Medica Central Coverage Policy

Policy Name:	**Genetic Testing - Specialty Testing: Multisystem Genetic Conditions**
Effective Date:	**01/01/2026**

Important Information – Please Read Before Using This Policy

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

Members may contact Medica Customer Service at the phone number listed on their member identification card to discuss their benefits more specifically. Providers with questions may call the Provider Service Center. Please use the Quick Reference Guide on the Provider Communications page for the appropriate phone number. https://mo-central.medica.com/Providers/SSM-employee-health-plan-for-IL-MO-OK-providers

Medica Central coverage policies are not medical advice. Members should consult with appropriate health care providers to obtain needed medical advice, care, and treatment.

OVERVIEW

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.

The tests, CPT codes, and ICD codes referenced in this policy are not comprehensive, and their inclusion does not represent a guarantee of coverage or non-coverage.

POLICY REFERENCE TABLE

COVERAGE CRITERIA SECTIONS	EXAMPLE TESTS (LABS)	COMMON BILLING CODES	SUPPORT
Broad Tests for Suspected Multisystem Genetic Conditions			

COVERAGE CRITERIA SECTIONS	EXAMPLE TESTS (LABS)	COMMON BILLING CODES	SUPPORT
Standard Exome Sequencing	Genomic Unity Exome Analysis - Proband (Variantyx, Inc.)	81415, 81416, F70-F79, F80.0-F89, G40.909, Q00.0-Q99.9, R56.9, R62.0, R62.50, R62.51	Rationale/ References
	Genomic Unity Exome Analysis - Comparator (Duo or Trio) (Variantyx, Inc.)		
	XomeDx - Proband (GeneDx)		
	Exome - Proband Only (Invitae Corporation)		
	XomeDx - Duo (GeneDx)		
	XomeDX - Trio (GeneDx)		
	Exome - Duo (Invitae Corporation)		
	Exome - Trio (Invitae Corporation)		
Reanalysis of Exome or Genome Sequencing Data	Exome Reanalysis (Ambry Genetics)	81417, 81427, F70-F79, F80-F89, G40.909, Q00.0-Q99.9, R56.9, R62.0, R62.50, R62.51	Rationale/ References
	Whole Genome Reanalysis (ARUP Laboratories)		
Rapid Exome Sequencing	XomeDxXpress (GeneDx)	81415, 81416, F70-F79, F80-F89, G40.909, Q00.0-Q99.9, R56.9, R62.0, R62.50, R62.51	Rationale/ References
	ExomeNext-Rapid (Ambry Genetics)		
	PGxome RAPID Exome Test (PreventionGenetics, part of Exact Sciences)		
Standard Genome Sequencing	Genomic Unity Whole Genome Analysis -	81425, 81426, 0212U, 0213U, 0265U, 0567U,	Rationale/ References

[COVERAGE CRITERIA SECTIONS](#)	EXAMPLE TESTS (LABS)	COMMON BILLING CODES	SUPPORT
	Proband - 0212U (Variantyx, Inc.)	F70-F79, F80-F89, G40.909, Q00.0-Q99.9, R56.9, R62.0, R62.50, R62.51	
	Genomic Unity Whole Genome Analysis - Comparator - 0213U (Variantyx, Inc.)		
	GenomeSeqDx (GeneDx)		
	TruGenome Trio (Illumina, Inc.)		
	Whole Genome Sequencing (Revvity)		
	MNGenome Proband Only Sequencing (MNG Laboratories)		
	Praxis Whole Genome Sequencing - 0265U (Praxis Genomics, LLC)		
	Genomic Unity 2.0 - 0567U (Variantyx, Inc.)		
Rapid Genome Sequencing	Rapid Whole Genome Sequencing - 0094U (Rady Children's Institute for Genomic Medicine)	81425, 81426, 0094U, 0425U, 0426U, 0532U, F70-F79, F80-F89, G40.909, Q00.0-Q99.9, R56.9, R62.0, R62.50, R62.51	Rationale/ References
	Rapid Whole Genome Sequencing, Comparator Genome - 0425U (Rady Children's Institute for Genomic Medicine)		
	Ultra-Rapid Whole Genome Sequencing - 0426U (Rady Children's		

COVERAGE CRITERIA SECTIONS	EXAMPLE TESTS (LABS)	COMMON BILLING CODES	SUPPORT
	Institute for Genomic Medicine)		
	Ultrarapid Genomic Testing (Revvity)		
	MNGenome STAT (MNG Laboratories)		
	Rapid Genome Sequencing Test - 0532U (University of California San Francisco Genomic Medicine Laboratory)		
Mitochondrial Genome Sequencing, Deletion/Duplication, and/or Nuclear Gene Panel	Mito Genome Sequencing & Deletion Testing (GeneDx)	81440, 81460, 81465, 0417U, E88.40, E88.41, E88.42, E88.49, G31.82, H49.811-H49.819	Rationale/ References
	Mitochondrial Full Genome Analysis, Next-Generation Sequencing (NGS), Varies (Mayo Clinic Laboratories)		
	Nuclear Mitochondrial Gene Panel, Next-Generation Sequencing, Varies (Mayo Clinic Laboratories)		
	Combined Mito Genome Plus Mito Focused Nuclear Gene Panel (GeneDx)		
	Genomic Unity Comprehensive Mitochondrial Disorders Analysis - 0417U (Variantyx, Inc)		

