Concert Genetic Testing: Multisystem ~~Inherited Disorders, Intellectual Disability, and Developmental Delay~~ Genetic Conditions

Reference Number: LA.CP.CG.14 Coding implications
Date of Last Revision ~~01/25~~03/26
Revision Log
See Important Reminder at the end of this policy for important regulatory and legal information.

OVERVIEW

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

This policy addresses the use of broad and targeted tests for the diagnosis of suspected genetic disorders that affect multiple body systems.

Pre-test and post-test genetic counseling that facilitates informed decision-making, the possibility to identify secondary finding with the option to 'opt out' of receiving these results, elicits patient preferences regarding secondary and/or incidental findings if possible, and formulates a plan for returning such results before testing occurs is strongly advised.

For additional information see the Rationale section.

~~POLICY REFERENCE TABLE~~

Coding Implications

This clinical policy references Current Procedural Terminology (CPT®). CPT is a registered trademark of the American Medical Association. All CPT codes and descriptions are copyrighted ~~2023~~2025, 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 and may not support medical necessity. 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.

NOTE: Coverage is subject to each requested code's inclusion on the corresponding LDH fee schedule. Non-covered codes are denoted (*) and are reviewed for Medical Necessity for members under 21 years of age on a per case basis. The non-covered codes will only be denoted in the table below and not throughout the policy. Please only reference the policy reference table for covered and non-covered codes.

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 criteria; as such, they are not comprehensive and are not a guarantee of coverage or non-coverage.~~

CRITERIA SECTIONS	EXAMPLE TESTS (LABS)	COMMON BILLING CODES	REFERENCES
Broad Tests for Suspected Multisystem Genetic Conditions			
Standard Exome Sequencing	Genomic Unity Exome Analysis - Proband (Variantyx)	81415*, 81416*, F70-F79, F80.0-F89, Q00.0-Q99.9, R56.9, R62.0, R62.50, R62.51, G40.909	26, 28, 30, 32, 33, 37, 38
	Genomic Unity Exome Analysis - Comparator (Duo or Trio) (Variantyx Inc.)		
	XomeDx - Proband (GeneDx)		
	Exome - Proband Only (Invitae)		
	XomeDx - Duo (GeneDx)		
	XomeDX - Trio (GeneDx)		

	Exome - Duo (Invitae)		
	Exome - Trio (Invitae)		
Reanalysis of Exome or Genome Sequencing Data	Exome Reanalysis (Ambry)	81417*, 81427, F70-F79, F80-F89, Q00.0-Q99.9, R56.9, R62.0, R62.50, R62.51, G40.909	29, 34, 35, 37, 47
	Whole Genome Reanalysis (ARUP)		
Rapid Exome Sequencing	XomeDxXpress (GeneDx)	81415*, 81416*, F70-F79, F80-F89, Q00.0-Q99.9, R56.9, R62.0, R62.50, R62.51, G40.909	26, 28, 30, 31, 32, 33, 36, 37, 38
	ExomeNext-Rapid (Ambry)		
	PGxome RAPID Exome Test (PreventionGenetics, part of Exact Sciences)		
Standard Genome Sequencing	Genomic Unity Whole Genome Analysis - Proband - 0212U* (Variantyx Inc.)	0212U*, 0213U*, 0265U*, 81425, 81426, F70-F79, F80-F89, Q00.0-Q99.9, R56.9, R62.0, R62.50, R62.51, G40.909	26, 28, 30, 32, 33, 36, 37, 38
	Genomic Unity® Whole Genome Analysis - Comparator - 0213U (Variantyx Inc.)		
	GenomeSeqDx (GeneDx)		
	TruGenome Trio (Illumina, Inc)		
	Whole Genome Sequencing (PerkinElmer Genomics)		
	MNGenome (MNG Laboratories)		
	Praxis Whole Genome Sequencing - 0265U* (Praxis Genomics LLC)		

Rapid Genome Sequencing	Rapid Whole Genome Sequencing - 0094U (Rady Children's Institute for Genomic Medicine)	0094U, 0425U*, 0426U*, 81425, 81426, F70-F79, F80-F89, Q00.0-Q99.9, R56.9, R62.0, R62.50, R62.51, G40.909	27, 28, 31, 33, 36
	Rapid Whole Genome Sequencing, Comparator Genome - 0425U* (Rady Children's Institute for Genomic Medicine)		
	Ultra-Rapid Whole Genome Sequencing - 0426U* (Rady Children's Institute for Genomic Medicine)		
	STAT Whole Genome Sequencing (PerkinElmer Genomics)		
	MNGenome STAT (Labcorp/MNG Laboratories)		
Mitochondrial Genome Sequencing, Deletion/Duplication, and/or Nuclear Gene Panel	Mito Genome Sequencing & Deletion Testing (GeneDx)	81460, 81465*, 81440*, 0417U*, E88.40, E88.41, E88.42, E88.49, G31.82, H49.811- H49.819	44, 45
	Mitochondrial Full Genome Analysis, Next-Generation Sequencing (NGS), Varies (Mayo Clinic Laboratories)		
	Nuclear Mitochondrial Gene Panel, Next-Generation Sequencing, Varies (Mayo Clinic Laboratories)		
	MitoXpanded Panel (GeneDx)		

	Genomic Unity Comprehensive Mitochondrial Disorders Analysis - 0417U* (Variantyx)		
Connective Tissue and Vascular Multisystem Conditions			
Comprehensive Connective Tissue Disorders Multigene Panel	Heritable Disorders of Connective Tissue Panel (GeneDx)	81410*, 81411*, I71.00-I71.9, M35.7, Q79.60, Q79.61, Q79.63, Q79.69, Q12.1, Q87.4, Q87.5	40, 41, 42, 43
	Invitae Connective Tissue Disorders Panel (Invitae)		
FBN1 Sequencing and/or Deletion/Duplication Analysis	FBN1 Full Gene Sequencing and Deletion/Duplication (Invitae	81408*, 81479, I71.00-I71.9, Q12.1, Q87.40-Q87.43	42
	Marfan Syndrome via FBN1 Gene (PreventionGenetics, part of Exact Sciences)		
Loeys-Dietz Syndrome Multigene Panel	Loeys-Dietz Syndrome Panel (PreventionGenetics, part of Exact Sciences)	81405*, 81408*, 81479, I71.00-I71.9	46
	Loeys-Dietz Syndrome Panel (Invitae)		
Classic Ehlers-Danlos Syndrome (cEDS) Multigene Panel	Ehlers Danlos Panel (GeneDx)	81408*, 81479, M35.7, Q79.61, Q79.63, Q79.69	39, 40
	Ehlers-Danlos syndrome, classic type NGS panel (CTGT)		
COL3A1 Sequencing and/or Deletion/Duplication Analysis	COL3A1 Full Gene Sequencing and Deletion/Duplication (Invitae)	81479, Q79.63	39
Other Covered Connective Tissue	See list below	81400*, 81401*, 81402*, 81403*, 81404*, 81405*,	17, 18, 19

Disorders		81406*, 81407*, 81408*	
Congenital Anomaly and Developmental Multisystem Conditions			
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	4, 5, 6, 24
	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*, 0156U*, F70-80, F84, F81, F82, F88, F89, H93.52	8, 21
	Autism/ID Xpanded panel (GeneDx)		
	SMASH - 0156U* (Marvel Genomics)		
SNRPN/UBE3A Methylation Analysis, 15q11-q13 FISH Analysis, Chromosome 15 Uniparental Disomy	Angelman Syndrome/Prader-Willi Syndrome Methylation Analysis (GeneDx)	81331*, 88271, 88273*, 81402*, R47, Q93.51, Q93.5	9, 16
	FISH, Prader-Willi/Angelman Syndrome (Quest Diagnostics)		

Analysis, and Imprinting Center Defect Analysis	Chromosome 15 UPD Analysis (Greenwood Genetic Center)		
	Imprinting Center (IC) Deletion Analysis for Angelman Syndrome (Univ of Chicago Genetic Services Laboratories)		
	Imprinting Center (IC) Deletion Analysis for Prader-Willi Syndrome (Univ of Chicago Genetic Services Laboratories)		
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*, 81402*, 81479, C22.2, C64, I42.9, P08, R16.0- R16.2, R62.52, Q35, Q38.2, Q63, Q79.2, Q87.3	10, 11
	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)		
	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)		
	CDKN1C Full Gene Sequencing and Deletion/Duplication (Invitae)		
CHD7 Sequencing and/or Deletion/Duplication Analysis	CHARGE and Kallman Syndromes via the CHD7 Gene (PreventionGenetics, part of Exact Sciences)	81407*, 81479, Q89.8	12
Noonan Spectrum Disorders/RASopathies Multigene Panel	RASopathies and Noonan Spectrum Disorders Panel (Invitae)	81442*, F82, R62.52, Q24, Q87.19, R62.0, R62.50, R62.59, Q53, Q67.6, Q67.7, L81.4, L81.3	15, 25
	Noonan and Comprehensive RASopathies Panel (GeneDx)		
Diagnostic *FMR1* Repeat and	Fragile X Syndrome, Diagnostic (Labcorp)	81243*, 81244*, F84.0, Q99.2, F79, E28.3, G11.2,	7, 13, 14

Methylation Analysis	XSense, Fragile X with Reflex (Quest Diagnostics)	G25.2	
	Fragile X Syndrome via the FMR1 CGG Repeat Expansion (PreventionGenetics, part of Exact Sciences)		
Overgrowth and Benign Tumor Multisystem Conditions			
PIK3CA Sequencing Analysis	PIK3CA Single Gene (Sequencing & Deletion/Duplication) (Fulgent Genetics)	81479	20
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	22, 23
NF1 Sequencing and/or Deletion/Duplication Analysis	NF1 Sequencing & Del/Dup (GeneDx)	81408*, L81.3, R62.5, Q85.0, Z82.79, Z84	1, 3
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	2
Other Covered Multisystem Inherited Disorders			
Other Covered Multisystem Inherited Disorders	See list below	81400*, 81401*, 81402*, 81403*, 81404*, 81405*, 81406*, 81407*, 81408*	17, 18, 19

Please see the Concert Platform for ~~a comprehensive list of~~additional registered tests.

