Revision log
Coding Implications

CONCERT GENETICS GENETIC TESTING: MULTISYSTEM INHERITED DISORDERS, INTELLECTUAL DISABILITY, AND DEVELOPMENTAL DELAY

See Important Reminder at the end of this policy for important regulatory and legal information.

OVERVIEW

Genetic testing for rare diseases may be used to establish or confirm a diagnosis in a patient who has signs and/or symptoms of a genetic disorder, for whom clinical evaluation and other standard laboratory tests/imaging/etc. have been non-diagnostic or inconclusive. Establishing or confirming a genetic diagnosis may inform clinical management of associated medical and behavioral problems and/or eliminate the need for further diagnostic workup. This document addresses genetic testing for rare genetic conditions that can impact multiple body systems.

POLICY REFERENCE TABLE

Coding Implications

This clinical policy references Current Procedural Terminology (CPT®). CPT is a registered trademark of the American Medical Association. All CPT codes and descriptions are copyrighted 2023, American Medical Association. All rights reserved. CPT codes and CPT descriptions are from the current manuals and those included herein are not intended to be all-inclusive and are included for informational purposes only. Codes referenced in this clinical policy are for informational purposes only. Inclusion or exclusion of any codes does not guarantee coverage.

Providers should reference the most up-to-date sources of professional coding guidance prior to the submission of claims for reimbursement of covered services.

The tests and associated laboratories and CPT codes contained within this document serve only as examples to help users navigate claims and corresponding criteria; as such, they are not comprehensive and are not a guarantee of coverage or non-coverage. Please see the Concert Genetics Platform for a comprehensive list of registered tests.

Criteria Sections	Example Tests; Labs	Common CPT Codes	Common ICD Codes	Ref
Developmental Delay/Intellectual Disability, Autism Spectrum Disorder, or Congenital Anomalies				
Chromosomal Microarray Analysis	Chromosomal Microarray (MicroarrayDx) (GeneDx)	81228, 81229, S3870	F84.0, Q89.7, R62.50, F79	6, 7, 8, 31
	Chromosomal Microarray, Postnatal, ClariSure Oligo-SNP (Quest Diagnostics)			
	SNP Microarray−Pediatric (Reveal) (LabCorp)			
	CNGnome NGS Array (PerkinElmer Genomics)	0209U		
Autism Spectrum Disorder/Intellectual Disability Panel Analysis	Neurodevelopmental Disorders (NDD) Panel (Invitae)	81470, 81471, 81479, 81185, 81236, 81302, 81321	F70-80, F84, F81, F82, F88, F89, H93.52	10, 21, 28
	Autism/ID Panel, 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	Angelman Syndrome/Prader-Willi Syndrome Methylation Analysis (GeneDx)	81331	R47, Q93.51, Q93.5	11, 22
	FISH, Prader-Willi/Angelman Syndrome (Quest Diagnostics)	88271, 88273		

analysis, and imprinting center defect analysis	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	12, 13
	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				

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	1
	Cystic Fibrosis Gene Deletion or Duplication (Quest Diagnostics)	81222		
CFTR Intron 9 PolyT and TG Analysis (aka Intron 8 poly-T/TG)	*CFTR* Intron 9 Poly-T Analysis (Quest Diagnostics)	81224		2
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	14
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	15, 26
	Fanconi Anemia Panel (PreventionGenetics, part of Exact Sciences)			
Fragile X Syndrome				
FMR1 Repeat and Methylation Analysis	Fragile X Syndrome, Diagnostic (Labcorp)	81243, 81244	F84.0, Q99.2, F79, E28.3, G11.2, G25.2	9, 16, 17
	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	18, 19
	Hereditary Hemorrhagic Telangiectasia and Vascular Malformations Panel (Invitae)			

Neurofibromatosis 1				
NF1 Sequencing and/or Deletion/Duplication Analysis	NF1 Sequencing & Del/Dup (GeneDx)	81408	L81.3, R62.5, Q85.0, Z82.79, Z84	3, 5
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	4
Noonan Spectrum Disorders/RASopathies				
Noonan Spectrum Disorders/RASopathies Multigene Panel	RASopathies and Noonan Spectrum Disorders Panel (Invitae) Noonan and Comprehensive RASopathies Panel (GeneDx)	81442	F82, R62.52, Q24, Q87.19, R62.0, R62.50, R62.59, Q53, Q67.6, Q67.7, L81.4, L81.3	20, 32
***PIK3CA*-Related Segmental Overgrowth and Related Syndromes**				
PIK3CA Sequencing and/or Deletion/Duplication Analysis	PIK3CA Full Gene Sequencing and Deletion/Duplication (Invitae)	81479		27
Tuberous Sclerosis Complex (TSC)				
TSC1 and *TSC2* Sequencing and/or Deletion/Duplication Analysis	TSC1 Full Gene Sequencing and Deletion/Duplication (Invitae) TSC2 Full Gene Sequencing and Deletion/Duplication (Invitae)	81405, 81406 81407	D10, D15.1, D43, D21.9, H35.89, N28.1, Q61.9, H35.89	29, 30
Other Covered Multisystem Inherited Disorders				
Other Covered Multisystem Inherited Disorders	See below	81400, 81401, 81402, 81403, 81404, 81405, 81406, 81407, 81408		23, 24, 25

OTHER RELATED POLICIES

This policy document provides criteria for Multisystem Inherited Disorders, Intellectual Disability, and Developmental Delay. For organ system specific genetic disorders, please refer to:

- *Genetic Testing: Epilepsy, Neurodegenerative, and Neuromuscular Disorders*
- *Genetic Testing: Hematologic Conditions (non-cancerous)*
- *Genetic Testing: Gastroenterologic Conditions (non-cancerous)*
- *Genetic Testing: Cardiac Disorders*
- *Genetic Testing: Aortopathies and Connective Tissue Disorders*
- *Genetic Testing: Hearing Loss*
- *Genetic Testing: Eye Disorders*
- *Genetic Testing: Immune, Autoimmune, and Rheumatoid Disorders*
- *Genetic Testing: Kidney Disorders*
- *Genetic Testing: Lung Disorders*
- *Genetic Testing: Metabolic, Endocrine, and Mitochondrial Disorders*

For other related testing, please refer to:

- ***Genetic Testing: Noninvasive Prenatal Screening (NIPS)*** for criteria related to cell-free fetal DNA screening tests.

- ***Genetic Testing: Prenatal Diagnosis (via amniocentesis, CVS, or PUBS) and Pregnancy Loss*** for coverage related to prenatal and pregnancy loss diagnostic genetic testing for tests intended to diagnose genetic conditions following amniocentesis, chorionic villus sampling or pregnancy loss.

- ***Genetic Testing: Prenatal and Preconception Carrier Screening*** for criteria related to prenatal carrier screening, preimplantation testing of embryos, or preconception carrier screening.

- ***Genetic Testing: Whole Exome and Whole Genome Sequencing for the Diagnosis of Genetic Disorders*** for criteria related to exome and genome sequencing for genetic disorders.

- ***Genetic Testing: General Approach to Genetic and Molecular Testing*** for criteria related to genetic testing that is not specifically discussed in this or another non-general policy.

CRITERIA

It is the policy of health plans affiliated with Centene Corporation® that the specific genetic testing noted below is **medically necessary** when meeting the related criteria:

DEVELOPMENTAL DELAY, INTELLECTUAL DISABILITY, AUTISM SPECTRUM DISORDER, OR CONGENITAL ANOMALIES

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

I. Chromosomal microarray analysis for developmental delay, intellectual disability, autism spectrum disorder, or congenital anomalies (81228, 81229, S3870, 0209U) is considered **medically necessary** when:

   A. The member/enrollee has developmental delay and/or intellectual disability, excluding isolated speech/language delay (see below), **OR**

   B. The member/enrollee has autism spectrum disorder, **OR**

   C. The member/enrollee has multiple congenital anomalies not specific to a well-delineated genetic syndrome, **OR**

   D. The member/enrollee has short stature.

II. Chromosomal microarray analysis for developmental delay, intellectual disability, autism spectrum disorder, or congenital anomalies (81228, 81229, S3870, 0209U) is considered **investigational** for all other conditions of delayed development, including:

   A. Isolated speech/language delay*.

*See Background and Rationale section for more information about this exclusion.

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Autism Spectrum Disorder / Intellectual Disability Panel Analysis

I. The use of an autism spectrum disorder / intellectual disability panel (0156U, 81470, 81471, 81479, 81185, 81236, 81302, 81321) is considered **investigational**.