COVERAGE CRITERIA SECTIONS	EXAMPLE TESTS (LABS)	COMMON BILLING CODES	SUPPORT
Combined Mitochondrial DNA Analysis and Exome Sequencing	Genomic Unity Exome PLUS Analysis (0214U)-Proband (Variantyx, Inc.) Genomic Unity Exome PLUS Analysis (0215U)-Comparator (Variantyx, Inc.)	0214U, 0215U, E88.40, E88.41, E88.42, E88.49, F70-F79, F80.0-F89, G40.909, G31.82, H49.811- H49.819, Q00.0-Q99.9, R56.9, R62.0, R62.50, R62.51	Rationale/ References
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, Q12.1, Q79.60, Q79.61, Q79.63, Q79.69, Q87.4, Q87.5	Rationale/ References
	Invitae Connective Tissue Disorders Panel (Invitae Corporation)		
FBN1 Sequencing and/or Deletion/Duplication Analysis	FBN1 Full Gene Sequencing and Deletion/Duplication (Invitae Corporation)	81408, 81479, I71.00-I71.9, Q12.1, Q87.40-Q87.43	Rationale/ References
	Marfan Syndrome via the 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	Rationale/ References
	Loeys-Dietz Syndrome Panel (Invitae Corporation)		
	Ehlers Danlos Panel (GeneDx)	81408, 81479, M35.7, Q79.61, Q79.63, Q79.69	Rationale/ References

COVERAGE CRITERIA SECTIONS	EXAMPLE TESTS (LABS)	COMMON BILLING CODES	SUPPORT
Classic Ehlers-Danlos Syndrome (cEDS) Multigene Panel	Ehlers-Danlos syndrome, classic type NGS panel (HNL Genomics)		
COL3A1 Sequencing and/or Deletion/Duplication Analysis	COL3A1 Full Gene Sequencing and Deletion/Duplication (Invitae Corporation)	81479, Q79.63	Rationale/ References
Other Covered Connective Tissue Disorders	See list below	81400, 81401, 81402, 81403, 81404, 81405, 81406, 81407, 81408	Additional References
Congenital Anomaly and Developmental Multisystem Conditions			
Chromosomal Microarray Analysis for Developmental Delay/Intellectual Disability, Autism Spectrum Disorder, or Congenital Anomalies	Chromosomal Microarray (MicroarrayDx) (GeneDx) Chromosomal Microarray, Postnatal, ClariSure Oligo-SNP (Quest Diagnostics) SNP Microarray−Pediatric (Reveal) (LabCorp) Genomic Unity Constitutional Genome-Wide Copy Number Variant Analysis (Variantyx)	81228, 81229, 81349, S3870, F79, F84.0, Q89.7, R62.50	Rationale/ References
Autism Spectrum Disorder/Intellectual Disability Panel Analysis	Neurodevelopmental Disorders (NDD) Panel (Invitae Corporation) Autism/ID Xpanded panel (GeneDx) SMASH - 0156U (New York Genome Center)	81185, 81236, 81302, 81321, 81470, 81471, 81479, 0156U, F70-80, F84, F81, F82, F88, F89, H93.52	Rationale/ References

COVERAGE CRITERIA SECTIONS	EXAMPLE TESTS (LABS)	COMMON BILLING CODES	SUPPORT
SNRPN/UBE3A Methylation Analysis, 15q11-q13 FISH Analysis, Chromosome 15 Uniparental Disomy Analysis, and Imprinting Center Defect Analysis	Angelman Syndrome/Prader-Willi Syndrome Methylation Analysis (GeneDx)	81331, 81402, 88271, 88273, Q93.51, Q93.5, R47	Rationale/ References
	FISH, Prader-Willi/Angelman Syndrome (Quest Diagnostics)		
	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 - Genetics Laboratory)	81401, 81402, 81479, C22.2, C64, I42.9, P08, Q35, Q38.2, Q63, Q79.2, Q87.3, R16.0- R16.2, R62.52	Rationale/ References
	Beckwith-Wiedemann: Methylation analysis of 11p15.5 only (University of Pennsylvania School of Medicine Genetic Diagnostic Laboratory)		

COVERAGE CRITERIA SECTIONS	EXAMPLE TESTS (LABS)	COMMON BILLING CODES	SUPPORT
	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 Corporation)		
CHD7 Sequencing and/or Deletion/Duplication Analysis	CHARGE and Kallman Syndromes via the CHD7 Gene (PreventionGenetics, part of Exact Sciences)	81407, 81479, Q89.8	Rationale/ References
Noonan Spectrum Disorders/RASopathies Multigene Panel	RASopathies and Noonan Spectrum Disorders Panel (Invitae Corporation)	81442, F82, L81.3, L81.4, Q24, Q53, Q67.6,	Rationale/ References

COVERAGE CRITERIA SECTIONS	EXAMPLE TESTS (LABS)	COMMON BILLING CODES	SUPPORT
	Noonan and Comprehensive RASopathies Panel (GeneDx)	Q67.7, Q87.19, R62.0, R62.50, R62.52, R62.59	
Diagnostic *FMR1* Repeat and Methylation Analysis	Fragile X Syndrome, Diagnostic (LabCorp)	81243, 81244, E28.3, F84.0, F79, G11.2, G25.2, Q99.2	Rationale/ References
	XSense, Fragile X with Reflex (Quest Diagnostics)		
	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	Rationale/ References
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	Rationale/ References
NF1 Sequencing and/or Deletion/Duplication Analysis	NF1 Single Gene (Sequencing & Deletion/Duplication) (Fulgent Genetics)	81408, 81479, L81.3, Q85.0, R62.5, Z82.79, Z84	Rationale/ References
NF2 Sequencing and/or Deletion/Duplication Analysis	Neurofibromatosis Type 2 via the NF2 Gene (PreventionGenetics, part of Exact Sciences)	81405, 81406, L81.3, Q85.0, R62.5, Z82.79, Z84	Rationale/ References
Other Covered Multisystem Inherited Disorders			

