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Dive deep with exome analysis

OeXome™ WES

Background

Exons comprise only ~1% of the genome [1] yet harbor 85% of known pathogenic variants [2]. Whole exome sequencing (WES) offers a high-yield, cost-effective solution for investigating complex genetic conditions where targeted sequencing is most likely to yield meaningful findings. With our self-developed experimental and bioinformatics pipeline, combined with the expertise of our team, we deliver high-quality, reliable results to support clinicians work with confidence.

OeXome™ WES

By combining our proprietary NanoWES™ library prep with our advanced bioinformatics pipeline, OeXome™ delivers in-depth, reliable results for analyzing patient phenotypes, fetal abnormalities, rare diseases, and research study.

Comprehensive Genomic Coverage

Moving beyond standard exome targeting, the proprietary OeXome™ NanoWES™ dsDNA capture probe (>65 Mb) is engineered to capture a broader spectrum of clinically relevant variants within a single test, including:

- Exome Regions
- Clinically Relevant Non-Coding Regions: Pathogenicity-defined intronic and regulatory regions (for >360 genes and 600 diseases)
- Mitochondrial Genome
- RefSeq Regions
- dmWES Upgrade: expand the analysis to include 13 repeat expansion disorders often missed by standard WES providers. This includes 8 Spinocerebellar Ataxia (SCA), 3 neuromuscular diseases, and 2 chorea

Optimized for "Hard-to-Map" Genes

Standard probes often struggle with complex genomic regions. NanoWES™ utilizes specialized probe designs to significantly improve capture efficiency for clinically critical, difficult-to-map genomics regions.

General WES - Rare Disease Diagnosis

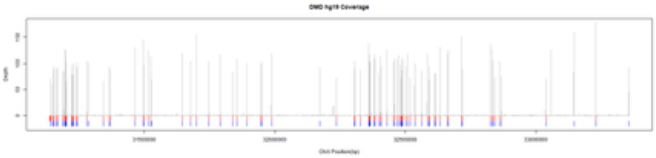
There are over 8,000 identified rare diseases and about 80% of them are genetic in origin [3]. Phenotype-based diagnosis is frequently challenging, leading to a "diagnostic odyssey" that can last years. This delay hinders timely management and incurs high healthcare costs. OeXome™ WES can provide the essential genetic basis for definitive clinical diagnosis, prognostic prediction, and precision management.

Prenatal WES - Prenatal Diagnostics

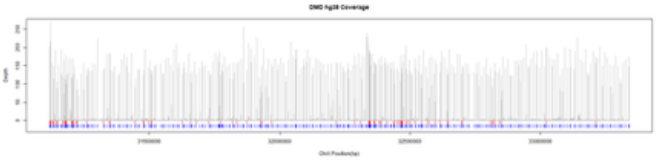
In fetuses with structural abnormalities, standard testing often leaves questions unanswered. Approximately 32% of cases are confirmed via Karyotype, and an additional 6% via Chromosomal Microarray (CMA) [4]. Recent studies demonstrate that WES significantly expands the diagnostic yield, identifying causative variants in an additional 8.5% – 10% of fetal structural abnormality cases [4-5].

Recommended Indications:
Indicated for cases presenting with fetal structural malformations, thickened NT (≥ 3.0 mm), severe IUGR/FGR (<10th percentile), fetal anemia, severe amniotic fluid abnormalities, hydrops fetalis, recurrent pregnancy loss, or unexplained products of conception (POC). Combined WES + CNV-seq is recommended for higher diagnostic rate.

Other probe without optimization
(*DMD* coverage, GRCh38/hg38)



NanoWES™ probe with optimization
(*DMD* coverage, GRCh38/hg38)



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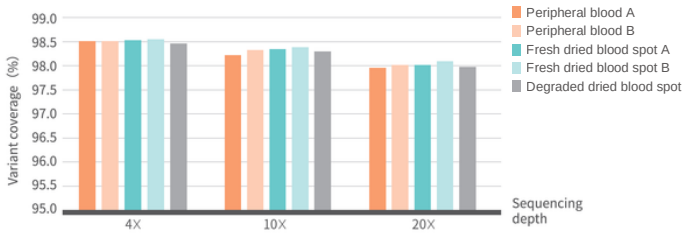
Patented NanoWES™ Technology

