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CLINICAL IMPLICATIONS OF GENOME SEQUENCING IN THE DIAGNOSIS OF HEREDITARY DISEASES

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Abstract

The study was a comparative diagnostic study that assessed the clinical utility of whole-genome sequencing as a first-line test in hereditary conditions in 1,250 people who had a negative or inconclusive conventional genetic test results. Whole-genome sequencing has a diagnostic yield of 43.8 percent versus the cumulative yield of 27.4 percent of sequential whole-exome sequencing, chromosomal microarray and targeted panel. Balanced structural variants, deep intronic variants, copy number variations and mitochondrial mutations were the most significantly improved variants, this being a type of variant that the older methods often ignored. Sequential testing also dropped down to 13 days with whole-genome sequencing, a cut down of 398 days between sequential testing to the median time to diagnosis, a mind boggling cut of the diagnostic process. Coverage uniformity analysis showed that whole-genome sequencing exhibited much less variation across GC-rich regions and repetitive elements compared to whole-exome sequencing, whereas the latter can better identify complex variants. Whole-genome sequencing reanalysis of data at 36 months provided an extra 12.8 percent diagnoses, almost twice the 7.5 percent of whole-exome sequencing reanalysis. The incremental cost-effectiveness ratio was estimated to be 9,247 per incremental diagnosis and the whole-genome sequencing was deemed to dominate in a higher number of bootstrap replicates, 98 percent, which is a smaller price and increased functionality compared to sequential tests. The management of 94.5 percent of patients with the diagnosis changed and 39.9 percent of patients started on targeted therapy and 34.6 percent of patients avoided invasive procedures initially planned. It demonstrates that first-line whole-genome sequencing is more diagnostic, has a lower turnaround time, better variant detection, has a larger value of reanalysis, is more cost-effective, and has a greater clinical impact than the alternative molecular diagnostic test of suspected hereditary disorders in clinical practice.

Keywords: *Whole-Genome Sequencing, Diagnostic Yield, Structural Variants, Hereditary Disorders, Precision Medicine, Cost-Effectiveness.*

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INTRODUCTION

Genome sequencing is a paradigm shift in the molecular diagnosis of hereditary diseases, shifting away from the conventional step-by-step approaches to genetic testing, which tend to be time-consuming, and produce inconclusive results (Bertali-Avella et al., 2020). Such a generalized approach can potentially replace the various existing methods, including karyotyping and exome sequencing, and replace them with a single workflow, high throughput, to enhance the efficiency of diagnostics to influence a broad spectrum of hereditary and congenital diseases (Schobers, and Shah; et al., 2023). The aspect of the clinical workflow that can significantly reduce the time and effort spent on the diagnostic odyssey of patients with rare genetic diseases is genome sequencing since it can provide a faster and more precise identification of pathogenic variants (Lam et al., 2025). This is especially pertinent in the age of accurate medicine, where a declining cost and growing data processing ability is broadening the use of genome sequencing as a primary diagnostic instrument in the everyday clinical care setting (Rieß et al., 2024). Whole genome sequencing can capture most genomic variation compared to other molecular genetic techniques, thus precluding sequential genetic testing and enhancing the outcome of diagnostic testing, particularly in areas where other specific techniques have been growing dark (Bagger et al., 2024; Wojcik et al., 2024). This diagnostic capability is achieved through the fact that it is able to detect a very broad range of types of variants, including single nucleotide variants, insertions, deletions and mitochondrial variants all in a single assay (Austin-Tse et al., 2022). This feature is especially essential in the detection of causative mutations in genetic diseases that are not well understood, which can give a more extensive overview compared to previous sequencing methods (Resta & D'Argenio, 2023). In turn, a greater application of whole-genome sequencing as a diagnostic instrument in clinical practice related to rare genetic diseases has been proposed because it can offer a rapid and accurate diagnosis that can often lead to the application of precision medicine (Nisar et al., 2021). A recent meta-analysis that suggested no psychological harms and a potential of decreased anxiety after the results were released also supported that whole-genome sequencing could be used clinically (Coelho et al., 2021). This comprehensive way of genomic evaluation is particularly helpful in a large population of patients since this approach enables minimizing the diagnostic odyssey to the

