CONCERT 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 hereditary diseases may be used to confirm a diagnosis in a patient who has signs and/or symptoms of a rare disease, but conventional diagnostic methods have been unsuccessful. Confirming the diagnosis may alter some aspects of management and may eliminate the need for further diagnostic workup. This document addresses genetic testing for rare genetic conditions that impact multiple body systems.

POLICY REFERENCE TABLE

Below are a list of higher volume tests and the associated laboratories for each coverage criteria section. This list is not all inclusive.

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 2022, 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.

Coverage Criteria Sections	Example Tests; Labs	Common CPT Codes	Common ICD Codes	Ref
Known Familial Variant Analysis for Multisystem Inherited Disorders				
Known Familial Variant Analysis for Multisystem Inherited Disorders	Targeted Mutation Analysis for a Known Familial Variant	81403, 81303, 81221		36
Developmental Delay/Intellectual Disability, Autism Spectrum Disorder, or Congenital Anomalies				
Chromosomal Microarray Analysis	Chromosomal Microarray (GenomeDx) (GeneDx)	81228, 81229, S3870	F84.0, Q89.7, R62.50, F79	6, 7, 8
	Chromosomal Microarray, Postnatal, ClariSure Oligo-SNP (Quest Diagnostics)			
	SNP Microarray−Pediatric (Reveal®) (LabCorp)			
Developmental Delay/Intellectual Disability, Autism Spectrum Disorder, or Congenital Anomalies Panel Analysis	Neurodevelopmental Panel (Invitae)	81470, 81471, 81479	F70 through 80, F84, F81, F82, F88, F89, H93.52	10, 26, 34
	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 analysis, and	Angelman Syndrome/Prader-Willi Syndrome Methylation Analysis (GeneDx)	81331	R47, Q93.51, Q93.5	11, 27
	FISH, Prader-Willi/Angelman Syndrome (Quest Diagnostics)	88271, 88273		
	Chromosome 15 UPD Analysis (Greenwood Genetic Center)	81402		

imprinting center defect analysis	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	Beckwith-Wiedemann Syndrome: H19 Methylation (EGL Laboratories)	81401	C22.2, C64, I42.9, P08, R16.0- R16.2, R62.52, Q35, Q38.2, Q63, Q79.2, Q87.3	14, 15
	Russell-Silver Syndrome: H19 Methylation (EGL Laboratories)			
	Beckwith-Wiedemann: Methylation analysis of 11p15.5 only (Univ of Pennsylvania Genetic Diagnostic Lab)			
	RSS: Methylation analysis of 11p15.5 only (Univ of Pennsylvania Genetic Diagnostic Lab)			
	Beckwith-Wiedemann: 11p15.5 high resolution copy number analysis only (aCGH) (Univ of Pennsylvania Genetic Diagnostic Lab)	81479		
	RSS: 11p15.5 high resolution copy number analysis only (aCGH) (Univ of Pennsylvania Genetic Diagnostic Lab)			
	Uniparental Disomy (Mayo Clinic Laboratories)	81402		
	CDKN1C Full Gene Sequencing and Deletion/Duplication (Invitae)	81479		
CADASIL				
NOTCH3 Sequencing and/or Deletion/Duplication Analysis	NOTCH3 Full Gene Sequencing and Deletion/Duplication (Invitae)	81406, 81479	I67.850, F02.80, F02.81	12, 13
Cystic Fibrosis				
CFTR Sequencing and/or Deletion/Duplication	Cystic Fibrosis Complete Rare Variant Analysis, Entire Gene Sequence (Quest Diagnostics)	81223	E84.0 through 9, P09, Q55.4, R94.8, Z13,	1, 2, 31

