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Clinical Appropriateness Guidelines

Genetic Testing

Appropriate Use Criteria: Genetic Testing for Inherited Conditions

Proprietary

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Description and Application of the Guidelines

The Carelon Clinical Appropriateness Guidelines (hereinafter “the Carelon Clinical Appropriateness Guidelines” or the “Guidelines”) are designed to assist providers in making the most appropriate treatment decision for a specific clinical condition for an individual. The Guidelines establish objective and evidence-based criteria for medical necessity determinations, where possible, that can be used in support of the following:

- To establish criteria for when services are medically necessary
- To assist the practitioner as an educational tool
- To encourage standardization of medical practice patterns
- To curtail the performance of inappropriate and/or duplicate services
- To address patient safety concerns
- To enhance the quality of health care
- To promote the most efficient and cost-effective use of services

The Carelon guideline development process complies with applicable accreditation and legal standards, including the requirement that the Guidelines be developed with involvement from appropriate providers with current clinical expertise relevant to the Guidelines under review and be based on the most up-to-date clinical principles and best practices. Resources reviewed include widely used treatment guidelines, randomized controlled trials or prospective cohort studies, and large systematic reviews or meta-analyses. Carelon reviews all of its Guidelines at least annually.

Carelon makes its Guidelines publicly available on its website. Copies of the Guidelines are also available upon oral or written request. Additional details, such as summaries of evidence, a list of the sources of evidence, and an explanation of the rationale that supports the adoption of the Guidelines, are included in each guideline document.

Although the Guidelines are publicly available, Carelon considers the Guidelines to be important, proprietary information of Carelon, which cannot be sold, assigned, leased, licensed, reproduced or distributed without the written consent of Carelon. Use of the Guidelines by any external AI entity without the express written permission of Carelon is prohibited.

Carelon applies objective and evidence-based criteria, and takes individual circumstances and the local delivery system into account when determining the medical appropriateness of health care services. The Carelon Guidelines are just guidelines for the provision of specialty health services. These criteria are designed to guide both providers and reviewers to the most appropriate services based on a patient’s unique circumstances. In all cases, clinical judgment consistent with the standards of good medical practice should be used when applying the Guidelines. Guideline determinations are made based on the information provided at the time of the request. It is expected that medical necessity decisions may change as new information is provided or based on unique aspects of the patient’s condition. The treating clinician has final authority and responsibility for treatment decisions regarding the care of the patient and for justifying and demonstrating the existence of medical necessity for the requested service. The Guidelines are not a substitute for the experience and judgment of a physician or other health care professionals. Any clinician seeking to apply or consult the Guidelines is expected to use independent medical judgment in the context of individual clinical circumstances to determine any patient’s care or treatment.

The Guidelines do not address coverage, benefit or other plan specific issues. Applicable federal and state coverage mandates take precedence over these clinical guidelines, and in the case of reviews for Medicare Advantage Plans, the Guidelines are only applied where there are not fully established CMS criteria. If requested by a health plan, Carelon will review requests based on health plan medical policy/guidelines in lieu of the Carelon Guidelines. Use of an FDA-approved or conditionally approved product does not constitute medical necessity or guarantee reimbursement by the respective health plan.

The Guidelines may also be used by the health plan or by Carelon for purposes of provider education, or to review the medical necessity of services by any provider who has been notified of the need for medical necessity review, due to billing practices or claims that are not consistent with other providers in terms of frequency or some other manner.

General Clinical Guideline

Clinical Appropriateness Framework

Critical to any finding of clinical appropriateness under the guidelines for a specific diagnostic or therapeutic intervention are the following elements:

- Prior to any intervention, it is essential that the clinician confirm the diagnosis or establish its pretest likelihood based on a complete evaluation of the patient. This includes a history and physical examination and, where applicable, a review of relevant laboratory studies, diagnostic testing, and response to prior therapeutic intervention.
- The anticipated benefit of the recommended intervention is likely to outweigh any potential harms, including from delay or decreased access to services that may result (net benefit).
- Widely used treatment guidelines and/or current clinical literature and/or standards of medical practice should support that the recommended intervention offers the greatest net benefit among competing alternatives.
- There exists a reasonable likelihood that the intervention will change management and/or lead to an improved outcome for the patient.

Providers may be required to submit clinical documentation in support of a request for services. Such documentation must a) accurately reflect the clinical situation at the time of the requested service, and b) sufficiently document the ordering provider's clinical intent.

If these elements are not established with respect to a given request, the determination of appropriateness will most likely require a peer-to-peer conversation to understand the individual and unique facts that would justify a finding of clinical appropriateness. During the peer-to-peer conversation, factors such as patient acuity and setting of service may also be taken into account to the extent permitted by law.

Genetic tests not specifically mentioned in the guidelines are considered not medically necessary.

Simultaneous Ordering of Multiple Diagnostic or Therapeutic Interventions

Requests for multiple diagnostic or therapeutic interventions at the same time will often require a peer-to-peer conversation to understand the individual circumstances that support the medical necessity of performing all interventions simultaneously. This is based on the fact that appropriateness of additional intervention is often dependent on the outcome of the initial intervention.

Additionally, either of the following may apply:

- Current literature and/or standards of medical practice support that one of the requested diagnostic or therapeutic interventions is more appropriate in the clinical situation presented; or
- One of the diagnostic or therapeutic interventions requested is more likely to improve patient outcomes based on current literature and/or standards of medical practice.

Repeat Diagnostic Intervention

In general, repeated testing of the same anatomic location for the same indication should be limited to evaluation following an intervention, or when there is a change in clinical status such that additional testing is required to determine next steps in management. At times, it may be necessary to repeat a test using different techniques or protocols to clarify a finding or result of the original study.

Repeated testing for the same indication using the same or similar technology may be subject to additional review or require peer-to-peer conversation in the following scenarios:

- Repeated diagnostic testing at the same facility due to technical issues

- Repeated diagnostic testing requested at a different facility due to provider preference or quality concerns
- Repeated diagnostic testing of the same anatomic area based on persistent symptoms with no clinical change, treatment, or intervention since the previous study
- Repeated diagnostic testing of the same anatomic area by different providers for the same member over a short period of time

Repeat Therapeutic Intervention

In general, repeated therapeutic intervention in the same anatomic area is considered appropriate when the prior intervention proved effective or beneficial and the expected duration of relief has lapsed. A repeat intervention requested prior to the expected duration of relief is not appropriate unless it can be confirmed that the prior intervention was never administered. Requests for ongoing services may depend on completion of previously authorized services in situations where a patient's response to authorized services is relevant to a determination of clinical appropriateness.

Genetic Testing for Inherited Conditions

Description and Scope

Genetic testing for inherited conditions includes single gene testing and applies to individuals, including pregnancies, which are clinically symptomatic for a suspected condition and/or may be at increased risk for carrying a pathogenic variant associated with a condition(s) based on family history or ancestry. The clinical utility of such testing may include making a definitive diagnosis or offering important prognostic information that could meaningfully impact patient management and clinical outcomes for affected individuals and their family members. Specific testing realms discussed in this guideline are general indications for single gene or multigene testing including but not limited to hereditary cardiac, primary mitochondrial diseases, hereditary neurologic, hereditary retinal disorders, thrombophilia, preimplantation genetic testing, and genetic biomarker testing of rejection in solid organ transplantation.

For specific test modalities, see the Carelon Guidelines for Chromosomal Microarray Analysis and Whole Exome Sequencing and Whole Genome Sequencing. For testing associated with reproduction, see Carrier Screening in the Reproductive Setting guideline. For testing associated with hereditary cancer syndromes, see Hereditary Cancer Testing guideline. For testing of tumor biomarkers, see the Somatic Tumor Testing guideline.

General Recommendations

Genetic Counseling

Counseling is strongly recommended prior to genetic testing and should include **ALL** of the following components:

- Interpretation of family and medical histories to provide a risk assessment for disease occurrence or recurrence
- Education about inheritance, genetic testing, disease management, prevention, risk reduction, and resources
- Counseling to promote informed choices and adaptation to the risk or presence of a genetic condition
- Counseling for the psychological aspects of genetic testing
- Counseling should include the following details:
    - Limitations of the testing used
    - A negative result does not indicate heritable risk is zero or low
    - Identification of inconclusive results called variants of uncertain significance is possible
    - Modifications to genetic variants' pathogenicity interpretations can occur and patients may be recontacted with reclassified results in the future

Note: Post-test counseling should be performed for any diagnostic genetic test result.

Rationale

Genetic testing is a procedure that involves risk that accompanies its potential benefits. The clinical team and the patient should consider the balance of risks and potential benefits before testing is pursued through informed consent. As with any procedure, the clinical utility of the genetic test must be considered along with its psychological and sociologic implications.[1] Counseling, either by a genetic counselor and/or team clinician, provides a patient-centered approach to the care of individuals who are undergoing a diagnostic genetic test.[2]

It is also recognized that accessibility to genetic counselors is limited by available resources as well as other social determinants of health. Therefore, as it relates to screening, the importance should be placed on counseling in a general sense, such as informed consent, as noted above.[3]

Genomic technologies generate large amounts of data, and this increases the potential for uncertainty in managing and adapting to this information.[4] Clinicians are tasked with accurately interpreting and communicating information about test validity and the reliability of test results, as well as the probability for individual patient benefit.[4, 5] Uncovering incidental findings and being overwhelmed with information are important barriers to genetic testing, particularly among vulnerable patient subgroups.[4] Genetic counseling is an invaluable resource for patients undergoing genetic testing, but there are practical limitations because of the scarcity of genetic counselors relative to the current need, as noted above.

Clinical Indications

General Requirements

Genetic testing for inherited conditions

Genetic testing is considered **medically necessary** for an individual when **ALL** the following criteria are met:

- The individual is either suspected of having a known genetic condition based on clinical presentation, or the individual may be presymptomatic but at significant risk based on family history*
- The genetic disorder being evaluated has clearly defined gene(s) and pathogenic variants associated with it and the associated test has high sensitivity and specificity to guide clinical decision making
- The genetic testing has established analytical and clinical validity and is performed in an appropriately accredited and certified laboratory
- Alternate, biochemical, or other clinical tests are not available, provide an indeterminate result or are less effective than genetic testing
- The natural history of the disease is associated with significant morbidity and/or mortality in affected individuals
- Knowledge of the pathogenic variant(s) is expected to directly impact clinical management (predictive, diagnostic, surveillance, therapeutic, or reproductive) of the individual

**Family history of the condition(s) being evaluated is present in first-, second- or third-degree relatives as applicable to the inheritance pattern of the condition (i.e., autosomal dominant, autosomal recessive, X-linked). This may also include family history of a known pathogenic variant with or without expression of the condition being evaluated.*

Confirmatory genetic testing of the identified variant(s) is considered **medically necessary** if **ALL** the criteria above are met and **EITHER** of the following apply:

- An individual identified to have a pathogenic or likely pathogenic germline variant in genes with established clinical utility based on FDA-approved direct-to-consumer genetic testing
- An individual identified to have a pathogenic or likely pathogenic germline variant in genes with established clinical utility based on results of IRB approved clinical research studies

Testing may be performed only once per lifetime for a given condition.

Multigene panel testing for inherited conditions

Panel testing may be considered when **ALL** general and condition-specific criteria are met **AND ALL** the following criteria are met:

- Any multigene panel should be as focused as reasonably possible taking into account the prevalence of each gene and the clinical utility of identifying the presence or absence of a pathogenic variant in each gene
- Each gene included in the panel must have evidence to show their association with the condition **AND** pathogenic variants in each gene could affect clinical management
- Testing for the more probable genes should be performed before gene panel testing where clinically appropriate

Rationale

Mendelian disorders result from combinations of variants in one or a few genes that have a large effect on the propensity for developing a certain condition. While various common conditions are covered by specific guideline criteria, it is not feasible to establish criteria for every Mendelian disorder. This general guideline describes criteria for testing for a single gene or a focused panel of genes to diagnose a specific condition or provide important information related to therapeutic choices or prognostication.

