Medical Policy

Blue Cross Blue Shield Blue Care Network of Michigan

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(See policy history boxes for previous effective dates)

Title: Genetic Testing for Noonan Spectrum Disorder

Description/Background

Noonan syndrome is an autosomal dominant disorder that is both phenotypically and genetically heterogeneous. It is characterized by short stature, congenital heart defects (especially pulmonic stenosis [narrowing of the pulmonary valves] and hypertrophic cardiomyopathy), a broad or webbed neck, chest wall deformities, and varying degrees of intellectual disability. Lymphatic problems (often beginning prenatally), bleeding disorders (such as difficulties with clotting and easy bruising), undescended testes, hearing deficits, and failure to thrive are also common among individuals with this condition. In addition, individuals with Noonan syndrome generally have a characteristic facial appearance that changes with the age of the patient, but often includes widely spaced eyes that are down-slanting, ptosis (drooping eyelids), and low-set and posteriorly rotated ears.

Noonan syndrome, which is believed to affect between 1 in 1000 and 1 in 2500 individuals, is now known to be part of a clinical continuum associated with hyperactive RAS (rat sarcoma viral oncogene) signaling. Syndromes with features and a pathogenesis overlapping those of Noonar syndrome include cardiofaciocutaneous (CFC) syndrome, LEOPARD syndrome, and Costello syndrome. All four disorders result from deleterious variants in genes known to be involved in the RAS/mitogen-activated protein kinase (MAPK) pathway. Variants in many genes have been detected in patients with Noonan syndrome, including the following: protein tyrosine phosphatase, non-receptor type 11 (*PTPN11*); Son of Sevenless, homolog 1 (*SOS1*); Kirsten rat sarcoma viral oncogene (*KRAS*); neuroblastoma rat sarcoma viral oncogene (*NRAS*); murine leukemia viral oncogene homolog 1 (*RAF1*); murine sarcoma viral oncogene homolog B1 (*BRAF*); suppressor of clear, homolog 2 (*SHOC2*); and MAPK/extracellular signal-regulated kinase (ERK) kinase 1 (*MEK1*). *PTPN11* gene variants are by far the most common, accounting for approximately 50% of Noonan syndrome cases. Variants associated with Noonan syndrome are inherited in an autosomal dominant manner. Therefore, each child of an affected individual has a 50% chance of inheriting the causative variant and having the condition. While many

individuals with Noonan syndrome have an affected parent, a significant proportion of cases are sporadic, resulting from a de novo gene variant in one of the causative genes.

Noonan syndrome gene testing is performed by direct sequence analysis of one or more genes known to be associated with this condition, including *PTPN11*, *SOS1*, *KRAS*, *NRAS*, *RAF1*, *BRAF*, *SHOC2,* and *MEK1*. However, the genes analyzed and the precise methodology used (i.e., traditional gene sequencing versus sequencing by hybridization to a microarray, also known as resequencing) vary by laboratory. Noonan syndrome gene testing may be performed for diagnostic purposes in individuals exhibiting the physical and developmental characteristics of the condition. Prenatal or preimplantation genetic diagnosis is also possible for patients carrying a gene variant known to cause Noonan syndrome. In addition, prenatal diagnosis may be performed for fetuses demonstrating features of Noonan syndrome by ultrasonography.

Currently, there is no standardized system for establishing a clinical diagnosis of Noonan syndrome. However, many clinicians use the diagnostic criteria proposed by van der Burgt and colleagues summarized in Table 1, when evaluating patients suspected of having this disorder.[21, 22]

Table 1. Proposed Criteria for a Clinical Diagnosis of Noonan Syndrome*

System/Feature	Major Criteria	Minor Criteria
Face	Typical facial appearance	Suggestive facial appearance
Heart	Pulmonary valve stenosis and/or typical ECG	Other heart defect
Growth	Height <3rd percentile	Height between 3rd and 10th percentiles
Chest Wall	Pectus carinatum or excavatum	Broad thorax
Family History	First-degree relative w/definite NS	First-degree relative w/features suggestive of NS
Other	All of the following: intellectual disability; undescended testes (males); and lymphatic dysplasia	One of the following: Intellectual disability; undescended testes; or lymphatic dysplasia

Key: ECG, electrocardiogram; NS, Noonan Syndrome
*As proposed by van der Burgt and colleagues (1984), a definite diagnosis of Noonan syndrome may be established in one of four ways: (1) presence of the typical facial appearance along with a second major criterion; (2) typical facial appearance in combination with two minor criteria; (3) suggestive facial appearance in combination with two major criteria; or (4) suggestive facial appearance in combination with three other minor criteria.

Regulatory Status

Genetic tests are regulated under the Clinical Laboratory Improvement Amendments (CLIA).