COVERAGE CRITERIA SECTIONS	EXAMPLE TESTS (LABS)	COMMON BILLING CODES	SUPPORT
Other Covered Multisystem Inherited Disorders	See list below	81400, 81401, 81402, 81403, 81404, 81405, 81406, 81407, 81408	Additional References

RELATED POLICIES

This policy document provides coverage criteria for multisystem inherited disorders, including intellectual disability and developmental delay. For organ system specific genetic disorders, please refer to:

- *Specialty Testing: Cardiovascular*
- *Specialty Testing: Dermatology*
- *Specialty Testing: Endocrinology*
- *Specialty Testing: Gastroenterology*
- *Specialty Testing: Hematology*
- *Specialty Testing: Immunology & Rheumatology*
- *Specialty Testing: Nephrology*
- *Specialty Testing: Neurology*
- *Specialty Testing: Nutrition and Metabolism*
- *Specialty Testing: Ophthalmology*
- *Specialty Testing: Orthopedics*
- *Specialty Testing: Otolaryngology*
- *Specialty Testing: Respiratory*

For other related testing, please refer to:

- ***General Approach to Laboratory Testing*** for coverage criteria related to multisystem genetic conditions, including known familial variant testing, that is not specifically discussed in this or another non-general policy.
- ***Reproductive Testing: Carrier Screening*** for coverage criteria related to parental carrier screening for genetic disorders before or during pregnancy.
- ***Reproductive Testing: Fertility*** for coverage criteria related to preimplantation diagnosis.
- ***Reproductive Testing: Prenatal Diagnosis*** for coverage criteria related to fetal diagnostic testing for genetic disorders during pregnancy.
- ***Reproductive Testing: Prenatal Screening*** for coverage criteria related to fetal screening for genetic disorders during pregnancy.

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COVERAGE CRITERIA

BROAD TESTS FOR SUSPECTED MULTISYSTEM GENETIC CONDITIONS

Standard Exome Sequencing

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

   A. The member 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 multigene panel testing is available, **AND**

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

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

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

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

      4. The member 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. Repeat standard exome sequencing is considered **investigational**.

III. Standard exome sequencing is considered **investigational** for all other indications, including screening asymptomatic/healthy individuals for genetic disorders.

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Reanalysis of Exome or Genome Sequencing Data

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

   A. The member had exome or genome sequencing at least 1 year ago, **OR**

   B. The member'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. Reanalysis of exome or genome sequencing data is considered **investigational** 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.

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Rapid Exome Sequencing

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

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

   B. The member 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 multigene panel testing is available, **AND**

   E. The member'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 meets at least one of the following criteria:

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

2. The member has global developmental delay, **OR**
3. The member was diagnosed with at least one congenital anomaly (functional and/or structural), **OR**
4. The member 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. Rapid exome sequencing (rES) is considered **investigational** for all other indications, including screening asymptomatic/healthy individuals for genetic disorders.

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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 multigene panel testing is available, **AND**

C. The member'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 meets at least one of the following clinical findings:

1. The member previously had uninformative exome sequencing (ES), **AND**
    a) Exome sequencing reanalysis is not possible, **OR**
2. The member has unexplained epilepsy diagnosed at any age, **OR**

3. The member has global developmental delay or intellectual disability with onset prior to age 18 years, **OR**
4. The member was diagnosed with at least one congenital anomaly (functional and/or structural), **OR**
5. The member 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. Repeat standard genome sequencing is considered **investigational**.

III. Standard genome sequencing is considered **investigational** 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**.**

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Rapid Genome Sequencing

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

    A. The member 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'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 meets at least one of the following clinical findings:

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

    2. The member has multiple congenital abnormalities (functional and/or structural) affecting unrelated organ systems, **OR**

    3. The member has epileptic encephalopathy, **OR**

    4. The member 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. Rapid genome sequencing (rGS) is considered **investigational** 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.

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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 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 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'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. Mitochondrial genome sequencing, deletion/duplication, and/or nuclear genes analysis to establish or confirm a diagnosis of a primary mitochondrial disorder is considered **investigational** for all other indications.

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Combined Mitochondrial DNA Analysis and Exome Sequencing

I. Combined[1] mitochondrial DNA sequence and deletion/duplication analysis and exome sequencing is considered **medically necessary** when:

   A. The member meets clinical criteria for Mitochondrial Genome Sequencing, Deletion/Duplication, and/or Nuclear Gene Panel, **AND**

   B. The member meets clinical criteria for Standard Exome Sequencing.

II. Combined mitochondrial DNA sequence and deletion/duplication analysis and exome sequencing is considered **investigational** for all other indications.

[1] This refers to tests for which exome sequencing (ES) and mitochondrial DNA (mtDNA) sequencing cannot be performed or billed separately (specifically 0214U and 0215U). Refer to Mitochondrial Genome Sequencing, Deletion/Duplication, and/or Nuclear Gene Panel or Standard Exome Sequencing for individual criteria that is billed separately.

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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 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. Comprehensive connective tissue disorders multigene panel analysis is considered **investigational** 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

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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 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 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. *FBN1* sequencing and/or deletion/duplication analysis to establish or confirm a molecular diagnosis of Marfan syndrome is considered **investigational** for all other indications.

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

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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 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 has a first-degree relative with a clinical diagnosis of LDS.

II. Loeys-Dietz syndrome (LDS) multigene panel analysis to establish or confirm a diagnosis of Loeys-Dietz syndrome is considered **investigational** for all other indications.