Analysis	Cystic Fibrosis Gene Deletion or Duplication (Quest Diagnostics)	81222	Z31, Z34, Z82.79, Z83, Z84	
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)	81407, 81479	Q89.8	16
Fanconi Anemia				
Fanconi Anemia Multigene Panel	FancZoom (DNA Diagnostic Laboratory - Johns Hopkins Hospital)	81162, 81216, 81307, 81479	C92, D46.9, D61.09, D61.89, D61.9, L81.3, L81.4 Q02, R62.52	17, 32
	Fanconi Anemia Panel (PreventionGenetics)			
Fragile X Syndrome				
FMR1 Repeat and Methylation Analysis	Fragile X, PCR and Southern Blot Analysis (Labcorp)	81243, 81244	F84.0, Q99.2, F79, E28.3, G11.2, G25.2	18, 19
	XSense, Fragile X with Reflex (Quest Diagnostics)			
	Fragile X Syndrome (Sema4)			
Hereditary Hemorrhagic Telangiectasia (HHT)				
Hereditary Hemorrhagic Telangiectasia Multigene Panel	HHTNext (Ambry Genetics)	81405, 81406, 81479	R04.0, Q27.30 through Q27.39	20, 22
	Hereditary Hemorrhagic Telangiectasia and Vascular Malformations Panel (Invitae)			
Legius Syndrome				
SPRED1 Sequencing and/or Deletion/Duplication Analysis	SPRED1 Full Gene Sequencing and Deletion/Duplication (Invitae)	81405, 81479	L81.3, Z82.79, Z84	22
	Legius Syndrome via the SPRED1 Gene (PreventionGenetics)			

Neurofibromatosis				
NF1 or ***NF2*** Sequencing and/or Deletion/Duplication Analysis or Multigene Panel	NF1 Sequencing & Del/Dup (GeneDx)	81408	L81.3, R62.5, Q85.0, Z82.79, Z84	3, 4, 5
	Neurofibromatosis Type 2 via the NF2 Gene (PreventionGenetics)	81405, 81406		
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	23
	Noonan and Comprehensive RASopathies Panel (GeneDx)			
***PIK3CA*-Related Segmental Overgrowth and Related Syndromes**				
PIK3CA Sequencing and/or Deletion/Duplication Analysis	PIK3CA Full Gene Sequencing and Deletion/Duplication (Invitae)	81479		33
Rett Syndrome				
MECP2 Sequencing and/or Deletion/Duplication Analysis	MECP2 Full Gene Sequencing and Deletion/Duplication (Invitae)	81302, 81304	F70 through F79, F80, F81, F82, F84, F88, F89, Z13.4, Z82.79, Z84	9, 25
	MECP2 Gene Sequencing & Del/Dup (GeneDx)			
	Genomic Unity MECP2 Analysis (Variantyx, Inc.)	0234U		
Tuberous Sclerosis Complex (TSC)				
TSC1 and ***TSC2*** Sequencing and/or Deletion/Duplication Analysis	TSC1 Full Gene Sequencing and Deletion/Duplication (Invitae)	81405, 81406 81407	D10, D15.1, D43, D21.9, H35.89, N28.1, Q61.9, H35.89	35, 37
	TSC2 Full Gene Sequencing and Deletion/Duplication (Invitae)			
Other Covered Multisystem Inherited Disorders				
Other Covered Multisystem Inherited Disorders	See below	81400 through 81408		28, 29, 30

OTHER RELATED POLICIES

This policy document provides coverage criteria for Multisystem Inherited Disorders, Intellectual Disability, and Developmental Delay. For 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 coverage 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 coverage 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 coverage criteria related to exome and genome sequencing for genetic disorders.

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:

KNOWN FAMILIAL VARIANT ANALYSIS FOR MULTISYSTEM INHERITED DISORDERS

I. Targeted mutation analysis for a known familial variant (81403, 81303, 81221) for a multisystem inherited disorder is considered **medically necessary** when:

   A. The member/enrollee has a close relative with a known pathogenic or likely pathogenic variant causing the condition.

II. Targeted mutation analysis for a known familial variant (81403, 81303, 81221) for a multisystem inherited disorder is considered **investigational** for all other indications.

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

Chromosomal Microarray Analysis

I. Chromosomal microarray analysis (81228, 81229, S3870) is considered **medically necessary** when:

   A. The member/enrollee has developmental delay and/ or intellectual disability, excluding: idiopathic growth delay and 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.