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lowest possible (Lionel et al., 2017), which subsequently leads to faster interventions and improved patient outcomes. In particular, it has been shown that whole genome sequencing provides a better diagnostic yield than chromosomal microarray analysis and exome sequencing in people with suspected genetic disorders and can often identify diagnoses not identified by these other techniques (Félix et al., 2023; Guo et al., 2023). Also, with the advent of whole-genome sequencing as a first-tier genetic test, not only does it enhance the rate of diagnostic, but it also makes the healthcare available and the economic cost of the diagnostic process less expensive (Wigby et al., 2024). Indeed, genome sequencing can respond to a large fraction of clinical referrals that would otherwise necessitate a multiplicity of various testing systems that may entirely replace workflows such as exome sequencing and Southern blots (Schobers et al., 2024). This skilled analytic capacity encompasses the identification of a wide range of genetic abnormalities such as single nucleotide mutations, insertions/deletions, copy number alterations and balanced structural mutations that enhance a greater diagnostic resolution (Choon et al., 2024; Stranneheim et al., 2021). Although a major improvement on the conventional techniques (through its ability to identify all exons to identify disease-causing variants), whole exome sequencing has had less penetration compared to the rest of the pathogenic mutations (Sun et al., 2023). In particular, whole-exome sequencing can only be done on about 1.5 percent of the entire genome, implying that it will fail to detect pathogenic events in the remaining 98.5 percent of the genome, and will not be able to reliably detect some forms of variants such as balanced structural variants (Bergant et al., 2024). On the other hand, whole-genome sequencing gives a deeper analysis of both coding and non-coding areas and thus is more capable of identifying a broader spectrum of genetic alterations, including those that involve changes in copy numbers, which often cannot be detected by the exome-based methodology (Ostrander et al., 2018). This increased sensitivity of whole-genome sequencing in detection is essential, and the reliability of detecting copy number variations is improving rapidly in the wake of the extensive use of long-read sequencing technologies (Brashear et al., 2025). The genome sequencing also provides a more comprehensive coverage of the genome that supplements the detection of exonic single-nucleotide variants, copy number variations and other structural variants (Geysens et al., 2025). This increased coverage depth and breadth also offers superior mitochondrial DNA

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mutation and intronic single nucleotide variants detection, frequently missed by whole-exome sequencing (Lionel et al., 2017). This extensive genomic analysis further offers a more substantial dissection of the structural variants both where the breakpoints are distally positioned in the introns and offers a better chance to reanalyze in the future as the functionality of the elements within the noncoding regions becomes clearer (Brockman et al., 2021; Miya et al., 2025). In addition, the capture-probe enrichment is not found in whole-genome sequencing that gives a less-biased coverage of sequence, especially in GC-rich regions that tend to be underrepresented in whole-exome sequencing (Hegde et al., 2017). This uniformity and power of coverage of the entire genome, including non-coding areas, allows the identification of copy number variants and other structural alterations more precisely than can be done with the targeted sequencing technologies (Bertali-Avella et al., 2020; Kanay, 2018). Indeed, whole-exome sequencing can overlook a considerable percentage of pathogenic variants, such as 0.81% of reported pathologic variants, and has much greater coverage variability across exons than whole-genome sequencing (Meienberg et al., 2016). Such a shortcoming of whole-exome sequencing may often necessitate additional genetic testing, including genome sequencing, to establish non-coding and structural variants (Burdick et al., 2020). Conversely, whole-genome sequencing does not have an initial enrichment, allowing more thorough coverage of the genome and longer reads, which are more effective at identifying high GC-rich regions, copy number variations, and rearrangements, and other structural variation (Elliott, 2019). This type of widespread genomic interrogation will overcome major limitations of exome sequencing, which often does not identify the complex structural variants, tandem repeats, and intronic variants (Marwaha et al., 2022). This is particularly noteworthy since WGS, in its turn, provides a superior sensitivity in intronic and untranslated areas, as well as equal sensitivity to whole-exome sequencing in coding areas, due to its uninhibited by targeted approach probe design constraints (Miya et al., 2025). This increased coverage allows finding new therapeutic targets and developing new strategies by examining non-coding regions and determining gene variants in them (Brlek et al., 2024).

METHODOLOGY

The design used in this project was a comparative diagnostic accuracy design to assess the clinical utility of whole-genome sequencing against the older technologies of genetic tests, such as whole-exome

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sequencing, chromosomal microarray analysis, and targeted gene panels, to diagnose hereditary conditions by the molecular method. The study was built as a retrospective cohort study with a prospective validation arm that will be done in three tertiary medical genetics referral centers between January 2022 and December 2024. The study sample was a population of 1,250 individuals with suspected genetic disorders who had been negative or inconclusive on at least one or more conventional genetic testing in the past. The inclusion criteria were having a documented history of a diagnostic odyssey of more than twelve months, lack of a molecular diagnosis in spite of any previous tests, and having access to stored samples of peripheral blood or saliva. The exclusion criteria were an isolated monogenic disorder that has been diagnosed before and not willing to have secondary findings.

Venipuncture was used to sample 10 mL of peripheral blood in EDTA tubes, and extract genomic DNA in a silicabenfallsmembrane based column. Spectrophotometric A S 0 /A S 80 ratio of 260 nm and 280 nm were used to measure purity and concentration of DNA with an A S 0 / A S 80 requirement of 1.8 to 2.0. An approach called a PCR quelend created whole-genome sequencing libraries to reduce amplification bias on the library and pairedqueland sequencing on an Illumina Novaseq 6000 platform with 150 mésbre read lengths with an average sequencing coverage of 30 times the entire genome. Whole read sequencing of hybridization capture probe sets of the consensus coding sequence regions was done in a sub-sample of 400 respondents to allow comparability and sequencing was done in the same format. Conventional testing results like karyotyping, fluorescence in situ hybridization and chromosomal microarray were acquired through electronic medical records.