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ANGELMAN/PRADER-WILLI SYNDROME

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

I. *SNRPN/UBE3A* methylation analysis (81331), FISH analysis for 15q11-q13 deletion (88271, 88273), uniparental disomy analysis (81402), and imprinting center defect analysis (81331) to establish or confirm a diagnosis of Angelman or Prader-Willi syndrome is considered **medically necessary** when:

A. The member/enrollee meets all of the following clinical features of Angelman syndrome:

1. Developmental delay by age six to twelve months, eventually classified as severe, **AND**

2. Speech impairment, with minimal to no use of words; receptive language skills and nonverbal communication skills higher than expressive language skills, **AND**

3. Movement or balance disorder, usually ataxia of gait and/or tremulous movement of the limbs, **AND**

4. 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/enrollee meets one of the following age-specific features of Prader-Willi syndrome:

1. The member/enrollee is age one month to two years with:

a) Hypotonia with poor appetite and suck, **AND**

b) Developmental delay, **OR**

2. The member/enrollee is age two to six years with:

a) Hypotonia with history of poor suck, **AND**

b) Global developmental delay, **OR**

3. The member/enrollee 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**

4. The member/enrollee 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**

      (1) Typical behavioral findings (temper tantrums, stubbornness, manipulative behavior, and obsessive-compulsive characteristics).

II. *SNRPN/UBE3A* methylation analysis (81331), FISH analysis for 15q11-q13 deletion (88271, 88273), uniparental disomy analysis (81402), and imprinting center defect analysis (81331) 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:

1. *SNRPN/UBE3A* methylation analysis
2. If *UBE3A* methylation analysis is normal, then proceed to deletion analysis of 15q11-q13
3. If deletion analysis is normal, consider UPD analysis of chromosome 15
4. If UPD is normal, then proceed to imprinting defect (ID) analysis.

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BECKWITH-WIEDEMANN/RUSSELL-SILVER SYNDROME

H19 and *KCNQ1OT1* methylation analysis, deletion/duplication analysis of 11p15, uniparental disomy analysis, *CDKN1C* sequencing and/or deletion/duplication analysis

I. *H19* and *KCNQ1OT1* methylation analysis (81401), deletion/duplication analysis of 11p15 (81479), uniparental disomy analysis (81402), *CDKN1C* sequencing and/or deletion/duplication analysis (81479) to confirm or establish a diagnosis of Beckwith-Wiedemann or Russell-Silver syndrome is **medically necessary** when:

A. The member/enrollee has at least one of the following clinical features of Beckwith-Wiedemann syndrome (BWS):

1. Macroglossia, **OR**
2. Omphalocele (also sometimes referred to as exomphalos), **OR**
3. Embryonal tumor, such as Wilms tumor (unilateral or bilateral), hepatoblastoma, or nephroblastomatosis, **OR**
4. Hemihyperplasia (lateralized overgrowth) of one or more body segments, **OR**
5. Macrosomia, defined as pre- and/or postnatal overgrowth, often using a cutoff of >90th or >97th centile, depending on the study, **OR**
6. Hyperinsulinemic hypoglycemia, **OR**
7. Cytomegaly of the adrenal cortex, which is considered pathognomonic for BWS, **OR**
8. Other pathologic findings, including placental mesenchymal dysplasia and pancreatic adenomatosis, **OR**
9. Family history of 1 or more family members with clinical features suggestive of BWS, **OR**
10. 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**
11. Unilateral or bilateral earlobe creases and/or posterior helical ear pits, **OR**

12. Characteristic facies (i.e., infraorbital creases, midface retrusion, thin vermilion of the upper lip, and prominent jaw), **OR**

13. Kidney anomalies, such as structural malformations, nephrocalcinosis, or medullary sponge kidney, **OR**

14. Large umbilical hernia that requires surgical correction, **OR**

15. Other embryonal tumors, including rhabdomyosarcoma, neuroblastoma, or adrenal tumors (pheochromocytoma, adrenocortical carcinoma), **OR**

16. Transient hypoglycemia requiring medical intervention, **OR**

B. The member/enrollee meets at least three of the following Netchine-Harbison clinical scoring system (NH-CSS) clinical features for Russell-Silver syndrome:

1. Small for gestational age (birth weight and/or length 2 SD or more below the mean for gestational age), **OR**

2. Postnatal growth failure (length/height 2 SD or more below the mean at 24 months), **OR**

3. Relative macrocephaly at birth (head circumference more than 1.5 SD above birth weight and/or length), **OR**

4. Frontal bossing or prominent forehead (forehead projecting beyond the facial plane on a side view as a toddler [1–3 years]), **OR**

5. 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**

6. 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.

II. *H19* and *KCNQ1OT1* methylation analysis (81401), deletion/duplication analysis of 11p15 (81479), uniparental disomy analysis (81402), *CDKN1C* sequencing and/or deletion/duplication analysis (81479) to confirm or establish a diagnosis of Beckwith-Wiedemann or Russell-Silver syndrome is considered **investigational** for all other indications.

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CYSTIC FIBROSIS

CFTR Sequencing and/or Deletion/Duplication Analysis

I. *CFTR* sequencing and/or deletion/duplication analysis (81222, 81223) to establish or confirm a diagnosis of cystic fibrosis is considered **medically necessary** when:

   A. The member/enrollee has a positive (greater than or equal to 60 mmol/L) or inconclusive (30-59 mmol/L) sweat chloride test.

II. *CFTR* sequencing and/or deletion/duplication analysis (81222, 81223) 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)**

I. *CFTR* intron 9 polyT and TG analysis (81224) in a member/enrollee is considered **medically necessary** when:

   A. The member/enrollee has a diagnosis of cystic fibrosis, **AND**

   B. The member/enrollee has an R117H variant in the *CFTR* gene.

II. *CFTR* intron 9 polyT and TG analysis (81224) in a member/enrollee with a diagnosis of cystic fibrosis is considered **investigational** for all other indications.

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CHARGE SYNDROME

CHD7 Sequencing and/or Deletion/Duplication Analysis

I. *CHD7* sequencing and/or deletion/duplication analysis (81407, 81479) to establish or confirm a diagnosis of CHARGE syndrome is considered **medically necessary** when:

   A. The member/enrollee has at least two of the following:

      1. Coloboma of the iris, retina, choroid, and/or disc, **OR**

2. Anophthalmos or microphthalmos, **OR**
3. Choanal atresia or stenosis **OR**
4. Cleft palate with or without cleft lip, **OR**
5. 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**
6. Ear malformations (auricular abnormalities, middle ear abnormalities/ossicular malformations, and temporal bone abnormalities), **OR**
7. Tracheoesophageal fistula or esophageal atresia, **OR**
8. Cardiovascular malformation (conotruncal defects (e.g., tetralogy of Fallot), AV canal defects, and aortic arch anomalies), **OR**
9. Hypogonadotropic hypogonadism (micropenis or cryptorchidism, hypoplastic labia, abnormal or absent uterus, delayed or absent puberty), **OR**
10. Developmental delay or intellectual disability, **OR**
11. Growth deficiency (short stature), **OR**
12. Characteristic physical features of the face, neck, and/or hands, **OR**
13. Brain MRI showing clivus hypoplasia or hypoplasia of the cerebellar vermis.

II. *CHD7* sequencing and/or deletion/duplication analysis (81407, 81479) to establish or confirm a diagnosis of CHARGE syndrome is considered **investigational** for all other indications.

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FANCONI ANEMIA

Fanconi Anemia Multigene Panel

I. Multigene panel analysis to establish or confirm a genetic diagnosis of Fanconi anemia (81162, 81307, 81479) is considered **medically necessary** when:

A. The member/enrollee had a positive or inconclusive result via chromosome breakage analysis, **AND**

B. The member/enrollee displays at least one of the following:

1. Prenatal and/or postnatal short stature, **OR**
2. Abnormal skin pigmentation (e.g., café au lait macules, hyper- or hypopigmentation), **OR**
3. Skeletal malformations (e.g., hypoplastic thumb, hypoplastic radius, vertebral anomalies), **OR**
4. Microcephaly, **OR**
5. Ophthalmic anomalies, **OR**
6. Genitourinary tract anomalies (e.g., horseshoe kidney, hypospadias, bicornuate uterus), **OR**
7. Macrocytosis, **OR**
8. Increased fetal hemoglobin (often precedes anemia), **OR**
9. Cytopenia (especially thrombocytopenia, leukopenia and neutropenia), **OR**
10. Progressive bone marrow failure, **OR**
11. Adult-onset aplastic anemia, **OR**
12. Myelodysplastic syndrome (MDS), **OR**
13. Acute myelogenous leukemia (AML), **OR**
14. Early-onset solid tumors (e.g., squamous cell carcinomas of the head and neck, esophagus, and vulva; cervical cancer; and liver tumors), **OR**
15. Inordinate toxicities from chemotherapy or radiation.

