Test Specific Guidelines

Noonan Spectrum Disorder Genetic Testing

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Introduction

Noonan spectrum disorder genetic testing is addressed by this guideline.

Procedures Addressed

The inclusion of any procedure code in this table is provided for informational purposes and is not a guarantee of coverage nor an indication that prior authorization is required.

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

Procedures addressed by this guideline	Procedure codes
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

What Is Noonan Spectrum Disorder?

Definition

Noonan spectrum disorders (NSDs) are a group of disorders that includes Noonan syndrome (NS), Cardiofaciocutaneous (CFC) syndrome, Noonan syndrome with multiple lentigines (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. 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 (~25%), KRAS (<2%), and MAP2K1.

NMSL or LEOPARD syndrome: Caused by mutations in PTPN11 (90%), RAF1 (<5%), BRAF, and MAP2K1.

Costello syndrome: Caused by mutations in HRAS (80-90%). This is the only causative gene reported to date.

Noonan syndrome-like disorder with loose anagen hair: Caused by mutations in SHOC2, particularly a recurrent 4A>G pathogenic variant. Sequencing of SHOC2 will detect a pathogenic variant in ~5% of individuals with NS, most of which have the 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; and eyes that are often wide-spaced, downslanted, and with epicanthal folds and fullness or droopiness 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, inferior pectus excavatum

Widely set nipples

Cryptorchidism in males

Lymphatic dysplasias of the lungs, intestines, and/or lower extremities

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: "high forehead, relative macrocephaly, bitemporal narrowing, hypoplasia of the supraorbital ridges, ocular hypertelorism, 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.[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 cardinal features listed above, 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), coarse facial features, curly or sparse, fine hair

Skin: loose and soft skin, increased pigmentation, deep palmar and plantar creases, papillomata of face and perianal region (typically absent in infancy but may appear in childhood), hyperkeratosis and calluses, premature aging, hair loss

Musculoskeletal system: diffuse hypotonia, joint laxity, 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 developing throughout childhood), positional foot deformity, vertical talus, kyphoscoliosis, pectus carinatum, pectus excavatum, asymmetric rib cage, developmental hip dysplasia

Cardiovascular system: cardiac hypertrophy, usually typical hypertrophic cardiomyopathy (i.e., idiopathic subaortic stenosis, asymmetric septal hypertrophy), although other forms (i.e., biventricular) have been reported; congenital heart defect, usually valvar pulmonic stenosis; arrhythmia, usually supraventricular tachycardia"; aortic dilation, mild; hypertension

"Neurologic: Chiari I malformation which may develop over time, hydrocephalus, syringomyelia, seizures, tethered cord

Tumors: increased occurrence of malignant solid tumors

Psychomotor development: developmental delay or intellectual disability, sociable, outgoing personality, findings suggestive of autism spectrum disorder in early infancy that improve by age four years."[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

Introduction

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 patient management, 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 PTPN11-related 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]

Guidelines and Evidence

Introduction

This section includes relevant guidelines and evidence pertaining to NSD testing.

American Academy of Family Physicians

The American Academy of Family Physicians (AAFP, 2014) stated that Noonan syndrome should be considered in anyone with two or more of the following:[16]

"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 AAFP also stated the following clinical recommendations:

“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."

Selected Relevant Publications

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 2019 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 (which does not require the clinician to determine which gene[s] are likely

involved) is the best option. Exome sequencing is the most commonly used genomic testing method; genome sequencing is also possible."

Gripp KW, et al (2019) stated the following regarding Costello syndrome:[17]

"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:[18]

"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."

A 2016 expert-authored review on CFC stated:[4]

"Consensus guidelines have been developed for genetic testing strategy for CFC syndrome.

Based on current published information, sequencing can be approached stepwise.

A multigene panel for RASopathies/Noonan spectrum disorders that includes BRAF, MAP2K1, MAP2K2, and KRAS and other genes of interest… is usually the preferred initial test.

If multigene panel testing is not available, serial single-gene testing is recommended, beginning with BRAF, MAP2K1, and MAP2K2, and KRAS; if no pathogenic variants are found follow with sequencing of HRAS (all exons) even though the patient appears to have a clinical diagnosis of CFC syndrome. Individuals who have an HRAS pathogenic variant by definition have Costello syndrome.

If no pathogenic variant is identified in these genes using sequencing analysis, gene-targeted deletion/duplication analysis or array CGH can be considered. Rare deletions in MEK genes (i.e., MAP2K1 and MAP2K2) may cause phenotypic features that are reminiscent of CFC syndrome."

More comprehensive genomic testing (when available) including exome sequencing or genome sequencing may be considered if serial single-gene testing (and/or use of a multigene panel that includes BRAF, MAP2K1, MAP2K2, and KRAS) fails to confirm a diagnosis in an individual with features of CFC syndrome."

A 2015 expert-authored review on NSML stated:[3]

"Molecular genetic testing approaches can include single-gene testing or use of a multigene panel." Single-gene testing should be "based on the order in which a pathogenic variant is most likely to be identified."

"Although gene-targeted deletion/duplication analysis could be considered, the variant detection frequency is unknown and expected to be extremely low."

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.[16,19-24]

Criteria

Introduction

Requests for NSD testing are reviewed using these 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, OR

Prenatal Testing for At-Risk Pregnancies:

Known familial disease-causing mutation identified in a biologic parent or affected sibling of the pregnancy, 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 lentigines, 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)

Pulmonary valve stenosis

Hypertrophic cardiomyopathy

A combination of TWO or more of the following: Polyhydramnios, distended jugular lymphatic sacs (JLS), pleural effusion, hydrops fetalis, 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 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 lentigines, follicular keratosis, etc.)

Pubertal delay and/or infertility, OR

Prenatal Testing:

Prenatal chromosome study is not diagnostic, and

Fetal imaging exhibits features of 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)

Pulmonary valve stenosis

Hypertrophic cardiomyopathy

A combination of TWO or more of the following: polyhydramnios, distended jugular lymphatic sacs (JLS), pleural effusion, hydrops fetalis, 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

Rendering laboratory is a qualified provider of service per the Health Plan policy

Deletion/Duplication Analysis

Due to the extremely low diagnostic yield of deletion/duplication analysis, this testing is not considered medically necessary and is therefore not reimbursable.

Note **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 - Solid Tumors*, 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 Considerations

When multiple CPT codes are billed for individual components of an NSD panel (e.g., Tier 1 MoPath codes 81200-81355 or Tier 2 MoPath codes 81400-81408), the entire panel will be approved if the above criteria are met. However, the laboratory will be redirected to the use of an appropriate panel code for billing purposes.

The billed amount should not exceed the list price of the test.

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

Genetic testing is only needed once per lifetime. Therefore, a single gene included in a panel may not be reimbursed if testing has been performed previously. Exceptions may be considered if technical advances in testing demonstrate significant advantages that would support a medical need to retest.

If a panel was previously performed and an updated, larger panel is being requested, only testing for the medically necessary, previously untested genes will be reimbursable. Therefore, only the most appropriate procedure codes for those additional genes will be considered for reimbursement.

If the laboratory will not accept redirection to a panel code, the medical necessity of 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 sequencing of the following genes may be considered for reimbursement, based on which NSD is most likely:

Classic NS: PTPN11, followed by SOS1, RAF1, RIT1 and KRAS 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.

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Introduction

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