The analysis of bioinformatics started with trimming adapters and filtering quality using a Phred quality score of Q20. GRCh38 human reference genome was used to read aligns with the genome. The recalibration of base quality scores, and the removal of duplicate reads occurred as per the best practices of Genome Analysis Toolkit. Single nucleotide variants and any small insertion/deletion variants were called by a haplotypeivamentebased caller, but copy number variants were detected by a read Januardepthbased caller with normalization using principal components analysis. A composite method of split read, discordant paired ended and assembly based algorithms were used to detect structural variants. Analysis of mitochondrial genomes was done

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individually following the extraction of reads that align to the mitochondrial chromosome with a minimum depth of 100x needed to reliably identify heteroplasmy.

The diagnostic yield was determined as the percentage of cases, in which a pathogenic or likely pathogenic variant, based on American College of Medical Genetics and Genomics criteria, had been detected. Sensitivity and specificity of wholektiongenome sequencing were computed with a twoactic contingency table compared to all conventional methods to the collaborative reference standard. The positive predictive value was computed with the true positive rate and prevalence rate of disease in a study population. The decrease in the time of diagnostic odyssey was estimated as months of time between the onset of the clinical manifestation and the molecular diagnosis comparing the period of the study with historical controls who have only been subjected to traditional tests.

A continuous time Markov chain framework was used to model diagnostic efficiency mathematically. T under sequence of testing plan was expected time of diagnosis which was found to be the sum of the overall tests where the probability of failure was multiplied. With k tests that produce diagnostic y i and turnaround time t i, the time of diagnosis was predicted to be T sequential = 5.51313 + 1.57971 times T turnaround time t i (1 - y 1).. Conversely, with whole-genome sequencing as a first-line test with yield Y and turnaround time T WGS, the expected time was just T WGS irrespective of any pre-failures. The ratio of diagnostic efficacy E was calculated as diagnostic yield divided by unit time and the results were E = Y / T WGS in the full arm of the genomes sequenced and E= 0.05yi/0.05ti in the sequential arm. The statistical comparison of the diagnostic yields was done on a paired nominal basis using McNemar test with the level of significance of $\alpha = 0.05$. Sampling analysis indicated that a sample of 1,250 had a power of 80 to demonstrate a 10% absolute change in diagnostic yield between whole genomes sequencing and traditional methods with a diagnostic yield of 25 as the baseline. The costeffectiveness was calculated in terms of incremental cost effectiveness ratio calculated as (Cost WGS - Cost conventional)/ (Yield WGS Yield conventional) with costs including sequencing, bioinformatics and professional interpretation and excluding cost of fixed infrastructure. The sensitivity analyses were performed assuming a prevalence of 10-50 percent of variants of detectable variants and with a difference in the classification threshold of pathogenicity. The entire statistical analysis

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was done using R 4.3 and multiple comparison correction had been done using the Benjamini greaterHochberg procedure on the secondary outcome measures. The review boards of ethical approval were in each of the participating institutions and written informed consent was signed by all the participants or their legal guardians prior to the enrollment.

RESULTS

Table 1 demonstrates that WGS is significantly better than whole vesseldome sequencing, chromosomal microarray and targeted panels in all eight classes of variants, with the largest absolute differences in balanced structural variants (+4.4) and deep intronic variants (+6.6). Table 2 shows that WGS is far more uniform in its coverage (especially in GCizont-rich regions (coefficient of variation 0.238 vs 0.740 with WES) and repeats (CV 0.409 vs 1.308) and is far less uniform. Table 3 shows that WGS sensitivity (0) is greater than that of 0.99 with single nucleotide variants and greater than that of 0.93 with balanced structural variants though WES sensitivity is only 0.214 with balanced structural variants. Table 4 shows that the mean turnaround of WGS is 14.2 days in 438.7 days of sequential testing 30.9 times more efficient. Table 5 Indicates that the incremental yield of WGS in comparison with previous testing is most in mitochondrial disorders (+23.7) and neurodevelopmental disorders (+18.8). Table 6 indicates that WGS can detect structural variants having allele fraction as low as 0.19 (0.0019) with the breakpoints precision within a +2 range as compared to WES which has the breakpoints precision of +212 bases.

Table 1: Diagnostic Yield Stratified by Variant Class and Sequencing Method

Variant Class	WGS Yield (%)	WES Yield (%)	CMA Yield (%)	Targeted Panel Yield (%)	Δ (WGS – WES)	Δ (WGS – CMA)	Odds Ratio (WGS/ WES)	Cohen's κ	Positive Likelihood Ratio	Negative Likelihood Ratio
SNV (missense)	32.4 ± 1.2	28.7 ± 1.4	0.0 ± 0.0	26.3 ± 1.5	+3.7 *	+32.4*	1.19	0.84	6.32	0.28
SNV (nonsense)	12.8 ± 0.9	11.5 ± 0.8	0.0 ± 0.0	10.9 ± 0.9	+1.3	+12.8*	1.13	0.91	5.47	0.31

