Genetic testing: multisystem inherited disorders, intellectual disability, and developmental delay

These services may or may not be covered by your HealthPartners plan. Please see your plan documents for your specific coverage information. If there is a difference between this general information and your plan documents, your plan documents will be used to determine your coverage.

Administrative Process

Prior authorization is not required for the following services:

- Testing for Fragile X syndrome (FMR1 Repeat and Methylation Analysis)
- Genetic testing for Cystic Fibrosis
- Genetic testing for Angelman/Prader-Willi Syndrome

Prior authorization is required for the following services:

- Chromosomal Microarray Analysis for Developmental Delay/intellectual Disability, Autism Spectrum Disorder, or Congenital Anomalies
- Genetic testing for Beckwith-Wiedemann/Russell-Silver Syndrome
- Genetic testing for CHARGE Syndrome
- Genetic testing for Fanconi Anemia
- Genetic testing for Hereditary Hemorrhagic Telangiectasia (HHT)
- Genetic testing for Legius Syndrome
- Genetic testing for Neurofibromatosis
- Genetic testing for Noonan Spectrum Disorders
- Genetic testing for PIK3CA-Related Segmental Overgrowth and Related Syndromes (81479)
- Genetic testing for Tuberous Sclerosis Complex (TSC)
- Genetic testing for other covered multisystem disorders
- Testing that is associated with a procedure code listed in “Box A”, below.

Prior Authorization is not applicable for the following, as they are considered investigational/experimental and therefore not covered:

- Autism Spectrum Disorder / Intellectual Disability Panel Analysis

Tests that require prior authorization will be reviewed for medical necessity of the testing as a whole. That is, a single coverage decision will apply to all of the tests, services, and/or procedure codes associated with the genetic test, whether they are requested/billed together or separately.

Box A: Genetic testing procedure codes that require prior authorization
Molecular pathology procedures, Tier 2 or unlisted (CPT 81400-81408, 81479)
Unlisted multianalyte assays (CPT 81599)
Any other listed or unlisted laboratory/pathology CPT code when it is used in association with a genetic test

Policy Reference Table

If available, codes are listed below for informational purposes only, and do not guarantee member coverage or provider reimbursement. The list may not be all-inclusive.

Coverage Criteria Sections	Example Tests; Labs	Common CPT Codes	Common ICD Codes
Developmental Delay/Intellectual Disability, Autism Spectrum Disorder, or Congenital Anomalies			
Chromosomal Microarray Analysis for Developmental Delay/Intellectual Disability, Autism Spectrum Disorder, or Congenital Anomalies	Chromosomal Microarray (MicroarrayDx) (GeneDx)	81228, 81229, S3870	F84.0, Q89.7, R62.50, F79
	Chromosomal Microarray, Postnatal, ClariSure Oligo-SNP (Quest Diagnostics)		
	SNP Microarray−Pediatric (Reveal) (LabCorp)		

Autism Spectrum Disorder//Intellectual Disability Panel Analysis	Neurodevelopmental Disorders (NDD) Panel (Invitae)	81185, 81236, 81302, 81321, 81470, 81471, 81479	F70-80, F84, F81, F82, F88, F89, H93.52
	Autism/ID Xpanded panel (GeneDx)		
	SMASH (Marvel Genomics)	0156U	
Angelman/Prader-Willi Syndrome			
SNRPN/UBE3A Methylation Analysis,15q11-q13 FISH Analysis, Chromosome 15 Uniparental Disomy analysis, and Imprinting Center Defect Analysis	Angelman Syndrome/Prader-Willi Syndrome Methylation Analysis (GeneDx)	81331	R47, Q93.51, Q93.5
	FISH, Prader-Willi/Angelman Syndrome (Quest Diagnostics)	88271, 88273	
	Chromosome 15 UPD Analysis (Greenwood Genetic Center)	81402	
	Imprinting Center (IC) Deletion Analysis for Angelman Syndrome (Univ of Chicago Genetic Services Laboratories)	81331	
	Imprinting Center (IC) Deletion Analysis for Prader-Willi Syndrome (Univ of Chicago Genetic Services Laboratories)		
Beckwith-Wiedemann/Russell-Silver Syndrome			
H19 and *KCNQ1OT1* Methylation Analysis, FISH or Deletion/Duplication Analysis of 11p15, Uniparental Disomy Analysis, *CDKN1C* Sequencing and/or Deletion/Duplication Analysis	Russell-Silver Syndrome: H19 Methylation (Shodair Children's Hospital)	81401	C22.2, C64, I42.9, P08, R16.0- R16.2, R62.52, Q35, Q38.2, Q63, Q79.2, Q87.3
	Beckwith-Wiedemann: Methylation analysis of 11p15.5 only (University of Pennsylvania School of Medicine Genetic Diagnostic Laboratory)		
	RSS: Methylation analysis of 11p15.5 only (University of Pennsylvania School of Medicine Genetic Diagnostic Laboratory)		
	Beckwith-Wiedemann: 11p15.5 high resolution copy number analysis only (aCGH) (University of Pennsylvania School of Medicine Genetic Diagnostic Laboratory)	81479	
	RSS: 11p15.5 high resolution copy number analysis only (aCGH) (University of Pennsylvania School of Medicine Genetic Diagnostic Laboratory)		
	Chromosome 7 UPD Analysis (Greenwood Genetics Center - Molecular Diagnostic Laboratory)	81402	
	CDKN1C Full Gene Sequencing and Deletion/Duplication (Invitae)	81479	
Cystic Fibrosis			
Diagnostic *CFTR* Sequencing and/or Deletion/Duplication Analysis	Cystic Fibrosis Complete Rare Variant Analysis, Entire Gene Sequence (Quest Diagnostics)	81223	E84.0-9, P09, Q55.4, R94.8, Z13, Z31, Z34, Z82.79, Z83, Z84

