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Expanding the horizons of embryo screening: performance and case studies of preimplantation genetic testing via whole genome sequencing

Benjamin Podgursky[1,†], Maria Katz[1,†], Shenglai Li[1,†], Thomas Giardina[1], Becca Girod[1], Dhruva Chandramohan[1], Qinnan Zhang[1], Michael Feinman[1], Barry Behr[2], Jerry Lanchbury[3], Noor Siddiqui[1], Funda Suer[1], Yuntao Xia[1,*]

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Abstract

Conventional preimplantation genetic testing for aneuploidy (PGT-A) and for monogenic disorders (PGT-M) is very limited in scope. These methods typically assess chromosomal ploidy or target only one or two specific variants carried by the parents. When the genetic variant is complex, testing often requires DNA samples from additional family members with a confirmed diagnosis, which complicates the process. In some cases, PGT laboratories may even decline testing due to the complexity of the condition. In 2024, we introduced the first PGT—whole genome sequencing (PGT-WGS), enabling the screening of thousands of genes as well as the detection of critical microdeletions and microduplications in one assay. Here, we present assay performance and two clinical case studies illustrate its utility: one showing high concordance between embryo and cord blood of a live-birth child for variants, and another identifying a previously unrecognized monogenic form of diabetes in embryos. These results demonstrate that PGT-WGS expands the clinical utility of preimplantation testing.

Keywords: *preimplantation genetic testing—whole genome sequencing, PGT-WGS, in vitro fertilization, IVF, case studies*

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1. Introduction

As in vitro fertilization (IVF) becomes increasingly common, parents and clinicians are seeking more accurate genetic tools to improve the health outcomes of their future children. Yet existing genetic testing methods, including carrier screening and current preimplantation genetic testing (PGT) techniques, often fail to detect serious, actionable conditions, particularly those arising from *de novo* variants or incompletely covered dominant genes [1–3]. Carrier screening is the primary method used to assess health risks for future children, but it only provides an indirect estimate of genetic risk by focusing on autosomal recessive variants in the parents. This approach can miss *de novo* and/or autosomal dominant pathogenic variants, such as those that cause Rett syndrome, that arrive spontaneously in embryos [4]. In contrast, PGT-WGS enables direct screening of thousands of genes in the embryos, addressing these gaps and offering families broader and more accurate genetic insights.

Historically, performing whole genome sequencing (WGS) on embryo biopsies is challenging because the amount of DNA obtained is usually less than 30 picograms. This quantity is ~10,000–20,000X less than the minimum quantity required for a direct sequencing, which typically requires around 100–500 nanograms. In practice, over 500 ng of DNA is often needed due to potential testing failures or the need for confirmatory testing. This process is further complicated by issues such as allele dropout and inconsistent gene coverage when whole genome amplification is used [5]. Several recent efforts have explored genome-wide screening in preimplantation embryos, such as multiple displacement amplification (MDA) and primary template-directed amplification (PTA). While promising, these methods have shown variable success rates and inconsistent coverage across clinically relevant genes. These limitations have constrained the clinical utility of WGS in preimplantation settings.

In 2021, we partnered with Stanford to develop a new method for genome-wide screening in PGT. By 2024, we had significantly enhanced the whole genome amplification (WGA) approach and validated its clinical application in PGT [6]. Improved WGA in theory enables detection of both inherited and *de novo* variants. This increased resolution also allows for the identification of clinically relevant microdeletions and microduplications that are often missed by traditional PGT methods and are significant contributors to birth defects and neurodevelopmental disorders. In this report, we present performance data and case studies demonstrating that our PGT-WGS method offers improved insight into embryo health and genetic risk, addressing key limitations of conventional screening.

[1]Orchid Health, Palo Alto, CA, USA.
[2]Department of Obstetrics & Gynecology—Reproductive Endocrinology and Infertility, Stanford University, Sunnyvale, CA, USA.
[3]Independent Researcher, Salt Lake City, UT, USA.
*email: yuntao@orchidhealth.com
†These authors contributed equally to this work.