Supports Various Sample Types with Consistent Detection

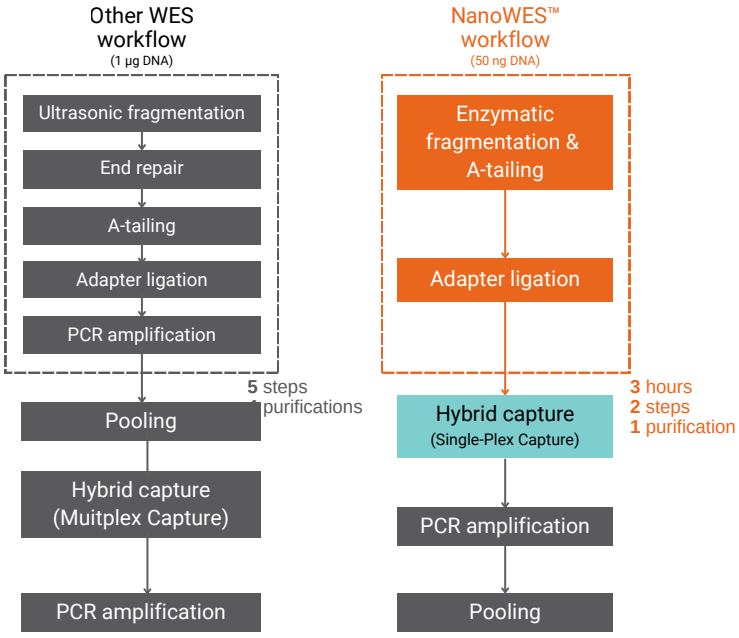
Under the NanoWES™ workflow, even with varying sample types, DNA quantities, and sample conditions, sequencing depth and coverage are maintained consistently. This increases flexibility in sample requirements without compromising the test, especially for investigating newborn cases with limited sample availability.



Pre-Capture PCR-free Workflow

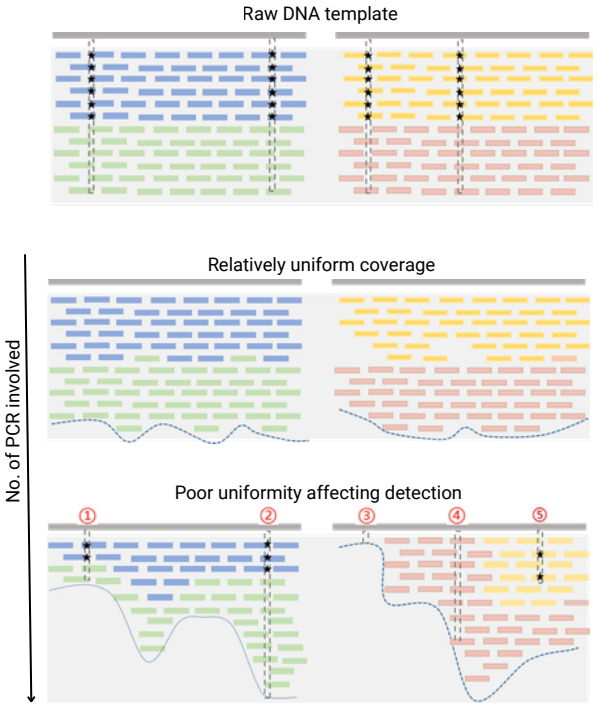
The NanoWES™ workflow is optimized for routine clinical testing, offering robust performance even with challenging sample types.

