

Noonan Spectrum Disorder Genetic Testing

MOL.TS.371.A

v2.0.2025

Noonan spectrum disorder (NSD) genetic testing is addressed by this guideline.

Procedures addressed

The inclusion of any procedure code in this table does not imply that the code is under management or requires prior authorization. Refer to the specific Health Plan's procedure code list for management requirements.

Procedures addressed by this guideline	Procedure codes
Known familial mutation analysis	81403
Noonan spectrum disorder gene analysis	81400 81401 81402 81403 81404 81405 81406 81407 81408 81479
Noonan spectrum disorders (eg, Noonan syndrome, cardio-facio-cutaneous syndrome, Costello syndrome, LEOPARD syndrome, Noonan-like syndrome), genomic sequence analysis panel, must include sequencing of at least 12 genes, including BRAF, CBL, HRAS, KRAS, MAP2K1, MAP2K2, NRAS, PTPN11, RAF1, RIT1, SHOC2, and SOS1	81442

Noonan Spectrum Disorder

Criteria

Introduction

Requests for Noonan spectrum disorder (NSD) genetic testing are reviewed using the following criteria.

Known Familial Mutation Analysis

- Genetic Counseling:
 - Pre and post-test genetic counseling by an appropriate provider (as deemed by the Health Plan policy), AND
- Previous Genetic Testing:
 - No previous genetic testing that would detect the familial mutation, AND
- Diagnostic Testing for Symptomatic Individuals:
 - Known familial mutation in a causative gene in a 1st-degree biologic relative, AND
- Rendering laboratory is a qualified provider of service per the Health Plan policy

Single Gene Sequence Analysis

- Genetic Counseling:
 - Pre and post-test genetic counseling by an appropriate provider (as deemed by the Health Plan policy), AND
- Previous Genetic Testing:
 - No previous testing of the requested gene, and
 - No known NSD mutation in a biologic relative, AND
- Diagnostic Testing for Symptomatic Individuals:
 - Two or more of the following major features:
 - Hypertrophic cardiomyopathy
 - Congenital pulmonary valve stenosis
 - Electrocardiogram characteristic of NSD associated with the requested gene
 - Facial dysmorphism suggestive of NSD associated with the requested gene
 - Stature less than 3rd percentile for age and gender
 - Pectus carinatum and/or excavatum
 - First-degree relative with known or suspected NSD associated with the requested gene, or
 - One major feature as listed above, in combination with one or more of the following:
 - Other cardiac abnormality suggestive of the Noonan Spectrum disorder associated with the requested gene (e.g., atrial septal defect, ventricular septal defect, branch pulmonary artery stenosis, tetralogy of Fallot, etc.)

- Stature 3rd to 10th percentile for age and gender
- Broad thorax/widely-spaced nipples
- Developmental delay, intellectual disability, or diagnosed learning disability
- Cryptorchidism
- Broad or webbed neck
- Lymphatic dysplasia
- Coagulopathy confirmed with hematologic studies
- Skin abnormality characteristic of the NSD associated with the requested gene (e.g. multiple lentiginos, follicular keratosis, etc.)
- Pubertal delay and/or infertility, OR
- Prenatal Testing:
 - Prenatal chromosome study is not diagnostic, and
 - Fetal ultrasound exhibits features of the NSD associated with the requested gene based on the presence of one or more of the following:
 - Nuchal edema (e.g., increased nuchal translucency, increased nuchal fold, or cystic hygroma) and/or hydrops fetalis
 - Pulmonary valve stenosis
 - Hypertrophic cardiomyopathy
 - A combination of TWO or more of the following: Polyhydramnios, distended jugular lymphatic sacs (JLS), pleural effusion, cardiac anomaly, renal anomaly, ascites, facial abnormalities suggestive of a NSD and/or first-degree relative known or suspected to have the associated NSD, and
 - No known cause for the above features (e.g., known genetic disorder, etc), and
 - The requested single gene sequencing test is appropriate due to one or more of following:
 - The requested gene is the only gene known to be associated with the suspected type of NSD (e.g., HRAS for Costello syndrome, etc.)
 - Mutations in the requested gene are the most common cause of the suspected type of NSD (e.g., PTPN11 for classic NS or NSML, etc.)
 - Sequencing of genes more frequently associated with the suspected Noonan Spectrum Disorder have been completed and was not diagnostic, AND
- Rendering laboratory is a qualified provider of service per the Health Plan policy