2. Methods

2.1. Sample collection and processing

The case study section presents two patient cases. The couple in Case 1 is covered under IRB approval (WCG Clinical #20222645), while the couples in Case 2 are clinical patients who consented for publication. Proper consent was obtained from all patients before including their data in the study. Embryos were biopsied on days 5–7 following standard PGT trophectoderm biopsy protocol [7]. Each biopsy contained approximately five cells and was collected in a 200 µl PCR tube with about 3 µl of biopsy buffer. Parental saliva samples were collected by patients using AccuGene AccuSaliva Collection Kits (Accugene, Incheon, Korea). Cord blood samples were collected in EDTA tubes and sequenced at Psomagen (CAP #8742212, CLIA #21D2062464) to 30X depth.

MDA and PTA were performed according to the vendors' instructions, while Orchid's WGA was carried out following internal laboratory developed protocol similar to industry single-cell amplification methods. In brief, for Orchid's WGA, 3 µl of alkaline lysis buffer was added to the embryo biopsy and incubated at 65 °C for 10 min to ensure efficient cell lysis and DNA denaturation. This was followed by the addition of 3 µl neutralization buffer to counteract excess base activity. Subsequently, 16 µl of reaction mix was added, and the sample was incubated in a thermocycler at 30 °C for 10 h. The reaction mix contained random primers, dNTP, phi29 polymerase to initiate DNA synthesis, and additional synthesized proprietary small molecules. Such small molecules perturb the phi29 during amplification and shorten the amplicon length; and the shortened length further promotes improved coverage, uniformity, and reduces allele dropout. It is important to note that the PTA method also shortens DNA but by adding irreversible terminators, specifically alpha-thiol ddNTPs; however, we found that irreversible terminators are harsh and can be replaced by other synthetic molecules. The resulting DNA yield was measured using a Qubit Flex fluorometer (ThermoFisher, Waltham, MA, USA), ensuring accurate quantification. For saliva samples, DNA was extracted using the QIAamp DSP DNA Blood Mini Kit (Qiagen, Germantown, MD, USA), a reliable and efficient method for obtaining high-quality DNA.

Between 250 and 500 nanograms of DNA were used to prepare the sequencing libraries using the KAPA HyperPlus kit from Roche Diagnostics (Indianapolis, IN, USA) in combination with Dual Index UMI adapters from Integrated DNA Technologies (IDT) (Coralville, IA, USA) following manufacturer recommendations. Library concentration was determined using the Qubit 1X dsDNA HS assay (ThermoFisher, Waltham, MA, USA), while library sizes were assessed with the Agilent 4150 Tapestation Genomic ScreenTape (Agilent, San Diego, CA, USA). Sequencing was performed on the Illumina NovaSeq X Plus (Illumina, San Diego, CA, USA) at 30X depth.

2.2. Ploidy calling

Aneuploidy screening was performed as previously described [6]. In brief, for low-pass aneuploidy screening, samples were sequenced to 0.05X depth for ploidy calling with a bin size of 500 kbp using NxClinical (Bionano, San Diego, CA, USA) and the open-source Ginkgo tool [8, 9]. For microduplication or microdeletion analysis, samples underwent 30X WGS and were loaded into NxClinical for manual review.

2.3. Variant calling

Individual sample Binary Alignment Map (BAM), SNP, and indel variant calls were generated using the Gencove human WGS pipeline GRCH37 v1.0 following best practices for germline variant calling [10]. To measure biopsy precision and sensitivity in the cord blood and embryo concordance, RTG Tools 3.12.1 was used. High-confidence *de novo* variants were filtered to heterozygous variants with 0.4 < VAF < 0.6 in cord blood, restricting DP to > 30 and restricting indels within 10 bp; and not present in mother or father.

2.4. Gini index of noise

The Gini coefficient, calculated according to the method described in [11, 12], quantified variance in genomic coverage across 500 kb bins. Numbers within each bin were normalized using data from five NA12878 samples, and the Gini Index was calculated for each autosome, then averaged across all 22 autosomes.

2.5. Sanger confirmation

Sanger sequencing and primer design was performed by Psomagen. Genotypes at the sites of interest were analyzed using in-house software on electropherograms.