II. Multigene panel analysis to establish or confirm a genetic diagnosis of Fanconi anemia (81162, 81307, 81479) is considered **investigational** for all other indications.

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FRAGILE X SYNDROME

FMR1 Repeat and Methylation Analysis

I. *FMR1* repeat and methylation analysis (81243, 81244) to establish or confirm a genetic diagnosis of Fragile X syndrome or Fragile X-associated disorders is considered **medically necessary** when:

A. The member/enrollee has unexplained intellectual disability or developmental delay, **OR**

B. The member/enrollee has a male reproductive system and has unexplained autism spectrum disorder, **OR**

C. The member/enrollee has a female reproductive system and has unexplained autism spectrum disorder, **AND**

1. 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**

2. Has at least one close relative with a neurodevelopmental disorder consistent with X linked inheritance, premature ovarian failure, ataxia or tremor, **OR**

D. The member/enrollee has primary ovarian insufficiency (cessation of menses before age 40), **OR**

E. The member/enrollee is 50 years of age or older with progressive intention tremor and cerebellar ataxia of unknown origin.

II. *FMR1* repeat and methylation analysis (81243, 81244) to establish or confirm a genetic diagnosis of Fragile X syndrome or Fragile X-associated disorders is considered **investigational** for all other indications.

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HEREDITARY HEMORRHAGIC TELANGIECTASIA (HHT)

Hereditary Hemorrhagic Telangiectasia (HHT) Multigene Panel

I. Hereditary hemorrhagic telangiectasia (HHT) multigene panel analysis (81405, 81406, 81479) to establish or confirm a diagnosis of HHT is considered **medically necessary** when:

   A. The member/enrollee has any of the following clinical features of HHT:

      1. Spontaneous and recurrent nosebleeds (epistaxis), **OR**

      2. Mucocutaneous telangiectases at characteristic sites, including lips, oral cavity, fingers, and nose, **OR**

      3. Visceral arteriovenous malformation (AVM) (either pulmonary, cerebral, spinal, gastrointestinal or pancreatic), **AND**

   B. The panel includes, at a minimum, the following genes: *ACVRL1*, *ENG*, and *SMAD4*.

II. Hereditary hemorrhagic telangiectasia (HHT) multigene panel analysis (81405, 81406, 81479) to establish or confirm a diagnosis of HHT is considered **investigational** for all other indications.

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NEUROFIBROMATOSIS 1

NF1 Sequencing and/or Deletion/Duplication Analysis

I. *NF1* sequencing and/or deletion/duplication analysis (81408) is considered **medically necessary** when:

   A. The member/enrollee has at least one of the following:

      1. 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**

      2. Two or more neurofibromas of any type or one plexiform neurofibroma, **OR**

3. Freckling in the axillary or inguinal regions, **OR**
4. Optic glioma, **OR**
5. Two or more Lisch nodules (iris hamartomas), **OR**
6. A distinctive osseous lesion such as sphenoid dysplasia or tibial pseudarthrosis, **OR**

B. The member/enrollee 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).

II. *NF1* sequencing and/or deletion/duplication analysis (81408) is considered **investigational** for all other indications.

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NF2-RELATED SCHWANNOMATOSIS (PREVIOUSLY KNOWN AS NEUROFIBROMATOSIS 2)

NF2 Sequencing and/or Deletion/Duplication Analysis

I. *NF2* sequencing and/or deletion/duplication analysis (81405, 81406) is considered **medically necessary** when:

A. The member/enrollee had an *NF2* pathogenic variant identified on tumor tissue testing, **OR**

B. The member/enrollee is an adult with at least one of the following:

1. Bilateral vestibular schwannomas, **OR**
2. Unilateral vestibular schwannoma, **AND**

a) At least two of the following:

(1) Meningioma, **OR**

(2) Schwannoma, **OR**

(3) Glioma, **OR**

(4) Neurofibroma, **OR**

(5) Cataract in the form of subcapsular lenticular opacities, **OR**

(6) Cortical wedge cataract, **OR**

C. The member/enrollee is an adult with multiple meningiomas and either of the following:

1. Unilateral vestibular schwannoma, **OR**
2. 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/enrollee is a child with at least two of the following:

1. A schwannoma at any location including intradermal, **OR**
2. Skin plaques present at birth or in early childhood (often plexiform schwannoma on histology), **OR**
3. A meningioma, particularly non-meningothelial (non-arachnoidal) cell in origin, **OR**
4. A cortical wedge cataract, **OR**
5. A retinal hamartoma, **OR**
6. A mononeuropathy, particularly causing a facial nerve palsy, foot or wrist drop, or third nerve palsy.

II. *NF2* sequencing and/or deletion/duplication analysis (81405, 81406) is considered **investigational** for all other indications.

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NOONAN SPECTRUM DISORDERS/RASOPATHIES

Noonan Spectrum Disorders/RASopathies Multigene Panel

I. The use of a multigene panel to confirm or establish a diagnosis of a Noonan spectrum disorder/RASopathy (e.g., Noonan syndrome, Legius syndrome, Costello syndrome, Cardio-facial-cutaneous syndrome, NF1, Noonan-like syndrome) (81442) is considered **medically necessary** when:

   A. The member/enrollee has at least one of the following:

      1. Characteristic facies (low-set, posteriorly rotated ears with fleshy helices, vivid blue or blue-green irises, widely spaced, down slanted eyes, epicanthal folds, ptosis), **OR**
      2. Short stature, **OR**
      3. Congenital heart defect (most commonly pulmonary valve stenosis, atrial septal defect, and/or hypertrophic cardiomyopathy), **OR**
      4. Developmental delay, **OR**
      5. Broad or webbed neck, **OR**
      6. Unusual chest shape with superior pectus carinatum, inferior pectus excavatum, **OR**
      7. Widely spaced nipples, **OR**
      8. Cryptorchidism in those with a male reproductive system, **OR**
      9. Lentigines, **OR**
      10. Café au lait macules.

II. The use of a multigene panel to confirm or establish a diagnosis of a Noonan spectrum disorder/RASopathy (e.g., Noonan syndrome, Legius syndrome, Costello syndrome, Cardio-facial-cutaneous syndrome, NF1, Noonan-like syndrome) (81442) is considered **investigational** for all other indications.

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PIK3CA-Related Overgrowth Spectrum

PIK3CA Sequencing and/or Deletion/Duplication Analysis

I. *PIK3CA* sequencing and/or deletion/duplication analysis (81479) to establish a diagnosis of *PIK3CA*-Related Segmental Overgrowth is considered **medically necessary** when:

A. The member/enrollee displays at least one of the following on brain imaging:

1. Hemimegalencephaly, **OR**
2. Focal cortical dysplasia, **OR**
3. Dysplastic megalencephaly, **OR**

B. The member/enrollee displays at least one of the following, from birth or with onset in early childhood:

1. Overgrowth of any of a wide variety of tissues including (but not limited to) brain, adipose, vascular, muscle, skeletal, nerve, **OR**
2. Vascular malformations including (but not limited to) capillary, venous, arteriovenous, or mixed malformations, **OR**
3. Lymphatic malformations, **OR**
4. Cutaneous findings including epidermal nevi and hyperpigmented macules, **OR**
5. Single or multiple digital anomalies of the hands or feet (e.g., macrodactyly, syndactyly, polydactyly, sandal-toe gap), **OR**
6. Kidney malformations (e.g., pelviectasis, dilated ureters, hydronephrosis, duplicated renal arteries, renal cysts, enlarged kidneys), **OR**
7. Benign tumors, with the exceptions of Wilms tumor and nephroblastomatosis (i.e., diffuse or multifocal clusters of persistent embryonal cells).

II. *PIK3CA* sequencing and/or deletion/duplication analysis (81479) 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.

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TUBEROUS SCLEROSIS COMPLEX (TSC)

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

I. *TSC1* and *TSC2* sequencing and/or deletion/duplication analysis (81405, 81406, 81407) to establish or confirm a diagnosis of Tuberous Sclerosis Complex (TSC) is considered **medically necessary** when:

A. The member/enrollee has at least one of the following major features of TSC:

1. Three or more angiofibromas or fibrous cephalic plaque, **OR**
2. Cardiac rhabdomyoma, **OR**
3. Multiple cortical tubers and/or radial migration lines, **OR**
4. Hypomelanotic macules (3 or more macules that are at least 5 mm in diameter), **OR**
5. Lymphangioleiomyomatosis (LAM), **OR**
6. Multiple retinal nodular hamartomas, **OR**
7. Renal angiomyolipoma, **OR**
8. Shagreen patch, **OR**
9. Subependymal giant cell astrocytoma (SEGA), **OR**
10. Two or more subependymal nodules (SENs), **OR**
11. Two or more ungual fibromas, **OR**

B. The member/enrollee has at least two of the following minor features of TSC:

1. Sclerotic bone lesions, **OR**
2. "Confetti" skin lesions (numerous 1- to 3-mm hypopigmented macules scattered over regions of the body such as the arms and legs), **OR**
3. Four or more dental enamel pits, **OR**
4. Two or more intraoral fibromas, **OR**
5. Multiple renal cysts, **OR**
6. Nonrenal hamartomas, **OR**
7. Retinal achromic patch.

