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Clinical Appropriateness Guidelines

Genetic Testing

Appropriate Use Criteria: Genetic Testing for Inherited Conditions

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Description and Application of the Guidelines

The Carelon Clinical Appropriateness Guidelines (hereinafter “the Carelon Clinical Appropriateness Guidelines” or the “Guidelines”) are designed to assist providers in making the most appropriate treatment decision for a specific clinical condition for an individual. As used by Carelon, the Guidelines establish objective and evidence-based criteria for medical necessity determinations where possible. In the process, multiple functions are accomplished:

- To establish criteria for when services are medically necessary (i.e., in general, shown to be effective in improving health outcomes and considered the most appropriate level of service)
- 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 advocate for 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 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. Relevant citations are included in the References section attached to each Guideline. Carelon reviews all of its Guidelines at least annually.

Carelon makes its Guidelines publicly available on its website twenty-four hours a day, seven days a week. Copies of the Carelon Clinical Appropriateness Guidelines are also available upon oral or written request. 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. If requested by a health plan, Carelon will review requests based on health plan medical policy/guidelines in lieu of the Carelon Guidelines. Pharmaceuticals, radiotracers, or medical devices used in any of the diagnostic or therapeutic interventions listed in the Guidelines must be FDA approved or conditionally approved for the intended use. However, 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 should outweigh any potential harms that may result (net benefit).
- Current literature and/or standards of medical practice should support that the recommended intervention offers the greatest net benefit among competing alternatives.
- Based on the clinical evaluation, current literature, and standards of medical practice, there exists a reasonable likelihood that the intervention will change management and/or lead to an improved outcome for the patient.

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 supersede the requirements set forth above. During the peer-to-peer conversation, factors such as patient acuity and setting of service may also be taken into account.

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.

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 ethnicity. The clinical utility of such testing may include making a definitive diagnosis or offering important prognostic information that may 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, hereditary cardiac, neurogenetic, thrombophilia testing, and genetic biomarkers 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 Prenatal 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

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

- Interpretation of family and medical histories to assess the probability of 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
- Post-test counseling for any positive screening test

Rationale

Genetic testing is a procedure that involves risk that accompanies its potential benefits. The clinician 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] Genetic counselors provide a patient-centered contribution to the care of individuals who are undergoing genetic testing. Genetic counseling is a communication process aimed at helping people understand and adapt to the medical, psychological, and familial implications of genetic contributions to disease.[2] Genetic counselors have advanced training in medical genetics and counseling which helps guide and support patients seeking more information about how inherited diseases and conditions might affect them or their families. This expertise is also applied to interpret genetic test results based on an individual's personal and family history. Genetic counselors are often specialized in prenatal, pediatric, oncology, neurology, ophthalmology, psychiatry, and many other areas.

The current literature demonstrates the clinical value of genetic counselor involvement in service delivery, including improvements in clinical management and positive psychological impact along with increased patient engagement. Physicians have varying levels of knowledge on how to interpret genetic and genomic information, and often express low confidence and high uncertainty in counseling about genetic testing findings.[3] Professional genetic counselors add unique value to the existing care team.

In the past decade, there has been explosive growth in the number of genetic tests available, the number and types of companies involved in providing these tests, diversity of the business models involved, and the diverse settings where genetic tests are accessed by consumers. There is access to some kinds of testing through direct-to-consumer channels, but most of the healthcare-associated testing is from full-service commercial laboratories, for-profit specialized laboratories, or not-for-profit laboratories, such as those associated with academic medical centers.[4] While laboratory business models vary widely, there is increasing interest in use of de-identified data from genetic testing for use in research and discovery and other business purposes beyond the application to individual patient care. These other uses of genetic information have partly fueled a trend for broader indications for testing and testing of larger panels of genes. Furthermore, while genetic counselors have traditionally been trained to counsel patients in healthcare settings prior to germline testing for diseases with a Mendelian inheritance pattern, their education and skills can also be readily adapted to other settings. Genetic testing services are now delivered both in person and via telehealth, and counselors may be employed not only by healthcare institutions but also by laboratories working under various distinct business models.