Multigene Panel Testing

When a multi-gene panel is requested and billed with the appropriate CPT panel code, 81442, the panel will be considered medically necessary when the following criteria are met:

- Genetic Counseling:

- Pre and post-test genetic counseling by an appropriate provider (as deemed by the Health Plan policy), AND
- Previous Genetic Testing:
 - No previous NSD panel testing, and
 - No known NSD mutation in a biologic relative, AND
- Diagnostic Testing for Symptomatic Individuals:
 - Two or more of the following major features:
 - Hypertrophic cardiomyopathy
 - Congenital pulmonary valve stenosis
 - Electrocardiogram characteristic of an NSD
 - Facial dysmorphism suggestive of an NSD
 - Stature less than 3rd percentile for age and gender
 - Pectus carinatum and/or excavatum
 - First-degree relative with known or suspected NSD, or
 - One major feature as listed above, in combination with one or more of the following:
 - Other cardiac abnormality suggestive of the NSD (e.g., atrial septal defect, ventricular septal defect, branch pulmonary artery stenosis, tetralogy of Fallot, etc.)
 - Stature 3rd to 10th percentile for age and gender
 - Broad thorax/widely-spaced nipples
 - Developmental delay, intellectual disability, or diagnosed learning disability
 - Cryptorchidism
 - Broad or webbed neck
 - Lymphatic dysplasia
 - Coagulopathy confirmed with hematologic studies
 - Skin abnormality characteristic of the NSD (e.g., multiple lentiginos, follicular keratosis, etc.)
 - Pubertal delay and/or infertility, OR
- Prenatal Testing:
 - Prenatal chromosome study is not diagnostic, and
 - Fetal imaging exhibits features of an NSD based on the presence of one or more of the following:
 - Nuchal edema (e.g. increased nuchal translucency, increased nuchal fold, or cystic hygroma) and/or hydrops fetalis
 - Pulmonary valve stenosis
 - Hypertrophic cardiomyopathy
 - A combination of TWO or more of the following: polyhydramnios, distended jugular lymphatic sacs (JLS), pleural effusion, cardiac anomaly, renal anomaly,

ascites, facial abnormalities suggestive of an NSD and/or first-degree relative known or suspected to have the associated NSD, and

- No known cause for the above features (e.g., known genetic disorder, etc), AND
- Rendering laboratory is a qualified provider of service per the Health Plan policy

Deletion/Duplication Analysis

Deletion/duplication analysis for NSD is not medically necessary due to the extremely low diagnostic yield.

Other Considerations

Broad NSD panels may not be medically necessary when a more targeted test is available and more appropriate based on clinical findings.

The criteria stated in this section applies only to germline diagnostic testing for NSDs. For information on somatic (tumor marker) testing, please refer to the appropriate test-specific guideline or to the guideline *Somatic Mutation Testing*, as this testing is not addressed here. For information on non-invasive screening, please refer to the guideline *Non-Invasive Prenatal Screening*, as this testing is not addressed here.

Billing and Reimbursement

Introduction

This section outlines the billing requirements for tests addressed in this guideline. These requirements will be enforced during the case review process whenever appropriate. Examples of requirements may include specific coding scenarios, limits on allowable test combinations or frequency and/or information that must be provided on a claim for automated processing. Any claims submitted without the necessary information to allow for automated processing (e.g. ICD code, place of service, etc.) will not be reimbursable as billed. Any claim may require submission of medical records for post service review.

- Deletion/Duplication analysis for NSD is not reimbursable.
- Any individual gene or multi-gene panel is only reimbursable once per lifetime.
- When otherwise reimbursable, the following limitations apply:
 - When a panel is being performed, it is only reimbursable when billed with a single, appropriate panel procedure code (e.g., 81442*).
 - When use of a panel code is not possible, each billed component procedure will be assessed independently.
 - In general, only a limited number of panel components that are most likely to explain the member's presentation will be reimbursable. The remaining panel components will not be reimbursable.

- When the test is billed with multiple stacked codes, only the following genes may be considered for reimbursement, based on which NSD is most likely:
 - Classic NS: PTPN11, followed by SOS1, RAF1, RIT1 and LZTR1 if PTPN11 sequencing is negative.
 - CFC syndrome: BRAF, followed by MAP2K1, MAP2K2, and KRAS if BRAF sequencing is negative.
 - NSML/LEOPARD syndrome: PTPN11, followed by RAF1, BRAF, and MAP2K1 if PTPN11 sequencing is negative.