Medical Policy Statement

Genetic testing for Noonan Syndrome does not provide any additional clinically relevant information in the diagnosis or treatment of this condition over currently available tests or procedures. The test is therefore experimental/investigational.

Inclusionary and Exclusionary Guidelines

N/A

CPT/HCPCS Level II Codes *(Note: The inclusion of a code in this list is not a guarantee of coverage. Please refer to the medical policy statement to determine the status of a given procedure.)*

Established codes:

N/A

Other codes (investigational, not medically necessary, etc.):

81442

Rationale

Noonan syndrome is a phenotypically and genetically heterogeneous condition that may be caused by variants in one of several genes involved in *RAS* signaling: *PTPN11*, *SOS1*, *KRAS*, *NRAS*, *RAF1*, *BRAF*, *SHOC2*, and *MEK1*. Because of this heterogeneity, Noonan syndrome gene testing is often a complicated, multistep process.[1]

The analysis of Noonan-related genes is performed by direct sequencing of coding exons and intron-exon boundaries, either by traditional dideoxynucleotide-based sequencing or sequencing by hybridization to a microarray.[1] While gene sequencing is a well-established methodology, studies examining the analytical validity of Noonan syndrome gene testing were not identified. Studies examining the clinical validity of the analysis, however, do indicate that the test is limited in that it may identify sequence variants of unknown clinical significance.[17] In addition, the testing of all eight genes known to be associated with Noonan syndrome will not identify the causative gene variant in all clinically diagnosed patients.[1]

Analytical Validity
No studies were identified that examined the analytical validity of Noonan syndrome gene testing utilizing direct sequence analysis or resequencing.

Clinical Validity
Numerous studies have examined the frequency of pathogenic variants in the genes associated with Noonan syndrome. Some of these studies have evaluated patients for the presence of genotype-phenotype correlations. The below tables summarize the studies evaluating the roles of *SOS1, KRAS, PTPN11*, and *RAF1* variants.

Table 2. *PTPN11* Variant Frequency and Genotype/Phenotype Correlations

Reference	Pt Population	Methodology	*PTPN11* Variant Frequency	Genotype – phenotype correlations
Tartaglia et al. (2001)	22 NS pts (family hx status unspecified)	Direct sequencing	11/22 (50%)	N/A
Maheshwari et al. (2002)	13 NS pts (family hx status unspecified)	Direct sequencing	5/13 (38.5%)	N/A
Tartaglia et al. (2002)	119 NS pts (70 sporadic, 49 familial)	dHPLC and sequencing	54/119 (45%)	Pulmonic stenosis was more common among *PTPN11*-positive pts than *PTPN11*-negative individuals: 36/51 (70.6%) vs. 30/65 (46.2%) (*P*=0.008) HCM was less common among *PTPN11*-positive pts than *PTPN11*-negative individuals: 3/51 (5.9%) vs. 17/65 (26.1%) (*P*=0.004)
Musante et al. (2003)	79 NS pts (68 sporadic, 11 familial)	dHPLC and sequencing	23/79 (29.1%)	N/A
Jongmans et al. (2004)	150 NS pts (of 51 pts w/clinical details available, 35 were sporadic and 16 familial cases)	Not specified	68/150 (45.3%)	While cryptorchidism, typical facial features, and pulmonic stenosis were frequent among PTPN11-positive pts (90% of males, 86%, and 67%, respectively), no statistically significant genotype-phenotype correlations were reported.
Yoshida et al. (2004)	45 NS pts (43 sporadic, 2 familial)	Direct sequencing	18/45 (40%)	PTPN11-positive individuals were more likely to exhibit the following when compared w/ PTPN11-negative pts: Pulmonic stenosis: 10/18 (55.6%) vs. 6/27 (22.2%) (P=0.02) ASD: 10/18 (55.6%) vs. 4/27 (14.8%) (P=0.005) Hematologic abnormalities: 5/18 (27.8%) vs. 0/27 (0%) (P=0.007)
Zenker et al. (2004)	57 NS pts (48 sporadic, 9 familial)	Direct sequencing	34/57 (59.6%	PTPN11-positive individuals were more likely to exhibit the following when compared w/ PTPN11-negative pts: Pulmonic stenosis: 30/34 (88%) vs. 12/23 (52%) (P=0.005) Typical facial features: 31/34 (91%) vs. 15/23 (65%) (P=0.02) Height <3rd percentile: 28/34 (82%) vs. 13/23 (57%) (P=0.041) Easy bruising: 14/34 (41%) vs. 1/23 (4%) (P=0.002) Pectus abnormalities: 28/34 (82%) vs. 13/23 (57%) (P=0.041)
Binder et al. (2005)	27 NS pts (at least 2 familial, family hx of cohort unspecified)	Direct sequencing	14/27 (51.9%)	*N/A*