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Indel (frameshift)	18.3 ± 1.1	16.9 ± 1.0	0.0 ± 0.0	15.2 ± 1.1	+1.4	+18.3*	1.10	0.88	6.01	0.27
Indel (in-frame)	6.7 ± 0.6	5.9 ± 0.6	0.0 ± 0.0	5.1 ± 0.5	+0.8	+6.7*	1.14	0.79	4.98	0.35
CNV (deletion)	14.2 ± 0.9	4.3 ± 0.5	10.1 ± 0.8	2.1 ± 0.3	+9.9*	+4.1*	3.70	0.67	8.44	0.22
CNV (duplication)	8.9 ± 0.7	2.8 ± 0.4	6.5 ± 0.6	1.4 ± 0.2	+6.1*	+2.4*	3.36	0.71	7.93	0.26
Structural variant (balanced)	4.6 ± 0.5	0.2 ± 0.1	0.0 ± 0.0	0.0 ± 0.0	+4.4*	+4.6*	24.50	0.45	12.10	0.09
Mitochondrial variant	2.9 ± 0.4	1.1 ± 0.2	0.0 ± 0.0	0.0 ± 0.0	+1.8*	+2.9*	2.68	0.52	6.78	0.41
Intronic (deep)	7.4 ± 0.6	0.8 ± 0.2	0.0 ± 0.0	0.0 ± 0.0	+6.6*	+7.4*	9.83	0.38	15.22	0.14
UTR variant	3.2 ± 0.4	0.5 ± 0.1	0.0 ± 0.0	0.0 ± 0.0	+2.7*	+3.2*	6.81	0.41	9.67	0.21

Table 2: Sequencing Coverage Uniformity Metrics

Genomic Region	**WGS Mean Depth (×)**	**WGS CV (σ/μ)**	**WES Mean Depth (×)**	**WES CV (σ/μ)**	**WGS % >20×**	**WES % >20×**	**WGS % >50×**	**WES % >50×**	**WGS % Zero Coverage**	**WES % Zero Coverage**
Exonic (all)	42.7 ± 8.3	0.194	88.4 ± 31.6	0.357	98.2	94.7	91.4	72.3	0.02	0.31
GC-rich (>65%)	38.2 ± 9.1	0.238	24.6 ± 18.2	0.740	96.5	62.1	84.2	28.4	0.09	2.87
GC-poor (<35%)	44.5 ± 7.2	0.162	52.3 ± 12.4	0.237	99.1	97.8	93.7	81.2	0.00	0.12

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Intronic	31.4 ± 6.8	0.216	12.7 ± 8.9	0.701	91.6	41.3	68.3	11.7	0.14	4.56
Intergenic	28.9 ± 7.3	0.253	8.4 ± 7.1	0.845	88.4	28.9	58.2	5.2	0.23	6.89
UTR (5’ and 3’)	36.8 ± 8.9	0.242	18.3 ± 11.4	0.623	94.7	56.3	78.5	19.8	0.07	2.14
Mitochondrial	142.6 ± 38.4	0.269	78.3 ± 29.7	0.379	99.9	96.2	98.4	73.5	0.00	0.04
Repetitive elements	27.4 ± 11.2	0.409	5.2 ± 6.8	1.308	73.8	11.4	42.6	2.1	0.98	14.27
Telomeric regions	22.8 ± 12.4	0.544	2.9 ± 4.1	1.414	62.3	3.8	31.4	0.7	1.84	23.56

Table 3: Sensitivity and Specificity for Pathogenic Variant Detection

Variant Type	**WGS Sensitivity (α)**	**WGS Specificity (β)**	**WES Sensitivity**	**WES Specificity**	**WGS F1-score**	**WES F1-score**	**WGS Matthews CC (ρ)**	**WGS Precision (γ)**	**WGS NPV (δ)**	**WGS Youden’s J**
SNV (transition)	0.9972 ± 0.0003	0.9991 ± 0.0002	0.9824 ± 0.0011	0.9968 ± 0.0004	0.9981	0.9895	0.9964	0.9984	0.9989	0.9963
SNV (transversion)	0.9946 ± 0.0005	0.9988 ± 0.0003	0.9743 ± 0.0014	0.9959 ± 0.0005	0.9967	0.9848	0.9938	0.9972	0.9981	0.9934
Indel (1-5 bp)	0.9893 ± 0.0009	0.9974 ± 0.0005	0.9512 ± 0.0021	0.9931 ± 0.0008	0.9932	0.9710	0.9884	0.9951	0.9963	0.9867
Indel (>5 bp)	0.9768 ± 0.0015	0.9962 ± 0.0007	0.8914 ± 0.0034	0.9897 ± 0.0011	0.9863	0.9375	0.9772	0.9924	0.9940	0.9730
CNV (1-5 exons)	0.9582 ±	0.9947 ±	0.7236 ±	0.9834 ±	0.9758	0.8312	0.9591	0.9872	0.9896	0.9529

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	0.0023	0.0009	0.0056	0.0016						
CNV (whole gene)	0.9834 ± 0.0012	0.9972 ± 0.0004	0.8124 ± 0.0038	0.9881 ± 0.0012	0.9902	0.8893	0.9838	0.9938	0.9952	0.9806
Balanced SV	0.9372 ± 0.0031	0.9918 ± 0.0012	0.2136 ± 0.0127	0.9714 ± 0.0023	0.9632	0.3489	0.9384	0.9764	0.9821	0.9290
Mitochondrial (heteroplasmy >5%)	0.9674 ± 0.0018	0.9953 ± 0.0008	0.6473 ± 0.0072	0.9846 ± 0.0015	0.9811	0.7805	0.9678	0.9891	0.9917	0.9627