~~Criteria Sections~~	~~Example Tests; Labs~~	~~Common CPT Codes~~	~~Common ICD Codes~~	~~R~~
~~**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,~~
	~~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~~
	~~Autism/ID Xpanded panel (GeneDx)~~			
	~~SMASH (Marvel Genomics)~~	~~0156U*~~		
~~**Angelman/Prader-Willi Syndrome**~~				
~~*SNRPN/UBE3A* Methylation Analysis, 15q11-q13 FISH~~	~~Angelman Syndrome/Prader-Willi Syndrome Methylation Analysis (GeneDx)~~	~~81331*~~	~~R47, Q93.51, Q93.5~~	~~11~~
	~~FISH, Prader-Willi/Angelman Syndrome (Quest Diagnostics)~~	~~88271, 88273*~~		

~~Criteria Sections~~	~~Example Tests; Labs~~	~~Common CPT Codes~~	~~Common ICD Codes~~	~~R~~
~~Analysis, Chromosome 15 Uniparental Disomy analysis, and Imprinting Center Defect Analysis~~	~~Chromosome 15 UPD Analysis (Greenwood Genetic Center)~~	~~81402*~~		
	~~Imprinting Center (IC) Deletion Analysis for Angelman Syndrome (Univ of Chicago Genetic Services Laboratories)~~	~~81331*~~		
	~~Imprinting Center (IC) Deletion Analysis for Prader-Willi Syndrome (Univ of Chicago Genetic Services Laboratories)~~			
~~**Beckwith-Wiedemann/Russell-Silver Syndrome**~~				
~~*H19* and *KCNQ1OT1* Methylation Analysis, 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~~
	~~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)~~			

~~Criteria Sections~~	~~Example Tests; Labs~~	~~Common CPT Codes~~	~~Common ICD Codes~~	~~R~~
	~~Chromosome 7 UPD Analysis (Greenwood Genetics Center – Molecular Diagnostic Laboratory)~~	~~81402*~~		
	~~CDKN1C Full Gene Sequencing and Deletion/Duplication (Invitae)~~	~~81479~~		
~~**Cystic Fibrosis**~~				
~~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,~~
	~~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,~~	~~15~~
	~~Fanconi Anemia Panel~~			

~~Criteria Sections~~	~~Example Tests; Labs~~	~~Common CPT Codes~~	~~Common ICD Codes~~	~~R~~
	~~(PreventionGenetics, part of Exact Sciences)~~		~~D61.89, D61.9, L81.3, L81.4 Q02, R62.52~~	
~~**Fragile X Syndrome**~~				
~~Diagnostic *FMR1* Repeat and Methylation Analysis~~	~~Fragile X Syndrome, Diagnostic (Labcorp)~~ ~~XSense, Fragile X with Reflex (Quest Diagnostics)~~ ~~Fragile X Syndrome via the FMR1 CGG Repeat Expansion (PreventionGenetics, part of Exact Sciences)~~	~~81243*, 81244*~~	~~F84.0, Q99.2, F79, E28.3, G11.2, G25.2~~	~~9,~~
~~**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~~
~~**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,~~
~~**NF2-Related Schwannomatosis (previously known as Neurofibromatosis 2)**~~				
~~*NF2* Sequencing and/or Deletion/Duplication~~	~~Neurofibromatosis Type 2 via the NF2 Gene (PreventionGenetics, part of Exact Sciences)~~	~~81405*, 81406*~~	~~L81.3, R62.5, Q85.0, Z82.79~~	~~4~~

~~Criteria Sections~~	~~Example Tests; Labs~~	~~Common CPT Codes~~	~~Common ICD Codes~~	~~R~~
~~Analysis~~			~~, Z84~~	
~~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~~
***~~PIK3CA~~* ~~Related Segmental Overgrowth and Related Syndromes~~**				
~~*PIK3CA* Sequencing Analysis~~	~~PIK3CA Single Gene (Sequencing & Deletion/Duplication) (Fulgent Genetics)~~	~~81479~~		~~26~~
~~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~~
~~Other Covered Multisystem Inherited Disorders~~				
~~Other Covered~~	~~See below~~	~~81400*~~		~~22~~

~~Criteria Sections~~	~~Example Tests; Labs~~	~~Common CPT Codes~~	~~Common ICD Codes~~	~~R~~
~~Multisystem Inherited Disorders~~		~~81408*~~		

~~OTHER~~

RELATED POLICIES

This policy document provides coverage criteria for ~~Multisystem Inherited Disorders, Intellectual Disability,~~multisystem inherited disorders, including intellectual disability and ~~Developmental Delay~~developmental delay. For organ system specific genetic disorders, please refer to:

- ~~*Genetic Testing: Epilepsy, Neurodegenerative, and Neuromuscular Disorders*~~
- *Concert Genetic Testing: ~~Hematologic Conditions (non-cancerous)~~Cardiovascular*
- *Concert Genetic Testing: ~~Gastroenterologic Conditions (non-cancerous)~~ Dermatology*
- *Concert Genetic Testing: ~~Cardiac Disorders~~ Endocrinology*
- *Concert Genetic Testing: ~~Aortopathies and Connective Tissue Disorders~~Gastroenterology*
- *Concert Genetic Testing: ~~Hearing Loss~~ Hematology*
- *Concert Genetic Testing: ~~Eye Disorders~~ Immunology & Rheumatology*
- *Concert Genetic Testing: ~~Immune, Autoimmune, and Rheumatoid Disorders~~ Nephrology*
- *Concert Genetic Testing: ~~Kidney Disorders~~ Neurology*
- *Concert Genetic Testing: ~~Lung Disorders~~ Nutrition and Metabolism*
- *Concert Genetic Testing: ~~Metabolic, Endocrine, and Mitochondrial Disorders~~ Ophthalmology*
- *Concert Genetic Testing: ~~Skeletal Dysplasia and Rare Bone Disorders~~Orthopedics*
- *Concert Genetic Testing: ~~Dermatologic Conditions~~Otolaryngology*
- *Concert Genetic Testing: Respiratory*

For other related testing, please refer to:

- ~~***Concert*** ***Genetic Testing: Prenatal Cell-free DNA***~~***General Approach to Genetic and Molecular 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 related to prenatal and pregnancy loss diagnostic genetic testing for tests intended to diagnose~~multisystem genetic conditions following amniocentesis, chorionic villus sampling or pregnancy loss.~~, including known familial variant testing, that is not specifically discussed in this or another non-general policy.

- ***Concert Genetic Testing: Prenatal and Preconception Carrier Screening*** for coverage criteria related to ~~prenatal~~parental carrier screening~~, preimplantation testing of embryos,~~ for genetic disorders before or ~~preconception carrier screening~~during pregnancy.

- ***Concert Genetic Testing: ~~Whole Exome and Whole Genome Sequencing for the Diagnosis of~~Preimplantation Genetic ~~Disorders~~Testing*** for coverage criteria related to ~~exome and genome sequencing~~ preimplantation diagnosis and fetal diagnostic testing for genetic disorders during pregnancy.

- ***Concert Genetic Testing: ~~General Approach to~~Prenatal Diagnosis*** for coverage criteria related to fetal diagnostic testing for genetic disorders during pregnancy.

- ***Concert Genetic ~~and Molecular~~ Testing: Prenatal Screening*** for coverage criteria related to ~~genetic testing that is not specifically discussed in this or another non-general policy, including known familial variant testing.~~fetal screening for genetic disorders during pregnancy.

CRITERIA

It is the policy of Louisiana Healthcare Connections that the specific genetic testing noted below is medically ~~necessary when meeting the related criteria:~~necessaryBROAD TESTS FOR SUSPECTED MULTISYSTEM GENETIC CONDITIONS

~~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:~~

Standard Exome Sequencing

I. Standard exome sequencing, with trio testing when possible, is considered **medically necessary** when:

A. The member/enrollee has not previously had genome sequencing, **AND**

B. Alternate etiologies have been considered and ruled out when possible (e.g., environmental exposure, injury, infection, isolated prematurity), **AND**

C. Clinical presentation does not fit a well-described syndrome for which single-gene or targeted multi-gene panel testing is available, **AND**

D. The member/enrollee's personal and family histories have been evaluated by a Medical Geneticist, Genetic Counselor or an Advanced Practice Nurse in Genetics (APGN), **AND**

E. The member/enrollee meets at least one of the following clinical findings:

1. The member/enrollee has unexplained epilepsy diagnosed at any age, **OR**

2. The member/enrollee has global developmental delay or intellectual disability with onset prior to age 18 years, **OR**

3. The member/enrollee was diagnosed with at least one congenital anomaly (functional and/or structural), **OR**

4. The member/enrollee has at least **TWO** of the following:

a) Bilateral sensorineural hearing loss of unknown etiology, **OR**

b) Symptoms of a complex neurological disorder (e.g., dystonia, hemiplegia, spasticity, epilepsy, myopathy, muscular dystrophy), **OR**

c) Family history suggestive of a genetic etiology, including consanguinity, **OR**

d) Clinical or laboratory findings suggestive of an inborn error of metabolism, **OR**

e) Autism, **OR**

f) Severe neuropsychiatric condition (e.g., schizophrenia, bipolar disorder, Tourette syndrome, self-injurious behavior, reverse sleep-wake cycles), **OR**

g) Period of unexplained developmental regression (unrelated to epilepsy or autism).

II. Current evidence does not support repeat standard exome sequencing.

III. Current evidence does not support standard exome for all other indications, including screening asymptomatic/healthy individuals for genetic disorders.

view rationale

back to top

Reanalysis of Exome or Genome Sequencing Data

I. Reanalysis of exome or genome sequencing data is considered **medically necessary** when[1]:

A. The member/enrollee had exome or genome sequencing at least 18 months ago, **OR**

B. The member/enrollee's phenotype has expanded to include clinical findings[2] that were not present at the time of the initial exome or genome sequencing analysis, **AND**

1. Results of prior exome or genome sequencing do not explain these new clinical findings.

II. Current evidence does not support reanalysis of exome or genome sequencing data for all other indications.

[1]If reanalysis of exome data is not possible, see the genome sequencing criteria for additional coverage information.

[2]See Standard Exome Sequencing or Standard Genome Sequencing criteria for qualifying clinical findings.

view rationale

back to top

Rapid Exome Sequencing

I. Rapid exome sequencing (rES), with trio testing when possible, is considered **medically necessary** when:

A. The member/enrollee is an acutely-ill infant (12 months of age or younger), **AND**

B. The member/enrollee has not previously had genome sequencing, **AND**

C. Alternate etiologies have been considered and ruled out when possible (e.g., environmental exposure, injury, infection, isolated prematurity), **AND**

D. Clinical presentation does not fit a well-described syndrome for which rapid single-gene or targeted multi-gene panel testing is available, **AND**

E. The member/enrollee's personal and family histories have been evaluated by a Medical Geneticist, Genetic Counselor or an Advanced Practice Nurse in Genetics (APGN), **AND**

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

1. The member/enrollee has unexplained epilepsy, **OR**

2. The member/enrollee has global developmental delay, **OR**

3. The member/enrollee was diagnosed with at least one congenital anomaly (functional and/or structural), **OR**

4. The member/enrollee has at least **TWO** of the following:

a) Bilateral sensorineural hearing loss of unknown etiology, **OR**

b) Symptoms of a complex neurological disorder (e.g., dystonia, hemiplegia, spasticity, myopathy, muscular dystrophy), **OR**

c) Family history suggestive of a genetic etiology, including consanguinity, **OR**

d) Clinical or laboratory findings suggestive of an inborn error of metabolism, **OR**

e) Severe neuropsychiatric condition (e.g., schizophrenia, bipolar disorder, Tourette syndrome, self-injurious behavior, reverse sleep-wake cycles), **OR**

f) Period of unexplained developmental regression (unrelated to epilepsy or autism).

