Clinical Policy: Genetic Testing Multisystem Inherited Disorders, Intellectual Disability, and Developmental Delay

Reference Number: CP.MP.230
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See Important Reminder at the end of this policy for important regulatory and legal information.

Description
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.

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

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## Clinical Policy

**Genetic Testing Multisystem Inherited Disorders Intellectual Disability and Developmental Delay**

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

- **CP.MP.218 Genetic Testing: Epilepsy, Neurodegenerative, and Neuromuscular Disorders**
- **CP.MP.224 Genetic Testing: Hematologic Conditions (non-cancerous)**
- **CP.MP.221 Genetic Testing: Gastroenterologic Conditions (non-cancerous)**
- **CP.MP.216 Genetic Testing: Cardiac Disorders**
- **CP.MP.215 Genetic Testing: Aortopathies and Connective Tissue Disorders**
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- **CP.MP.223 Genetic Testing: Hearing Loss**
- **CP.MP.220 Genetic Testing: Eye Disorders**
- **CP.MP.226 Genetic Testing: Immune, Autoimmune, and Rheumatoid Disorders**
- **CP.MP.227 Genetic Testing: Kidney Disorders**
- **CP.MP.228 Genetic Testing: Lung Disorders**
- **CP.MP.229 Genetic Testing: Metabolic, Endocrine, and Mitochondrial Disorders**

For other related testing, please refer to:

- **CP.MP.231 Genetic Testing: Noninvasive Prenatal Screening (NIPS)** for criteria related to cell-free fetal DNA screening tests.
- **CP.MP.235 Genetic Testing: Prenatal Diagnosis (via amniocentesis, CVS, or PUBS) and Pregnancy Loss** for criteria related to prenatal and pregnancy loss diagnostic genetic testing for tests intended to diagnose genetic conditions following amniocentesis, chorionic villus sampling or pregnancy loss.
- **CP.MP.234 Genetic Testing: Prenatal and Preconception Carrier Screening** for criteria related to prenatal carrier screening, preimplantation testing of embryos, or preconception carrier screening.
- **CP.MP.219 Genetic Testing: Exome and Genome Sequencing for the Diagnosis of Genetic Disorders** for criteria related to exome and genome sequencing for genetic disorders.

**Policy/Criteria**

**Known Familial Variant Analysis for Multisystem Inherited Disorders**

I. It is the policy of health plans affiliated with Centene Corporation® that 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\(^1\) with a known pathogenic or likely pathogenic variant causing the condition.

II. It is the policy of health plans affiliated with Centene Corporation® that current evidence does not support targeted mutation analysis for a known familial variant (81403, 81303, 81221) for a multisystem inherited disorder for all other indications.

**Developmental Delay/Intellectual Disability, Autism Spectrum Disorder, Or Congenital Anomalies**

**Chromosomal Microarray Analysis**

I. It is the policy of health plans affiliated with Centene Corporation® that chromosomal microarray analysis (81228, 81229, S3870) is considered medically necessary when meeting any of the following:

   A. The member/enrollee has developmental delay/intellectual disability;
B. The member/enrollee has autism spectrum disorder;
C. The member/enrollee has multiple congenital anomalies not specific to a well-delineated genetic syndrome.

II. It is the policy of health plans affiliated with Centene Corporation® that current evidence does not support chromosomal microarray 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. It is the policy of health plans affiliated with Centene Corporation® that current evidence does not support the use of autism spectrum disorder, intellectual disability, or developmental delay multigene panel analysis (0156U, 81470, 81471, 81479).

Angelman/Prader-Willi Syndrome
SNRPN/UBE3A Methylation Analysis, 15q11-Q13 FISH Analysis, Chromosome 15 Uniparental Disomy Analysis, And Imprinting Center Defect Analysis

I. It is the policy of health plans affiliated with Centene Corporation® that 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 meeting any of the following:

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

1. Developmental delay by age six to 12 months, eventually classified as severe;
2. Speech impairment, with minimal to no use of words; receptive language skills and nonverbal communication skills higher than expressive language skills;
3. Movement or balance disorder, usually ataxia of gait and/or tremulous movement of the limbs;
4. Unique behavior, including any combination of frequent laughter/smiling; apparent happy demeanor; excitability, often with hand-flapping movements and hypermotoric behavior;

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;

2. The member/enrollee is age two to six years with both of the following characteristics:
   a) Hypotonia with history of poor suck;
   b) Global developmental delay;

3. The member/enrollee is age six to 12 years with all of the following characteristics:
   a) History of hypotonia with poor suck (hypotonia often persists);
   b) Global developmental delay;
   c) Excessive eating with central obesity if uncontrolled;

4. The member/enrollee is age 13 years to adulthood with all of the following characteristics:
   a) Cognitive impairment, usually mild intellectual disability;
   b) Excessive eating with central obesity if uncontrolled;
   c) Hypogonadism.