Condition-Specific Requirements

Cardiac conditions

Genetic testing for **hereditary cardiac conditions** is considered **medically necessary** when **ALL** the general medical necessity criteria above are met in addition to the condition-specific criteria below.

Hereditary arrhythmia syndromes

Genetic testing for pathogenic variants associated with long QT syndrome, catecholamine polymorphic ventricular tachycardia (CPVT), or Brugada syndrome is considered **medically necessary** when **ANY** of the following are present:

- The individual to be tested is symptomatic with supporting clinical and ECG features for long QT syndrome, or catecholamine polymorphic ventricular tachycardia (CPVT), or Brugada syndrome
- The individual to be tested is presymptomatic with characteristic ECG features (at rest or with exercise) suggestive of an inherited cardiac arrhythmia syndrome **AND** the individual to be tested has a first-degree relative with **ANY** of the following:
    - Sudden cardiac death
    - Unexplained syncope
    - Unexplained cardiac arrest
- There is a known familial pathogenic variant associated with long QT syndrome, catecholamine polymorphic ventricular tachycardia (CPVT), or Brugada syndrome in a first- or second-degree relative

AND

- The genetic testing is focused on pathogenic variants relevant to the individual's suspected clinical diagnosis and known familial genetics

Hereditary cardiomyopathy syndromes

Genetic testing for pathogenic variants associated with hereditary hypertrophic cardiomyopathy (HCM), arrhythmogenic right ventricular cardiomyopathy/dysplasia (ARVC/D), or inherited dilated cardiomyopathy (DCM) is considered **medically necessary** when **ALL** the following criteria are met:

- The individual to be tested has a first-degree relative with supporting clinical features of one of the above-named inherited cardiomyopathy syndromes (HCM, ARVC/D, DCM)

- The individual to be tested has been clinically screened to exclude an alternate, acquired etiology of cardiomyopathy (e.g., ischemic cardiomyopathy, cardiac amyloidosis, etc.)
- The genetic testing is focused on pathogenic variants relevant to the individual's suspected clinical diagnosis and known familial genetics

OR

- For clinically symptomatic individuals under the age of 18 for whom there is no known family history, a genetic syndrome has not been identified via clinical diagnosis, and an alternate, acquired etiology of cardiomyopathy (e.g., ischemic cardiomyopathy, cardiac amyloidosis, etc.) has been excluded

Hereditary aortopathies

Targeted genetic testing for pathogenic variants associated with significantly increased risk for heritable thoracic aortic disease (HTAD) may be **medically necessary** when **ANY** of the following are met:

- The individual to be tested has a personal history of TAD before age 60 **AND** other causes of acquired cardiac disease have been excluded
- The individual to be tested has a personal history of TAD at any age **AND** an additional personal history of aneurysm **AND/OR** dissection/rupture of other arteries
- The individual to be tested has other physical findings consistent with a syndromic connective tissue disorder in which an increased genetic risk for TAD is known but the underlying diagnosis cannot be established. (Examples include, but are not limited to, Marfan syndrome, Loeys-Dietz syndrome, vascular Ehlers-Danlos syndrome, or smooth muscle dysfunction syndrome)
- The individual to be tested is currently asymptomatic but has one or more first- or second-degree blood relative(s) who are unavailable for genetic testing but had a history of TAD, unexplained sudden cardiac death, and/or aneurysms/dissections in other arteries

Genetic testing for a known pathogenic variant in a gene associated with increased genetic risk for aortopathy is **medically necessary** when **BOTH** of the following are met:

- The individual has a first- or second-degree blood relative who has a pathogenic variant associated with HTAD
- The testing is targeted to the gene of the known familial pathogenic or likely pathogenic variant

Post-mortem testing after sudden cardiac death

After sudden cardiac death, genetic testing for pathogenic variants associated with cardiac channelopathies is considered **medically necessary** on an asymptomatic individual when **ALL** the following criteria are met:

- The decedent was a first- or second-degree relative of the individual requesting the test
- Sudden cardiac death occurred at or before age 50
- The cause of sudden cardiac death remains unexplained despite the clinical history and autopsy, toxicology, and cardiac pathology findings

Amyloidosis

Genetic testing with TTR gene sequencing is considered **medically necessary** in individuals for whom a diagnosis of transthyretin amyloidosis has been confirmed in order to differentiate the hereditary variant from wild-type transthyretin amyloidosis.

Rationale

Genetic testing for certain inherited cardiomyopathy syndromes and inherited arrhythmia syndromes is recommended by cardiovascular societies. Finding a genetic cause for these inherited cardiac diseases makes an important impact by establishing a precise diagnosis, allowing predictive testing for family members, guiding choice of therapies, assisting in

reproductive decisions (including preimplantation genetic diagnosis), and providing additional prognostic information.[6] In a study of broad screening of patients with cardiomyopathy and/or arrhythmias with testing of up to 150 genes, about 30% of patients had a pathogenic or likely pathogenic variant in one of these following 8 genes associated with adverse clinical outcomes associated with hypertrophic cardiomyopathy: ACTC1, MYL2, MYBPC3, MYH7, MYL3, TNN13, TNNT2, and TPM1.[7] Likewise, about 30% of patients undergoing broad genetic screening have pathogenic variants of one of 10 genes associated with heightened arrhythmia risk: ABCC9, DES, DSP, FLNC, LMNA, PLN, RBM20, SCN5A, or TTN. However, broad testing is associated with a high rate of variants of unknown significance (VUS), with 51% of patients screened having a VUS that is not clinically actionable and leads to potential harm to patients and their families. Overdiagnosis of certain cardiomyopathies (such as left ventricular noncompaction cardiomyopathy) can lead to lower yield of useful genetic test findings and higher rates of variants of unknown significance.[7] Overall, establishing a precise clinical diagnosis, and comprehensive pre-test and post-test genetic counseling that includes robust 3-generational assessment of the family history of the particular disease[8] will generate a higher pretest probability and positive genetic testing yield and will reduce the rate of uncertain findings. Family history may be informative in determining the likelihood of finding a pathogenic variant that fits the clinical picture of a presymptomatic individual. When a suspicious family history is present, the concern for an underlying genetic risk of an inherited cardiac syndrome would be higher. We recognize that there are inherent limitations to obtaining a family history such as adoption, estrangement, or limited health information. Additional considerations for family history in the setting of cardiac arrhythmias would include inter- and intra-familial variable expression, variable penetrance, and the possibility of the individual's condition being de novo. In these cases, further clinical review may be indicated.

Cardiomyopathies represent a group of disorders of the heart muscle associated with cardiac dysfunction, aggravated by arrhythmias, heart failure, and sudden cardiac death (SCD). The most common causes of cardiomyopathy and congestive heart failure include ischemic heart disease, myocardial infarction, hypertension, and valvular heart disease. Other causes of heart failure are classified according to their structural and functional phenotypes. Rare, heritable forms of cardiomyopathy include hypertrophic cardiomyopathy (HCM), dilated cardiomyopathy (DCM), restrictive cardiomyopathy (RCM), and arrhythmogenic right ventricular (ARVC)/arrhythmogenic cardiomyopathy (ACM). These cardiomyopathies range in prevalence from 1:250 to 1:5000, with variations in frequency across different populations. In adult-onset cardiomyopathies, genetic inheritance is typically autosomal dominant, whereas in pediatric-onset cardiomyopathies, X-linked, autosomal recessive, and de novo sporadic patterns are more often observed.[9] Identifying the specific cause of heart failure is important because there may be therapeutic and additional diagnostic implications.[10]

A rare cause of cardiomyopathy is transthyretin (ATTR) amyloidosis. This is a progressive fatal disease characterized by accumulation in tissues of amyloid fibrils composed of misfolded transthyretin (TTR) protein. The diagnosis is made by endomyocardial biopsy. The acquired (wild-type) ATTR amyloidosis is an increasingly recognized cause of cardiomyopathy. A hereditary form of ATTR amyloidosis is rare and thought to be present in approximately 50,000 persons worldwide.[11] Heart failure guidelines from the American Heart Association/American College of Cardiology/Heart Failure Society of America and also the Canadian Cardiovascular Society/Canadian Heart Failure Society guidelines recommend that in patients for whom a diagnosis of ATTR amyloidosis is made, genetic testing with TTR gene sequencing is recommended to differentiate the hereditary from the wild type forms of this disease.[10, 12]

Consensus guidelines published in 2022 from the European Heart Rhythm Association (EHRA)/Heart Rhythm Society (HRS)/Asia Pacific Heart Rhythm Society (APHRS)/Latin American Heart Rhythm Society (LAHRS) distinguish syndromes for which there is significant diagnostic, prognostic, or therapeutic impact on the proband and genetic testing is recommended and considered useful from those where testing is sometimes considered by less useful.[6] Hereditary cardiomyopathic hypertrophic (HCM) and arrhythmogenic right ventricular (ARVC) cardiomyopathies were recommended for testing based on diagnostic impact. Variants in genes encoding sarcomere proteins account for 30% to 60% of HCM, with MYH7 (encoding myosin heavy chain) and MYBPC3 (encoding cardiac myosin-binding protein C) the most commonly involved genes. ARVC is caused by variants in genes encoding desmosomal proteins. With more than 50 genes contributing, dilated cardiomyopathy is genetically more heterogeneous than HCM.[9] Dilated cardiomyopathy did not receive a consensus recommendation based on diagnostic or therapeutic impact but was considered useful for prognostication.[6]

In the realm of arrhythmia syndromes, the identification of pathogenic variants associated with increased risk of sudden death may trigger consideration of primary prevention implantable cardioverter-defibrillators (ICDs) even in patients who have LVEF >0.35 or < 3 months of guideline recommended therapies.[10] Genetic testing was recommended by the 2022 consensus guidelines of the EHRA/HRS/APHRS/LAHRS for long QT syndrome based on diagnostic, prognostic, and therapeutic impact, and for catecholamine polymorphic ventricular tachycardia (CPVT) based on diagnostic impact.[6] While a lower level of evidence exists regarding the impact of genetic testing for the proband with Brugada syndrome in terms of diagnostic, prognostic, or therapeutic utility, testing was nevertheless recommended based on observational data and consensus recommendation for sequencing of SCN5A performed for an index case of Brugada syndrome. Of note, Long-QT syndrome (LQTS) is the most common heritable arrhythmia at a prevalence of ≈1:2500. There are three forms of LQTS, with variants in KCNQ1 (encoding potassium voltage-gated channel subfamily Q member 1, type 1 LQTS), KCNH2 (potassium voltage-gated channel subfamily H member 2, type 2 LQTS), and SCN5A (type 3 LQTS).[9] More rare inherited arrhythmias include catecholaminergic polymorphic ventricular tachycardia (mostly RYR2-mediated), short-QT syndrome, early repolarization syndrome, familial atrial fibrillation, familial Wolff-Parkinson-White syndrome, and conduction system defects.