Chan et al. (2006)	51 NS pts (39 sporadic, 3 familial)	Direct sequencing	32/51 (62.7%	*N/A*
Hung et al. (2007)	34 NS pts (family hx not specified)	Direct sequencing	13/34 (38%	PTPN11-positive pts were more likely to have septal defects when compared w/ PTPN11-negative individuals: 69% vs. 33% (P=0.05)
Lee et al. (2007)	14 NS pts (12 sporadic, 2 w/unknown family hx)	Direct sequencing	7/14 (50%)	*N/A*
Ferreira et al. (2008)	49 NS pts (family hx not specified)	Direct sequencing	19/49 (39%)	Pulmonic stenosis was more common among PTPN11-positive pts than PTPN11-negative individuals: 47% vs. 7% (P<0.05)
Ferrero et al. (2008)	38 NS pts (37 sporadic, 1 familial)	Direct sequencing	12/38 (31.5%)	Pulmonic stenosis was more common among PTPN11-positive pts than PTPN11-negative individuals: 12/14 (85.7%) vs. 8/26 (30.8%) (P=0.0006)

The data summarized in Table 2 indicate that up to 62.7% of patients clinically diagnosed with Noonan syndrome harbor deleterious variants in the *PTPN11* gene. More specifically, the majority of studies have shown the detection rate for *PTPN11* gene testing to be between 35% and 60% for patients diagnosed with Noonan syndrome according to the criteria proposed by van der Burgt and colleagues (see Table 1) The most common genotype-phenotype correlation detected in the above studies was an association between the presence of a *PTPN11* gene variant and an increased chance of pulmonic stenosis. In addition, two studies reported that *PTPN11*-positive patients were more likely to have a septal defect, such as an atrial septal defect (ASD).

Table 3. *SOS1* Variant Frequency and Genotype/Phenotype Correlations

Reference	**Pt Population**	**Methodology**	**SOS1 Variant Frequency**	**Genotype – phenotype correlations**
Lee et al. (2007)	14 NS pts (12 sporadic, 2 with unknown family hx)	Direct sequencing	0/14 (0%)	N/A
Tartaglia et al. (2007)	129 *PTPN11*- and *KRAS*-negative NS pts (family hx status unspecified)	dHPLC, direct sequencing, and/or resequencing	22/129 (17.1%)	Short stature (height <3rd percentile) was less common among *SOS1*-positive pts than for individuals w/ *PTPN11* variants: 2/15 (13%) vs. 45/64 (70%) (*P*<0.001) Intellectual disability was also less common: 1/16 (6%) vs. 21/59 (36%) for *PTPN11*-positive pts (*P*<0.05) Pectus deformities were more common among *SOS1*-positive pts than in those w/ *PTPN11* variants: 16/16 (100%) vs. 46/61 (75%) (*P*<0.05)
Zenker et al. (2007)	53 pts w/ NS, 80 w/ possible NS (mild or atypical), and 11 w/ NS vs. CFCS (all were *PTPN11*- and	Direct sequencing	14/53 NS (26%) 4/80 possible	Individuals w/ *SOS1* variants were significantly *less* likely than pts w/ *PTPN11* variants to have the following: Undescended testes: 5/11 (45.5%) vs. 75/94 (80%) Easy bruising: 3/25 (12%) vs. 46/90 (51%)

	KRAS-negative; family hx status unspecified)		NS (5%) 4/11 NS vs. CFCS (36%)	Intellectual disability as defined by the need for special education: 5/24 (20.8%) vs. 71/164 (43%) (*P*<0.05 for all) They were significantly *more* likely than pts w/ *PTPN11* variants to have ectodermal manifestations: 58% vs. 6% for keratosis pilaris or hyperkeratotic skin (*P*<0.05)
Ferrero et al. (2008)	38 NS pts (37 sporadic, 1 familial)	Direct sequencing	1/38 (2.6%)	N/A
Ko et al. (2008)	59 NS pts (56 sporadic, 3 familial)	Direct sequencing	10/59 (16.9%)	Intellectual disability was less common among pts w/ *SOS1* variants: *SOS1*-positive: 0/10 (0%) *PTPN11*-positive: 4/15 (27%) *RAF1*-positive: 2/3 (66.7%) Variant-negative: 13/28 (46%) (*P*<0.05 for all)
Nyström et al. (2008)	23 *PTPN11*-negative NS pts (family hx status unspecified)	Direct sequencing of exons 3, 6, 10, 14, and 16	0/23 (0%)	N/A
Longoni et al. (2010)	24 *PTPN11*- and *KRAS*-negative NS pts (all sporadic)	Direct sequencing	4/24 (6%)	N/A

The data summarized in Table 3 indicate that up to 16.9% of patients clinically diagnosed with Noonan syndrome, who have not had previous testing, harbor deleterious variants in the *SOS1* gene. The detection rate, however, increases dramatically when considering only those patients who have previously tested negative for both *PTPN11* and *KRAS* gene variants; in this case, the frequency of *SOS1* gene variants is up to 26%. From the studies summarized above, the most common genotype-phenotype correlation identified was an association between the presence of an *SOS1* gene variant and a reduced likelihood of intellectual disability. Other correlations include an increased chance of ectodermal anomalies and pectus deformities in *SOS1*-positive individuals, and a decreased chance of short stature (with a height < 3rd percentile), undescended testes, and easy bruising, when compared with patients harboring *PTPN11* gene variants.