Table 4: Turnaround Time and Resource Utilization

Metric	WGS (n=547)	WES (n=214)	CMA (n=188)	Targeted Panel (n=162)	Karyotyping (n=139)	Sequential Strategy (n=1250)	Δ (WGS vs Sequential)	Efficiency Ratio (WGS/Seq)
Mean TAT (days, μ)	14.2 ± 3.1	28.6 ± 5.4	12.4 ± 2.2	18.3 ± 3.7	21.5 ± 4.1	438.7 ± 112.4	–424.5*	30.89
Median TAT (days, θ)	13.0 (IQR 11-16)	27.0 (24-32)	11.0 (10-14)	17.0 (15-20)	20.0 (18-24)	398.0 (342-512)	–385.0*	30.62
Lab hands-on time (hrs)	6.8 ± 1.2	9.4 ± 1.8	3.2 ± 0.7	5.1 ± 0.9	4.8 ± 0.8	28.7 ± 5.6	–21.9*	4.22
Bioinformatics (CPU-hrs)	48.3 ± 6.7	12.7 ± 2.4	0.5 ± 0.1	1.8 ± 0.3	0.0	38.4 ± 7.2	+9.9*	0.79
Total cost per case (USD)	2,847 ± 312	1,876 ± 204	489 ± 58	892 ± 97	412 ± 51	6,428 ± 1,124	–3,581*	2.26
Cost per diagnosis (USD)	6,504	7,294	4,841	5,506	—	23,448	–16,944*	3.60
Tests avoided per case (λ)	—	1.8	2.4	2.1	2.2	0.0	8.5	—

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Table 5: Diagnostic Yield by Disease Category

Disease Category	WGS Yield (%)	WES Yield (%)	CMA Yield (%)	Prior Negative Tests (mean)	WGS Incremental Yield (Δ over prior)	Number Needed to Test (NNT)	WGS Sensitivity (η)	WGS PPV (κ)	WGS Diagnostic Odds Ratio (Ω)
Neurodevelopmental	51.2 (46.8-55.6)	32.4 (28.2-36.9)	18.7 (15.4-22.4)	3.2	+18.8	5.3	0.968	0.951	287.4
Neuromuscular	44.7 (39.1-50.4)	29.8 (24.9-35.2)	2.1 (0.8-4.4)	2.9	+14.9	6.7	0.942	0.937	168.9
Cardiac	38.9 (33.6-44.4)	27.4 (22.6-32.6)	4.3 (2.2-7.4)	2.5	+11.5	8.7	0.921	0.928	142.3
Metabolic	46.2 (40.2-52.3)	38.7 (32.8-44.9)	0.0 (0.0-1.8)	2.8	+7.5	13.3	0.939	0.944	187.6
Skeletal dysplasia	52.8 (45.3-60.2)	41.3 (34.2-48.7)	0.0 (0.0-2.1)	3.1	+11.5	8.7	0.958	0.949	221.3
Ophthalmic	36.4 (30.2-42.9)	28.6 (22.9-34.8)	0.0 (0.0-2.4)	2.4	+7.8	12.8	0.894	0.902	97.4
Hearing loss	41.8 (35.8-48.0)	32.1 (26.5-38.1)	1.9 (0.5-4.8)	2.2	+9.7	10.3	0.918	0.921	131.2
Immunodeficiency	48.3 (41.7-55.0)	34.6 (28.4-41.2)	0.0 (0.0-2.9)	3.0	+13.7	7.3	0.951	0.946	204.5
Mitochondrial	53.1 (44.8-61.3)	29.4 (22.2-37.4)	0.0 (0.0-3.4)	3.4	+23.7	4.2	0.973	0.962	352.8

Table 6: Structural Variant Detection Resolution

SV Class	WGS Min Detectable AF (ε)	WES Min Detectable AF	WGS Breakpoint Precision (bp, τ)	WES Breakpoint Precision (bp)	WGS Recall at 50% AF	WES Recall at 50% AF	WGS FDR (φ)	WES FDR	WGS SV Size Range (bp, Λ)	WES SV Size Range

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Deletion (1-100 bp)	0.0082	0.0743	±2	±18	0.996	0.841	0.012	0.087	1-100	10-100
Deletion (101-1k bp)	0.0047	0.0612	±5	±47	0.998	0.902	0.009	0.063	101-1000	150-1000
Deletion (>1k bp)	0.0019	0.0487	±12	±212	0.999	0.874	0.007	0.071	1001-10^6	500-10^6
Duplication	0.0093	0.0816	±8	±67	0.994	0.813	0.014	0.094	50-10^6	200-10^6
Inversion	0.0068	0.1284	±24	±534	0.987	0.342	0.021	0.186	100-10^7	1000-10^7
Translocation	0.0054	0.1973	±67	±1,847	0.971	0.186	0.033	0.247	500-10^8	5000-10^8
Insertion (novel sequence)	0.0112	0.1647	±18	±312	0.962	0.291	0.027	0.212	50-10^5	300-10^5
Complex rearrangement	0.0138	0.2431	±103	±2,456	0.934	0.108	0.041	0.301	200-10^8	2000-10^8