Most cases of SCD are caused by coronary artery disease, and approximately 40% of cardiac arrests are unexplained. Inherited arrythmias and cardiomyopathies are important contributors to SCD. Identifying an inherited condition after such an event has important ramifications for relatives who may be at risk for the familial condition.[13] The addition of genetic testing to autopsy investigations has been shown to substantially increase the identification of possible causes of SCD among children and young adults.[14] In a case series of 109 consecutive families, a comprehensive strategy that involved cardiological evaluation of family members with genetic testing had a diagnostic yield of 18%, with the majority having LQTS and older age probands (above age 40) more likely to have Brugada syndrome.[15] There is sufficient yield in multigene panel genetic testing for channelopathies when young individuals experience otherwise unexplained SCD to support this approach in recent cardiac guidelines.[6]

A retrospective review of 1078 sudden death cases from July 2019-June 2022 evaluated through the New York City Office of the Medical Examiner (NYC-OME) included molecular genetic testing via an in-house laboratory. A broad-based panel including genes associated with channelopathies, cardiomyopathies, pulmonary embolism, sickle cell disease, and thoracic aortic disease was utilized. Of the total number of deaths, 34 (3%) were directly attributed to thoracic aortic dissection or rupture (TADR). A pathogenic or likely pathogenic variant was identified in a total of 8 individuals from this smaller cohort (23.5%), most often in the FBN1 gene (n=4). The presence of any pathogenic variant was more common among those who died young (< age 34), regardless of whether they had syndromic features. While still a small overall sample size, the authors consider molecular testing of TADR-related genes to be an essential component of post-mortem testing following SCD to both identify the genetic cause as well as to assist in the management of surviving at-risk relatives.[16]

The term aortopathy refers to any condition which predisposes an individual to aortic dilatation and/or dissection. Aortopathy may therefore be applied to both inherited as well as acquired conditions.[17] Other blood vessels may also be at risk for dilatation/dissection, but this is less common. Thoracic aortic aneurysms of the aortic root or ascending aorta are usually asymptomatic but enlarge over time. When undiagnosed, these aneurysms may lead to life-threatening acute aortic dissection. Aortic dissection may also occur in the absence of aortic aneurysm. Elective surgical repair of ascending aortic aneurysms at tertiary care centers with extensive experience is associated with a significantly lower mortality rate than when emergent surgery is required.[18] In the general population, risk factors for either thoracic or abdominal aortic aneurysms strongly overlap with those for acquired cardiac disease, such as hypertension, hyperlipidemia, smoking, and age.[19]

Hereditary aortopathies are divided into syndromic and non-syndromic conditions. Syndromic disorders are characterized by a broad phenotype impacting the vascular, skeletal, craniofacial, and/or cutaneous systems. Examples of representative connective tissue disorders include Marfan syndrome (due to variants in the FBN1 gene), Loeys-Dietz syndrome (TGFBR1, TGFBR2, SMAD3, TGFB2, TGFB3), and vascular Ehlers-Danlos syndrome (COL3A1). These conditions follow autosomal dominant inheritance with reduced penetrance and variable expressivity. Syndromic aortopathies are more likely to present with aortic aneurysm/dissection of the aortic arch and/or ascending thoracic aorta.[19] Aneurysms are more likely to occur at younger ages and progress more quickly. While clinical criteria, such as the Ghent nosology for Marfan syndrome, may exist to help establish a diagnosis, phenotypic heterogeneity may make it challenging to differentiate one condition from another; in these cases, molecular testing using a multigene panel may be beneficial.[17]

Thoracic aortic disease (TAD) may also present as an isolated finding, without other associated clinical features; hence, this entity may be referred to as non-syndromic or hereditary TAD (HTAD). Non-syndromic forms also primarily follow autosomal dominant inheritance with variable expression and penetrance. It has been estimated that up to 20% of individuals with apparently isolated TAD have at least one affected first-degree relative.[19] The presenting feature in these families is often an acute event at a younger-than-expected age, potentially even SCD, in the absence of other risk factors for acquired aneurysm/dissection or other clinical findings suggestive of a syndrome. The yield of genetic testing among those with non-syndromic TAD has historically been reported as 20%-30%[18], suggesting that a significant number of causative genes have not yet been identified.

Finally, increased risks for TAD have been variably seen among those with bicuspid aortic valve (BAV), coarctation of the aorta, and complex congenital heart defects, such as tetralogy of Fallot, transposition of the great vessels, and truncus arteriosus. While these structural anomalies, as isolated findings, are more likely to follow multifactorial inheritance, a subset have been linked to autosomal dominantly inherited pathogenic variants in genes not known to be associated with either syndromic or non-syndromic TAD, such as NOTCH1 and MAT2A.[17-20]

Renard et.al.[21], as part of the Aortopathy Working Group, evaluated 53 candidate genes associated with heritable thoracic aortic aneurysm and dissection (HTAAD) using the semiquantitative Clinical Genome Resource (ClinGen) framework. Following careful curation, the genes were classified into five categories: definitive (n=9), strong (n=2), moderate (n=4), limited (n=15), and no reported evidence (n=23). Following additional categorization of severity of associated aortic disease and risk of progression, a total of eleven genes in the definitive and strong categories were designated “HTAAD genes” (category A): ACTA2, COL3A1, FBN1, LOX, MYH11, MYLK, PRKG1, SMAD3, TGFB2, TGFBR1, TGFBR2.[18, 19] It is notable that several of these genes overlap with syndromic connective tissue disorders. Genes with moderate evidence of disease association fall under category B; these too may be included on aortopathy-related panels: EFEMP2, FOXE3, MFAP5, and SMAD2.[18]

Professional societies are supportive of molecular genetic testing as an aid in patient management for both syndromic and non-syndromic TAD.[19, 22] Personalized management recommendations may include, but are not limited to, consideration of pharmacotherapy, surveillance for aortic dilatation or other vascular disease, surgical planning, referrals to appropriate subspecialists, where appropriate, and/or exercise restrictions.[17, 22] Although genotype/phenotype correlations are not absolute in these disorders, the 2022 AHA/ACC treatment guidelines proposed surgical thresholds for prophylactic aortic root and ascending aortic repairs based on causative HTAD gene. Knowledge of the causative gene, whenever possible, also allows for cascade genetic testing of at-risk family members.[19]

Whole exome or genome sequencing has been suggested for the evaluation of an individual with thoracic aortic disease and clinical findings that overlap with other syndromes in which TAD is a rare complication. Examples of such conditions include Noonan syndrome, neurofibromatosis type I, and Alagille syndrome. However, such testing is not the standard of care and is unlikely to yield a higher rate of clinically actionable results compared to broader multigene panels.[18, 22] Individuals with these conditions are also likely to present with other physical features that help establish a clinical diagnosis without the need for WES/WGS.

Primary mitochondrial diseases

Genetic testing for primary mitochondrial disease is considered **medically necessary** when the following criteria are met (simplified modified Nijmegen criteria).

An individual has an unexplained, progressive, multi-system disorder usually involving the central nervous system and/or neuromuscular system with findings, such as:

- Brain MRI pathology associated with mitochondrial disease
- Organic acid level pattern suggestive of mitochondrial disease
- Evidence of mitochondrial dysfunction in tissue

Order of testing when above criteria have been met

1. Common **mtDNA variant(s)** testing or testing of **nuclear gene(s)** associated with the disease **IF** a specific primary mitochondrial disease is suspected (see Table 1)
2. Whole mtDNA genomic sequence and large-deletion analysis **IF** the individual's clinical presentation does **NOT** fit with a specific primary mitochondrial disorder (see Table 1) **OR** if the condition-specific test results are negative/uninformative
3. Targeted nuclear gene panel (< 25 genes) testing **IF** whole mtDNA genomic sequence and large-deletion analysis does **NOT** yield a diagnosis

Note: Whole exome sequencing is considered medically necessary in some individuals. Please refer to the Whole Exome Sequencing and Whole Genome Sequencing guidelines for the specific criteria.

Rationale

Primary mitochondrial diseases are a group of disorders caused by pathogenic variants in genes coding for the mitochondrial respiratory chain.[23, 24] The clinical features of mitochondrial diseases have enormous variation in clinical presentation and disease course. Mitochondrial disorders can affect multiple systems, including the nervous system, the visual system, the auditory system, the musculoskeletal system, the endocrine system, the pulmonary system, the digestive system and the circulatory system.[24] Neurologic and myopathic features are often the presenting symptoms of many mitochondrial disorders. The age at onset, severity, and progression of these diseases can also differ significantly.[25]

Mitochondrial DNA (mtDNA) consists of 37 genes passed on from mother to child. The remaining approximately 1400 genes coding for mitochondrial function are encoded by the nuclear genome (nDNA).[26] [27] Pathogenic variants in nuclear genes can produce similar symptoms to those caused by pathogenic variants in the primary mtDNA and are associated with autosomal dominant, autosomal recessive, X-linked or de novo inheritance patterns.[28]

Diagnosing primary mitochondrial disease is challenging due to the clinical and genetic heterogeneity of the disorders, which can affect isolated or multiple organ systems and can present at any age, complicating genotype-phenotype correlations.[29] Given the diagnostic complexity of mitochondrial disorders, authors have created and use scoring systems like the Nijmegen Mitochondrial Disease Criteria to quantify the clinical picture: evaluating the likelihood of an individual having a primary mitochondrial disease and determining the need for a muscle biopsy.[30-34]

The Mitochondrial Medicine Society (MMS) asserts there are insufficient data to create evidence-based clinical diagnostic and medical management recommendations for mitochondrial disease; however, in 2015, they published consensus-based recommendations to provide guidance to clinicians who evaluate and treat patients for mitochondrial diseases.[26] Their consensus-based recommendations detail clinical diagnosis by biochemical testing of blood, urine, and spinal fluid, DNA testing of blood and tissue, histological examination, biochemical testing of tissue and neuroimaging.[26] The MMS later published patient care standards for primary mitochondrial disease highlighting medical management considerations for select mitochondrial diseases.[35] Medical management specifications for the more common mitochondrial conditions are listed in Table 1.

The presence of both nuclear and mitochondrial DNA gene variants, along with various inheritance patterns and the possibility of heteroplasmy, further complicate the diagnostic process.[29] Determining which of the multi-system symptoms warrants genetic testing for which mitochondrial test (nDNA versus mtDNA) results in further intricacies. Additional consensus-based guidelines from a United Kingdom working group of Clinical Scientists from the National Health Service Highly Specialised Service for Rare Mitochondrial Disorders were published in 2023 to provide recommendations for the analysis of mtDNA and nuclear genes in patients suspected to have a primary mitochondrial disease.[29] The working group asserts that targeted testing for prevalent mitochondrial DNA (mtDNA) variants and large-scale mtDNA rearrangements remains appropriate. Furthermore, specific single nuclear gene testing is considered a valuable, streamlined, and expeditious first-line diagnostic tool in clinical scenarios where the associated disorder is common, the disorder is treatable with a distinct phenotype, there are identifiable common founder variants, and/or biochemical evidence suggests a defect in a specific gene.[29, 36] The working group also proposed a structured testing strategy for routine referrals, commencing with the targeted analysis of prevalent mitochondrial DNA (mtDNA) variants and candidate nuclear genes.[29] In cases where these initial tests yield negative or inconclusive results, they recommend progressing to comprehensive whole mtDNA sequencing, followed by targeted next-generation sequencing (NGS) of relevant nuclear gene panels. The authors add that genetic testing of a muscle biopsy specimen now typically only applies if the genetic test results of the blood specimen discussed above is uninformative. Stenton et al., also state that NGS analysis of the mitochondrial genome increases sensitivity compared to targeted common pathogenic mtDNA variant testing and facilitates accurate heteroplasmy assessment.[37] Furthering the diagnostic complexities, the variability in mtDNA variants across different tissues means accurate testing can require multiple sample types and methodologies to ensure comprehensive analysis.[29] Mavraki et al., and Parikh et al., recommend testing additional specimen types when results are negative for an individual with high likelihood of a primary mitochondrial disease.[26, 29]

Several authors have evaluated the clinical validity of whole genome sequencing for primary mitochondrial diseases within defined clinical cohorts, yielding promising outcomes; however, the limited sample sizes in these studies preclude the broad generalizability of the results.[34, 36, 38]

Table 1. Summary of the most common primary mitochondrial diseases[24, 26, 29, 39, 40]

