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

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.

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	Targeted Mutation Analysis for a Known Familial Variant	81403, 81303, 81221		
Developmental Delay/Intellectual Disability, Autism Spectrum Disorder, or Congenital Anomalies				
Chromosomal Microarray Analysis	Chromosomal Microarray, Congenital, Blood (Mayo Medical Laboratories)	81228, 81229, S3870	F84.0, Q89.7, R62.50, F79	8, 9, 10, 11, 12, 13

	Chromosomal Microarray, Postnatal, ClariSure Oligo-SNP (Quest Diagnostics)			
	Rapid Chromosomal Microarray via aCGH and SNP Test (PreventionGenetics)			
	SNP Microarray–Pediatric (Reveal®) (LabCorp)			
Developmental Delay/Intellectual Disability, Autism Spectrum Disorder, or Congenital Anomalies Panel Analysis	Intellectual Disability (IDNext) (Ambry Genetics)	81470, 81471, 81479	F70-80, F84, F81, F82, F88, F89, H93.52	9, 13, 14
	AutismNext (Ambry Genetics)			
	Autism/ID Panel (GeneDx)			
	Intellectual Disability, Epilepsy, and Autism (IDEA) Panel - Patient Only (IDEA panel of patient) (PreventionGenetics)			
	SMASH (Marvel Genomics)	0156U		
Angelman/Prader-Willi Syndrome				
SNRPN/UBE3A methylation analysis, 15q11-q13 FISH analysis, chromosome 15 uniparental disomy analysis, and imprinting center defect analysis	SNRPN/UBE3A Methylation Analysis	81331	R47, Q93.51, Q93.5	15, 16, 40
	15q11-q13 FISH Analysis	88271		
	Uniparental Disomy Analysis	81402		
	Imprinting Center Defect Analysis	81479		
Beckwith-Wiedemann/Russell-Silver Syndrome				
H19 and *KCNQ1OT1* methylation analysis, FISH or deletion/duplication analysis of 11p15, uniparental disomy analysis, CDKN1C	H19 and KCNQ1OT1 Methylation Analysis	81401	C64, I42.9, P08, R16.0-R16.2, Q35, Q38.2, Q63, Q79.2, Q87.3	20, 21, 41
	11p15 FISH Analysis	88271		
	11p15 Deletion/Duplication Analysis	81479		
	Uniparental Disomy Analysis	81402		
	CDKN1C Sequencing Analysis	81479		

sequencing and/or deletion/duplication analysis	CDKN1C Deletion/Duplication Analysis			
CADASIL				
NOTCH3 Sequencing and/or Deletion/Duplication Analysis	NOTCH3 Sequencing Analysis	81406,	I67.850, F02.80, F02.81	17, 18, 19
	NOTCH3 Deletion/Duplication Analysis	81479		
Cystic Fibrosis				
CFTR Sequencing and/or Deletion/Duplication Analysis	CFTR Sequencing Analysis	81222, S3835	E84.0-9, P09, Q55.4, R94.8, Z13, Z31, Z34, Z82.79, Z83, Z84	1, 2, 3, 49
	CFTR Deletion/Duplication Analysis	81223		
CFTR Intron 9 PolyT and TG Analysis (aka Intron 8 poly-T/TG)	*CFTR* Intron 9 (8) Poly-T Analysis	81224		
CHARGE Syndrome				
CHD7 Sequencing and/or Deletion/Duplication Analysis	CHD7 Sequencing Analysis	81407	Q89.8	22, 23
	CHD7 Deletion/Duplication Analysis	81479		
Fanconi Anemia				
Fanconi Anemia Multigene Panel	FancZoom (DNA Diagnostic Laboratory - Johns Hopkins Hospital)	81167, 81216, 81479	C92, D46.9, D61.09, D61.89, D61.9, L81.3, L81.4 Q02, R62.52	26, 50
	Fanconi Anemia NGS Panel (Sequencing & Deletion/Duplication) (Fulgent Genetics)			
	Invitae Fanconi Anemia Panel (Invitae)			
Fragile X Syndrome				
FMR1 Repeat and Methylation Analysis	FMR1 Repeat Analysis FMR1 Methylation Analysis FMR1 Repeat & Methylation Analysis	81243, 81244	F84.0, Q99.2, F79, R56.9, Q89.7	12, 26, 27
Hereditary Hemorrhagic Telangiectasia (HHT)				