II. It is the policy of health plans affiliated with Centene Corporation® that current evidence does not support 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 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

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. It is the policy of health plans affiliated with Centene Corporation® that 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 meeting either of the following:
A. The member/enrollee meets at least 4 of the following 6 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 ≥ 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,

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 >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 member/enrollees 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. It is the policy of health plans affiliated with Centene Corporation® that current evidence does not support HI9 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 for all other indications.

CADASIL NOTCH3 Sequencing and/or Deletion/Duplication Analysis  
I. It is the policy of health plans affiliated with Centene Corporation® that 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 meeting either of the following:

A. Unexplained white matter hyperintensities and a family history of stroke and/or vascular dementia;  

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

1. At least one of the following clinical features of CADASIL:  
   a) Transient ischemic attacks and ischemic stroke  
   b) Cognitive impairment, manifesting initially with executive dysfunction, with a concurrent stepwise deterioration due to recurrent strokes to vascular dementia  
   c) Migraine with aura (mean age of onset of 30 years)  
   d) Psychiatric disturbances, most frequently mood disturbances and apathy,  

2. At least one of the following brain imaging findings of CADASIL:  
   a) Symmetric and progressive white matter hyperintensities, often involving the anterior temporal lobes and external capsules  
   b) Lacunes of presumed vascular origin  
   c) Recent subcortical infarcts  
   d) Dilated perivascular spaces, sometimes referred to as subcortical lacunar lesions
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e) Brain atrophy
f) Cerebral microbleeds

II. It is the policy of health plans affiliated with Centene Corporation® that current evidence does not support 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) for all other indications.

Cystic Fibrosis

CFTR Sequencing and/or Deletion/Duplication Analysis

I. It is the policy of health plans affiliated with Centene Corporation® that 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 meeting either of the following:

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

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

II. It is the policy of health plans affiliated with Centene Corporation® that current evidence does not support CFTR sequencing and/or deletion/duplication analysis (81220, 81222, 81223, S3835) to establish or confirm a diagnosis of cystic fibrosis for all other indications.

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

I. It is the policy of health plans affiliated with Centene Corporation® that CFTR intron 9 polyT and TG analysis (81224) in a member/enrollee with a diagnosis of cystic fibrosis is considered medically necessary when meeting both of the following:

A. The member/enrollee has a diagnosis of cystic fibrosis;

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

II. It is the policy of health plans affiliated with Centene Corporation® that current evidence does not support CFTR intron 9 polyT and TG analysis (81224) in a member/enrollee with a diagnosis of cystic fibrosis for all other indications.

Charge Syndrome

CHD7 Sequencing and/or Deletion/Duplication Analysis

I. It is the policy of health plans affiliated with Centene Corporation® that 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

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. It is the policy of health plans affiliated with Centene Corporation® that current evidence does not support CHD7 sequencing and/or deletion/duplication analysis (81407, 81479) to establish or confirm a diagnosis of CHARGE syndrome for all other indications.
Fanconi Anemia
Fanconi Anemia Multigene Panel
   I. It is the policy of health plans affiliated with Centene Corporation® that multigene panel analysis to establish or confirm a genetic diagnosis of Fanconi anemia (81167, 81216, 81479) is considered medically necessary when meeting all of the following:
      A. The member/enrollee has had a positive or inconclusive chromosome breakage analysis;
      B. The member/enrollee 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;
      C. The panel includes, at a minimum, the following genes: FANCA, FANCC, and FANCG.

   II. It is the policy of health plans affiliated with Centene Corporation® that current evidence does not support multigene panel analysis to establish or confirm a genetic diagnosis of Fanconi anemia (81167, 81216, 81479) for all other indications.

Fragile X Syndrome
FMR1 Repeat and Methylation Analysis
   I. It is the policy of health plans affiliated with Centene Corporation® that 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 meeting any of the following:
      A. The member/enrollee has unexplained speech and/or language delay, intellectual disability, or autism spectrum disorder;
B. The member/enrollee is a female with primary ovarian insufficiency (cessation of menses before age 40);

C. The member/enrollee is ≥ 50 years with progressive intention tremor and cerebellar ataxia of unknown origin.

II. It is the policy of health plans affiliated with Centene Corporation® that current evidence does not support \textit{FMR1} repeat and methylation analysis (81243, 81244) to establish or confirm a genetic diagnosis of Fragile X syndrome or Fragile X-associated disorders for all other indications.

\subsection*{Hereditary Hemorrhagic Telangiectasia (HHT) Multigene Panel}

I. It is the policy of health plans affiliated with Centene Corporation® that hereditary hemorrhagic telangiectasia (HHT) multigene panel analysis (81405, 81406, 81479) to establish or confirm a diagnosis of HHT is considered \textit{medically necessary} when meeting both of the following:

A. The member/enrollee 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),

B. The panel includes, at a minimum, the following genes: \textit{ACVRL1} and \textit{ENG}.

II. It is the policy of health plans affiliated with Centene Corporation® that current evidence does not support hereditary hemorrhagic telangiectasia (HHT) multigene panel analysis (81405, 81406, 81479) to establish or confirm a diagnosis of HHT for all other indications.