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

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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 has skin hyperextensibility and atrophic scarring, **AND**

   B. The member 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. Classic Ehlers-Danlos syndrome multigene panel analysis to establish or confirm a diagnosis of cEDS is considered **investigational** 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.

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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 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 has a close relative with a clinical diagnosis of vEDS, **OR**

6. The member 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. *COL3A1* sequencing and/or deletion/duplication analysis to establish or confirm a diagnosis of vEDS is considered **investigational** 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.

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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 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.

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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 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.

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CONGENITAL ANOMALY AND DEVELOPMENTAL MULTISYSTEM CONDITIONS

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 is considered **medically necessary** when:

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

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

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

D. The member has short stature.

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

A. Isolated speech/language delay[1]

[1] See Rationale section for more information about this exclusion.

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Autism Spectrum Disorder/Intellectual Disability Panel Analysis

I. The use of an autism spectrum disorder / intellectual disability panel is considered **investigational** for all indications.

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

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

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

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

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

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

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

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

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

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

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

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

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

         b) Developmental delay, **OR**

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

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

         b) Developmental delay, **OR**

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

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

b) Developmental delay, **AND**

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

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

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

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

c) At least one of the following:

(1) Hypothalamic hypogonadism, **OR**

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

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

NOTE: The following is the recommended testing strategy:

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

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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, deletion/duplication analysis of 11p15, chromosome 7 uniparental disomy analysis, or *CDKN1C* sequencing and/or deletion/duplication analysis to confirm or establish a diagnosis of Beckwith-Wiedemann or Russell-Silver syndrome is **medically necessary** when:

A. The member has at least one of the following clinical features of Beckwith-Wiedemann syndrome (BWS):

1. Macroglossia, **OR**

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

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

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

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

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

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CHD7 Sequencing and/or Deletion/Duplication Analysis

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

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

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

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

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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) is considered **medically necessary** when:

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

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

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

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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 has unexplained intellectual disability or developmental delay, **OR**

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

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

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

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

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

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

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

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OVERGROWTH AND BENIGN TUMOR MULTISYSTEM CONDITIONS

***PIK3CA* Sequencing Analysis**

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

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

   1. Hemimegalencephaly, **OR**

   2. Focal cortical dysplasia, **OR**

   3. Dysplastic megalencephaly, **OR**

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

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

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

   3. Lymphatic malformations, **OR**

4. Cutaneous findings including epidermal nevi and hyperpigmented macules, **OR**
5. Single or multiple digital anomalies of the hands or feet (e.g., macrodactyly, syndactyly, polydactyly, sandal-toe gap), **OR**
6. Kidney malformations (e.g., pelviectasis, dilated ureters, hydronephrosis, duplicated renal arteries, renal cysts, enlarged kidneys), **OR**
7. Benign tumors, with the exceptions of Wilms tumor and nephroblastomatosis (i.e., diffuse or multifocal clusters of persistent embryonal cells).

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

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

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

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

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

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

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

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

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NF1 Sequencing and/or Deletion/Duplication Analysis

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

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

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

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

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_NF2_ Sequencing and/or Deletion/Duplication Analysis

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

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

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

    1. Bilateral vestibular schwannomas, **OR**

    2. Unilateral vestibular schwannoma, **AND**

      a) At least two of the following:

        (1) Meningioma, **OR**

        (2) Schwannoma, **OR**

        (3) Glioma, **OR**

        (4) Neurofibroma, **OR**

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

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

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

    1. Unilateral vestibular schwannoma, **OR**

    2. At least two of the following:

      a) Schwannoma, **OR**

      b) Ependymoma, **OR**

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

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

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

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

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

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

4. A cortical wedge cataract, **OR**
5. A retinal hamartoma, **OR**
6. A mononeuropathy, particularly causing a facial nerve palsy, foot or wrist drop, or third nerve palsy.

II. *NF2* sequencing and/or deletion/duplication analysis is considered **investigational** for all other indications.

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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 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 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.

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PRIOR AUTHORIZATION

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

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RATIONALE AND REFERENCES

Standard Exome Sequencing

American College of Medical Genetics and Genomics (ACMG)

In 2021, ACMG 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)

Manickam K, McClain MR, Demmer LA, et al. Exome and genome sequencing for pediatric patients with congenital anomalies or intellectual disability: an evidence-based clinical guideline of the American College of Medical Genetics and Genomics (ACMG). Genet Med. 2021;23(11):2029-2037. doi:10.1038/s41436-021-01242-6

In 2022, ACMG 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).

Li MM, Tayoun AA, DiStefano M, et al. Clinical evaluation and etiologic diagnosis of hearing loss: A clinical practice resource of the American College of Medical Genetics and Genomics (ACMG). Genet Med. 2022;24(7):1392-1406. doi:10.1016/j.gim.2022.03.018

National Society for Genetic Counselors (NSGC)

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.

Secondary and Incidental Findings in Genetic Testing. Position Statement from National Society of Genetic Counselors. https://www.nsgc.org/Policy-Research-and-Publications/Position-Statements/Position-Statements/Post/secondary-and-incidental-findings-in-genetic-testing-1. Released September 27, 2013. Updated March 23, 2020. Reaffirmed 2023.

The National Society of Genetic Counselors (NSGC) published evidence-based practice guidelines for individuals with unexplained epilepsy (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.

Smith L, Malinowski J, Ceulemans S, et al. Genetic testing and counseling for the unexplained epilepsies: An evidence-based practice guideline of the National Society of Genetic Counselors. J Genet Couns. 2023;32(2):266-280. doi:10.1002/jgc4.1646

Patient-Centered Laboratory Utilization Guidance Services (PLUGS)

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.