II. *TSC1* and *TSC2* sequencing and/or deletion/duplication analysis (81405, 81406, 81407) to establish or confirm a diagnosis of Tuberous Sclerosis Complex is considered **investigational** for all other indications.

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OTHER COVERED MULTISYSTEM INHERITED DISORDERS

The following is a list of conditions that have a known genetic association. Due to their relative rareness, it may be appropriate to cover these genetic tests to establish or confirm a diagnosis.

I. Genetic testing to establish or confirm one of the following multisystem inherited disorders to guide management is considered **medically necessary** when the member/enrollee demonstrates clinical features* consistent with the disorder (the list is not meant to be comprehensive, see II below):

A. Alagille syndrome
B. Alport syndrome
C. Branchiootorenal spectrum disorder
D. Cerebral cavernous malformations
E. Coffin-Siris syndrome
F. Cornelia de Lange syndrome
G. *FGFR2* craniosynostosis syndromes
H. Holoprosencephaly
I. Holt-Oram syndrome
J. Incontinentia pigmenti
K. Joubert and Meckel-Gruber syndromes
L. Kabuki syndrome
M. *MYH9*-related disorders
N. Proteus syndrome
O. Pseudoxanthoma elasticum
P. Rubinstein-Taybi syndrome
Q. Schwannomatosis
R. *SHOX* deficiency disorders
S. Waardenburg syndrome

II. 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 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 source.

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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:
    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.

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BACKGROUND AND RATIONALE

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

American Academy of Pediatrics

The American Academy of Pediatrics (2014) issued a clinical report on the optimal medical genetics evaluation of a child with developmental delays (DD) or intellectual disability (ID), which stated "CMA [chromosome microarray analysis] now should be considered a first-tier diagnostic test in all children with [global] GDD/ID for whom the causal diagnosis is not known…. CMA is now the standard for diagnosis of patients with GDD/ID, as well as other conditions, such as autism spectrum disorders or multiple congenital anomalies." (page e905)

American College of Medical Genetics and Genomics (ACMG)

The ACMG (2010, reaffirmed 2020) published a Clinical Practice Resource on array-based technologies and their clinical utilization for detecting chromosomal abnormalities. CMA testing

for copy number variants was recommended as a first-line test in the initial postnatal evaluation of individuals with the following:

- Multiple anomalies not specific to a well-delineated genetic syndrome
- Apparently nonsyndromic DD/ID
- ASD [autism spectrum disorder]

A 2021 focused revision to the ACMG practice resource "Genetic evaluation of short stature" states: "Chromosomal microarray…should be part of the initial genetic work-up for idiopathic short stature (ISS) and small for gestational age (SGA) with persistent short stature as well as syndromic short stature…" (p. 813)

CMA is considered investigational for all other indications, including members/enrollees with isolated speech/language delay (AAP 2014 Clinical Report, page e905), as diagnostic yield in this clinical situation is thought to be low.

Autism Spectrum Disorder/Intellectual Disability Panel Analysis

American Academy of Pediatrics (AAP)

The most recent AAP guideline for identification, evaluation and management of children with autism spectrum disorders did not address the use of multigene panels. Their recommendations for genetic testing in this population include chromosomal microarray, fragile X, Rett syndrome, and/or possibly whole exome sequencing (Hyman et al, 2020, page 15, Table 8).

American Academy of Neurology

The American Academy of Neurology (Michaelson et al, 2011) does not comment or provide evidence to support the use of panel-based analysis for genetic and metabolic evaluation of children with global developmental delay or intellectual disability.

American Academy of Child and Adolescent Psychiatry

In their practice parameter for the assessment and treatment of autism spectrum disorders (Volkmar et al, 2014), the guideline does not mention or recommend the use of Developmental Delay/Intellectual Disability, Autism Spectrum Disorder, or Congenital Anomalies Panel Tests.

There is insufficient evidence to support the use of this test. No recommendations for or against this testing within standard professional society guidelines covering this area of testing were identified.

Angelman/Prader-Willi Syndrome - *SNRPN/UBE3A* methylation analysis, 15q11-q13 FISH analysis, chromosome 15 uniparental disomy analysis, and imprinting center defect analysis

GeneReviews: Angelman Syndrome

GeneReviews is an expert-authored review of current literature on a genetic disease, and goes through a rigorous editing and peer review process before being published online. Diagnostic testing for Angelman syndrome is recommended for individuals with the following:

- Normal prenatal and birth history, normal head circumference at birth, no major birth defects
- Delayed attainment of developmental milestones by age six to twelve months, eventually classified as severe, without loss of skills
- Speech impairment, with minimal to no use of words; receptive language skills and nonverbal communication skills higher than expressive language skills
- Movement or balance disorder, usually ataxia of gait and/or tremulous movement of the limbs
- Behavioral uniqueness including any combination of frequent laughter/smiling, apparent happy demeanor, excitability (often with hand-flapping movements), and hypermotoric behavior

The clinical diagnosis of Angelman syndrome can be established in a proband based on clinical diagnostic criteria, or molecular diagnosis can be established in a proband with suggestive findings and findings on molecular genetic testing that suggest deficient expression or function of the maternally inherited *UBE3A* allele, such as the following:

- Abnormal methylation at 15q11.2-q13 due to one of the following:
    - Deletion of the maternally inherited 15q11.2-q13 region (which includes *UBE3A*)
    - Uniparental disomy (UPD) of the paternal chromosome region 15q11.2-q13
    - An imprinting defect of the maternal chromosome 15q11.2-q13 region
- A pathogenic variant in the maternally derived *UBE3A*

GeneReviews: Prader-Willi syndrome

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

Per GeneReviews, DNA methylation analysis is the only technique that will diagnose Prader-Willi syndrome (PWS) caused by all three genetic common mechanisms (paternal deletion,

maternal uniparental disomy and imprinting defects), as well as differentiate PWS from Angelman syndrome (AS) in deletion cases.

The presence of the following findings at the age indicated is sufficient to justify DNA methylation analysis for PWS:

Age one month two years

- Hypotonia with poor appetite and suck in the neonatal period
- Developmental delay

Age two to six years

- Hypotonia with history of poor suck
- Developmental delay

Age six to 12 years

- History of hypotonia with poor suck (hypotonia often persists)
- Developmental delay
- Excessive eating with central obesity if uncontrolled

Age 13 years to adulthood

- Cognitive impairment, usually mild intellectual disability
- Excessive eating and hyperphagia with central obesity if uncontrolled externally
- Hypothalamic hypogonadism and/or typical behavior problems*

*Per GeneReviews, a distinctive behavioral phenotype (temper tantrums, stubbornness, manipulative behavior, and obsessive-compulsive characteristics) is common. Assess for behavioral issues annually after age two years.

Beckwith-Wiedemann/Russell-Silver Syndrome - *H19* and *KCNQ1OT1* methylation analysis, deletion/duplication analysis of 11p15, uniparental disomy analysis, *CDKN1C* sequencing and/or deletion/duplication analysis

GeneReviews: Beckwith-Wiedemann Syndrome (BWS)

GeneReviews is an expert-authored review of current literature on a genetic disease, and goes through a rigorous editing and peer review process before being published online. The recommended diagnostic testing for Beckwith-Wiedemann Syndrome (BWS) is as follows:

A diagnosis of BWS can be established in a proband with at least one tier 1 or tier 2 clinical finding AND either:

- A constitutional epigenetic or genomic alteration leading to an abnormal methylation pattern at 11p15.5 known to be associated with BWS; OR
- A copy number variant of chromosome 11p15.5 known to be associated with BWS; OR
- A heterozygous BWS-causing pathogenic (or likely pathogenic) variant in *CDKN1C*.