Note:

*The panel code(s) listed here may not be all-inclusive. For further discussion of what is considered an appropriate panel code, please refer to the guideline *Laboratory Billing and Reimbursement*.

What is Noonan spectrum disorder?

Noonan spectrum disorders (NSDs) are a group of disorders that includes Noonan syndrome (NS), Cardiofaciocutaneous (CFC) syndrome, Noonan syndrome with multiple lentiginos (NSML or LEOPARD syndrome), Costello syndrome, Noonan syndrome-like disorder with loose anagen hair, and Noonan syndrome-like disorder with or without juvenile myelomonocytic leukemia (JMML). These disorders are often referred to as “RASopathies” due the associated gene products being involved in the Ras/MAPK-pathway.¹⁻⁴

Prevalence

The prevalence of NS is between 1:1,000 and 1:2,500 individuals. Though mild expression of the condition is likely to be overlooked. Other NSDs are relatively rare.¹⁻⁴

Symptoms

NSDs are multisystem disorders characterized by facial features, short stature, cardiovascular abnormalities (particularly pulmonary valve stenosis and hypertrophic cardiomyopathy), and developmental delay of variable degree.¹⁻⁴

Cause

NSDs are associated with mutations in a number of genes involved in the Ras/MAPK-pathway, with genetic overlap between many of the NSD types.¹⁻⁴

- NS: Causative mutations are found in PTPN11 (50%), SOS1 (10-13%), LZTR1 (~8%), RAF1 (5%), RIT1 (5%), and KRAS (<5%). BRAF, MAP2K1, MRAS, NRAS, RASA2, RRAS2, and SOS2 mutations each account for 4% or fewer cases.

- CFC: Caused by mutations in BRAF (~75%), MAP2K2/MEK2 and MAP2K1 (~25%), KRAS (<2%), and rarely YWHAZ.
- NSML or LEOPARD syndrome: Caused by mutations in PTPN11 (>95%), RAF1 (<3%), BRAF, and MAP2K1.
- Costello syndrome: Caused by mutations in HRAS (~99%).
- Noonan syndrome-like disorder with loose anagen hair: Caused by mutations in SHOC2, particularly a recurrent 4A>G pathogenic variant. Pathogenic variants in SHOC2 are often associated with classic loose anagen hair. This is also caused by mutation in PPP1CB.
- JMML: Caused by mutations in the CBL gene.

Inheritance

Inheritance is autosomal dominant, with the exception of mutations in LZTR1, which can be inherited in either an autosomal dominant or autosomal recessive manner.¹⁻⁴

Individuals with NS and NSML may have an affected parent. In contrast, CFC and Costello syndrome are almost always the result of a de novo mutation.¹⁻⁴

Autosomal dominant inheritance

In autosomal dominant inheritance, individuals have 2 copies of the gene and only one mutation is required to cause disease. When a parent has a mutation, each offspring has a 50% risk of inheriting the mutation. Males and females are equally likely to be affected.

Autosomal recessive inheritance

In autosomal recessive inheritance, individuals have 2 copies of the gene and an individual typically inherits a gene mutation from both parents. Usually only siblings are at risk for also being affected. Males and females are equally affected. Individuals who inherit only one mutation are called carriers. Carriers do not typically show symptoms of the disease, but have a 50% chance, with each pregnancy, of passing on the mutation to their children. If both parents are carriers of a mutation, the risk for each pregnancy to be affected is 1 in 4, or 25%.

Diagnosis

The diagnosis of an NSD is established with molecular testing, which can be accomplished with the use of a multigene panel or serial single-gene testing. Once the causative mutation in the family has been identified, prenatal diagnosis is possible via CVS or amniocentesis.