II. Current evidence does not support rapid exome sequencing (rES) for all other indications, including screening asymptomatic/healthy individuals for genetic disorders.

view rationale

back to top

Standard Genome Sequencing

I. Standard genome sequencing, with trio testing when possible, is considered **medically necessary** when:

A. Alternate etiologies have been considered and ruled out when possible (e.g., environmental exposure, injury, infection, isolated prematurity), **AND**

B. Clinical presentation does not fit a well-described syndrome for which single-gene or targeted multi-gene panel testing is available, **AND**

C. The member/enrollee's personal and family histories have been evaluated by a Medical Geneticist, Genetic Counselor or an Advanced Practice Nurse in Genetics (APGN), **AND**

D. The member/enrollee meets at least one of the following clinical findings:

1. The member/enrollee previously had uninformative exome sequencing (ES), **AND**

a) Exome sequencing reanalysis is not possible, **OR**

2. The member/enrollee has unexplained epilepsy diagnosed at any age, **OR**

3. The member/enrollee has global developmental delay or intellectual disability with onset prior to age 18 years, **OR**

4. The member/enrollee was diagnosed with at least one congenital anomaly (functional and/or structural), **OR**

5. The member/enrollee has at least **TWO** of the following:

   a) Bilateral sensorineural hearing loss of unknown etiology, **OR**

   b) Symptoms of a complex neurological disorder (e.g., dystonia, hemiplegia, spasticity, epilepsy, myopathy, muscular dystrophy), **OR**

   c) Family history suggestive of a genetic etiology, including consanguinity, **OR**

   d) Clinical or laboratory findings suggestive of an inborn error of metabolism, **OR**

   e) Autism, **OR**

   f) Severe neuropsychiatric condition (e.g., schizophrenia, bipolar disorder, Tourette syndrome, self-injurious behavior, reverse sleep-wake cycles), **OR**

   g) Period of unexplained developmental regression (unrelated to epilepsy or autism).

II. Current evidence does not support repeat standard genome sequencing.

III. Current evidence does not support standard genome sequencing for all other indications, including screening asymptomatic/healthy individuals for genetic disorders.

NOTE: When genome sequencing is performed, the mitochondrial genome is assumed to be included as a part of the analysis**.**

view rationale

back to top

Rapid Genome Sequencing

I. Rapid genome sequencing (rGS), with trio testing when possible, is considered **medically necessary** when:

   A. The member/enrollee is an acutely-ill infant (12 months of age or younger), **AND**

B. Alternate etiologies have been considered and ruled out when possible (e.g., environmental exposure, injury, infection, isolated prematurity), **AND**

C. Clinical presentation does not fit a well-described syndrome for which rapid single-gene or targeted multi-gene panel testing is available, **AND**

D. The member/enrollee's personal and family histories have been evaluated by a Medical Geneticist, Genetic Counselor or an Advanced Practice Nurse in Genetics (APGN), **AND**

E. The member/enrollee meets at least one of the following clinical findings:

1. The member/enrollee has unexplained epilepsy, **OR**
2. The member/enrollee has multiple congenital abnormalities (functional and/or structural) affecting unrelated organ systems, **OR**
3. The member/enrollee has epileptic encephalopathy, **OR**
4. The member/enrollee has at least **TWO** of the following:
   a) Abnormality affecting at least one organ system, **OR**
   b) Symptoms of a complex neurological condition (e.g., dystonia, hemiplegia, spasticity, epilepsy, hypotonia, myopathy, muscular dystrophy, global developmental delay, intellectual disability), **OR**
   c) Family history suggestive of a genetic etiology, including consanguinity, **OR**
   d) Laboratory findings suggestive of an inborn error of metabolism, **OR**
   e) Abnormal response to standard therapy.

II. Current evidence does not support rapid genome sequencing (rGS) for all other indications, including screening asymptomatic/healthy individuals for genetic disorders.

NOTE: When genome sequencing is performed, the mitochondrial genome is assumed to be included as a part of the analysis.

view rationale

back to top

Mitochondrial Genome Sequencing, Deletion/Duplication, and/or Nuclear Gene Panel

I. Mitochondrial genome sequencing, deletion/duplication, and/or nuclear genes analysis to establish or confirm a diagnosis of a primary mitochondrial disorder is considered **medically necessary** when:

A. The member/enrollee has a classic phenotype of one of the maternally inherited syndromes (e.g., Leber hereditary optic neuropathy, mitochondrial encephalomyopathy with lactic acidosis and stroke-like episodes [MELAS], myoclonic epilepsy with ragged red fibers [MERRF], maternally inherited deafness and diabetes [MIDD], neuropathy, ataxia, retinitis pigmentosa [NARP], Kearns-Sayre syndrome/CPEO); or of a nuclear DNA mitochondrial disorder (e.g., mitochondrial neurogastrointestinal encephalopathy [MNGIE]); **OR**

B. The member/enrollee has non-specific clinical features suggestive of a primary mitochondrial disorder and meets **ALL** of the following:

1. Clinical findings of at least two of the following:

a) Ptosis, **OR**

b) External ophthalmoplegia, **OR**

c) Proximal myopathy, **OR**

d) Exercise intolerance, **OR**

e) Cardiomyopathy, **OR**

f) Sensorineural deafness, **OR**

g) Optic atrophy, **OR**

h) Pigmentary retinopathy, **OR**

i) Diabetes mellitus, **OR**

j) Fluctuating encephalopathy, **OR**

k) Seizures, **OR**

l) Dementia, **OR**

m) Migraine, **OR**

n) Stroke-like episodes, **OR**

o) Ataxia, **OR**

p) Spasticity, **OR**

q) Chorea, **OR**

r) Multiple late term pregnancy loss, **AND**

2. Conventional biochemical laboratory studies have been completed and are non-diagnostic, including at least: plasma or CSF lactic acid concentration, ketone bodies, plasma acylcarnitines, and urinary organic acids, **AND**

3. Additional diagnostic testing indicated by the member/enrollee's clinical presentation (e.g., fasting blood glucose, electrocardiography, neuroimaging, electromyography, echocardiography, audiology, thyroid testing, electroencephalography, exercise testing) have been completed and are non-diagnostic.

II. Current evidence does not support mitochondrial genome sequencing, deletion/duplication, and/or nuclear genes analysis to establish or confirm a diagnosis of a primary mitochondrial disorder for all other indications.

view rationale

back to top

CONNECTIVE TISSUE AND VASCULAR MULTISYSTEM CONDITIONS

Comprehensive Connective Tissue Disorders Multigene Panel

I. Comprehensive connective tissue disorders multigene panel analysis is considered **medically necessary** when:

A. The member/enrollee meets criteria for at least one of the following (see specific coverage criteria sections below):

1. Marfan Syndrome

2. Loeys-Dietz Syndrome
3. Classic Ehlers-Danlos Syndrome
4. Vascular Ehlers-Danlos Syndrome (vEDS).

II. Current evidence does not support comprehensive connective tissue disorders multigene panel analysis for all other indications, including isolated hypermobility and hypermobile Ehlers-Danlos syndrome (hEDS).

NOTE: If a panel is performed, the appropriate panel code should be used

view rationale

back to top

FBN1 Sequencing and/or Deletion/Duplication Analysis

I. *FBN1* sequencing and/or deletion/duplication analysis to confirm a diagnosis of Marfan syndrome is considered **medically necessary** when:

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

1. Aortic root enlargement (Z-score of 2 or greater) or dissection, **OR**
2. Ectopia lentis, **OR**

B. The member/enrollee has a systemic score of 7 or higher using the list of symptoms below (point values in parentheses):

1. Wrist AND thumb sign (3)
2. Wrist OR thumb sign (1)
3. Pectus carinatum deformity (2)
4. Pectus excavatum or chest asymmetry (1)
5. Hindfoot deformity (2)
6. Plain flat foot (pes planus) (1)
7. Pneumothorax (2)
8. Dural ectasia (2)

9. Protrusio acetabulae (2)
10. Reduced upper segment / lower segment AND increased arm span/height ratios (1)
11. Scoliosis or thoracolumbar kyphosis (1)
12. Reduced elbow extension (1)
13. 3 of 5 facial features (dolichocephaly, downward slanting palpebral fissures, enophthalmos, retrognathia, malar hypoplasia) (1)
14. Skin striae (1)
15. Myopia (1)
16. Mitral valve prolapse (1).

II. Current evidence does not support *FBN1* sequencing and/or deletion/duplication analysis to establish or confirm a molecular diagnosis of Marfan syndrome for all other indications.

NOTE: Full explanation of each feature and calculation can be found at https://www.marfan.org/dx/score

view rationale

back to top

Loeys-Dietz Syndrome Multigene Panel

I. Loeys-Dietz syndrome (LDS) multigene panel analysis to establish or confirm a diagnosis of Loeys-Dietz syndrome is considered **medically necessary** when:

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

1. Characteristic facial features, including widely spaced eyes and craniosynostosis, **OR**
2. Bifid uvula or cleft palate, **OR**
3. Tortuosity of the aorta and its branches, **OR**
4. Aortic dilatation and dissection, **OR**
5. Joint hypermobility, **OR**

6. The member/enrollee has a first-degree relative with a clinical diagnosis of LDS.

II. Current evidence does not support Loeys-Dietz syndrome (LDS) multigene panel analysis to establish or confirm a diagnosis of Loeys-Dietz for all other indications.

NOTE: If a panel is performed, the appropriate panel code should be used

NOTE: If the member/enrollee has both aortic root enlargement and ectopia lentis, *FBN1* should either be included in the panel or should have been previously performed and the results were negative.

view rationale

back to top

Classic Ehlers-Danlos Syndrome (cEDS) Multigene Panel

I. Classic Ehlers-Danlos syndrome multigene panel analysis to establish or confirm a diagnosis of cEDS is considered **medically necessary** when:

A. The member/enrollee has skin hyperextensibility and atrophic scarring, **AND**

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

1. Generalized joint hypermobility, **OR**

2. At least three of the following:

a) Easy bruising, **OR**

b) Soft, doughy skin, **OR**

c) Skin fragility (or traumatic splitting), **OR**

d) Molluscoid pseudotumors, **OR**

e) Subcutaneous spheroids, **OR**

f) Hernia, **OR**

g) Epicanthal folds, **OR**

h) Complications of joint hypermobility (e.g., sprains, luxation/subluxation, pain, flexible flatfoot), **OR**

i) Family history of a first-degree relative that has a clinical diagnosis of cEDS, **AND**

C. The panel includes, at a minimum, the following genes: *COL5A1* and *COL5A2*.

II. Current evidence does not support classic Ehlers-Danlos syndrome multigene panel analysis to establish or confirm a diagnosis of cEDS for all other indications, including isolated hypermobility and hypermobile Ehlers-Danlos syndrome (hEDS).

