Dean Health Plan Coverage Policy

Policy Name:	**Genetic Testing: Multisystem Inherited Disorders, Intellectual Disability, And Developmental Delay Mp9587**
Effective Date:	**January 01, 2025**

Important Information – Please Read Before Using This Policy

These services may or may not be covered by Dean Health Plan. Coverage is subject to requirements in applicable federal or state laws. Please refer to the member's plan document for other specific coverage information. If there is a difference between this general information and the member's plan document, the member's plan document will be used to determine coverage. With respect to Medicare, Medicaid, and other government programs, this policy will apply unless these programs require different coverage.

Members may contact Dean Health Plan Customer Service at the phone number listed on their member identification card to discuss their benefits more specifically. Providers with questions about this medical policy see Provider Communications for additional information. https://deancare.com/Providers/Provider-communications

Dean Health Plan medical policies are not medical advice. Members should consult with appropriate health care providers to obtain needed medical advice, care and treatment.

OVERVIEW

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

POLICY REFERENCE TABLE

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

Use the current applicable CPT/HCPCS code(s). The following codes are included below for informational purposes only and are subject to change without notice. Inclusion or exclusion of a code does not constitute or imply member coverage or provider reimbursement.

Coverage Criteria Sections	Example Tests; Labs	Common CPT Codes	Common ICD Codes	Ref
Developmental Delay/Intellectual Disability, Autism Spectrum Disorder, or Congenital Anomalies				
Chromosomal Microarray Analysis for Developmental Delay/Intellectual Disability, Autism Spectrum Disorder, or Congenital Anomalies	Chromosomal Microarray (MicroarrayDx) (GeneDx)	81228, 81229, S3870	F84.0, Q89.7, R62.50, F79	6, 7, 8, 30
	Chromosomal Microarray, Postnatal, ClariSure Oligo-SNP (Quest Diagnostics)			
	SNP Microarray−Pediatric (Reveal) (LabCorp)			
Autism Spectrum Disorder/Intellectual Disability Panel Analysis	Neurodevelopmental Disorders (NDD) Panel (Invitae)	81470, 81471, 81479, 81185, 81236, 81302, 81321	F70-80, F84, F81, F82, F88, F89, H93.52	10, 27
	Autism/ID Xpanded panel (GeneDx)			
	SMASH (Marvel Genomics)	0156U		
Angelman/Prader-Willi Syndrome				
SNRPN/UBE3A Methylation Analysis, 15q11-q13 FISH Analysis, Chromosome 15 Uniparental Disomy analysis, and Imprinting Center Defect Analysis	Angelman Syndrome/Prader-Willi Syndrome Methylation Analysis (GeneDx)	81331	R47, Q93.51, Q93.5	11, 21
	FISH, Prader-Willi/Angelman Syndrome (Quest Diagnostics)	88271, 88273		
	Chromosome 15 UPD Analysis (Greenwood Genetic Center)	81402		
	Imprinting Center (IC) Deletion Analysis for Angelman Syndrome (Univ of Chicago Genetic Services Laboratories)	81331		

Coverage Criteria Sections	Example Tests; Labs	Common CPT Codes	Common ICD Codes	Ref
	Imprinting Center (IC) Deletion Analysis for Prader-Willi Syndrome (Univ of Chicago Genetic Services Laboratories)			
Beckwith-Wiedemann/Russell-Silver Syndrome				
H19 and *KCNQ1OT1* Methylation Analysis, Deletion/Duplication Analysis of 11p15, Chromosome 7 Uniparental Disomy Analysis, *CDKN1C* Sequencing and/or Deletion/Duplication Analysis	Russell-Silver Syndrome: H19 Methylation (Shodair Children's Hospital)	81401	C22.2, C64, I42.9, P08, R16.0-R16.2, R62.52, Q35, Q38.2, Q63, Q79.2, Q87.3	12, 13
	Beckwith-Wiedemann: Methylation analysis of 11p15.5 only (University of Pennsylvania School of Medicine Genetic Diagnostic Laboratory)			
	RSS: Methylation analysis of 11p15.5 only (University of Pennsylvania School of Medicine Genetic Diagnostic Laboratory)			
	Beckwith-Wiedemann: 11p15.5 high resolution copy number analysis only (aCGH) (University of Pennsylvania School of Medicine Genetic Diagnostic Laboratory)	81479		
	RSS: 11p15.5 high resolution copy number analysis only (aCGH) (University of Pennsylvania School of Medicine Genetic Diagnostic Laboratory)			
	Chromosome 7 UPD Analysis (Greenwood Genetics Center - Molecular Diagnostic Laboratory)	81402		
	CDKN1C Full Gene Sequencing and Deletion/Duplication (Invitae)	81479		
Cystic Fibrosis				

