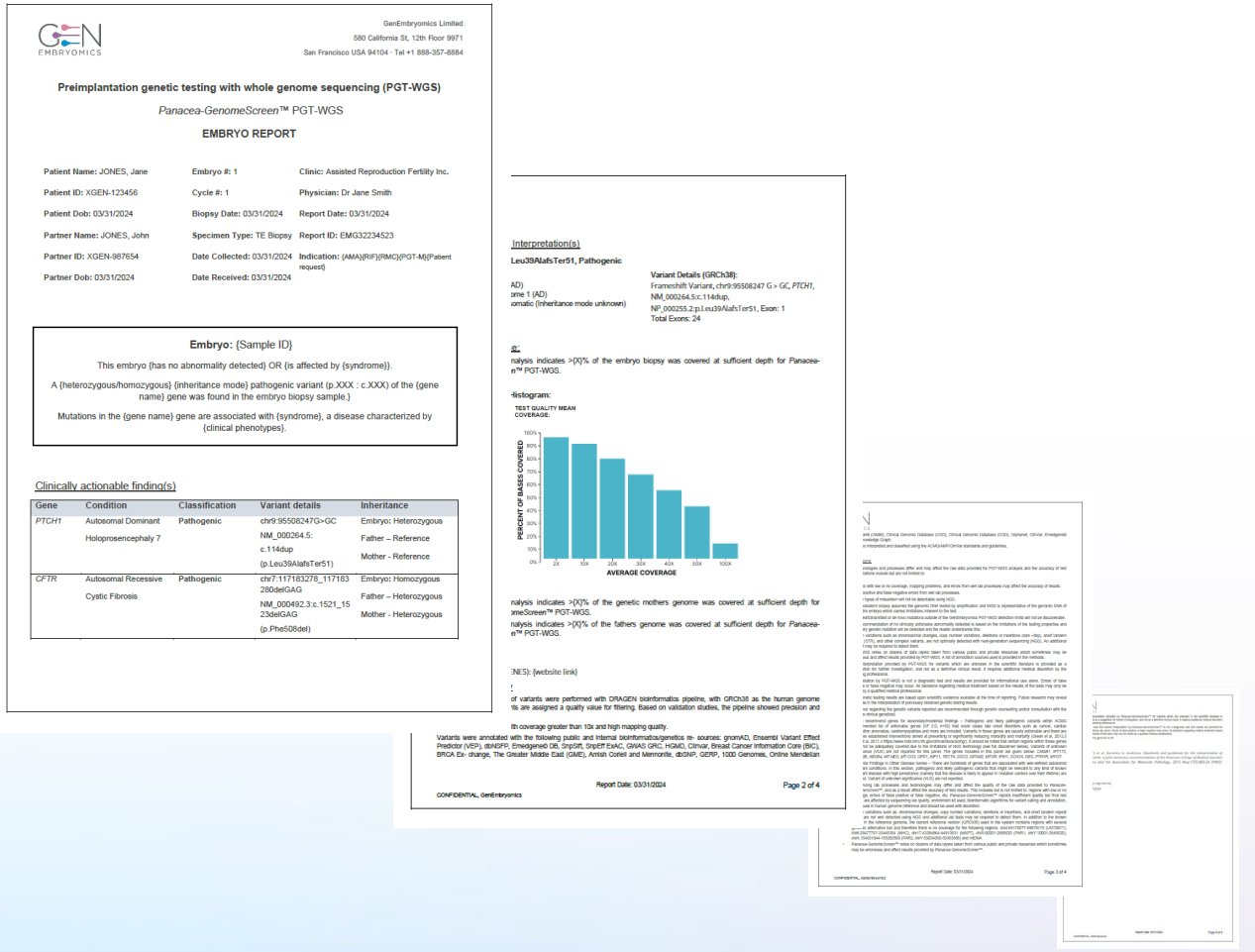
# Reporting

- Patient info
- Single embryo report
- No parent findings
- Coverage histogram
- Limitations
- Cycle summary report provided



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**Preimplantation genetic testing with whole genome sequencing (PGT-WGS)**

*Panacea-GenomeScreen™* PGT-WGS

**EMBRYO REPORT**

**Patient Name:** JONES, Jane
**Patient ID:** XGEN-123456
**Patient Dob:** 03/31/2024
**Partner Name:** JONES, John
**Partner ID:** XGEN-987654
**Partner Dob:** 03/31/2024

**Embryo #:** 1
**Cycle #:** 1
**Biopsy Date:** 03/31/2024
**Specimen Type:** TE Biopsy
**Date Collected:** 03/31/2024
**Date Received:** 03/31/2024

**Clinic:** Assisted Reproduction Fertility Inc.
**Physician:** Dr Jane Smith
**Report Date:** 03/31/2024
**Report ID:** EMG32234523
**Indication:** {AMA}{RIF}{RMC}{PGT-M}{Patient request}

**Embryo:** {Sample ID}

This embryo {has no abnormality detected} OR {is affected by {syndrome}}.