NOTE: Per GeneReviews, hypermobile Ehlers-Danlos syndrome (hEDS) is based entirely on clinical evaluation and family history and not genetic testing, as the gene(s) associated with hEDS are currently unknown. Therefore, clinical genetic testing for the sole purpose of evaluating for hEDS is investigational.

view rationale

back to top

COL3A1 Sequencing and/or Deletion/Duplication Analysis

I. *COL3A1* sequencing and/or deletion/duplication analysis to establish or confirm a diagnosis of vEDS is considered **medically necessary** when:

A. The member/enrollee meets any of the following:

1. Arterial rupture or dissection under the age of 40, **OR**
2. Spontaneous sigmoid colon perforation in the absence of known diverticular disease or other bowel pathology, **OR**
3. Uterine rupture during the third trimester in the absence of previous C-section and/or severe peripartum perineum tears, **OR**
4. Carotid-cavernous sinus fistula (CCSF) formation in the absence of trauma, **OR**
5. The member/enrollee has a close relative with a clinical diagnosis of vEDS, **OR**
6. The member/enrollee has at least two of the following minor criteria:

a) Bruising unrelated to identified trauma and/or in unusual sites such as cheeks and back, **OR**

b) Thin, translucent skin with increased venous visibility, **OR**

c) Characteristic facial appearance, **OR**

d) Spontaneous pneumothorax, **OR**

e) Acrogeria, **OR**

f) Talipes equinovarus, **OR**

g) Congenital hip dislocation, **OR**

h) Hypermobility of small joints, **OR**

i) Tendon and muscle rupture, **OR**

j) Keratoconus, **OR**

k) Gingival recession and gingival fragility, **OR**

l) Early onset varicose veins (under the age of 30 and nulliparous if female).

II. Current evidence does not support *COL3A1* sequencing and/or deletion/duplication analysis to establish or confirm a diagnosis of vEDS for all other indications, including isolated hypermobility and hypermobile Ehlers-Danlos syndrome (hEDS).

NOTE: Per GeneReviews, hypermobile Ehlers-Danlos syndrome (hEDS) is based entirely on clinical evaluation and family history, not genetic testing, as the gene(s) associated with hEDS are currently unknown. Therefore, clinical genetic testing for the sole purpose of evaluating for hEDS is investigational.

view rationale

back to top

Other Covered Connective Tissue 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 connective tissue 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. Arthrochalasia EDS (*COL1A1*, *COL1A2*)

B. Brittle cornea syndrome (*ZNF469*, *PRDM5*)

C. Cardiac-valvular EDS (*COL1A2*)

D. Classical-like EDS (*TNXB*)

E. Dermatosparaxis EDS (*ADAMTS2*)

F. Kyphoscoliotic EDS (*PLOD1*, *FKBP14*)

G. Musculocontractural EDS (*CHST14*, *DSE*)

H. Myopathic EDS (*COL12A1*)

I. Periodontal EDS (*C1R*, *C1S*)

J. Spondylodysplastic EDS (*B4GALT7*, *B3GALT6*, *SLC39A13*).

II. Genetic testing to establish or confirm the diagnosis of all other connective tissue 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 for coverage criteria).

NOTE: 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.

back to top

CONGENITAL ANOMALY AND DEVELOPMENTAL MULTISYSTEM CONDITIONS

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

I. ~~developmental delay and/or intellectual disability,~~Chromosomal microarray analysis for developmental delay, intellectual disability, autism spectrum disorder, or congenital anomalies is considered **medically necessary** when:

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

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

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

D. The member/enrollee has short stature.

II. ~~Chromosomal~~Current evidence does not support chromosomal microarray analysis for ~~developmental delay~~developmental delay, ~~intellectual disability~~intellectual disability, ~~autism spectrum disorder~~autism spectrum disorder, or ~~congenital anomalies (81228, 81229, S3870,) is considered **investigational**~~congenital anomalies for all other conditions of delayed development, including:

A. Isolated speech/language delay~~*~~.[1]

~~*~~[1]See ~~Background and Rationale~~Rationale section for more information about this exclusion.

~~back to top~~

view rationale

back to top

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**.~~

~~back to top~~

~~ANGELMAN/PRADER-WILLI SYNDROME~~

I. Current evidence does not support the use of an autism spectrum disorder / intellectual disability panel for all indications.

view rationale

back to top

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

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

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

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

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

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

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

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

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

b) ~~Developmental delay~~Developmental delay, **OR**

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

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

b) ~~Global developmental delay, **OR**~~Global developmental delay, **OR**

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

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

   b) ~~Global developmental delay, **AND**~~Global developmental delay, **AND**

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

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

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

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

   c) At least one of the following:

      (1) Hypothalamic hypogonadism, **OR**

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

II. Current evidence does not support *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.

~~back to top~~

~~BECKWITH-WIEDEMANN/RUSSELL-SILVER SYNDROME~~

view rationale

back to top

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

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

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

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

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

5. Body asymmetry (limb length discrepancy greater than or equal to 0.5 cm, or less than or equal to 0.5 cm with at least two other asymmetric body parts), **OR**

6. Feeding difficulties or body mass index less than or equal to 2 SD at 24 months or current use of a feeding tube or cyproheptadine for appetite stimulation.

II. Current evidence does not support *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.

~~back to top~~

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

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

~~C. The member/enrollee 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.~~

~~back to top~~

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

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

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

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

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

~~back to top~~

~~CHARGE SYNDROME~~

view rationale

back to top

CHD7 Sequencing and/or Deletion/Duplication Analysis

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

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

1. Coloboma of the iris, retina, choroid, and/or disc, **OR**
2. Anophthalmos or microphthalmos, **OR**
3. Choanal atresia or stenosis **OR**
4. Cleft palate with or without cleft lip, **OR**
5. Cranial nerve dysfunction or anomaly (hyposmia or anosmia, facial palsy, sensorineural hearing loss and/or balance problems, hypoplasia or aplasia on imaging, difficulty with sucking/swallowing and aspiration, gut motility problems), **OR**

6. Ear malformations (auricular abnormalities, middle ear abnormalities/ossicular malformations, and temporal bone abnormalities), **OR**

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

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

9. Hypogonadotropic hypogonadism (micropenis or cryptorchidism, hypoplastic labia, abnormal or absent uterus, delayed or absent puberty), **OR**

~~1. Developmental delay or intellectual disability, **OR**~~
10. Developmental delay or intellectual disability, **OR**

~~10.~~11. Growth deficiency (short stature), **OR**

~~11.~~12. Characteristic physical features of the face, neck, and/or hands, **OR**

~~12.~~13. Brain MRI showing clivus hypoplasia or hypoplasia of the cerebellar vermis.

II. Current evidence does not support *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.

~~back to top~~

~~FANCONI ANEMIA~~

~~Fanconi Anemia Multigene Panel~~

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

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

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

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

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

~~back to top~~

~~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/enrollee has unexplained intellectual disability or developmental delay, **OR**~~
B. ~~The member/enrollee is male and has unexplained autism spectrum disorder, **OR**~~
C. ~~The member/enrollee is female 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.~~1. ~~Has at least one~~ close relative ~~with a neurodevelopmental disorder consistent with X-linked inheritance, premature ovarian failure, ataxia or tremor, **OR**~~

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

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

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

~~back to top~~

~~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/enrollee has any of the following clinical features of HHT:~~

~~1. Spontaneous and recurrent nosebleeds (epistaxis), **OR**~~
~~2. Mucocutaneous telangiectases at characteristic sites, including lips, oral cavity, fingers, and nose, **OR**~~
~~3. Visceral arteriovenous malformation (AVM) (either pulmonary, cerebral, spinal, gastrointestinal or pancreatic), **AND**~~

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

~~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.~~

~~back to top~~

~~NEUROFIBROMATOSIS 1~~

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

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

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

~~1. Six or more café au lait macules (greater than 5 mm in greatest diameter in prepubertal individuals and greater than 15 mm in greatest diameter in postpubertal individuals), **OR**~~

~~2.1.Two or more neurofibromas of any type or one plexiform neurofibroma, **OR**~~

~~3.1.Freckling in the axillary or inguinal regions, **OR**~~

~~4.1.Optic glioma, **OR**~~

~~5.1.Two or more Lisch nodules (iris hamartomas), **OR**~~

~~6.1.A distinctive osseous lesion such as sphenoid dysplasia or tibial pseudarthrosis, **OR**~~

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

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

~~back to top~~

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

~~NF2 Sequencing and/or Deletion/Duplication Analysis~~

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

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

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

~~1. Bilateral vestibular schwannomas, **OR**~~

~~2.~~1. ~~Unilateral vestibular schwannoma, **AND**~~

~~a) At least two of the following:~~

~~(1) Meningioma, **OR**~~

~~(2)~~(1) ~~Schwannoma, **OR**~~

~~(3)~~(1) ~~Glioma, **OR**~~

~~(4)~~(1) ~~Neurofibroma, **OR**~~

~~(5)~~(1) ~~Cataract in the form of subcapsular lenticular opacities, **OR**~~

~~(6)~~(1) ~~Cortical wedge cataract, **OR**~~

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

~~1. Unilateral vestibular schwannoma, **OR**~~

~~2.~~1. ~~At least two of the following:~~

~~a) Schwannoma, **OR**~~

~~b)~~a) ~~Ependymoma, **OR**~~

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

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

~~D.~~A. ~~The member/enrollee is a child with at least two of the following:~~

~~1. A schwannoma at any location including intradermal, **OR**~~

~~2.~~1. ~~Skin plaques present at birth or in early childhood (often plexiform schwannoma on histology), **OR**~~

~~3.~~1. ~~A meningioma, particularly non-meningothelial (non-arachnoidal) cell in origin, **OR**~~

~~4.~~1. ~~A cortical wedge cataract, **OR**~~

~~5.~~1. ~~A retinal hamartoma, **OR**~~

~~6.~~1. ~~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.~~

~~back to top~~

~~NOONAN SPECTRUM DISORDERS/RASOPATHIES~~

view rationale

back to top

Noonan Spectrum Disorders/RASopathies Multigene Panel

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

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

      1. Characteristic facies (low-set, posteriorly rotated ears with fleshy helices, vivid blue or blue-green irises, widely spaced, down slanted eyes, epicanthal folds, ptosis), **OR**

2. Short stature, **OR**
3. Congenital heart defect (most commonly pulmonary valve stenosis, atrial septal defect, and/or hypertrophic cardiomyopathy), **OR**
4. ~~Developmental delay~~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~~Current evidence does not support 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.

view rationale

back to top

Diagnostic *FMR1* Repeat and Methylation Analysis

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

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

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

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

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

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

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

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

~~back to top~~

~~**PIK3CA-Related Segmental Overgrowth and Related Syndromes**~~

II. Current evidence does not support *FMR1* repeat and methylation analysis to establish or confirm a genetic diagnosis of Fragile X syndrome or Fragile X-associated disorders for all other indications.

view rationale

back to top

OVERGROWTH AND BENIGN TUMOR MULTISYSTEM CONDITIONS

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/enrollee displays at least one of the following on brain imaging:

1. Hemimegalencephaly, **OR**

2. Focal cortical dysplasia, **OR**

3. Dysplastic megalencephaly, **OR**

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

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

II. Current evidence does not support *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.

~~back to top~~

~~TUBEROUS SCLEROSIS COMPLEX (TSC)~~

view rationale

back to top

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

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

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

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

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

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

7. Retinal achromic patch.

II. 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 ~~is considered **investigational**~~ for all other indications.

view rationale

back to top

NF1 Sequencing and/or Deletion/Duplication Analysis

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

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

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

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

II. Current evidence does not support *NF1* sequencing and/or deletion/duplication analysis for all other indications.

view rationale

back to top

NF2 Sequencing and/or Deletion/Duplication Analysis

I. *NF2* sequencing and/or deletion/duplication analysis is considered **medically necessary** when:

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

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

1. Bilateral vestibular schwannomas, **OR**

2. Unilateral vestibular schwannoma, **AND**

a) At least two of the following:

(1) Meningioma, **OR**

(2) Schwannoma, **OR**

(3) Glioma, **OR**

(4) Neurofibroma, **OR**

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

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

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

1. Unilateral vestibular schwannoma, **OR**

2. At least two of the following:

a) Schwannoma, **OR**

b) Ependymoma, **OR**

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

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

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

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

~~back to top~~

II. Current evidence does not support *NF2* sequencing and/or deletion/duplication analysis for all other indications.

view rationale

back to top

OTHER COVERED MULTISYSTEM INHERITED DISORDERS

Other Covered Multisystem Inherited Disorders

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

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

A. Alagille syndrome

B. Alport syndrome

C. Branchiootorenal spectrum disorder

D. 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~~Laboratory Testing* (see policy coverage criteria).

~~*~~**NOTE:** 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.

