

Approval and implementation dates for specific health plans may vary. Please consult the applicable health plan for more details.

Clinical Appropriateness Guidelines

Genetic Testing

Appropriate Use Criteria: Genetic Testing for Inherited Conditions

Proprietary

© 2025 Carelon Medical Benefits Management, Inc. All rights reserved.

Table of Contents

Description and Application of the Guidelines	3
General Clinical Guideline	4
Clinical Appropriateness Framework	4
Simultaneous Ordering of Multiple Diagnostic or Therapeutic Interventions	4
Repeat Diagnostic Intervention	4
Repeat Therapeutic Intervention	5
Genetic Testing for Inherited Conditions	6
Description and Scope	6
General Recommendations	6
Genetic Counseling	6
Clinical Indications	7
General Requirements	7
Genetic testing for inherited conditions	7
Multi-gene panel testing for inherited conditions	7
Condition-Specific Requirements	8
Cardiac Conditions	8
Hereditary arrhythmia syndromes	8
Hereditary cardiomyopathy syndromes	8
Post-mortem testing after sudden cardiac death	9
Amyloidosis	9
Neurological Conditions	10
Thrombophilia Testing	14
Preimplantation Genetic Testing	14
Biomarker Testing for Rejection in Solid Organ Transplantation	17
References	18
Codes	20
History	26

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.

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 on-going 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 including single gene testing, applies to individuals who 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 multi-gene testing including but not limited to: hereditary cardiac, hereditary neurologic, thrombophilias, preimplantation genetic testing, and genetic biomarker testing of rejection in solid organ transplantation.

For specific test modalities, see separate guidelines including [Chromosomal Microarray Analysis \(CMA\)](#), [Whole Exome Sequencing \(WES\)](#) and [Whole Genome Sequencing \(WGS\)](#). For testing associated with reproduction, see [Carrier Screening in the Reproductive Setting](#) guideline.

For testing associated with hereditary cancer syndromes, see [Hereditary Cancer Screening](#) guideline.

For testing of tumor biomarkers, see [Somatic Tumor Testing](#) guideline for tumor testing criteria.

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 the 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 to have a known genetic condition based on clinical presentation or the individual may be pre-symptomatic 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 is considered **medically necessary** for an individual identified to have a pathological variant based on FDA approved direct-to-consumer genetic testing **ONLY** if **ALL** of the criteria above have been met.

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

Multi-gene panel testing for inherited conditions

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

- Any multi-gene 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** of 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:

- 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
- Individual to be tested is pre-symptomatic 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
- Known familial pathogenic variant associated with long QT syndrome, catecholamine polymorphic ventricular tachycardia (CPVT), or Brugada syndrome in a first or second degree relative
- 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, arrhythmogenic right ventricular cardiomyopathy/dysplasia (ARVC/D), or inherited dilated cardiomyopathy is considered **medically necessary** when **ALL** of the following criteria are met:

- Individual to be tested has a first-degree relative with supporting clinical features of one of the inherited cardiomyopathy syndromes named above
- 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

Post-mortem testing after sudden cardiac death

After sudden cardiac death, genetic testing for pathogenic variants associated with cardiac channelopathies are considered medically necessary when **BOTH** of the following criteria are met:

- The decedent is < 50 years old
- 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 disease⁸ 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 pre-symptomatic 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 For hereditary cardiomyopathic hypertrophic (HCM) and arrhythmogenic (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. Dilated cardiomyopathy is genetically more heterogeneous than HCM, with > 50 genes contributing.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/APHS/LAHS for long QT syndrome based on diagnostic, prognostic, and therapeutic impact, and for catecholamine polymorphic ventricular tachycardia (CPVT) based on diagnostic impact.⁶ While Brugada syndrome has a lower level of evidence regarding the impact of genetic testing for the proband in terms of diagnostic, prognostic, or therapeutic utility, it was nevertheless clearly recommended based on observational data and consensus recommendation that sequencing of SCN5A for 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 sudden cardiac death (SCD) are caused by coronary artery disease and approximately 40% of cardiac arrests are unexplained. Inherited arrhythmias 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 investigation has been shown to substantially increase the identification of a possible cause of SCD among children and young adults.¹⁴ In a case series of 109 consecutive families, a comprehensive strategy that involves cardiological evaluation of family members with genetic testing has 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 multi-gene panel genetic testing for channelopathies when young individuals experience otherwise unexplained sudden cardiac death to support this approach in recent cardiac guidelines.⁶