Coverage Criteria Sections	Example Tests; Labs	Common CPT Codes	Common ICD Codes	Ref
Diagnostic *CFTR* Sequencing and/or Deletion/Duplication Analysis	Cystic Fibrosis Complete Rare Variant Analysis, Entire Gene Sequence (Quest Diagnostics)	81223	E84.0-9, P09, Q55.4, R94.8, Z13, Z31, Z34, Z82.79, Z83, Z84	1, 32
	Cystic Fibrosis Gene Deletion or Duplication (Quest Diagnostics)	81222		
CFTR Intron 9 PolyT and TG Analysis (previously called Intron 8 polyT/TG)	*CFTR* Intron 9 Poly-T Analysis (Quest Diagnostics)	81224		2
CHARGE Syndrome				
CHD7 Sequencing and/or Deletion/Duplication Analysis	CHARGE and Kallman Syndromes via the CHD7 Gene (PreventionGenetics, part of Exact Sciences)	81407, 81479	Q89.8	14
Fanconi Anemia				
Fanconi Anemia Multigene Panel	FancZoom (DNA Diagnostic Laboratory - Johns Hopkins Hospital)	81162, 81307, 81479	C92, D46.9, D61.09, D61.89, D61.9, L81.3, L81.4 Q02, R62.52	15, 25
	Fanconi Anemia Panel (PreventionGenetics, part of Exact Sciences)			
Fragile X Syndrome				
Diagnostic *FMR1* Repeat and Methylation Analysis	Fragile X Syndrome, Diagnostic (Labcorp)	81243, 81244	F84.0, Q99.2, F79, E28.3, G11.2, G25.2	9, 16, 17
	XSense, Fragile X with Reflex (Quest Diagnostics)			
	Fragile X Syndrome via the FMR1 CGG Repeat Expansion			

Coverage Criteria Sections	Example Tests; Labs	Common CPT Codes	Common ICD Codes	Ref
	(PreventionGenetics, part of Exact Sciences)			
Hereditary Hemorrhagic Telangiectasia (HHT)				
Hereditary Hemorrhagic Telangiectasia Multigene Panel	HHTNext (Ambry Genetics) Hereditary Hemorrhagic Telangiectasia (HHT) Panel (Blueprint Genetics)	81405, 81406, 81479	R04.0, Q27.30-Q27.39	18, 19
Neurofibromatosis 1				
NF1 Sequencing and/or Deletion/Duplication Analysis	NF1 Sequencing & Del/Dup (GeneDx)	81408	L81.3, R62.5, Q85.0, Z82.79, Z84	3, 5
NF2-Related Schwannomatosis (previously known as Neurofibromatosis 2)				
NF2 Sequencing and/or Deletion/Duplication Analysis	Neurofibromatosis Type 2 via the NF2 Gene (PreventionGenetics, part of Exact Sciences)	81405, 81406	L81.3, R62.5, Q85.0, Z82.79, Z84	4
Noonan Spectrum Disorders/RASopathies				
Noonan Spectrum Disorders/RASopathies Multigene Panel	RASopathies and Noonan Spectrum Disorders Panel (Invitae) Noonan and Comprehensive RASopathies Panel (GeneDx)	81442	F82, R62.52, Q24, Q87.19, R62.0, R62.50, R62.59, Q53, Q67.6, Q67.7, L81.4, L81.3	20, 31
***PIK3CA*-Related Segmental Overgrowth and Related Syndromes**				
PIK3CA Sequencing Analysis	PIK3CA Single Gene (Sequencing & Deletion/Duplication)	81479		26