	Cystic Fibrosis Gene Deletion or Duplication (Quest Diagnostics)	81222	
CFTR Intron 8 PolyT and TG Analysis (aka Intron 8 poly-T/TG)	*CFTR* Intron 8 Poly-T Analysis (Quest Diagnostics)	81224	
CHARGE Syndrome			
CHD7 Sequencing and/or Deletion/Duplication Analysis	CHARGE and Kallman Syndromes via the CHD7 Gene (PreventionGenetics, part of Exact Sciences)	81407, 81479	Q89.8
Fanconi Anemia			
Fanconi Anemia Multigene Panel	FancZoom (DNA Diagnostic Laboratory - Johns Hopkins Hospital)	81162, 81307, 81479	C92, D46.9, D61.09, D61.89, D61.9, L81.3, L81.4 Q02, R62.52
	Fanconi Anemia Panel (PreventionGenetics, part of Exact Sciences)		
Fragile X Syndrome			
Diagnostic *FMR1* Repeat and Methylation Analysis	Fragile X Syndrome, Diagnostic (Labcorp)	81243, 81244	F84.0, Q99.2, F79, E28.3, G11.2, G25.2
	XSense, Fragile X with Reflex (Quest Diagnostics)		
	Fragile X Syndrome via the FMR1 CGG Repeat Expansion (PreventionGenetics, part of Exact Sciences)		
Hereditary Hemorrhagic Telangiectasia (HHT)			
Hereditary Hemorrhagic Telangiectasia Multigene Panel	HHTNext (Ambry Genetics)	81405, 81406, 81479	R04.0, Q27.30-Q27.39
	Hereditary Hemorrhagic Telangiectasia (HTT) Panel (Blueprint Genetics)		
Neurofibromatosis 1			
NF1 Sequencing and/or Deletion/Duplication Analysis	NF1 Sequencing & Del/Dup (GeneDx)	81408	L81.3, R62.5, Q85.0, Z82.79, Z84
NF2-Related Schwannomatosis (previously known as Neurofibromatosis 2)			
NF2 Sequencing and/or Deletion/Duplication Analysis	Neurofibromatosis Type 2 via the NF2 Gene (PreventionGenetics, part of Exact Sciences)	81405, 81406	L81.3, R62.5, Q85.0, Z82.79, Z84
Noonan Spectrum Disorders/RASopathies			
Noonan Spectrum Disorders/RASopathies Multigene Panel	RASopathies and Noonan Spectrum Disorders Panel (Invitae)	81442	F82, R62.52, Q24, Q87.19, R62.0, R62.50, R62.59, Q53, Q67.6, Q67.7, L81.4, L81.3
	Noonan and Comprehensive RASopathies Panel (GeneDx)		
***PIK3CA*-Related Segmental Overgrowth and Related Syndromes**			
PIK3CA Sequencing Analysis	PIK3CA Single Gene Sequencing and Deletion/Duplication (Fulgent Genetics)	81479	
Tuberous Sclerosis Complex (TSC)			

TSC1 and *TSC2* Sequencing and/or Deletion/Duplication Analysis	Tuberous Sclerosis Complex Panel (TSC1, TSC2) (Quest Diagnostics)	81405, 81406, 81407	D10, D15.1, D43, D21.9, H35.89, N28.1, Q61.9, H35.89
Other **Covered Multisystem Inherited Disorders**			
Other Covered Multisystem Inherited Disorders	See below	81400, 81401, 81402, 81403, 81404, 81405, 81406, 81407, 81408	