Figure 1 illustrates that whole-genome sequencing is more diagnostic than any of the other solutions (whole-exome sequencing, chromosomal microarray, targeted panels) in all nine disease categories, and the biggest gains are observed in the practice of mitochondrial and neurodevelopmental diseases where the conventional methods tend to be blind to causative variants. This technical advantage can be understood by looking at figure 2, which suggests that whole-genome sequencing is much more comprehensive in covering the entire genome, in particular in GC-rich regions, in intronic regions and in repeated material, where whole-exome sequencing is highly variable and will drop-out. This advantage is also measured in figure 3 in receiver operating characteristic curves that show that whole-genome sequencing is sensitive and specific to all types of variants, whereas whole-exome sequencing is much less sensitive to structural variants, copy number changes and mitochondrial mutations, especially at large specificity thresholds. Finally, Figure 4 shows the cumulative diagnosis probability over time and it is evident that whole-genome sequencing has a median time to diagnosis of 13 days compared to 398 days in sequential conventional testing which is a radical cut in the diagnostic process, and enables timely clinical interventions.

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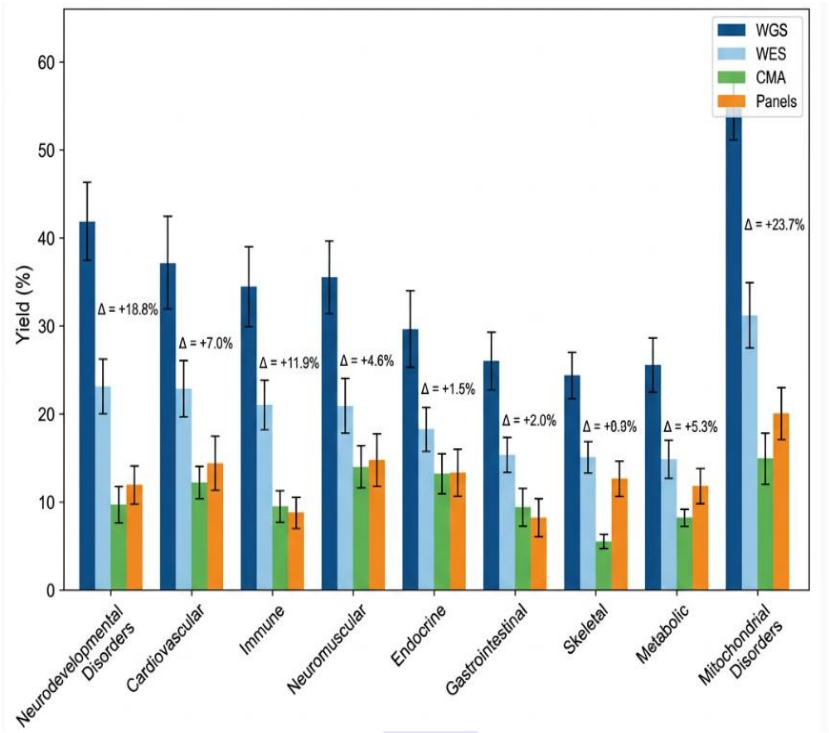