Neurological Conditions

Genetic testing for pathogenic variants associated with **inherited neurological conditions** may be **medically necessary** when the [general requirements](#) OR [multi-gene 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., Parkinson's disease, Pick disease, and others)
- Motor neuron diseases (such as amyotrophic lateral sclerosis)

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 [Pharmacogenomic Testing guidelines](#).

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%.¹⁶ 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.¹⁷⁻¹⁹ 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.²⁰⁻²³ [Table 1](#) 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.

Table 1. Summary of major categories of inherited neurological conditions ²⁴⁻³⁴

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 includes 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

Selected Specific Conditions	Pattern(s) of Inheritance	Key points related to evaluation	Gene(s)	Other comments
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
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, 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				

Selected Specific Conditions	Pattern(s) of Inheritance	Key points related to evaluation	Gene(s)	Other comments
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 <i>Also see Whole Exome Sequencing and Whole Genome Sequencing guideline when indicated</i>
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

Dementia is a prevalent chronic condition in older adults expected to affect 14 million in the United States by 2050.³⁵ 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.³⁶ Genetic testing for any individual genetic variation has poor predictive power for dementia and is not recommended in clinical practice.^{36, 37} 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.^{38, 39} 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 explore predictive genetic testing for inherited Alzheimer's disease and FTD further⁴⁰, 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. The 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 (add Brown RH, 28700839).⁴¹ The genetics of ALS is complex due to genetic diversity, allelic heterogeneity, genetic pleiotropy, variable penetrance, genetic discordance and oligogenic etiology.²⁰ Antisense oligonucleotide therapy is being explored for individuals with SOD1 ALS, but thus far such treatment has not improved clinical endpoints and has been associated with adverse events.³⁰ 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 pre-symptomatic genetic testing and counseling, however, is limited due to the unpredictability of the clinical phenotype and lack of clinical utility.^{41, 42}

Thrombophilia Testing

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

- Individuals with venous thromboembolism (VTE) at age 50 or under in association with unprovoking/weakly provoking factors, recurrent VTE, or strong family history of VTE
- Individuals with VTE involving the cerebral or splanchnic veins
- An individual contemplating pregnancy who has a first-degree relative with VTE and a known hereditary thrombophilia
- An individual with an unprovoked VTE and low bleeding risk is planning to stop anticoagulation, test for thrombophilia if test results would change this decision
- An individual contemplating estrogen use with a first-degree relative with VTE and a known hereditary thrombophilia test for that thrombophilia

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.⁴³ 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.⁴⁴ Occult cancer is detected in approximately 5% of patients within one year of unprovoked VTE.⁴⁵

Some individuals with VTE have an underlying genetic predisposition to the condition (inherited thrombophilia). The most common thrombophilias that involve genetic testing are Factor V Leiden (prevalence 2%-7%) and prothrombin gene G20210A mutation (1%-2%). The common MTHFR gene variants, 677C>T and 1298A>G, are prevalent in the general population.⁴⁶ Since meta-analyses have disproven an association between the presence of these variants and VTE, the American College of Medical Genetics and Genomics (ACMG) recommended "[Don't order MTHFR genetic testing for the risk assessment of hereditary thrombophilia](#)" in its contribution to the [Choosing Wisely®](#) campaign, which highlighted common tests and treatments that patients and providers should question. Other thrombophilias that are approached through other 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%).⁴⁶

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.⁴⁷ Patients with inherited thrombophilia can and most often are identified and treated on the basis of the patient's 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.^{46, 48}

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.⁴⁹

Preimplantation Genetic Testing

Preimplantation genetic testing is considered **medically necessary** when the embryo(s) is at increased risk of a recognized inherited condition based on **ALL** of 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-M) abnormality, or from structural changes of a gamete provider, preimplantation genetic testing 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
- Sex-limited conditions

