

Noonan Spectrum Disorders/RASopathies Multigene Panel

- I. The use of a multigene panel to confirm or establish a diagnosis of a Noonan spectrum disorder/RASopathy (e.g., Noonan syndrome, Legius syndrome, Costello syndrome, Cardio-facial-cutaneous syndrome, NF1, Noonan-like syndrome) is considered **medically necessary** when:
 - A. The member has at least one of the following:
 1. Characteristic facies (low-set, posteriorly rotated ears with fleshy helices, vivid blue or blue-green irises, widely spaced, down slanted eyes, epicanthal folds, ptosis), **OR**
 2. Short stature, **OR**
 3. Congenital heart defect (most commonly pulmonary valve stenosis, atrial septal defect, and/or hypertrophic cardiomyopathy), **OR**
 4. [Developmental delay](#), **OR**
 5. Broad or webbed neck, **OR**
 6. Unusual chest shape with superior pectus carinatum, inferior pectus excavatum, **OR**
 7. Widely spaced nipples, **OR**
 8. Cryptorchidism in males, **OR**
 9. Lentigines, **OR**
 10. Café au lait macules.
- II. The use of a multigene panel to confirm or establish a diagnosis of a Noonan spectrum disorder/RASopathy (e.g., Noonan syndrome, Legius syndrome, Costello syndrome, Cardio-facial-cutaneous syndrome, NF1, Noonan-like syndrome) is considered **investigational** for all other indications.

RATIONALE AND REFERENCES

Noonan Spectrum Disorders/RASopathies Multigene Panel

GeneReviews: Noonan Syndrome

GeneReviews is an expert-authored review of current literature on a genetic disease, and goes through a rigorous editing and peer review process before being published online.

It is recommended that diagnostic testing for Noonan Spectrum Disorders via multigene panel be performed as follows:

Noonan syndrome (NS) should be suspected in individuals with the following clinical, laboratory, and family history findings.

- Characteristic facies. The facial appearance of NS shows considerable change with age, being most striking in young and middle childhood, and most subtle in adulthood. Key features found regardless of age include the following:
 - Low-set, posteriorly rotated ears with fleshy helices
 - Vivid blue or blue-green irises
 - Widely spaced and down slanted palpebral fissures
 - Epicanthal folds
 - Fullness or drooping of the upper eyelids (ptosis)
- Short stature for sex and family background
- Congenital heart defects, most commonly pulmonary valve stenosis, atrial septal defect, and/or hypertrophic cardiomyopathy
- Developmental delay of variable degree
- Broad or webbed neck
- Unusual chest shape with superior pectus carinatum and inferior pectus excavatum
- Widely spaced nipples
- Cryptorchidism in males
- Lymphatic dysplasia of the lungs, intestines, and/or lower extremities

When the phenotypic findings suggest the diagnosis of Noonan Syndrome (NS), molecular genetic testing approaches usually include the use of a multi-gene panel testing as it is more efficient and cost effective than serial single-gene testing. Approximately 50% of individuals with NS have a pathogenic missense variant in *PTPN11*; therefore, single-gene testing starting with *PTPN11* would be the next best first test.

Roberts AE. Noonan Syndrome. 2001 Nov 15 [Updated 2022 Feb 17]. In: Adam MP, Mirzaa MP, Pagon RA, et al., editors. GeneReviews [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2025. Available from: <https://www.ncbi.nlm.nih.gov/books/NBK1124/>

Rauen

Per the NIH, the RASopathies are comprised of the following conditions: neurofibromatosis type 1, Noonan syndrome, Noonan syndrome with multiple lentigines, capillary malformation–arteriovenous malformation syndrome, Costello syndrome, cardio-facio-cutaneous syndrome, and Legius syndrome.

Rauen KA. The RASopathies. Annu Rev Genomics Hum Genet. 2013;14:355-369.
doi:10.1146/annurev-genom-091212-153523

DEFINITIONS

1. **Developmental delay (DD)** is defined as slow-to-meet or not reaching milestones in one or more of the areas of development (communication, motor, cognition, social-emotional, or adaptive skills) in the expected way for a child's age.