Additionally, NSDs are usually diagnosed on clinical grounds based on the presence of key features. Clinical diagnostic criteria are available for NSML. No formal diagnostic

criteria exist for NS, CFC or Costello syndrome. The diagnosis should be suspected in individuals with the following:¹⁻⁴

- **NS:**
 - Characteristic facies: "low-set, posteriorly rotated ears with fleshy helices; vivid blue or blue-green irises; widely spaced and downslanted palpebral fissures; epicanthal folds; fullness or droopiness of the upper eyelids (ptosis)."¹
 - "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"¹
 - "Coagulation defects"¹
 - Per a recent expert summary, "No consensus clinical diagnostic criteria for Noonan syndrome have been published."¹ However, diagnostic scoring systems for NS were developed by van der Burgt and published in 2007.⁵ These are also embedded in the Dyscerene 2010 guidelines for NS, and similar recommendations were provided by Romano et al 2010 and Roberts et al 2013.⁶⁻⁸ Each feature has a major finding and minor finding as indicated below. Per the scoring systems, a clinical diagnosis of NS is definitive when an individual has: two major signs OR one major sign plus two minor signs OR three minor signs.
 - Facial
 - Major: typical face dysmorphology
 - Minor: suggestive face dysmorphology
 - Cardiac
 - Major: pulmonary valve stenosis, HOCM [hypertrophic obstructive cardiomyopathy] and/or ECG typical of NS
 - Minor: other defect
 - Height
 - Major: height less than third percentile for age
 - Minor: height less than tenth percentile for age
 - Chest wall
 - Major: pectus carinatum/excavatum
 - Minor: broad thorax
 - Family history

- Major: first degree relative with definite NS
- Minor: first degree relative with suggestive NS
- Other
 - Major: intellectual disability, cryptorchidism, and lymphatic dysplasia
 - Minor: intellectual disability, cryptorchidism, and/or lymphatic dysplasia
- **CFC:**
 - Cardiac features: pulmonic stenosis, atrial septal defects, ventricular septal defects, hypertrophic cardiomyopathy, heart valve anomalies, and rhythm disturbances.
 - Craniofacial features: "relative macrocephaly, triangular facies, bitemporal narrowing, hypoplasia of the supraorbital ridges, widely spaced eyes, telecanthus, downslanting palpebral fissures, epicanthal folds, ptosis, short nose with depressed bridge and anteverted nares, ear lobe creases, low-set ears that may be posteriorly rotated, deep philtrum, cupid's bow configuration of the upper lip, high-arched palate, relative micrognathia."
 - Ectodermal features: characteristic skin, hair, and nail abnormalities.
 - Neurological features: developmental delay, intellectual disability, epilepsy, hypotonia, abnormal brain MRIs.
 - Gastrointestinal and growth features: feeding problems, failure to thrive, growth delays, gastrointestinal dysmotility.⁴
- **NSML (previously LEOPARD) syndrome:**
 - "Lentigines
 - Cardiac abnormalities, particularly hypertrophic cardiomyopathy
 - Poor linear growth/short stature
 - Pectus deformity"
 - Craniofacial features including widely spaced eyes and ptosis
 - Clinical diagnostic criteria are:
 - "Multiple lentigines plus two of the other cardinal features, OR
 - In the absence of lentigines, three of the other cardinal features plus a first-degree relative with NSML"³
- **Costello syndrome:**
 - Prenatal findings: "increased nuchal thickness, polyhydramnios (>90%), characteristic ulnar deviation of the wrists, short humeri and femurs, fetal tachycardia (various forms of atrial tachycardia), preterm delivery
 - Postnatal findings: severe postnatal feeding difficulties extending throughout early childhood, failure to thrive, short stature, macrocephaly (relative or absolute), coarse facial features, curly or sparse, fine hair
 - Skin: loose, soft skin, increased pigmentation, deep palmar and plantar creases, papillomata of face and/or perianal region (typically absent in infancy but may appear in childhood), hyperkeratosis and calluses, premature aging with hair loss

- Musculoskeletal system: diffuse hypotonia, joint laxity, and low muscle mass, ulnar deviation of wrists and fingers; splayed fingers resulting in characteristic hand posture, spatulate finger pads, abnormal fingernails, tight Achilles tendons (often evolving throughout childhood), positional foot deformity, vertical talus, kyphoscoliosis, pectus carinatum, pectus excavatum, asymmetric rib cage, developmental hip dysplasia
- Cardiovascular system: cardiac hypertrophy, usually hypertrophic cardiomyopathy (i.e., idiopathic subaortic stenosis, asymmetric septal hypertrophy), although other forms (e.g., biventricular hypertrophy) have been reported; congenital heart defects, usually valvar pulmonic stenosis; arrhythmia, usually supraventricular tachycardia (known as non-reentrant tachycardias); aortic dilation (typically mild, noted in fewer than 10% of individuals); hypertension
- Neurologic: Chiari I malformation (may develop over time), hydrocephalus, syringomyelia, tethered cord, seizures
- Tumors: increased occurrence of malignant solid tumors including rhabdomyosarcoma and neuroblastoma in young children and transitional cell carcinoma of the bladder in adolescents and young adults
- Psychomotor development: developmental delay or intellectual disability, findings suggestive of autism spectrum disorder in early infancy (that typically improve by age four years), sociable, outgoing personality, anxiety"²