II. Chromosomal microarray analysis (81229) is considered **investigational** for all other conditions of delayed development, including:

   A. Idiopathic growth delay
   B. Isolated speech/language delay.

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

Developmental Delay/intellectual Disability, Autism Spectrum Disorder, or Congenital Anomalies Panel Analysis

I. The use of autism spectrum disorder, intellectual disability, or developmental delay multigene panel analysis (0156U, 81470, 81471, 81479) 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 birth to two years with hypotonia with poor suck, **OR**
2. The member/enrollee is age two to six years with both of the following characteristics:
    a) Hypotonia with history of poor suck, **AND**
    b) Global developmental delay, **OR**
3. The member/enrollee is age six to twelve years with all of the following characteristics:
    a) History of hypotonia with poor suck (hypotonia often persists), **AND**
    b) Global developmental delay, **AND**
    c) Excessive eating with central obesity if uncontrolled, **OR**
4. The member/enrollee is age thirteen years or older with all of the following characteristics:
    a) Cognitive impairment, usually mild intellectual disability, **AND**
    b) Excessive eating with central obesity if uncontrolled, **AND**
    c) Hypogonadism.

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, FISH or deletion/duplication analysis of 11p15, uniparental disomy analysis, *CDKN1C* sequencing and/or deletion/duplication analysis

I. ***H19*** and ***KCNQ1OT1*** methylation analysis (81401), FISH or 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 meets at least 4 of the following 6 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 to 3 years]), **OR**

      5. Body asymmetry (limb length discrepancy greater than 0.5 cm, or less than 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, **OR**

   B. The member/enrollee meets at least one or more of the following major and/or minor clinical features of Beckwith-Wiedemann syndrome (BWS):

      1. Major criteria for BWS:

         a) Macrosomia (traditionally defined as weight and length/height above the 97th centile)
         b) Macroglossia
         c) Hemihyperplasia (asymmetric overgrowth of one or more regions of the body)

d) Omphalocele (also called exomphalos) or umbilical hernia
e) Embryonal tumor (e.g., Wilms tumor, hepatoblastoma, neuroblastoma, rhabdomyosarcoma)
f) Visceromegaly involving one or more intra-abdominal organs including liver, spleen, kidneys, adrenal glands, and/or pancreas
g) Cytomegaly of the fetal adrenal cortex (pathognomonic)
h) Renal abnormalities including structural abnormalities, nephromegaly, nephrocalcinosis, and/or later development of medullary sponge kidney
i) Anterior linear earlobe creases and/or posterior helical ear pits
j) Placental mesenchymal dysplasia
k) Cleft palate (rare in BWS)
l) Cardiomyopathy (rare in BWS)
m) Positive family history (1 or more family members with a clinical diagnosis of BWS or a history or features suggestive of BWS)

2. Minor criteria for BWS:

a) Pregnancy-related findings including polyhydramnios and prematurity
b) Neonatal hypoglycemia
c) Vascular lesions including nevus simplex (typically appearing on the forehead, glabella, and/or back of the neck) or hemangiomas (cutaneous or extracutaneous)
d) Characteristic facies including midface retrusion and infraorbital creases
e) Structural cardiac anomalies or cardiomegaly
f) Diastasis recti
g) Advanced bone age (common in overgrowth/endocrine disorders)

II. ***H19*** and ***KCNQ1OT1*** methylation analysis (81401), FISH or 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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CADASIL

NOTCH3 Sequencing and/or Deletion/Duplication Analysis

I. ***NOTCH3*** sequencing and/or deletion/duplication analysis (81406, 81479) to establish or confirm a diagnosis of CADASIL (cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy) is considered **medically necessary** when:

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

1. Unexplained white matter hyperintensities and a family history of stroke and/or vascular dementia, **OR**

2. At least one of the following clinical features of CADASIL:

a) Transient ischemic attacks and ischemic stroke, **OR**
b) Cognitive impairment, manifesting initially with executive dysfunction, with a concurrent stepwise deterioration due to recurrent strokes to vascular dementia, **OR**
c) Migraine with aura (mean age of onset of 30 years), **OR**
d) Psychiatric disturbances, most frequently mood disturbances and apathy, **AND**

B. The member/enrollee has at least one of the following brain imaging findings of CADASIL:

1. Symmetric and progressive white matter hyperintensities, often involving the anterior temporal lobes and external capsules, **OR**
2. Lacunes of presumed vascular origin, **OR**
3. Recent subcortical infarcts, **OR**
4. Dilated perivascular spaces, sometimes referred to as subcortical lacunar lesions, **OR**
5. Brain atrophy, **OR**
6. Cerebral microbleeds.

