

The Utility of Comprehensive Genetic Testing to Resolve the Diagnostic Odyssey for Adult Patients

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Background

- Rare disease diagnosis continues to improve as genetic testing becomes more comprehensive and accessible to patients and providers.
- Guidelines from professional organizations such as the American College of Medical Genetics and Genomics (ACMG) and American Academy of Pediatrics (AAP) have strengthened access to comprehensive genetic testing by endorsing genome sequencing (GS) and exome sequencing (ES) as first-tier genetic tests for pediatric patients with congenital anomalies (CA), developmental delays (DD), and intellectual disability (ID).^{1,2}
- Additional GS and ES guidelines specific to adult patients, especially those that became adults before the availability of clinical GS and ES, could help clinicians and payors better serve adult patients through increased access, diagnostic yield, and faster turn around time to results.
- We present a case series of adult patients whose long diagnostic odysseys were ultimately resolved by GS or ES.

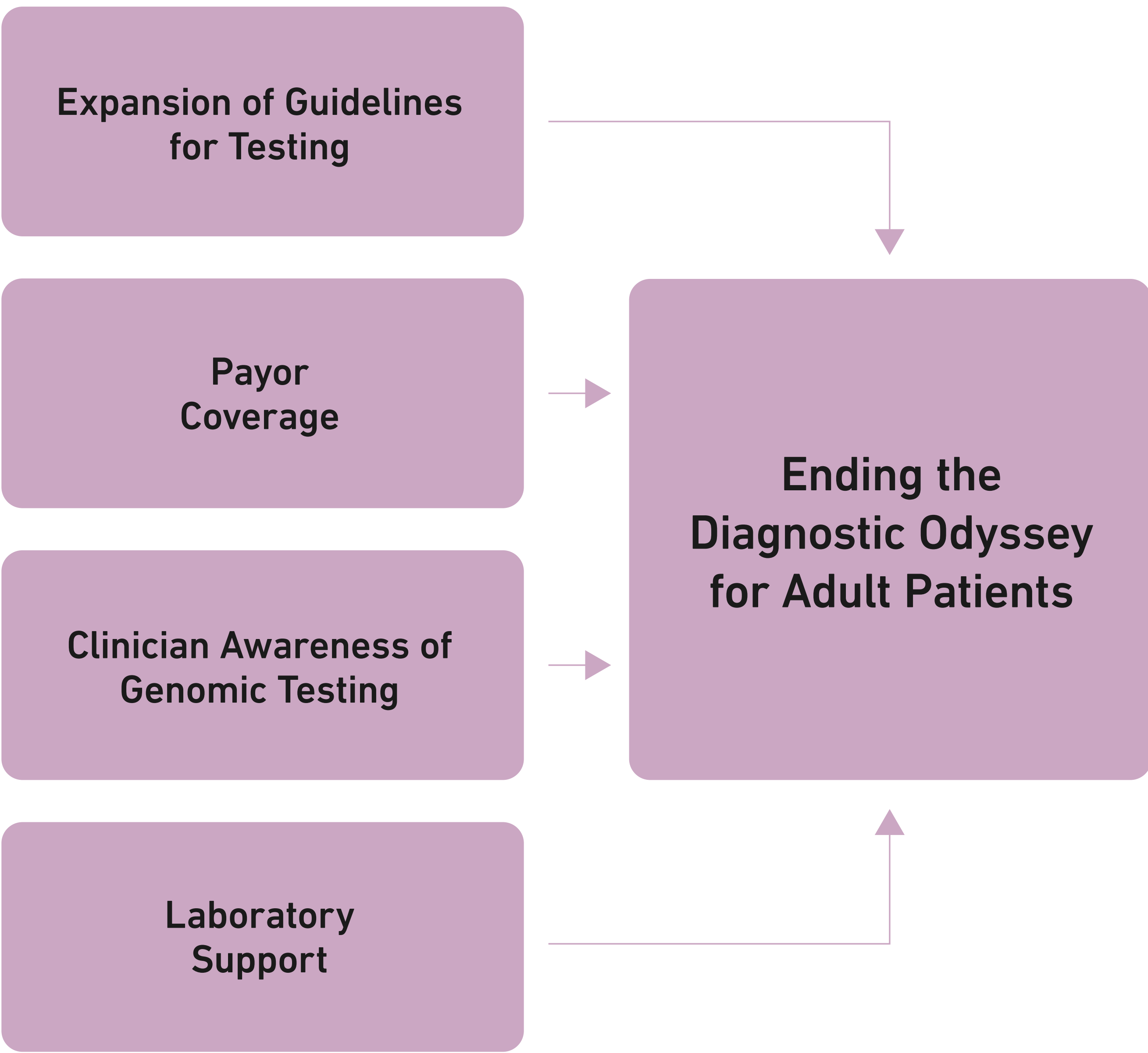
PATIENT HISTORY	PRIOR TESTING	GS/ES RESULTS	IMPACT
52-year-old non-verbal with DD, ID, and end-stage renal disease	1990: Positive PWS testing 2000s: Negative PWS testing 2023: Het pathogenic <i>TMEM231</i> variant on panel testing	2024: The previously-identified <i>TMEM231</i> variant was seen in trans with a 1.1kb single exon <i>TMEM231</i> deletion on proband ES, consistent with Joubert Syndrome 20	GS and ES can have a higher sensitivity for single exon copy number variants compared to CMA
41-year-old with autistic behavior, seizures, global DD, ID, sparse hair, and dysmorphic facial features	1990s: Karyotype and CMA with paternally inherited chromosome 15;16 translocation and maternally inherited chromosome 6 abnormality reported (not available for review)	2025: De novo heterozygous LP 3kb single exon deletion within the <i>ARID1B</i> gene (on chromosome 6) was detected on trio GS, consistent with Coffin-Siris Syndrome 1	
30-year-old with DD, ID, peripheral neuropathy, hearing loss, gait disturbance, and consanguinity	1990s: Clinical diagnosis of “Down Syndrome,” but no genetic testing performed	2025: Trio GS identified hom LP variants in <i>MANF</i> , associated with Diabetes, Deafness, Developmental Delay, and Short Stature Syndrome	The diagnostic odyssey was ultimately resolved through GS after previous nondiagnostic testing
38-year-old with hearing loss, DD, autism, short stature, and end-stage renal disease	1990s: Negative PWS testing	2024: De novo het pathogenic <i>KMT2D</i> variant and maternally inherited KCNJ5 VUS with trio GS, consistent with Kabuki Syndrome 1	
37-year-old with global DD, minimal speech, abnormal movements, and contractures	Early 2024: Nondiagnostic CMA and PWS/AS testing	Late 2024: Het de novo LP <i>NALCN</i> variant detected on trio GS, associated with Congenital Contractures of the Limbs and Face, Hypotonia, and Developmental Delay	GS results can provide answers for the patient and family members
