

Genome-wide Sequencing (WES/WGS) as a Diagnostic Test Society Statements Table

	ACMG [*]	CMDA [§]	RACP ^β	ESHG [#]	AAP [¥]
Date of latest publication	July 2021 ¹	June 2019 ²	February 2021 ³	May 2022 ⁴	June 2025 ⁵
Publication Type	Practice Guideline	Expert Consensus	Viewpoint	Recommendations	Clinical Report
Sequencing Type	WES/WGS	WGS	WES/WGS	WGS	WGS
Eligible patients	Patients with one or more congenital anomalies prior to one year of age OR with intellectual disability with onset prior to age 18	Non-specific phenotype associated with intellectual disability and/or developmental delay; multiple congenital anomalies; clear clinical diagnosis associated with high level of genetic heterogeneity; previously negative WES or CMA	Any child < 10 years with: facial dysmorphism AND ≥ 1 congenital structural anomaly; OR global developmental delay/ intellectual disability (moderate to severe); Test must be requested by clinical geneticist OR pediatrician following consultation with clinical geneticist	It is recommended to introduce WGS analysis in a diagnostic setting when it is a relevant improvement on quality, efficiency and/or diagnostic yield	Global developmental delay/intellectual disability (GDD/IDD) Phenotype-driven approach should be used when possible. Agnostic approach when distinguishing features are not evidence.
Tier	First or second tier test	First or second tier test	Second tier: Negative routine blood tests if indicated, negative CMA required	Not specified	Tiered approach outlined: First-tier WGS/WES or CMA in agnostic approach. If WGS not performed first, consider follow-up after other testing is negative (ie. WES/CMA/Fragile X).
Reporting	Not specified	Report on pathogenic, likely pathogenic, and variants of unknown clinical significance associated with the patient phenotype	Not specified	Laboratory should include the following on a report: diagnostic strategy, types of genetic variants detected, their reportable range, analytical sensitivity, and precision. A VUS should only be reported if phenotype of gene matches the patient.	Not specified
Informed Consent and Pretest Counseling	Set expectations, establish understanding of benefits/limitations/potential harms of testing such as limited disease-known associations	Discuss purpose of test, test limitations, possible results, possibility of secondary findings; possibility of data reanalysis	Explain possible outcomes to manage patient/parent expectations, address potential for incidental (secondary) findings, address possibility of certain types of insurance discrimination	Pre-test genetic counseling should be performed prior to obtaining informed consent. This counseling should be performed by a qualified expert (ie. clinician, genetic counselor).	Pre-test counseling should include discussion of potential results, including variants of uncertain significance, incidental or secondary findings.

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Posttest Counseling	Discuss pathogenic and likely pathogenic results, benign results, and variants of uncertain clinical significance, secondary findings, detection of nonpaternity or consanguinity, limits of testing	Counselor should explain results of test, provide information about treatment/management/risk to family members and future children, and provide patient support materials.	Results disclosure need tailored approach, should include discussion of pathogenic, likely pathogenic, and variants of uncertain significance	WGS reports should be delivered to the referring physician. Advice on referring to the patient and family for genetic counselling must be included in the report.	Significance of a variant may be reinterpreted over time. Geneticist should help to provide as much clarification as possible to the family and HCP.
Secondary Findings	Patient can opt out with informed consent	Patient can opt out with informed consent	Referred to as Incidental Findings; Authors do not endorse the intentional clinical analysis of disease genes not related to primary indication.	Recommended to only search for pathogenic variants in genes associated with the phenotype of the patient. The option for analyzing other genes for secondary findings depends on local policy. (As reported previously)®	Potential for should be included in pretest counseling.
Reevaluation/Reanalysis	Value in reanalysis; frequency/strategy not specified	Not specified	In the event of a variant of uncertain significance, recommend reanalysis in 18 months, up to twice after the initial test is performed. Some situations warrant shorter reanalysis interval.	Reanalysis should be triggered by the clinician and not by the diagnostic laboratory. Patients should be aware of and provide consent to reanalysis.	Not specified
WGS versus WES+CMA	WGS provides coverage of both array and exome targets with further coverage of clinically relevant regions of the genome	Not specified	Not specified	Not specified	Not specified

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2. Chinese Medical Doctor Association Medical Genetics Branch. Expert consensus on the clinical application of whole-genome sequencing in the detection of genetic diseases. *Chinese Journal of Pediatrics*, 2019, 57(6): 419-423
3. Sachdev R, Field M, Baynam GS, et al. Paediatric genomic testing: Navigating medicare rebatable genomic testing. *J Paediatr Child Health*. 2021 Apr;57(4):477-483.
4. Souche E, Beltran S, Brosens E, et al. Recommendations for whole genome sequencing in diagnostics for rare diseases [published online ahead of print, 2022 May 16]. *Eur J Hum Genet*. 2022;10.1038/s41431-022-01113-x. doi:10.1038/s41431-022-01113-x
5. Rodan LH, Stoler J, Chen E, et al. Genetic evaluation of the child with intellectual disability or global developmental delay: Clinical report. *Pediatrics*. 2025; 156(1):e2025072219.

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* American College of Medical Genetics and Genomics
 § Chinese Medical Doctor Association, Medical Genetics Branch
 β Royal Australasian College of Physicians, Paediatric and Child Health Division
 #European Society of Human Genetics
 ¥ American Academy of Pediatrics
 WES = Whole-Exome Sequencing
 WGS = Whole-Genome Sequencing
 CMA = Chromosomal Microarray

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