InformedDNA®
Genetics, Decoded.

General Genetic Testing

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Scope

This evidence-based guideline addresses genetic testing for rare single gene disorders including hereditary arrhythmias and cardiomyopathies; mitochondrial disorders; thrombophilia; connective tissue disorders and thoracic aortic aneurysm/dissection. The use of polygenic risk scores is also addressed.

This guideline's coverage criteria delineate medically necessary clinical scenarios for molecular testing and may include specific situations when testing is considered never medically necessary. In general, molecular testing is considered never medically necessary when evidence demonstrating its ability to improve diagnosis, management, or clinical outcomes is lacking in peer-reviewed literature.

- Please refer to the separate genetic testing guidelines for more specific information related to reproductive genetics; hereditary cancer; pharmacogenomics; somatic tumor testing; oncology screening tests; organ transplantation; and whole genome copy number variant analysis (chromosomal microarray analysis), whole exome sequencing, and whole genome sequencing.

State Biomarker Legislation

Medical necessity determinations must also take into consideration controlling state coverage mandates that may supersede these guidelines when applicable. When state biomarker legislation requirements impact coverage decisions, this guideline will initially be applied to determine if criteria are met for approval. If an approval cannot be granted based on the criteria in this guideline, some or all of the following sources will be reviewed, as defined by applicable state legislation, to determine if test coverage is supported in a manner that is consistent with the state biomarker legislation requirements:

- Medicare National Coverage Determinations (NCDs)
- Medicare Local Coverage Determinations (LCDs)
- U.S. Food and Drug Administration (FDA) approved or cleared tests
- Tests indicated for an FDA-approved drug
- Nationally recognized clinical practice guidelines
- Consensus statements

Guideline Coverage Criteria

Germline Genetic Testing

Genetic testing is medically necessary when all of the following criteria are met (*see additional indication-specific testing criteria listed below*):

- The test is clinically reasonable:

    - Symptoms and presentation are consistent with the suspected condition
    - Results are expected to lead to a change in medical management
    - If testing guidelines exist, the clinical scenario falls within those recommendations
    - The test is customarily recognized as clinically and technically appropriate in the diagnosis and/or treatment of the suspected condition
- The clinical benefit of testing outweighs the potential risk of psychological or medical harm to the individual being tested
- The test is as targeted as possible for the clinical situation (e.g., familial pathogenic or likely pathogenic (P/LP) variant testing, common variants, genes related to phenotype)
- The testing methodology* has been clinically validated and is the most accurate method unless technical limitations (e.g., poor sample quality) necessitate the need for alternate testing strategies
- The clinical presentation warrants testing of multiple genes when a multi-gene panel is requested

*The testing methodology may target DNA and/or RNA.

Genetic Testing for Connective Tissue Disorders *and* Thoracic Aortic Aneurysm and Dissection

Single gene or targeted multi-gene panel testing is medically necessary in any of the following scenarios:

- Thoracic aortic dissection (TAD)
    - At age 70 or younger in an individual with hypertension
    - At any age in the absence of hypertension
- Thoracic aortic aneurysm (TAA)
    - At age >18 when z-score is >3.5 or aortic diameter is ≥4.5 cm regardless of hypertension
    - At age <18 when z-score is ≥3 or aortic diameter is ≥4 cm
    - At age >70 in an individual whose z-score is 2.5-3.5 or aortic diameter is 4.0-4.4 cm in the absence of hypertension
    - At age 70 or younger in an individual whose z-score is 2.5-3.5 or aortic diameter is 4.0-4.4 cm regardless of hypertension
    - At age <18 in an individual whose z-score is >2 and other systemic features are present or z-score progression is documented
- An individual with at least one first degree relative who meets the TAA or TAD criteria above but is unavailable for testing
- An individual with additional systemic features suggestive of a connective tissue disorder, e.g. Marfan syndrome, Loeys-Dietz syndrome, or Ehlers Danlos syndrome, who does not meet the above criteria.
    - Genetic testing should be targeted to the suspected condition(s).

- An individual with no evidence of aortic dilatation and features suggestive of a connective tissue disorder, e.g. Marfan syndrome, Loeys-Dietz syndrome, or Ehlers Danlos syndrome
    - Genetic testing should be targeted to the suspected condition(s).

Genetic testing is never medically necessary in an individual when only hypermobile Ehlers Danlos syndrome is suspected.