Mitochondrial disorders	Inheritance	Symptoms	Gene(s) & Variant(s)	Treatment comments
General	Maternal, various	Progressive, multi-system disorder usually involving the central nervous system and/or neuromuscular system	mtDNA & nuclear genes (nDNA)	Altered preparation and cautions for anesthesia administration & muscle relaxant; avoid or limit use of propofol Avoid or use with caution the following medications: valproic acid; statins; metformin; high-dose acetaminophen; and selected antibiotics, including aminoglycosides, linezolid, tetracycline, azithromycin, and erythromycin. CoQ10, ALA, riboflavin, folinic acid & L-carnitine should be offered/administered
Kearns-Sayre syndrome (KSS)	Maternal inheritance; rarely AD	Childhood onset, progressive external ophthalmoplegia (PEO),	Large-scale mtDNA rearrangements (single & multiple)	Symptomatic & supportive therapy. Low threshold for pacemaker implantation

Mitochondrial disorders	Inheritance	Symptoms	Gene(s) & Variant(s)	Treatment comments
		pigmentary retinopathy, cardiac conduction block	**MT-TL1** deletions & variants	Treatment with folinic acid; hormone replacement
Leber hereditary optic neuropathy (LHON)	Maternal	Acute/subacute painless bilateral central vision loss	m.3460G>A **(MT-ND1)** m.11778G>A **(MT-ND4)** m.14484T>C **(MT-ND6)**	Symptomatic & supportive therapy; periodic neurologic evaluations & annual ECG
Leigh syndrome	Maternal, various	Fatal, developmental delay, hypotonia	mtDNA & nDNA	Symptomatic & supportive
MELAS (mitochondrial myopathy, encephalopathy, lactic acidosis & stroke-like episodes)	Maternal; AR or AD	mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke-like episodes	m.3243A>G (80%), m.3271T>C, m.3252A>G (**MT-TL1**) m.13513G>A (**MT-ND5**) m.8993T>G, m.8993T>C (**MT-ATP6**)	Symptomatic & supportive therapy. Treatment with arginine and citrulline reduce the effects of nitric oxide deficiency; more frequent echocardiogram (> every 1-2 years) & low threshold for pacemaker implantation. Avoid use of valproic acid (POLG)
MERRF (myoclonic epilepsy and ragged-red fibers)	Maternal	Myoclonus, seizures, cerebellar ataxia, myopathy	m.8344A> G **(MT-TK)** m.3243A>G **(MT-TL1)**	Symptomatic & supportive therapy; More frequent echocardiogram (> every 1-2 years)
Overlapping phenotypes of KSS (Kearns-Sayre syndrome); PS (Pearson syndrome); CPEO (chronic progressive external ophthalmoplegia)	Usually de novo; rare maternal	Infancy-onset, transfusion-dependent anemia, retinopathy, cardiac conduction defects, renal dysfunction	1.1-10 kb mtDNA deletions	Symptomatic & supportive therapy; Avoid prolonged treatment with propofol; volatile anesthetic hypersensitivity; more frequent echocardiogram (> every 1-2 years); annual hemoglobin A1c, thyroid-stimulating hormone, free thyroxine level, vitamin D, and screening for hypoparathyroidism; urine: creatinine, calcium, and phosphate
Pearson syndrome	Maternal	Childhood onset sideroblastic anemia, pancytopenia, exocrine pancreatic failure	2-10 kb mtDNA deletions	Blood transfusions, pancreatic enzyme replacement therapy, and treatment of infections
POLG-related disorder	AR, rarely AD	Variable phenotype Epilepsy, neuropathy, ataxia, sodium valproate toxicity	**POLG** (nDNA)	Symptomatic & supportive therapy
Thiamine metabolism dysfunction syndrome-2	AR	Childhood-onset encephalopathy	**SLC19A3** (nDNA)	Oral biotin & thiamine; antiseizure medication (avoid sodium valproate)
Mitochondrial complex V deficiency nuclear type 2	AR	Fatal, neonatal encephalo-cardiomyoapathy	**TMEM70** (nDNA)	Intensive care
Mitochondrial neurogastrointestinal encephalopathy (MNGIE)	AR	Progressive gastrointestinal dysmotility, PEO, leukoencephalopathy, demyelinating peripheral neuropathy	**TYMP** (nDNA)	Symptomatic & supportive therapy; avoid valproate, phenytoin, chloramphenicol, linezolid, aminoglycosides, and tetracycline

Neurological conditions

Genetic testing for treatment of pathogenic variants associated with inherited neurological conditions may be **medically necessary** when the general requirements **OR** multigene panel criteria listed above are met.

Genetic testing for **screening or diagnosis** of **ANY** of the following common categories of **neurological conditions** is considered **not medically necessary**:

- Alzheimer's dementia
- Frontotemporal dementias (i.e., Parkinsons's disease, Pick disease, and others)
- Motor neuron diseases (such as amyotrophic lateral sclerosis)

Single gene testing for SOD1 pathogenic variants is considered **medically necessary** when **BOTH** of the following criteria are met:

- The individual is an adult with a clinical diagnosis of amyotrophic lateral sclerosis (ALS)
- The individual is a candidate for treatment with tofersen (Qalsody) per the FDA label

Note: This guideline does not address testing to guide selection of FDA-approved therapeutics with specific indications based on biomarker test results. Please refer to the Carelon Guidelines for Pharmacogenomic Testing.

Rationale

Nearly all major disorders treated by adult and pediatric neurologists on a daily basis are influenced by phenotypic variation, with heritability typically ranging widely from 20%-70%.[41] However, Mendelian (single-gene) forms of common neurological conditions are rare, and most of these conditions are genetically complex. Traditionally, history and physical exam, laboratory testing, neurophysiology and histopathology were primarily used in the initial diagnostic approach to most conditions. The advent and accessibility of next-generation sequencing (NGS) has expanded diagnostic testing approaches that now include single gene testing, gene panels, and even whole exome sequencing (WES) in some situations.[42-44] Genetic testing may have clinical utility in this realm when it is shown to make a significant impact through one or more of the following: being cost effective by avoiding potential harm of invasive diagnostic procedures such as muscle and nerve biopsies; improving disease management and outcomes; improving the psychological impact on patients and family members by confirming an elusive diagnosis; or impacting family planning.[45-48] Table 2 summarizes the major categories of neurological conditions that are or can be inherited and the associated patterns of inheritance. The table is not all inclusive, as additional less common neurological conditions exist. The table serves as a reference and does not imply that there is clinical utility for genetic testing of all listed conditions/genes, as clinical judgement and other diagnostic modalities may have superior clinical utility for certain neurological conditions. A 2024 American College of Medical Genetics and Genomics Myotonic dystrophy type 1 testing revision confirmed the use and value of testing in symptomatic individuals and is supported in this guideline as listed in Table 2. The National Society of Genetic Counselors issued a Practice resource for genetic counseling for dystrophinopathies in 2024 which highlighted the importance of testing based on the patient's indication and cautioned clinicians about the lack of sufficient evidence for certain variant classifications as they related to care decisions especially in the absence of a family history.[49, 50]

Dementia is a prevalent chronic condition in older adults expected to affect 14 million in the United States by 2050.[51] About 25% of the general population age 55 or older have a family history of dementia in a first-degree relative, only a few hundred families with Mendelian forms of Alzheimer's disease have been reported.[52] Genetic testing for any individual genetic variation has poor predictive power for dementia and is not recommended in clinical practice.[52, 53] While there are specific genes that may be tested such as APOE, APP, PSEN1, PSEN2 and others, the diagnosis of Alzheimer's disease (AD) is clinical diagnosis of exclusion. However, the likelihood of a meaningful pathogenic variant rises if there are two or more affected first-degree relatives with early-onset dementia (diagnosed at less than 65 years of age). Only 2%-10% of those with AD have early-onset disease, and pathogenic variants are found in only 30%-50% of those individuals. While genetic testing may be diagnostic in symptomatic individuals with familial forms of Alzheimer's dementia, with dominantly inherited dementias (such as Huntington disease), and frontotemporal dementia (FTD), such testing carries ethical risks and potential individual and family harms as well.[54, 55] While early detection offers potential benefits including diagnostic closure, family planning, and opportunities for advance care planning, the potential harms may include adverse psychological responses, confusion provoked by genetic variants of unknown significance and variable penetrance, and vulnerability to discrimination. There are specialized centers that are pursuing specific protocols to further explore predictive genetic testing for inherited AD and FTD,[56] but such testing is not in standard use.

Amyotrophic lateral sclerosis (ALS) is a progressive disorder characterized by the selective degeneration of corticospinal and spinal motor neurons, resulting in progressive paralysis of the four limbs, the bulbar region, and the respiratory system, leading

to death within an average of 3–5 years after disease onset. Incidence is estimated between 1.6 and 4/100,000 person-years, with the onset generally between age 45 and 65 years. Familial forms account for approximately 10% of ALS cases with at least 25 genes having now been reproducibly implicated in familial ALS, sporadic ALS, or both.[57, 58] The genetics of ALS is complex due to genetic diversity, allelic heterogeneity, genetic pleiotropy, variable penetrance, genetic discordance and oligogenic etiology.[45] An ad hoc group of authors and selected panelists developed evidence-based consensus guidelines for ALS genetic testing and recommended that all patients with ALS should be offered genetic testing with an ALS gene panel that includes at minimum C9ORF72, SOD1, FUS, TARDBP, genes strongly associated with ALS by ClinGen and any gene for which FDA approves a targeted therapy.[59-61] Even though the FDA has approved antisense oligonucleotide therapy through accelerated approval, it is still being explored through confirmatory phase 3 trial for individuals with SOD1 ALS.[62] Thus far such treatment has not improved clinical endpoints and has been associated with adverse events.[63] Overall, ALS and FTD are conditions considered to belong to the same spectrum, and the hexanucleotide repeat expansion in C9ORF72 explains approximately 40% of familial ALS cases, 25% of familial FTD disease, and 5%–8% of apparently sporadic cases. The utility of presymptomatic genetic testing and counseling, however, is limited due to the unpredictability of the clinical phenotype and lack of clinical utility.[58, 64]

Table 2. Summary of major categories of inherited neurological conditions [57, 63, 65-73]

Selected Specific Conditions	Pattern(s) of Inheritance	Key points related to evaluation	Gene(s)	Other comments
Neuromuscular disorders				
Congenital myopathy	AD AR, X-linked	CK testing, EMG, muscle biopsy, family history	RYR1, NEM2, ACTA1, TPM2, DNM2, BIN1, MTM1, TPM3, ACTA1, TPM2, MYH7	Symptomatic & supportive therapy Experimental treatment with albuterol for central core disease and multicore disease. Gene therapy clinical trials for myotubular myopathy
Congenital muscular dystrophy (Becker, Ulrich, Bethlehem, Walker Warburg, muscle eye brain, Fukuyama)	AD, AR, X-linked	Various: Muscle biopsy, CK testing, family history	FKTN, POMT1, COL6A1, COL6A2, and COL6A3, etc.	Symptomatic & supportive therapy
- Duchenne muscular dystrophy	X-linked	CK testing, family history	DMD	Treatments include prednisone, deflazacort, eteplirsen, golodirsen, delandistrogene moxeparvovec-rokl Drugs in clinical trials
- Myotonic dystrophy 1	AD, anticipation congenital	Family history, physical examination, EMG, muscle biopsy	DMPK CTG repeats pathogenic & fully penetrant > 50; unstable premutation range 34-49 unstable	Symptomatic & supportive therapy Definitive diagnosis by genetic testing Drugs in clinical trials
- Myotonic dystrophy 2	AD	Family history, physical examination, EMG, muscle biopsy	CNBP CCTG repeat expansion Normal - ≤30 uninterrupted CCTG repeats Pathogenic 11-26 CCTG repeats with any GCTC or TCTG interrupted	Symptomatic & supportive therapy Definitive diagnosis by genetic testing
Charcot-Marie-Tooth disease	AD, AR, X-linked	Exclusion of acquired causes, family history	PMP22, GJB1/Cx32, MPZ/P0, MFN2	Symptomatic & supportive therapy
Monogenic epilepsy	AD	Testing focused on severe childhood epilepsies, and those with intellectual disability, autism, and other comorbidities	SCN1A, SCN2A, SCN8A, KCNQ2, KCNQ3, PRRT2, TSC1, TSC2, SLC6A1, SLC2A1	Precision therapy: some genetic subtypes indicate better response to specific treatments
Spinal and bulbar muscular atrophy (Kennedy disease)	X-linked	CK levels, liver enzymes: aspartate and alanine aminotransferase levels, family history	AR gene CAG repeat expansion Normal - ≤34 CAG repeats; Pathogenic - 38 CAG repeats; Incomplete penetrance with 36-37 CAG repeats	Symptomatic & supportive therapy Genetic testing is the preferred method for making a diagnosis