II. ***NOTCH3*** sequencing and/or deletion/duplication analysis (81406, 81479) to establish or confirm a diagnosis of CADASIL (cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy) 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 60mmol/L) or inconclusive sweat chloride test (30 to 59mmol/L), **OR**

   B. The member/enrollee has unexplained acute recurrent (2 or more episodes) or chronic pancreatitis with documented elevated amylase or lipase levels.

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 is considered **medically necessary** when:

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

   B. The member/enrollee is known to have 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, and/or anophthalmos or microphthalmos, **OR**

2. Choanal atresia or stenosis, which may be unilateral or bilateral, **OR**

3. Cranial nerve dysfunction or anomaly (hyposmia or anosmia, facial palsy (unilateral or bilateral), sensorineural hearing loss and/or balance problems, hypoplasia or aplasia on imaging, difficulty with sucking/ swallowing and aspiration, gut motility problems), **OR**

4. Ear malformations (the following are the most common):

    a) 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
    b) Middle ear. Ossicular malformations (resulting in a typical wedge-shaped audiogram due to mixed sensorineural and conductive hearing loss)
    c) Temporal bone abnormalities (most commonly determined by temporal bone CT scan). Mondini defect of the cochlea (cochlear hypoplasia), absent or hypoplastic semicircular canals, **OR**

5. Tracheoesophageal fistula or esophageal atresia, **OR**

6. Cardiovascular malformation, including conotruncal defects (e.g., tetralogy of Fallot), AV canal defects, and aortic arch anomalies, **OR**

7. Hypogonadotropic hypogonadism with delayed or absent puberty, **OR**

8. Developmental delay / intellectual disability, **OR**

9. Growth deficiency (short stature), **OR**

10. Distinctive features (the following are the most common):

    a) 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)
    b) Neck: Short and wide with sloping shoulders

c) Hands:. Typically, short, wide palm with hockey-stick crease, short fingers, and finger-like thumb; polydactyly and reduction defects in a small percentage, **OR**

11. Brain MRI showing clival hypoplasia, hypoplasia of 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, 81216, 81307, 81479) is considered **medically necessary** when:

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

B. The member/enrollee displays any of the following clinical features of Fanconi anemia:

1. Prenatal and/or postnatal short stature, **OR**
2. Abnormal skin pigmentation (e.g., café au lait macules, hypopigmentation), **OR**
3. Skeletal malformations (e.g., hypoplastic thumb, hypoplastic radius), **OR**
4. Microcephaly, **OR**
5. Ophthalmic anomalies, **OR**
6. Genitourinary tract anomalies, **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, **AND**

C. The panel includes, at a minimum, the following genes: ***FANCA***, ***FANCC***, and ***FANCG***.

II. Multigene panel analysis to establish or confirm a genetic diagnosis of Fanconi anemia (81162, 81216, 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 is male and has unexplained autism spectrum disorder, **OR**

C. The member/enrollee is female with unexplained autism spectrum disorder and has one of the following:

1. Phenotype compatible with Fragile X syndrome (examples: ADHD and/or other behavioral differences, typical facies [long face, prominent forehead, large ears, prominent jaw], mitral valve prolapse, aortic root dilatation), **OR**

2. 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 (small blanchable red spots that are focal dilatations of post-capillary venules or delicate, lacy red vessels composed of markedly dilated and convoluted venules) at characteristic sites, including lips, oral cavity, fingers, and nose, **OR**

3. Visceral arteriovenous malformation (AVM), **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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LEGIUS SYNDROME

SPRED1 Sequencing and/or Deletion/Duplication Analysis

I. ***SPRED1*** sequencing and/or deletion/duplication analysis (81405, 81479) to establish or confirm a diagnosis of Legius syndrome is considered **medically necessary** when:

A. The member/enrollee has multiple café au lait macules, **AND**

B. The member's/enrollee's personal history does not include any of the non-pigmentary clinical diagnostic manifestations of neurofibromatosis type 1 (NF1) (e.g., Lisch nodules, neurofibromas, optic nerve glioma, sphenoid wing dysplasia, long bone dysplasia), **AND**

C. The member/enrollee has previously undergone genetic testing of ***NF1*** and the results were negative.

II. ***SPRED1*** sequencing and/or deletion/duplication analysis (81405, 81479) to establish or confirm a diagnosis of Legius syndrome is considered **investigational** for all other indications.