Genomic Sequencing for Rare Disease. Seattle Children's Hospital Patient-centered Laboratory Utilization Guidance Services. https://www.schplugs.org/wp-content/uploads/Genomic-Sequencing-in-Rare-Disease_2023_FINAL.pdf. Effective July 2023.

Belanger, et al

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American Academy of Pediatrics (AAP)

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Rodan LH, Stoler J, Chen E, Geleske T; Council on Genetics. Genetic evaluation of the child with intellectual disability or global developmental delay: clinical report. Pediatrics. 2025;156(1):e2025072219. doi:10.1542/peds.2025-072219

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Reanalysis of Exome or Genome Sequencing Data

American Academy of Pediatrics (AAP)

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Rodan LH, Stoler J, Chen E, Geleske T; Council on Genetics. Genetic evaluation of the child with intellectual disability or global developmental delay: clinical report. Pediatrics. 2025;156(1):e2025072219. doi:10.1542/peds.2025-072219

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).

Alfares A, Aloraini T, Subaie LA, et al. Whole-genome sequencing offers additional but limited clinical utility compared with reanalysis of whole-exome sequencing. *Genet Med*. 2018;20(11):1328-1333. doi:10.1038/gim.2018.41

American College of Medical Genetics (ACMG)

A statement from ACMG (2019, reaffirmed 2023) included considerations for case-level exome reanalysis, 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).

Deignan JL, Chung WK, Kearney HM, et al. Points to consider in the reevaluation and reanalysis of genomic test results: a statement of the American College of Medical Genetics and Genomics (ACMG). Genet Med. 2019;21(6):1267-1270. doi:10.1038/s41436-019-0478-1

Reddi HV, Avenarius MR, Bean LJH, et al. Addendum: Points to consider in the reevaluation and reanalysis of genomic test results: A statement of the American College of Medical Genetics and Genomics (ACMG). Genetics in Medicine. 2024;26(5):101100. doi:10.1016/j.gim.2024.101100

Patient-Centered Laboratory Utilization Guidance Services (PLUGS)

The PLUGS guidelines entitled “Genomic Sequencing for Rare Disease” (2023) 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).

Genomic Sequencing for Rare Disease. Seattle Children's Hospital Patient-centered Laboratory Utilization Guidance Services. https://www.schplugs.org/wp-content/uploads/Genomic-Sequencing-in-Rare-Disease_2023_FINAL.pdf. Effective July 2023.

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Rapid Exome Sequencing

American College of Medical Genetics and Genomics (ACMG)

In 2021, ACMG 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).

Manickam K, McClain MR, Demmer LA, et al. Exome and genome sequencing for pediatric patients with congenital anomalies or intellectual disability: an evidence-based clinical guideline of the American College of Medical Genetics and Genomics (ACMG). Genet Med. 2021;23(11):2029-2037. doi:10.1038/s41436-021-01242-6

In 2020, ACMG 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).

Malinowski J, Miller DT, Demmer L, et al. Systematic evidence-based review: outcomes from exome and genome sequencing for pediatric patients with congenital anomalies or intellectual disability. Genet Med. 2020;22(6):986-1004. doi:10.1038/s41436-020-0771-z

In 2022, ACMG 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).

Li MM, Tayoun AA, DiStefano M, et al. Clinical evaluation and etiologic diagnosis of hearing loss: A clinical practice resource of the American College of Medical Genetics and Genomics (ACMG). Genet Med. 2022;24(7):1392-1406. doi:10.1016/j.gim.2022.03.018

National Society for Genetic Counselors (NSGC)

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.

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The National Society of Genetic Counselors (NSGC) published evidence-based practice guidelines for individuals with unexplained epilepsy (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.

Smith L, Malinowski J, Ceulemans S, et al. Genetic testing and counseling for the unexplained epilepsies: An evidence-based practice guideline of the National Society of Genetic Counselors. J Genet Couns. 2023;32(2):266-280. doi:10.1002/jgc4.1646

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Rehm, et al.

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).

Rehm HL, Alaimo JT, Aradhya S, et al. The landscape of reported VUS in multi-gene panel and genomic testing: Time for a change. Genet Med. 2023 Dec;25(12):100947. Epub 2023 Jul 30. doi:10.1016/j.gim.2023.100947.

Kingsmore, et al

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).

Kingsmore SF, Cakici JA, Clark MM, et al. A Randomized, Controlled Trial of the Analytic and Diagnostic Performance of Singleton and Trio, Rapid Genome and Exome Sequencing in Ill Infants. Am J Hum Genet. 2019;105(4):719-733. doi:10.1016/j.ajhg.2019.08.009

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Standard Genome Sequencing

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Rapid Genome Sequencing

Patient-Centered Laboratory Utilization Guidance Services (PLUGS)

PLUGS released a guideline entitled “Rapid Genome Sequencing” in June of 2022. The authors specify 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).

Rapid Genome Sequencing. Seattle Children's Hospital Patient-centered Laboratory Utilization Guidance Services. https://www.schplugs.org/wp-content/uploads/Rapid-Genome-Sequencing-Policy_June-2022-FINAL.pdf Effective June 2022.

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

Mitochondrial Medicine Society

In 2015, the Mitochondrial Medicine Society published the following consensus recommendations for DNA testing for mitochondrial disorders:

- 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.
- 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.

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

Parikh S, Goldstein A, Koenig MK, et al. Diagnosis and management of mitochondrial disease: a consensus statement from the Mitochondrial Medicine Society. Genet Med. 2015;17(9):689-701. doi:10.1038/gim.2014.177

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 disorder 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.