- Validated for inputs as low as 50 ng, ensuring consistent library quality from difference sample types such as amniotic fluid and Dried Blood Spots (DBS)
- Our pre-capture PCR-free approach reduces hand-on time without sacrificing quality
- Utilizing 1 single-plex capture (1 sample per reaction) ensures data consistency across different samples



Parameters	Description
Technology	Targeted sequencing, paired-end
Platform	illumina or Salus SBS sequencing system
Sample type	gDNA from blood, CVS, amniotic fluid, cord blood/tissue, product of conception, etc.
Operation Time	Library preparation: total 23.5 hours (Include 16 hours overnight capture)
Coverage	Targeting protein-coding regions, pathogenicity-defined intronic and regulatory regions, RefSeq regions, and the mitochondrial genome Standard Data Volume ~8-10 Gb (Can be customized under request), with ≥97.5% coverage of target regions at a depth of ≥20x

Amplification errors induced during library preparation



1. Low coverage depth leads to false-negatives
2. Allele imbalance causes false-negatives
3. Lack of coverage results in false-negatives
4. Loss of information for one allele
5. Detection of erroneous variants

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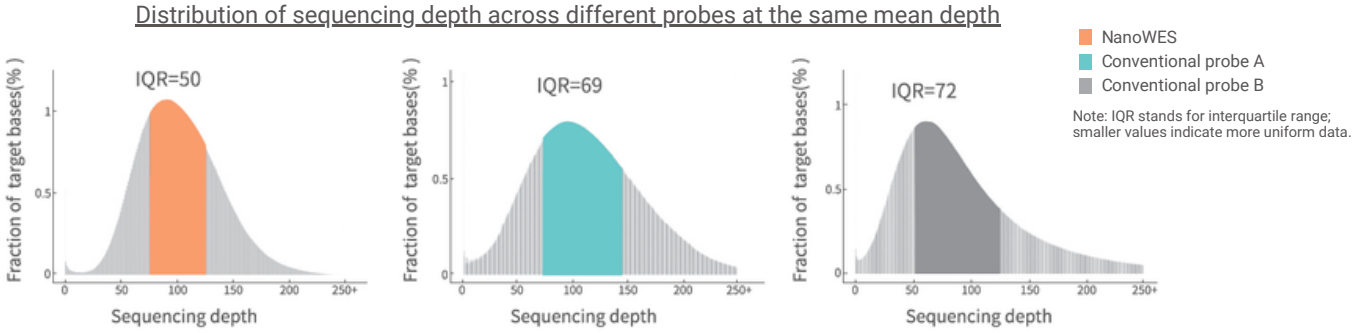
The Result: Industry-Leading Uniformity, Lowering the Sequencing Cost

By eliminating pre-capture amplification, NanoWES™ reduce amplification bias, resulting in lower error and duplication rates.

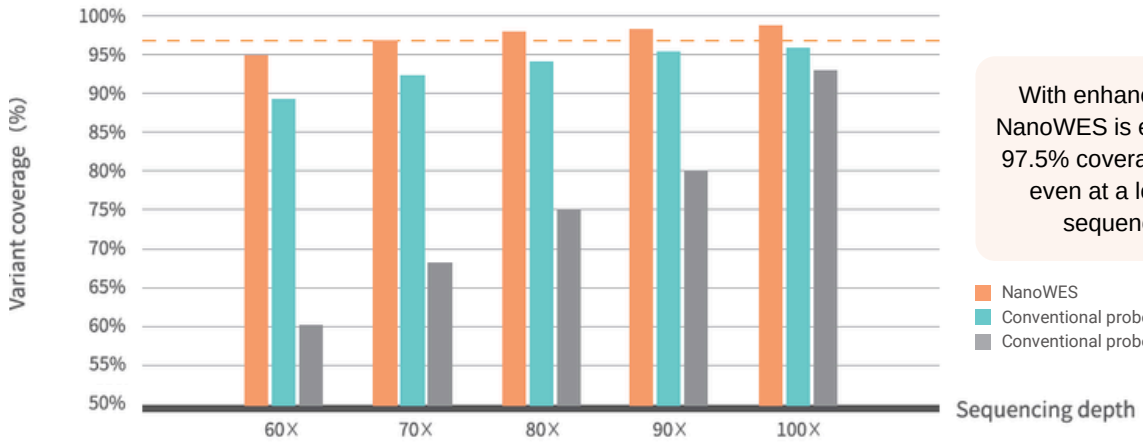
- Delivers uniform coverage, minimizing data waste
- Improved uniformity makes variant calling more accurate, particularly for exon-CNVs (which require highly uniform depth across exons) and low-level mosaicism (distinguish from noise)

Distribution of sequencing depth across different probes at the same mean depth



Note: IQR stands for interquartile range; smaller values indicate more uniform data.