Management

Surveillance is indicated for anomalies in any organ system, particularly the cardiovascular system. Heart defects are usually treated the same as in the general population. Developmental delay is addressed by early intervention programs and individualized education strategies. Growth hormone (GH) treatment may be used to increase growth velocity. Coagulation screening, including CBC with differential and PT/PTT, and treatment of serious bleeding problems as needed.^{1-4,6,8} Some genotype-phenotype correlations are present, which may help to guide medical management.⁹

Survival

An individual with an NSD can have a normal lifespan. However, lifespan can vary depending on the medical complications, such as cardiovascular defects, present in the affected individual.¹⁻⁴

Test information

Testing for NSDs may include known familial mutation analysis, next generation sequencing, or multigene panel testing.

Known Familial Mutation (KFM) Testing

Known familial mutations analysis is performed when a causative mutation has been identified in a close biological relative of the individual requesting testing. Analysis for known familial mutations typically includes only the single mutation. However, if available, a targeted mutation panel that includes the familial mutation may be performed.

Next Generation Sequencing Assay

Next generation sequencing (NGS), which is also sometimes called massively parallel sequencing, was developed in 2005 to allow larger scale and more efficient gene sequencing. NGS relies on sequencing many copies of small pieces of DNA simultaneously and using bioinformatics to assemble the sequence. Sequence analysis detects single nucleotide substitutions and small (several nucleotide) deletions and insertions. Regions analyzed typically include the coding sequence and intron/exon boundaries. Promoter regions and intronic sequences may also be sequenced if disease-causing mutations are known to occur in these regions of a gene.

Multi-Gene Testing Panels

The efficiency of NGS has led to an increasing number of large, multi-gene testing panels. NGS panels that test several genes at once are particularly well-suited to conditions caused by more than one gene or where there is considerable clinical overlap between conditions making it difficult to reliably narrow down likely causes. Additionally, tests should be chosen to maximize the likelihood of identifying mutations in the genes of interest, contribute to alterations in management for an individual, and/or minimize the chance of finding variants of uncertain clinical significance.

- Research has demonstrated that postnatal NGS panel testing in symptomatic individuals has a diagnostic yield of 19-47%.¹⁰⁻¹²
- One study of multigene NSD panel testing in individuals with apparently isolated cardiomyopathy (per clinical information obtained from test requisition forms) demonstrated a detection rate of 0.6%.¹³ NSDs are estimated to account for ~6% of pulmonary valve stenosis.¹⁴
- Approximately 3-15% of fetuses with normal chromosomes and increased nuchal translucency are estimated to have NS.¹
- Nearly all pathogenic mutations associated with an NSD are detected with sequence analysis. Very rare cases of duplication and/or deletion have been reported in some genes; the yield of such testing is expected to be extremely low.¹⁻⁴ There is also some question as to whether these case reports with copy number variation did indeed have a clinical diagnosis of an NSD.¹⁵

- Roughly 10% of individuals who fit the clinical diagnosis of an NSD do not have an identifiable pathogenic mutation in any of the known genes, suggesting that additional genes are involved.¹⁶

Guidelines and evidence

Selected Relevant Publications

A 2023 expert-authored review on CFC stated:⁴

- "The diagnosis of CFC syndrome is established in a proband with suggestive findings by the identification of a heterozygous pathogenic (or likely pathogenic) variant in BRAF, MAP2K1, MAP2K2, or KRAS by molecular genetic testing."
- "Molecular genetic testing approaches can include a combination of gene-targeted testing (multigene panel) and comprehensive genomic testing (exome sequencing, genome sequencing) depending on the phenotype. Gene-targeted testing requires that the clinician determine which gene(s) are likely involved, whereas genomic testing does not."
- "A RASopathy multigene panel... is most likely to identify the genetic cause of the condition while limiting identification of variants of uncertain significance and pathogenic variants in genes that do not explain the underlying phenotype."