Genetic Testing for Hereditary Arrhythmias and Cardiomyopathies

Confirmatory or diagnostic genetic testing for select hereditary arrhythmias and cardiomyopathies (i.e., Brugada syndrome [BrS], catecholaminergic polymorphic ventricular tachycardia [CPVT], long QT syndrome [LQTS], short QT syndrome [SQTS], arrhythmogenic right ventricular cardiomyopathy [ARVC], dilated cardiomyopathy [DCM], hypertrophic cardiomyopathy [HCM], left ventricular non-compaction cardiomyopathy [LVNC], or restrictive cardiomyopathy [RCM]) is medically necessary when all of the following criteria are met:

- The individual has a clinical diagnosis or suspected syndromic presentation of a hereditary cardiomyopathy or arrhythmia listed above
- The requested testing is as targeted as possible to a specific subset of genes with a demonstrated gene/disease association with the individual's diagnosed or suspected condition

Genetic testing of asymptomatic individuals is medically necessary when testing is targeted to the known familial pathogenic or likely pathogenic (P/LP) variant in a gene associated with a hereditary cardiomyopathy or arrhythmia listed above.

Genetic Testing in the Evaluation of Unexplained Sudden Cardiac Arrest

Cardiac genetic testing ("multi-condition" panel testing) of an individual with an unexplained sudden cardiac arrest is medically necessary when all of the following criteria are met:

- Comprehensive clinical cardiac evaluation (heart rhythm monitoring, cardiac imaging, provocative testing, etc.) has not confirmed a diagnosis of a specific underlying heritable cardiac condition (e.g., ARVC, HCM, LQTS, etc.)
- Non-genetic causes of sudden cardiac arrest have been ruled out (toxicology, ischemic coronary artery disease, etc.)

Post-Mortem Cardiac Genetic Testing

Post-mortem cardiac genetic testing of an individual with sudden unexplained death, whose first-degree family member is a covered member, is medically necessary in the following circumstances:

- When the autopsy reveals evidence for a *specific* underlying heritable cardiac condition (e.g., ARVC, HCM, DCM, RCM):
    - The corresponding targeted testing is ordered (e.g., HCM panel testing in cases where autopsy revealed evidence for HCM)

- When the deceased individual is less than 40 years old at the time of death and the cause of death remains unknown after completion of autopsy and toxicology testing ('autopsy negative' cases)
    - "Multi-condition" panel testing may be ordered

Genetic Testing for Mitochondrial Disorders

Genetic testing for mitochondrial disorders (i.e., targeted analysis *when a specific mitochondrial disorder is suspected*, full sequencing and deletion/duplication analysis of mitochondrial DNA, multi-gene nuclear DNA panels) is medically necessary when any of the following criteria are met:

- An individual has documented unexplained lactic acidosis (in the absence of sepsis, heart failure, etc.)
- An individual has multisystem involvement suggestive of a mitochondrial disorder by exhibiting at least two of the following:
    - elevated lactate
    - proximal myopathy/exercise intolerance and cardiomyopathy
    - ptosis, external ophthalmoplegia or optic atrophy
    - encephalopathy
    - seizures
    - migraine
    - stroke-like episodes
    - ataxia
    - peripheral neuropathy
    - sensorineural hearing loss
    - spasticity
    - dysphagia, vomiting or gastroparesis
- An individual has a mitochondrial disease criteria score of 2 or more (Whitters et al., 2018)

If whole exome/whole genome sequencing is requested in conjunction with mitochondrial testing, please see the Whole Exome Sequencing, Whole Genome Sequencing, and Genome Wide Copy Number Variant Analysis coverage guideline to determine if criteria for this testing is met.

Repeat mitochondrial DNA testing is medically necessary when clinical suspicion persists for a mitochondrial disorder following negative or non-diagnostic testing and subsequent testing is now being performed on different tissue.

Factor V (*F5*) and Prothrombin (*F2*) Genetic Testing

Testing for common variants in factor V (*F5*) and prothrombin (*F2*) related to venous thromboembolism (VTE) is medically necessary for any of the following indications:

- Individual with VTE provoked by pregnancy/postpartum or pregnant individual who has a personal history of a VTE
- Individual who has a first-degree relative with *F5* or *F2* thrombophilia and one of the following:
    - Surgery is planned
    - Individual is pregnant or postpartum
    - Individual is considering estrogen contraception or hormone replacement therapy and results would influence the decision to use estrogen

Genetic testing of *F2* and/or *F5* is not medically necessary in any other clinical scenario, e.g. recurrent pregnancy loss or infertility.