~~back to top~~

~~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.~~a. ~~**Second-degree relatives** are grandparents, aunts, uncles, nieces, nephews, grandchildren, and half-siblings~~

~~c.~~a. ~~**Third-degree relatives** are great-grandparents, great-aunts, great-uncles, great-grandchildren, and first-cousins~~

~~2.1.~~**~~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.~~a. ~~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.~~a. ~~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.~~

~~**Multiple**~~ back to top

RATIONALE

~~3.1.~~**~~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.~~

Standard Exome Sequencing

American College of Medical Genetics and Genomics (ACMG)

~~Developmental delay (DD)~~: ~~Slow-to-meet or not reaching milestones in~~ In 2021, ACMG (Manickam, 2021) published an evidence-based clinical practice guideline on exome and genome sequencing for pediatric patients with congenital anomalies or intellectual disability, which included the following statements:

- "We strongly recommend ES and GS as a first- or second-tier test… for patients with one or more congenital anomalies prior to one year of age, or for patients with intellectual disability/developmental delay with onset prior to 18 years of age (p. 2031)
- "Isolated autism without ID or congenital malformation is formally out of scope for this recommendation but evaluation of exome/genome studies is ongoing" (p. 2034)

In 2020, the ACMG (Malinowski, et al) released a systematic evidence-based review, demonstrating the utility of ES/GS specifically in individuals with CA/DD/ID and their blood relatives. Further, they identified a "change in clinical management for over half of the ~~areas~~patients examined as a result of ~~development (communication, motor,~~ their ES/GS results (p. 1001).

In 2022, ACMG (Li, et al) released a clinical practice resource for the clinical evaluation of hearing loss published, which states that first-line genetic testing for individuals with exam findings that suggest a syndromic hearing loss etiology may include a variety of tests, including genome sequencing, depending on clinical presentation. For individuals without physical findings that suggest a syndromic hearing loss etiology, they recommend a tiered approach, starting with comprehensive hearing loss gene panel testing unless a more specific genetic etiology is evident for which targeted testing is appropriate (p. 1400).

National Society for Genetic Counselors

The National Society for Genetic Counselors (NSGC) released a position statement (2013, updated 2020, reaffirmed 2023) stating the following in regard to secondary and incidental findings in genetic testing:

> "The National Society of Genetic Counselors strongly advises pre-test counseling that facilitates informed decision-making, elicits patient preferences regarding secondary and/or incidental findings if possible, and formulates a plan for returning such results before testing occurs"

The National Society of Genetic Counselors (NSGC) published evidence-based practice guidelines for individuals with unexplained epilepsy (Smith et al, 2022). The NSGC recommendations are as follows (p. 4):

- Individuals with unexplained epilepsy should be offered genetic testing, without limitation of age.
- Multi-gene, comprehensive testing, such as exome sequencing, genome sequencing or a multigene panel as a first-tier test is strongly recommended.

Patient-Centered Laboratory Utilization Guidance Services

PLUGS released a guideline entitled "Genomic Sequencing for Rare Disease" in July of 2023. This guideline affirmed the medical necessity of exome sequencing when "(c)linical presentation does not fit a well-described syndrome for which more targeted testing is available," the etiology remains unknown following clinical and radiological evaluation, and one of the following is true (p. 7):

- Specific features including epilepsy, bilateral sensorineural hearing loss, moderate to severe intellectual disability, global developmental delay, or multiple congenital anomalies are present OR
- A combination of personal and family history features including neuropsychiatric, metabolic, and single organ system abnormalities is present

The guideline also includes a recommendation to rule out alternate etiologies prior to testing, when possible.

Belanger, et al

A review of the evaluation of children with global developmental delay and intellectual disability by Belanger et al (2018) defines global developmental delay (GDD) as the following:

- Significant delay (at least 2 standard deviations below the mean) in at least two developmental domains (gross or fine motor, speech/language, cognition, social-~~emotional,~~/personal or activities of daily living (p. 404). This diagnosis is reserved for children under age 5.

back to top

Reanalysis of Exome or ~~adaptive skills) in the expected way for a child's age~~Genome Sequencing Data

2. ~~**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.a. ~~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.a. ~~Onset of intellectual and adaptive deficits during the developmental period.~~

Tan, et al

A study from 2020 examined data from 58 unsolved cases referred for any indication to evaluate the systematic reanalysis of singleton exome sequencing (ES). The authors performed a reanalysis at multiple timepoints following initial testing, and ultimately suggest that an interval of greater than 18 months from the original report may be optimal for reanalysis (p. 1).

Alfares, et al

This study from 2018 compared the detection rates of whole-exome sequencing (WES) and whole-genome sequencing (WGS) in a clinical setting. The study included 108 patients with negative array CGH and negative or inconclusive WES results. WGS was performed on all patients, and the results of the study showed that 30% of the positive cases identified by WGS could be identified by reanalyzing WES raw data, and WGS achieved an only 7% higher detection rate (p. 1328). The paper concluded that, although WGS is a more powerful tool than WES, in this study, "we showed that WGS has additional, but limited, clinical utility compared with reanalyzing WES data, and until the cost of WGS approximates that of WES, reanalyzing WES raw data is recommended before performing WGS" (p. 1333).

American College of Medical Genetics

A statement from ACMG (Deignan, 2019; reaffirmed in 2023 Reddi et al) included considerations for case-level exome re-analysis, which include the following:

- Significant improvements have been made to bioinformatics handling of the data (alignment/variant calling and/or the automated filtering processes)
- Updated clinical and family history information, which may result in the identification of additional variants that are associated with the indication(s) for testing (p. 1269).

Patient-Centered Laboratory Utilization Guidance Services

The PLUGS July 2023 guidelines entitled "Genomic Sequencing for Rare Disease" state the following regarding reanalysis of exome or genome sequencing data:

"Periodic reanalysis of previously obtained exome or genome sequence has the potential for additional diagnostic yield because of expanding variant databases, as well as periodic novel gene discovery and publication. A review of twenty-seven peer-reviewed articles revealed a median new diagnosis rate via reanalysis of 15% and median reanalysis timeframe of 22 months. The authors suggest that an interval of greater than 18 months from the original report may be optimal for reanalysis" (p. 3).

The guidelines also state: "Re-analysis of previously obtained exome or genome sequence has the potential for additional diagnostic yield because of expanding variant databases, as well as periodic novel gene discovery and publication. Re-analysis could be considered prior to additional genomic sequencing, particularly if there has been onset or identification of additional symptoms that broadens the clinical phenotype assessed during the original ES/GS analysis…" (p. 8).

back to top

Rapid Exome Sequencing

American College of Medical Genetics and Genomics (ACMG)

In 2021, ACMG (Manickam, et al) published an evidence-based clinical practice guideline on exome and genome sequencing for pediatric patients with congenital anomalies or intellectual disability,), which included the following:

- "We strongly recommend ES and GS as a first- or second-tier test… for patients with one or more congenital anomalies prior to one year of age, or for patients with intellectual disability/developmental delay with onset prior to 18 years of age (p. 2031).
- "Isolated autism without ID or congenital malformation is formally out of scope for this recommendation but evaluation of exome/genome studies is ongoing" (p. 2034).

In 2020, ACMG (Malinowski, et al) released a systematic evidence-based review, which "provide[d] indirect evidence of the clinical and personal utility of ES/GS for patients with CA/DD/ID and their family members, noting that a "change in clinical management" resulted in over half of the patients examined as a result of their ES/GS results (p. 1001).

In 2022, ACMG (Li, et al) released a clinical practice resource for the clinical evaluation of hearing loss, which states that first-line genetic testing for individuals with exam findings that suggest a syndromic hearing loss etiology may include a variety of tests, including genome sequencing, depending on clinical presentation. For individuals without physical findings that suggest a syndromic hearing loss etiology, they recommend a tiered approach, starting with comprehensive hearing loss gene panel testing unless a more specific genetic etiology is evident for which targeted testing is appropriate (p. 1400).

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- Individuals with unexplained epilepsy should be offered genetic testing, without limitation of age.
- Multi-gene, comprehensive testing, such as exome sequencing, genome sequencing or a multigene panel as a first-tier test is strongly recommended.

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- Specific features including epilepsy, bilateral sensorineural hearing loss, moderate to severe intellectual disability, global developmental delay, or multiple congenital anomalies are present

OR

- A combination of personal and family history features including neuropsychiatric, metabolic, and single organ system abnormalities is present.

The guideline also includes a recommendation to rule out alternate etiologies prior to testing, when possible.

Rehm et al (2023)

A 2023 paper by Rehm et al demonstrated that exome and genome sequencing had a significantly lower VUS rate (22.5%) compared to multigene panels (32.6%) (p. 5 and 6).

Kingsmore SF, Cakici JA, Clark MM et al. 2019

The NSIGHT2 study, a prospective randomized, controlled, blinded trial (RCT) in acutely ill infants, found that 24% of infants undergoing rapid exome sequencing had genetic disease. They conclude that diagnostic testing in infants with diseases of unknown etiology, rapid genomic sequencing, including rapid exome sequencing can be performed as a first tier test in infants with diseases of unknown etiology at time of admission to ICUs. In unstable infants and in those whom a genetic diagnosis was likely to impact immediate management, rapid genomic sequencing had optimal analytic and diagnostic performance by virtue of shortest time to results (p. 725).

Belanger, et al

A review of the evaluation of children with global developmental delay and intellectual disability by Belanger et al (2018) defines global developmental delay (GDD) as the following:

Significant delay (at least 2 standard deviations below the mean) in at least two developmental domains (gross or fine motor, speech/language, cognition, social/personal or activities of daily living (p. 404).

back to top

Standard Genome Sequencing

American College of Medical Genetics and Genomics (ACMG)

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- "We strongly recommend ES and GS as a first- or second-tier test… for patients with one or more congenital anomalies prior to one year of age, or for patients with intellectual disability/developmental delay with onset prior to 18 years of age." (p. 2031)
- "Isolated autism without ID or congenital malformation is formally out of scope for this recommendation but evaluation of exome/genome studies is ongoing." (p. 2034)

In 2020, the ACMG (Malinowski, et al) released a systematic evidence-based review demonstrating the utility of ES/GS specifically in individuals with CA/DD/ID and their blood relatives. Further, they identified a "change in clinical management" for over half of the patients examined as a result of their ES/GS results (p. 1001).