Variant coverage at depth 20x across different probes and varying average sequencing depths



With enhanced uniformity, NanoWES is easier to achieve 97.5% coverage at depth 20x even at a lower average sequencing depth

Ideal for exon-CNVs (WES-CNVs) and Mosaic Samples which Require Superior Data Quality

OeXome™ is capable of analyzing pathogenic WES-CNVs with a relatively higher resolution in size (down to exon-level) than low-coverage whole genome sequencing (e.g. Xromate™ CNV-seq) due to its higher sequencing depth and excellent coverage uniformity. This allows physicians to identify or rule out causative CNVs from different aspects, saving costs when investigating the genetic factors behind uncommon clinical cases.

WES-CNVs analysis can enhance the clinical diagnosis of rare disease

n a retrospective analysis on 75 children with neurodevelopmental disorders. OeXome™ demonstrated an overall diagnostic yield of 54.05% (40/74) when combining SNVs/InDels and WES-CNVs analysis. Specifically, 35.13% (26/74) of diagnoses were from SNVs/InDels analysis, and 18.92% (14/74) were from WES-CNVs analysis. [6]

WES + CNV-seq strategy can enhance the prenatal diagnosis

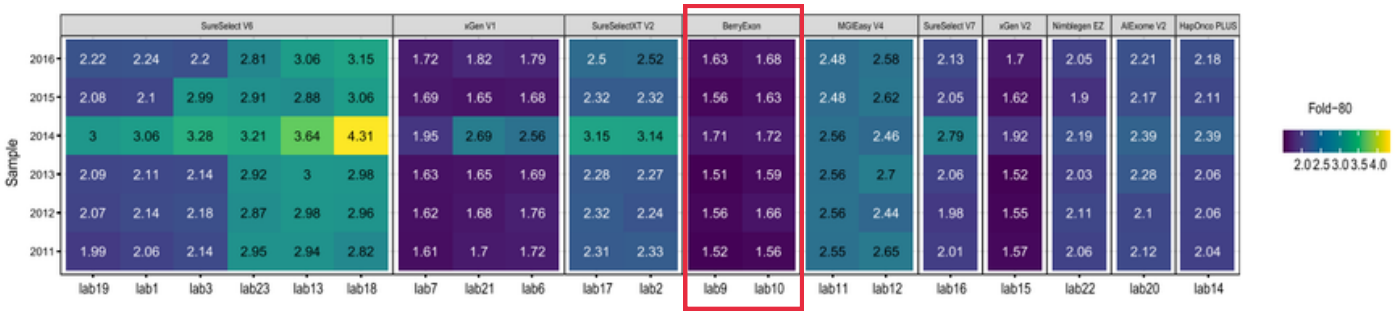
A combined OeXome™ + Xromate™ strategy enables efficient prenatal diagnosis by compressing turnaround time (TAT) and facilitating faster results. In a cohort study of 959 trios with fetuses displaying structural anomalies or increased nuchal translucency (NT), 227 pathogenic or likely pathogenic alterations were identified, including 10 double diagnoses (cases with both CNVs and variants), which would be missed if OeXome™ and Xromate™ were performed sequentially. The overall diagnostic rate was 23.67%. [7]

OeXome™ Leads in Quality: Proficiency Testing

To systematically assess the comparability of clinical WES testing results under routine conditions, the National Center for Clinical Laboratories (NCCL) conducted a proficiency test across 24 participating laboratories. [21] Two of Berry Genomics' laboratories (BerryExon, lab 9 and 10) outperformed other commercial laboratories in terms of breadth of coverage, coverage uniformity, and bioinformatic reproducibility.

The Top Performer in Uniformity and Breadth of Coverage at Depth ≥ 20X

Fold-80 base penalty score of each sample across all laboratories that were grouped by capture methods



Note:
Fold-80 is a metric used to evaluate uniformity. A lower Fold-80 indicates efficient capture and minimizes over-sequencing.
Fold-80 = [average depth] / [depth at which ≥80% of bases is covered], indicating the fold of additional sequencing required to ensure that 80% of the bases reach the average coverage depth.