Chinnery PF. Primary Mitochondrial Disorders Overview. 2000 Jun 8 [Updated 2021 Jul 29]. In: Adam MP, Ardinger HH, Pagon RA, et al., editors. GeneReviews [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2025. Available from: https://www.ncbi.nlm.nih.gov/books/NBK1224/

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Combined Mitochondrial DNA Analysis and Exome Sequencing

Mavraki, et al.

In 2022, Mavraki, et al. published best practice guidelines regarding genetic testing for mitochondrial disease. They discuss strategies for both targeted testing and comprehensive next generation sequencing (NGS) testing for mitochondrial DNA disease (mtDNA) (p. 150) and state that for urgent or phenotypically complex referrals“simultaneous testing of both mtDNA and nuclear DNA”, if possible, is appropriate as first line testing (p. 149).

Mavraki E, Labrum R, Sergeant K, et al. Genetic testing for mitochondrial disease: the United Kingdom best practice guidelines. Eur J Hum Genet. 2023;31(2):148-163. doi:10.1038/s41431-022-01249-w

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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.

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…”

Malfait F, Symoens S, Syx D. Classic Ehlers-Danlos Syndrome. 2007 May 29 [Updated 2024 Feb 1]. In: Adam MP, Ardinger HH, Pagon RA, et al., editors. GeneReviews [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2025. Available from: https://www.ncbi.nlm.nih.gov/books/NBK1244/

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.

Levy HP. Hypermobile Ehlers-Danlos Syndrome. 2004 Oct 22 [Updated 2024 Feb 22]. In: Adam MP, Ardinger HH, Pagon RA, et al., editors. GeneReviews[Internet]. Seattle (WA): University of Washington, Seattle; 1993-2025. Available from: https://www.ncbi.nlm.nih.gov/books/NBK1279/

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”.

Dietz H. FBN1-Related Marfan Syndrome. 2001 Apr 18 [Updated 2022 Feb 17]. In: Adam MP, Ardinger HH, Pagon RA, et al., editors. GeneReviews [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2025. Available from: https://www.ncbi.nlm.nih.gov/books/NBK1335/

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.

Loeys BL, Dietz HC. Loeys-Dietz Syndrome. 2008 Feb 28 [Updated 2024 Sep 12]. In: Adam MP, Ardinger HH, Pagon RA, et al., editors. GeneReviews [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2025. Available from: https://www.ncbi.nlm.nih.gov/books/NBK1133/

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FBN1 Sequencing and/or Deletion/Duplication 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:

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

Dietz H. FBN1-Related Marfan Syndrome. 2001 Apr 18 [Updated 2022 Feb 17]. In: Adam MP, Ardinger HH, Pagon RA, et al., editors. GeneReviews [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2025. Available from: https://www.ncbi.nlm.nih.gov/books/NBK1335/

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Loeys-Dietz Syndrome Multigene Panel

American College of Medical Genetics and Genomics (ACMG)

In 2012, ACMG 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).

Pyeritz RE; American College of Medical Genetics and Genomics. Evaluation of the adolescent or adult with some features of Marfan syndrome. Genet Med. 2012;14(1):171-177. doi:10.1038/gim.2011.48

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Classic Ehlers-Danlos Syndrome (cEDS) Multigene Panel

International EDS Consortium

The 2017 International Classification of the Ehlers-Danlos Syndromes (2017) included the following clinical features for the associated conditions:

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

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).

Malfait F, Francomano C, Byers P, et al. The 2017 international classification of the Ehlers-Danlos syndromes. Am J Med Genet C Semin Med Genet. 2017;175(1):8-26. doi:10.1002/ajmg.c.31552

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”.

Malfait F, Symoens S, Syx D. Classic Ehlers-Danlos Syndrome. 2007 May 29 [Updated 2024 Feb 1]. In: Adam MP, Ardinger HH, Pagon RA, et al., editors. GeneReviews [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2025. Available from: https://www.ncbi.nlm.nih.gov/books/NBK1244/

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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).

Malfait F, Francomano C, Byers P, et al. The 2017 international classification of the Ehlers-Danlos syndromes. Am J Med Genet C Semin Med Genet. 2017;175(1):8-26. doi:10.1002/ajmg.c.31552

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

American Academy of Pediatrics (AAP)

The American Academy of Pediatrics issued a clinical report on the optimal medical genetics evaluation of a child with developmental delays (DD) or intellectual disability (ID) (2014, reaffirmed 2020), 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).

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

Moeschler JB, Shevell M; Committee on Genetics. Comprehensive evaluation of the child with intellectual disability or global developmental delays. Pediatrics. 2014;134(3):e903-e918. Reaffirmed March 2020. doi:10.1542/peds.2014-1839

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]

Manning M, Hudgins L; Professional Practice and Guidelines Committee. Array-based technology and recommendations for utilization in medical genetics practice for detection of chromosomal abnormalities. Genet Med. 2010;12(11):742-745. doi:10.1097/GIM.0b013e3181f8baad

Manning M, Hudgins L; American College of Medical Genetics and Genomics (ACMG) Professional Practice and Guidelines Committee. Addendum: Array-based technology and recommendations for utilization in medical genetics practice for detection of chromosomal abnormalities [published online ahead of print, 2020 Jun 8]. Genet Med. 2020;10.1038/s41436-020-0848-8. doi:10.1038/s41436-020-0848-8

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).

Mintz CS, Seaver LH, Irons M, Grimberg A, Lozano R, ACMG Professional Practice and Guidelines Committee. Focused Revision: ACMG practice resource: Genetic evaluation of short stature. Genet Med. 2021;23(5):813-815.