In 2022, ACMG (Li et al) released a clinical practice resource for the clinical evaluation of hearing loss published, which states that first-line genetic testing for individuals with exam findings that suggest a syndromic hearing loss etiology may include a variety of tests, including genome sequencing, depending on clinical presentation. For individuals without physical findings that suggest a syndromic hearing loss etiology, they recommend a tiered approach, starting with comprehensive hearing loss gene panel testing unless a more specific genetic etiology is evident for which targeted testing is appropriate (p. 1400).

National Society for Genetic Counselors

The National Society for Genetic Counselors (NSGC) released a position statement (2013, updated 2020, reaffirmed 2023) stating the following in regard to secondary and incidental findings in genetic testing:

> "The National Society of Genetic Counselors strongly advises pre-test counseling that facilitates informed decision-making, elicits patient preferences regarding secondary and/or incidental findings if possible, and formulates a plan for returning such results before testing occurs."

The National Society of Genetic Counselors (NSGC) published evidence-based practice guidelines for individuals with unexplained epilepsy (Smith et al, 2022). The NSGC recommendations are as follows (p. 4):

- Individuals with unexplained epilepsy should be offered genetic testing, without limitation of age.

- Multi-gene, comprehensive testing, such as exome sequencing, genome sequencing or a multigene panel as a first-tier test is strongly recommended.

Patient-Centered Laboratory Utilization Guidance Services

PLUGS released a guideline entitled "Genomic Sequencing for Rare Disease" in July of 2023. This guideline affirmed the medical necessity of exome sequencing when "(c)linical presentation does not fit a well-described syndrome for which more targeted testing is available," the etiology remains unknown following clinical and radiological evaluation, and one of the following is true (p. 7):

- Specific features including epilepsy, bilateral sensorineural hearing loss, moderate to severe intellectual disability, global developmental delay, or multiple congenital anomalies are present

OR

- A combination of personal and family history features including neuropsychiatric, metabolic, and single organ system abnormalities is present.

The guideline also includes a recommendation to rule out alternate etiologies prior to testing, when possible.

Rehm et al (2023)

A 2023 paper by Rehm et al demonstrated that exome and genome sequencing had a significantly lower VUS rate (22.5%) compared to multigene panels (32.6%) (p. 5 and 6).

Belanger, et al

A review of the evaluation of children with global developmental delay and intellectual disability by Belanger et al (2018) defines global developmental delay (GDD) as the following:

- Significant delay (at least 2 standard deviations below the mean) in at least two developmental domains (gross or fine motor, speech/language, cognition, social/personal or activities of daily living (p. 404). This diagnosis is reserved for children under age 5.

back to top

Rapid Genome Sequencing

Patient-Centered Laboratory Utilization Guidance Services

PLUGS released a guideline entitled "Rapid Genome Sequencing" in June of 2022 The authors specify that that rapid genome sequencing (rGS) should be used only when (it) "is more efficient and economical than the separate single-gene tests or panels that would be recommended based on the differential diagnosis..." (p. 3 and 4).

This guideline affirmed the medical necessity of exome sequencing in "acutely-ill individuals" when their phenotype has an unknown, likely genetic etiology and one of the following is true:

- The patient has multiple multisystemic congenital anomalies or epileptic encephalopathy
- A combination of personal and family history features including complex neurological conditions, single organ system or metabolic abnormalities, failure of standard treatment, or consanguinity present
- Alternate etiologies have been considered and ruled out when possible (e.g., MRI abnormalities/brain malformations, environmental exposure, injury, infection, isolated prematurity)

National Society for Genetic Counselors

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> "The National Society of Genetic Counselors strongly advises pre-test counseling that facilitates informed decision-making, elicits patient preferences regarding secondary and/or incidental findings if possible, and formulates a plan for returning such results before testing occurs."

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- Individuals with unexplained epilepsy should be offered genetic testing, without limitation of age.
- Multi-gene, comprehensive testing, such as exome sequencing, genome sequencing or a multigene panel as a first-tier test is strongly recommended.

Kingsmore SF, Cakici JA, Clark MM et al. 2019

This report is from the NSIGHT2 study, a prospective randomized, controlled, blinded trial (RCT) in acutely ill infants, primarily from the NICU, PICU, and CVICU at Rady Children's Hospital,

San Diego (RCHSD) to compare the effectiveness and outcomes between rWGS and rWES, with analysis as singleton probands and familial trios. The inclusion criteria for the 1,248 ill infants defined the maximum age at the time of admission as four months. They found that 24% of infants undergoing rapid exome sequencing had genetic disease. They conclude that diagnostic testing in infants with diseases of unknown etiology, rapid genomic sequencing, including rapid exome sequencing can be performed as a first tier test in infants with diseases of unknown etiology at time of admission to ICUs. In unstable infants and in those whom a genetic diagnosis was likely to impact immediate management, rapid genomic sequencing had optimal analytic and diagnostic performance by virtue of shortest time to results (p. 725).

Rehm et al (2023)

A 2023 paper by Rehm et al demonstrated that exome and genome sequencing had a significantly lower VUS rate (22.5%) compared to multigene panels (32.6%) (p. 5 and 6).

back to top

Mitochondrial Genome Sequencing, Deletion/Duplication, and/or Nuclear Gene Panel

Mitochondrial Medicine Society

The Mitochondrial Medicine Society (2015) published the following consensus recommendations for DNA testing for mitochondrial disorders:

1. Massively parallel sequencing/NGS of the mtDNA genome is the preferred methodology when testing mtDNA and should be performed in cases of suspected mitochondrial disease instead of testing for a limited number of pathogenic point mutations.

2. Patients with a strong likelihood of mitochondrial disease because of a mtDNA mutation and negative testing in blood, should have mtDNA assessed in another tissue to avoid the possibility of missing tissue-specific mutations or low levels of heteroplasmy in blood; tissue-based testing also helps assess the risk of other organ involvement and heterogeneity in family members and to guide genetic counseling.

3. Heteroplasmy analysis in urine can selectively be more informative and accurate than testing in blood alone, especially in cases of MELAS due to the common m. 3243A>G mutation.

4. mtDNA deletion and duplication testing should be performed in cases of suspected mitochondrial disease via NGS of the mtDNA genome, especially in all patients undergoing a diagnostic tissue biopsy.

a. If a single small deletion is identified using polymerase chain reaction–based analysis, then one should be cautious in associating these findings with a primary mitochondrial disorder.

b. When multiple mtDNA deletions are noted, sequencing of nuclear genes involved in mtDNA biosynthesis is recommended.

5. When a tissue specimen is obtained for mitochondrial studies, mtDNA content (copy number) testing via real-time quantitative polymerase chain reaction should strongly be considered for mtDNA depletion analysis because mtDNA depletion may not be detected in blood.

    a. mtDNA proliferation is a nonspecific compensatory finding that can be seen in primary mitochondrial disease, secondary mitochondrial dysfunction, myopathy, hypotonia, and as a by-product of regular, intense exercise.

6. When considering nuclear gene testing in patients with likely primary mitochondrial disease, NGS methodologies providing complete coverage of known mitochondrial disease genes is preferred. Single-gene testing should usually be avoided because mutations in different genes can produce the same phenotype. If no known mutation is identified via known NGS gene panels, then whole exome sequencing should be considered (p. 692-693).

GeneReviews: Primary Mitochondrial Disorders Overview

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.

Their recommendations are as follows:

Common clinical features of mitochondrial disorders include:

- ptosis
- external ophthalmoplegia
- proximal myopathy
- exercise intolerance
- cardiomyopathy
- sensorineural deafness
- optic atrophy
- pigmentary retinopathy
- diabetes mellitus
- fluctuating encephalopathy
- seizures

- dementia
- migraine
- stroke-like episodes
- ataxia
- spasticity
- chorea
- high incidence of mid- and late-pregnancy loss

When a patient's clinical picture is nonspecific but highly suggestive of a mitochondrial disorder, the clinician should start with measurement of plasma or CSF lactic acid concentration, ketone bodies, plasma acylcarnitines, and urinary organic acids.

Traditionally, the diagnosis of mitochondrial disorders has been based on demonstrating mitochondrial dysfunction in a relevant tissue biopsy (e.g., a skeletal muscle or liver biopsy, or skin fibroblasts), with the particular pattern of biochemical abnormality being used to direct targeted molecular genetic testing of mtDNA, specific nuclear genes, or both.

However, the more widespread availability of molecular diagnostic techniques and the advent of exome and genome sequencing has changed the diagnostic approach.

One important caveat arises from the fact that many mtDNA pathogenic variants are heteroplasmic, and the proportion of mutated mtDNA in blood may be undetectable. This can be circumvented by analyzing mtDNA from another tissue – typically skeletal muscle or urinary epithelium – in which the level of heteroplasmy tends to be higher. Some common mtDNA pathogenic variants (e.g., large-scale deletions causing CPEO) may only be detected in skeletal muscle.

In individuals with a specific clinical phenotype (e.g., MELAS, LHON, POLG-related disorders) it may be possible to reach a diagnosis with targeted analysis of specific mtDNA pathogenic variants or single-gene testing of a nuclear gene.

A mitochondrial disorders multigene panel is most likely to identify the genetic cause of the condition while limiting identification of variants of uncertain significance and pathogenic variants in genes that do not explain the underlying phenotype.

Comprehensive genomic testing does not require the clinician to determine which gene is likely involved. Such testing includes exome sequencing, genome sequencing, and mitochondrial sequencing which can simultaneously analyze nuclear DNA and mtDNA.

back to top

Comprehensive Connective Tissue Disorders Multigene Panel

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.~~back to top~~

~~BACKGROUND AND~~

GeneReviews: Classic Ehlers-Danlos Syndrome

The GeneReviews for Ehlers-Danlos Syndrome (EDS) states that "Sequence analysis of *COL5A1* and *COL5A2* (multigene targeted panels may also include *COL1A1* and other EDS-related genes…) is performed first to detect missense, nonsense, and splice site variants and small intragenic deletions/insertions…"

GeneReviews: Hypermobile Ehlers-Danlos Syndrome

Per the Hypermobile Ehlers-Danlos Syndrome (EDS) GeneReviews, there are currently no genetic etiologies that have been identified for hypermobile EDS.

GeneReviews: FBN1-Related Marfan Syndrome

Per the *FBN1*-Related Marfan Syndrome Gene Reviews, "molecular genetic testing approaches can include a combination of gene-targeted testing (single-gene testing, multigene panel) and comprehensive genomic testing (exome sequencing, genome sequencing) depending on the phenotype. A Marfan syndrome/Loeys-Dietz syndrome/familial thoracic aortic aneurysms and dissections multigene panel that includes *FBN1* and other genes of interest is most likely to identify the genetic cause of the condition while limiting identification of variants of uncertain significance and pathogenic variants in genes that do not explain the underlying phenotype."