A {heterozygous/homozygous} {inheritance mode} pathogenic variant (p.XXX : c.XXX) of the {gene name} gene was found in the embryo biopsy sample.}

Mutations in the {gene name} gene are associated with {syndrome}, a disease characterized by {clinical phenotypes}.

Clinically actionable finding(s)

| Gene | Condition | Classification | Variant details | Inheritance |
|---|---|---|---|---|
| *PTCH1* | Autosomal Dominant Holoprosencephaly 7 | Pathogenic | chr9:95508247G>GC NM_000264.5: c.114dup (p.Leu39AlafsTer51) | Embryo: Heterozygous Father – Reference Mother - Reference |
| *CFTR* | Autosomal Recessive Cystic Fibrosis | Pathogenic | chr7:117183278_117183280delGAG NM_000492.3:c.1521_1523delGAG (p.Phe508del) | Embryo: Homozygous Father – Heterozygous Mother - Heterozygous |

Interpretation(s)

**Leu39AlafsTer51, Pathogenic**

Variant Details (GRCh38):
Frameshift Variant, chr9:95508247 G > GC, *PTCH1*, NM_000264.5:c.114dup, NP_000255.2:p.Leu39AlafsTer51, Exon: 1
Total Exons: 24

TEST QUALITY MEAN COVERAGE:

PERCENT OF BASES COVERED

AVERAGE COVERAGE

Variants were annotated with the following public and internal bioinformatics/genetics re- sources: gnomAD, Ensembl Variant Effect Predictor (VEP), dbNSFP, Emedgene/i-DB, SnpGR, SnpEff EvaC, GWAS GRC, HGMD, Clinvar, Breast Cancer Information Core (BIC), BRCA Ex- change, The Greater Middle East (GME), Amish Cortiel and Mennonite, dbSNP, GERP, 1000 Genomes, Online Mendelian

Report Date: 03/31/2024 Page 2 of 4

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Deans *et al*. Recommendations for reporting results of diagnostic genomic testing, (2022)

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# Genetic Counseling Process for PGT-WGS

- Pre-test Counseling:
  - PGT-WGS capabilities and limitations, potential detection of *de novo,* rare variants & thresholds
  - Discuss reproductive options based on screening and patient values
- Results Interpretation and Delivery:
  - Consider implications for genetic contributors and family
  - Align results with patient's preferences and values
- Post-test Counseling:
  - Coordinate care with providers and genetics team, provide support for expanded results
- Benefits and Limitations of PGT-WGS:
  - Comprehensive screening in a single test, Improved detection of clinically significant findings
  - Limited detection of certain disorders (e.g. repeat expansions, methylation defects)
  - Missing regions, no or low coverage

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# PGT-WGS – tool for research & test development

- Large clinical & WGS data collections (e.g. UKBiobank):
    - Pathogenic mutations, common mutations
    - Thousands of lifestyle, clinical, genetic, drug, diet, biochemical etc data fields
- TBD – Collaborative ‘Early in Life’ BioBank
    - Multi-ethnic WGS data on parents, live births, embryo biopsies and/or SCM, POC
    - IVF datapoints of successes, failures
    - Embryo culture
    - Outcomes & follow-up
- Pure R&D and clinical grade test development & validation

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# Concluding remarks

- “Technology is the Fuel.”
  - Hughes, M., PGDIS, 2024
- "Over 80% of all individuals with severe developmental disorders have *de novo* mutations. Are they possible to detect? Do we want to?"
  - Vermeesch, J., PGDIS, 2024
- “The aim is not just to have a baby, but to have a healthy baby.”
  - Martin, D., PGDIS, 2024

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# Concluding remarks

Selecting euploid embryos for transfer should improve ongoing pregnancy rates per transfer (Munné, *et al*. 1993)

Selecting embryos **free of clinically significant genetic variants** should improve ongoing pregnancy rates per transfer.

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# Concluding remarks

- PGT-WGS simplifies the screening of embryos
- Standardisation of a hierarchy of reporting of IVF embryo screening
- Recommendation: a ‘Biobank for reproduction research’

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