Polygenic Risk Scores

The use of polygenic risk scores to determine risk for disease, aid in diagnosis, or guide treatment decision-making for multifactorial conditions is considered never medically necessary.

Key Terms and Definitions

Common variants are genetic changes that occur at a relatively high frequency in the population.
Connective tissue disorders are a group of inherited conditions affecting the tissues that support or connect various structures and organs in the body including the heart, eyes and skin.
Deoxyribonucleic acid (DNA) is a molecule that contains the genetic instructions for all living organisms and plays a crucial role in the development and susceptibility to diseases.
First-degree relative refers to a biological parent, sibling, or child.
Genes are segments of DNA that contain the instructions for specific traits, characteristics, or functions within an organism.
Genetic (molecular) testing examines a person's DNA or RNA to identify variations that can aid in the diagnosis of disease and/or provide valuable information about a person's risk of developing certain diseases.
Germline genetic testing involves examining the DNA found in every cell of the body derived from reproductive cells (eggs or sperm).
Hereditary arrhythmias are a group of inherited conditions in which individuals have an abnormal heart rhythm known as arrhythmia.
Hereditary cardiomyopathies are a diverse group of disorders affecting the heart muscle's mechanical or electrical function, making it harder for the heart to pump blood to the rest of the body.
Mendelian disorders are inherited diseases that result from pathogenic variants in a single gene.
Mitochondrial disorders are a group of conditions that can include muscle weakness, exercise intolerance, eye findings and neurological symptoms.
Multifactorial conditions are health conditions that result from a combination of genetic and environmental factors, e.g. cancer, heart disease, and hypertension.

Multi-gene panels simultaneously analyze multiple genes associated with a particular condition or a group of related conditions.
Pathogenic/likely pathogenic variants are specific genetic changes that are known or highly likely to cause a particular genetic disorder, which can aid in diagnosis and/or guide treatment and management strategies.
Phenotype refers to the observable characteristics or features of a genetic disorder.
Polygenic risk scores are numerical scores that estimate a person's risk for developing a particular trait or disease based on information from multiple contributing genetic variants.
Ribonucleic acid (RNA) is a molecule that plays a crucial role in various cellular processes within living organisms, such as cell functioning and regulation.
Sudden cardiac arrest is when the heart abruptly stops pumping due to an electrical disturbance; it is distinct from a heart attack, in which there is disrupted cardiac function due to the loss of blood flow to cardiac tissue.
Syndromic presentation refers to a combination of clinical features that occur together as part of a recognizable pattern or syndrome.
Thoracic aortic aneurysm is when the diameter of the aorta is larger than normal.
Thoracic aortic dissection is a life threatening event that occurs when a tear arises in the aorta.
Thrombophilia is a blood disorder that increases the risk for the blood in a person's vessels (arteries/veins) to clot.
Venous thromboembolism (VTE) is a common, complex disease in which blood clots form within the veins, leading to the obstruction of blood flow.

CPT® Codes

Medical necessity review of claims may include evaluation of the submitted codes. Laboratories must accurately represent their services using the most applicable and specific CPT code(s). Tier 1 molecular pathology procedure codes or Proprietary Laboratory Analyses (PLA) codes should be used when available for the specific test. Tier 2 molecular pathology procedure codes should only be used if the American Medical Association (AMA) has specifically assigned the performed test to such a code. Genomic sequencing procedures (GSP) codes (e.g., CPT codes 81410-81471) were developed by the AMA to represent multi-gene panels utilizing DNA or RNA analysis for specific clinical scenarios (e.g., carrier screening, tumor testing, etc.) and should be utilized when applicable.

Coding guidelines can be found in the AMA's CPT manual as well as the Centers for Medicare and Medicaid Services (CMS) National Correct Coding Initiative (NCCI) policy manuals. NCCI General Correct Coding Policy states that procedures should be reported with the most comprehensive CPT code describing the services performed and that the services described by a CPT code cannot be unbundled into multiple less specific codes. Additionally, GSP codes should be utilized when appropriate for the described test and should not be submitted along with other CPT codes that represent components of the GSP code.