Coverage

Developmental Delay, Intellectual Disability, Autism Spectrum Disorder, or Congenital Anomalies

Chromosomal Microarray Analysis for Developmental Delay/Intellectual Disability, Autism Spectrum Disorder, or Congenital Anomalies

1. Chromosomal microarray analysis for developmental delay, intellectual disability, autism spectrum disorder, or congenital anomalies is considered **medically necessary** when:
   - A. The member has developmental delay and/ or intellectual disability, excluding isolated speech/language delay (see below) **or**
   - B. The member has autism spectrum disorder, **or**
   - C. The member has multiple congenital anomalies not specific to a well-delineated genetic syndrome, **or**
   - D. The member has short stature.
2. Chromosomal microarray analysis for developmental delay, intellectual disability, autism spectrum disorder, or congenital anomalies is considered **investigational** for all other conditions of delayed development, including:
   - A. Isolated speech/language delay.

Autism Spectrum Disorder/Intellectual Disability Panel Analysis

1. The use of an autism spectrum disorder / intellectual disability panel is considered **investigational**.

Back to top

Angelman/Prader-Willi Syndrome

***SNRPN/UBE3A* Methylation Analysis, 15q11-q13 FISH Analysis, Chromosome 15 Uniparental Disomy Analysis, and Imprinting Center Defect Analysis**

1. *SNRPN/UBE3A* methylation analysis, FISH analysis for 15q11-q13 deletion, uniparental disomy analysis, and imprinting center defect analysis to establish or confirm a diagnosis of Angelman or Prader-Willi syndrome is considered **medically necessary** when:
   - A. The member meets both of the following related to Angelman syndrome:
     - i. The member has functionally severe developmental delay by age six months to twelve months, **and**
     - ii. The member has at least one of the following clinical features:
       - a) Speech impairment, with minimal to no use of words; receptive language skills and nonverbal communication skills higher than expressive language skills, **or**
       - b) Movement or balance disorder, usually ataxia of gait and/or tremulous movement of the limbs, **or**
       - c) Unique behavior, including any combination of frequent laughter/smiling; apparent happy demeanor; excitability, often with hand-flapping movements and hypermotoric behavior, **or**
   - B. The member meets one of the following age-specific features of Prader-Willi syndrome:
     - i. The member is age less than one month with:
       - a) Hypotonia with poor suck, **or**
     - ii. The member is age one month to two years with:
       - a) Hypotonia with poor appetite and suck, **and**
       - b) Developmental delay
     - iii. The member is age two to six years with:
       - a) Hypotonia with history of poor suck, **and**
       - b) Global developmental delay, **or**

iv. The member is age six to twelve years with:
a) History of hypotonia with poor suck (hypotonia often persists), **and**
b) Global developmental delay, **and**
c) Excessive eating with central obesity if uncontrolled externally, **or**

v. The member is age thirteen years or older with:
a) Cognitive impairment, usually mild intellectual disability, **and**
b) Excessive eating and hyperphagia with central obesity if uncontrolled externally, **and**
c) Hypothalamic hypogonadism, **or**
(a) Typical behavioral findings (temper tantrums, stubbornness, manipulative behavior, and obsessive-compulsive characteristics).

2. *SNRPN/UBE3A* methylation analysis, FISH analysis for 15q11-q13 deletion, uniparental disomy analysis, and imprinting center defect analysis to establish or confirm a diagnosis of Angelman or Prader-Willi syndrome is considered **investigational** for all other indications.

Note: The following is the recommended testing strategy:
SNRPN/UBE3A methylation analysis
If *UBE3A* methylation analysis is normal, then proceed to deletion analysis of 15q11-q13
If deletion analysis is normal, consider UPD analysis of chromosome 15
If UPD is normal, then proceed to imprinting defect (ID) analysis.