Hereditary Hemorrhagic Telangiectasia Multigene Panel	HHTNext (Ambry Genetics)	81405, 81406, 81479	R04.0, Q27.30-Q27.39	28, 30, 31
	Hereditary hemorrhagic telangiectasia panel - NGS Panel + CNV (Centogene)			
	Hereditary Hemorrhagic Telangiectasia (HHT), Proband (LabCorp)			
	Hereditary Hemorrhagic Telangiectasia Panel (PerkinElmer Genomics)			
Legius Syndrome				
SPRED1 Sequencing and/or Deletion/Duplication Analysis	SPRED1 Sequencing SPRED1 Deletion/Duplication	81405	L81.3, Z82.79, Z84	34
Neurofibromatosis				
NF1 or *NF2* Sequencing and/or Deletion/Duplication Analysis or Multigene Panel	NF1 Sequencing Analysis	81408	L81.3, R62.5, Q87.1, Q85.0, Z82.79, Z84	4, 5, 6, 7
	NF2 Sequencing Analysis NF2 Deletion/Duplication Analysis	81405, 81406		
Noonan Spectrum Disorders				
Noonan Spectrum Disorders Multigene Panel	NoonanNext (Ambry Genetics)	81442	F82, R62.52, Q24, Q87.19, R62.0, R62.50, R62.59, Q53, Q67.6, Q67.7, L81.4, L81.3	32, 33, 34
	Noonan Spectrum Disorder NGS Panel (CTGT)			
	Noonan and Comprehensive RASopathies Panel (GeneDx)			
	Noonan Spectrum Disorders/Rasopathies Panel (PreventionGenetics)			
***PIK3CA*-Related Segmental Overgrowth and Related Syndromes**				
PIK3CA Sequencing and/or Deletion/Duplication	PIK3CA Sequencing Analysis PIK3CA Deletion/Duplication Analysis	81479		51, 52

Analysis				
Rett Syndrome				
MECP2 Sequencing and/or Deletion/Duplication Analysis	MECP2 Sequencing Analysis	81302	F70-F79, F80, F81, F82, F84, F88, F89, Z13.4, Z82.79, Z84	35, 36, 37, 38, 39
	MECP2 Deletion/Duplication Analysis	81304		
	Genomic Unity MECP2 Analysis (Variantyx, Inc.)	0234U		
Tuberous Sclerosis Complex (TSC)				
TSC1 and *TSC2* Sequencing and/or Deletion/Duplication Analysis	TSC1 Sequencing Analysis TSC1 Deletion/Duplication Analysis TSC2 Sequencing Analysis TSC2 Deletion/Duplication Analysis	81405, 81406, 81407	D10, D15.1, D43, D21.9, H35.89, N28.1, Q61.9, H35.89	42
Other Covered Multisystem Inherited Disorders				
Other Covered Multisystem Inherited Disorders	See below	81400-81408		43, 44, 45

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.

COVERAGE 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 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 has developmental delay/intellectual disability, excluding isolated speech/language delay **OR**

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

   C. The member has multiple congenital anomalies not specific to a well-delineated genetic syndrome.

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

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

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), uniparental disomy analysis (81402), and imprinting center defect analysis (81479) to establish or confirm a diagnosis of Angelman or Prader-Willi syndrome is considered **medically necessary** when:

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

      1. Developmental delay by age six to 12 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 meets one of the following age-specific features of Prader-Willi syndrome:

      1. The member is age birth to two years with hypotonia with poor suck, **OR**

      2. The member 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 is age six to 12 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 is age 13 years to adulthood 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), uniparental disomy analysis (81402), and imprinting center defect analysis (81479) 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 (88271, 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 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 below the mean for gestational age)
2. Postnatal growth failure (length/height ≥2 SD below the mean at 24 months)
3. Relative macrocephaly at birth (head circumference >1.5 SD above birth weight and/or length)
4. Frontal bossing or prominent forehead (forehead projecting beyond the facial plane on a side view as a toddler [1–3 years])
5. Body asymmetry (limb length discrepancy ≥0.5 cm, or <0.5 cm with ≥2 other asymmetric body parts)
6. Feeding difficulties or body mass index ≤2 SD at 24 months or current use of a feeding tube or cyproheptadine for appetite stimulation, **OR**