Claims may not be approved if the submitted codes are not the most appropriate for the described procedure (i.e., as accurate and specific as available).

The following codes(s) are medically necessary when coverage criteria are met. This list is not all inclusive.

Code	Description
81161	DMD (dystrophin) (eg, Duchenne/Becker muscular dystrophy) deletion analysis, and duplication analysis, if performed
81171	AFF2 (ALF transcription elongation factor 2 [FMR2]) (eg, fragile X intellectual disability 2 [FRAXE]) gene analysis; evaluation to detect abnormal (eg, expanded) alleles
81172	AFF2 (ALF transcription elongation factor 2 [FMR2]) (eg, fragile X intellectual disability 2 [FRAXE]) gene analysis; characterization of alleles (eg, expanded size and methylation status)
81173	AR (androgen receptor) (eg, spinal and bulbar muscular atrophy, Kennedy disease, X chromosome inactivation) gene analysis; full gene sequence
81174	AR (androgen receptor) (eg, spinal and bulbar muscular atrophy, Kennedy disease, X chromosome inactivation) gene analysis; known familial variant
81177	ATN1 (atrophin 1) (eg, dentatorubral-pallidoluysian atrophy) gene analysis, evaluation to detect abnormal (eg, expanded) alleles
81178	ATXN1 (ataxin 1) (eg, spinocerebellar ataxia) gene analysis, evaluation to detect abnormal (eg, expanded) alleles
81179	ATXN2 (ataxin 2) (eg, spinocerebellar ataxia) gene analysis, evaluation to detect abnormal (eg, expanded) alleles
81180	ATXN3 (ataxin 3) (eg, spinocerebellar ataxia, Machado-Joseph disease) gene analysis, evaluation to detect abnormal (eg, expanded) alleles
81181	ATXN7 (ataxin 7) (eg, spinocerebellar ataxia) gene analysis, evaluation to detect abnormal (eg, expanded) alleles
81182	ATXN8OS (ATXN8 opposite strand [non-protein coding]) (eg, spinocerebellar ataxia) gene analysis, evaluation to detect abnormal (eg, expanded) alleles
81183	ATXN10 (ataxin 10) (eg, spinocerebellar ataxia) gene analysis, evaluation to detect abnormal (eg, expanded) alleles
81184	CACNA1A (calcium voltage-gated channel subunit alpha1 A) (eg, spinocerebellar ataxia) gene analysis; evaluation to detect abnormal (eg, expanded) alleles
81185	CACNA1A (calcium voltage-gated channel subunit alpha1 A) (eg, spinocerebellar ataxia) gene analysis; full gene sequence
81186	CACNA1A (calcium voltage-gated channel subunit alpha1 A) (eg, spinocerebellar ataxia) gene analysis; known familial variant
81187	CNBP (CCHC-type zinc finger nucleic acid binding protein) (eg, myotonic dystrophy type 2) gene analysis, evaluation to detect abnormal (eg, expanded) alleles
81188	CSTB (cystatin B) (eg, Unverricht-Lundborg disease) gene analysis; evaluation to detect abnormal (eg, expanded) alleles
81189	CSTB (cystatin B) (eg, Unverricht-Lundborg disease) gene analysis; full gene sequence
81190	CSTB (cystatin B) (eg, Unverricht-Lundborg disease) gene analysis; known familial variant(s)
81200	ASPA (aspartoacylase) (eg, Canavan disease) gene analysis, common variants (eg, E285A, Y231X)
81204	AR (androgen receptor) (eg, spinal and bulbar muscular atrophy, Kennedy disease, X chromosome inactivation) gene analysis; characterization of alleles (eg, expanded size or methylation status)