\subsection*{Legius Syndrome}

\textit{SPRED1} Sequencing and/or Deletion/Duplication Analysis

I. It is the policy of health plans affiliated with Centene Corporation® that \textit{SPRED1} sequencing and/or deletion/duplication analysis (81405) to establish or confirm a diagnosis of Legius syndrome is considered \textit{medically necessary} when meeting all of the following:

A. The member/enrollee has multiple café au lait macules;

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

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

II. It is the policy of health plans affiliated with Centene Corporation® that current evidence does not support SPRED1 sequencing and/or deletion/duplication analysis (81405, 81479) to establish or confirm a diagnosis of Legius syndrome for all other indications.

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

I. It is the policy of health plans affiliated with Centene Corporation® that 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/enrollee 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 two of the following:

   a) Meningioma;
   b) Schwannoma;
   c) Glioma;
   d) Neurofibroma;
   e) Cataract in the form of subcapsular lenticular opacities,
   f) Cortical wedge cataract
9. Multiple meningiomas and either of the following:
   a) Unilateral vestibular schwannoma;
   b) Any two of the following: schwannoma, glioma, neurofibroma, cataract in the form of subcapsular lenticular opacities or cortical wedge cataract

II. It is the policy of health plans affiliated with Centene Corporation® that current evidence does not support NF1 or NF2 sequencing and/or deletion/duplication analysis (81408) or multigene panel analysis for all other indications.

Noonan Spectrum Disorders
Noonan Spectrum Disorders Multigene Panel
I. It is the policy of health plans affiliated with Centene Corporation® that 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 meeting both of the following:

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)
   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. It is the policy of health plans affiliated with Centene Corporation® that current evidence does not support 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) for all other indications.
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PIK3CA-Related Segmental Overgrowth and Related Syndromes

**PIK3CA Sequencing and/or Deletion/Duplication Analysis**

I. It is the policy of health plans affiliated with Centene Corporation® that *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 clinical features of one of the following PIK3CA-related Segmental Overgrowth phenotypes:

      1. CLOVES syndrome
      2. Megalencephaly-capillary malformation syndrome (MCAP syndrome)
      3. Fibroadipose hyperplasia
      4. Hemimegalencephaly

II. It is the policy of health plans affiliated with Centene Corporation® that current evidence does not support *PIK3CA* sequencing and/or deletion/duplication analysis (81479) to establish a diagnosis of PIK3CA-Related Segmental Overgrowth 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.

Rett Syndrome

**MECP2 Sequencing and/or Deletion/Duplication Analysis**

I. It is the policy of health plans affiliated with Centene Corporation® that *MECP2* sequencing and/or deletion/duplication analysis (81302, 81304, 0234U) to establish or confirm a diagnosis of Rett syndrome is considered **medically necessary** when meeting all of the following:

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

   B. The member/enrollee 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;

   C. The member/enrollee does **not** have either of the following:
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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. It is the policy of health plans affiliated with Centene Corporation® that current evidence does not support MECP2 sequencing and/or deletion/duplication analysis (81302, 81304, 0234U) to establish or confirm a diagnosis of Rett syndrome for all other indications.

Tuberous Sclerosis Complex (TSC)

TSC1 and TSC2 Sequencing and/or Deletion Duplication Analysis

I. It is the policy of health plans affiliated with Centene Corporation® that 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 meeting either of the following:

A. The member/enrollee 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;

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)
2. Four or more Dental enamel pits
3. Two or more Intraoral fibromas
4. Multiple renal cysts
5. Nonrenal hamartomas
6. Retinal achromatic patch
7. Sclerotic bone lesions

II. It is the policy of health plans affiliated with Centene Corporation® that current evidence does not support TSC1 and TSC2 sequencing and/or deletion/duplication analysis (81405, 81406, 81407) to establish or confirm a diagnosis of Tuberous Sclerosis Complex 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, these genetic tests may be appropriate to establish or confirm a diagnosis.

I. It is the policy of health plans affiliated with Centene Corporation® that 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. 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. It is the policy of health plans affiliated with Centene Corporation® that 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 CP.MP.222 General Approach to Genetic Testing (see policy criteria).

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

Notes and Definitions
1. Close relatives include first, second, and third degree blood relatives:
   a. First-degree relatives are parents, siblings, and children

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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

**Background**

**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

Fanconi Anemia

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
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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).

Neurofibromatosis Type 1 and Neurofibromatosis Type 2

American Academy of Pediatrics
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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 member/enrollees 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

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.

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 2021, 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.
References


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44. Online Mendelian Inheritance in Man, OMIM®. McKusick-Nathans Institute of Genetic Medicine, Johns Hopkins University (Baltimore, MD). World Wide Web URL: https://omim.org/


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

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

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

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

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

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

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