B. The member 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 >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 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 (88271, 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. Unexplained white matter hyperintensities and a family history of stroke and/or vascular dementia, **OR**

   B. The member has at least one of the following clinical features of CADASIL:

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

   C. The member 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
      2. Lacunes of presumed vascular origin
      3. Recent subcortical infarcts
      4. Dilated perivascular spaces, sometimes referred to as subcortical lacunar lesions
      5. Brain atrophy
      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 (81220, 81222, 81223, S3835) to establish or confirm a diagnosis of cystic fibrosis is considered **medically necessary** when:

   A. The member has a positive (≥60mmol/L) or inconclusive sweat chloride test (30-59mmol/L), **OR**

   B. The member 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 (81220, 81222, 81223, S3835) 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 with a diagnosis of cystic fibrosis is considered **medically necessary** when:

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

   B. The member is known to have an R117H variant in the *CFTR* gene.

II. *CFTR* intron 9 polyT and TG analysis (81224) in a member 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 has at least two of the following:

1. Coloboma of the iris, retina, choroid, and/or disc, and/or anophthalmos or microphthalmos
2. Choanal atresia or stenosis, which may be unilateral or bilateral.
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)
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
5. Tracheoesophageal fistula or esophageal atresia
6. Cardiovascular malformation, including conotruncal defects (e.g., tetralogy of Fallot), AV canal defects, and aortic arch anomalies
7. Hypogonadotropic hypogonadism with delayed or absent puberty

8. Developmental delay / intellectual disability
9. Growth deficiency (short stature)
10. Distinctive features:
    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
11. Brain MRI showing clivus 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 (81167, 81216, 81479) is considered **medically necessary** when:

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

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

1. Prenatal and/or postnatal short stature
2. Abnormal skin pigmentation (e.g., café au lait macules, hypopigmentation)

3. Skeletal malformations (e.g., hypoplastic thumb, hypoplastic radius)
4. Microcephaly
5. Ophthalmic anomalies
6. Genitourinary tract anomalies
7. Macrocytosis
8. Increased fetal hemoglobin (often precedes anemia)
9. Cytopenia (especially thrombocytopenia, leukopenia and neutropenia)
10. Progressive bone marrow failure
11. Adult-onset aplastic anemia
12. Myelodysplastic syndrome (MDS)
13. Acute myelogenous leukemia (AML)
14. Early-onset solid tumors (e.g., squamous cell carcinomas of the head and neck, esophagus, and vulva; cervical cancer; and liver tumors)
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 (81167, 81216, 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 has unexplained speech and/or language delay, intellectual disability, or autism spectrum disorder, **OR**

B. The member is a female with primary ovarian insufficiency (cessation of menses before age 40), **OR**

C. The member is ≥ 50 years 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 has any of the following clinical features of HHT:

1. Spontaneous and recurrent nosebleeds (epistaxis)

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.

3. Visceral arteriovenous malformation (AVM), **AND**

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

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) to establish or confirm a diagnosis of Legius syndrome is considered **medically necessary** when:

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

   B. The member's personal and family history do 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 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 (81405, 81406, 81407, 81479) is considered **medically necessary** when:

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

      1. Six or more café au lait macules (>5 mm in greatest diameter in prepubertal individuals and >15 mm in greatest diameter in postpubertal individuals)

2. Two or more neurofibromas of any type or one plexiform neurofibroma
3. Freckling in the axillary or inguinal regions
4. Optic glioma
5. Two or more Lisch nodules (iris hamartomas)
6. A distinctive osseous lesion such as sphenoid dysplasia or tibial pseudarthrosis
7. Bilateral vestibular schwannomas
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
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 (81408) or multigene panel analysis is considered **investigational** for all other indications.