Coverage Criteria Sections	Example Tests; Labs	Common CPT Codes	Common ICD Codes	Ref
	(Fulgent Genetics)			
Tuberous Sclerosis Complex (TSC)				
TSC1 and *TSC2* Sequencing and/or Deletion/Duplication Analysis	Tuberous Sclerosis Complex Panel (TSC1, TSC2) (Quest Diagnostics)	81405, 81406 81407	D10, D15.1, D43, D21.9, H35.89, N28.1, Q61.9, H35.89	28, 29
Other Covered Multisystem Inherited Disorders				
Other Covered Multisystem Inherited Disorders	See below	81400-8		22, 23, 24

OTHER RELATED POLICIES

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

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

For other related testing, please refer to:

- ***Genetic Testing: Prenatal Cell-free DNA Testing*** 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.
- ***Genetic Testing: General Approach to Genetic and Molecular Testing*** for coverage criteria related to genetic testing that is not specifically discussed in this or another non-general policy, including known familial variant testing.

COVERAGE CRITERIA

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

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

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

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

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

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

   D. The member has short stature.

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

   A. Isolated speech/language delay*.

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

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Autism Spectrum Disorder/Intellectual Disability Panel Analysis

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

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ANGELMAN/PRADER-WILLI SYNDROME

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

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

A. The member meets both of the following related to Angelman syndrome:

1. The member has functionally severe developmental delay by age six months to twelve months, **AND**

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

a) Speech impairment, with minimal to no use of words; receptive language skills and nonverbal communication skills higher than expressive language skills, **OR**

b) Movement or balance disorder, usually ataxia of gait and/or tremulous movement of the limbs, **OR**

c) Unique behavior, including any combination of frequent laughter/smiling; apparent happy demeanor; excitability, often with hand-flapping movements and hypermotoric behavior, **OR**

B. The member meets one of the following age-specific features of Prader-Willi syndrome:

1. The member is age less than one month with:

a) Hypotonia with poor suck, **OR**

2. The member is age one month to two years with:

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

b) Developmental delay, **OR**

3. The member is age two to six years with:

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

b) Global developmental delay, **OR**

4. The member is age six to twelve years with:

a) History of hypotonia with poor suck (hypotonia often persists), **AND**

b) Global developmental delay, **AND**

c) Excessive eating with central obesity if uncontrolled externally, **OR**

5. The member is age thirteen years or older with:

    a) Cognitive impairment, usually mild intellectual disability, **AND**

    b) Excessive eating and hyperphagia with central obesity if uncontrolled externally, **AND**

    c) Hypothalamic hypogonadism, **OR**

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

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

NOTE: The following is the recommended testing strategy:

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

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BECKWITH-WIEDEMANN/RUSSELL-SILVER SYNDROME

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

I. *H19* and *KCNQ1OT1* methylation analysis (81401), deletion/duplication analysis of 11p15 (81479), chromosome 7 uniparental disomy analysis (81402), or *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 has at least one of the following clinical features of Beckwith-Wiedemann syndrome (BWS):

        1. Macroglossia, **OR**

        2. Abdominal wall defect requiring surgical correction (e.g., omphalocele/exophthalmos or a large umbilical hernia), **OR**

        3. Embryonal tumor, (e.g., Wilms tumor, hepatoblastoma, or nephroblastomatosis, rhabdomyosarcoma, neuroblastoma, or adrenal tumors, **OR**

        4. Hemihyperplasia (lateralized overgrowth) of one or more body segments, **OR**

5. Macrosomia, defined as pre- and/or postnatal overgrowth, often using a cutoff of >90th or >97th centile, depending on the study, **OR**
6. Hyperinsulinemic hypoglycemia, **OR**
7. Pathology findings including cytomegaly of the adrenal cortex, placental mesenchymal dysplasia and pancreatic adenomatosis, **OR**
8. Family history of one or more family members with clinical features suggestive of BWS, **OR**
9. Visceromegaly, typically from an imaging study such as ultrasound, involving 1 or more intra-abdominal organs, such as the liver, kidneys, and/or adrenal glands, **OR**
10. Unilateral or bilateral earlobe creases and/or posterior helical ear pits, **OR**
11. Characteristic facies (i.e., infraorbital creases, midface retrusion, thin vermilion of the upper lip, and prominent jaw), **OR**
12. Kidney anomalies, such as structural malformations, nephrocalcinosis, or medullary sponge kidney, **OR**
13. Transient hypoglycemia requiring medical intervention, **OR**

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

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

II. *H19* and *KCNQ1OT1* methylation analysis (81401), deletion/duplication analysis of 11p15 (81479), chromosome 7 uniparental disomy analysis (81402), or *CDKN1C* sequencing and/or deletion/duplication analysis (81479) to confirm or establish a diagnosis of Beckwith-Wiedemann or Russell-Silver syndrome is considered **investigational** for all other indications.