81205	BCKDHB (branched-chain keto acid dehydrogenase E1, beta polypeptide) (eg, maple syrup urine disease) gene analysis, common variants (eg, R183P, G278S, E422X)
81209	BLM (Bloom syndrome, RecQ helicase-like) (eg, Bloom syndrome) gene analysis, 2281del6ins7 variant
81220	CFTR (cystic fibrosis transmembrane conductance regulator) (eg, cystic fibrosis) gene analysis; common variants (eg, ACMG/ACOG guidelines)
81221	CFTR (cystic fibrosis transmembrane conductance regulator) (eg, cystic fibrosis) gene analysis; known familial variants
81222	CFTR (cystic fibrosis transmembrane conductance regulator) (eg, cystic fibrosis) gene analysis; duplication/deletion variants
81223	CFTR (cystic fibrosis transmembrane conductance regulator) (eg, cystic fibrosis) gene analysis; full gene sequence
81224	CFTR (cystic fibrosis transmembrane conductance regulator) (eg, cystic fibrosis) gene analysis; intron 8 poly-T analysis (eg, male infertility)
81234	DMPK (DM1 protein kinase) (eg, myotonic dystrophy type 1) gene analysis; evaluation to detect abnormal (expanded) alleles
81238	F9 (coagulation factor IX) (eg, hemophilia B), full gene sequence
81239	DMPK (DM1 protein kinase) (eg, myotonic dystrophy type 1) gene analysis; characterization of alleles (eg, expanded size)
81240	F2 (prothrombin, coagulation factor II) (eg, hereditary hypercoagulability) gene analysis, 20210G>A variant
81241	F5 (coagulation factor V) (eg, hereditary hypercoagulability) gene analysis, Leiden variant
81242	FANCC (Fanconi anemia, complementation group C) (eg, Fanconi anemia, type C) gene analysis, common variant (eg, IVS4+4A>T)
81243	FMR1 (fragile X messenger ribonucleoprotein 1) (eg, fragile X syndrome, X-linked intellectual disability [XLID]) gene analysis; evaluation to detect abnormal (eg, expanded) alleles
81244	FMR1 (fragile X messenger ribonucleoprotein 1) (eg, fragile X syndrome, X-linked intellectual disability [XLID]) gene analysis; characterization of alleles (eg, expanded size and promoter methylation status)
81247	G6PD (glucose-6-phosphate dehydrogenase) (eg, hemolytic anemia, jaundice), gene analysis; common variant(s) (eg, A, A-)
81248	G6PD (glucose-6-phosphate dehydrogenase) (eg, hemolytic anemia, jaundice), gene analysis; known familial variant(s)
81249	G6PD (glucose-6-phosphate dehydrogenase) (eg, hemolytic anemia, jaundice), gene analysis; full gene sequence
81250	G6PC (glucose-6-phosphatase, catalytic subunit) (eg, Glycogen storage disease, type 1a, von Gierke disease) gene analysis, common variants (eg, R83C, Q347X)
81251	GBA (glucosidase, beta, acid) (eg, Gaucher disease) gene analysis, common variants (eg, N370S, 84GG, L444P, IVS2+1G>A)
81252	GJB2 (gap junction protein, beta 2, 26kDa, connexin 26) (eg, nonsyndromic hearing loss) gene analysis; full gene sequence
81253	GJB2 (gap junction protein, beta 2, 26kDa, connexin 26) (eg, nonsyndromic hearing loss) gene analysis; known familial variants
81254	GJB6 (gap junction protein, beta 6, 30kDa, connexin 30) (eg, nonsyndromic hearing loss) gene analysis, common variants (eg, 309kb [del(GJB6-D13S1830)] and 232kb [del(GJB6-D13S1854)])
81255	HEXA (hexosaminidase A [alpha polypeptide]) (eg, Tay-Sachs disease) gene analysis, common variants (eg,