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NOONAN SPECTRUM DISORDERS

Noonan Spectrum Disorders 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 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)
2. Short stature
3. Congenital heart defect (most commonly pulmonary valve stenosis, atrial septal defect, and/or hypertrophic cardiomyopathy)
4. Developmental delay
5. Broad or webbed neck
6. Unusual chest shape with superior pectus carinatum, inferior pectus excavatum
7. Widely set nipples
8. Cryptorchidism in males
9. Lentigines
10. Café au lait macules

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 displays two or more of the following clinical features

      1. Sporadic and mosaic overgrowth in adipose, muscle, nerve, or skeletal tissues

      2. Vascular malformations including capillary, venous, arteriovenous malformation, or lymphatic.

      3. Epidermal nevus, **OR**

   B. The member displays one or more of the following clinical features, with a congenital or early childhood onset

      1. Large isolated lymphatic malformation

      2. Isolated macrodactyly OR overgrown splayed feet/ hands, overgrown limbs

      3. Truncal adipose overgrowth

      4. Hemimegalencephaly (bilateral)/ dysplastic megalencephaly/ focal cortical dysplasia

      5. Epidermal nevus

      6. Seborrheic keratoses

   C. 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 experienced a period of developmental regression (range: ages 1-4 years) followed by recovery or stabilization (range: ages 2-10 years), **AND**

   B. The member has any of the following:

      1. Partial or complete loss of acquired purposeful hand skills

      2. Partial or complete loss of acquired spoken language or language skill (e.g., babble)

      3. Gait abnormalities: impaired (dyspraxic) or absence of ability

      4. Stereotypic hand movements including hand wringing/squeezing, clapping/tapping, mouthing, and washing/rubbing automatisms, **AND**

   C. The member 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

      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, 0234U) 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 is considered **medically necessary** when:

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

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

B. The member has at least one 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)
2. Four or more Dental enamel pits
3. Two or more Intraoral fibromas
4. Multiple renal cysts
5. Nonrenal hamartomas

6. Retinal achromic patch
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 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. Capillary malformation-arteriovenous malformation syndrome (CM-AVM syndrome)
E. Cerebral cavernous malformations
F. Coffin-Siris syndrome
G. Cornelia de Lange syndrome
H. *FGFR2* craniosynostosis syndromes
I. Holoprosencephaly
J. Holt-Oram syndrome
K. Hypohidrotic ectodermal dysplasia
L. Incontinentia pigmenti
M. Joubert and Meckel-Gruber syndromes
N. Kabuki syndrome
O. *MYH9*-related disorders
P. Proteus syndrome

Q. Pseudoxanthoma elasticum
R. Rubinstein-Taybi syndrome
S. Schwannomatosis
T. *SHOX* deficiency disorders
U. 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 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.

BACKGROUND AND RATIONALE

Practice Guidelines and Position Statements

Chromosomal Microarray Analysis, DD/ID/ASD panels

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 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."

American College of Medical Genetics

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

The guideline revisions from ACMG (2013) stated that a stepwise or tiered approach to the clinical genetic diagnostic evaluation of ASD is recommended, with the first tier including fragile X syndrome and CMA, and the second tier MECP2 and PTEN testing. The guidelines stated that, "This approach will evolve with continued advancements in diagnostic testing and improved understanding of the ASD phenotype. Multiple additional conditions have been reported in association with an ASD phenotype, but none of these has been evaluated in a large prospective cohort. Therefore, a future third tier of evaluation is a distinct possibility. Further studies would be needed to elevate the evidence to the point of recommended testing. Alternatively, advances in technology may permit bundling of individual tests into an extended, more readily accessible, and less expensive platform. The accumulating evidence using next-generation sequencing (third-tier testing) will increase the diagnostic yield even more over the next few years."

Cystic Fibrosis

American Society for Reproductive Medicine in partnership with the Society for Male Reproduction and Urology

Consensus-based guidelines from the American Society for Reproductive Medicine in partnership with the Society for Male Reproduction and Urology (2008) recommend cystic fibrosis testing for men with CAVD and their partners, stating that "A man with CBAVD should be assumed to harbor a CFTR mutation. Therefore, before any treatments using his sperm, testing should be offered to the female partner to exclude the possibility (approximately 4%) that she too may be a carrier. All such couples should be offered genetic counseling."

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."