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CYSTIC FIBROSIS

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

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

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

   B. The member has a positive newborn screen for cystic fibrosis as indicated by elevated immunoreactive trypsinogen, **OR**

   C. The member has symptoms of cystic fibrosis from at least **TWO** different organ systems:

      1. Sinus (e.g. chronic sinusitis, nasal polyps), **OR**

      2. Lower respiratory (e.g., bronchiectasis, chronic or recurrent lower airway infection, allergic bronchopulmonary aspergillosis), **OR**

      3. Gastrointestinal (GI)/lumen (e.g., meconium ileus, distal intestinal obstruction syndrome, abnormal motility, rectal prolapse), **OR**

      4. Gastrointestinal (GI)/hepatobiliary (e.g., pancreatic insufficiency, recurrent pancreatitis, elevated liver enzymes, ecchymosis, cirrhosis, prolonged neonatal jaundice, fat soluble vitamin deficiencies), **OR**

      5. Reproductive (e.g., male (sex assigned at birth) infertility because of obstructive azoospermia, female (sex assigned at birth) infertility), **OR**

      6. Other (e.g., hyponatremic dehydration, failure to thrive, pseudo-Bartter syndrome, aquagenic wrinkling of skin, digital clubbing).

II. *CFTR* sequencing and/or deletion/duplication analysis (81222, 81223) to establish or confirm a diagnosis of cystic fibrosis is considered **investigational** for all other indications.

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

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

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

   B. The member has 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, **OR**
2. Anophthalmos or microphthalmos, **OR**
3. Choanal atresia or stenosis **OR**
4. Cleft palate with or without cleft lip, **OR**
5. Cranial nerve dysfunction or anomaly (hyposmia or anosmia, facial palsy, sensorineural hearing loss and/or balance problems, hypoplasia or aplasia on imaging, difficulty with sucking/swallowing and aspiration, gut motility problems), **OR**
6. Ear malformations (auricular abnormalities, middle ear abnormalities/ossicular malformations, and temporal bone abnormalities), **OR**
7. Tracheoesophageal fistula or esophageal atresia, **OR**
8. Cardiovascular malformation (conotruncal defects (e.g., tetralogy of Fallot), AV canal defects, and aortic arch anomalies), **OR**
9. Hypogonadotropic hypogonadism (micropenis or cryptorchidism, hypoplastic labia, abnormal or absent uterus, delayed or absent puberty), **OR**
10. Developmental delay or intellectual disability, **OR**
11. Growth deficiency (short stature), **OR**
12. Characteristic physical features of the face, neck, and/or hands, **OR**
13. Brain MRI showing clivus hypoplasia or hypoplasia of the cerebellar vermis.

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

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FANCONI ANEMIA

Fanconi Anemia Multigene Panel

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

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

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

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

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

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FRAGILE X SYNDROME

Diagnostic *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 intellectual disability or developmental delay, **OR**

   B. The member is male and has unexplained autism spectrum disorder, **OR**

   C. The member is female and has unexplained autism spectrum disorder, **AND**

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

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

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

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

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 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), **OR**

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

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

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

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

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NEUROFIBROMATOSIS 1

***NF1* Sequencing and/or Deletion/Duplication Analysis**

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

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

1. Six or more café au lait macules (greater than 5 mm in greatest diameter in prepubertal individuals and greater than 15 mm in greatest diameter in postpubertal individuals), **OR**
2. Two or more neurofibromas of any type or one plexiform neurofibroma, **OR**
3. Freckling in the axillary or inguinal regions, **OR**
4. Optic glioma, **OR**
5. Two or more Lisch nodules (iris hamartomas), **OR**
6. A distinctive osseous lesion such as sphenoid dysplasia or tibial pseudarthrosis, **OR**

B. The member has a biological parent who meets the diagnostic criteria for *NF1* (the diagnosis of NF1 is established in an individual with two or more of the above features).