2.6. Haplotype analysis

For known or suspected inherited variants, a pairwise haplotype linkage analysis within the embryo cohort was performed as a confirmatory test to support sequencing results [13]. This analysis involved identifying informative single-nucleotide polymorphisms (SNPs)—those present in only one parent—with a population frequency of 1–5% in the target sample, located within a 1 million base pair window surrounding the target variant in the parental gVCF. The variants in each pair of embryos were then compared to determine if the haplotype inheritance (sharing one, two, or both haplotypes) at a given locus was consistent with the genotypes identified through direct calls and the presumed parental origin. In cases where the gamete source of the variant was unknown, two separate analyses were conducted to confirm consistency with either maternal or paternal inheritance.

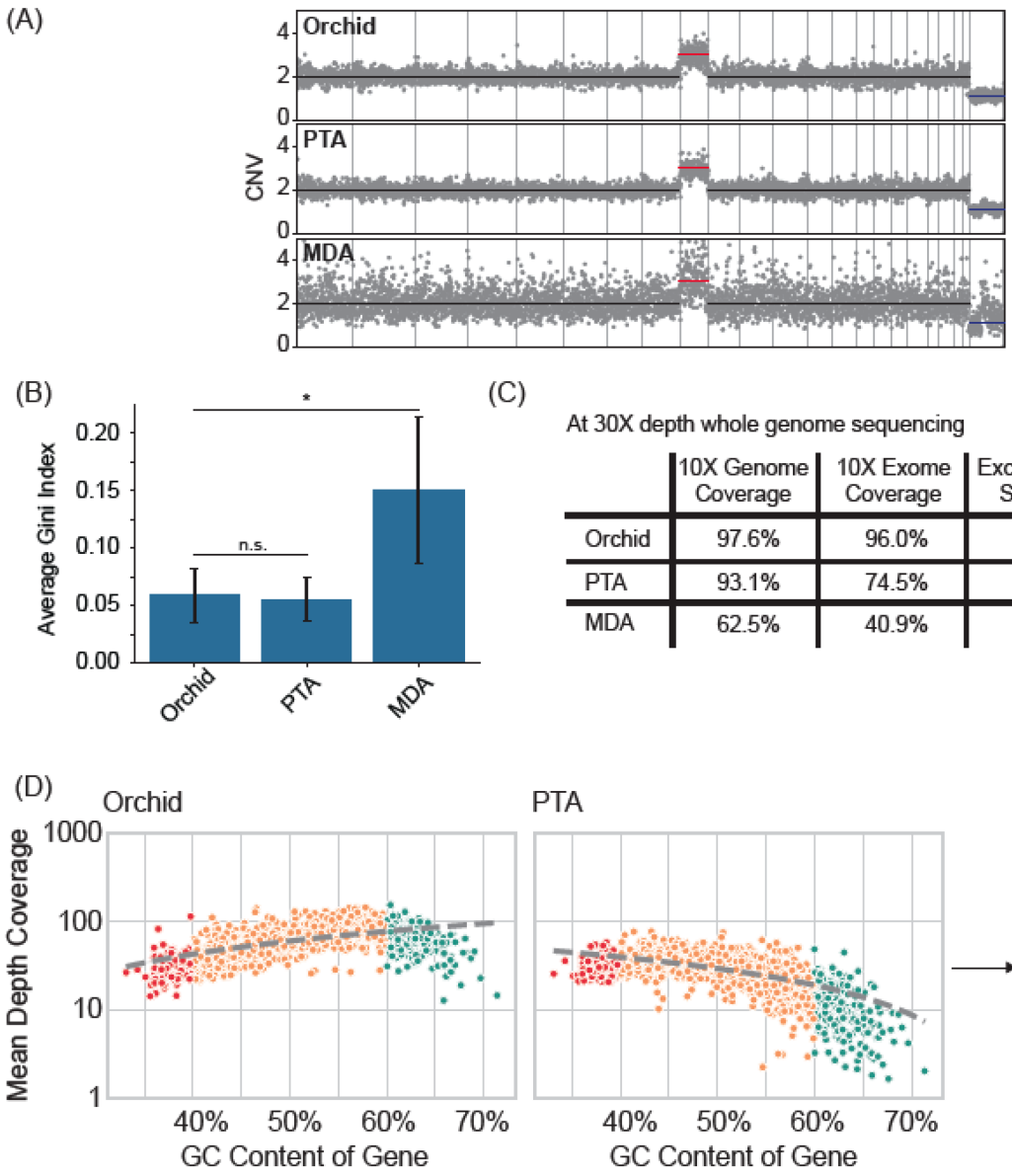
2.7. Gene list and variant classification