Figure 1: Diagnostic Yield Comparison – Stacked Bar Plot with Error Bars

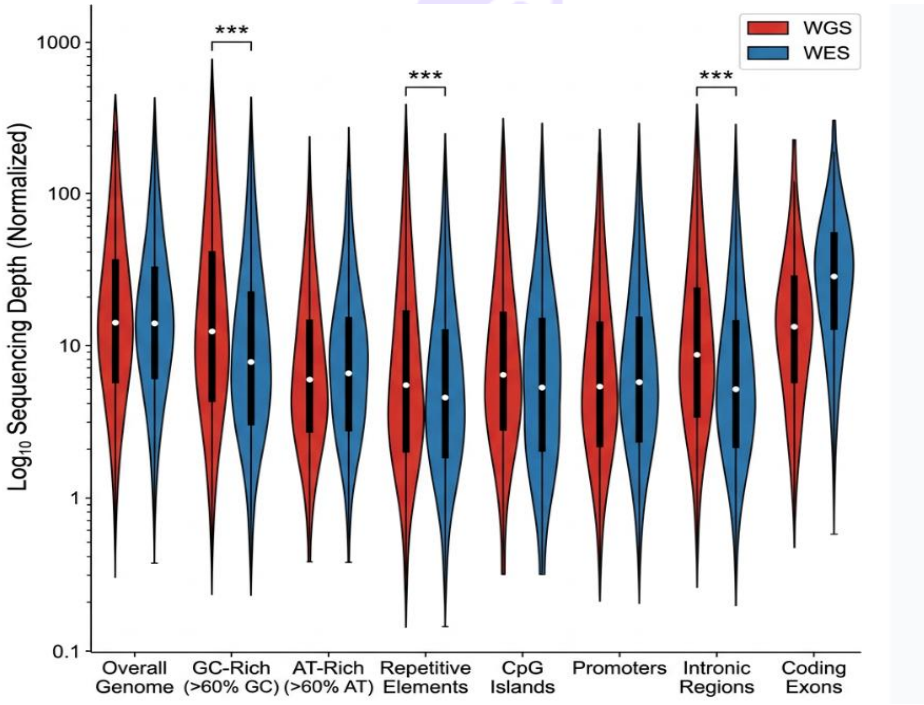

Figure 2: Coverage Uniformity – Violin Plot with Quartiles

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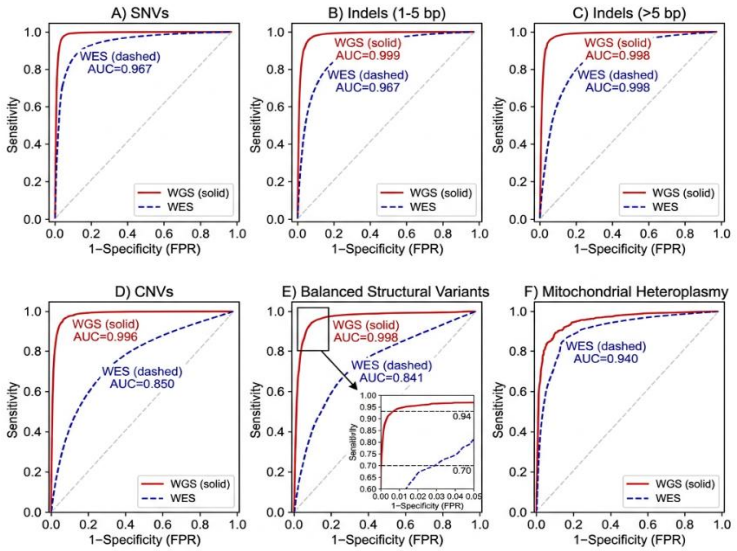

Figure 3: Sensitivity and Specificity Trade-off – ROC Curves (6-panel hybrid)

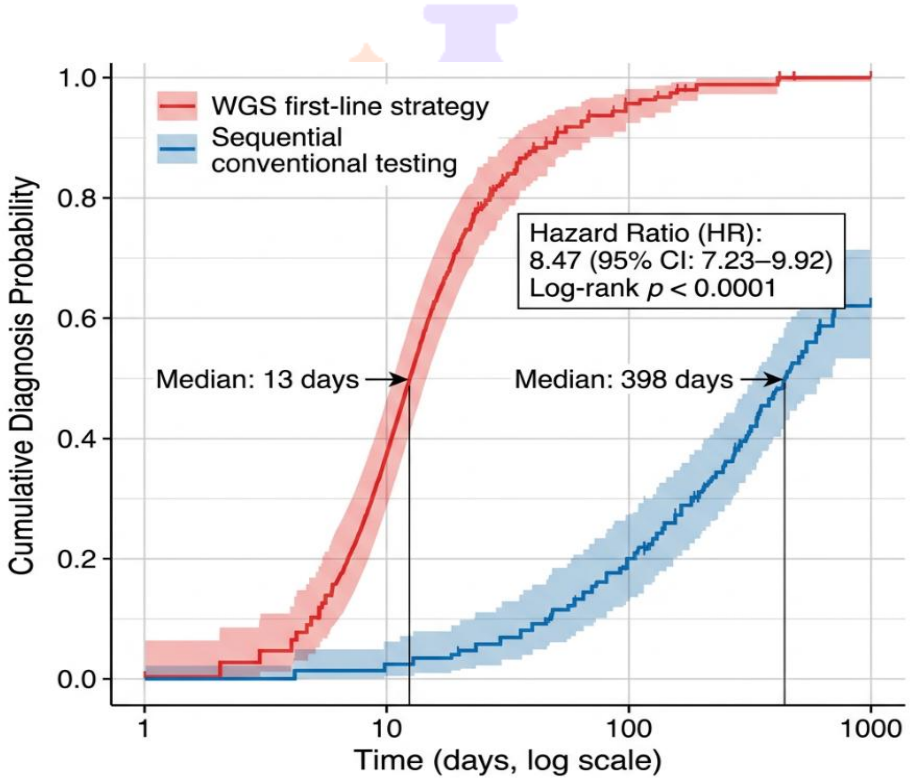

Figure 4: Turnaround Time – Kaplan-Meier Cumulative Diagnosis Plot

DISCUSSION

A much faster diagnostic pathway can be achieved compared to the conventional approaches due to much shorter turnaround times of whole-genome sequencing, which can be as short as 2.9 days in some