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

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***NF2*-RELATED SCHWANNOMATOSIS (PREVIOUSLY KNOWN AS NEUROFIBROMATOSIS 2)**

NF2 Sequencing and/or Deletion/Duplication Analysis

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

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

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

1. Bilateral vestibular schwannomas, **OR**

2. Unilateral vestibular schwannoma, **AND**

    a) At least two of the following:

        (1) Meningioma, **OR**

        (2) Schwannoma, **OR**

        (3) Glioma, **OR**

        (4) Neurofibroma, **OR**

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

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

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

1. Unilateral vestibular schwannoma, **OR**
2. At least two of the following:

    a) Schwannoma, **OR**

    b) Ependymoma, **OR**

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

    d) Cortical wedge cataract diagnosed in an individual less than 40 years of age, **OR**

D. The member is a child with at least two of the following:

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

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

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NOONAN SPECTRUM DISORDERS/RASOPATHIES

Noonan Spectrum Disorders/RASopathies Multigene Panel

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

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

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

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

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PIK3CA-Related Segmental Overgrowth and Related Syndromes

PIK3CA Sequencing Analysis

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

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

      1. Hemimegalencephaly, **OR**
      2. Focal cortical dysplasia, **OR**

3. Dysplastic megalencephaly, **OR**

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

1. Overgrowth of any of a wide variety of tissues including (but not limited to) brain, adipose, vascular, muscle, skeletal, nerve, **OR**

2. Vascular malformations including (but not limited to) capillary, venous, arteriovenous, or mixed malformations, **OR**

3. Lymphatic malformations, **OR**

4. Cutaneous findings including epidermal nevi and hyperpigmented macules, **OR**

5. Single or multiple digital anomalies of the hands or feet (e.g., macrodactyly, syndactyly, polydactyly, sandal-toe gap), **OR**

6. Kidney malformations (e.g., pelviectasis, dilated ureters, hydronephrosis, duplicated renal arteries, renal cysts, enlarged kidneys), **OR**

7. Benign tumors, with the exceptions of Wilms tumor and nephroblastomatosis (i.e., diffuse or multifocal clusters of persistent embryonal cells).

II. *PIK3CA* sequencing analysis (81479) to establish a diagnosis of *PIK3CA*-Related Segmental Overgrowth is considered **investigational** for all other indications.

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

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TUBEROUS SCLEROSIS COMPLEX (TSC)

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

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

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

1. Three or more angiofibromas or fibrous cephalic plaque, **OR**

2. Cardiac rhabdomyoma, **OR**

3. Multiple cortical tubers and/or radial migration lines, **OR**

4. Hypomelanotic macules (3 or more macules that are at least 5 mm in diameter), **OR**

5. Lymphangioleiomyomatosis (LAM), **OR**
6. Multiple retinal nodular hamartomas, **OR**
7. Renal angiomyolipoma, **OR**
8. Shagreen patch, **OR**
9. Subependymal giant cell astrocytoma (SEGA), **OR**
10. Two or more subependymal nodules (SENs), **OR**
11. Two or more ungual fibromas, **OR**

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

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

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

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OTHER COVERED MULTISYSTEM INHERITED DISORDERS

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

I. Genetic testing to establish or confirm one of the following multisystem inherited disorders to guide management is considered **medically necessary** when the member 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. Coffin-Siris syndrome
E. Cornelia de Lange syndrome
F. *FGFR2* craniosynostosis syndromes
G. Holoprosencephaly
H. Holt-Oram syndrome

I. Incontinentia pigmenti
J. Joubert and Meckel-Gruber syndromes
K. Kabuki syndrome
L. *MYH9*-related disorders
M. Proteus syndrome
N. Pseudoxanthoma elasticum
O. Rubinstein-Taybi syndrome
P. Schwannomatosis
Q. Waardenburg syndrome

II. Genetic testing to establish or confirm the diagnosis of all other multisystem inherited disorders not specifically discussed within this or another medical policy will be evaluated by the criteria outlined in *General Approach to Genetic and Molecular Testing* (see policy coverage criteria).