34-year-old with autism, ID, seizures, dolichocephaly, brain abnormalities, sister w/ similar phenotype and multiple relatives with ID and autism	2010s: Negative CMA	2024: Hom pathogenic variants in <i>DOCK7</i> on trio GS consistent with Developmental and Epileptic Encephalopathy 23; sister was also hom	
42-year-old with speech delay, Tetralogy of Fallot, vertebral abnormalities, ID, peripheral neuropathy, and paternal relatives who passed from heart issues	–	2024: Proband GS revealed a het LP <i>TNPO3</i> variant, associated with Limb-Girdle Muscular Dystrophy 2	Paired with GS or ES, RNA sequencing enhances variant classification
20-year-old with connective tissue disorder and limited fhx	2019: Negative aortopathy/EDS panel 2021: ES with mtDNA analysis revealed two mitochondrial VUS; muscle biopsy inconclusive 2024: <i>COL4A3</i> VUS on ES reanalysis	2025: Proband GS identified the same <i>COL4A3</i> VUS; the variant was reclassified by RNA sequencing to LP and is associated with <i>COL4A3</i> -Related Disorders	
31-year-old with fetal alcohol syndrome, learning delay, eczema, recurrent infection, and limited fhx	–	2025: Compound het pathogenic variants in <i>RNU4ATAC</i> on proband GS, associated with <i>RNU4ATAC</i> Spectrum Disorder	Noncoding variants often have limited, if any, coverage by non-GS testing methods

fhx: family history; PWS/AS: Prader-Willi Syndrome/Angelman Syndrome; VUS: variant of uncertain significance; LP: likely pathogenic; het: heterozygous; hom: homozygous; CMA: chromosomal microarray; EDS: Ehlers-Danlos Syndrome

On average, patients in our cohort took 21.1 years to reach a diagnosis after their first genetic test

From a cohort of 1297 adult patients tested with GS or ES at our laboratory³:

- The overall diagnostic yield was 25%, and ~40% of adults (age 18 – 44) with DD or ID received a diagnosis; these yields are comparable to pediatric patients with these phenotypes.
- Most of this cohort were adults prior to the guidelines existing, with diagnostic odysseys spanning decades.



Conclusions

- The cases within this series highlight the comprehensive nature of GS and ES and their utility for ending what sometimes has been a decades-long diagnostic odyssey for adult patients who would have met ACMG and AAP criteria for genetic testing as children.
- Identifying a correct molecular diagnosis could guide clinical care and inform reproductive risks for relatives, such as adult siblings.
- As access to clinical genomic and multiomic technologies expands, this case series supports adult patients having the same access to GS and ES that pediatric patients do. Increased clinical awareness and expansion of genetic testing guidelines is imperative to support this goal.

References:

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