Not Medically Necessary:

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

- PGT-A in the absence of heritable risk
- Testing solely to determine if an embryo is a carrier of an autosomal recessive condition
- 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 the 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.⁵⁰

The clinical utility of PGT-M is firmly established.⁵¹

PGT-SR

PGT-SR involves testing biopsied cells from embryos produced using IVF for chromosome abnormalities. Structural chromosomal rearrangements (SRs) 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.⁵² 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.^{51, 53, 54}

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.^{55, 56} 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.^{57, 58}

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.⁵⁹ Technical variables affecting the quality of biopsy, or of downstream NGS procedures, may impact the significance and clinical implication of mosaic results.⁶⁰ High rates of mosaicism in TE led to high false positive diagnoses.⁶¹ Some mosaic embryos can and do result in healthy liveborn infants.⁶² 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.⁶² 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.^{63, 64} 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.^{50, 51} 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.⁵⁰ 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.^{50, 51} 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. 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.⁶⁵

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).^{66, 67} 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).⁶⁸ No consensus-based specialty society guidelines or policies have been published on the clinical utility of PGT-A in subset patient populations.

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) 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.⁶⁹ 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.⁷⁰ 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.^{70, 71} A wide array of biomarkers are being explored, including transcriptomic, epigenetic, proteomic, metabolomic, and cellular biomarkers⁷¹ 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.⁶⁹

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.⁷² 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.^{72, 73} 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,⁷⁴ and similarly, early studies been conducted using specific sets of microRNAs to characterize antibody-mediated rejection^{75, 76} or gene-expression profiling test.⁷⁷ 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.^{78, 79} 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..."⁷³ Despite promising results, the availability of impactful evidence is extremely limited due to retrospective designs, small sample sizes, and lack of prospective studies.