A 2022 expert-authored review on NS stated:¹

- "When the phenotypic findings suggest the diagnosis of Noonan syndrome, molecular genetic testing approaches usually include the use of a multigene panel."
- "Serial single-gene testing can be considered if panel testing is not feasible. 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. Appropriate serial single-gene testing if PTPN11 testing is not diagnostic can be determined by the individual's phenotype (e.g., RIT1 if there is hypertrophic cardiomyopathy, LZTR1 if autosomal recessive inheritance is suspected); however, continued sequential single-gene testing is not recommended as it is less efficient and more costly than panel testing."
- "Since Noonan syndrome occurs through a gain-of-function mechanism and large intragenic deletions or duplications have not been reported, testing for intragenic deletions or duplications is unlikely to result in a diagnosis; however, rare cases have been reported for some genes."
- "Molecular genetic testing approaches can include a combination of gene-targeted testing (multigene panel) and comprehensive genomic testing (exome sequencing or genome sequencing) depending on the phenotype."
- "When the diagnosis of Noonan syndrome has not been considered because an individual has atypical phenotypic features or if some but not all characteristic phenotypic features are present (e.g., a "Noonan-like" phenotype), comprehensive

genomic testing, which does not require the clinical to determine which gene is likely involved, may be used. Exome sequencing is most commonly used; genome sequencing is also possible."

A 2022 expert-authored review on NSML stated:³

- "Molecular genetic testing approaches can include a combination of gene-targeted testing (multigene panel) and comprehensive genomic testing (exome sequencing, genome sequencing) depending on the phenotype."
- "Although gene-targeted deletion/duplication analysis could be considered, the variant detection frequency is unknown and expected to be extremely low."

A 2023 expert-authored review on Costello syndrome stated:²

- "When the clinical findings suggest the diagnosis of Costello syndrome, molecular genetic testing approaches can include single-gene testing or use of a multigene panel."
- "When the diagnosis of Costello syndrome is not considered because an individual has atypical phenotypic features, comprehensive genomic testing does not require the clinician to determine which gene is likely involved. Exome sequencing is most commonly used; genome sequencing is also possible."

A 2014 expert-authored review on NS made the following recommendations:¹⁷

- Noonan syndrome should be considered in anyone with two or more of the following:
 - "Characteristic facial features
 - Developmental delay and/or learning disability
 - Heart defect
 - Pubertal delay and/or infertility
 - Short stature
 - Typical chest deformity
 - Undescended testes
 - First-degree relative who has Noonan syndrome or any of the above features"
- "The diagnosis of Noonan syndrome should be considered in all fetuses with a normal karyotype and increased nuchal translucency, especially when cardiac anomaly, polyhydramnios, and/or multiple effusions are observed [Evidence rating: C]."
- "Management of patients with Noonan syndrome is optimized by adherence to age-specific guidelines that emphasize screening and testing for common health issues [Evidence rating: C]. U.S. and United Kingdom age-specific guidelines are available."
- "Referral to a clinical geneticist for assistance in diagnosis and management of Noonan syndrome is helpful [Evidence rating: C]."
- "The appropriateness and sequence of genetic testing should be determined by a clinical geneticist [Evidence rating: C]. Mutation testing will prove a diagnosis in approximately 70% of cases. Mutation testing may benefit a family if reproductive decisions depend on this information."

Gripp KW, et al (2019) stated the following regarding Costello syndrome:¹⁸

- "Genetic testing coordinated by a genetics professional is important to confirm the diagnosis.
 - HRAS sequencing, or common mutation panel followed by full analysis if common panel is negative.
 - Multi-gene RASopathies panel if diagnosis is unclear or negative HRAS testing.
 - Additional testing may be considered by medical genetics professionals including chromosome microarray and exome testing."

Tafazoli A, et al (2017) stated:¹⁹

- "All cases should be confirmed by molecular testing for appropriate specific treatments and follow-up procedures in addition to making correct genotype-phenotype correlations...Karyotype and copy number analysis are suggested only in cases with intense neurocognitive involvement and are not performed routinely for patients with typical phenotypes of NS."

