Testing for Genetic Syndromes Related to Developmental Delay, Intellectual Disability, and Autism Spectrum Disorder

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INDICATIONS FOR TESTING
DD, ID, and/or ASD
AND/OR
One or more comorbidities (eg, dysmorphic features, seizures, congenital defects, psychiatric disorders, family history of recurrent miscarriages)

Conduct comprehensive medical history, family history, physical examination, and neurologic examination

Down syndrome, trisomy 13, or trisomy 18 suspected

ORDER
Chromosome analysis with reflex to genomic microarray

DD/ID/ASD of unknown etiology

Specific disorder suspected

ORDER
Disorder-specific testing

First-Tier Testing

ORDER
Genomic microarray

AND
Fragile X (*FMR1*) testing[a]

CONSIDER
Testing for metabolic and/or mitochondrial disorders (if clinical indicators are present)[b]

AND

Medical genetics/genetic counseling referral

Second-Tier Testing

- Consider additional specific molecular studies to assess for:
  - Rett syndrome, if the patient is female
  - *PTEN*-related disorders, if the patient has ASD and macrocephaly (head circumference >2.5 SDs above the mean)
- X-linked disorder testing, if indicated by clinical and family history
- Whole exome sequencing
- Brain imaging studies

Abbreviations

ASD	Autism spectrum disorder
DD	Developmental delay
ID	Intellectual disability
SD	Standard deviation

[a]The American College of Medical Genetics and Genomics suggests fragile X syndrome screening for male and female patients with compatible clinical features and family history. The American Academy of Pediatrics and the American Academy of Neurology recommend screening in all cases.
[b]Consider metabolic testing (eg, acylcarnitine, amino acids, creatine, mucopolysaccharides, organic acids, creatine disorders panel, very long-chain and branched-chain fatty acids profile, uric acid, pyridoxine-dependent epilepsy panel [includes pipecolic acid and total AASA-P6C]) and review of newborn screening results even if there is low incidence/suspicion because intervention may be possible. Clinical indicators may include poor feeding, vomiting, dehydration, lethargy, hypotonia, and seizures in the newborn period. Clinical indicators outside of the newborn period exhibit marked variability and may be episodic and/or progressive.

References

- Michelson DJ, Shevell MI, Sherr EH, et al. Evidence report: Genetic and metabolic testing on children with global developmental delay: report of the Quality Standards Subcommittee of the American Academy of Neurology and the Practice Committee of the Child Neurology Society. *Neurology*. 2011;77(17):1629-1635.
- Moeschler J, Shevell M, Committee on Genetics. Comprehensive evaluation of the child with intellectual disability or global developmental delays. *Pediatrics*. 2014;134(3):e903-e918.
- Schaefer B, Mendelsohn NJ, Professional Practice and Guidelines Committee. Clinical genetics evaluation in identifying the etiology of autism spectrum disorders: 2013 guideline revisions [published correction appears in *Genet Med*. 2013;1(8):669]. *Genet Med*. 2013;15(5):399-407.