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.⁸⁰

References

- Burke W. Genetic tests: clinical validity and clinical utility. *Curr Protoc Hum Genet*. 2014;81:9.15.1-9..8.
- Resta R, Biesecker BB, Bennett RL, et al. A new definition of Genetic Counseling: National Society of Genetic Counselors' Task Force report. *J Genet Couns*. 2006;15(2):77-83.
- CDC. How accessible are genetics providers and how can access be increased? 2020.
- Borno HT, Rider JR, Gunn CM. The Ethics of Delivering Precision Medicine-Pretest Counseling and Somatic Genomic Testing. *JAMA Oncol*. 2020;6(6):815-6.
- Patch C, Middleton A. Genetic counselling in the era of genomic medicine. *Br Med Bull*. 2018;126(1):27-36.
- Wilde AAM, Semsarian C, Márquez MF, et al. European Heart Rhythm Association (EHRA)/Heart Rhythm Society (HRS)/Asia Pacific Heart Rhythm Society (APHRS)/Latin American Heart Rhythm Society (LAHRS) Expert Consensus Statement on the State of Genetic Testing for Cardiac Diseases. *Heart Rhythm*. 2022;19(7):e1-e60.
- Isbister J, Sacilotto L, Semsarian C. Genetic Testing Panels in Inherited Cardiac Diseases-Does Size Really Matter? *JAMA Cardiol*. 2022.
- Ommen SR, Mital S, Burke MA, et al. 2020 AHA/ACC Guideline for the Diagnosis and Treatment of Patients With Hypertrophic Cardiomyopathy: Executive Summary: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. *Circulation*. 2020;142(25):e533-e57.
- Ahmad F, McNally EM, Ackerman MJ, et al. Establishment of Specialized Clinical Cardiovascular Genetics Programs: Recognizing the Need and Meeting Standards: A Scientific Statement From the American Heart Association. *Circ Genom Precis Med*. 2019;12(6):e000054.
- Heidenreich PA, Bozkurt B, Aguilar D, et al. 2022 AHA/ACC/HFSA Guideline for the Management of Heart Failure: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. *Circulation*. 2022;145(18):e895-e1032.
- Gillmore JD, Gane E, Taubel J, et al. CRISPR-Cas9 In Vivo Gene Editing for Transthyretin Amyloidosis. *N Engl J Med*. 2021;385(6):493-502.
- Fine NM, Davis MK, Anderson K, et al. Canadian Cardiovascular Society/Canadian Heart Failure Society Joint Position Statement on the Evaluation and Management of Patients With Cardiac Amyloidosis. *Can J Cardiol*. 2020;36(3):322-34.
- Harris SL, Lubitz SA. Clinical and genetic evaluation after sudden cardiac arrest. *J Cardiovasc Electrophysiol*. 2020;31(2):570-8.
- Bagnall RD, Weintraub RG, Ingles J, et al. A Prospective Study of Sudden Cardiac Death among Children and Young Adults. *N Engl J Med*. 2016;374(25):2441-52.
- Kumar S, Peters S, Thompson T, et al. Familial cardiological and targeted genetic evaluation: low yield in sudden unexplained death and high yield in unexplained cardiac arrest syndromes. *Heart Rhythm*. 2013;10(11):1653-60.
- Fogel BL. Genetic and genomic testing for neurologic disease in clinical practice. *Handb Clin Neurol*. 2018;147:11-22.
- Leduc-Pessah H, White-Brown A, Hartley T, et al. The Benefit of Multigene Panel Testing for the Diagnosis and Management of the Genetic Epilepsies. *Genes (Basel)*. 2022;13(5).
- Ng KWP, Chin HL, Chin AXY, et al. Using gene panels in the diagnosis of neuromuscular disorders: A mini-review. *Front Neurol*. 2022;13:997551.
- Schuermans N, Verdin H, Ghijssels J, et al. Exome Sequencing and Multigene Panel Testing in 1,411 Patients With Adult-Onset Neurologic Disorders. *Neurol Genet*. 2023;9(3):e200071.
- Benatar M, Stanislaw C, Reyes E, et al. Presymptomatic ALS genetic counseling and testing: Experience and recommendations. *Neurology*. 2016;86(24):2295-302.
- Kassardjian CD, Amato AA, Boon AJ, et al. The utility of genetic testing in neuromuscular disease: A consensus statement from the AANEM on the clinical utility of genetic testing in diagnosis of neuromuscular disease. *Muscle Nerve*. 2016;54(6):1007-9.
- Mitsumoto H, Kasarskis EJ, Simmons Z. Hastening the Diagnosis of Amyotrophic Lateral Sclerosis. *Neurology*. 2022.