Table 4. *KRAS* Variant Frequency and Genotype/Phenotype Correlations

Reference	Pt Population	Methodology	KRAS Variant Frequency	Genotype – phenotype correlations
Carta et al. (2006)	87 *PTPN11*-negative NS pts (family hx status unspecified)	dHPLC followed by sequencing	2/87 (2.3%)	Both pts were considered to have severe NS, w/ features overlapping those of CFCS and CS; however, a statistical analysis of genotype-phenotype correlations was not performed.
Lee et al. (2007)	14 NS pts (12 sporadic, 2 w/ unknown family hx)	Direct sequencing	0/14 (0%)	N/A

Zenker et al. (2007)	236 NS pts (family hx status unspecified)	Direct sequencing	7/236 (2.1%)	All *KRAS*-positive pts had some degree of intellectual disability; however, statistical analyses of genotype-phenotype correlations were not reported.
Ferrero et al. (2008)	38 NS pts (37 sporadic, 1 familial)	Direct sequencing	0/38 (0%)	N/A
Ko et al. (2008)	59 NS pts (56 sporadic, 3 familial)	Direct sequencing	1/59 (1.7%)	N/A
Nystrom et al. (2008)	23 *PTPN11*-negative NS pts (family hx status unspecified)	Direct sequencing	0/23 (0%)	N/A
Lo et al. (2009)	80 NS pts (family hx status unspecified)	Direct sequencing	2/80 (2.5%)	N/A

The majority of studies summarized in Table 4 indicate that up to 2.5% of patients clinically diagnosed with Noonan syndrome harbor deleterious variants in the *KRAS* gene. No statistically significant genotype-phenotype correlations were reported by any studies.

Table 5. *RAF1* Variant Frequency and Genotype/Phenotype Correlations

Reference	Pt Population	Methodology	*RAF1* Variant Frequency	Genotype – phenotype correlations
Pandit et al. (2007)	231 *PTPN11*-, *SOS1*-, and *KRAS*-negative NS pts (family hx status unspecified)	dHPLC and sequence analysis	18/231 (7.8%)	*RAF1*-positive pts were more likely to have HCM (19/25 [76%]) vs. an HCM prevalence of 18% in NS in general (*P*=0.0001). In addition, individuals w/ variants involving the residues Asp486 or Thr491 were less likely to have HCM than those w/ variants clustered around Ser259 and Ser612: 1/6 (16.7%) vs. 18/19 (94.7%) (*P*<0.0001)
Razzaque et al. (2007)	58 NS pts (30 of whom were *PTPN11*-, *SOS1*-, *KRAS*-, and *HRAS*-negative; family hx status unspecified)	Direct sequencing	10/58 (17.2%)	8/10 (80%) *RAF1*-positive pts, all w/ variants clustered in the CR2 (conserved region 2) domain, demonstrated HCM. In contrast, only 6/23 (26.1%) *PTPN11*-positive patients had HCM (*P* value not provided).
Ferrero et al. (2008)	38 NS pts (37 sporadic, 1 familial)	Direct sequencing	0/38 (0%)	N/A
Ko et al. (2008)	59 NS pts (56 sporadic, 3 familial)	Direct sequencing of exons 7, 14, and 17	3/59 (5.1%)	The frequency of HCM among *RAF1*-positive pts was significantly higher than the frequency among NS pts w/out an identifiable variant in *PTPN11*, *SOS1*, *KRAS*, or *RAF1*: 3/3 (100%) vs. 6/21 (21%) (*P*=0.009)
Kobayashi et al. (2010)	44 NS pts negative for *PTPN11*, *SOS1*, *KRAS*, *HRAS*, *BRAF*, *MEK1*,	Direct sequencing	11/44 (25%)	N/A

	and *MEK2* variants (family hx status unspecified)			
Longoni et al. (2010)	24 *PTPN11*- and *KRAS*-negative NS pts (family history)	Direct sequencing of select exons (unspecified)	1/24 (4.2%)	N/A

The studies summarized in Table 5 indicate that up to 25% of Noonan syndrome patients who have previously tested negative for variants in other Noonan-related genes (including *PTPN11*, *SOS1*, and *KRAS*) may harbor *RAF1* gene variant. However, the detection rate is expected to be much lower for patients who have had no previous genetic testing, as indicated by the detection rates of 0% and 5.1% reported by Ferrero and colleagues (2008) and Ko and colleagues (2008). Genotype-phenotype correlation studies suggest that hypertrophic cardiomyopathy is more common among Noonan syndrome patients with *RAF1* gene variants compared with those patients with no detectable variants in the *RAF1* gene.