> When at least one characteristic feature is present, a diagnosis of CF can be confirmed by:
> - Two abnormal sweat chloride values
> - Identification of two CFTR gene mutations
> - Characteristic transepithelial nasal potential difference (NPD)
>
> In the absence of symptoms, a CF diagnosis can be established in:
> - A newborn with two CFTR gene mutations identified via newborn screening
> - A pregnancy found to have two CFTR mutations on prenatal testing

<u>Fanconi Anemia</u>

Fanconi Anemia Research Foundation

The Fanconi Anemia Research Foundation (2014) issued guidelines on diagnosis and management of the disease, which stated the following in regard to genetic testing:

> "In the last few years, the development of next-generation sequencing (NGS) methodology, also referred to as massively parallel sequencing, has transformed the field of genetic testing because it enables detailed analysis of thousands of genes simultaneously (i.e., in parallel). Such analyses would be too time-consuming and costly to attempt using classic DNA sequencing methodologies, such as Sanger sequencing, that analyze a single gene at a time. Many laboratories have developed targeted panels of genes to be assessed by NGS to search for mutations among a group of genes that have been previously documented or have been suggested to be important in a particular disease. Such panels may include anywhere from a few genes to greater than 500. The number of genes examined varies from laboratory to laboratory depending on the testing platform and algorithm being used."

Fragile X Syndrome

American College of Medical Genetics and Genomics

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.
- Affected individuals or their relatives in the context of a positive cytogenetic fragile X test result who are seeking further counseling related to the risk of carrier status among themselves or their relatives. The cytogenetic test was used before the identification of the FMR1 gene and is significantly less accurate than the current DNA test. DNA testing on such individuals is warranted to accurately identify premutation carriers and to distinguish premutation from full mutation carrier women.
- In the clinical genetics evaluation to identify the etiology of autism spectrum disorders, ACMG recommends testing for FXS as part of the first-tier testing.

According to the ACMG recommendations, the following is the preferred approach to testing:

- DNA analysis is the method of choice if one is testing specifically for fragile X syndrome (FXS) and associated trinucleotide repeat expansion in the FMR1 gene.

- For isolated cognitive impairment, DNA analysis for FXS should be performed as part of a comprehensive genetic evaluation that includes routine cytogenetic evaluation. Cytogenetic studies are critical since constitutional chromosome abnormalities have been identified as frequently or more frequently than fragile X mutations in mentally retarded individuals referred for fragile X testing.
- Fragile X testing is not routinely warranted for children with isolated attention-deficit/hyperactivity disorder (see Subcommittee on Attention-Deficit/Hyperactivity Disorder, Steering Committee on Quality Improvement, & Steering Committee on Quality Improvement Management, 2011).
- For individuals who are at risk due to an established family history of fragile X syndrome, DNA testing alone is sufficient. If the diagnosis of the affected relative was based on previous cytogenetic testing for fragile X syndrome, at least one affected relative should have DNA testing.
- If a woman has ovarian failure before the age of 40, DNA testing for premutation size alleles should be considered as part of an infertility evaluation and prior to in vitro fertilization.
- If a patient has cerebellar ataxia and intentional tremor, DNA testing for premutation size alleles, especially among men, should be considered as part of the diagnostic evaluation.

American College of Obstetricians and Gynecologists

The American College of Obstetricians and Gynecologists (2017) recommended that screening for FXS be offered to women with a family history suggestive of FXS and to women with a medical history suggestive of being a fragile X carrier (ie, ovarian insufficiency or failure or an elevated follicle-stimulating hormone level before age 40).

<u>Neurofibromatosis Type 1 and Neurofibromatosis Type 2</u>

American Academy of Pediatrics

The American Academy of Pediatrics (2019) published diagnostic and health supervision guidance for children with neurofibromatosis type 1 (NF1), which stated the following regarding genetic testing:

"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

PIK3CA Sequencing and/or Deletion/Duplication Analysis

Keppler-Noreiul 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.

Rett Syndrome

American Academy of Pediatrics

A 2007 policy statement from the American Academy of Pediatrics, reaffirmed in 2014, recommended MECP2 testing to confirm a diagnosis of suspected Rett syndrome (RTT), especially when the diagnosis was unclear from symptoms alone.

Neither the American Academy of Neurology nor the American Academy of Pediatrics has provided recommendations on when to use CDKL5 or FOXG1 testing.

American College of Medical Genetics and Genomics

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.

Tuberous Sclerosis

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."

"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."

"Definite TSC: 2 major features or 1 major feature with 2 minor features.

Possible TSC: either 1 major feature or 2 minor features."

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