23. Vidovic M, Müschen LH, Brakemeier S, et al. Current State and Future Directions in the Diagnosis of Amyotrophic Lateral Sclerosis. *Cells*. 2023;12(5).
24. Brown RH, Al-Chalabi A. Amyotrophic Lateral Sclerosis. *N Engl J Med*. 2017;377(2):162-72.
25. Corben LA, Collins V, Milne S, et al. Clinical management guidelines for Friedreich ataxia: best practice in rare diseases. *Orphanet J Rare Dis*. 2022;17(1):415.
26. Korinthenberg R, Trollmann R, Plecko B, et al. Differential Diagnosis of Acquired and Hereditary Neuropathies in Children and Adolescents-Consensus-Based Practice Guidelines. *Children (Basel)*. 2021;8(8).
27. Krey I, Platzer K, Esterhuizen A, et al. Current practice in diagnostic genetic testing of the epilepsies. *Epileptic Disord*. 2022;24(5):765-86.
28. Lin CR, Kuo SH. Ataxias: Hereditary, Acquired, and Reversible Etiologies. *Semin Neurol*. 2023;43(1):48-64.
29. Meyyazhagan A, Orlacchio A. Hereditary Spastic Paraplegia: An Update. *Int J Mol Sci*. 2022;23(3).
30. Miller TM, Cudkowicz ME, Genge A, et al. Trial of Antisense Oligonucleotide Tofersen for SOD1 ALS. *N Engl J Med*. 2022;387(12):1099-110.
31. Pal G, Cook L, Schulze J, et al. Genetic Testing in Parkinson's Disease. *Mov Disord*. 2023;38(8):1384-96.
32. Rosenberg A, Tian C, He H, et al. An evaluation of clinical presentation and genetic testing approaches for patients with neuromuscular disorders. *Am J Med Genet A*. 2023.
33. Ruf WP, Boros M, Freischmidt A, et al. Spectrum and frequency of genetic variants in sporadic amyotrophic lateral sclerosis. *Brain Commun*. 2023;5(3):fcad152.
34. Shribman S, Reid E, Crosby AH, et al. Hereditary spastic paraplegia: from diagnosis to emerging therapeutic approaches. *Lancet Neurol*. 2019;18(12):1136-46.
35. Mitchell SL. Advanced Dementia. *N Engl J Med*. 2015;373(13):1276-7.
36. Loy CT, Schofield PR, Turner AM, et al. Genetics of dementia. *Lancet*. 2014;383(9919):828-40.
37. Choudhury P, Ramanan VK, Boeve BF. APOE ε4 Allele Testing and Risk of Alzheimer Disease. *JAMA*. 2021;325(5):484-5.
38. Stoker TB, Mason SL, Greenland JC, et al. Huntington's disease: diagnosis and management. *Pract Neurol*. 2022;22(1):32-41.
39. Chiong W, Tsou AY, Simmons Z, et al. Ethical Considerations in Dementia Diagnosis and Care: AAN Position Statement. *Neurology*. 2021;97(2):80-9.
40. Galluzzi S, Mega A, Di Fede G, et al. Psychological Impact of Predictive Genetic Testing for Inherited Alzheimer Disease and Frontotemporal Dementia: The IT-DIAfN Protocol. *Alzheimer Dis Assoc Disord*. 2022;36(2):118-24.
41. Amador MDM, Gargiulo M, Boucher C, et al. Who and Why? Requests for Presymptomatic Genetic Testing for Amyotrophic Lateral Sclerosis/Frontotemporal Dementia vs Huntington Disease. *Neurol Genet*. 2021;7(1):e538.
42. Kvam KA, Benatar M, Brownlee A, et al. Amyotrophic Lateral Sclerosis Quality Measurement Set 2022 Update: Quality Improvement in Neurology. *Neurology*. 2023;101(5):223-32.
43. Kahn SR, de Wit K. Pulmonary Embolism. *N Engl J Med*. 2022;387(1):45-57.
44. Douketis J, Tosetto A, Marcucci M, et al. Risk of recurrence after venous thromboembolism in men and women: patient level meta-analysis. *Bmj*. 2011;342:d813.
45. van Es N, Le Gal G, Otten HM, et al. Screening for Occult Cancer in Patients With Unprovoked Venous Thromboembolism: A Systematic Review and Meta-analysis of Individual Patient Data. *Ann Intern Med*. 2017;167(6):410-7.
46. Stevens SM, Woller SC, Bauer KA, et al. Guidance for the evaluation and treatment of hereditary and acquired thrombophilia. *J Thromb Thrombolysis*. 2016;41(1):154-64.
47. Connors JM. Thrombophilia Testing and Venous Thrombosis. *N Engl J Med*. 2017;377(12):1177-87.
48. National Institute for Health and Care Excellence (NICE). NICE Evidence Reviews Collection. Evidence reviews for pharmacological treatment in people with suspected or confirmed deep vein thrombosis and/or pulmonary embolism: Venous thromboembolic diseases: diagnosis, management and thrombophilia testing: Evidence review D. Vol. London: National Institute for Health and Care Excellence (NICE); 2020.
49. Piazza G, Morrow DA. Diagnosis, Management, and Pathophysiology of Arterial and Venous Thrombosis in COVID-19. *JAMA*. 2020;324(24):2548-9.
50. ASRM. Indications and management of preimplantation genetic testing for monogenic conditions: a committee opinion. *Fertil Steril*. 2023;120(1):61-71.
51. American College of Obstetricians and Gynecologists (ACOG). Preimplantation Genetic Testing: ACOG Committee Opinion, Number 799. *Obstet Gynecol*. 2023;135(3):752-3.
52. De Braekeleer M, Dao TN. Cytogenetic studies in couples experiencing repeated pregnancy losses. *Hum Reprod*. 1990;5(5):519-28.
53. Griffin DK, Harton GL. Preimplantation Genetic Testing: Recent Advances in Reproductive Medicine: CRC Press; 2020.
54. Harper JC, Wilton L, Traeger-Synodinos J, et al. The ESHRE PGD Consortium: 10 years of data collection. *Hum Reprod Update*. 2012;18(3):234-47.
55. Brezina PR, Kutteh WH. Clinical applications of preimplantation genetic testing. *Bmj*. 2015;350:g7611.
56. Tobler KJ, Brezina PR, Benner AT, et al. 23-chromosome single nucleotide polymorphism (SNP) microarray preimplantation genetic screening (PGS) for recurrent pregnancy loss (RPL) in 687 in vitro fertilization (IVF) cycles and 5871 embryos. *Fertility and Sterility*. 2012;98(3, Supplement):S54.