Target region coverage and average coverage depth per sample of each laboratory grouped by capture methods

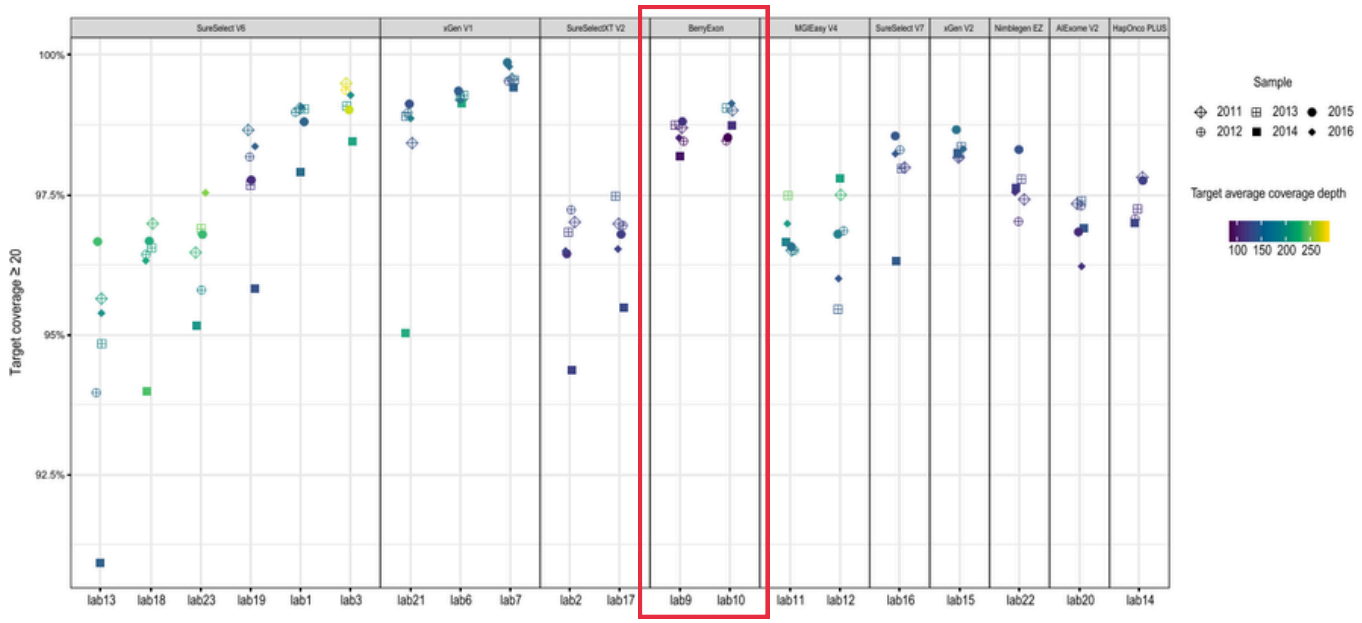


Figure adopted from reference [8] with modification

Covering the ACMG genes with >95% Breadth of Coverage at Depth ≥ 20x

The mean breadth of coverage for ACMG 71 genes with read depth ≥ 20x of three NAI2878 samples

High Reproductivity on Small Variant Detection

Reproducibility of detected variants among three NAI2878 samples between NCCL pipeline and laboratories' in-house pipeline