Roberts AE, et al (2013) stated:⁷

- "Genetic testing can be useful in several scenarios. Because the presentation of cardiofaciocutaneous and Costello syndromes overlaps substantially in the first year of life, genotyping can aid diagnosis. If a patient has a mild or atypical presentation, genotyping could establish the diagnosis. For an adult with suspected Noonan syndrome, establishing the molecular genetic cause will enable preimplantation, prenatal, or postnatal testing if desired. The specific genotype of a child with Noonan syndrome is useful to know in order to provide specific guidance—for example, to address the increased prevalence of hypertrophic cardiomyopathy in RAF1-associated Noonan syndrome or short stature and growth hormone abnormalities in PTPN11-associated Noonan syndrome."

Romano, AA et al (2010) stated:⁸

- "If sequential molecular testing is determined to be indicated (rather than simultaneous chip based analysis):
 - PTPN11 sequencing should be performed first, because this gene explains the highest number of cases
 - If normal, phenotype should be used to guide the choice of the next gene to sequence
 - If developmental delays are absent or mild, CFC syndrome–like skin and hair findings are present, and/or patient is of normal stature, consider SOS1 sequencing
 - If HCM is present, consider RAF1 sequencing
 - For significant developmental delays or cognitive issues, consider KRAS sequencing
 - For sparse, thin, slow-growing hair, consider SHOC2 sequencing
 - If a variant is found, consider testing the parents to provide accurate recurrence risks."

- "...routine karyotyping or copy-number analysis is not recommended at this time for typical NS cases. It may be considered for atypical cases or when there is particularly severe neurocognitive involvement."

Special Considerations

There is considerable debate about when genetic testing for an NSD should be pursued in a pregnancy with abnormal ultrasound findings and absence of a known family history. Some authors recommend that testing for NS be undertaken for any pregnancy with an increased nuchal translucency and normal chromosome studies, even if there are no additional associated abnormalities, while others recommend that testing only be performed if there is at least one additional ultrasound finding, such as polyhydramnios, hydrops fetalis, renal anomalies, distended JLS, hydrothorax, cardiac anomalies or ascites.^{17,20-28}

Note:

This benefit/harm statement only applies to those jurisdictions that do not have Medicare guidance. Based upon the guidelines and evidence provided in the clinical policy, following EviCore's criteria for Noonan spectrum disorder testing will ensure that testing will be available to those members most likely to benefit from a genetic diagnosis. For those not meeting criteria, it ensures alternate diagnostic strategies are considered. However, it is possible that some members who have the condition, but have non-standard features, will not receive an immediate approval for testing.

References

1. Roberts AE. Noonan Syndrome. 2001 Nov 15 [Updated 2022 Feb 17]. In: Adam MP, Feldman J, Mirzaa GM, et al., editors. GeneReviews [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2024. Available at: <https://www.ncbi.nlm.nih.gov/books/NBK1124/>
2. Gripp KW and Rauen KA. HRAS-Costello Syndrome. 2006 Aug 29 [Updated 2023 Dec 21]. In: Adam MP, Feldman J, Mirzaa GM, et al., editors. GeneReviews [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2024. Available at: <https://www.ncbi.nlm.nih.gov/books/NBK1507/>
3. Gelb BD and Tartaglia M. Noonan Syndrome with Multiple Lentigines. 2007 Nov 30 [Updated 2022 June 30]. In: Adam MP, Feldman J, Mirzaa GM, et al., editors. GeneReviews [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2024. Available at: <https://www.ncbi.nlm.nih.gov/books/NBK1383/>
4. Rauen KA. Cardiofaciocutaneous Syndrome. 2007 Jan 18 [Updated 2023 Feb 9]. In: Adam MP, Feldman J, Mirzaa GM, et al., editors. GeneReviews [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2024. Available at: <https://www.ncbi.nlm.nih.gov/books/NBK1186/>
5. van der Burgt I. Noonan syndrome. *Orphanet J Rare Dis*. 2007;2:4.
6. Noonan Syndrome Guideline Development Group. Management of Noonan Syndrome – A Clinical Guideline. University of Manchester: DYSCERNE. Available at: https://rasopathiesnet.org/wp-content/uploads/2014/01/265_Noonan_Guidelines.pdf
7. Roberts AE, Allanson JE, Tartaglia M, Gelb BD. Noonan syndrome. *Lancet*. 2013;381(9863):333-342.
8. Romano AA, Allanson JE, Dahlgren J, et al. Noonan syndrome: Clinical features, diagnosis, and management guidelines. *Pediatrics*. 2010;126:746-759.