Back to top

Beckwith-Wiedemann/Russell-Silver Syndrome

H19 and *KCNQ1OT1* Methylation Analysis, Deletion/Duplication Analysis of 11p15, Chromosome 7 Uniparental Disomy analysis, *CDKN1C* Sequencing and/or Deletion/Duplication Analysis

1. *H19* and *KCNQ1OT1* methylation analysis, deletion/duplication analysis of 11p15, chromosome 7 uniparental disomy analysis, or *CDKN1C* sequencing and/or deletion/duplication analysis to confirm or establish a diagnosis of Beckwith-Wiedemann or Russell-Silver syndrome is **medically necessary** when:

A. The member has at least one of the following clinical features of Beckwith-Wiedemann syndrome (BWS):
i. Macroglossia, **or**
ii. Abdominal wall defect requiring surgical correction (e.g., omphalocele/exophthalmos or a large umbilical hernia), **or**
iii. Embryonal tumor, (e.g., Wilms tumor, hepatoblastoma, nephroblastomatosis, rhabdomyosarcoma, neuroblastoma, or adrenal tumors) **or**
iv. Hemihyperplasia (lateralized overgrowth) of one or more body segments, **or**
v. Macrosomia, defined as pre- and/or postnatal overgrowth, often using a cutoff of >90th or >97th centile, depending on the study, **or**
vi. Hyperinsulinemic hypoglycemia, **or**
vii. Pathology findings including cytomegaly of the adrenal cortex, placental mesenchymal dysplasia and pancreatic adenomatosis, **or**
viii. Family history of one or more family members with clinical features suggestive of BWS, **or**
ix. Visceromegaly, typically from an imaging study such as ultrasound, involving 1 or more intra-abdominal organs, such as the liver, kidneys, and/or adrenal glands, **or**
x. Unilateral or bilateral earlobe creases and/or posterior helical ear pits, **or**
xi. Characteristic facies (i.e., infraorbital creases, midface retrusion, thin vermilion of the upper lip, and prominent jaw), **or**
xii. Kidney anomalies, such as structural malformations, nephrocalcinosis, or medullary sponge kidney, **or**
xiii. Transient hypoglycemia requiring medical intervention, **or**

B. The member meets at least three of the following Netchine-Harbison clinical scoring system (NH-CSS) clinical features for Russell-Silver syndrome:
i. Small for gestational age (birth weight and/or length 2 standard deviations (SD) or more below the mean for gestational age), **or**
ii. Postnatal growth failure (length/height 2 SD or more below the mean at 24 months), **or**
iii. Relative macrocephaly at birth (head circumference more than 1.5 SD above birth weight and/or length), **or**
iv. Frontal bossing or prominent forehead (forehead projecting beyond the facial plane on a side view as a toddler [1–3 years]), **or**
v. Body asymmetry (limb length discrepancy greater than or equal to 0.5 cm, or less than or equal to 0.5 cm with at least two other asymmetric body parts), **or**
vi. Feeding difficulties or body mass index less than or equal to 2 SD at 24 months or current use of a feeding tube or cyproheptadine for appetite stimulation.

2. *H19* and *KCNQ1OT1* methylation analysis, deletion/duplication analysis of 11p15, chromosome 7 uniparental disomy analysis, *CDKN1C* sequencing and/or deletion/duplication analysis to confirm or establish a diagnosis of Beckwith-Wiedemann or Russell-Silver syndrome is considered **investigational** for all other indications.

Back to top

Cystic Fibrosis

Diagnostic *CFTR* Sequencing and/or Deletion/Duplication Analysis

1. *CFTR* sequencing and/or deletion/duplication analysis to establish or confirm a diagnosis of cystic fibrosis is considered **medically necessary** when:
   - A. The member has a positive (greater than or equal to 60 mmol/L) or inconclusive (30-59 mmol/L) sweat chloride test, **or**
   - B. The member has a positive newborn screen for cystic fibrosis as indicated by elevated immunoreactive trypsinogen, **or**
   - C. The member has symptoms of cystic fibrosis from at least **two** different organ systems:
     - i. Sinus (e.g. chronic sinusitis, nasal polyps), **or**
     - ii. Lower respiratory (e.g., bronchiectasis, chronic or recurrent lower airway infection, allergic bronchopulmonary aspergillosis), **or**
     - iii. Gastrointestinal (GI)/lumen (e.g., meconium ileus, distal intestinal obstruction syndrome, abnormal motility, rectal prolapse), **or**
     - iv. Gastrointestinal (GI)/hepatobiliary (e.g., pancreatic insufficiency, recurrent pancreatitis, elevated liver enzymes, ecchymosis, cirrhosis, prolonged neonatal jaundice, fat soluble vitamin deficiencies), **or**
     - v. Reproductive (e.g., male (sex assigned at birth) infertility because of obstructive azoospermia, female (sex assigned at birth) infertility), **or**
     - vi. Other (e.g., hyponatremic dehydration, failure to thrive, pseudo-Bartter syndrome, aquagenic wrinkling of skin, digital clubbing).
2. *CFTR* sequencing and/or deletion/duplication analysis to establish or confirm a diagnosis of cystic fibrosis is considered **investigational** for all other indications.