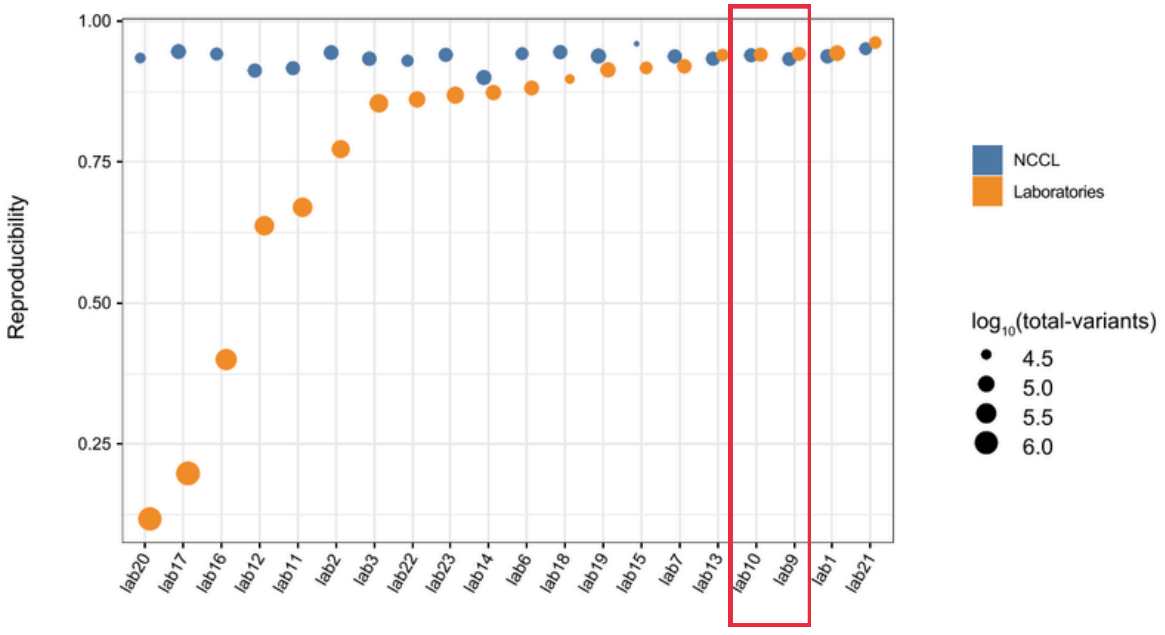


Figure adopted from reference [8] with modification

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Appendix:
General OeXome™ WES Reporting Scope from Berry Genomics Clinical Labs

(Fully adaptable for in-house laboratory integration, and large-scale custom projects)

Session	Description
Main Findings	• P or LP variants with the expected inheritance pattern, including incomplete penetrance • Compound heterozygote where one variant is rated as P or LP while the other is rated as Variant of Uncertain Significance (VUS) • Heterozygous P or LP variants potentially forming compound heterozygotes with WES-CNVs • X-linked recessive (XLR) or X-linked dominant (XLD), P or LP hemizygous/ heterozygous variants • Phenotypically related and highly pathogenic WES-CNVs, mitochondrial variants, dynamic mutations/repeat expansion in the *ATXN1*, *ATXN2*, *ATXN3*, *CACNA1A*, *ATXN7*, *PPP2R2B*, *ATXN8OS/ATXN8*, *ATN1*, *AR*, *DMPK*, *HTT*, *JPH3*, and *PABPN1* genes, or uniparental disomy (UPD) located in critical regions of chromosomes 6, 7, 11, 14, 15, and 20
Potential Relevant Findings	• Phenotypically related VUS variants with the expected inheritance pattern (which classification might change if more information provided, incomplete penetrance) • Phenotypically related, XLR or XLD, VUS hemizygous/ heterozygous single variant • Phenotypically related, P or LP or VUS variants but does not confirm to family co-segregation • Phenotypically related, autosomal recessive (AR) variants • Specific variants or genes of interest by the physicians • Unexcluded diseases/phenotypes susceptibility, highly suspected P or LP or VUS variants with the expected inheritance pattern
ACMG Secondary Findings	P or LP variants identified from the ACMG Secondary Findings gene list are unrelated to the patient's primary phenotype and do not overlap with the Main Findings or Potentially Relevant Findings

Reporting variants: SNVs, InDels < 50 bp, Aneuploidy, WES-CNVs ≥ 3 exons, Mitochondrial SNVs > 1% heteroplasmy, UPD (*Trio* only) in selected regions, and Dynamic mutations (trinucleotide repeats) of selected genes

Appendix (Opt-in):
Customized insights beyond the standard WES report are available on request to deliver a more comprehensive analysis.
For example:

- Carrier status
- Partially phenotypically related AR heterozygous single variant
- Partially phenotypically related autosomal dominant (AD) VUS variants, with a significant population carrying that heterozygous variants according gnomAD
- Selected top causative variants