	1278insTATC, 1421+1G>C, G269S)
81256	HFE (hemochromatosis) (eg, hereditary hemochromatosis) gene analysis, common variants (eg, C282Y, H63D)
81257	HBA1/HBA2 (alpha globin 1 and alpha globin 2) (eg, alpha thalassemia, Hb Bart hydrops fetalis syndrome, HbH disease), gene analysis; common deletions or variant (eg, Southeast Asian, Thai, Filipino, Mediterranean, alpha3.7, alpha4.2, alpha20.5, Constant Spring)
81258	HBA1/HBA2 (alpha globin 1 and alpha globin 2) (eg, alpha thalassemia, Hb Bart hydrops fetalis syndrome, HbH disease), gene analysis; known familial variant
81259	HBA1/HBA2 (alpha globin 1 and alpha globin 2) (eg, alpha thalassemia, Hb Bart hydrops fetalis syndrome, HbH disease), gene analysis; full gene sequence
81260	IKBKAP (inhibitor of kappa light polypeptide gene enhancer in B-cells, kinase complex-associated protein) (eg, familial dysautonomia) gene analysis, common variants (eg, 2507+6T>C, R696P)
81269	HBA1/HBA2 (alpha globin 1 and alpha globin 2) (eg, alpha thalassemia, Hb Bart hydrops fetalis syndrome, HbH disease), gene analysis; duplication/deletion variants
81271	HTT (huntingtin) (eg, Huntington disease) gene analysis; evaluation to detect abnormal (eg, expanded) alleles
81274	HTT (huntingtin) (eg, Huntington disease) gene analysis; characterization of alleles (eg, expanded size)
81284	FXN (frataxin) (eg, Friedreich ataxia) gene analysis; evaluation to detect abnormal (expanded) alleles
81285	FXN (frataxin) (eg, Friedreich ataxia) gene analysis; characterization of alleles (eg, expanded size)
81286	FXN (frataxin) (eg, Friedreich ataxia) gene analysis; full gene sequence
81289	FXN (frataxin) (eg, Friedreich ataxia) gene analysis; known familial variant(s)
81290	MCOLN1 (mucolipin 1) (eg, Mucolipidosis, type IV) gene analysis, common variants (eg, IVS3-2A>G, del6.4kb)
81302	MECP2 (methyl CpG binding protein 2) (eg, Rett syndrome) gene analysis; full sequence analysis
81303	MECP2 (methyl CpG binding protein 2) (eg, Rett syndrome) gene analysis; known familial variant
81304	MECP2 (methyl CpG binding protein 2) (eg, Rett syndrome) gene analysis; duplication/deletion variants
81312	PABPN1 (poly[A] binding protein nuclear 1) (eg, oculopharyngeal muscular dystrophy) gene analysis, evaluation to detect abnormal (eg, expanded) alleles
81324	PMP22 (peripheral myelin protein 22) (eg, Charcot-Marie-Tooth, hereditary neuropathy with liability to pressure palsies) gene analysis; duplication/deletion analysis
81325	PMP22 (peripheral myelin protein 22) (eg, Charcot-Marie-Tooth, hereditary neuropathy with liability to pressure palsies) gene analysis; full sequence analysis
81326	PMP22 (peripheral myelin protein 22) (eg, Charcot-Marie-Tooth, hereditary neuropathy with liability to pressure palsies) gene analysis; known familial variant
81330	SMPD1(sphingomyelin phosphodiesterase 1, acid lysosomal) (eg, Niemann-Pick disease, Type A) gene analysis, common variants (eg, R496L, L302P, fsP330)
81331	SNRPN/UBE3A (small nuclear ribonucleoprotein polypeptide N and ubiquitin protein ligase E3A) (eg, Prader-Willi syndrome and/or Angelman syndrome), methylation analysis
81332	SERPINA1 (serpin peptidase inhibitor, clade A, alpha-1 antiproteinase, antitrypsin, member 1) (eg, alpha-1-antitrypsin deficiency), gene analysis, common variants (eg, *S and *Z)
81333	TGFBI (transforming growth factor beta-induced) (eg, corneal dystrophy) gene analysis, common variants (eg, R124H, R124C, R124L, R555W, R555Q)
81336	SMN1 (survival of motor neuron 1, telomeric) (eg, spinal muscular atrophy) gene analysis; full gene