Rather than screening all 20,000 genes in the human genome, the monogenic gene list is selected based on several criteria: well-documented, high or moderate penetrance, and having variants known to cause clinically relevant conditions such as neurodevelopmental disorders, birth defects, and pediatric and adult hereditary cancers.

We follow the recommendation set by the American College of Medical Genetics and Genomics (ACMG) for variant classification [11, 14]. Our screening process focuses exclusively on well-documented pathogenic variants sourced from clinical databases and the literature (via Varsome Clinical). This approach differs from diagnostic methods that explore variants of uncertain significance (VUS), as we aim to report only variants with solid evidence of causing phenotypes. Additionally, carrier status is not reported unless specifically requested, as carriers typically remain asymptomatic. Therefore, for autosomal recessive (AR) conditions, if a variant is found in a heterozygous state in an embryo, it is not reported, as it is unlikely result in a phenotype.

2.8. Comparison of different WGA approaches

The statistics in **Figure 1A** were based on the Genome in a Bottle (GIAB) cell line NA12878. WGA was performed using MDA, PTA, or Orchid, starting with 50 pg of DNA. Then, 500 ng of the resulting DNA was subjected to 30X WGS. The results for each WGA method represented averages from five independent samples. As the National Institute of Standards and Technology (NIST) provides benchmark variants for NA12878, we used it as a reference to calculate sensitivity and precision. In the analysis, we observed 19,890 true positive variants on the exome, 374 false positives, and 424 false negatives with Orchid WGA on the exome. Using equations sensitivity = TP/(TP + FN) and precision = TP/(TP + FP), we obtained a sensitivity of 0.9791 and a precision of 0.9815. The same calculation method was applied to PTA, where we observed 15,167 true positives, 363 false positives, and 5040 false negatives, resulting in a sensitivity of 0.7506 and a precision of 0.9766. More validation results of cell lines and embryos can be found in [6].



At 30X depth whole genome sequencing	10X Genome Coverage	10X Exome Coverage	Exome Variant Sensitivity	Exome Variant Precision
Orchid	97.6%	96.0%	97.9%	98.2%
PTA	93.1%	74.5%	75.1%	97.7%
MDA	62.5%	40.9%	N/A	N/A

Figure 1 • Comparison of WGA methods. (**A**) Copy number visualization on the same trisomy 9 sample NA09286. (**B**) A quantitative measurement of uniformity in (**A**) using the Gini index (n.s. not significant, * significant). (**C**) Sequencing coverage, sensitivity, and precision between PTA, MDA, and Orchid. (**D**) Orchid and PTA coverage on low (red), medium (orange), and high (green) GC genes.

3. Results

3.1. Performance comparison of current WGA approaches

As the basis of a well-performing PGT is the amplification method, we compared two common WGA approaches (multiple displacement amplification (MDA) [15] and primary templated amplification (PTA) [16]) to Orchid. We observed that MDA has poor uniformity across the genome as indicated by high noise in copy number plots (**Figure 1A**) and large Gini index, a parameter to quantify uniformity (**Figure 1B**) [12]. Due to the poor genomic coverage (**Figure 1C**) and uniformity of MDA, it is not suitable for PGT-WGS. As a result, further analysis of MDA was omitted.