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Appendix:
Prenatal OeXome™ WES Reporting Scope from Berry Genomics Clinical Labs

(Fully adaptable for in-house laboratory integration, and large-scale custom projects)

Session	Description
Main Findings	SNVs/InDels: • The clinical features and expected inheritance pattern of the disease associated with the variant are consistent with the primary clinical phenotype and zygosity of the tested individual, respectively, and the variant is classified as LP or P. CNVs: • The expected inheritance pattern of the segment is consistent with the tested individual's zygosity, and the variant is classified as LP or P. • The expected inheritance pattern of the segment is consistent with the tested individual's zygosity, and the variant is a *DMD* exon deletion/duplication classified as a VUS or higher. UPD (for *trio* only): • Within the UPD reporting scope (isodisomy greater than 5Mb on chromosomes 6, 7, 11, 14, 15, and 20) that is classified as a definitively pathogenic
Potential Relevant Findings	SNVs/InDels: • The primary clinical features of the disease associated with the variant are consistent with the primary clinical phenotype of the tested individual, but the variant is classified as a VUS, or the expected inheritance pattern does not match the detected zygosity • The gene associated with the variant is on the incidental findings list (genotype-driven analysis for variants that are difficult to detect via fetal imaging, are unrelated to the current presented phenotype, and are associated with birth defects that severely impact the quality of life in infants and young children), the expected inheritance pattern is consistent with the detected zygosity, and the variant has a high likelihood of being pathogenic.
ACMG Secondary Findings	P or LP variants in ACMG Secondary Findings gene list associated with monogenic diseases. (The zygosity and the inheritance pattern of the associated disease must be consistent).

Reporting variants: SNVs, InDels < 50 bp, Aneuploidy, WES-CNVs ≥ 3 exons, and UPD (*Trio* only) in selected regions
Note: Mitochondrial variants and dynamic mutations (trinucleotide repeats) are not reported.
It is recommended that the test be submitted as a family-based WES (prenatal WES-*Trio*). If only a singleton fetal sample is submitted for prenatal WES testing, the origin of the variants cannot be determined. This limitation may affect the test results.

Appendix (Opt-in):
Customized insights beyond the standard prenatal WES report are available on request to deliver a more comprehensive analysis.
For example:

- Variants with Insufficient Evidence for Genetic Pathogenicity: Variants with a low degree of consistency with the tested individual's phenotype or with insufficient evidence

References:
[1] Ng SB, Turner EH, Robertson PD, et al. Targeted capture and massively parallel sequencing of 12 human exomes. *Nature*. 2009;461(7261):272-276.
[2] Choi M, Scholl UI, Ji W, et al. Genetic diagnosis by whole exome capture and massively parallel DNA sequencing. *Proc Natl Acad Sci U S A*. 2009;106(45):19096-19101.
[3] Rare genetic diseases. *National Human Genome Research Institute*. Accessed January 2026. https://www.genome.gov/dna-day/15-ways/rare-genetic-diseases.
[4] Petrovski S, Aggarwal V, Giordano JL, et al. Whole-exome sequencing in the evaluation of fetal structural anomalies: a prospective cohort study. *Lancet*. 2019;393(10173):758-767.
[5] Lord J, McMullan DJ, Eberhardt RY, et al. Prenatal exome sequencing analysis in fetal structural anomalies detected by ultrasonography (PAGE): a cohort study. *Lancet*. 2019;393(10173):747-757.
[6] Zhai Y, Zhang Z, Shi P, Martin DM, Kong X. Incorporation of exome-based CNV analysis makes trio-WES a more powerful tool for clinical diagnosis in neurodevelopmental disorders: A retrospective study. *Hum Mutat*. 2021;42(8):990-1004.
[7] Chen X, Jiang Y, Chen R, et al. Clinical efficiency of simultaneous CNV-seq and whole-exome sequencing for testing fetal structural anomalies. *J Transl Med*. 2022;20(1):10.
[8] Zhang K, Yu L, Lin G, Li J. A multi-laboratory assessment of clinical exome sequencing for detection of hereditary disease variants: 4441 ClinVar variants for clinical genomic test development and validation. *Clin Chim Acta*. 2022;535:99-107.

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