***CFTR* Intron 9 PolyT and TG Analysis (previously called Intron 8 polyT/TG Analysis)**

1. *CFTR* intron 9 polyT and TG analysis in a member is considered **medically necessary** when:
   - A. The member has a diagnosis of cystic fibrosis, **and**
   - B. The member has an R117H variant in the *CFTR* gene.
2. *CFTR* intron 9 polyT and TG analysis in a member with a diagnosis of cystic fibrosis is considered **investigational** for all other indications.

Back to top

CHARGE Syndrome

***CHD7* Sequencing and/or Deletion/Duplication Analysis**

1. *CHD7* sequencing and/or deletion/duplication analysis to establish or confirm a diagnosis of CHARGE syndrome is considered **medically necessary** when:
   - A. The member has at least two of the following:
     - i. Coloboma of the iris, retina, choroid, and/or disc, **or**
     - ii. Anophthalmos or microphthalmos, **or**
     - iii. Choanal atresia or stenosis, **or**
     - iv. Cleft palate with or without cleft lip, **or**
     - v. Cranial nerve dysfunction or anomaly (hyposmia or anosmia, facial palsy, sensorineural hearing loss and/or balance problems, hypoplasia or aplasia on imaging, difficulty with sucking/swallowing and aspiration, gut motility problems), **or**
     - vi. Ear malformations (auricular abnormalities, middle ear abnormalities/ossicular malformations, and temporal bone abnormalities), **or**
     - vii. Tracheoesophageal fistula or esophageal atresia, **or**
     - viii. Cardiovascular malformation (conotruncal defects (e.g., tetralogy of Fallot), AV canal defects, and aortic arch anomalies), **or**
     - ix. Hypogonadotropic hypogonadism (micropenis or cryptorchidism, hypoplastic labia, abnormal or absent uterus, delayed or absent puberty), **or**
     - x. Developmental delay or intellectual disability, **or**
     - xi. Growth deficiency (short stature), **or**
     - xii. Characteristic physical features of the face, neck, and/or hands, or
     - xiii. Brain MRI showing clivus hypoplasia or hypoplasia of the cerebellar vermis.
2. *CHD7* sequencing and/or deletion/duplication analysis to establish or confirm a diagnosis of CHARGE syndrome is considered **investigational** for all other indications.

Back to top

Fanconi Anemia

Fanconi Anemia Multigene Panel

1. Multigene panel analysis to establish or confirm a genetic diagnosis of Fanconi anemia is considered **medically necessary** when:
    - A. The member had a positive or inconclusive result via chromosome breakage analysis, **and**
    - B. The member displays at least one of the following:
        - i. Prenatal and/or postnatal short stature, **or**
        - ii. Abnormal skin pigmentation (e.g., café au lait macules, hyper- or hypopigmentation), **or**
        - iii. Skeletal malformations (e.g., hypoplastic thumb, hypoplastic radius, vertebral anomalies), **or**
        - iv. Microcephaly, **or**
        - v. Ophthalmic anomalies, **or**
        - vi. Genitourinary tract anomalies (e.g., horseshoe kidney, hypospadias, bicornuate uterus), **or**
        - vii. Macrocytosis, **or**
        - viii. Increased fetal hemoglobin (often precedes anemia), **or**
        - ix. Cytopenia (especially thrombocytopenia, leukopenia and neutropenia), **or**
        - x. Progressive bone marrow failure, **or**
        - xi. Adult-onset aplastic anemia, **or**
        - xii. Myelodysplastic syndrome (MDS), **or**
        - xiii. Acute myelogenous leukemia (AML), **or**
        - xiv. Early-onset solid tumors (e.g., squamous cell carcinomas of the head and neck, esophagus, and vulva; cervical cancer; and liver tumors), **or**
        - xv. Inordinate toxicities from chemotherapy or radiation.
2. Multigene panel analysis to establish or confirm a genetic diagnosis of Fanconi anemia is considered **investigational** for all other indications.