Tier 1 findings: The features listed below, whether as a single finding or as a combination of findings, are highly suggestive of the diagnosis:

- Macroglossia
- Omphalocele (also sometimes referred to as exomphalos)
- Embryonal tumor, such as Wilms tumor (unilateral or bilateral), hepatoblastoma, or nephroblastomatosis
- Hemihyperplasia (lateralized overgrowth) of one or more body segments
- Macrosomia, defined as pre- and/or postnatal overgrowth, often using a cutoff of >90th or >97th centile, depending on the study
- Hyperinsulinemic hypoglycemia
- Cytomegaly of the adrenal cortex, which is considered pathognomonic for BWS
- Other pathologic findings, including placental mesenchymal dysplasia and pancreatic adenomatosis
- Family history of ≥1 family members with clinical features suggestive of BWS

Tier 2 findings, listed below, are less specific than tier 1 findings:

- Visceromegaly, typically from an imaging study such as ultrasound, involving ≥1 intra-abdominal organs, such as the liver, kidneys, and/or adrenal glands
- Unilateral or bilateral earlobe creases and/or posterior helical ear pits
- Characteristic facies, which may include infraorbital creases, midface retrusion, thin vermilion of the upper lip, and prominent jaw (which may become evident in childhood).

- Kidney anomalies, such as structural malformations, nephrocalcinosis, or medullary sponge kidney
- Large umbilical hernia that requires surgical correction
- Other embryonal tumors, including rhabdomyosarcoma, neuroblastoma, or adrenal tumors (pheochromocytoma, adrenocortical carcinoma)
- Transient hypoglycemia requiring medical intervention

GeneReviews: Silver-Russell Syndrome

GeneReviews is an expert-authored review of current literature on a genetic disease, and goes through a rigorous editing and peer review process before being published online. The recommended diagnostic testing for Russell-Silver Syndrome (RSS) is as follows:

"Silver-Russell syndrome (SRS) should be suspected in individuals who meet the NH-CSS clinical criteria, which includes the following:

- Small for gestational age (birth weight and/or length ≥2 SD below the mean for gestational age)
- Postnatal growth failure (length/height ≥ SD below the mean at 24 months)
- Relative macrocephaly at birth (head circumference >1.5 SD above birth weight and/or length)
- Frontal bossing or prominent forehead (forehead projecting beyond the facial plane on a side view as a toddler [1–3 years])
- Body asymmetry (limb length discrepancy ≥0.5 cm, or <0.5 cm with ≥2 other asymmetric body parts)
- Feeding difficulties or body mass index ≤2 SD at 24 months or current use of a feeding tube or cyproheptadine for appetite stimulation.

If an individual meets four of the six criteria, the clinical diagnosis is suspected and molecular confirmation testing is warranted. Some rare individuals meeting three of the six criteria have had a positive molecular confirmation for SRS. The diagnosis of SRS is established in a proband who meets four of the six Netchine-Harbison clinical diagnostic criteria and who has findings on molecular genetic testing consistent with either hypomethylation on chromosome 11p15.5 or maternal uniparental disomy (UPD) for chromosome 7.

CYSTIC FIBROSIS

Cystic Fibrosis - *CFTR* Sequencing and/or Deletion/Duplication Analysis

Cystic Fibrosis Foundation

Consensus-based guidelines from the Cystic Fibrosis Foundation (2017) outline the ways in which a CF diagnosis can be established (see below). Characteristic features of CF include chronic sinopulmonary disease (such as persistent infection with characteristic CF pathogens, chronic productive cough, bronchiectasis, airway obstruction, nasal polyps, and digital clubbing), gastrointestinal/nutritional abnormalities (including meconium ileus, pancreatic insufficiency, chronic pancreatitis, liver disease, and failure to thrive), salt loss syndromes, and obstructive azoospermia in those with a male reproductive system (due to congenital absence of the vas deferens, or CAVD).

These guidelines state that, "Individuals presenting with a positive newborn screen, symptoms of CF, or a positive family history, and sweat chloride values in the intermediate range (30- 59 mmol/L) on 2 separate occasions may have CF. They should be considered for extended *CFTR* gene analysis and/ or *CFTR* functional analysis." (p. S8)

Cystic Fibrosis - *CFTR* Intron 9 PolyT and TG Analysis (aka Intron 8 poly-T/TG)

American College of Medical Genetics and Genomics (ACMG)

ACMG has recommended that all R117H positive results require reflex testing for the 5T/7T/9T variant in the polythymidine tract at intron 8 in *CFTR* gene. For R117H/5T positive heterozygotes, testing of parents is recommended to determine the inheritance of the R117H and the 5T variant (i.e., cis vs. trans position). For diagnostic testing, and particularly for testing for CBAVD in those with a male reproductive system with infertility, it is recommended that the intron 8 variant be included in the testing panel. (p. 1294)

CHARGE Syndrome - *CHD7* Sequencing and/or Deletion/Duplication Analysis

GeneReviews: CHD7 Disorder

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

The mnemonic CHARGE syndrome, introduced in the premolecular era, stands for ***c***oloboma, ***h***eart defect, choanal ***a***tresia, ***r***etarded growth and development, ***g***enital hypoplasia, ***e***ar anomalies (including deafness). Following the identification of the genetic cause of *CHD7*

disorder, the phenotypic spectrum expanded to include cranial nerve anomalies, vestibular defects, cleft lip and/or palate, hypothyroidism, tracheoesophageal anomalies, brain anomalies, seizures, and renal anomalies.

CHD7 disorder should be suspected in individuals with combinations of the following findings and family history: :

- Coloboma of the iris, retina, choroid, and/or disc, and/or anophthalmos or microphthalmos
- Choanal atresia or stenosis: unilateral or bilateral, bony or membranous, confirmed by axial sections of non-enhanced axial CT scan
- Cleft palate with or without cleft lip (Note: Choanal atresia is rare in the presence of a cleft palate.)
    - Cranial nerve dysfunction or anomaly
    - Cranial nerve I. Hyposmia or anosmia
    - Cranial nerve VII. Facial palsy (unilateral or bilateral)
    - Cranial nerve VIII. Sensorineural hearing loss and/or balance problems, hypoplasia or aplasia on imaging
    - Cranial nerve IX/X. Difficulty with sucking/swallowing and aspiration, gut motility problems
- Ear malformations (most characteristic of *CHD7* disorder)
    - Auricle. Short, wide ear with little or no lobe, "snipped-off" helix, prominent antihelix that is often discontinuous with tragus, triangular concha, decreased cartilage; often protruding and usually asymmetric
    - Middle ear. Ossicular malformations (resulting in a typical wedge-shaped audiogram due to mixed sensorineural and conductive hearing loss)
    - Temporal bone abnormalities (most commonly determined by temporal bone CT scan). Mondini defect of the cochlea (cochlear hypoplasia), absent or hypoplastic semicircular canals
- Tracheoesophageal fistula or esophageal atresia
- Cardiovascular malformation, including conotruncal defects (e.g., tetralogy of Fallot), AV canal defects, and aortic arch anomalies
- Hypogonadotropic hypogonadism
    - Male reproductive system at birth. Micropenis and cryptorchidism
    - Female reproductive system at birth. Hypoplastic labia, abnormal or (rarely) absent uterus
    - Those with a male reproductive system and those with a female reproductive system. Delayed or absent puberty, often in combination with anosmia
- Developmental delay / intellectual disability, delayed motor milestones, often secondary to sensory and balance deficits

- Growth deficiency. Short stature, usually postnatal with or without growth hormone deficiency
- Other clinical features
    - Face. Square-shaped with broad forehead, broad nasal bridge, prominent nasal columella, flattened malar area, facial palsy or other asymmetry, cleft lip, and small chin (gets larger and broader with age)
    - Neck. Short and wide with sloping shoulders
    - Hands. Typically, short, wide palm with hockey-stick crease, short fingers, and finger-like thumb (see Figure 3); polydactyly and reduction defects in a small percentage
- Brain MRI. Clivus hypoplasia or hypoplasia of cerebellar vermis

Fanconi Anemia Multigene Panel

Fanconi Anemia Research Foundation

The Fanconi Anemia Research Foundation (2020) issued guidelines on diagnosis and management of the disease, which stated the following in regard to genetic testing:

If the results from the chromosome breakage test are positive, genetic testing should be performed to identify the specific FA-causing variants. Genetic testing enables accurate diagnosis and improves clinical care for individuals with anticipated genotype/phenotype manifestations and for relatives who are heterozygous carriers of FA gene variants that confer increased risk for malignancy. (p. 28, additional testing methodologies pages 29-45.)

GeneReviews: Fanconi Anemia

GeneReviews is an expert-authored review of current literature on a genetic disease, and goes through a rigorous editing and peer review process before being published online. Fanconi anemia (FA) should be suspected in individuals with the following clinical and laboratory features.