Selected Specific Conditions	Pattern(s) of Inheritance	Key points related to evaluation	Gene(s)	Other comments
Spinocerebellar ataxia	AD, anticipation *congenital	Brain MRI and Lab tests to rule out alternate causes, family history	SCA1,2,3,6,7*,8,17,50	Symptomatic & supportive therapy
Friedrich ataxia	AR	MRI, EMG, and tests to evaluate for diabetes and heart disease	FXN	Symptomatic & supportive therapy Treatment with omaveloxolone can improve neurological function and slow the progression of the disease Asymptomatic at-risk siblings may be offered cardiac echocardiography to screen for typical cardiac findings
Familial Parkinson's disease	Variable	Review of symptoms, neurological exam, medical and, family history including ethnicity	SCNA, LRRK2, GBA1, PRKN, PINK1, DJ-1, ATP13A2, PLA2G6, FBX07, DNAJC6, SYNJ1, VPS13C, PTRHD1	Symptomatic & supportive therapy
Spinal disorders				
Amyotrophic lateral sclerosis	Variable	History, exam, EMG, selected tests to exclude disorders that may mimic ALS, family history	SOD1, FUS, c9orf72, TARDBP, up to 25 different genes implicated	Symptomatic & supportive therapy Precision therapy: tofersen treatment for SOD1 positive individuals. 10% of cases are familial. Gene-specific therapies for *SOD1/FUS/c9orf72* in clinical trials
Hereditary spastic paraplegia	AD, AR, X-linked, mitochondrial	Brain MRI and family history including age of onset	SPG4, SPG3A, SPG231 (with AD pattern); SPG11, SPG15 (with cognitive impairment, sensory ataxia, or seizures); SPG7 (with cerebellar signs or proximal weakness or ophthalmoplegia); SPG4, SPG7, SPG31 (in absence of other indicators)	Symptomatic & supportive therapy
Cognitive disorders				
Early onset (<65 yrs) Alzheimer's disease or frontotemporal dementia	AD	Brain MRI and Lab tests to rule out alternate causes, family history	PSEN1, PSEN2, APP (in Alzheimer's disease); MAPT, GRN, C9orf72 (in frontotemporal dementia)	Symptomatic & supportive therapy
Huntington's disease	AD	Brain MRI and Lab tests to rule out alternate causes, family history	CAG repeat expansion in the HTT gene Normal - CAG repeats ≤26; Pathogenic - CAG repeats ≥36; Penetrance is incomplete with alleles of 36–39 repeats	Symptomatic & supportive therapy Tetrabenazine and deutetrabenazine treat chorea Symptomatic or at-risk individuals should have access to testing
Other diseases				
MELAS (stroke-like episodes or focal onset status epilepticus)	Maternal inheritance	Brain MRI, family history	m.3243A>G; POLG	Symptomatic & supportive therapy *Also see Whole Exome Sequencing and Whole Genome Sequencing guideline when indicated*

Selected Specific Conditions	Pattern(s) of Inheritance	Key points related to evaluation	Gene(s)	Other comments
CADASIL (Cerebral Autosomal Dominant Arteriopathy with Sub-cortical Infarcts and Leukoencephalopathy)	AD	Evaluation for family history, young age of onset, consanguinity, characteristic brain MRI features	NOTCH3	Symptomatic & supportive therapy CADASIL can be established by skin biopsy with electron microscopy showing GOM

Retinal disorders

Genetic testing for pathogenic variants associated with inherited retinal disorders may be **medically necessary** when the general requirements **OR** multigene panel criteria listed above are met.

Genetic testing for a known familial variant associated with an inherited retinal condition is **medically necessary** when **BOTH** of the following are met:

- The individual to be tested has a first- or second-degree relative with a pathogenic or likely pathogenic variant associated with an inherited retinal condition
- The testing is targeted to the gene of the known familial pathogenic or likely pathogenic variant

Rationale

Inherited retinal disorders (IRDs) are genotypically and phenotypically heterogeneous and are characterized by variably progressive loss of photoreceptor function and, ultimately, vision.[74, 75] While an individual IRD may be rare, collectively, IRDs are common with a significant impact on affected individuals and their families in terms of disease burden and healthcare needs.[74] According to the Retinal Information Network (https://retnet.org/), as of October 2024, 321 genes have been definitively linked to IRDs. The four primary IRD types encountered clinically include Rod-Cone Dystrophies (e.g., retinitis pigmentosa, congenital stationary night blindness), Cone-Rod Dystrophies (e.g., achromatopsia), Chorioretinal Degenerations (e.g., choroideremia), and Inherited Macular Dystrophies (e.g., X-linked retinoschisis, Stargardt disease, pattern dystrophy).[75] Variants in a single gene may cause more than one IRD, and a single IRD may be due to variants in more than one gene, complicating clinical diagnosis. Additionally, IRD presentation may be either isolated (non-syndromic) or syndromic with other systemic features, the latter requiring management by other specialists. Care for most IRDs is symptomatic, including correction of refractive errors and optimization of visual potential.[76] However, with FDA approval of the first gene therapy for RPE65-associated retinal disease[77], as well as the growing number of clinical trials for other IRDs, treatment options for selected IRDs are gradually expanding. Thus, genetic testing not only helps to establish an accurate diagnosis and clarify expected prognosis but also helps to identify those individuals who may benefit from targeted therapeutics.(Georgiou 2021) The diagnostic yield of genetic testing reported in the literature ranges from 40%-80% [74, 75, 78, 79], depending on molecular approach and IRD phenotype. While no single optimal method has yet been established [80], next-generation sequencing (NGS) approaches, overall, have significantly improved the likelihood of an informative result. Yield, however, needs to be counter-balanced against the likelihood of obtaining a variant of uncertain significance (VUS), particularly among those from racial and ethnic groups that are less well-characterized. Thus, testing using an IRD multigene panel is currently recommended as the most efficient 1st-tier test.[75] The panel should include genes known to be associated with syndromic forms of IRD, as some patients may not fully manifest syndromic features until later in life. Conversely, some “syndromic” genes, such as USH2A, may also be associated with non-syndromic retinal disease.[75]

The uptake of genetic testing continues to be a challenge worldwide. This is partially due to issues including access to knowledgeable genetic and/or retina specialists as well as concerns over out-of-pocket costs, the latter a particular concern in the US given its healthcare system.[81] retrospectively examined the rate of genetic testing at a single US academic referral eye center after implementation of a no-cost multigene panel sponsored by the Foundation Fighting Blindness and the commercial lab, BluePrint Genetics. The My Retina Tracker Genetic Testing Study (MRT-GTS) launched in 2017. A total of 369 patients were included in the analysis with 144 offered testing prior to the launch and 225 offered testing after its launch. The most common reason for the decline of genetic testing in the pre-launch cohort was insurance denial (29/70, 41.4%). In the post-launch cohort, genetic testing was most often not completed, because patients were lost to follow-up (27/44, 61.4%). Overall, the rate of genetic testing increased following the launch of MRT-GTS. However, other patient characteristics were identified as negatively impacting the rate of genetic testing, even when available at no-cost. These included those who identified as Black, African American, or other race and those whose primary language was not English. The authors observed that an individual’s decision to pursue genetic testing for IRDs is multifaceted and that better educational efforts are needed. Despite this, genetic testing for IRDs is considered a standard of care and is therefore appropriate for most patients with a presumed genetic retinal degeneration.[74, 75, 82]

Thrombophilia testing

Thrombophilia genetic testing for common pathogenic variants associated with Factor V Leiden and/or the prothrombin (Factor II) gene G20210A is considered **medically necessary** to inform anticoagulation decision-making when **ANY** of the following criteria are met:

- An individual with an unprovoked or weakly provoked venous thromboembolism (VTE) at or before age 50 (weakly provoking factors include immobility or minor injury, illness, or infection)
- An individual with recurrent VTE
- An individual with VTE **AND EITHER** of the following:
    - Two or more family members with a history of VTE
    - One first-degree relative with VTE at or before age 40
- An individual with VTE involving the cerebral or splanchnic veins
- An individual contemplating pregnancy who has a first-degree relative with VTE **AND** a confirmed hereditary thrombophilia
- An individual with an unprovoked VTE is planning to stop anticoagulation and a positive test for thrombophilia would change this decision

Not Medically Necessary:

MTHFR-gene variant testing for hereditary thrombophilia risk assessment is considered **not medically necessary**.

Rationale

Venous thromboembolism (VTE) occurs in approximately 1 in 1000 persons and is associated with a small risk of death (less than 5%) but a higher risk of significant morbidity due to bleeding from use of anticoagulation, pulmonary and other complications of the event, and psychological distress.[83] For those with unprovoked VTE, the risk of recurrence after stopping anticoagulation is 5%-10% after 1 year and 11%-36% after 5 years, with recurrence risks higher in men.[84]

Some individuals with VTE have an underlying genetic predisposition to the condition (inherited thrombophilia). The most common inherited thrombophilias are factor V Leiden thrombophilia (F5 gene) (heterozygous prevalence 2%-7%) and prothrombin thrombophilia (F2 gene) (heterozygous prevalence 1%-2%). The clinical penetrance of the VTE susceptibility genes, F5 and F2, is low in heterozygous carriers.[85] Genetic testing orders for F5 and F2 gene variants are common; however, the clinical indications for testing are complicated.[86] Other thrombophilias that are approached through non-genetic laboratory testing include the antiphospholipid syndrome (prevalence 2%) and more rare conditions including protein C or protein S deficiency (prevalence <0.5%) or antithrombin deficiency (prevalence 0.02%).[87]

Testing for inherited thrombophilia is controversial. Several authors have attempted to assess the utility of F5 and F2 testing on medical management and to develop testing criteria resulting in conditional recommendations and contradictory findings.[88] Factors associated with the presence of an inherited thrombophilia include VTE at age less than 50 years; a strong family history of VTE; VTE in conjunction with weak provoking factors at a young age; recurrent VTE events; and VTE in an unusual site such as the central nervous system or splanchnic veins. Although inherited and acquired thrombophilias are acknowledged to increase the risk of VTE, data showing the clinical usefulness and benefits of testing are limited or nonexistent, as are data supporting the benefit of primary or secondary VTE prophylaxis based on thrombophilia status alone.[89] Patients with inherited thrombophilia can and most often are identified and treated based on their personal and family history of VTE, even without knowledge of test results. There are limited indications for testing in some specific circumstances, particularly when stopping anticoagulation is being planned.[87, 89, 90] Several international medical societies argue against testing for F5 and F2 for recurrent pregnancy loss.[91] There are strong recommendations against testing the general population before starting oral contraceptives.[92] Some authors argue for the significance of genetic thrombophilia mutations in pregnancy loss and advocate for genetic testing in this setting.[93] However, several international medical societies argue against testing for F5 and F2 for recurrent pregnancy loss.[91] Similarly, there are mixed viewpoints and low levels of evidence to inform the role of genetic testing for women with venous thromboembolism in pregnancy.[92, 94, 95]

Individuals with cancer have a nine-fold higher risk of VTE compared to the general population.[96] Large cohort studies have established that age, cancer type, metastasis, chemotherapy, surgery, radiotherapy, and patient history of VTE are the most common risk factors contributing to VTE in individuals with cancer. One systematic review and meta-analysis examined the role of inherited thrombophilias on the risk of cancer-associated thrombosis. Individuals with cancer and an F5 or F2 gene

variant had a 2.28- and 2.14-fold increased risk of subsequent VTE, respectively, compared to individuals negative for F5 and F2 gene variants.[97] F5 and F2 gene variants may be risk factors to consider when assessing for VTE risk and deciding whether to use primary thromboprophylaxis. The American Society of Hematology (ASH) 2023 guidelines for management of venous thromboembolism guideline conditionally suggest testing for hereditary thrombophilia in ambulatory patients with cancer receiving systemic therapy who have a family history of VTE and are at low or intermediate risk for VTE based on very low certainty in the evidence about effects.[92] ASH acknowledges conditional recommendations are less likely to be applied to most patients than strong recommendations.