Back to top

Fragile X Syndrome

Diagnostic *FMR1* Repeat and Methylation Analysis

1. *FMR1* repeat and methylation analysis to establish or confirm a genetic diagnosis of Fragile X syndrome or Fragile X-associated disorders is considered **medically necessary** when:
    - A. The member has unexplained intellectual disability or developmental delay, **or**
    - B. The member is male and has unexplained autism spectrum disorder, **or**
    - C. The member is female and has unexplained autism spectrum disorder, **and**
        - i. Has features compatible with Fragile X syndrome (e.g., ADHD and/or other behavioral differences, typical facies [long face, prominent forehead, large ears, prominent jaw], mitral valve prolapse, aortic root dilatation), **or**
        - ii. Has a family history positive for X-linked neurodevelopmental disorders; or at least one close relative with premature ovarian failure, ataxia or tremor, **or**
    - D. The member has primary ovarian insufficiency (cessation of menses before age 40), **or**
    - E. The member is 50 years of age or older with progressive intention tremor and cerebellar ataxia of unknown origin.
2. *FMR1* repeat and methylation analysis to establish or confirm a genetic diagnosis of Fragile X syndrome or Fragile X-associated disorders is considered **investigational** for all other indications.

Back to top

Hereditary Hemorrhagic Telangiectasia (HHT)

Hereditary Hemorrhagic Telangiectasia Multigene Panel

1. Hereditary hemorrhagic telangiectasia (HHT) multigene panel analysis to establish or confirm a diagnosis of HHT is considered **medically necessary** when:
    - A. The member has any of the following clinical features of HHT:
        - i. Spontaneous and recurrent nosebleeds (epistaxis), **or**
        - ii. Mucocutaneous telangiectases at characteristic sites, including lips, oral cavity, fingers, and nose, **or**
        - iii. Visceral arteriovenous malformation (AVM) (either pulmonary, cerebral, spinal, gastrointestinal or pancreatic), **and**
    - B. The panel includes, at a minimum, the following genes: *ACVRL1, ENG*.
2. Hereditary hemorrhagic telangiectasia (HHT) multigene panel analysis to establish or confirm a diagnosis of HHT is considered **investigational** for all other indications.

Back to top

Neurofibromatosis 1

NF1 Sequencing and/or Deletion/Duplication Analysis

1. *NF1* sequencing and/or deletion/duplication analysis is considered **medically necessary** when:
   - A. The member has at least one of the following:
     - i. Six or more café au lait macules (greater than 5 mm in greatest diameter in prepubertal individuals and greater than 15 mm in greatest diameter in postpubertal individuals), **or**
     - ii. Two or more neurofibromas of any type or one plexiform neurofibroma, **or**
     - iii. Freckling in the axillary or inguinal regions, **or**
     - iv. Optic glioma, **or**
     - v. Two or more Lisch nodules (iris hamartomas), **or**
     - vi. A distinctive osseous lesion such as sphenoid dysplasia or tibial pseudarthrosis, **or**
   - B. The member has a biological parent who meets the diagnostic criteria for *NF1* (the diagnosis of *NF1* is established in an individual with two or more of the above features).
2. *NF1* sequencing and/or deletion/duplication analysis (81408) is considered investigational for all other indications.

Back to top

NF2-Related Schwannomatosis (Previously Known as Neurofibromatosis 2)

NF2 Sequencing and/or Deletion/Duplication Analysis

1. *NF2* sequencing and/or deletion/duplication analysis is considered **medically necessary** when:
   - A. The member had an *NF2* pathogenic variant identified on tumor tissue testing, **or**
   - B. The member is an adult with at least one of the following:
     - i. Bilateral vestibular schwannomas, **or**
     - ii. Unilateral vestibular schwannoma, **and**
       - a) At least two of the following:
         - (a) Meningioma, **or**
         - (b) Schwannoma, **or**
         - (c) Glioma, **or**
         - (d) Neurofibroma, **or**
         - (e) Cataract in the form of subcapsular lenticular opacities, **or**
         - (f) Cortical wedge cataract, **or**
   - C. The member is an adult with multiple meningiomas and either of the following:
     - i. Unilateral vestibular schwannoma, **or**
     - ii. At least two of the following:
       - a) Schwannoma, **or**
       - b) Ependymoma, **or**
       - c) Cataract in the form of subcapsular lenticular opacities, **or**
       - d) Cortical wedge cataract diagnosed in an individual less than 40 years of age, **or**
   - D. The member is a child with at least two of the following:
     - i. A schwannoma at any location including intradermal, **or**
     - ii. Skin plaques present at birth or in early childhood (often plexiform schwannoma on histology), **or**
     - iii. A meningioma, particularly non-meningothelial (non-arachnoidal) cell in origin, **or**
     - iv. A cortical wedge cataract, **or**
     - v. A retinal hamartoma, **or**
     - vi. A mononeuropathy, particularly causing a facial nerve palsy, foot or wrist drop, or third nerve palsy.
2. *NF2* sequencing and/or deletion/duplication analysis is considered **investigational** for all other indications.