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NEUROFIBROMATOSIS

NF1 or *NF2* Sequencing and/or Deletion/Duplication Analysis or Multigene Panel

I. ***NF1*** or ***NF2*** sequencing and/or deletion/duplication analysis (81405, 81406, 81408) or multigene panel analysis is considered **medically necessary** when:

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

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**

7. Bilateral vestibular schwannomas, **OR**
8. Unilateral vestibular schwannoma, **AND**
    a) Any two of the following: meningioma, schwannoma, glioma, neurofibroma, cataract in the form of subcapsular lenticular opacities or cortical wedge cataract, **OR**
9. Multiple meningiomas, **AND**
    a) Unilateral vestibular schwannoma, **OR**
    b) Any two of the following: schwannoma, glioma, neurofibroma, cataract in the form of subcapsular lenticular opacities or cortical wedge cataract.

II. ***NF1*** or ***NF2*** sequencing and/or deletion/duplication analysis (81405, 81406, 81408) or multigene panel analysis 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 (e.g., Noonan syndrome, Legius syndrome, Costello syndrome, Cardio-facial-cutaneous syndrome, NF1-related Noonan syndrome) (81442) is considered **medically necessary** when:

A. The member/enrollee has any of the following clinical features of Noonan spectrum disorders:

1. Characteristic facies (low-set, posteriorly rotated ears with fleshy helices, vivid blue or blue-green irises, wide-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 set nipples, **OR**
8. Cryptorchidism in males, **OR**
9. Lentigines, **OR**
10. Café au lait macules, **AND**

B. The panel includes, at a minimum, the following genes: ***PTPN11***, ***SOS1***, ***RAF1***, and ***RIT1.***

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

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PIK3CA-Related Segmental Overgrowth and Related Syndromes

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 two or more of the following clinical features:

1. Sporadic and mosaic overgrowth in adipose, muscle, nerve, or skeletal tissues, **OR**
2. Vascular malformations including capillary, venous, arteriovenous malformation, or lymphatic, **OR**
3. Epidermal nevus, **OR**

B. The member/enrollee displays a congenital or early childhood onset of one or more of the following clinical features:

1. Large isolated lymphatic malformation, **OR**
2. Isolated macrodactyly OR overgrown splayed feet/ hands, overgrown limbs, **OR**
3. Truncal adipose overgrowth, **OR**
4. Hemimegalencephaly (bilateral)/ dysplastic megalencephaly/ focal cortical dysplasia, **OR**
5. Epidermal nevus, **OR**
6. Seborrheic keratoses, **OR**
7. Benign lichenoid keratoses.

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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RETT SYNDROME

MECP2 Sequencing and/or Deletion/Duplication Analysis

I. ***MECP2*** sequencing and/or deletion/duplication analysis (81302, 81304, 0234U) to establish or confirm a diagnosis of Rett syndrome is considered **medically necessary** when:

A. The member/enrollee experienced a period of developmental regression (range: ages 1 through 4 years) followed by recovery or stabilization (range: ages 2 through 10 years), **AND**

B. The member/enrollee has any of the following:

1. Partial or complete loss of acquired purposeful hand skills, **OR**
2. Partial or complete loss of acquired spoken language or language skill (e.g., babble), **OR**
3. Gait abnormalities: impaired (dyspraxic) or absence of ability, **OR**
4. Stereotypic hand movements including hand wringing/squeezing, clapping/tapping, mouthing, and washing/rubbing automatisms, **AND**

C. The member/enrollee does **not** have either of the following:

1. Brain injury secondary to peri- or postnatal trauma, neurometabolic disease, or severe infection that causes neurologic problems, **OR**
2. Grossly abnormal psychomotor development in the first six months of life, with early milestones not being met.