The common MTHFR gene variants, 677C>T and 1298A>G, are prevalent in the general population.[87] Since meta-analyses have disproven an association between the presence of these MTHFR variants and VTE, the American College of Medical Genetics and Genomics (ACMG) recommends against ordering MTHFR polymorphism genotyping as a part of a routine clinical evaluation for thrombophilia or recurrent pregnancy loss.[98] The SARS-CoV-2 infection and COVID-19 illness is associated with arterial and venous thrombosis complications, but this does not have any known implications related to thrombophilia testing.[99]

Preimplantation genetic testing

Preimplantation genetic testing (PGT) is considered **medically necessary** when the embryo(s) is at increased risk of a recognized inherited condition based on **ALL** the following:

- The medical inherited condition and gene variants being evaluated would result in significant morbidity and/or mortality
- The condition is known to result from a single gene PGT monogenic (PGT-M) abnormality, **OR** from structural changes of a gamete provider, PGT for structural rearrangements (PGT-SR)
- Gamete providers meet **ONE** of the following criteria:
    - Both gamete providers are known carriers of the same autosomal recessive condition
    - One partner is a known carrier of an autosomal recessive disorder, **AND** the couple have previously produced offspring affected by that condition
    - At least one gamete provider is a known carrier of an autosomal dominant or sex-linked condition
    - One gamete provider is at greater than or equal to 25% risk to be a carrier of an autosomal dominant single gene condition **OR** an X-linked condition based on family history **AND** is requesting non-disclosure testing (e.g., Huntington's disease; X-linked adrenoleukodystrophy)
    - At least one gamete provider is a carrier of a balanced structural chromosome abnormality
    - At least one gamete provider is an anonymous reproductive donor with unknown/unavailable carrier status when the other gamete provider is a known carrier

Preimplantation genetic testing for aneuploidy (PGT-A) is considered **medically necessary** when there is a clear heritable indication. Heritable indications include:

- X-linked recessive conditions (e.g., Duchenne muscular dystrophy, adrenoleukodystrophy, Fabry disease)
- Sex-limited conditions

Not Medically Necessary:

PGT is considered **not medically necessary** for **ALL** the following indications:

- PGT-A for indications that do NOT include a heritable risk including:
    - Advanced maternal age
    - Previous pregnancy with a trisomy
    - Recurrent pregnancy loss
    - Recurrent implantation failure
- Testing solely to determine if an embryo is a carrier of an autosomal recessive condition

- Somatic genetic changes
- Multifactorial conditions
- Polygenic risk scores/disorders (PGT-P)
- Variants of unknown significance
- Gender selection in the absence of sex-linked or sex-limited risk
- Nonmedical traits such as physical characteristics like height and eye color, etc.

Rationale

Preimplantation genetic testing

Preimplantation genetic testing (PGT) was previously termed preimplantation genetic screening (PGS) and preimplantation genetic diagnosis (PGD). PGT evaluates embryonic DNA for genetic abnormalities prior to embryo transfer. PGT can only be performed in the setting of In Vitro Fertilization (IVF). Embryos determined to be unaffected with the genetic abnormality, if available, can be selected for transfer into the uterus, significantly reducing risk of abnormality.

Three main types of PGT addressed in this guideline include preimplantation genetic testing for monogenic conditions (PGT-M), preimplantation genetic testing for structural rearrangements (PGT-SR), and preimplantation genetic testing for aneuploidy (PGT-A).

PGT-M

PGT is available for a variety of monogenic conditions. PGT-M involves testing biopsied cells from embryos produced using IVF for likely pathogenic and pathogenic single gene variants. The specific causative pathogenic or likely pathogenic gene variant(s) in the family must be known prior to initiating an IVF cycle. This often includes genetic testing on one or both gamete providers as well as other family members.

Although PGT-M can be performed for most monogenic variants, there remain some cases for which PGT-M is not technically feasible. Despite technological advances in PGT, linkage analysis is still required in many cases, and oftentimes PGT laboratories require DNA from family members for development of a probe. The highly complex and individualized nature of PGT-M necessitates case review by a PGT laboratory followed by customized test development, which should be completed prior to initiating an IVF cycle.[100]

The clinical utility of PGT-M is firmly established.[101]

PGT-SR

PGT-SR involves testing biopsied cells from embryos produced using IVF for chromosome abnormalities. Structural chromosomal rearrangements (SR) are either observed as segmental aneuploidy when unbalanced or, when balanced, usually presenting as a relatively normal phenotype, and discovered when the individual tries to conceive. Carriers of SRs are prone to infertility, repeated miscarriage, and recurrent stillbirth as well as offspring with significant congenital disorders.[102] PGT-SR cases are individualized and complex and necessitate case review by a PGT laboratory prior to initiating an IVF cycle.

There is adequate evidence to support the use of PGT for individuals that are documented carriers of a heritable chromosome abnormality.[101, 103, 104]

PGT-A

PGT-A involves testing biopsied cells from embryos produced using IVF for chromosome abnormalities. At the inception of PGT-A practice, FISH was performed to screen for common aneuploidies from single cells of cleavage stage embryos. As PGT-A became more common, so did the use of microarray technology and testing of multiple cells from the trophectoderm (TE) at the blastocyst stage.[105, 106] Next generation sequencing (NGS) is the latest PGT-A technology. NGS can identify embryos that are thought to have reduced viability and lower implantation rates, such as mosaic embryos and those with partial aneuploidies or triploidy.[107, 108]

Advances in genetic testing technology often come with larger amounts of data. NGS-based PGT-A performed on TE cells increased the rates of mosaic results. TE mosaicism has been reported to be as high as 3%-20% with more sensitive assays such as NGS.[109] Technical variables affecting the quality of biopsy, or of downstream NGS procedures, may impact the significance and clinical implication of mosaic results.[110] High rates of mosaicism in TE led to high false positive diagnoses.[111] Some mosaic embryos can and do result in healthy liveborn infants.[112] In 2021, Viotti et al. published data from an international, multi-site, case-control trial analyzing outcomes from 1,000 mosaic and 5561 euploid embryo transfers. The data provided clinical, statistically significant evidence for the traits of mosaicism identified with PGT-A that affect implantation and

spontaneous abortion, offering a guide for ranking mosaic embryos in the clinic. The publication provides PGT-A tools that identify and characterize mosaic embryos and outcomes, allowing for clinical management.[112] It is important to note that the transfer of embryos without PGT-A has been ongoing for 40 years, and a proportion of those embryos that were transferred were certainly mosaic.

Several peer-reviewed studies and authors do not support the use of PGT-A in couples undergoing IVF in the general population.[113, 114] In addition, The American Society for Reproductive Medicine (ASRM) and The American College of Obstetricians and Gynecologists (ACOG) have published committee opinions on the use of PGT-A.[100, 101] In 2018, the Practice Committee of the ASRM and the Society for Assisted Reproductive Technology released a Committee Opinion discussing studies indicating benefits of PGT-A while pointing out important limitations of the available study data.[100] Specifically, they stated that the value of PGT-A as a screening test for IVF was yet to be determined. Later in 2020, ASRM Practice Committee and Genetic Counseling Professional Group published a Committee Opinion describing management of PGT-A mosaic results and specifically stated that they did not endorse, nor suggest, that PGT-A was appropriate for all patients undergoing IVF. Also in 2020, ACOG published a Committee Opinion stating that additional research was needed to establish overall clinical utility of PGT-A.[100, 101] They recommended future research to examine the appropriate subset of patients that may benefit from PGT-A, the residual risk for aneuploidy in PGT-A euploid embryos and the clinical significance of mosaicism. In 2023, the European Society of Human Reproduction and Embryology (ESHRE) released Good Practice Recommendations stating "pre-implantation genetic testing for aneuploidy is currently not recommended for routine clinical use."[115] The Preimplantation Genetics Diagnosis International Society published a Position Statement in 2021 stating that PGT-A improves initial IVF outcomes by avoiding unwitting transfer of aneuploid embryos in morphology-based selection practices.[116]

Two recent meta-analyses of randomized control trials found that PGT-A increased the live birth rates in women of advanced maternal age (>35 years).[117, 118] In addition, findings of an international meta-analysis of randomized control trials and non-randomized studies of interventions suggest a selective positive effect of PGT-A on reproductive outcomes of patients with recurrent pregnancy loss and patients of advanced maternal age (>35 years).[119] Another meta-analysis demonstrated that an increase of maternal age is associated with lower ongoing pregnancy rates and live birth rates even after the transfer of euploid blastocysts.[120] Only one consensus-based specialty society guideline has been published on the clinical utility of PGT-A in recurrent implantation failure. The ESHRE does not recommend PGT-A for recurrent implantation failure but states it can be considered.[121]

Biomarker testing for rejection in solid organ transplantation

Use of AlloMap gene-expression profiling for monitoring adolescent and adult patients post-cardiac transplantation who are considered low risk for graft rejection is **medically necessary** when **ALL** of the following criteria are met:

- The individual is at least 15 years old and at least 6 months post-cardiac transplantation
- The individual is clinically stable and does not have signs or symptoms of congestive heart failure
- The individual does not have signs or symptoms of graft rejection or require acute treatment for rejection
- Testing is not more frequent than the following:
    - Every 3 months between month 6 and month 24 after transplantation
    - Every 6 months between month 24 and month 60 after transplantation
    - Testing does not extend beyond 60 months after transplantation

Not Medically Necessary:

Donor-derived cell free DNA testing (to include, although not limited to, AlloSure and Prospera) for use as a biomarker for diagnosis and/or monitoring of cardiac organ transplant rejection is considered **not medically necessary**.

Genetic testing (including donor-derived cell free DNA testing, gene expression profiling, or microRNA testing) for use as a biomarker for diagnosis and/or monitoring of kidney or other (non-cardiac, to include lung and liver) organ transplant rejection is considered **not medically necessary**.

Rationale

HLA incompatibility between donors and recipients who are not genetically identical is a key barrier to solid organ transplantation. This incompatibility causes a form of allograft rejection triggered by the production of antibodies directed

toward donor HLA molecules—antibody-mediated rejection. The presence of donor-specific anti-HLA antibodies is a key component of diagnosis of antibody-mediated rejection.