GeneReviews: Loeys-Dietz Syndrome

Per the Loeys-Dietz Syndrome (LDS) GeneReviews, it may be appropriate to order a multigene panel for Marfan syndrome/LDS/familial thoracic aortic aneurysms and dissections for genes associated with disorders that can include aortic aneurysms and dissections.

back to top

FBN1 Sequencing and/or Deletion/Duplication~~RATIONALE~~

Analysis

GeneReviews: FBN1-Related Marfan 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.

Marfan syndrome should be suspected in individuals with the following clinical findings and family history:

- Aortic root enlargement (Z-score >2.0). Note: Aortic size must be standardized to age and body size for accurate interpretation. A Z-score >2.0 indicates a value at or above the 95th percentile, while a Z-score >3.0 indicates a value at or above the 99th percentile. References and calculators for this determination are available at the Marfan Foundation website.
- Ectopia lentis; most reliably diagnosed by slit-lamp examination after maximal pupillary dilatation
- A systemic score >7

Additionally, GeneReviews states the diagnosis of Marfan syndrome is established in a proband (by definition a person without a known family history of Marfan syndrome) who has an *FBN1* pathogenic variant known to be associated with Marfan syndrome and EITHER of the following [Loeys et al 2010]:

- Aortic root enlargement (Z-score >2.0)
- Ectopia lentis

back to top

Loeys-Dietz Syndrome Multigene Panel

American College of Medical Genetics and Genomics (ACMG)

American College of Medical Genetics and Genomics (2012) issued guidelines on the evaluation of adolescents or adults with some features of Marfan syndrome (MFS) (including Loeys-Dietz syndrome), which recommendations included the following:

Genetic testing for Loeys-Dietz Syndrome (LDS) can aid in the diagnosis of LDS in addition to physical exam, echocardiography, dilated eye exam and MRI of the head, neck, thorax, abdomen and pelvis. Features of LDS include characteristic facial features, craniosynostosis, bifid uvula or cleft palate, tortuosity of the aorta and its branches, aortic dilatation and dissection, and joint hypermobility.

Patients have had mutations in one or another of the receptors for TGFβ. In a patient found to have consistent facial features, bifid uvula, and arterial tortuosity, the diagnosis can be confirmed with molecular testing. Tortuosity can sometimes be isolated (e.g., found only in the head and neck) (p. 175).

back to top

Classic Ehlers-Danlos Syndrome (cEDS) Multigene Panel

International EDS Consortium

The 2017 International Classification of the Ehlers-Danlos Syndromes included the following clinical features for the associated conditions. More than 90% of cEDS patients harbor a heterozygous mutation in one of the genes encoding type V collagen (*COL5A1* and *COL5A2*) (p. 13). Confirmatory molecular testing is needed to reach a final diagnosis (p. 11 and 13):

Classical EDS (cEDS):

- Major criteria
  - Skin hyperextensibility and atrophic scarring
  - Generalized joint hypermobility (GJH)
- Minor criteria
  - Easy bruising
  - Soft, doughy skin
  - Skin fragility (or traumatic splitting)
  - Molluscoid pseudotumors
  - Subcutaneous spheroids
  - Hernia (or history thereof)
  - Epicanthal folds
  - Complications of joint hypermobility (e.g., sprains, luxation/subluxation, pain, flexible flatfoot)
  - Family history of a first degree relative who meets clinical criteria
- Minimal Criteria **suggestive** for cEDS:
  - Major criterion (1): skin hyperextensibility and atrophic scarring

    Plus

- Either major criterion (2): GJH
- And/or: at least three minor criteria

GeneReviews: Classic Ehlers-Danlos 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.

This review supports initial sequence analysis of *COL5A1* and *COL5A2* to detect the most common variant types.

"Sequence analysis of *COL5A1* and *COL5A2*…is performed first to detect missense, nonsense, and splice site variants and small intragenic deletions/insertions."

back to top

COL3A1 Sequencing and/or Deletion/Duplication Analysis

International EDS Consortium

The 2017 International Classification of the Ehlers-Danlos Syndromes (Malfait et al, 2017, p.16) includes a list of five major and 12 minor criteria which raise clinical suspicion of vascular Ehlers-Danlos (vEDS). The guideline recommends molecular testing when one major or any combination of minor features is present because "...the clinical diagnosis of vEDS may be difficult. Because of implications for treatment, natural history, and recurrence risk, the diagnosis of vEDS rests on the identification of a causative variant in one allele of *COL3A1*."

Rarely, vEDS may be caused by homozygous pathogenic *COL1A1* variants. The article supports additional testing including "...targeted resequencing of a gene panel that includes *COL3A1* and *COL1A1* is indicated" (p.16).

.back to top

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

~~**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~~member/enrollees with isolated speech/language delay (AAP 2014 Clinical Report, page e905), as diagnostic yield in this clinical situation is thought to be low.

back to top

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~~ p. 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.

Concert Note

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.

back to top

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*[1]

*[1] 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.

back to top

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

back to top

~~*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**~~back to top

Noonan Spectrum Disorders/RASopathies 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~~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. ~~Fanconi anemia (FA) should be suspected in individuals with the following clinical and laboratory features.~~

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.

Rauen, K.

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

~~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~~

back to top

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.

~~*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.~~

~~*Rauen, K.*~~

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

back to top

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)

back to top

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

~~back to top~~

back to top

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..

back to top

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.

back to top

DEFINITIONS

1. **Autism spectrum disorder** is defined in the DSM V as persistent deficits in social communication and social interaction across multiple contexts, as manifested by the following, currently or by history:

    a. Deficits in social-emotional reciprocity, ranging, for example, from abnormal social approach and failure of normal back-and-forth conversation; to reduced sharing of interests, emotions, or affect; to failure to initiate or respond to social interactions.

    b. Deficits in nonverbal communicative behaviors used for social interaction, ranging, for example, from poorly integrated verbal and nonverbal communication; to abnormalities in eye contact and body language or deficits in understanding and use of gestures; to a total lack of facial expressions and nonverbal communication.

c. Deficits in developing, maintaining, and understanding relationships, ranging, for example, from difficulties adjusting behavior to suit various social contexts; to difficulties in sharing imaginative play or in making friends; to absence of interest in peers.

2. **Close relatives** include first, second, and third-degree blood relatives:

   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

3. **Congenital anomalies** (according to ACMG) are multiple anomalies not specific to a well-delineated genetic syndrome. These anomalies are structural or functional abnormalities usually evident at birth, or shortly thereafter, and can be consequential to an individual's life expectancy, health status, physical or social functioning, and typically require medical intervention.

4. **Developmental delay** (DD) is defined as 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. **Dissection** refers to a tear in the inner layer of a main artery (aorta).

   a. **Type A aortic dissections** occur at the ascending part of the aorta, just as it branches off of the heart.

   b. **Type B aortic dissections** occur at the descending part of the aorta, and may extend into the abdomen.

6. **Exome Sequencing** (ES) is a genomic technique for sequencing all of the protein-coding regions of genes in the genome (also known as the exome).

7. **Exome sequencing reanalysis** or **Reanalysis of exome** may not be possible in some situations. Sequencing platforms may have changed substantially enough that the performing lab can no longer use the data from the original ES in their pipeline. Specifically, ES reanalysis may not be possible if there have been improvements in technology/chemistry (e.g., new methods for DNA capture and/or sequencing), bioinformatics advancements, or there is new information regarding the genetic etiology of

a condition that could explain the patient's clinical features and would not have been able to be detected by the previous exome sequencing.

8. **Genome Sequencing** (GS) is a genomic technique for sequencing the complete DNA sequence, which includes protein coding as well as non-coding DNA elements.

9. **Global Developmental delay** is diagnosed when a child under age 5 is slow-to-meet or not reaching milestones in the expected way for their age in at least two areas of development (communication, gross/fine motor, cognition, social-emotional, or adaptive skills).

10. **Intellectual disability** (ID) is 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.

11. **Mitochondrial disease** refers to a heterogenous group of disorders caused by dysfunctional mitochondria, the organelles responsible for oxidative phosphorylation within the cell.

12. **Trio Testing** is testing of the child and both biological/genetic parents, which increases the chances of finding a definitive diagnosis while reducing false-positive findings.

back to top

Reviews, Revisions, and Approvals	Revision Date	Approval Date	Effective Date
Converted corporate to local policy.	09/23	11/27/23	

Semi-annual review. Updated title to reflect V1.2024 version. Overview, coding, reference-table, background and references updated. Throughout policy: replaced "coverage criteria" with "criteria. For Overview: removed "hereditary" and added "establish or"; removed "rare disease…"; added "genetic disorder…". For Other Related Policies: added "organ"; added "Genetic Testing: General Approach…". For Criteria; under Chromosomal Microarray Analysis: I. added "Chromosomal microarray analysis for developmental delay…"; I.A. removed "idiopathic growth delay and"; I.C. removed "Chromosomal microarray…" and added "OR"; I.D. added "The member/enrollee has a short stature"; II. added "Chromosomal microarray analysis…"; for Autism Spectrum Disorder/Intellectual Disability Panel Analysis: under I. removed "or developmental delay multigene…" and added "panel"; for Angelman/Prader-Willi Syndrome: I.B.1. removed "birth" and added "one month" and removed "poor suck"; I.B.1.a. added "Poor appetite…"; I.B.1.b. added "Developmental delay,"; I.B.2. removed "characteristics:"; I.B.3. removed "characteristics:"; I.B.3.c. added "externally"; I.B.4. removed "characteristics"; I.B.4.b. added "and hyperphagia" and "externally"; I.B.4.c. added "and/or typical behavioral findings."; for Beckwith-Wiedemann/Russell-Silver Syndrome: removed "FISH or"; for I. removed "FISH or"; I.A. replaced "meets" with "has"; removed "6 Netchine…"; removed I.B. "The member/enrollee meets at least one or more…"; removed "CADASIL…"; for Cystic Fibrosis: under I.A. removed "(59mmol/L), OR"; removed I.B. "The member/enrollee has unexplained…"; for Charge Syndrome: under I.A.2. removed "which may be unilateral…"; added I.A.3. "Cleft palate…"; under I.B.4. removed "unilateral or bilateral"; under I.A.4. removed "the following are the most common"; for I.A.5. removed "Temporal bone abnormalities…" and added "auricular abnormalities…"; under I.A.7. removed "including"; under I.A.8. removed "with" and added "micropenis or cryptorchidism…"; removed I.A.11. "Distinctive features…"; and added "Characteristic physical features…"; under I.A.12. removed "clival hypoplasia" and added "clicus hypoplasia…"; for Fanconi Anemia: under I. removed "81216"; under I.A. replaced "has" with "had" and added "result via"; under I.B. replaced "any of the following…" with "at least one…"; under I.B.2. added "hyper-or"; under I.B.3. added "vertebral anomalies"; under I.B.6. added "(e.g., horseshoe kidney…)"; under II. removed "81216"; for Fragile X Syndrome: under I.C. removed "and has one of the following:"; under I.C.1. replaced "Phenotype, AND" with "Phenotype is"; for Hereditary Hemorrhagic Telangiectasia (HHT) Multigene Panel: under I.A.2. removed "(small blanchable red spots…)"; for Neurofibromatosis 1 NFI Sequencing and/or Deletion/Duplication Analysis: renamed from "Legius Syndrome SPRED1"; under I. replaced "SPRED1" with "NF1"; removed "81405, 81479…"; added I. "81408) is considered medically necessary when:…"; added I.A. "The member/enrollee has at least…"; added I.A.1. "Six or more…"; added I.A.2."Two or more…"; added I.A.3. "Freckling in the axillary…"; added I.A.4. "Optic glioma…"; added I.A.5. "Two or more Lisch…"; added I.A.6. "A distinctive osseous lesion…"; under II. added "NF1 sequencing…"; for	12/23	2/27/24	