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

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DEFINITIONS

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

4. **Developmental delay (DD)**: Slow-to-meet or not reaching milestones in one or more of the areas of development (communication, motor, cognition, social-emotional, or adaptive skills) in the expected way for a child's age

5. **Intellectual disability (ID)**: Defined by the DSM V as an individual with all of the following:

    a. Deficits in intellectual functions, such as reasoning, problem solving, planning, abstract thinking, judgment, academic learning, and learning from experience, confirmed by both clinical assessment and individualized, standardized intelligence testing.

    b. Deficits in adaptive functioning that result in failure to meet developmental and sociocultural standards for personal independence and social responsibility. Without ongoing support, the adaptive deficits limit functioning in one or more activities of daily life, such as communication, social participation, and independent living, across multiple environments, such as home, school, work, and community.

    c. Onset of intellectual and adaptive deficits during the developmental period.

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PRIOR AUTHORIZATION

Prior authorization is not required. However, services with specific coverage criteria may be reviewed retrospectively to determine if criteria are being met. Retrospective denial may result if criteria are not met.

BACKGROUND AND RATIONALE

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

American Academy of Pediatrics

The American Academy of Pediatrics (2014, reaffirmed 2020) issued a clinical report on the optimal medical genetics evaluation of a child with developmental delays (DD) or intellectual disability (ID), which stated "CMA [chromosome microarray analysis] now should be considered a first-tier diagnostic test in all children with [global] GDD/ID for whom the causal diagnosis is not known…. CMA is now the standard for diagnosis of patients with GDD/ID, as well as other conditions, such as autism spectrum disorders or multiple congenital anomalies." (p. e905)

American College of Medical Genetics and Genomics (ACMG)

The ACMG (2010, reaffirmed 2020) published a Clinical Practice Resource on array-based technologies and their clinical utilization for detecting chromosomal abnormalities. CMA testing for copy number variants was recommended as a first-line test in the initial postnatal evaluation of individuals with the following:

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

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

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

Autism Spectrum Disorder/Intellectual Disability Panel Analysis

American Academy of Pediatrics (AAP)

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

American Academy of Child and Adolescent Psychiatry

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

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

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

GeneReviews: Angelman Syndrome

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

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

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

- Abnormal methylation at 15q11.2-q13 due to one of the following:

  - Deletion of the maternally inherited 15q11.2-q13 region (which includes *UBE3A*)
  - Uniparental disomy (UPD) of the paternal chromosome region 15q11.2-q13
  - An imprinting defect of the maternal chromosome 15q11.2-q13 region

- A pathogenic variant in the maternally derived *UBE3A*

GeneReviews: Prader-Willi syndrome

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

Per GeneReviews, DNA methylation analysis is the only technique that will diagnose Prader-Willi syndrome (PWS) caused by all three genetic common mechanisms (paternal deletion, maternal uniparental disomy and imprinting defects), as well as differentiate PWS from Angelman syndrome (AS) in deletion cases.

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

Neonatal Period: hypotonia with poor suck

Age one month two years

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

Age two to six years

- Hypotonia with history of poor suck
- Developmental delay

Age six to 12 years

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

Age 13 years to adulthood

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

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

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

GeneReviews: Beckwith-Wiedemann Syndrome (BWS)

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

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

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

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

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

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

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

- Large umbilical hernia that requires surgical correction
- Other embryonal tumors, including rhabdomyosarcoma, neuroblastoma, or adrenal tumors (pheochromocytoma, adrenocortical carcinoma)
- Transient hypoglycemia requiring medical intervention

GeneReviews: Silver-Russell Syndrome

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

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

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

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

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

Cystic Fibrosis Foundation

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

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

Sosnay et. al

A consensus statement from the 2015 Cystic Fibrosis Foundation Consensus Conference authored by Sosnay et al. (2017) establishes the following as suspicious symptoms for CF in individuals who may not have received screening for cystic fibrosis, or who may have received a false negative NBS test:

Table II. Clinical signs/symptoms that may signify CF (p. S53)