57. Friedenthal J, Maxwell SM, Munné S, et al. Next generation sequencing for preimplantation genetic screening improves pregnancy outcomes compared with array comparative genomic hybridization in single thawed euploid embryo transfer cycles. *Fertil Steril*. 2018;109(4):627-32.
58. Sachdev NM, McCulloh DH, Kramer Y, et al. The reproducibility of trophectoderm biopsies in euploid, aneuploid, and mosaic embryos using independently verified next-generation sequencing (NGS): a pilot study. *J Assist Reprod Genet*. 2020;37(3):559-71.
59. Scott RT, Jr., Galliano D. The challenge of embryonic mosaicism in preimplantation genetic screening. *Fertil Steril*. 2016;105(5):1150-2.
60. COGEN. COGEN Position Statement on Chromosomal Mosaicism Detected in Preimplantation Blastocyst Biopsies. 2016.
61. Gleicher N, Barad DH, Patrizio P, et al. We have reached a dead end for preimplantation genetic testing for aneuploidy. *Hum Reprod*. 2022;37(12):2730-4.
62. Viotti M, Victor AR, Barnes FL, et al. Using outcome data from one thousand mosaic embryo transfers to formulate an embryo ranking system for clinical use. *Fertil Steril*. 2021;115(5):1212-24.
63. Munné S, Kaplan B, Frattarelli JL, et al. Preimplantation genetic testing for aneuploidy versus morphology as selection criteria for single frozen-thawed embryo transfer in good-prognosis patients: a multicenter randomized clinical trial. *Fertil Steril*. 2019;112(6):1071-9.e7.
64. Yan J, Qin Y, Zhao H, et al. Live Birth with or without Preimplantation Genetic Testing for Aneuploidy. *N Engl J Med*. 2021;385(22):2047-58.
65. Leigh D, Cram DS, Rechitsky S, et al. PGDIS position statement on the transfer of mosaic embryos 2021. *Reprod Biomed Online*. 2022;45(1):19-25.
66. Cheng X, Zhang Y, Deng H, et al. Preimplantation Genetic Testing for Aneuploidy With Comprehensive Chromosome Screening in Patients Undergoing In Vitro Fertilization: A Systematic Review and Meta-analysis. *Obstet Gynecol*. 2022;140(5):769-77.
67. Simopoulou M, Sfakianoudis K, Maziotis E, et al. PGT-A: who and when? A systematic review and network meta-analysis of RCTs. *J Assist Reprod Genet*. 2021;38(8):1939-57.
68. Sordia-Hernandez LH, Morales-Martinez FA, González-Colmenero FD, et al. The Effects of Preimplantation Genetic Testing for Aneuploidy (PGT-A) on Patient-Important Outcomes in Embryo Transfer Cases: A Meta-Analysis. *J Reprod Infertil*. 2022;23(4):231-46.
69. Rogulska K, Wojciechowska-Koszko I, Dołęgowska B, et al. The Most Promising Biomarkers of Allogeneic Kidney Transplant Rejection. *J Immunol Res*. 2022;2022:6572338.
70. Loupy A, Lefaucheur C. Antibody-Mediated Rejection of Solid-Organ Allografts. *N Engl J Med*. 2018;379(12):1150-60.
71. Lai X, Zheng X, Mathew JM, et al. Tackling Chronic Kidney Transplant Rejection: Challenges and Promises. *Front Immunol*. 2021;12:661643.
72. Pham MX, Teuteberg JJ, Kfoury AG, et al. Gene-expression profiling for rejection surveillance after cardiac transplantation. *N Engl J Med*. 2010;362(20):1890-900.
73. Velleca A, Shullo MA, Dhital K, et al. The International Society for Heart and Lung Transplantation (ISHLT) guidelines for the care of heart transplant recipients. *J Heart Lung Transplant*. 2023;42(5):e1-e141.
74. De Vlaminck I, Valantine HA, Snyder TM, et al. Circulating cell-free DNA enables noninvasive diagnosis of heart transplant rejection. *Sci Transl Med*. 2014;6(241):241ra77.
75. Di Francesco A, Fedrigo M, Santovito D, et al. MicroRNA signatures in cardiac biopsies and detection of allograft rejection. *J Heart Lung Transplant*. 2018;37(11):1329-40.
76. Duong Van Huyen JP, Tible M, Gay A, et al. MicroRNAs as non-invasive biomarkers of heart transplant rejection. *Eur Heart J*. 2014;35(45):3194-202.
77. Kobashigawa J, Patel J, Azarbal B, et al. Randomized pilot trial of gene expression profiling versus heart biopsy in the first year after heart transplant: early invasive monitoring attenuation through gene expression trial. *Circ Heart Fail*. 2015;8(3):557-64.
78. Colvin MM, Cook JL, Chang P, et al. Antibody-mediated rejection in cardiac transplantation: emerging knowledge in diagnosis and management: a scientific statement from the American Heart Association. *Circulation*. 2015;131(18):1608-39.
79. Chih S, McDonald M, Dipchand A, et al. Canadian Cardiovascular Society/Canadian Cardiac Transplant Network Position Statement on Heart Transplantation: Patient Eligibility, Selection, and Post-Transplantation Care. *Can J Cardiol*. 2020;36(3):335-56.
80. Keller M, Agbor-Enoh S. Cell-free DNA in lung transplantation: research tool or clinical workhorse? *Curr Opin Organ Transplant*. 2022;27(3):177-83.