While copy number plots indicate that both PTA and Orchid uniformly cover the whole genome at chromosomal resolution (binned each 500 kbp; **Figure 1A**), PGT-WGS requires single base pair resolution with good coverage (ideally >10X depth) on exome for a reliable variant capture and interpretation. PTA has a bias towards intronic regions and loses ~25% coverage on exome. Because of that, we observed only 75% sensitivity on exonic variants (**Figure 1C**). This means that if there are 100 variants on exons, PTA is only able to capture 75 of them. By contrast, Orchid maintained a sensitivity greater than 97% and a low false positive rate (precision > 98%) across the exome (**Figure 1C**). Such performance made PGT-WGS feasible in clinical practice.

A key challenge with WGA methods is the efficacy of covering the genes with high guanine and cytosine content (GC content) in the DNA sequence. To compare Orchid vs. PTA, the gene list was separated into genes with low GC content (≤40%, red), medium GC content (40–60%, orange), and high GC content (≥60%, green) in **Figure 1D**. There are 1200 genes in our screen panels that cover neurodevelopmental disorders, hereditary cancer, and birth defects (**Table S1**). These genes have various GC contents. Orchid covered all 1200 genes at a depth of 10X or higher using 30x whole genome sequencing (**Figure 1D**). In contrast, when processed with PTA, there is a trend that genes with higher GC content are more poorly covered (**Figure 1D**). Since many genes associated with birth defects and neurodevelopmental disorders have high GC content [17], Orchid's WGA approach becomes the only feasible solution.

Other common WGA methods, such as Malbac and DOP-PCR, have demonstrated lower performance and are not discussed in this study. For example, DOP-PCR typically achieves a maximum genomic coverage of only 40%, significantly below the PGT-WGS requirements [5, 16].

3.1.1. Case 1: Concordance analysis of trophectoderm biopsy to the cord blood of the resulting child

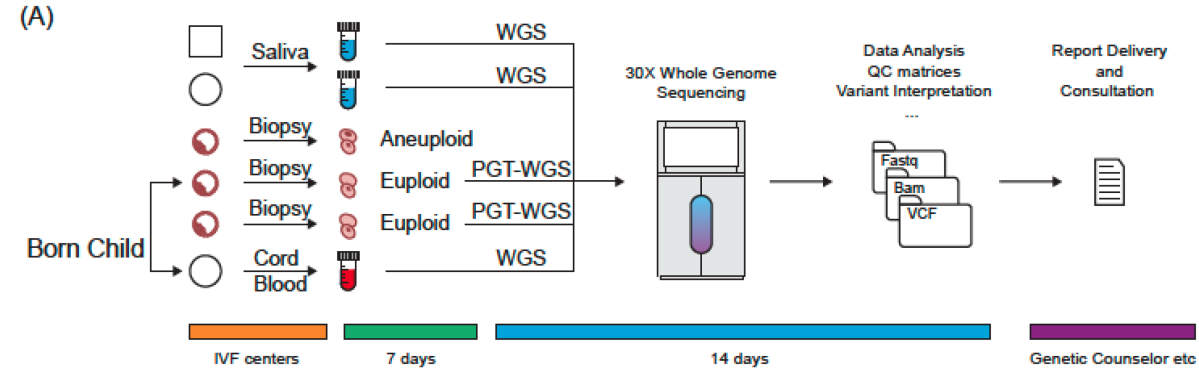
As part of an ongoing study assessing concordance between embryo PGT-WGS results and the genomic data of resulting children, we present the first case here as a proof of concept (**Figure 2A**). The couple is of European ancestry. The female was 41 and the male 37 at the time of IVF. Both individuals are healthy but looking for more comprehensive screening beyond PGT-A.

Following the IVF cycle of the couple, three embryos were biopsied and underwent PGT-WGS including chromosome analysis and screening of ~50 targeted disease-causing microdeletions/microduplications, monogenic for a set list of ~1200 single gene disorders. One embryo biopsy was aneuploid (monosomy 20 and trisomy 21) and two embryo biopsies were euploid. The euploid embryos screened negative for the additional analysis including microdup/dels. Embryo 1 was transferred and resulted in a successful pregnancy and live birth. To assess the accuracy of PGT-WGS, parental DNA and fetal cord blood were collected after delivery and sequenced WGS to 30X depth to enable comparison with PGT-WGS results (**Figure 2A**). The QC metrics of Embryo 1 are presented in **Figure 2B**. With a Gini index of 0.140, the result marginally met our QC threshold (<0.15), making this a suitable example to demonstrate lower bound performance. However, even at this quality, 10X coverage of the Orchid's gene panels (1200 genes) remained over 96%, adequate for variant analysis.