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Autism Spectrum Disorder/Intellectual Disability Panel Analysis

Concert Evidence Review for Coverage Determination (Published 06/01/2025)

This review focused on a search for evidence-based guidelines and peer-reviewed, published evidence of the clinical validity and utility of autism spectrum disorder/intellectual disability multigene panel tests. The review was limited to literature published between 05/21/2024 to 05/21/2025. A total of 112 abstracts were identified and 7 full text publications were fully reviewed, none of which met the inclusion criteria.

There were no new guidelines identified and no peer-reviewed literature identified to include in the evidence review.

There is INSUFFICIENT EVIDENCE in published guidelines and peer-reviewed literature to definitively demonstrate improved health outcomes from the use of autism spectrum disorder/intellectual disability multigene panel tests, as compared to the current standard of care. At this time, the available evidence does not support health plan coverage of these tests compared to other, guideline-supported testing methodologies.

Concert Evidence Review for Coverage Determination for Autism Spectrum Disorder/Intellectual Disability Panels. Published 06/01/2025.

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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*

Dagli AI, Mathews J, Williams CA. Angelman Syndrome. 1998 Sep 15 [Updated 2021 Apr 22]. In: Adam MP, Ardinger HH, Pagon RA, et al., editors. GeneReviews [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2025. Available from: https://www.ncbi.nlm.nih.gov/books/NBK1144/

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 main technique used to 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. If methylation is abnormal, than other techniques such as FISH oroligo-SNP combination array are used to identify the molecular cause in most individuals (either a 15q11.2-q13 deletion/duplication, imprinting center deletion, and uniparental isodisomy or segmental isodisomy).

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 externally

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.

Driscoll DJ, Miller JL, Schwartz S, et al. Prader-Willi Syndrome. 1998 Oct 6 [Updated 2024 Dec 5]. In: Adam MP, Ardinger HH, Pagon RA, et al., editors. GeneReviews [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2025. Available from: https://www.ncbi.nlm.nih.gov/books/NBK1330/

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

GeneReviews: Beckwith-Wiedemann Syndrome (BWS)

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

The recommended diagnostic testing for Beckwith-Wiedemann Syndrome (BWS) is as follows:

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

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

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

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

Shuman C, Beckwith JB, Weksberg R. Beckwith-Wiedemann Syndrome. 2000 Mar 3 [Updated 2023 Sept 21]. In: Adam MP, Ardinger HH, Pagon RA, et al., editors. GeneReviews [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2025. Available from: https://www.ncbi.nlm.nih.gov/books/NBK1394/

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.

Per GeneReviews, molecular diagnostic testing for Silver-Russell Syndrome (SRS) should be performed in individuals with at least four of the following Netchine-Harbison clinical diagnostic criteria (NH-CSS) clinical criteria:

- 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.

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. Some rare individuals meeting three of the six criteria have had a positive molecular confirmation for SRS.

Saal HM, Harbison MD, Netchine I. Silver-Russell Syndrome. 2002 Nov 2 [Updated 2025 Jan 9]. In: Adam MP, Ardinger HH, Pagon RA, et al., editors. GeneReviews [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2025. Available from: https://www.ncbi.nlm.nih.gov/books/NBK1324/

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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

van Ravenswaaij-Arts CM, Hefner M, Blake K, et al. CHD7 Disorder. 2006 Oct 2 [Updated 2022 Sep 29]. In: Adam MP, Ardinger HH, Pagon RA, et al., editors. GeneReviews [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2025. Available from: https://www.ncbi.nlm.nih.gov/books/NBK1117/

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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 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.

Roberts AE. Noonan Syndrome. 2001 Nov 15 [Updated 2022 Feb 17]. In: Adam MP, Mirzaa MP, Pagon RA, et al., editors. GeneReviews [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2025. Available from: https://www.ncbi.nlm.nih.gov/books/NBK1124/

Rauen

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.

Rauen KA. The RASopathies. Annu Rev Genomics Hum Genet. 2013;14:355-369. doi:10.1146/annurev-genom-091212-153523

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Diagnostic *FMR1* Repeat and Methylation Analysis

American College of Medical Genetics and Genomics (ACMG)

In 2005, the ACMG 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).

Sherman S, Pletcher BA, Driscoll DA. Fragile X syndrome: diagnostic and carrier testing. Genet Med. 2005;7(8):584-587. doi:10.1097/01.gim.0000182468.22666.dd

In 2013, the ACMG 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).

Schaefer GB, Mendelsohn NJ; Professional Practice and Guidelines Committee. Clinical genetics evaluation in identifying the etiology of autism spectrum disorders: 2013 guideline revisions [published correction appears in Genet Med. 2013 Aug;15(8):669]. Genet Med. 2013;15(5):399-407. doi:10.1038/gim.2013.32

GeneReviews: FMR1 Disorders

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

The recommended testing for *FMR1*-related disorders is as follows:

GeneReviews 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

Hunter JE, Berry-Kravis E, Hipp H, et al. FMR1 Disorders. 1998 Jun 16 [Updated 2024 May 16]. In: Adam MP, Ardinger HH, Pagon RA, et al., editors. GeneReviews [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2025. Available from: https://www.ncbi.nlm.nih.gov/books/NBK1384/

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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)

Mirzaa G, Graham JM Jr, Keppler-Noreuil K. PIK3CA-Related Overgrowth Spectrum. 2013 Aug 15 [Updated 2023 Apr 6]. In: Adam MP, Mirzaa GM, Pagon RA, et al., editors. GeneReviews [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2025. Available from: https://www.ncbi.nlm.nih.gov/books/NBK153722/#.