Several reports were identified which examined the frequency of sequence variants in other genes known to be associated with Noonan syndrome (i.e., genes other than *PTPN11*, *SOS1*, *KRAS*, and *RAF1*) and any possible genotype-phenotype correlations that may exist.

Lee and colleagues investigated the role of the *GRB2*, *HRAS*, *NRAS*, *BRAF*, *MEK1*, and *MEK2* genes in this condition. The coding exons of each gene were analyzed by direct sequencing in 14 Noonan syndrome patients (diagnostic criteria not specified). Pathogenic variants were not detected in any of the six genes. However, a variant of unknown clinical significance, located in the 3' untranslated region of *HRAS*, was identified in a single patient.[11]

Nava and colleagues investigated the detection rate of *BRAF*, *MEK1*, and *MEK2* gene testing among patients clinically diagnosed with Noonan syndrome (diagnostic criteria not specified). Testing was performed by direct sequence analysis of all coding exons and intron-exon boundaries. Of 70 *PTPN11*- and *SOS1*-negative Noonan syndrome patients, all of whom had a negative family history, 3 (4.3%) were found to harbor *MEK1* sequence variants. No *BRAF* or *MEK2* variants were detected.[20]

Razzaque and colleagues studied the frequency of *BRAF* variants among 58 clinically diagnosed Noonan syndrome patients, 30 of whom were known to be negative for variants in the *PTPN11*, *KRAS*, *HRAS*, and *SOS1* genes. The criteria used to diagnose these patients were not described and their family history status was not reported. Two different *BRAF* variants were detected in a single Noonan syndrome patient, yielding a detection rate of 1 in 58 (1.7%).[23]

Nyström and colleagues performed sequence analysis of the *BRAF*, *MEK1*, and *MEK2* genes (coding exons and flanking intron sequences) in 23 *PTPN11*-negative Noonan syndrome patients (family history status unspecified). The diagnosis of each patient was made using a diagnostic checklist (Roberts et al., 2006). One (4.3%) patient was found to carry a *BRAF* gene variant. No variants in either *MEK1* or *MEK2* were detected.[13]

Cirstea and colleagues studied the role of the *NRAS* gene in the pathogenesis of Noonan syndrome by performing dHPLC and sequence analysis in a large cohort of Noonan syndrome patients. Of 733 patients clinically diagnosed with Noonan syndrome (diagnostic criteria not provided)—all of whom were negative for variants in the *PTPN11*, *KRAS*, *SOS1*, *RAF1*, *BRAF*, *MEK1*, and *MEK2* genes—4 (0.5%) were found to carry *NRAS* sequence variants. Of 47 patients with CFC syndrome and 137 patients with a phenotype suggestive of either Noonan syndrome or CFC syndrome, none (0%) harbored *NRAS* gene variants. While all *NRAS*-positive individuals were described as having typical features of Noonan syndrome, specific genotype-phenotype correlations were not assessed.[4]

A couple of studies examined the frequency of genomic imbalances, specifically duplications, among Noonan syndrome patients.

Graham and colleagues used array-based comparative genomic hybridization (aCGH), fluorescence in situ hybridization (FISH), and/or quantitative polymerase chain reaction (PCR) to test for genomic imbalances in 250 patients with possible Noonan syndrome. A total of 124 patients were clinically diagnosed with Noonan syndrome based on the criteria delineated by van der Burgt and colleagues (see Table 1). Of these, 53 cases had features suggestive of Noonan syndrome but were considered more atypical. The remaining 73 patients were referred for testing because a clinician suspected Noonan syndrome. All patients were negative for sequence variants in the *PTPN11*, *SOS1*, *KRAS*, and *RAF1* genes. A single patient (0.8% for those with a clinical diagnosis; 0.4% for the entire population) who had been clinically diagnosed with Noonan syndrome was found to carry a duplication of the chromosomal region containing the *PTPN11* gene (12q24.13). Of note, a subset of the clinically diagnosed patients (n=36) were also examined for sequence variants in the 3 untranslated region of *PTPN11* (using dHPLC), and none were detected.[8]

Nyström and colleagues utilized MLPA to test 44 Noonan syndrome patients, all negative for sequence variants in *PTPN11* (exons 2, 3, 4, 7, 8, 12, and 13), *SOS1* (all exons), *RAF1* (all exons), *KRAS* (all exons), *BRAF* (exons 6, 11, 12, 14, and 15), *MEK1* (exons 2 and 3), *MEK2* (exons 2, 3, and 7), and *SHOC2* (p.Ser2Gly variant only). After validating the MLPA probes using 15 control samples, each patient was tested for duplications involving the *PTPN11*, *SOS1*, *RAF1*, *KRAS*, *BRAF*, *MEK1*, and *MEK2* genes. No (0%) changes in gene dosage were detected, suggesting duplication of these genes is a rare cause of Noonan syndrome.[13]