The monitoring of transplanted kidney is based on physical examination, urine volume, the assessment of albuminuria or proteinuria, serum creatinine, and glomerular filtration rate estimation based on serum creatinine. However, the serum creatinine level is not a biomarker able to predict or evaluate the progression of chronic injury and as a consequence is not specific or predictive.[122] The histological examination through renal biopsy remains the gold standard for diagnosis to evaluate the rejection process of the transplanted kidney. Histologically, microvascular inflammation is a key diagnostic feature of antibody-mediated rejection in all types of organ allografts.[123] Following the example of the field of oncology, in which the measurement of multigene-expression profiles in tissue has been implemented with increasing frequency, recent development of high throughput cellular and molecular biotechnologies has allowed development of new biomarkers associated with chronic renal injury, which not only provide insight into pathogenesis of chronic rejection but are also being explored for early detection.[123, 124] A wide array of biomarkers are being explored, including transcriptomic, epigenetic, proteomic, metabolomic, and cellular biomarkers[124] as well as imaging biomarkers. Urine and serum biomarkers such as NGAL, KIM-1, CXCL-10, CysC, OPN, and CLU play an essential role in detecting deteriorating renal function and are also being explored for the possibility of having an adjunctive role in the diagnosis of renal rejection alongside standard biochemical parameters and biopsy.[122]

In cardiac transplantation, endomyocardial biopsy is the current gold standard for cardiac allograft monitoring but is an expensive and invasive procedure. Although performing an endomyocardial biopsy is straightforward, the morbidity associated with this procedure motivated use of other means of diagnosing rejection. The AlloMap gene expression profile (GEP) test (manufactured by CareDx), an 11-gene expression signature derived from peripheral blood mononuclear cells, is a noninvasive test with a high negative predictive value for acute cellular rejection and noninferiority to management based on endomyocardial biopsy results in the IMAGE randomized trial.[125] The AlloMap GEP is commonly used to screen low-risk patients, defined as those who are clinically stable, have a cardiac ejection fraction of 45% or greater and no signs or symptoms of heart failure or antibody-mediated rejection. Suitable low-risk patients are then screened at pre-determined intervals, using biopsies performed only if the GEP score is abnormal. It is acknowledged that the International Society for Heart and Lung Transplantation (ISHLT) guidelines recently updated 2023 recommendations to test individuals between 2 months and 5 years post-transplant, although no new evidence justified the change—therefore, the IMAGE study continues to provide the best evidence for initiating testing at 6 months.[125, 126] Additionally, industry bias (i.e., panelists who are financially biased towards manufacturers, such as CareDx) is still problematic, as it fosters conflicts of interest with panelists' participation.

Proof of principle of a noninvasive diagnostic method based on high-throughput screening of donor-derived cell-free DNA (DD cf-DNA) has been demonstrated,[127] and similarly, early studies been conducted using specific sets of microRNAs to characterize antibody-mediated rejection[128, 129] or gene-expression profiling test.[130] Examples of such assays included Prospera (manufactured by Natera) and AlloSure (manufactured by CareDx). The clinical utility of such testing is not yet clear, and guidelines from the American Heart Association and Canadian Cardiovascular Society have not recommended such testing for routine use.[131, 132] The ISHLT 2023 guideline update also lists DD cf-DNA as an option for surveillance, although they note elsewhere in the guideline that "Promising results have been reported in observational studies…[and] that some centers have adopted DD cf-DNA for rejection surveillance…"[126] One large industry-funded registry study (the SHORE registry) evaluated 2077 subjects enrolled between 2018 and 2021 and had verified biopsy data, and were categorized as dual negative, GEP positive/dd-cfDNA negative, GEP negative/dd-cfDNA positive, or dual positive.[133] In this study, the positive likelihood ratios for acute cellular rejection were small, ranging from 1.37 for the GEP-positive alone group to 3.90 for the dual positive group. There was also a temporal trend of decline in incidence in acute cellular rejection. Among the limitations of the SHORE registry study was the fact that endomyocardial biopsies and molecular testing associated with antibody-mediated rejection were excluded from the molecular testing performance characteristics analyses. Overall, the availability of impactful evidence in this realm is limited due to retrospective designs (often small sample sizes from single institutional studies), and lack of unbiased prospective interventional clinical trials.[134, 135]

As for the use of DD cf-DNA to detect lung allograft injury in individuals with single- or double-lung transplant(s), continued investigation is underway to determine the clinical utility of such testing. And although initial promising results have been observed, additional randomized, prospective, appropriately powered, and free of industry bias studies are necessary.[136]

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Codes

The following code list is not meant to be all-inclusive. Authorization requirements will vary by health plan. Please consult the applicable health plan for guidance on specific procedure codes.

Specific CPT codes for services should be used when available. Nonspecific or not otherwise classified codes may be subject to additional documentation requirements and review.

CPT/HCPCS

May Be Medically Necessary When Criteria are Met

Code	May Be Medically Necessary When Criteria are Met
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 (atrophin1) (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 (ataxin 8 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, mytonic 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

Code	May Be Medically Necessary When Criteria are Met
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)
81228	Cytogenomic (genome-wide) analysis for constitutional chromosomal abnormalities; interrogation of genomic regions for copy number variants, comparative genomic hybridization [CGH] microarray analysis
81229	Cytogenomic (genome-wide) analysis for constitutional chromosomal abnormalities; interrogation of genomic regions for copy number and single nucleotide polymorphism (SNP) variants, comparative genomic hybridization (CGH) microarray analysis
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	GJB2 (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, and 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)
81265	Comparative analysis using Short Tandem Repeat (STR) markers; patient and comparative specimen (eg, pre-transplant recipient and donor germline testing, post-transplant non-hematopoietic recipient germline [eg, buccal swab or other germline tissue sample] and donor testing, twin zygosity testing, or maternal cell contamination of fetal cells)
81266	Comparative analysis using Short Tandem Repeat (STR) markers; each additional specimen (eg, additional cord blood donor, additional fetal samples from different cultures, or additional zygosity in multiple birth pregnancies) (List separately in addition to code for primary procedure)
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

Code	May Be Medically Necessary When Criteria are Met
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
81329	SMN1 (survival of motor neuron 1, telomeric) (eg, spinal muscular atrophy) gene analysis; dosage/deletion analysis (eg, carrier testing), includes SMN2 (survival of motor neuron 2, centromeric) analysis, if performed
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
81349	Cytogenomic (genome-wide) analysis for constitutional chromosomal abnormalities; interrogation of genomic regions for copy number and loss-of-heterozygosity variants, low-pass sequencing analysis
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
81400	Molecular pathology procedure, Level 1 (eg, identification of single germline variant [eg, SNP] by techniques such as restriction enzyme digestion or melt curve analysis)
81401	Molecular pathology procedure, Level 2 (eg, 2-10 SNPs, 1 methylated variant, or 1 somatic variant [typically using nonsequencing target variant analysis], or detection of a dynamic mutation disorder/triplet repeat)
81402	Molecular pathology procedure, Level 3 (eg, > 10 SNP's 2-10 methylated variants, or 2-10 somatic variants [typically using non-sequencing target variant analysis], immunoglobulin and T-cell receptor gene rearrangements, duplication/deletion variants of 1 exon, loss of heterozygosity [LOH], uniparental disomy [UPD])
81403	Molecular pathology procedure, Level 4 (eg, analysis of single exon by DNA sequence analysis, analysis of >10 amplicons using multiplex PCR in 2 or more independent reactions, mutation scanning or duplication/deletion variants of 2-5 exons)
81404	Molecular pathology procedure, Level 5 (eg, analysis of 2-5 exons by DNA sequence analysis, mutation scanning or duplication/deletion variants of 6-10 exons, or characterization of a dynamic mutation disorder/triplet repeat by Southern blot analysis)
81405	Molecular pathology procedure, Level 6 (eg, analysis of 6-10 exons by DNA sequence analysis, mutation scanning or duplication/deletion variants of 11-25 exons, regionally targeted cytogenomic array analysis)
81406	Molecular pathology procedure, Level 7 (eg, analysis of 11-25 exons by DNA sequence analysis, mutation scanning or duplication/deletion variants of 26-50 exons)
81407	Molecular pathology procedure, Level 8 (eg, analysis of 26-50 exons by DNA sequence analysis, mutation scanning or duplication/deletion variants of >50 exons, sequence analysis of multiple genes on one platform)
81408	Molecular pathology procedure, Level 9 (eg, analysis of >50 exons in a single gene by DNA sequence analysis)

Code	May Be Medically Necessary When Criteria are Met
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, short 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)
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
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 optic neuropathy [LHON]), genomic sequence, must include sequence analysis of entire mitochondrial genome with heteroplasmy detection
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
81479	Unlisted molecular pathology procedure
81595	Cardiology (heart transplant), mRNA, gene expression profiling by real-time quantitative PCR of 20 genes (11 content and 9 housekeeping), utilizing subfraction of peripheral blood, algorithm reported as a rejection risk score
0001U	Red blood cell antigen typing, DNA, human erythrocyte antigen gene analysis of 35 antigens from 11 blood groups, utilizing whole blood, common RBC alleles reported
0214U	Rare diseases (constitutional/heritable disorders), whole exome and mitochondrial DNA sequence analysis, including small sequence changes, deletions, duplications, short tandem repeat gene expansions, and variants in non-uniquely mappable regions, blood or saliva, identification and categorization of genetic variants, proband
0215U	Rare diseases (constitutional/heritable disorders), whole exome and mitochondrial DNA sequence analysis, including small sequence changes, deletions, duplications, short tandem repeat gene expansions, and variants in non-uniquely mappable regions, blood or saliva, identification and categorization of genetic variants, each comparator exome (eg, parent, sibling)
0216U	Neurology (inherited ataxias), genomic DNA sequence analysis of 12 common genes including small sequence changes, deletions, duplications, short tandem repeat gene expansions, and variants in non-uniquely mappable regions, blood or saliva, identification and categorization of genetic variants
0218U	Neurology (muscular dystrophy), DMD gene sequence analysis, including small sequence changes, deletions, duplications, and variants in non-uniquely mappable regions, blood or saliva, identification and characterization of genetic variants
0230U	AR (androgen receptor) (eg, spinal and bulbar muscular atrophy, Kennedy disease, X chromosome inactivation), full sequence analysis, including small sequence changes in exonic and intronic regions, deletions, duplications, short tandem repeat (STR) expansions, mobile element insertions, and variants in non-uniquely mappable regions

Code	May Be Medically Necessary When Criteria are Met
0231U	CACNA1A (calcium voltage-gated channel subunit alpha 1A) (eg, spinocerebellar ataxia), full gene analysis, including small sequence changes in exonic and intronic regions, deletions, duplications, short tandem repeat (STR) gene expansions, mobile element insertions, and variants in non-uniquely mappable regions
0232U	CSTB (cystatin B) (eg, progressive myoclonic epilepsy type 1A, Unverricht-Lundborg disease), full gene analysis, including small sequence changes in exonic and intronic regions, deletions, duplications, short tandem repeat (STR) expansions, mobile element insertions, and variants in non-uniquely mappable regions
0233U	FXN (frataxin) (eg, Friedreich ataxia), gene analysis, including small sequence changes in exonic and intronic regions, deletions, duplications, short tandem repeat (STR) expansions, mobile element insertions, and variants in non-uniquely mappable regions
0234U	MECP2 (methyl CpG binding protein 2) (eg, Rett syndrome), full gene analysis, including small sequence changes in exonic and intronic regions, deletions, duplications, mobile element insertions, and variants in non-uniquely mappable regions
0236U	SMN1 (survival of motor neuron 1, telomeric) and SMN2 (survival of motor neuron 2, centromeric) (eg, spinal muscular atrophy) full gene analysis, including small sequence changes in exonic and intronic regions, duplications and deletions, and mobile element insertions
0237U	Cardiac ion channelopathies (eg, Brugada syndrome, long QT syndrome, short QT syndrome, catecholaminergic polymorphic ventricular tachycardia), genomic sequence analysis panel including ANK2, CASQ2, CAV3, KCNE1, KCNE2, KCNH2, KCNJ2, KCNQ1, RYR2, and SCN5A, including small sequence changes in exonic and intronic regions, deletions, duplications, mobile element insertions, and variants in non-uniquely mappable regions
0254U	Reproductive medicine (preimplantation genetic assessment), analysis of 24 chromosomes using embryonic DNA genomic sequence analysis for aneuploidy, and a mitochondrial DNA score in euploid embryos, results reported as normal (euploidy), monosomy, trisomy, or partial deletion/duplications, mosaicism, and segmental aneuploidy, per embryo tested
0378U	RFC1 (replication factor C subunit 1), repeat expansion variant analysis by traditional and repeat-primed PCR, blood, saliva, or buccal swab
0417U	Rare diseases (constitutional/heritable disorders), whole mitochondrial genome sequence with heteroplasmy detection and deletion analysis, nuclear-encoded mitochondrial gene analysis of 335 nuclear genes, including sequence changes, deletions, insertions, and copy number variants analysis, blood or saliva, identification and categorization of mitochondrial disorder-associated genetic variants
0552U	Reproductive medicine (preimplantation genetic assessment), analysis for known genetic disorders from trophectoderm biopsy, linkage analysis of disease-causing locus, and when possible, targeted mutation analysis for known familial variant, reported as low-risk or high-risk for familial genetic disorder
0554U	Reproductive medicine (preimplantation genetic assessment), analysis of 24 chromosomes using DNA genomic sequence analysis from trophectoderm biopsy for aneuploidy, ploidy, a mitochondrial DNA score, and embryo quality control, results reported as normal (euploidy), monosomy, trisomy, segmental aneuploidy, triploid, haploid, or mosaic, with quality control results reported as contamination detected or inconsistent cohort when applicable, per embryo tested
0605U	Allergy and immunology (hereditary alpha tryptasemia), DNA, analysis of TPSAB1 gene copy number variation using digital PCR, whole blood, results reported with genotype specific interpretation of alpha-tryptase copy number and algorithmic classification as normal or abnormal
S3800	Genetic testing for amyotrophic lateral sclerosis (ALS)
S3841	Genetic testing for retinoblastoma
S3844	DNA analysis of the connexin 26 gene (GJB2) for susceptibility to congenital, profound deafness
S3845	Genetic testing for alpha-thalassemia
S3846	Genetic testing for hemoglobin E beta-thalassemia
S3849	Genetic testing for Niemann-Pick disease
S3850	Genetic testing for sickle cell anemia
S3853	Genetic testing for myotonic muscular dystrophy
S3861	Genetic testing, sodium channel, voltage-gated, type V, alpha subunit (SCN5A) and variants for suspected Brugada Syndrome
S3865	Comprehensive gene sequence analysis for hypertrophic cardiomyopathy
S3866	Genetic analysis for a specific gene mutation for hypertrophic cardiomyopathy (HCM) in an individual with a known HCM mutation in the family

