Genomic Diagnosis and Treatment Impact in Epilepsy: Insights from Rapid Whole Genome Sequencing

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INTRODUCTION

- Genetic factors play an impactful role in the etiology of many seizure disorders and epilepsies, with over 1500 related genes identified.[1]
- Rapid whole genome sequencing (rWGS) offers genome-wide analysis of many types of genetic variants in just a few days and is increasingly employed in the diagnostic evaluation of epilepsy. Results can inform clinical management, including the implementation of targeted therapies.
- The National Society of Genetic Counselors and the American Epilepsy Society strongly recommend genome sequencing as first-tier testing for all individuals with unexplained epilepsy.[2]
- This study presents a clinical cohort of patients with seizures and/or epilepsy to demonstrate the clinical utility of rWGS in guiding treatment decisions.

METHODS

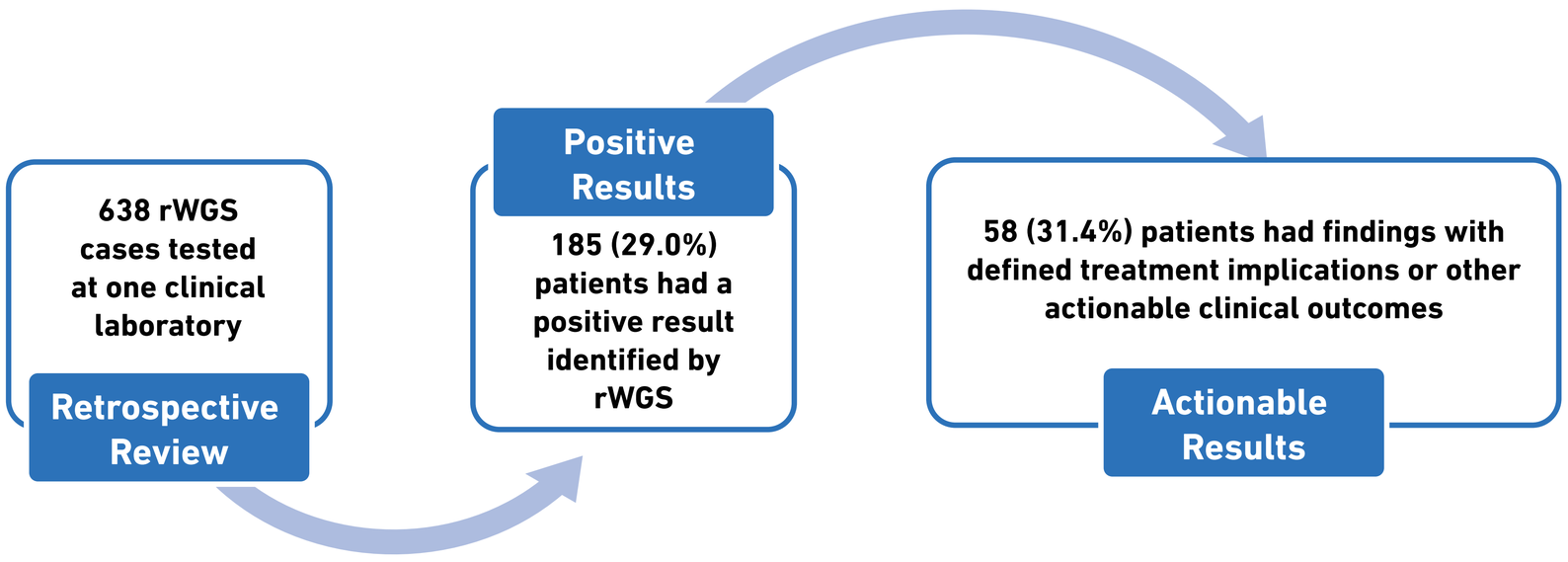
Study Design: Retrospective review of rWGS results

Inclusion Criteria:

- rWGS completed at one clinical laboratory
- Clinical indication includes epilepsy or infantile spasms

Analysis:

- We reviewed the clinical and genetic data to determine the frequency of "positive" results (defined as pathogenic and likely pathogenic variants associated with epilepsy or seizures) detected by rWGS.
- Among positive results, genes with known treatment or management implications were identified via literature review.



Among all positive results, variant types included single nucleotide variants (SNVs), copy number variants (CNVs), mitochondrial genome variants (mtDNA), and short tandem repeats (STRs). Whole exome sequencing (WES) has limited capability to capture CNVs, mtDNA, and STRs.

Selected Genes and Actionable Outcomes	
SCN1A **(Dravet syndrome)**	Patients with *SCN1A*-related disorders may respond positively to stiripentol (Diacomit®), cannabidiol, and fenfluramine (Fintepla®) as well as a ketogenic diet.[3] Antisense oligonucleotides are also being investigated as a potential therapy but are not currently available for clinical use.[4]
POLG**-related disorders**	Treatment is largely based on symptoms, but valproic acid, sodium divalproate, and medications that rely heavily on liver metabolism should be avoided.[5]
ALDH7A1 **(pyridoxine-dependent epilepsy)**	Conventional antiepileptic drugs are ineffective - the condition must be treated with vitamin B6 (pyridoxine) supplementation. Combining pyridoxine with lysine reduction therapy is associated with improved outcomes.[6]
MECP2 **(Rett syndrome)**	Trofinetide (Daybue®) is an approved treatment for patients with Rett syndrome.[7]

Variant type	Number of findings	Would WES capture?
SNVs	148	Likely*
CNVs	30	Limited
mtDNA	5	No
STRs	2 (*ATXN8OS*, *DMPK*)	No

*Deep intronic and non-coding variants may not be captured by WES

CONCLUSIONS

- rWGS identified a genetic diagnosis within days in approximately 1 in 3 patients with seizure-related concerns; one-third of these cases involved conditions with actionable medical management implications.
- Several positive findings likely would have been missed by panel-based or exome sequencing.
- rWGS is an important tool to reduce time to diagnosis and inform treatment decisions in patients with seizures.

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Reference:
1) PMID 37777370. 2) PMID 36281494. 3) PMID 35156171. 4) PMID 32848094. 5) PMID 31799506.
6) PMID 35279367. 7) PMID 37291210.