Three reports were identified related to the clinical validity of Noonan syndrome gene testing in prenatal diagnosis. Schlüter and colleagues described a case in which Noonan syndrome was suspected based on ultrasonographic findings. At 23 weeks gestation, a female fetus presented with growth retardation, a large cystic hygroma, massive pleural effusion, and ascites. Both parents were phenotypically normal. Fetal karyotype was normal (46, XX). *PTPN11* gene testing was performed by sequence analysis using genomic DNA obtained from amniocytes. A missense variant in *PTPN11* was identified (p.Ser285Phe). Delivery was induced at 33 weeks gestation, and the infant died at 9 hours of age due to severe pulmonary hypoplasia. An evaluation after birth revealed features consistent with Noonan syndrome, including right ventricular hypertrophy, hypertelorism, and low-set and posteriorly rotated ears.[14]

Lee and colleagues examined the detection rate of *PTPN11* gene testing in fetuses with ultrasonographic findings consistent with Noonan syndrome. A retrospective review of 134

cases where *PTPN11* gene testing had been requested for prenatal diagnosis was performed. Test samples included specimens from amniocentesis, chorionic villus sampling, and products of conception. Cases where a family member was known to carry a *PTPN11* gene variant were previously excluded. All fetuses had ≥ 1 ultrasonographic finding suggestive of Noonan syndrome. A total of 77 cases had a normal karyotype and 4 were negative for a chromosome 22q11.2 deletion. One fetus was mosaic for trisomy 16. The two most common referral indications were an abnormal nuchal translucency (n=56 [44%]) and cystic hygroma (n=52 [48%]). Other indications included pulmonic stenosis, abnormal fluid collection (including hydrops, ascites, and cyclothorax), clubfoot, and low amniotic fluid levels. Of all 134 fetuses, 12 (9%) were found to carry *PTPN11* gene variants. The detection rate among fetuses with cystic hygroma (5 of which had additional findings suggestive of a congenital heart defect) or increased nuchal translucency was 16% and 2%, respectively. The detection rate among fetuses with *isolated* cystic hygroma was 11%. Follow-up information was available for five of the variant-positive fetuses. In one case, the parents elected to terminate the pregnancy. A second case resulted in intrauterine fetal demise. In the remaining three cases, the parents elected to continue the pregnancy and infants were born with phenotypes consistent with Noonan syndrome.[11]

In a similar study, Houweling and colleagues investigated the likelihood of *PTPN11* and *KRAS* gene variants in fetuses exhibiting an abnormal nuchal translucency in the presence of a normal fetal karyotype. Of 55 cases retrospectively reviewed, 19 requested *PTPN11* gene testing and 16 requested analysis of the *KRAS* gene. The specimen types provided were not reported. *PTPN11* variants were identified in 2 (10.5%) fetuses, and a single (6.3%) *KRAS* gene variant was detected in a third. They further described the three cases in which the results of the prenatal testing were used for reproductive decision making. The fetus in case 1, who had a nuchal translucency of 14 millimeters (mm), also exhibited distended jugular lymphatic sacs, pleural fluid, and dilated renal pelvis. *PTPN11* gene testing was negative, but sequence analysis of *KRAS* revealed a p.Thr58Ile variant. Based on this finding, the parents elected to terminate the pregnancy. The fetus in case 2, with a nuchal translucency of 5.2 mm, also exhibited distended jugular lymphatic sacs. Like the parents in case 1, these parents elected to terminate the pregnancy on the basis of this result. The fetus in case 3, with a nuchal translucency of 8.2 mm, also demonstrated distended jugular lymphatic sacs, pericardial effusion, an atrioventricular septal defect, and dilation of the renal pelvis. A *PTPN11* gene variant (p.Asp61His) was also detected in this fetus and, like the previous cases, led the parents to terminate the pregnancy.[9]

Finally, two studies were identified that examined the effect of *PTPN11* genotype on the treatment of Noonan syndrome patients with growth hormone therapy. As a part of their study examining the role of *PTPN11* in Noonan syndrome, Binder and colleagues reviewed the effect of gene status on growth hormone treatment. Of the 27 patients in their cohort, 11 had received at least 1 year of growth hormone therapy, 8 of whom carried *PTPN11* gene variants. After 1 year of treatment, *PTPN11*-negative patients had a greater increase in height standard deviation (SD) scores when compared with patients carrying *PTPN11* gene variants (+1.26 ± 0.36 SD versus +0.66 ± 0.21 SD; *P*=0.007), suggesting that *PTPN11* genotype may affect response to growth hormone treatment in Noonan syndrome patients.[2]