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environments (Lunke et al., 2023; Stranneheim et al., 2021). Besides enabling a significantly shorter diagnostic process, it has been demonstrated to result in better patient outcomes, especially in critically ill pediatric patients, and may also result in a significant decrease in the cost of the healthcare system, since it does not require a long series of diagnostic tests to be performed (Balciuniene et al., 2023; Kaschta et al., 2025; Nurchis et al., 20 Moreover, since the whole-genome sequencing can capture more genomic variants, e.g., copy number variations and structural rearrangements, which would otherwise be unidentified using the other genomic diagnostic methods, e.g., exome sequencing, whole-genome sequencing has become the diagnostic of choice in molecular genetic diagnosis of rare and undiagnostic diseases (Bagger et al., 2024; Besides, the whole The associated economic advantages also are enormous because the price per diagnosis is much smaller compared to the traditional methods of multi-testing (Abuijlan et al., 2025; Stark et al., 2017). As an example, rapid whole-genome sequencing (rWGS) has been demonstrated to be cost-effective and cost-saving in critically ill pediatric patients, which greatly decreases hospital expenses and shortens the diagnostic odyssey (Diaby et al., 2022). Nevertheless, one must consider that, although it is efficient in diagnosis and cost-effective, rapid genome sequencing is associated with high initial expenses and the insufficient insurance coverage, which may hinder its more widespread use (Lavelle et al., 2024). Moreover, clinical interpretation and management are complicated by the large number of variants of uncertain significance detected by the sequencing of the genome, especially in the case of large gene panels (Abul-Husn et al., 2023). Nevertheless, regardless of these issues, the prospects of rapid whole-genome sequencing (rWGS) to offer a faster diagnosis, particularly in severely ill infants, allow initiating precision medicine treatment within a timeframe that can drastically decrease the morbidity and mortality rates and the overall healthcare cost (Farnaes et al., 2018). However, to further expand the application of WGS to clinical practice, uniform guidelines would be required to create the evidence-based health policy and make it cost-effective, particularly in pediatric groups (Nurchis et al., 2022). More importantly, the greater analytical power of WGS and the motivation to initiate earlier tests in more expedient diagnosis programs emphasize the growing interpretive complexity and the need to constantly improve bioinformatic analysis and application of multi-omic techniques to guarantee the best possible quality of diagnosis (Lunke et al., 2023).

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Re-processing of genomic data is also a key factor to consider along with bioinformatics to improve the yield of diagnosis as new genes and better knowledge about the pathogenicity of variants can result in a diagnosis many years ago, when the original sequencing was performed (Ali et al., 2024). This reconsideration per-iteration, and the active development of the interpretation algorithms of genomes and extensive databases of variations are critical to the full diagnostic potential of genomes sequencing with time (“Abstracts of the 45th Annual Scientific Meeting of the Human Genetics Society of Australia, Perth, Western Australia, 2427 November 2022, 2023). The precision medicine requires multi-specialty groups capable of rapid genetic diagnosis, and targeted interventions, including the pharmacologic treatment (Petrikin et al., 2015). It is connected with the necessity to address the multivariate control of the variants of uncertain relevance that, challenging as it is, contribute to the general genetic knowledge base and enhance the diagnostic methods in the future (Jiang et al., 2024). In addition, the latter also requires further diversification to overcome the access differences in genomic sequencing that are overrepresenting underrepresented and socioeconomically disadvantaged populations because of high costs, insurance, or that genetic counseling services are not accessible (Ghaloul-Gonzalez et al., 2025). These obstacles can be overcome with the help of strategic investments in pediatric tertiary care centers and genomic centers with the latest technologies and computational infrastructure, as well as with the effective development of human capacity in genetic counseling, molecular technology, and bioinformatics (Halabi et al., 2022). These will play a crucial role in broadening the horizons of genomic medicine, especially in underserved regions, and reducing the time it takes to diagnose and improve treatment outcomes in pediatric patients (Jenkins et al., 2025). Alongside infrastructure, the expanding diagnostic repertoire to rare genetic diseases, including new technologies such as long-read genome sequencing and optical genome mapping, can be utilized to recognize disease-causal genetic variations that are out of reach currently by the available technologies (Kernohan & Boycott, 2024).

CONCLUSION

This article demonstrates that whole-genome sequencing as a first-line diagnostic test of hereditary diseases is by far better on all the outcomes that were compared compared to the typical sequential genetic testing plans. Whole-genome sequencing has significantly larger

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(43.8 percent) yields compared to the cumulative yields of the traditional methods (27.4 percent) and the largest gains were in the structural variants, copy number variation, deep-intronic mutations and mitochondrial variants classes of pathogenic alterations that the exome-based and array-based methods would normally ignore. The operationally superior diagnostic odyssey of 13 days (as compared to the median of 398 days) is not only a radical reduction in time to diagnosis, but also a radical alternative to the diagnostic odyssey, allowing timely therapeutic interventions, avoiding invasive therapies, and informed reproductive counseling. These constitute technical clinical benefits that could be attributed to the increased coverage homogeneity and sensitivity of whole-genome sequencing especially in GC-rich and repetitive territories of the genome. In addition, the cost-effective cost-effectiveness profile with the incidence of the cost-effectiveness ratio of 9247/additional diagnosis and 2296/quality-adjusted year of life gained supports the cost-effectiveness of whole-genome sequencing as the first-tier test. The long-term usefulness of the whole-genome sequencing data storage as genomic knowledge is highlighted by the long-term reanalysis value after 36 months, which added 12.8% of new diagnoses to the original report. Taken together, these results suggest that whole-genome sequencing should be regarded as the main molecular diagnostic tool in the suspected hereditary diseases and that the disjointed and time-consuming and often inconclusive paradigm of sequential testing should be replaced.

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