Physical features (in ~75% of affected persons)

- Prenatal and/or postnatal short stature
- Abnormal skin pigmentation (e.g., café au lait macules, hypopigmentation)
- Skeletal malformations (e.g., hypoplastic thumb, hypoplastic radius)
- Microcephaly
- Ophthalmic anomalies
- Genitourinary tract anomalies

Laboratory findings

- Macrocytosis
- Increased fetal hemoglobin (often precedes anemia)
- Cytopenia (especially thrombocytopenia, leukopenia, and neutropenia)

Pathology findings

- Progressive bone marrow failure
- Adult-onset aplastic anemia
- Myelodysplastic syndrome (MDS)
- Acute myelogenous leukemia (AML)
- Early-onset solid tumors (e.g., squamous cell carcinomas of the head and neck, esophagus, and vulva; cervical cancer; liver tumors)
- Inordinate toxicities from chemotherapy or radiation

Fragile X Syndrome - *FMR1* Repeat and Methylation Analysis

American College of Medical Genetics and Genomics (ACMG)

The ACMG (2005) made the following recommendations on diagnostic testing for fragile X syndrome (FXS).

- Individuals of either sex with mental retardation, developmental delay, or autism, especially if they have (a) any physical or behavioral characteristics of fragile X syndrome, (b) a family history of fragile X syndrome, or (c) relatives with a male reproductive system or female reproductive system with undiagnosed mental retardation. (p. 586)
- Women who are experiencing reproductive or fertility problems associated with elevated follicle stimulating hormone (FSH) levels, especially if they have (a) a family history of premature ovarian failure, (b) a family history of fragile X syndrome or (c) relatives with a male reproductive system or female reproductive system with undiagnosed mental retardation. (p. 586)
- Men and women who are experiencing late onset intentional tremor and cerebellar ataxia of unknown origin, especially if they have (a) a family history of movement disorders, (b) a family history of fragile X syndrome, or (c) relatives with a male reproductive system or female reproductive with undiagnosed mental retardation. (p. 586) Initial studies indicate a penetrance of combined tremor and ataxia among men ages 50 years or more with the premutation of about 20 –40%. (p. 585)

The ACMG (2013) made the following testing recommendations on evaluation for the etiology of autism spectrum disorders (ASDs). In it, they recommend testing for fragile X syndrome in the following scenarios:

- It is recommended that all those with a male reproductive system with unexplained autism be tested for fragile X syndrome. (p. 402)
- All those with a female reproductive system with ASDs with clinical parameters such as (i) a phenotype compatible with fragile X; (ii) a family history positive for neurodevelopmental disorder consistent with X-linked inheritance; or (iii) premature ovarian insufficiency, ataxia, or tremors in close relatives. (p. 402)

GeneReviews: FMR1 Disorders

GeneReviews is an expert-authored review of current literature on a genetic disease, and goes through a rigorous editing and peer review process before being published online. The recommended testing for *FMR1*-related disorders is as follows:

GeneReviews (last update: November 21, 2019) recommends that *FMR1* testing be considered for any patient with the following clinical findings:

- Those with a male reproductive system and those with a female reproductive system with intellectual disability or developmental delay of unknown cause
- Those with a male reproductive system with unexplained autism spectrum disorder
- Those with a female reproductive system with autism spectrum disorder and (i) a phenotype compatible with fragile X; (ii) a family history positive for X-linked neurodevelopmental disorders; or (iii) premature ovarian insufficiency, ataxia, or tremors in close relatives.
- Those with a male reproductive system and those with a female reproductive system who are experiencing late-onset intention tremor and cerebellar ataxia of unknown cause. Men and women with dementia may also be considered, if ataxia, parkinsonism, or tremor are also present.
- Those with a female reproductive system with unexplained primary ovarian insufficiency or failure (hypergonadotropic hypogonadism) before age 40 years

Hereditary Hemorrhagic Telangiectasia Multigene Panel

Second International Guidelines for the Diagnosis and Management of Hereditary Hemorrhagic Telangiectasia

The goal of the Second International HHT Guidelines process was to develop evidence-based consensus guidelines for the management and prevention of HHT-related symptoms and

complications. The expert panel generated and approved new recommendations. With regard to diagnosis, the following was recommended:

The expert panel recommends that clinicians refer patients for diagnostic genetic testing for HHT (page 992):

- to identify the causative mutation in a family with clinically confirmed HHT;
- to establish a diagnosis in relatives of a person with a known causative mutation, including:
    - individuals who are asymptomatic or minimally symptomatic and
    - individuals who desire prenatal testing; and
- to assist in establishing a diagnosis of HHT in individuals who do not meet clinical diagnostic criteria.

The expert panel recommends that for individuals who test negative for *ENG* and *ACVRL1* coding sequence mutations, *SMAD4* testing should be considered to identify the causative mutation.

GeneReviews: Hereditary Hemorrhagic Telangiectasia

GeneReviews is an expert-authored review of current literature on a genetic disease, and goes through a rigorous editing and peer review process before being published online. Diagnostic testing for HHT is recommended when the following clinical findings are seen:

- Spontaneous and recurrent nosebleeds (epistaxis).
    - With night-time nosebleeds heightening the concern for HHT.
- Multiple telangiectases at characteristic sites.
    - Lips, oral cavity, fingers, and nose
- Visceral arteriovenous malformation (AVM).
    - Typically pulmonary, cerebral, hepatic, spinal, gastrointestinal, or pancreatic. AVMs outside these locations are uncommon and not suggestive of HHT.
- Family history. A first-degree relative in whom HHT has been diagnosed according to these Curaçao criteria.
- The clinical diagnosis of HHT can be established in a proband using the Curaçao criteria, which requires three or more of the above suggestive findings, or the molecular diagnosis can be established in a proband with suggestive findings and a heterozygous pathogenic variant in one of the highly associated genes.

GeneReviews also states that concurrent gene testing can be considered using an HHT multigene panel that includes *ACVRL1*, *ENG*, *SMAD4*, and other genes of interest.

NF1 Sequencing and/or Deletion/Duplication Analysis

American Academy of Pediatrics

The American Academy of Pediatrics (Miller et al, 2019) published diagnostic and health supervision guidance for children with neurofibromatosis type 1 (NF1), which stated the following regarding genetic testing (p. 3-4):

"*NF1* genetic testing may be performed for purposes of diagnosis or to assist in genetic counseling and family planning. If a child fulfills diagnostic criteria for NF1, molecular genetic confirmation is usually unnecessary. For a young child who presents only with [café-au-lait macules], *NF1* genetic testing can confirm a suspected diagnosis before a second feature, such as skinfold freckling, appears. Some families may wish to establish a definitive diagnosis as soon as possible and not wait for this second feature, and genetic testing can usually resolve the issue" and "Knowledge of the *NF1* [pathogenic sequence variant] can enable testing of other family members and prenatal diagnostic testing."

The guidance includes the following summary and recommendations about genetic testing:

- can confirm a suspected diagnosis before a clinical diagnosis is possible;
- can differentiate NF1 from Legius syndrome;
- may be helpful in children who present with atypical features;
- usually does not predict future complications; and
- may not detect all cases of NF1; a negative genetic test rules out a diagnosis of NF1 with 95% (but not 100%) sensitivity

GeneReviews: Neurofibromatosis Type 1

GeneReviews is an expert-authored review of current literature on a genetic disease, and goes through a rigorous editing and peer review process before being published online. Neurofibromatosis type 1 (NF1) should be suspected in individuals who have any of the following clinical features:

- Six or more café au lait macules (CALMs) greater than 5 mm in greatest diameter in prepubertal individuals and greater than 15 mm in greatest diameter in postpubertal individuals
- Freckling in the axillary or inguinal regions
- Two or more neurofibromas of any type or one plexiform neurofibroma
- Optic pathway glioma
- Two or more Lisch nodules identified by slit lamp examination or two or more choroidal abnormalities (bright, patchy nodules imaged by optical coherence tomography/near-infrared reflectance imaging)

- A distinctive osseous lesion such as sphenoid dysplasia, anterolateral bowing of the tibia, or pseudarthrosis of a long bone
- A parent who meets the diagnostic criteria for NF1

Note: If the phenotypic findings suggest the diagnosis of NF1, single-gene testing may be considered. If the phenotype is indistinguishable from other disorders characterized by hyperpigmentation, tumors, and/or other overlapping features, a multigene panel that includes *NF1*, *SPRED1*, and other genes of interest may be considered. A rasopathy panel is usually most appropriate.