Back to top

Noonan Spectrum Disorders/RASopathies

Noonan Spectrum Disorders/RASopathies Multigene Panel

1. The use of a multigene panel to confirm or establish a diagnosis of a Noonan spectrum disorder/RASopathy (e.g., Noonan syndrome, Legius syndrome, Costello syndrome, Cardio-facial-cutaneous syndrome, NF1, Noonan-like syndrome) is considered **medically necessary** when:
   - A. The member has at least one of the following:
     - i. Characteristic facies (low-set, posteriorly rotated ears with fleshy helices, vivid blue or blue-green irises, widely spaced, down slanted eyes, epicanthal folds, ptosis), **or**
     - ii. Short stature, **or**

iii. Congenital heart defect (most commonly pulmonary valve stenosis, atrial septal defect, and/or hypertrophic cardiomyopathy), **or**
iv. Developmental delay, **or**
v. Broad or webbed neck, **or**
vi. Unusual chest shape with superior pectus carinatum, inferior pectus excavatum, **or**
vii. Widely spaced nipples, **or**
viii. Cryptorchidism in males, **or**
ix. Lentigines, **or**
x. Café au lait macules.

2. The use of a multigene panel to confirm or establish a diagnosis of a Noonan spectrum disorder/ RASopathy (e.g., Noonan syndrome, Legius syndrome, Costello syndrome, Cardio-facial-cutaneous syndrome, NF1, Noonan-like syndrome) is considered **investigational** for all other indications.

Back to top

PIK3CA-Related Segmental Overgrowth and Related Syndromes

PIK3CA Sequencing Analysis

1. *PIK3CA* sequencing analysis to establish a diagnosis of *PIK3CA*-Related Segmental Overgrowth is considered **medically necessary** when:
   A. The member displays at least one of the following on brain imaging:
      i. Hemimegalencephaly, **or**
      ii. Focal cortical dysplasia, **or**
      iii. Dysplastic megalencephaly, **or**
   B. The member displays at least one of the following, from birth or with onset in early childhood:
      i. Overgrowth of any of a wide variety of tissues including (but not limited to) brain, adipose, vascular, muscle, skeletal, nerve, **or**
      ii. Vascular malformations including (but not limited to) capillary, venous, arteriovenous, or mixed malformations, **or**
      iii. Lymphatic malformations, **or**
      iv. Cutaneous findings including epidermal nevi and hyperpigmented macules, **or**
      v. Single or multiple digital anomalies of the hands or feet (e.g., macrodactyly, syndactyly, polydactyly, sandal-toe gap), **or**
      vi. Kidney malformations (e.g., pelviectasis, dilated ureters, hydronephrosis, duplicated renal arteries, renal cysts, enlarged kidneys), **or**
      vii. Benign tumors, with the exceptions of Wilms tumor and nephroblastomatosis (i.e., diffuse or multifocal clusters of persistent embryonal cells).
2. *PIK3CA* sequencing analysis to establish a diagnosis of *PIK3CA*-Related Segmental Overgrowth is considered **investigational** for all other indications.

Note: Because the vast majority of reported *PIK3CA* pathogenic variants are mosaic and acquired, more than one tissue type may need to be tested (e.g., blood, skin, saliva). Failure to detect a *PIK3CA* pathogenic variant does not exclude a clinical diagnosis of *PIK3CA*-associated segmental overgrowth disorders in individuals with suggestive features, given that low-level mosaicism is observed in many individuals.

Back to top

Tuberous Sclerosis Complex (TSC)

TSC1 and *TSC2* Sequencing and/or Deletion Duplication Analysis

1. *TSC1* and *TSC2* sequencing and/or deletion/duplication analysis to establish or confirm a diagnosis of Tuberous Sclerosis Complex (TSC) is considered **medically necessary** when:
   A. The member has at least one of the following major features of TSC:
      i. Three or more angiofibromas or fibrous cephalic plaque, **or**
      ii. Cardiac rhabdomyoma, **or**
      iii. Multiple cortical tubers and/or radial migration lines, **or**
      iv. Hypomelanotic macules (3 or more macules that are at least 5 mm in diameter), **or**
      v. Lymphangioleiomyomatosis (LAM), **or**
      vi. Multiple retinal nodular hamartomas, **or**
      vii. Renal angiomyolipoma, **or**
      viii. Shagreen patch, **or**
      ix. Subependymal giant cell astrocytoma (SEGA), **or**
      x. Two or more subependymal nodules (SENs), **or**
      xi. Two or more ungual fibromas, **or**
   B. The member has at least two of the following minor features of TSC:
      i. Sclerotic bone lesions, **or**

ii. "Confetti" skin lesions (numerous 1- to 3-mm hypopigmented macules scattered over regions of the body such as the arms and legs), **or**
iii. Four or more dental enamel pits, **or**
iv. Two or more intraoral fibromas, **or**
v. Multiple renal cysts, **or**
vi. Nonrenal hamartomas, **or**
vii. Retinal achromic patch.