II. ***MECP2*** sequencing and/or deletion/duplication analysis (81302, 81304) to establish or confirm a diagnosis of Rett syndrome is considered **investigational** for all other indications.

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

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 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 source.

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NOTES AND 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**: is 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. **Congenital anomalies** according to ACMG are multiple anomalies 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** is a 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) is 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.

6. **Idiopathic growth delay** is a deficit in the height or growth of a person for which no underlying cause has been identified.

BACKGROUND AND RATIONALE

Known Familial Variant Analysis for Multisystem Inherited Disorders

Genetic Support Foundation

The Genetic Support Foundation's Genetics 101 information on inheritance patterns says the following about testing for familial pathogenic variants:

> Genetic testing for someone who may be at risk for an inherited disease is always easier if we know the specific genetic cause. Oftentimes, the best way to find the genetic cause is to start by testing someone in the family who is known or strongly suspected to have the disease. If their testing is positive, then we can say that we have found the familial pathogenic (harmful) variant. We can use this as a marker to test other members of the family to see who is also at risk.

Chromosomal Microarray Analysis

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) published guidelines 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]

CMA is considered investigational for all other indications, including members/enrollees with idiopathic growth delay (ACMG 2010 Practice Guideline, p. 744; reaffirmed in 2020 and reclassified as a Clinical Practice Resource) and isolated speech/language delay (AAP 2014 Clinical Report, page e905), as diagnostic yield in these clinical situations is thought to be low.

Developmental Delay/Intellectual Disability, Autism Spectrum Disorder, or Congenital Anomalies Panel Analysis

American Academy of Pediatrics (AAP)

The AAP most recent 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.

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. The recommended diagnostic testing for Angelman syndrome is for individuals with the following history:

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

Birth to age two years

- Hypotonia with poor suck (neonatal period)

Age two to six years

- Hypotonia with history of poor suck
- Global developmental delay

Age six to 12 years

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

Age 13 years to adulthood

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

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

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:

"Beckwith-Wiedemann syndrome (BWS) should be suspected in individuals who have one of the above mentioned major and/or minor findings (listed above in corresponding Coverage Criteria). Diagnosis of BWS is established when there is a an epigenetic or genomic alteration leading to abnormal methylation at 11p15.5 or a heterozygous BWS-causing pathogenic variant in CDKN1C in the presence of one or more clinical findings."

GeneReviews: Russell-Silver Syndrome (RSS)

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, as noted above in corresponding Coverage Criteria. If an individuals 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."

CADASIL - NOTCH3 Sequencing and/or Deletion/Duplication Analysis

European Academy of Neurology

Consensus recommendations from the European Academy of Neurology states that CADASIL diagnosis can be established by skin biopsy with electron microscopy showing GOM, but genetic testing should be the first diagnostic line of investigation. (p. 918)

GeneReviews: CADASIL

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.

CADASIL should be suspected in individuals with unexplained white matter hyperintensities and a family history of stroke and/or vascular dementia; however, lack of an apparent family history of CADASIL does not preclude the diagnosis. The following clinical signs and neuroimaging findings can be observed in CADASIL.

Clinical signs

- Transient ischemic attacks and ischemic stroke
- Cognitive impairment, manifesting initially with executive dysfunction, with a concurrent stepwise deterioration due to recurrent strokes to vascular dementia
- Migraine with aura, with a mean age of onset of 30 years
- Psychiatric disturbances, most frequently mood disturbances and apathy

Brain imaging

- Symmetric and progressive white matter hyperintensities, often involving the anterior temporal lobes and external capsules
- Lacunes of presumed vascular origin
- Recent subcortical infarcts
- Dilated perivascular spaces, sometimes referred to as subcortical lacunar lesions
- Brain atrophy
- Cerebral microbleeds