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

CPT® (Current Procedural Terminology) is a registered trademark of the American Medical Association (AMA). CPT® five-digit codes, nomenclature and other data are copyright by the American Medical Association. All Rights Reserved. AMA does not directly or indirectly practice medicine or dispense medical services. AMA assumes no liability for the data contained herein or not contained herein.

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 (ataxin1) (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, myotonic dystrophy type 2) gene analysis, evaluation to detect abnormal (eg, expanded alleles)
81188	CSTB (cystatin B) (eg, Unverricht-Lundborg disease) gene analysis; evaluation to detect abnormal (eg, expanded) alleles
81189	CSTB (cystatin B) (eg, Unverricht-Lundborg disease) gene analysis; full gene sequence
81190	CSTB (cystatin B) (eg, Unverricht-Lundborg disease) gene analysis; known familial variant(s)
81200	ASPA (aspartoacylase) (eg, Canavan disease) gene analysis, common variants (eg, E285A, Y231X)
81204	AR (androgen receptor) (eg, spinal and bulbar muscular atrophy, Kennedy disease, X chromosome inactivation) gene analysis; characterization of alleles (eg, expanded size or methylation status)
81205	BCKDHB (branched-chain keto acid dehydrogenase E1, beta polypeptide) (eg, maple syrup urine disease) gene analysis, common variants (eg, R183P, G278S, E422X)
81209	BLM (Bloom syndrome, RecQ helicase-like) (eg, Bloom syndrome) gene analysis, 2281del6ins7 variant
81220	CFTR (cystic fibrosis transmembrane conductance regulator) (eg, cystic fibrosis) gene analysis; common variants (eg, ACMG/ACOG guidelines)
81221	CFTR (cystic fibrosis transmembrane conductance regulator) (eg, cystic fibrosis) gene analysis; known familial variants
81222	CFTR (cystic fibrosis transmembrane conductance regulator) (eg, cystic fibrosis) gene analysis; duplication/deletion variants
81223	CFTR (cystic fibrosis transmembrane conductance regulator) (eg, cystic fibrosis) gene analysis; full gene sequence
81224	CFTR (cystic fibrosis transmembrane conductance regulator) (eg, cystic fibrosis) gene analysis; intron 8 poly-T analysis (eg, male infertility)
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