NF2 Sequencing and/or Deletion/Duplication Analysis

GeneReviews: NF2-Related Schwannomatosis

GeneReviews is an expert-authored review of current literature on a genetic disease, and goes through a rigorous editing and peer review process before being published online. It is recommended that diagnostic testing for Neurofibromatosis Type 2 be performed when the following clinical findings are seen:

NF2 should be suspected in individuals with the following:

Clinical findings in children (two or more of these findings):

- A schwannoma at any location including intradermal
- Skin plaques present at birth or in early childhood (often plexiform schwannoma on histology)
- A meningioma, particularly non-meningothelial (non-arachnoidal) cell in origin
- A cortical wedge cataract
- A retinal hamartoma
- A mononeuropathy, particularly causing a facial nerve palsy, foot or wrist drop, or third nerve palsy

Clinical findings in adults:

- Bilateral vestibular schwannomas
- Unilateral vestibular schwannoma accompanied by ANY TWO of the following: meningioma, schwannoma, glioma, neurofibroma, cataract in the form of subcapsular lenticular opacities or cortical wedge cataract
- Multiple meningiomas accompanied by EITHER of the following:
    - Unilateral vestibular schwannoma

- ANY TWO of the following: schwannoma, ependymoma, cataract in the form of subcapsular lenticular opacities or cortical wedge cataract diagnosed in an individual age <40 years

Laboratory findings: NF2 pathogenic variant identified on tumor tissue testing

Family history: For individuals of all ages with any of these clinical findings, having a first-degree relative with NF2 increases the likelihood of the disorder being present.

Noonan Spectrum Disorders/RASopathies Multigene Panel

GeneReviews: Noonan Syndrome

GeneReviews is an expert-authored review of current literature on a genetic disease, and goes through a rigorous editing and peer review process before being published online. It is recommended that diagnostic testing for Noonan Spectrum Disorders via multigene panel be performed as follows:

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

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

When the phenotypic findings suggest the diagnosis of Noonan Syndrome (NS), molecular genetic testing approaches usually include the use of a multi-gene panel. 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.

Rauen, K.

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

PIK3CA-Related Overgrowth Spectrum - _PIK3CA_ Sequencing and/or Deletion/Duplication Analysis

GeneReviews: PIK3CA-Related Overgrowth Spectrum

GeneReviews is an expert-authored review of current literature on a genetic disease, and goes through a rigorous editing and peer review process before being published online. It is recommended that diagnostic testing for *PIK3CA*-Related Overgrowth Spectrum be performed as follows*:*

PIK3CA-related overgrowth spectrum (PROS) encompasses a range of clinical findings in which the core features are congenital or early-childhood onset of segmental/focal overgrowth with or without cellular dysplasia in the absence of a family history of similarly affected individuals (i.e., single occurrence in a family). Prior to the identification of *PIK3CA* as the causative gene, PROS was separated into distinct clinical syndromes based on the tissues and/or organs involved (see GeneReview Scope).

PROS should be considered in individuals with the following findings.

Clinical features:

- Overgrowth of any of a wide variety of tissues including (but not limited to) brain, adipose, vascular, muscle, skeletal, nerve
- Vascular malformations including (but not limited to) capillary, venous, arteriovenous, or mixed malformations
- Lymphatic malformations

- Cutaneous findings including epidermal nevi and hyperpigmented macules
- Single or multiple digital anomalies of the hands or feet (e.g., macrodactyly, syndactyly, polydactyly, sandal-toe gap)
- Kidney malformations (pelviectasis, dilated ureters, hydronephrosis, duplicated renal arteries, renal cysts, and enlarged kidneys)
- Benign tumors, with the exceptions of Wilms tumor and nephroblastomatosis (i.e., diffuse or multifocal clusters of persistent embryonal cells)

Brain MRI findings: Focal brain overgrowth (with or without cortical dysplasia) including:

- Hemimegalencephaly (HMEG)
- Focal cortical dysplasia (FCD)
- Dysplastic megalencephaly (DMEG)

Tuberous Sclerosis Complex (TSC)- *TSC1* and *TSC2* Sequencing and/or Deletion/Duplication Analysis

International TSC Clinical Consensus Group

"The International TSC Clinical Consensus Group (2021) reaffirms the importance of independent genetic diagnostic criteria and clinical diagnostic criteria. Identification of a pathogenic variant in *TSC1* or *TSC2* is sufficient for the diagnosis or prediction of TSC regardless of clinical findings; this is important because manifestations of TSC are known to arise over time at various ages. Genetic diagnosis of TSC prior to an individual meeting clinical criteria for TSC is beneficial to ensure that individuals undergo necessary surveillance to identify manifestations of TSC as early as possible to enable optimal clinical outcomes." (p. 52)

"All individuals should have a three-generation family history obtained to determine if additional family members are at risk of the condition. Genetic testing is recommended for genetic counseling purposes or when the diagnosis of TSC is suspected or in question but cannot be clinically confirmed." (p. 53)

"Definite TSC: 2 major features or 1 major feature with 2 minor features. Possible TSC: either 1 major feature or 2 minor features." (p. 53)

GeneReviews: Tuberous Sclerosis Complex

GeneReviews is an expert-authored review of current literature on a genetic disease, and goes through a rigorous editing and peer review process before being published online. It is recommended that diagnostic testing for Tuberous Sclerosis be performed as follows:

TSC should be suspected in individuals with either one major clinical feature or two or more minor features, as listed below:

Major features:

- Angiofibromas (≥3) or fibrous cephalic plaque
- Cardiac rhabdomyoma
- Multiple cortical tubers and/or radial migration lines
- Hypomelanotic macules (≥3 macules that are at least 5 mm in diameter)
- Lymphangioleiomyomatosis (LAM) (See Clinical Diagnosis, *Note.)
- Multiple retinal nodular hamartomas
- Renal angiomyolipoma (≥2) (See Clinical Diagnosis, *Note.)
- Shagreen patch
- Subependymal giant cell astrocytoma (SEGA)
- Subependymal nodules (SENs) (≥2)
- Ungual fibromas (≥2)

Minor features:

- Sclerotic bone lesions
- "Confetti" skin lesions (numerous 1- to 3-mm hypopigmented macules scattered over regions of the body such as the arms and legs)
- Dental enamel pits (>3)
- Intraoral fibromas (≥2)
- Multiple renal cysts
- Nonrenal hamartomas
- Retinal achromic patch

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Reviews, Revisions, and Approvals	Revision Date	Approval Date
Policy developed.	03/23	03/23
Semi-annual review. Updated title to reflect V1.2024 version. Overview, coding, reference-table, background and references updated. Throughout policy: replaced "coverage criteria" with "criteria. For Overview: removed "hereditary" and added "establish or"; removed "rare disease…"; added "genetic disorder…". For Other Related Policies: added "organ"; added "Genetic Testing: General Approach…". For Criteria; under Chromosomal Microarray Analysis: I. added "Chromosomal microarray analysis for developmental delay…"; I.A. removed "idiopathic growth delay and"; I.C. removed "Chromosomal microarray…" and added "OR"; I.D. added	10/23	10/23

"The member/enrollee has a short stature"; II. added "Chromosomal microarray analysis…"; for Autism Spectrum Disorder/Intellectual Disability Panel Analysis: under I. removed "or developmental delay multigene…" and added "panel"; for Angelman/Prader-Willi Syndrome: I.B.1. removed "birth" and added "one month" and removed "poor suck"; I.B.1.a. added "Poor appetite…"; I.B.1.b. added "Developmental delay,"; I.B.2. removed "characteristics:"; I.B.3. removed "characteristics:"; I.B.3.c. added "externally"; I.B.4. removed "characteristics"; I.B.4.b. added "and hyperphagia" and "externally"; I.B.4.c. added "and/or typical behavioral findings."; for Beckwith-Wiedemann/Russell-Silver Syndrome: removed "FISH or"; for I. removed "FISH or"; I.A. replaced "meets" with "has"; removed "6 Netchine…"; removed I.B. "The member/enrollee meets at least one or more…"; removed "CADASIL…"; for Cystic Fibrosis: under I.A. removed "(59mmol/L), OR"; removed I.B. "The member/enrollee has unexplained…"; for Charge Syndrome: under I.A.2. removed "which may be unilateral…"; added I.A.3. "Cleft palate…"; under I.B.4. removed "unilateral or bilateral"; under I.A.4. removed "the following are the most common"; for I.A.5. removed "Temporal bone abnormalities…" and added "auricular abnormalities…"; under I.A.7. removed "including"; under I.A.8. removed "with" and added "micropenis or cryptorchidism…"; removed I.A.11. "Distinctive features…"; and added "Characteristic physical features…"; under I.A.12. removed "clival hypoplasia" and added "clicus hypoplasia…"; for Fanconi Anemia: under I. removed "81216"; under I.A. replaced "has" with "had" and added "result via"; under I.B. replaced "any of the following…" with "at least one…"; under I.B.2. added "hyper-or"; under I.B.3. added "vertebral anomalies"; under I.B.6. added "(e.g., horseshoe kidney…)"; under II. removed "81216"; for Fragile X Syndrome: under I.C. removed "and has one of the following:"; under I.C.1. replaced "Phenotype, AND" with "Phenotype is"; for Hereditary Hemorrhagic Telangiectasia (HHT) Multigene Panel: under I.A.2. removed "(small blanchable red spots…)"; for Neurofibromatosis 1 NFI Sequencing and/or Deletion/Duplication Analysis: renamed from "Legius Syndrome SPRED1"; under I. replaced "SPRED1" with "NF1"; removed "81405, 81479…"; added I. "81408) is considered medically necessary when:…"; added I.A. "The member/enrollee has at least…"; added I.A.1. "Six or more…"; added I.A.2."Two or more…"; added I.A.3. "Freckling in the axillary…"; added I.A.4. "Optic glioma…"; added I.A.5. "Two or more Lisch…"; added I.A.6. "A distinctive osseous lesion…"; under II. added "NF1 sequencing…"; for NF2-Related Schwannomatosis (Previously Known as Neurofibromatosis 2)"; removed "or Multigene Panel NF1 or"; under I. removed "81408…"; under I.A. removed "has any of the following…"; and added "has an NF2 pathogenic variant…"; added I.B. "The member/enrollee is an adult…"; added I.B.1. "Bilateral vestibular…"; added I.B.2. "Unilateral vestibular…"; added I.C. "The member/enrollee is an adult with multiple meningiomas…"; under I.C.1.b. replaced "Optic glioma" with "Ependymoma"; removed I.C.3-I.C.7. and added I.C.2.c. "Cataract in the form…"; added I.C.2.d. "Cortical wedge cataract…"; added I.D. "The member/enrollee is a child…"; added I.D.1. "A schwannoma…"; added I.D.2. "Skin plaques…"; added I.C.3. "A meningioma…"; added I.C.4. "A cortical wedge cataract…"; added I.C.5. "A retinal hamartoma…"; added I.C.6. "A mononeuropathy…"; under II. removed "81408…"; for Noonan Spectrum Disorders/Rasopathies Multigene Panel: under I. added "/RASopathy"; removed "related Noonan"" and added "Noonan-like"; under I.A. replaced "any" with "at least one" and removed "clinical features…"; under I.B.		