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 males (due to 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. Refer to model reports for carrier screening presented in the ACMG statement.1 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). If the R117H and 5T variant are determined to be in cis, then the report should reflect that this mutation has been associated with a variable phenotype when R117H/5T (cis) or another CFTR mutation is present in patients with CF. If the R117H mutation and 5T are determined to be in trans, the report should indicate that the individual carries a relatively benign CF mutation that is not generally associated with the phenotype of typical CF patients but has been associated with CBAVD, leading to infertility in males and no known clinical features in females. In addition, the report should reflect that the 5T variant on one chromosome, in combination with a CFTR mutation on the opposite chromosome, may lead to male infertility due to CBAVD, with or without mild or atypical symptoms of CF, and that there is no known clinical significance of 5T in females. The penetrance of 5T is reduced, and thus it is difficult to predict the clinical significance of the 5T variant. For individuals who are R117H positive and 5T negative, the report should indicate that the R117H mutation is not expected to lead to a typical CF clinical phenotype. How- ever, R117H has been associated with CBAVD. In all above cases, genetic counseling is recommended. For diagnostic testing, and particularly for testing for CBAVD in males with infertility, it is recommended that the intron 8 variant be included in the testing panel. (p. 389)

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. It is recommended that diagnostic testing for CHARGE syndrome be performed when the following clinical and imaging findings are seen:

- Coloboma of the iris, retina, choroid, and/or disc, and/or anophthalmos or microphthalmos
- Choanal atresia or stenosis, which may be unilateral or bilateral.
- Cranial nerve dysfunction or anomaly (hyposmia or anosmia, facial palsy (unilateral or bilateral), sensorineural hearing loss and/or balance problems, hypoplasia or aplasia on imaging, difficulty with sucking/swallowing and aspiration, gut motility problems)
- Ear malformations (the following are the most common):
    - 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 with delayed or absent puberty
- Developmental delay / intellectual disability
- Growth deficiency (short stature)
- Distinctive 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; polydactyly and reduction defects in a small percentage
- Brain MRI showing clivus hypoplasia, hypoplasia of cerebellar vermis

Fanconi Anemia Multigene Panel

Fanconi Anemia Research Foundation

The Fanconi Anemia Research Foundation (2022) 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 through 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

Per Table 1 in GeneReviews, germline mutations in FANCA, FANCC, and FANCG represent 84 to 94% of cases of Fanconi anemia.

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) male or female relatives 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) male or female relatives 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) male or female relatives with undiagnosed mental retardation. (p. 586)

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

- It is recommended that all males with unexplained autism be tested for fragile X syndrome. (p. 402)
- All females 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:

- Males and females with intellectual disability or developmental delay of unknown cause
- Males with autism spectrum disorder
- Females 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.
- Males and females 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.
- Females 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. It is recommended that diagnostic testing for HHT be performed 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.

Legius Syndrome - SPRED1 Sequencing and/or Deletion/Duplication Analysis

GeneReviews: Legius 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 Legius Syndrome should be suspected when the following clinical findings are seen:

- Has pigmentary dysplasia consisting of café au lait macules, with or without intertriginous freckling; and

- Lacks the nonpigmentary clinical diagnostic manifestations of neurofibromatosis type 1 (NF1) (e.g., Lisch nodules, neurofibromas, optic pathway glioma, sphenoid wing dysplasia, long bone dysplasia).

Opinions differ on the appropriate approach when clinical information and family history cannot distinguish between NF1 and Legius syndrome. This is the case in individuals with only café au lait macules with or without freckling but no other signs of NF1. The assessment of pros and cons of molecular testing requires consideration of the circumstances unique to each individual, including (but not limited to) the following:

- Clinical findings and family history
- Age of the individual
- Differences in recommended clinical management when the diagnosis of NF1 or Legius syndrome is established with certainty vs when the diagnosis of neither can be established with confidence
- Psychological burden of a diagnosis or lack thereof
- Costs of testing and surveillance
- Odds of identifying a diagnosis of NF1 vs Legius syndrome in those with phenotype limited to pigmentary findings