	sequence
81337	SMN1 (survival of motor neuron 1, telomeric) (eg, spinal muscular atrophy) gene analysis; known familial sequence variant(s)
81343	PPP2R2B (protein phosphatase 2 regulatory subunit Bbeta) (eg, spinocerebellar ataxia) gene analysis, evaluation to detect abnormal (eg, expanded) alleles
81344	TBP (TATA box binding protein) (eg, spinocerebellar ataxia) gene analysis, evaluation to detect abnormal (eg, expanded) alleles
81361	HBB (hemoglobin, subunit beta) (eg, sickle cell anemia, beta thalassemia, hemoglobinopathy); common variant(s) (eg, HbS, HbC, HbE)
81362	HBB (hemoglobin, subunit beta) (eg, sickle cell anemia, beta thalassemia, hemoglobinopathy); known familial variant(s)
81363	HBB (hemoglobin, subunit beta) (eg, sickle cell anemia, beta thalassemia, hemoglobinopathy); duplication/deletion variant(s)
81364	HBB (hemoglobin, subunit beta) (eg, sickle cell anemia, beta thalassemia, hemoglobinopathy); full gene sequence
81410	Aortic dysfunction or dilation (eg, Marfan syndrome, Loeys Dietz syndrome, Ehler Danlos syndrome type IV, arterial tortuosity syndrome); genomic sequence analysis panel, must include sequencing of at least 9 genes, including FBN1, TGFBR1, TGFBR2, COL3A1, MYH11, ACTA2, SLC2A10, SMAD3, and MYLK
81411	Aortic dysfunction or dilation (eg, Marfan syndrome, Loeys Dietz syndrome, Ehler Danlos syndrome type IV, arterial tortuosity syndrome); duplication/deletion analysis panel, must include analyses for TGFBR1, TGFBR2, MYH11, and COL3A1
81413	Cardiac ion channelopathies (eg, Brugada syndrome, long QT syndrome, catecholaminergic polymorphic ventricular tachycardia); genomic sequence analysis panel, must include sequencing of at least 10 genes, including ANK2, CASQ2, CAV3, KCNE1, KCNE2, KCNH2, KCNJ2, KCNQ1, RYR2, and SCN5A
81414	Cardiac ion channelopathies (eg, Brugada syndrome, long QT syndrome, catecholaminergic polymorphic ventricular tachycardia); duplication/deletion gene analysis panel, must include analysis of at least 2 genes, including KCNH2 and KCNQ1
81419	Epilepsy genomic sequence analysis panel, must include analyses for ALDH7A1, CACNA1A, CDKL5, CHD2, GABRG2, GRIN2A, KCNQ2, MECP2, PCDH19, POLG, PRRT2, SCN1A, SCN1B, SCN2A, SCN8A, SLC2A1, SLC9A6, STXBP1, SYNGAP1, TCF4, TPP1, TSC1, TSC2, and ZEB2
81430	Hearing loss (eg, nonsyndromic hearing loss, Usher syndrome, Pendred syndrome); genomic sequence analysis panel, must include sequencing of at least 60 genes, including CDH23, CLRN1, GJB2, GPR98, MTRNR1, MYO7A, MYO15A, PCDH15, OTOF, SLC26A4, TMC1, TMPRSS3, USH1C, USH1G, USH2A, and WFS1
81431	Hearing loss (eg, nonsyndromic hearing loss, Usher syndrome, Pendred syndrome); duplication/deletion analysis panel, must include copy number analyses for STRC and DFNB1 deletions in GJB2 and GJB6 genes
81434	Hereditary retinal disorders (eg, retinitis pigmentosa, Leber congenital amaurosis, cone-rod dystrophy), genomic sequence analysis panel, must include sequencing of at least 15 genes, including ABCA4, CNGA1, CRB1, EYS, PDE6A, PDE6B, PRPF31, PRPH2, RDH12, RHO, RP1, RP2, RPE65, RPGR, and USH2A
81439	Hereditary cardiomyopathy (eg, hypertrophic cardiomyopathy, dilated cardiomyopathy, arrhythmogenic right ventricular cardiomyopathy), genomic sequence analysis panel, must include sequencing of at least 5 cardiomyopathy-related genes (eg, DSG2, MYBPC3, MYH7, PKP2, TTN)
81440	Nuclear encoded mitochondrial genes (eg, neurologic or myopathic phenotypes), genomic sequence panel, must include analysis of at least 100 genes, including BCS1L, C10orf2, COQ2, COX10, DGUOK, MPV17, OPA1, PDSS2, POLG, POLG2, RRM2B, SCO1, SCO2, SLC25A4, SUCLA2, SUCLG1, TAZ, TK2, and TYMP