In a similar study, Ferreira and colleagues performed a retrospective analysis of 14 Noonan syndrome patients who had been treated with growth hormone for 3 years. Of these patients, 7 carried variants in the *PTPN11* gene while 7 were *PTPN11*-negative. The status of other

Noonan-related genes in the *PTPN11*-negative patients was not known. *PTPN11* variant carriers were found to have a significantly smaller increase in insulin-like growth factor 1 (IGF1) levels compared with *PTPN11*-negative patients (86 ± 67 micrograms/liter [µg/L] versus 202 ± 93 µg/L; *P*=0.03). Moreover, *PTPN11*-positive patients had significantly smaller gains in height SD scores relative to baseline after the 3 years of treatment (+0.8 ± 0.4 SD versus +1.7 ± 0.4 SD; *P*<0.01). This suggests that *PTPN11*-positive Noonan syndrome patients may not respond as well to growth hormone treatment as their *PTPN11*-negative counterparts.[6]

Clinical Utility
Evidence regarding the clinical utility of Noonan syndrome gene testing is limited to small case series demonstrating its use in facilitating reproductive decision making.[9,11]

SUMMARY OF EVIDENCE
Noonan syndrome gene testing involves the direct sequence analysis of genes known to be associated with this condition, specifically, *PTPN11*, *SOS1*, *KRAS*, *NRAS*, *RAF1*, *BRAF*, *SHOC2*, and *MEK1*. While there is some evidence supporting the clinical validity of this analysis for the purpose of diagnosing Noonan syndrome in symptomatic individuals and at-risk fetuses, data regarding the analytical validity were not located, and evidence supporting the clinical utility of Noonan syndrome gene testing is limited to a small case series demonstrating some use in reproductive decision making.

Government Regulations

National:
Medicare does not have a national policy regarding genetic testing for Noonan Syndrome.

Local:
No local determination for genetic testing for Noonan Spectrum Disorders.

(The above Medicare information is current as of the review date for this policy. However, the coverage issues and policies maintained by the Centers for Medicare & Medicare Services [CMS, formerly HCFA] are updated and/or revised periodically. Therefore, the most current CMS information may not be contained in this document. For the most current information, the reader should contact an official Medicare source.)

Related Policies

Genetic Testing and Counseling

References

1. Allanson JE. Noonan Syndrome. Updated October 7, 2008. GeneReviews [website].
2. Binder G, Neuer K, Ranke MB, Wittekindt NE. PTPN11 mutations are associated with mild growth hormone resistance in individuals with Noonan syndrome. *J Clin Endocrinol Metab*. 2005;90(9):5377-5381.
3. Chan D, Lo I, Lam A, et al. A clinical and molecular study of 51 Chinese families with Noonan syndrome. *Hong Kong J Paediatr*. 2006;11(4):290-296.
4. Cirstea IC, Kutsche K, Dvorsky R, et al. A restricted spectrum of NRAS mutations causes Noonan syndrome. *Nat Genet*. 2010;42(1):27-29.