Compared to the cord blood, which exhibited 1422 variants across the 1200 genes in our analysis, we identified 1385 true positive variants, 37 false negatives, and 32 false positives, culminating in a sensitivity of 97.7% and a precision of 97.4% (**Figure 2C**). Variants from the father, mother, embryo, and cord blood were independently analyzed and interpreted. In the cord blood, two inherited AR variants were seen, *PAH* (NM_000277.3):c.1074A>T,p.L358F and *MEFV* (NM_000243.3):c.2084A>G,p.K695R, consistent with the results from PGT-WGS and the parents' carrier screening results (**Figure 2D**).

Since no pathogenic *de novo* variants were detected in either the cord blood or PGT-WGS, a supplementary *de novo* analysis involving the father, mother, and cord blood was conducted on benign variants to assess if *de novo* variants in cord blood are captured by PGT-WGS. This analysis revealed 16 intronic *de novo* variants in the cord blood. Due to the limited availability of DNA, we randomly selected and confirmed five of these variants through Sanger sequencing (**Figure S1**). Re-examining the PGT-WGS data from the embryo biopsy, all five *de novo* variants were accurately detected through PGT-WGS (**Figure 2D**). Again, these variants were not reported because they are classified as benign—not due to a failure of detection.

While a larger sample size is needed, this preliminary and proof-of-concept analysis shows high concordance between PGT-WGS results from trophectoderm cells and cord blood. It detects both *de novo* and inherited variants in this case.



(B)

QC Matrices

Sample	Test Performed	10X Genome Coverage	10X 1200 Gene Panel Coverage	QC Pass?	MitoDNA Content
Mother	Saliva-WGS	99.6%	99.7%	Yes	<1%
Father	Saliva-WGS	99.5%	98.7%	Yes	<1%
Born Child	Cord Blood-WGS	99.6%	99.0%	Yes	<1%
Embryo 1	PGT-WGS	93.0%	96.1%	Yes (Gini=0.14)	8.6%
Embryo 2	PGT-WGS	97.2%	98.5%	Yes	2%

(C)

Oveview: Concordance between Embryo and Cord Blood through Direct Calling

Gene Region	True Variants	False Positives	False Negatives	Assay Sensitivity	Assay Precision
1200 Gene Panel	1385	32	37	97.7%	97.4%

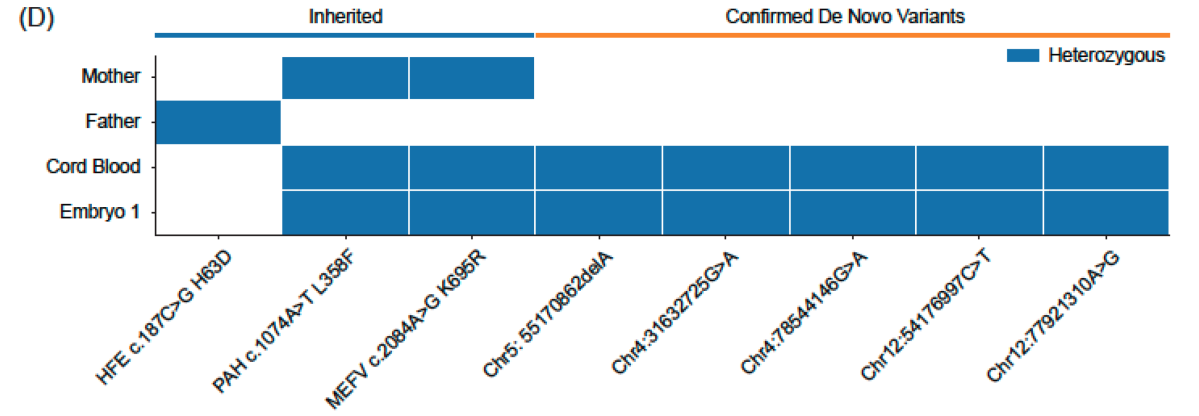


Figure 2 • Case 1: Concordance analysis between trophectoderm biopsy and resulting child's cord blood. (**A**) Study workflow. (**B**) QC metrics. (**C**) Sensitivity and precision of 1200 gene screening panel. (**D**) Clinically relevant inherited variants and *de novo* benign variants in the father, mother, cord blood, and embryo.