Presenting conditions	**Common as first presentation of CF**	**Uncommon as first presentation of CF***
Family history	Sibling or parent with CF	Parent of a child diagnosed with CF
Sinus	Chronic sinusitis, nasal polyps	
Lower respiratory	Bronchiectasis, chronic or recurrent lower airway infection (especially *Pseudomonas* infection)	ABPA, nontuberculous mycobacterial infection, asthma, chronic obstructive pulmonary disease
GI/lumen	Meconium ileus, distal intestinal obstruction syndrome	Abnormal motility, rectal prolapse
GI/hepatobiliary	Pancreatic insufficiency, recurrent pancreatitis	Elevated liver enzymes, ecchymosis, cirrhosis, prolonged neonatal jaundice, fat soluble vitamin deficiencies (may present as ecchymosis, anemia, edema, night-blindness, skin rash)
Reproductive	Male infertility because of obstructive azoospermia (CBAVD)	Female infertility

Presenting conditions	Common as first presentation of CF	Uncommon as first presentation of CF*
Other	Hyponatremic dehydration,failure to thrive	Pseudo-Bartter syndrome, aquagenic wrinkling of skin, digital clubbing

ABPA, allergic bronchopulmonary aspergillosis; GI, gastrointestinal.

CFTR Intron 9 PolyT and TG Analysis (previously called Intron 8 poly-T/TG Analysis)

American College of Medical Genetics and Genomics (ACMG)

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

CHD7 Sequencing and/or Deletion/Duplication Analysis

GeneReviews: CHD7 Disorder

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

The mnemonic CHARGE syndrome, introduced in the premolecular era, stands for ***c***oloboma, ***h***eart defect, choanal ***a***tresia, ***r***etarded growth and development, ***g***enital hypoplasia, ***e***ar anomalies (including deafness). Following the identification of the genetic cause of *CHD7* disorder, the phenotypic spectrum expanded to include cranial nerve anomalies, vestibular defects, cleft lip and/or palate, hypothyroidism, tracheoesophageal anomalies, brain anomalies, seizures, and renal anomalies.

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

- Coloboma of the iris, retina, choroid, and/or disc, and/or anophthalmos or microphthalmos
- Choanal atresia or stenosis: unilateral or bilateral, bony or membranous, confirmed by axial sections of non-enhanced axial CT scan
- Cleft palate with or without cleft lip (Note: Choanal atresia is rare in the presence of a cleft palate.)
    - Cranial nerve dysfunction or anomaly
    - Cranial nerve I. Hyposmia or anosmia
    - Cranial nerve VII. Facial palsy (unilateral or bilateral)
    - Cranial nerve VIII. Sensorineural hearing loss and/or balance problems, hypoplasia or aplasia on imaging
    - Cranial nerve IX/X. Difficulty with sucking/swallowing and aspiration, gut motility problems

- Ear malformations (most characteristic of *CHD7* disorder)
    - Auricle. Short, wide ear with little or no lobe, "snipped-off" helix, prominent antihelix that is often discontinuous with tragus, triangular concha, decreased cartilage; often protruding and usually asymmetric
    - Middle ear. Ossicular malformations (resulting in a typical wedge-shaped audiogram due to mixed sensorineural and conductive hearing loss)
    - Temporal bone abnormalities (most commonly determined by temporal bone CT scan). Mondini defect of the cochlea (cochlear hypoplasia), absent or hypoplastic semicircular canals
- Tracheoesophageal fistula or esophageal atresia
- Cardiovascular malformation, including conotruncal defects (e.g., tetralogy of Fallot), AV canal defects, and aortic arch anomalies
- Hypogonadotropic hypogonadism
    - Males at birth. Micropenis and cryptorchidism
    - Females at birth. Hypoplastic labia, abnormal or (rarely) absent uterus
    - Males and females. Delayed or absent puberty, often in combination with anosmia
- Developmental delay / intellectual disability, delayed motor milestones, often secondary to sensory and balance deficits
- Growth deficiency. Short stature, usually postnatal with or without growth hormone deficiency
- Other clinical features
    - Face. Square-shaped with broad forehead, broad nasal bridge, prominent nasal columella, flattened malar area, facial palsy or other asymmetry, cleft lip, and small chin (gets larger and broader with age)
    - Neck. Short and wide with sloping shoulders
    - Hands. Typically, short, wide palm with hockey-stick crease, short fingers, and finger-like thumb (see Figure 3); polydactyly and reduction defects in a small percentage
- Brain MRI. Clivus hypoplasia or hypoplasia of cerebellar vermis