81441	Inherited bone marrow failure syndromes (IBMFS) (eg, Fanconi anemia, dyskeratosis congenita, Diamond-Blackfan anemia, Shwachman-Diamond syndrome, GATA2 deficiency syndrome, congenital amegakaryocytic thrombocytopenia) sequence analysis panel, must include sequencing of at least 30 genes, including BRCA2, BRIP1, DKC1, FANCA, FANCB, FANCC, FANCD2, FANCE, FANCF, FANCG, FANCI, FANCL, GATA1, GATA2, MPL, NHP2, NOP10, PALB2, RAD51C, RPL11, RPL35A, RPL5, RPS10, RPS19, RPS24, RPS26, RPS7, SBDS, TERT, and TINF2
81442	Noonan spectrum disorders (eg, Noonan syndrome, cardio-facio-cutaneous syndrome, Costello syndrome, LEOPARD syndrome, Noonan-like syndrome), genomic sequence analysis panel, must include sequencing of at least 12 genes, including BRAF, CBL, HRAS, KRAS, MAP2K1, MAP2K2, NRAS, PTPN11, RAF1, RIT1, SHOC2, and SOS1
81448	Hereditary peripheral neuropathies (eg, Charcot-Marie-Tooth, spastic paraplegia), genomic sequence analysis panel, must include sequencing of at least 5 peripheral neuropathy-related genes (eg, BSCL2, GJB1, MFN2, MPZ, REEP1, SPAST, SPG11, SPTLC1)
81460	Whole mitochondrial genome (eg, Leigh syndrome, mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes [MELAS], myoclonic epilepsy with ragged-red fibers [MERFF], neuropathy, ataxia, and retinitis pigmentosa [NARP], Leber hereditary op
81465	Whole mitochondrial genome large deletion analysis panel (eg, Kearns-Sayre syndrome, chronic progressive external ophthalmoplegia), including heteroplasmy detection, if performed
81470	X-linked intellectual disability (XLID) (eg, syndromic and non-syndromic XLID); genomic sequence analysis panel, must include sequencing of at least 60 genes, including ARX, ATRX, CDKL5, FGD1, FMR1, HUWE1, IL1RAPL, KDM5C, L1CAM, MECP2, MED12, MID1, OCRL, RPS6KA3, and SLC16A2
81471	X-linked intellectual disability (XLID) (eg, syndromic and non-syndromic XLID); duplication/deletion gene analysis, must include analysis of at least 60 genes, including ARX, ATRX, CDKL5, FGD1, FMR1, HUWE1, IL1RAPL, KDM5C, L1CAM, MECP2, MED12, MID1, OCRL, RPS6KA3, and SLC16A2
0318U	Pediatrics (congenital epigenetic disorders), whole genome methylation analysis by microarray for 50 or more genes, blood

The following code(s) are considered never medically necessary. This list is not all inclusive.

Code	Description
81493	Coronary artery disease, mRNA, gene expression profiling by real-time RT-PCR of 23 genes, utilizing whole peripheral blood, algorithm reported as a risk score
81554	Pulmonary disease (idiopathic pulmonary fibrosis [IPF]), mRNA, gene expression analysis of 190 genes, utilizing transbronchial biopsies, diagnostic algorithm reported as categorical result (eg, positive or negative for high probability of usual interstitial pneumonia [UIP])
81291	MTHFR (5,10-methylenetetrahydrofolate reductase) (eg, hereditary hypercoagulability) gene analysis, common variants (eg, 677T, 1298C)

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Change Summary

Version	Review Date	Effective Date	Summary of Revisions
Created	CSC: 8/11/2022 PAB: 9/12/2022	November 2022	Not applicable

v1.2023	COOC: 2/15/2023 PAB: 3/16/2023	April 1, 2023	Semi-annual review. No criteria changes.
v2.2023	COOC: 8/16/2023 PAB: 9/25/2023	October 1, 2023	Semi-annual review. SQTS was added to the list of hereditary arrhythmias for which targeted molecular testing is medically necessary. Thrombophilia criteria were expanded.
v1.2024	COOC: 2/14/2024 PAB: 3/25/2024	April 1, 2024	Semi-annual review. Coverage criteria were added for genetic testing for mitochondrial disorders, connective tissue disorders and thoracic aortic aneurysm/dissection. Clarifications were made to the Scope and CPT Code sections. References were updated.
v2.2024	COOC: 8/19/2024 PAB: 9/20/2024	October 1, 2024	Semi-annual review. Criteria were clarified for CTD and TAA/TAAD testing to include aortic diameter measurements. *F2*/*F5* testing criteria were clarified for pregnant/postpartum individuals with first degree relatives. CPT codes and references were updated.
v1.2025	COOC: 2/17/2025 PAB: 3/24/2025	July 3, 2025	Semi-annual review. Criteria were updated for Genetic Testing for Connective Tissue Disorders and Thoracic Aortic Aneurysm and Dissection and Factor V (F5) and Prothrombin (F2) Genetic Testing. References were updated.