3.1.2. Case 2: Identification of a pathogenic variant linked to maturity-onset diabetes of the young (MODY) in a trophectoderm biopsy, consistent with family history

The female partner reported a family history of atypical diabetes but did not undergo diagnostic testing. Her carrier screening returned negative for diabetes; however, such screening only tested autosomal recessive genes. The female is of Hispanic descent; the male did not disclose his ethnicity. At the time of IVF, the female was 31 and the male was 57. The female has a family history of diabetes.

Pre-test PGT genetic counseling was provided to the couple. During the consultation, potential monogenic findings were discussed, including monogenic forms of diabetes and other conditions that could lead to early- or late-onset disease.

Eighteen embryo biopsies were received and screened through PGT-WGS. The male and female partners also provided saliva samples. In total, 12 of 18 embryos were euploid, negative in microdup/del screening, and then underwent monogenic analysis on Orchid panels (1200 genes). Among the euploid embryos, 8 of the 12 were found to carry an AD pathogenic variant within the *GCK*(NM_033507.3):c.562G>A, p.A188T (**Figure 3**). The GCK gene encodes the protein glucokinase, and disruptions in this gene can result in AD forms of MODY and AR neonatal diabetes mellitus [18].

Genotype status on GCK c.562G>A in euploid embryos

Order	Embryo ID	Direct NGS Call on GCK c.562G>A	Haplotyping
1	2	Heterozygous	Hap.1 Hap.3
2	5	Heterozygous	Hap.1 Hap.4
3	6	Not Detected	Hap.2 Hap.3
4	7	Not Detected	Hap.2 Hap.4
5	8	Heterozygous	Hap.1 Hap.4
6	9	Heterozygous	Hap.1 Hap.3
7	10	Heterozygous	Hap.1 Hap.4
8	11	Heterozygous	Hap.1 Hap.3
9	14	Not Detected	Hap.2 Hap.4
10	15	Heterozygous	Hap.1 Hap.3
11	16	Not Detected	Hap.2 Hap.3
12	17	Heterozygous	Hap.1 Hap.3

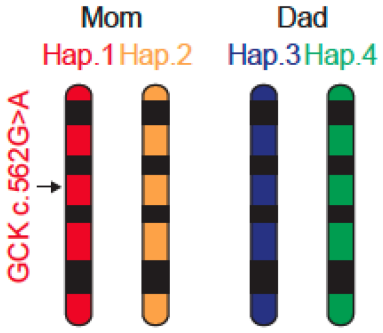


Figure 3 • Case with positive findings. Case 2: Confirmatory haplotyping analysis across embryo cohort-matched NGS calls.

Since the *GCK* variant was present in multiple samples, it was likely to be inherited from either parent. As parental DNA was provided, haplotype analysis was completed to confirm whether directly detected variants were consistent with inherited haplotypes; all embryo genotypes were confirmed and agreed with NGS calls (**Figure 3**).

Upon the patient's request, subsequent diagnostic testing confirmed that the mother carried the *GCK* variant consistent with her family history of atypical diabetes. During post-test genetic counseling, the patient was advised to share her results with family members and consult an endocrinologist for guidance on medical management. The importance of sharing this information with future obstetricians was highlighted, as GCK-MODY can impact pregnancy management when the pregnant individual is affected by the condition [19]. One euploid embryo, which screened negative for the pathogenic *GCK* variant, was transferred and resulted in the birth of an apparently healthy child.

Embryo screening cannot replace traditional genetic testing and regular checkups with primary care physicians. Nevertheless, this case gives an example of how PGT-WGS can uncover previously missed genetic conditions, resulting in clinically valuable information for the mother's care team and for managing the health of future children.