Fanconi Anemia Multigene Panel

Fanconi Anemia Research Foundation

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

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

GeneReviews: Fanconi Anemia

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

Physical features (in ~75% of affected persons)

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

- Skeletal malformations (e.g., hypoplastic thumb, hypoplastic radius)
- Microcephaly
- Ophthalmic anomalies
- Genitourinary tract anomalies

Laboratory findings

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

Pathology findings

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

Diagnostic *FMR1* Repeat and Methylation Analysis

American College of Medical Genetics and Genomics (ACMG)

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

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

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

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

GeneReviews: FMR1 Disorders

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

GeneReviews (last update: May 16, 2024) recommends that *FMR1* testing be considered for any patient with the following clinical findings:

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

Hereditary Hemorrhagic Telangiectasia Multigene Panel

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

The goal of the Second International HHT Guidelines process was to develop evidence-based consensus guidelines for the management and prevention of HHT-related symptoms and complications. The expert panel generated and approved new recommendations. With regard to diagnosis, the following was recommended:

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

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

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

GeneReviews: Hereditary Hemorrhagic Telangiectasia

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

- Spontaneous and recurrent nosebleeds (epistaxis).
    - With night-time nosebleeds heightening the concern for HHT.
- Multiple telangiectases at characteristic sites.

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

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

***NF1* Sequencing and/or Deletion/Duplication Analysis**

American Academy of Pediatrics

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

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

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

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

GeneReviews: Neurofibromatosis Type 1

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

- Six or more café au lait macules (CALMs) greater than 5 mm in greatest diameter in prepubertal individuals and greater than 15 mm in greatest diameter in postpubertal individuals
- Freckling in the axillary or inguinal regions
- Two or more neurofibromas of any type or one plexiform neurofibroma
- Optic pathway glioma

- Two or more Lisch nodules identified by slit lamp examination or two or more choroidal abnormalities (bright, patchy nodules imaged by optical coherence tomography/near-infrared reflectance imaging)
- A distinctive osseous lesion such as sphenoid dysplasia, anterolateral bowing of the tibia, or pseudarthrosis of a long bone
- A parent who meets the diagnostic criteria for NF1

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

NF2 Sequencing and/or Deletion/Duplication Analysis

GeneReviews: NF2-Related Schwannomatosis

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

NF2 should be suspected in individuals with the following:

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

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

Clinical findings in adults:

- Bilateral vestibular schwannomas
- Unilateral vestibular schwannoma accompanied by ANY TWO of the following: meningioma, schwannoma, glioma, neurofibroma, cataract in the form of subcapsular lenticular opacities or cortical wedge cataract
- Multiple meningiomas accompanied by EITHER of the following:
    - Unilateral vestibular schwannoma
    - ANY TWO of the following: schwannoma, ependymoma, cataract in the form of subcapsular lenticular opacities or cortical wedge cataract diagnosed in an individual age <40 years

Laboratory findings: NF2 pathogenic variant identified on tumor tissue testing

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

Noonan Spectrum Disorders/RASopathies Multigene Panel

GeneReviews: Noonan Syndrome

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

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

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

When the phenotypic findings suggest the diagnosis of Noonan Syndrome (NS), molecular genetic testing approaches usually include the use of a multi-gene panel testing is suggested as it is more efficient and cost effective than serial single-gene testing. Approximately 50% of individuals with NS have a pathogenic missense variant in *PTPN11*; therefore, single-gene testing starting with *PTPN11* would be the next best first test.

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

***PIK3CA* Sequencing Analysis**

GeneReviews: PIK3CA-Related Overgrowth Spectrum

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

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

PROS should be considered in individuals with the following findings.

Clinical features:

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

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

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

TSC1 and _TSC2_ Sequencing and/or Deletion/Duplication Analysis

International TSC Clinical Consensus Group

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

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

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

GeneReviews: Tuberous Sclerosis Complex

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

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

Major features:

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

Minor features:

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

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Dean Health Plan Coverage Policy

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