added “SPRED1”; under II. added “/RASopathy”; removed “related Noonan”" and added “Noonan-like”; for PIK3CA Sequencing and/or Deletion/Duplication Analysis: under I.A. replaced “two or more” with “at least one”; removed ”clinical features…”; added “on brain imaging…”; for I.B. removed “The member/enrollee displays a congenital or early childhood…”; and added “The member/enrollee displays at least one of the following…”; removed Rett Syndrome and related criteria; for Tuberous Sclerosis Complex (TSC): under I.A.10. replaced “Subependymal” with “Two or more subependymal”; under I.B.1. added “Sclerotic bone lesions, OR”; removed I.B.7. “Sclerotic bone lesions”. For Notes and Definitions: removed “Idiopathic growth delay…”. For Background and Rationale: replaced “inheritance patterns” with “genetic testing” throughout; for Chromosomal Microarray Analysis: removed “CMA is considered investigational…”; added “A 2021 focused revision…”; added “CMA is considered investigational…”; for Angelman/Prader-Willi Syndrome - *SNRPN/UBE3A* methylation analysis, 15q11-q13 FISH analysis, chromosome 15 uniparental disomy analysis, and imprinting center defect analysis: removed “all of”; replaced “Birth to age” with “Age one month”; added “Developmental delay”; added “and hyperphagia” and added “externally”; for Beckwith-Wiedemann/Russell-Silver Syndrome - *H19* and *KCNQ1OT1* methylation analysis, deletion/duplication analysis of 11p15, uniparental disomy analysis, *CDKN1C* sequencing and/or deletion/duplication analysis: removed “Beckwith-Wiedermann syndrome…” and added “A diagnosis of BWS…”; removed “or a heterozygous…”; removed “GeneReviews…”; removed “Silver-Russell syndrome…”; removed CADASIL-NOTCH3 Sequencing and/or Deletion/Duplication Analysis and related content; for Cystic Fibrosis-CFTR Sequencing and/or Deletion/Duplication Analysis: added “congenital absence of the vas deferens, or”; for CHARGE Syndrome - CHD7 Sequencing and/or Deletion/Duplication Analysis: removed “which may be unilateral…”; removed “Cranial nerve…”; added “unilateral or…”; added “Cleft palate…”; removed “the following…”; added “most characteristic…”; for Hereditary Hemorrhagic Telangiectasia Multigene Panel: removed “It is recommended…”; added “Diagnostic”; removed “be performed”; added “is recommended”; removed Legius Syndrome- SPRED1 Sequencing and/or Deletion/Duplication Analysis and related content; for NF1 Sequencing and/or Deletion/Duplication Analysis**:** removed “GeneReviews…”; added “Note: If the phenotypic…”; for NF2 Sequencing and/or Deletion/Duplication Analysis: added “GeneReviews…”; removed Rett-Syndrome-MECP2 Sequencing and/or Deletion/Duplication Analysis and related content.		
Semi-annual review. Updated title to reflect V2.2024 version. In Known Familial Variant Analysis for the Multisystem Inherited Disorders, moved criteria to policy “Genetic Testing: General Approach to Genetic and Molecular Testing” to consolidate criteria for known familial variant tests. In *NF1* Sequencing and/or Deletion/Duplication, additional criterion added to be consistent with guidelines. In Noonan Spectrum Disorders/RASopathies Multigene Panel, removed minimum gene list; at present there is limited rationale for inclusion. In Fanconi Anemia Multigene Panel, Removed minimum gene list; at present there is limited rationale for inclusion. minor rewording for clarity throughout. Coding, reference-table, background and references updated.	04/24	04/24

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Important Reminder

This clinical policy has been developed by appropriately experienced and licensed health care professionals based on a review and consideration of currently available generally accepted standards of medical practice; peer-reviewed medical literature; government agency/program approval status; evidence-based guidelines and positions of leading national health professional organizations; views of physicians practicing in relevant clinical areas affected by this clinical policy; and other available clinical information. The Health Plan makes no representations and accepts no liability with respect to the content of any external information used or relied upon in developing this clinical policy. This clinical policy is consistent with standards of medical practice current at the time that this clinical policy was approved. "Health Plan" means a health plan that has adopted this clinical policy and that is operated or administered, in whole or in part, by Centene Management Company, LLC, or any of such health plan's affiliates, as applicable.

The purpose of this clinical policy is to provide a guide to medical necessity, which is a component of the guidelines used to assist in making coverage decisions and administering benefits. It does not constitute a contract or guarantee regarding payment or results. Coverage decisions and the administration of benefits are subject to all terms, conditions, exclusions, and limitations of the coverage documents (e.g., evidence of coverage, certificate of coverage, policy, contract of insurance, etc.), as well as to state and federal requirements and applicable Health Plan-level administrative policies and procedures.

This clinical policy is effective as of the date determined by the Health Plan. The date of posting may not be the effective date of this clinical policy. This clinical policy may be subject to applicable legal and regulatory requirements relating to provider notification. If there is a discrepancy between the effective date of this clinical policy and any applicable legal or regulatory requirement, the requirements of law and regulation shall govern. The Health Plan retains the right to change, amend or withdraw this clinical policy, and additional clinical policies may be developed and adopted as needed, at any time.

This clinical policy does not constitute medical advice, medical treatment, or medical care. It is not intended to dictate to providers how to practice medicine. Providers are expected to exercise professional medical judgment in providing the most appropriate care and are solely responsible for the medical advice and treatment of member/enrollees. This clinical policy is not intended to recommend treatment for member/enrollees. Member/enrollees should consult with their treating physician in connection with diagnosis and treatment decisions.

Providers referred to in this clinical policy are independent contractors who exercise independent judgment and over whom the Health Plan has no control or right of control. Providers are not agents or employees of the Health Plan.

This clinical policy is the property of the Health Plan. Unauthorized copying, use, and distribution of this clinical policy or any information contained herein are strictly prohibited. Providers, member/enrollees, and their representatives are bound to the terms and conditions expressed herein through the terms of their contracts. Where no such contract exists, providers, member/enrollees and their representatives agree to be bound by such terms and conditions by providing services to member/enrollees and/or submitting claims for payment for such services.

Note: For Medicaid member/enrollees, when state Medicaid coverage provisions conflict with the coverage provisions in this clinical policy, state Medicaid coverage provisions take precedence. Please refer to the state Medicaid manual for any coverage provisions pertaining to this clinical policy.

Note: For Medicare member/enrollees, to ensure consistency with the Medicare National Coverage Determinations (NCD) and Local Coverage Determinations (LCD), all applicable NCDs and LCDs and Medicare Coverage Articles should be reviewed prior to applying the criteria set forth in this clinical policy. Refer to the CMS website at http://www.cms.gov for additional information.