Why *trio* testing matters

When a genetic cause is suspected, including parental samples from the outset can directly impact variant classification and reduce delays in reaching a diagnosis.

Trio testing can increase diagnostic yield by 7-15%[1-4] compared to testing that does not include biological relative samples.

This can enable syndrome-specific management, surveillance, educational supports, and resources sooner.

Developmental delay without a clear cause

Birth

Meet Harper.* At delivery, Harper displayed severe torticollis and was discharged without additional concerns.

12 months

Her early developmental milestones were attained as expected. However, Harper's speech and ambulation became a concern after 12 months. Following a normal hearing test, her pediatrician recommended OT and PT to assist with attaining the milestones of talking and walking.

3 years

By age 3, she demonstrated further developmental delays and was referred to pediatric neurology. On assessment, there were no obvious dysmorphic features or additional neurological concerns. A brain MRI and genetic testing were recommended to help determine etiology.

*Case study is based on GeneDx patient testing, with all identifying information removed.

References: 1. Clark MM, Stark Z, Farnaes L, et al. Meta-analysis of the diagnostic and clinical utility of genome and exome sequencing and chromosomal microarray in children with suspected genetic diseases. NPJ Genom Med. 2018 Jul 9;3:16. doi: 10.1038/s41525-018-0053-8. eCollection 2018. **2.** Lee H, Deignan JL, Dorrani N, et al. Clinical exome sequencing for genetic identification of rare Mendelian disorders. JAMA. 2014 Nov 12;312(18):1880-7. doi: 10.1001/jama.2014.14604. **3.** Farwell KD, Shahmirzadi L, El-Khechen D, et al. Enhanced utility of family-centered diagnostic exome sequencing with inheritance model-based analysis: results from 500 unselected families with undiagnosed genetic conditions. Genet Med. 2015 Jul;17(7):578-86. doi: 10.1038/gim.2014.154. **4.** Sawyer SL, Hartley T, Dyment DA, et al. Utility of whole-exome sequencing for those near the end of the diagnostic odyssey: time to address gaps in care. Clin Genet. 2016 Mar;89(3):275-84. doi: 10.1111/cge.12654

GeneDx®

The impact of trio testing on diagnosis

Report without trio test

- Proband exome sequencing identified an *SOS1* variant
- Without familial context to help clarify significance, the *SOS1* variant was reported as a **variant of uncertain significance**

Next steps

- Diagnostic uncertainty remains
- Delayed access to syndrome-specific management recommendations
- Clinical follow-up required

Report with trio test

- Sequencing identified a *SOS1* variant. Inheritance information confirmed the variant was de novo, increasing suspicion for pathogenicity
- Trio exome sequencing reported the *SOS1* variant as **likely pathogenic**, leading to a diagnosis of Noonan syndrome

Next steps

- Referral for echocardiogram, ECG, renal ultrasound and ophthalmology assessment
- Growth monitoring using Noonan-specific growth charts
- Ongoing developmental, behavioral and psychological assessments
- Monitoring for vision, hearing, dermatological, hematological, neurological, and musculoskeletal concerns
- De novo variant results in low recurrence risk for her parents' family planning

The impact of trio testing

Trio testing provided inheritance information which was integral to classifying Harper's *SOS1* variant as likely pathogenic, allowing for a clinical diagnosis of Noonan syndrome.

Harper's healthcare team is able to provide clarity to her family regarding prognosis, plan for syndrome-specific surveillance, connect them to disease-specific support groups, and refer to specialists as indicated.

Start with trio testing to maximize diagnostic yield and help families get answers sooner.

Learn more about convenient options to order trio testing.
genedx.co/how-to-order

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