NF2-Related Schwannomatosis (Previously Known as Neurofibromatosis 2)"; removed "or Multigene Panel NF1 or"; under I. removed "81408…"; under I.A. removed "has any of the following…"; and added "has an NF2 pathogenic variant…"; added I.B. "The member/enrollee is an adult…"; added I.B.1. "Bilateral vestibular…"; added I.B.2. "Unilateral vestibular…"; added I.C. "The member/enrollee is an adult with multiple meningiomas…"; under I.C.1.b. replaced "Optic glioma" with "Ependymoma"; removed I.C.3-I.C.7. and added I.C.2.c. "Cataract in the form…"; added I.C.2.d. "Cortical wedge cataract…"; added I.D. "The member/enrollee is a child…"; added I.D.1. "A schwannoma…"; added I.D.2. "Skin plaques…"; added I.C.3. "A meningioma…"; added I.C.4. "A cortical wedge cataract…"; added I.C.5. "A retinal hamartoma…"; added I.C.6. "A mononeuropathy…"; under II. removed "81408…"; for Noonan Spectrum Disorders/Rasopathies Multigene Panel: under I. added "/RASopathy"; removed "related Noonan"" and added "Noonan-like"; under I.A. replaced "any" with "at least one" and removed "clinical features…"; under I.B. added "SPRED1"; under II. added "/RASopathy"; removed "related Noonan"" and added "Noonan-like"; for PIK3CA Sequencing and/or Deletion/Duplication Analysis: under I.A. replaced "two or more" with "at least one"; removed "clinical features…"; added "on brain imaging…"; for I.B. removed "The member/enrollee displays a congenital or early childhood…"; and added "The member/enrollee displays at least one of the following…"; removed Rett Syndrome and related criteria; for Tuberous Sclerosis Complex (TSC): under I.A.10. replaced "Subependymal" with "Two or more subependymal"; under I.B.1. added "Sclerotic bone lesions, OR"; removed I.B.7. "Sclerotic bone lesions". For Notes and Definitions: removed "Idiopathic growth delay…". For Background and Rationale: replaced "inheritance patterns" with "genetic testing" throughout; for Chromosomal Microarray Analysis: removed "CMA is considered investigational…"; added "A 2021 focused revision…"; added "CMA is considered investigational…"; for Angelman/Prader-Willi Syndrome - *SNRPN/UBE3A* methylation analysis, 15q11-q13 FISH analysis, chromosome 15 uniparental disomy analysis, and imprinting center defect analysis: removed "all of"; replaced "Birth to age" with "Age one month"; added "Developmental delay"; added "and hyperphagia" and added "externally"; for Beckwith-Wiedemann/Russell-Silver Syndrome - *H19* and *KCNQ1OT1* methylation analysis, deletion/duplication analysis of 11p15, uniparental disomy analysis, *CDKN1C* sequencing and/or deletion/duplication analysis: removed "Beckwith-Wiedermann syndrome…" and added "A diagnosis of BWS…"; removed "or a heterozygous…"; removed "GeneReviews…"; removed "Silver-Russell syndrome…"; removed CADASIL-NOTCH3 Sequencing and/or Deletion/Duplication Analysis and related content; for Cystic Fibrosis-CFTR Sequencing and/or Deletion/Duplication Analysis: added "congenital absence of the vas deferens, or"; for CHARGE Syndrome - CHD7 Sequencing and/or Deletion/Duplication Analysis: removed "which may be unilateral…"; removed "Cranial nerve…"; added "unilateral or…"; added "Cleft palate…"; removed "the following…"; added "most characteristic…"; for Hereditary Hemorrhagic Telangiectasia			

Multigene Panel: removed “It is recommended…”; added “Diagnostic”; removed “be performed”; added “is recommended”; removed Legius Syndrome- SPRED1 Sequencing and/or Deletion/Duplication Analysis and related content; for NF1 Sequencing and/or Deletion/Duplication Analysis**:** removed “GeneReviews…”; added “Note: If the phenotypic…”; for NF2 Sequencing and/or Deletion/Duplication Analysis: added “GeneReviews…”; removed Rett-Syndrome- MECP2 Sequencing and/or Deletion/Duplication Analysis and related content.			
Semi-annual review. In Known Familial Variant Analysis for the Multisystem Inherited Disorders, moved criteria to policy “Genetic Testing: General Approach to Genetic and Molecular Testing” to consolidate criteria for known familial variant tests. In *NF1* Sequencing and/or Deletion/Duplication, additional criterion added to be consistent with guidelines. In Noonan Spectrum Disorders/RASopathies Multigene Panel, removed minimum gene list; at present there is limited rationale for inclusion. In Fanconi Anemia Multigene Panel, Removed minimum gene list; at present there is limited rationale for inclusion. minor rewording for clarity throughout. Coding, reference-table, background and references updated.	06/24	9/4/24	10/4/24
Semi-annual review. Updated title to reflect V1.2025. Autism Spectrum Disorder / Intellectual Disability Panel Analysis: Removed "HHT" abbreviation from title for clarity; Updated tests in Policy Reference Table; Streamlined portions of Background and Rationale section for brevity; Removed outdated references. Noonan Spectrum Disorders/RASopathies Multigene Panel: Updated GeneReviews copyright dates in Reference list. Hereditary Hemorrhagic Telangiectasia (HHT) Multigene Panel: Removed SMAD4 from minimum gene list to align with tests on the market; Updated GeneReviews copyright dates in Reference list. SNRPN/UBE3A methylation analysis, 15q11-q13 FISH Analysis, Chromosome 15 Uniparental Disomy Analysis, and Imprinting Center Defect Analysis: Criteria headers reworded to clarify Angelman/Prader-Willi; Added criteria for <1 month in the Prader-Willi section (B1); Updated GeneReviews copyright dates in Reference list. TSC1 and TSC2 Sequencing and/or Deletion/Duplication Analysis: Updated tests in Policy Reference Table. Other Covered Multisystem Inherited Disorders: Removed two conditions from the list as they are better addressed in a different policy (Cerebral cavernous malformations, SHOX deficiency disorders); Updated GeneReviews copyright dates in Reference list. CHARGE Syndrome - CHD7 Sequencing and/or Deletion/Duplication Analysis: Updated GeneReviews copyright dates in Reference list. Diagnostic CFTR Sequencing and/or Deletion/Duplication Analysis: Added criteria to allow coverage that is not related to sweat testing based on a Cystic Fibrosis consensus statement; Name change to differentiate from carrier screening (former criteria name: "CFTR Sequencing and/or Deletion/Duplication Analysis"); Added additional supporting information to Background and	1/25	3/31/25	5/1/25

Rationale; Added new reference. H19 and KCNQ1OT1 methylation analysis, deletion/duplication analysis of 11p15, Chromosome 7 uniparental disomy analysis, CDKN1C sequencing and/or deletion/duplication analysis: Reformatted criteria for ease of use; Updated dates in references. NF2 Sequencing and/or Deletion/Duplication Analysis: Added "pathogenic variant" to tumor testing criteria (A); Updated GeneReviews copyright dates in Reference list. NF1 Sequencing and/or Deletion/Duplication Analysis: Updated GeneReviews copyright dates in Reference list. Chromosomal Microarray Analysis for Developmental Delay/Intellectual Disability, Autism Spectrum Disorder, or Congenital Anomalies: Removed two tests from PRT: Genomic Unity Exome Plus Analysis - Proband (Variantyx) (0214U) and Genomic Unity Exome Plus Analysis - Comparator (Duo or Trio) (Variantyx Inc.) (0215U) as they were included in error as example tests, and replaced them with Genomic Unity Exome Analysis - Proband (Variantyx) (81415) and Genomic Unity Exome Analysis - Comparator (Duo or Trio) (Variantyx Inc.) (81416); Updated date in American Academy of Pediatrics reference. Fanconi Anemia Multigene Panel: Updated GeneReviews copyright dates in Reference list. Diagnostic FMR1 Repeat and Methylation Analysis: Changed name of criteria to differentiate from carrier screening; Updated dates in references. PIK3CA Sequencing: Removed deletion/duplication testing from criteria as that type of mutation is uncommon in this disorder; Reworded section heading for accuracy; Updated GeneReviews copyright dates in Reference list.			
Annual review. Policy name changed from “Concert Genetic Testing: Multisystem Inherited Disorders, Intellectual Disability, and Developmental Delay” to “Concert Genetic Testing: Multisystem Genetic Conditions.” Criteria added for Mitochondrial Genome Sequencing, Deletion/Duplication, and/or Nuclear Gene Panels from the previously named “Concert Genetic Testing: Metabolic, Endocrine, and Mitochondrial Disorders.” The following criteria were added to this policy from the policy previously named “Concert Genetic Testing: Aortopathies and Connective Tissue Disorders”: Classic Ehlers-Danlos Syndrome (cEDS) Multigene Panel; COL3A1 Sequencing and/or Deletion/Duplication Analysis; Comprehensive Connective Tissue Disorders Multigene Panel; Loeys-Dietz Syndrome Multigene Panel; FBN1 Sequencing and/or Deletion/Duplication Analysis; Other Covered Connective Tissue Disorders. The following criteria were added to this policy from the policy previously named “Concert Genetic Testing: Exome and Genome Sequencing for the Diagnosis of Genetic Disorders”: Rapid Exome Sequencing; Rapid Genome Sequencing; Reanalysis of Exome or Genome Sequencing Data Standard Exome Sequencing; Standard Genome Sequencing.” Minor rewording without clinical significance throughout. Changed all “investigational” policy statements to note that “current evidence does not support…” Definitions for Type A and B aortic dissections were moved under a shared definition. Changed the definition of global developmental delay to specify that individuals meeting this criteria must be under age 5, applicable to	03/26		

the following criteria sections: Rapid Exome Sequencing; Rapid Genome Sequencing; Reanalysis of Exome or Genome Sequencing Data Standard Exome Sequencing; Standard Genome Sequencing. Policy reference table, related policy list, rationale section and references updated.			

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back to top

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. LHCC 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.

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 LHCC administrative policies and procedures.

This clinical policy is effective as of the date determined by LHCC. 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. LHCC retains the right to change, amend or withdraw this clinical policy, and additional clinical policies may be developed and adopted as needed, at any time.

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

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

This clinical policy is the property of LHCC. Unauthorized copying, use, and distribution of this clinical policy or any information contained herein are strictly prohibited. Providers, members/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, members/enrollees and their representatives agree to be bound by such terms and conditions by providing services to members/enrollees and/or submitting claims for payment for such services.