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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)

Northrup H, Aronow ME, Bebin EM, et al. Updated International Tuberous Sclerosis Complex Diagnostic Criteria and Surveillance and Management Recommendations. Pediatr Neurol. 2021;123:50-66. doi:10.1016/j.pediatrneurol.2021.07.011

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

Northrup H, Koenig MK, Pearson DA, et al. Tuberous Sclerosis Complex. 1999 Jul 13 [Updated 2021 Dec 9]. In: Adam MP, Everman DB, Mirzaa GM, et al., editors. GeneReviews [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2025. Available from: https://www.ncbi.nlm.nih.gov/books/NBK1220/

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NF1 Sequencing and/or Deletion/Duplication Analysis

American Academy of Pediatrics (AAP)

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

Miller DT, Freedenberg D, Schorry E, et al. Health Supervision for Children With Neurofibromatosis Type 1. Pediatrics. 2019;143(5):e20190660. doi:10.1542/peds.2019-0660

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.

Friedman JM. Neurofibromatosis 1. 1998 Oct 2 [Updated 2022 Apr 21]. In: Adam MP, Mirzaa GM, Pagon RA, et al., editors. GeneReviews [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2025. Available from: https://www.ncbi.nlm.nih.gov/books/NBK1109/

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

International Consensus Group on Neurofibromatosis Criteria (I-NF-DC)

In 2022, the I-NF-DC published a consensus recommendation, using a modified Delphi approach, to update the diagnostic criteria for *NF2*-related schwannomatosis (previously known as Neurofibromatosis type II). Table 1 outlines the diagnostic criteria for *NF2*-related schwannomatosis, which include the following:

- An individual with bilateral vestibular schwannomas
- An individual with an *NF2* pathogenic variant (PV) in at least 2 primary *NF2*-related tumors, which include schwannoma, meningioma, and/or ependymoma)
- Either 2 major features or 1 major feature and 2 minor features, as described below:

- Major features:
  - Unilateral vestibular schwannoma
  - First-degree relative (NOT a sibling) with *NF2*-related schwannomatosis
  - 2 or more meningiomas "(Note: single meningioma qualifies as minor criteria)"
  - *NF2* pathogenic variant in an unaffected tissue such as blood (Note: if the VAF is clearly <50%, the diagnosis is mosaic
- Minor features that can be counted more than once:
  - Ependymoma
  - Meningioma "(Note: multiple meningiomas qualify as a major criteria)"
  - Schwannoma "(Note: if the major criterion is unilateral VS, at least 1 schwannoma must be dermal in location)"
- Minor features that can be counted only once:
  - Juvenile subcapsular or cortical cataract
  - Retinal hamartoma
  - Epiretinal membrane in a person aged <40 years
  - Meningioma (p. 1971)

Plotkin SR, Messiaen L, Legius E, et al. Updated diagnostic criteria and nomenclature for neurofibromatosis type 2 and schwannomatosis: An international consensus recommendation. Genet Med. 2022;24(9):1967-1977. doi:10.1016/j.gim.2022.05.007

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.

GeneReviews states that NF2 should be suspected in individuals with specific clinical features, as well as for individuals with a pathogenic variant in *NF2* identified in a tumor.

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

Evans DG. NF2-Related Schwannomatosis. 1998 Oct 14 [Updated 2023 Apr 20]. In: Adam MP, Mirzaa GM, Pagon RA, et al., editors. GeneReviews [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2025 Available from: https://www.ncbi.nlm.nih.gov/books/NBK1201/

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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 anomalies not specific to a well-delineated genetic syndrome. These are structural or functional abnormalities requiring medical intervention that are usually evident at birth, or shortly thereafter, and are consequential to an individual's life expectancy, health status, or physical/social functioning.
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. **Genome Sequencing** (GS) is a genomic technique for sequencing the complete DNA sequence, which includes protein coding as well as non-coding DNA elements.

8. **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). Examples include (but are not limited to): not sitting independently by 9 months; not crawling or rolling over by a year; not walking by 18 months (based on CDC Developmental milestones).

9. **Intellectual disability (ID)** is defined by the DSM V as an individual age 5 or older with either an IQ score of 70 or below, OR with a clinical diagnosis of intellectual disability per the DSM V, which includes 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.

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

11. **Reanalysis of exome sequencing (ES) (aka exome sequencing reanalysis) or genome sequencing (GS) (aka genome sequencing reanalysis)** involves a bioinformatic re-review of both reported and unreported variants detected by the original assay. This is typically performed when (1) the patient’s phenotype has changed and the changes are not explainable by the original result or (2) the original test was not diagnostic and the clinician or laboratory suspect that advances in variant classification or analysis pipelines may result in a diagnosis. Reanalysis may not be possible or useful in some situations due to changes in bioinformatic pipeline compatibility or new information regarding the genetic etiology of a condition that could explain the patient’s clinical features but would not have been captured by previous ES or GS sequencing methods. **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.

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.

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ADDITIONAL REFERENCES

1. Adam MP, Ardinger HH, Pagon RA, et al., editors. GeneReviews [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2025. Available from: https://www.ncbi.nlm.nih.gov/books/NBK1116/
2. Online Mendelian Inheritance in Man, OMIM. McKusick-Nathans Institute of Genetic Medicine, Johns Hopkins University (Baltimore, MD). World Wide Web URL: https://omim.org/
3. MedlinePlus [Internet]. Bethesda (MD): National Library of Medicine (US). Available from: https://medlineplus.gov/genetics/.

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Note: The Health Plan uses the genetic testing clinical criteria developed by Concert Genetics, an industry-leader in genetic testing technology assessment and policy development.

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