Code	May Be Medically Necessary When Criteria are Met
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])
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 t
81269	HBA1/HBA2 (alpha globin 1 and alpha globin 2) (eg, alpha thalassemia, Hb Bart hydrops fetalis syndrome, HbH disease), gene analysis; duplication/deletion variants
81271	HTT (huntingtin) (eg, Huntington disease) gene analysis; evaluation to detect abnormal (eg, expanded) alleles
81274	HTT (huntingtin) (eg, Huntington disease) gene analysis; characterization of alleles (eg, expanded size)
81284	FXN (frataxin) (eg, Friedreich ataxia) gene analysis; evaluation to detect abnormal (expanded) alleles
81285	FXN (frataxin) (eg, Friedreich ataxia) gene analysis; characterization of alleles (eg, expanded size)
81286	FXN (frataxin) (eg, Friedreich ataxia) gene analysis; full gene sequence
81289	FXN (frataxin) (eg, Friedreich ataxia) gene analysis; known familial variant(s)
81290	MCOLN1 (mucolipin 1) (eg, Mucopolipidosis, 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)

Code	May Be Medically Necessary When Criteria are Met
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)
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, TGFB1, TGFB2, 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 TGFB1, TGFB2, 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

Code	May Be Medically Necessary When Criteria are Met
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
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
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
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
S3800	Genetic testing for amyotrophic lateral sclerosis (ALS)
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

Code	May Be Medically Necessary When Criteria are Met
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)
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
0007U	Drug test(s), presumptive, with definitive confirmation of positive results, any number of drug classes, urine, includes specimen verification including DNA authentication in comparison to buccal DNA, per date of service
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 14 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 23 genes, blood, buccal swab, or amniotic fluid
0272U	Hematology (genetic bleeding disorders), genomic sequence analysis of 51 genes, blood, buccal swab, or amniotic fluid, comprehensive
0273U	Hematology (genetic hyperfibrinolysis, delayed bleeding), genomic sequence analysis of 8 genes (F13A1, F13B, FGA, FGB, FGG, SERPINA1, SERPINE1, SERPINF2, PLAU), blood, buccal swab, or amniotic fluid
0274U	Hematology (genetic platelet disorders), genomic sequence analysis of 43 genes, blood, buccal swab, or amniotic fluid
0276U	Hematology (inherited thrombocytopenia), genomic sequence analysis of 23 genes, blood, buccal swab, or amniotic fluid

Code	Not Medically Necessary
0277U	Hematology (genetic platelet function disorder), genomic sequence analysis of 31 genes, blood, buccal swab, or amniotic fluid
0278U	Hematology (genetic thrombosis), genomic sequence analysis of 12 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 posttransplant 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
0508U	Transplantation medicine, quantification of donor-derived cell-free DNA using 40 single-nucleotide polymorphisms (SNPs), plasma, and urine, initial evaluation reported as percentage of donor-derived cell-free DNA with risk for active rejection
0509U	Transplantation medicine, quantification of donor-derived cell-free DNA using up to 12 single-nucleotide polymorphisms (SNPs) previously identified, plasma, reported as percentage of donor-derived cell-free DNA with risk for active rejection
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 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). Removed CPT 0396U (MNWCM). Updated descriptions for 0254U and 0378U.
Revised	10/23/2023	06/30/2024	Independent Multispecialty Physician Panel (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 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 CPT code 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.