9. Tartaglia M, Gelb BD, and Zenker M. Noonan syndrome and clinically related disorders. *Best Pract Res Clin Endocrinol Metab.* 2011;25(1):161-179.
10. Lepri FR, Scavelli R, Digilio MC, et al. Diagnosis of Noonan syndrome and related disorders using target next generation sequencing. *BMC Med Genet.* 2014;15:14.
11. Bhoj EJ, Yu Z, Guan Q, et al. Phenotypic predictors and final diagnoses in patients referred for RASopathy testing by targeted next-generation sequencing. *Genet Med.* 2017;19(6):715-718.
12. Leach NT, Wilson Mathews DR, Rosenblum LS, et al. Comparative assessment of gene-specific variant distribution in prenatal and postnatal cohorts tested for Noonan syndrome and related conditions. *Genet Med.* 2019;21:417-425.
13. Ceyhan-Birsoy O, Miatkowski MM, Hynes E, et al. NGS testing for cardiomyopathy: Utility of adding RASopathy-associated genes. *Hum Mutat.* 2018;39:954-958.
14. Anderson K, Cnota J, James J, et al. Prevalence of Noonan spectrum disorders in a pediatric population with valvar pulmonary stenosis. *Congenit Heart Dis.* 2019;14:264-273.
15. Lisowski C, Kant SG, Stark Z, et al. Copy number variants including RAS pathway genes – How much RASopathy is in the phenotype? *Am J Med Genet Part A.* 2015;167A:2685-2690.
16. Aoki Y, Niihori T, Inoue S, Matsubara Y. Recent advances in RASopathies. *J Hum Genet.* 2016 Jan;61(1):33-9. doi: 10.1038/jhg.2015.114. Epub 2015 Oct 8.
17. Bhambhani V and Muenke M. Noonan Syndrome. *Am Fam Physician.* 2014;89(1):37-43.
18. Gripp KW, Morse LA, Axelrad M, et al. Costello syndrome: Clinical phenotype, genotype and management guidelines. *Am J Med Genet.* 2019;179A:1725-1744.
19. Tafazoli A, Eshraghi P, Koleti ZK, and Abbaszadegan M. Noonan syndrome – a new survey. *Arch Med Sci.* 2017;13(1):215-222.
20. Houweling AC, de Mooij YM, van der Burgt I, et al. Prenatal detection of Noonan syndrome by mutation analysis of the PTPN11 and KRAS genes. *Prenat Diagn.* 2010;30:284-286.
21. Alamillo CML, Fiddler M, and Pergament E. Increased nuchal translucency in the presence of normal chromosomes: what's next? *Cur Opin Obstet Gynecol.* 2012;24(2):102-108.
22. Bakker M, Pajkrt E, Mathijssen IB, and Bilardo CM. Targeted ultrasound examination and DNA testing for Noonan syndrome, in fetuses with increased nuchal translucency and normal karyotype. *Prenat Diagn.* 2011;31:833-840.
23. Croonen EA, Nillesen WM, Stuurman KE, et al. Prenatal diagnostic testing of the Noonan syndrome: genes in fetuses with abnormal ultrasound findings. *Eur J Hum Genet.* 2013;21:936-942.
24. Stuurman KE, Joosten M, van der Burgt I, et al. Prenatal ultrasound findings of rasopathies in a cohort of 424 fetuses: update on genetic testing in the NGS era. *J Med Genet.* 2019;0:1-8.
25. Hakami F, Dillon MW, Lebo M, and Mason-Suares H. Retrospective study of prenatal ultrasound findings in newborns with a Noonan spectrum disorder. *Prenat Diagn.* 2016;36:418-423.
26. Quinn AM, Valcarcel BN, Makhmreh MM, et al. A systematic review of monogenic etiologies of nonimmune hydrops fetalis. *Genet Med.* 2021 Jan;23(1):3-12. doi: 10.1038/s41436-020-00967-0.
27. Mardy AH, Chetty SP, Norton ME, Sparks TN. A system-based approach to the genetic etiologies of non-immune hydrops fetalis. *Prenat Diagn.* 2019 Aug;39(9):732-750. doi: 10.1002/pd.5479.
28. Wagner T, Fahham D, Frumkin A, et al. The many etiologies of nonimmune hydrops fetalis diagnosed by exome sequencing. *Prenat Diagn.* 2022 Jun;42(7):881-889. doi: 10.1002/pd.5977.