4. Discussion

Many patients choose PGT-WGS because (1) patients have been diagnosed with complex genetic conditions and were rejected by many PGT-M labs, as PGT-WGS is able to accommodate a significant portion of these cases, and/or (2) patients want to screen for more than PGT-A [20].

A significant concern with PGT-WGS is gene selection and variant curation. As described in the Methods section, PGT-WGS focuses on well-documented diseases from clinical databases, literature, and clinically available testing panels. Similarly to carrier screening criteria, only pathogenic or likely pathogenic variants with strong evidence are reported, while variants of uncertain significance (VUS) are excluded from the report. Additionally, carrier status is not reported to ensure that only clinically actionable results are reported in embryos.

With regard to technical limitations, it is important to note that, aside from Fragile X syndrome, repeat expansion disorders remain difficult to detect using PGT-WGS. For trinucleotide repeat expansion-related diseases, traditional linkage analysis is recommended. This approach requires samples from both parents as well as an affected family member. Linkage analysis can then be used to identify which embryos carry the affected allele from the parents.

Furthermore, microdeletions and microduplications smaller than 400 kb are difficult to detect consistently via PGT-WGS. In such cases, traditional PGT-M with linkage may offer greater resolution and remains the more appropriate approach.

De novo variants play a substantial role in many genetic diseases, especially in neurodevelopmental and autosomal dominant conditions. PGT-WGS offers the unique advantage of directly screening for *de novo* pathogenic variants in embryos, which cannot be achieved through traditional PGT-M that relies on prior family history or parental genotype data. This potential broadens the clinical utility of PGT, particularly in cases using donor gametes, without known parental variants or with sporadic presentations.

5. Conclusions

PGT-WGS allows for direct variant screening across the entire genome, filling the technical gaps of current PGT, accommodating cases that traditional PGT-M cannot accept, and facilitating the screening for *de novo* variants.

Preliminary data from case studies demonstrates a high concordance between PGT-WGS findings in embryos and the resulting children, including identification of *de novo* variants. However, given that these findings are based on a limited number of cases, broader validation in larger, diverse cohorts is needed to confirm the accuracy, sensitivity, and clinical utility of PGT-WGS.

It is critical that physicians and genetic counselors provide comprehensive guidance to patients regarding the capabilities, limitations, and ethical implications of PGT-WGS. For instance, as shown in Case 2, incidental findings may reveal previously unknown genetic information about the parents. Therefore, robust informed consent and thorough pre-test counseling are essential to ensure that patients fully understand the scope and impact of this testing.

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Author contributions

Conceptualization, N.S. and Y.X.; methodology, B.P., S.L. and Y.X.; software, T.G. and D.G.; formal analysis, S.L., Y.X., T.G., B.P.; resources, Q.Z.; data curation, S.L. and B.P.; writing–original draft preparation, M.K. and B.P.; writing–review & editing, B.B., J.L., B.G., Q.Z. and M.K.; visualization, Y.X. and S.L.; project administration, Y.X. and N.S. All authors have read and agreed to the published version of the manuscript.

Conflict of interest

The authors declare that B.P., M.K., S.L., T.G., B.G., D.C., Q.Z., M.F., N.S., F.S. and Y.X. are employees of Orchid Health (Palo Alto, CA, USA), and B.B. and J.L. were scientific advisors at the time of writing. Orchid is a clinical lab providing PGT-WGS.

Data availability statement

All data supporting the findings of this publication are available within this article and/or its supplementary materials.

Institutional review board statement

The study was conducted according to the guidelines of the Declaration of Helsinki. Case 1 was approved by the Institutional Review Board of WCG Clinical (protocol code #20222645, approved on 2022 May 12). Ethical review and approval were waived for Case 2, because it was a routine clinical patient and only the description of the patient case was included. No research interventions were performed.

Informed consent statement

Informed consent for participation was obtained from all subjects involved in the study.

Supplementary materials

The supplementary materials are available at https://doi.org/10.20935/AcadMolBioGen7874.

Additional information

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