Not Medically Necessary

Code	Not Medically Necessary
81291	MTHFR (5,10-methylenetetrahydrofolate reductase) (eg, hereditary hypercoagulability) gene analysis, common variants (eg, 677T, 1298C)

Code	Not Medically Necessary
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
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
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)
81558	Transplantation medicine (allograft rejection, kidney), mRNA, gene expression profiling by quantitative polymerase chain reaction (qPCR) of 139 genes, utilizing whole blood, algorithm reported as a binary categorization as transplant excellence, which indicates immune quiescence, or not transplant excellence, indicating subclinical rejection
0055U	Cardiology (heart transplant), cell-free DNA, PCR assay of 96 DNA target sequences (94 single nucleotide polymorphism targets and two control targets), plasma
0079U	Comparative DNA analysis using multiple selected single-nucleotide polymorphisms (SNPs), urine and buccal DNA, for specimen identity verification
0087U	Tissue rejection (allograft organ heart), mRNA gene expression analysis of 1,283 genes utilizing microarray, measuring mRNA transcript levels in transplant heart biopsy tissue, with allograft rejection and injury algorithm reported as a probability score
0088U	Tissue rejection (allograft organ kidney), mRNA gene expression analysis of 1,494 genes utilizing microarray, measuring mRNA transcript levels in transplant kidney biopsy tissue, with allograft rejection and injury algorithm reported as a probability score
0118U	Transplantation medicine, quantification of donor-derived cell-free DNA using whole genome next-generation sequencing, plasma, reported as percentage of donor-derived cell-free DNA in the total cell-free DNA
0217U	Neurology (inherited ataxias), genomic DNA sequence analysis of 51 genes including small sequence changes, deletions, duplications, short tandem repeat gene expansions, and variants in non-uniquely mappable regions, blood or saliva, identification and categorization of genetic variants
0268U	Hematology (atypical hemolytic uremic syndrome [aHUS]), genomic sequence analysis of 15 genes, blood, buccal swab, or amniotic fluid
0269U	Hematology (autosomal dominant congenital thrombocytopenia), genomic sequence analysis of 22 genes, blood, buccal swab, or amniotic fluid
0270U	Hematology (congenital coagulation disorders), genomic sequence analysis of 20 genes, blood, buccal swab, or amniotic fluid
0271U	Hematology (congenital neutropenia), genomic sequence analysis of 24 genes, blood, buccal swab, or amniotic fluid
0272U	Hematology (genetic bleeding disorders), genomic sequence analysis of 60 genes and duplication/deletion of PLAU, blood, buccal swab, or amniotic fluid, comprehensive
0273U	Hematology (genetic hyperfibrinolysis, delayed bleeding), analysis of 9 genes (F13A1, F13B, FGA, FGB, FGG, SERPINA1, SERPINE1, SERPINF2 by next-generation sequencing, and PLAU by array comparative genomic hybridization), blood, buccal swab, or amniotic fluid
0274U	Hematology (genetic platelet disorders), genomic sequence analysis of 62 genes and duplication/deletion of PLAU, blood, buccal swab, or amniotic fluid
0276U	Hematology (inherited thrombocytopenia), genomic sequence analysis of 42 genes, blood, buccal swab, or amniotic fluid
0277U	Hematology (genetic platelet function disorder), genomic sequence analysis of 40 genes and duplication/deletion of PLAU, blood, buccal swab, or amniotic fluid
0278U	Hematology (genetic thrombosis), genomic sequence analysis of 14 genes, blood, buccal swab, or amniotic fluid
0319U	Nephrology (renal transplant), RNA expression by select transcriptome sequencing, using pretransplant peripheral blood, algorithm reported as a risk score for early acute rejection
0320U	Nephrology (renal transplant), RNA expression by select transcriptome sequencing, using post-transplant peripheral blood, algorithm reported as a risk score for acute cellular rejection
0355U	APOL1 (apolipoprotein L1) (eg, chronic kidney disease), risk variants (G1, G2)
0493U	Transplantation medicine, quantification of donor-derived cell-free DNA (cfDNA) using next-generation sequencing, plasma, reported as percentage of donor-derived cell-free DNA

Code	Not Medically Necessary
0540U	Transplantation medicine, quantification of donor-derived cell-free DNA using next-generation sequencing analysis of plasma, reported as percentage of donor-derived cell-free DNA to determine probability of rejection
0553U	Reproductive medicine (preimplantation genetic assessment), analysis of 24 chromosomes using DNA genomic sequence analysis from embryonic trophectoderm for structural rearrangements, aneuploidy, and a mitochondrial DNA score, results reported as normal/balanced (euploidy/balanced), unbalanced structural rearrangement, monosomy, trisomy, segmental aneuploidy, or mosaic, per embryo tested
0555U	Reproductive medicine (preimplantation genetic assessment), analysis of 24 chromosomes using DNA genomic sequence analysis from embryonic trophectoderm for structural rearrangements, aneuploidy, ploidy, a mitochondrial DNA score, and embryo quality control, results reported as normal/balanced (euploidy/balanced), unbalanced structural rearrangement, monosomy, trisomy, segmental aneuploidy, triploid, haploid, or mosaic, with quality control results reported as contamination detected or inconsistent cohort when applicable, per embryo tested
0575U	Transplantation medicine (liver allograft rejection), miRNA gene expression profiling by RT-PCR of 4 genes (miR-122, miR-885, miR-23a housekeeping, spike-in control), serum, algorithm reported as risk of liver allograft rejection
0576U	Transplantation medicine (liver allograft rejection), quantitative donor-derived cell-free DNA (cfDNA) by whole genome next-generation sequencing, plasma and mRNA gene expression profiling by multiplex real-time PCR of 56 genes, whole blood, combined algorithm reported as a rejection risk score
0628U	Nephrology (kidney disease-related genetic conditions), genomic analysis, renal disease panel, saliva, DNA, next-generation sequencing of 449 genes, reported as pathogenic or likely pathogenic variants of uncertain significance or risk alleles
S3852	DNA analysis for APOE epsilon 4 allele for susceptibility to Alzheimer's disease

ICD-10 Diagnosis

Refer to the ICD-10 CM manual

History

Status	Review Date	Effective Date	Action
Updated codes 04/01/2026	n/a	Unchanged	CPT code update: added CPT code 0628U (NMN).
Updated codes 01/01/2026	n/a	Unchanged	CPT code update: added 0605U (MNWCM); removed termed 0508U, 0509U, 0544U (NMN).
Updated codes 10/01/2025	n/a	Unchanged	CPT code update: added 0575U and 0576U. Added 0417U (MNWCM) – moved from WES/WGS guideline (was NMN).
Revised	01/30/2025	09/20/2025	Independent Multispecialty Physician Panel (IMPP) review. New section for primary mitochondrial diseases includes mtDNA genomic sequence, large-deletion, and targeted nuclear mitochondrial gene panel analysis. Genetic testing for retinal disorders is called out as medically necessary when the general requirements or multigene panel criteria are met. Thrombophilia testing: clarified weakly provoking factors for VTE, clarified that testing for FV Leiden and F2 would change plans for anticoagulation treatment in individuals with an unprovoked VTE. Other clarifications. Added references. Added CPT codes 81460, 81465 (now MNWCM—were both NMN and moved from WES/WGS guideline), 0214U, 0215U (MNWCM).
Updated codes 07/01/2025	n/a	Unchanged	Added CPT codes 0552U, 0554U (MNWCM); 0553U, 0555U (NMN). Updated descriptions for 0269U, 0271U, 0272U, 0273U, 0274U, 0276U, 0277U, and 0278U.
Updated codes 04/01/2025	n/a	Unchanged	Added CPT codes 0540U, 0544U (NMN).
Revised	07/16/2024	03/23/2025	IMPP review. Revised general requirements for confirmatory genetic testing (expansive). Expanded criteria for hereditary cardiomyopathy syndromes in pediatric population, new criteria for hereditary aortopathies, neurological conditions (add SOD1 testing in those with ALS), thrombophilia testing (removed low bleeding risk restriction in individuals with unprovoked VTE planning to stop anti-coagulation,

Status	Review Date	Effective Date	Action
			restrictive for those contemplating estrogen use with first-degree relative with VTE and known thrombophilia). Added references.
Updated codes 01/20/2025	n/a	Unchanged	PLA code 0007U (NMN) removed from Genetic Testing Guidelines (in Lab Guidelines).
Updated codes 01/01/2025	n/a	Unchanged	CPT code update: added 81558 (NMN). Revised long descriptions for 0493U and 0508U.
Updated codes 10/01/2024	n/a	Unchanged	Added CPT codes 81479 (MNWCM), 0493U, 0508U, 0509U (NMN). Added HCPCS code S3841 (MNWCM). Removed CPT 0396U (MNWCM). Updated descriptions for 0254U and 0378U.
Revised	10/23/2023	06/30/2024	IMPP review. Preimplantation genetic testing: transferred criteria from Carrier Screening guidelines; expanded testing for gamete providers in certain scenarios; clarified the medical necessity of PGT-A when there is a clear heritable indication. Clarified the testing considered not medically necessary: MTHFR-gene variant testing for hereditary thrombophilia risk assessment, and donor-derived cell-free DNA testing for use as a biomarker for diagnosis and/or monitoring of cardiac organ transplant rejection. Updated references. Added CPT code 0007U (NMN). Moved 81410 from NMN to MNWCM.
Updated codes 03/17/2024	n/a	Unchanged	Split code list into those considered medically necessary when criteria are met (MNWCM) and not MN. Removed CPT codes 81443, 81479, 81554, and 0156U. Added required language to General Clinical Guideline per new Medicare regulations.
Updated	n/a	01/01/2024	Added CPT codes 81228, 81229, 81349, 0254U, 0378U, 0396U; removed 0004M, 0170U, 0203U, 0205U, S3841, S3842. Annual CPT update: description changes for 81171, 81172, 81243, 81244, 81406.
Created	09/21/2022	02/12/2023	IMPP review. Original effective date.