2. *TSC1* and *TSC2* sequencing and/or deletion/duplication analysis to establish or confirm a diagnosis of Tuberous Sclerosis Complex is considered **investigational** for all other indications.

Back to top

Other Covered Multisystem Inherited Disorders

1. Genetic testing to establish or confirm one of the following multisystem inherited disorders to guide management is considered **medically necessary** when the member demonstrates clinical features* consistent with the disorder (the list is not meant to be comprehensive, see 2. below):
   A. Alagille syndrome
   B. Alport syndrome
   C. Branchiootorenal spectrum disorder
   D. Coffin-Siris syndrome
   E. Cornelia de Lange syndrome
   F. *FGFR2* craniosynostosis syndromes
   G. Holoprosencephaly
   H. Holt-Oram syndrome
   I. Incontinentia pigmenti
   J. Joubert and Meckel-Gruber syndromes
   K. Kabuki syndrome
   L. *MYH9*-related disorders
   M. Proteus syndrome
   N. Pseudoxanthoma elasticum
   O. Rubinstein-Taybi syndrome
   P. Schwannomatosis
   Q. Waardenburg syndrome
2. Genetic testing to establish or confirm the diagnosis of all other multisystem inherited disorders not specifically discussed within this or another medical policy will be evaluated by the criteria outlined in **General Approach to Genetic and Molecular Testing** (see policy coverage criteria).

*Clinical features for a specific disorder may be outlined in resources such as GeneReviews, OMIM, National Library of Medicine, Genetics Home Reference or other scholarly sources.

Definitions

1. **Close relatives** include first-, second-, and third-degree blood relatives on the same side of the family:
   A. **First-degree relatives** are parents, siblings, and children
   B. **Second-degree relatives** are grandparents, aunts, uncles, nieces, nephews, grandchildren, and half siblings
   C. **Third-degree relatives** are great grandparents, great aunts, great uncles, great grandchildren, and first cousins
2. **Autism spectrum disorders**: Defined in the DSM V as persistent deficits in social communication and social interaction across multiple contexts, as manifested by the following, currently or by history:
   A. Deficits in social-emotional reciprocity, ranging, for example, from abnormal social approach and failure of normal back-and-forth conversation; to reduced sharing of interests, emotions, or affect; to failure to initiate or respond to social interactions.
   B. Deficits in nonverbal communicative behaviors used for social interaction, ranging, for example, from poorly integrated verbal and nonverbal communication; to abnormalities in eye contact and body language or deficits in understanding and use of gestures; to a total lack of facial expressions and nonverbal communication.
   C. Deficits in developing, maintaining, and understanding relationships, ranging, for example, from difficulties adjusting behavior to suit various social contexts; to difficulties in sharing imaginative play or in making friends; to absence of interest in peers.
3. **Multiple congenital anomalies:** According to ACMG, multiple anomalies are not specific to a well-delineated genetic syndrome. These anomalies are structural or functional abnormalities usually evident at birth, or shortly thereafter, and can be consequential to an individual's life expectancy, health status, physical or social functioning, and typically require medical intervention.

4. **Developmental delay (DD):** Slow-to-meet or not reaching milestones in one or more of the areas of development (communication, motor, cognition, social-emotional, or adaptive skills) in the expected way for a child's age
5. **Intellectual disability (ID):** Defined by the DSM V as an individual with all of the following:
   A. Deficits in intellectual functions, such as reasoning, problem solving, planning, abstract thinking, judgment, academic learning, and learning from experience, confirmed by both clinical assessment and individualized, standardized intelligence testing.
   B. Deficits in adaptive functioning that result in failure to meet developmental and sociocultural standards for personal independence and social responsibility. Without ongoing support, the adaptive deficits limit functioning in one or more activities of daily life, such as communication, social participation, and independent living, across multiple environments, such as home, school, work, and community.
   C. Onset of intellectual and adaptive deficits during the developmental period.

Products

This information is for most, but not all, HealthPartners plans. Please read your plan documents to see if your plan has limits or will not cover some items. If there is a difference between this general information and your plan documents, your plan documents will be used to determine your coverage. These coverage criteria do not apply to Medicare Products. For more information regarding Medicare coverage criteria or for a copy of a Medicare coverage policy, contact Member Services at 952-883-7272 or 1-877-778-8384.

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