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Highlights from American College of Medical Genetics and Genomics (ACMG)

Evidence-based Guideline: Exome and genome sequencing (ES/GS) for pediatric patients with congenital anomalies or intellectual disability/ developmental delay (ID/DD)[1]

What indications are included in this guideline?

Patients with one or more congenital anomalies before one year of age OR patients with intellectual disability or developmental delay prior to 18 years of age.

Why are these indications important?

Congenital anomalies, developmental delay and intellectual disability are among the most common indications for genetic referral in the pediatric population and comprise a heterogeneous group of conditions that can impact a child's physical, learning, or behavioral function.

What methodology was used for this guideline?

The American College of Medical Genetics and Genomics published a systematic evidence review in 2020 on 167 publications related to exome and genome sequencing. This guideline is based on findings from that systematic evidence review.[2]

Key Highlights

- **Strong recommendation for ES/GS as a first- or second-tier test in:**
  - Pediatric patients with one or more contenital anomalies (CA) before one year of age
  - Pediatric patients with intellectual disability/developmental delay (ID/DD) prior to 18 years of age
- **There is evidence of clinical utility of ES/GS in these indications**
  - There are desirable effects of ES/GS on active and long-term clinical management of patients with CA/DD/ID
  - There is value to family-focused and reproductive planning with ES/GS
  - There is limited evidence for harm (eg. insurance discrimination, psychosocial/family impact, financial burden) or negative outcomes following ES/GS
- **Feasibility and acceptance of ES/GS have been demonstrated by relevant stakeholders**
  - Healthcare and laboratory providers are uniformly in favor of ES/GS
  - ES/GS are technically and logistically feasible

Additional Points

- Guideline still suggests targeted testing for patients with indications highly suggestive of specific condition
- ES/GS for other indications, (e.g. hereditary cardiomyopathies, autism, neuropathies) are expected to yield similar clinical utility
- Rapid GS should be made available if clinical utility indications are met
- Whole-genome sequencing (WGS) provides coverage of both array and exome targets, and further coverage of clinically relevant non-exome regions of the genome
- Patients/parents recognize the value of a diagnosis in cases of CA/DD/ID and are generally in favor of genomic sequencing
- Preliminary evidence shows diagnostic yield is similar with GS compared to ES + chromosomal microarray (CMA) or other targeted test with a potential lower cost for GS
- In theory, if ES/GS can provide a diagnosis in fewer visits, care disparities could decrease in patients at a lower socioeconomic status

1. Manickam, K., McClain, et al. Exome and genome sequencing for pediatric patients with congenital anomalies or intellectual disability: an evidence-based clinical guideline of the American College of Medical Genetics and Genomics (ACMG). Genet Med (2021). https://doi.org/10.1038/s41436-021-01242-6

2. Malinowski, J., Miller, D.T., Demmer, L. et al. Systematic evidence-based review: outcomes from exome and genome sequencing for pediatric patients with congenital anomalies or intellectual disability. Genet Med 22, 986–1004 (2020). https://doi.org/10.1038/s41436-020-0771-z

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