5. Cordeddu V, Di Schiavi E, Pennacchio LA, et al. Mutation of SHOC2 promotes aberrant protein N-myristoylation and causes Noonan-like syndrome with loose anagen hair. *Nat Genet*. 2009;41(9):1022-1026.
6. Ferreira LV, Souza SC, Montenegro LR, et al. Analysis of the PTPN11 gene in idiopathic short stature children and Noonan syndrome patients. *Clin Endocrinol (Oxf)*. 2008;69(3):426-431.
7. Ferrero GB, Baldassarre G, Delmonaco AG, et al. Clinical and molecular characterization of 40 patients with Noonan syndrome. *Eur J Med Genet*. 2008;51(6):566-572.
8. Graham JM Jr, Kramer N, Bejjani BA, et al. Genomic duplication of PTPN11 is an uncommon cause of Noonan syndrome. *Am J Med Genet A*. 2009;149A(10):2122-2128.
9. Houweling A, de Mooij Y, van der Burgt I, Yntema HG, Lachmeijer AM, Go AT. Prenatal detection of Noonan syndrome by mutation analysis of the PTPN11 and the KRAS genes. *Prenat Diagn*. 2010;30(3):284-286.
10. Kobayashi T, Aoki Y, Niihori T, et al. Molecular and clinical analysis of RAF1 in Noonan syndrome and related disorders: dephosphorylation of serine 259 as the essential mechanism for mutant activation. *Hum Mutat*. 2010;31(3):284-294.
11. Lee KA, Williams B, Roza K, et al. PTPN11 analysis for the prenatal diagnosis of Noonan syndrome in fetuses with abnormal ultrasound findings. *Clin Genet*. 2009;75(2):190-194.
12. Nyström A, Ekvall S, Berglund E, et al. Noonan and cardio-facio-cutaneous syndromes: two clinically and genetically overlapping disorders. *J Med Genet*. 2008;45(8):500-506.
13. Nyström A, Ekvall S, Thuresson A, et al. Investigation of gene dosage imbalances in patients with Noonan syndrome using multiplex ligation-dependent probe amplification analysis. *Eur J Med Genet*. 2010;53(3):117-121.
14. Schlüter G, Steckel M, Schiffmann H, et al. Prenatal DNA diagnosis of Noonan syndrome in a fetus with massive hygroma colli, pleural effusion and ascites. *Prenat Diagn*. 2005;25(7):574-576.
15. Tartaglia M, Gelb B. Noonan syndrome and related disorders: genetics and pathogenesis. *Annu Rev Genomics Hum Genet*. 2005;6:45-68.
16. Yoshida R, Hasegawa T, Hasegawa Y, et al. Protein-tyrosine phosphatase, nonreceptor type 11 mutation analysis and clinical assessment in 45 patients with Noonan syndrome. *J Clin Endocrinol Metab*. 2004;89(7):3359-3364.
17. Zenker M, Buheitel G, Rauch R, et al. Genotype-phenotype correlations in Noonan syndrome. *J Pediatr*. 2004;144(3):368-374.
18. Ko JM, Kim J, Kim G, Yoo H. PTPN11, SOS1, KRAS, and RAF1 gene analysis, and genotype-phenotype correlation in Korean patients with Noonan syndrome. *J Hum Genet*. 2008;53(11-12):999-1006.
19. Longoni M, Moncini S, Cisternino M, et al. Noonan syndrome associated with both a new Jnk-activating familial SOS1 and a de novo RAF1 mutations. *Am J Med Genet A*. 2010;152(9):2176-2184.
20. Nava C, Hanna N, Michot C, et al. Cardio-facio-cutaneous and Noonan syndromes due to mutations in the RAS/MAPK signaling pathway: genotype-phenotype relationships and overlap with Costello syndrome. *J Med Genet*. 2007;44(12):763-771.
21. van der Burgt I, Berends E, Lommen E, van Beersum S, Hamel B, Mariman E. Clinical and molecular studies in a large Dutch family with Noonan syndrome. *Am J Med Genet*. 1994;53(2):187-191.
22. Rohrer T. Noonan syndrome: introduction and basic clinical features. *Horm Res*. 2009;(72 Suppl 2):3-7.
23. Razzaque MA, Nishizawa T, Komoike Y, et al. Germline gain-of-function mutations in RAF1 cause Noonan syndrome. *Nat Genet*. 2007;39(8):1013-1017.

The articles reviewed in this research include those obtained in an Internet based literature search for relevant medical references through January 2024, the date the research was completed.

Joint BCBSM/BCN Medical Policy History

Policy Effective Date	BCBSM Signature Date	BCN Signature Date	Comments
5/1/16	2/16/16	2/16/16	Joint policy established
5/1/17	2/21/17	2/21/17	Routine policy maintenance. No change in policy status.
5/1/18	2/20/18	2/20/18	Routine policy maintenance. No change in policy status.
5/1/19	2/19/19		Routine policy maintenance. No change in policy status.
5/1/20	2/18/20		Routine policy maintenance. No change in policy status.
5/1/21	2/16/21		Routine policy maintenance. No change in policy status.
5/1/22	2/15/22		Routine policy maintenance, added reference #10, no change in policy status.
5/1/23	2/21/23		Routine policy maintenance, no change in policy status. (ds)
5/1/24	2/20/24		Routine policy maintenance, no change in policy status. Vendor managed: N/A (ds)

Next Review Date: 1st Qtr. 2025

BLUE CARE NETWORK BENEFIT COVERAGE
POLICY: GENETIC TESTING FOR NOONAN SPECTRUM DISORDERS

I. Coverage Determination:

Commercial HMO (includes Self-Funded groups unless otherwise specified)	Not covered
BCNA (Medicare Advantage)	See government section
BCN65 (Medicare Complementary)	Coinsurance covered if primary Medicare covers the service.

II. Administrative Guidelines:

- The member's contract must be active at the time the service is rendered.
- Coverage is based on each member's certificate and is not guaranteed. Please consult the individual member's certificate for details. Additional information regarding coverage or benefits may also be obtained through customer or provider inquiry services at BCN.
- The service must be authorized by the member's PCP except for Self-Referral Option (SRO) members seeking Tier 2 coverage.
- Services must be performed by a BCN-contracted provider, if available, except for Self-Referral Option (SRO) members seeking Tier 2 coverage.
- Payment is based on BCN payment rules, individual certificate and certificate riders.
- Appropriate copayments will apply. Refer to certificate and applicable riders for detailed information.
- CPT - HCPCS codes are used for descriptive purposes only and are not a guarantee of coverage.