Neurofibromatosis type 1 (NF1) is most frequently confused with Legius syndrome, as some individuals with Legius syndrome fulfill the clinical diagnostic criteria for NF1. About 8% of children with six or more café au lait spots and no other clinical features of NF1 have Legius syndrome. Distinguishing Legius syndrome from NF1 is sometimes impossible on the basis of clinical features alone in a young child because the multiple cutaneous neurofibromas and Lisch nodules characteristic of NF1 do not usually arise until later in childhood or adolescence. Examination of the parents for signs of Legius syndrome or NF1 may distinguish the two conditions, but in simplex cases reevaluation of the proband after adolescence or molecular testing may be necessary to establish the diagnosis

NF1 and NF2 Sequencing and/or Deletion/Duplication Analysis or Multigene Panel

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 through 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

GeneReviews: Neurofibromatosis Type 2

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:

Because the phenotype of NF2 is broad, individuals with the distinctive findings and suggestive findings and adults who meet the consensus diagnostic criteria, are likely to be diagnosed using sequence analysis of NF2 followed by chromosome microarray if sequencing is normal to detect variations that sequencing cannot identify (p. 3). Suggestive findings of NF2 include schwannoma, skin plaques presenting at birth or in childhood, meningioma, cataract, retinal hamartoma, mononeuropathy, vestibular schwannoma, glioma, neurofibroma and subcapsular lenticular opacities.

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 droopiness of the upper eyelids (ptosis)
- Short stature for sex and family background
- Congenital heart defects, most commonly pulmonary valve stenosis, atrial septal defect, and/or hypertrophic cardiomyopathy
- Developmental delay of variable degree
- Broad or webbed neck
- Unusual chest shape with superior pectus carinatum and inferior pectus excavatum
- Widely spaced nipples
- Cryptorchidism in males
- 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.

PIK3CA-Related Segmental Overgrowth and Related Syndromes - *PIK3CA* Sequencing and/or Deletion/Duplication Analysis

Keppler-Noreuil et al (2015)

Keppler-Noreuil et al published outcomes from a workshop that included experts on PIK3CA syndromes, and established clinical criteria for diagnosis and treatment of this collection of disorders. They propose the umbrella term of "PIK3CA-Related Overgrowth Spectrum (PROS)", which includes macrodactyly, FAO, HHML, CLOVES, and related megalencephaly conditions. Identification of a ***PIK3CA*** mutation is included as part of the clinical criteria. (p. 290)

Rett Syndrome - *MECP2* Sequencing and/or Deletion/Duplication Analysis

American College of Medical Genetics and Genomics (ACMG)

The American College of Medical Genetics and Genomics (2013) revised its evidence-based guidelines for clinical genetics evaluation of autism spectrum disorders. Testing for ***MECP2*** genetic variants was recommended as part of the diagnostic workup of females who present with an autistic phenotype. Routine ***MECP2*** testing in males with autism spectrum disorders was not recommended). However, geneticists should be alert to the features of ***MECP2*** duplications and consider ***MECP2*** duplication testing in boys with autism and such features. (p. 402)

GeneReviews: MECP2 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.

Most distinguishing finding: A period of regression (range: ages 1 to 4 years) followed by recovery or stabilization (range: ages 2 to 10 years; mean: age 5 years)

- Main findings
    - Partial or complete loss of acquired purposeful hand skills
    - Partial or complete loss of acquired spoken language or language skill (e.g., babble)
    - Gait abnormalities: impaired (dyspraxic) or absence of ability
    - Stereotypic hand movements including hand wringing/squeezing, clapping/tapping, mouthing, and washing/rubbing automatisms
- Exclusionary findings
    - Brain injury secondary to peri- or postnatal trauma, neurometabolic disease, or severe infection that causes neurologic problems
    - Grossly abnormal psychomotor development in the first six months of life, with early milestones not being met

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

International TSC Clinical Consensus Group

"The International TSC Clinical Consensus Group 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

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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 members/enrollees. This clinical policy is not intended to recommend treatment for members/enrollees. Members/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.

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expressed herein through the terms of their contracts. Where no such contract exists, providers, members/enrollees and their representatives agree to be bound by such terms and conditions by providing services to members/enrollees and/or submitting claims for payment for such services.

Note: For Medicaid members/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 members/enrollees, to ensure consistency with the Medicare National Coverage Determinations (NCD) and Local Coverage Determinations (LCD), all applicable NCDs, 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.