Genomic technologies generate large amounts of data, and this increases the potential for uncertainty in managing and adapting to this information. 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.[5] Uncovering incidental findings and being overwhelmed with information are important barriers to genetic testing, particularly among vulnerable patient subgroups.[6] 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. Clinicians are often required to stretch their skillsets and play a role in providing basic counseling about genetic testing and will need more training and skills to do so effectively. Further research is needed regarding the use of clinical practice tools to enhance patient care and uphold the clinical and ethical ideals of medical care in this complicated realm of care delivery.

The use of genetic counseling by professionals not employed by testing laboratories is strongly recommended for a wide variety of common clinical scenarios across all realms of medicine. Genetic counseling is considered mandatory for a subset of clinical scenarios related to germline or somatic testing where the stakes are predictably high in terms of the potential medical and psychological consequences of the testing process. The specific scenarios for which genetic counseling is mandatory and the minimum expected qualifications for genetic counseling providers may vary by health plan.

Clinical Indications

General Requirements

Genetic testing for inherited conditions

Genetic testing is considered **medically necessary** for an individual when **ALL** of 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 screened for 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 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, or therapeutic) of the individual

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.

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

**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.*

Multi-gene panel testing for inherited conditions

Panel testing may be considered when all general and condition-specific criteria are met as well as all of the following:

- 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 must have evidence to show their association with the condition as well as important in management.
- A tiered approach to testing, with reflex to more detailed testing, should be undertaken where clinically appropriate

Rationale

Mendelian disorders and monogenic traits result from combinations of variants in 1 or a few genes that have a large effect on the propensity for developing a certain condition or characteristic. While various common conditions are covered by specific guideline criteria, it is not feasible to establish criteria for every Mendelian disorder and monogenic trait. This general guideline describes criteria for testing for a single gene or a focused panel of genes in order 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 ALL 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: Hereditary cardiac conditions

Genetic testing for certain inherited cardiomyopathy syndromes and inherited arrhythmia syndromes are 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.[7] 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.[8] 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.[8] Overall, establishing a precise clinical diagnosis, and comprehensive pre-test and post-test genetic counseling that includes robust 3-generational assessment of the family history of the particular disease[9] 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.[10] Identifying the specific cause of heart failure is important because there may be therapeutic and additional diagnostic implications.[11]

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.[12] 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.[11, 13]

Consensus guidelines published in 2022 from the European Heart Rhythm Association (EHRA)/HeartRhythm Society (HRS)/Asia Pacific Heart RhythmSociety (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.[7] 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 .[10] Dilated cardiomyopathy did not receive a consensus recommendation based on diagnostic or therapeutic impact but was considered useful for prognostication.[7]

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.[11] Genetic testing was recommended by the 2022 consensus guidelines of the EHRA/HRS/APHRS/LAHRS for long QT syndrome based on diagnostic, prognostic, and therapeutic impact, and for catecholamine polymorphic ventricular tachycardia (CPVT) based on diagnostic impact.[7] 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, is 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).[10] 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 arrythmias and cardiomyopathies are important contributors to SCD. Identifying an inherited condition after such an event has important ramifications for relatives who may be at risk for the familial condition.[14] 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.[15] 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.[16] 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.[7]

Neurologic conditions

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

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

Rationale: Hereditary neurologic conditions

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%.[17] However, Mendelian (single-gene) forms of common neurological conditions are rare and most of these conditions are genetically complex. For example, although 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.[18] Genetic testing for any individual genetic variation has poor predictive power for dementia and is not recommended in clinical practice.[18] 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). However, only 2%-10% of those with AD have early-onset disease, and genetic mutations 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, and with dominantly inherited dementias (such as Huntington disease) frontotemporal dementia, such testing carries ethical risks ad potential individual and family harms as well.[19] 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.

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 4 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.[20] ALS and frontotemporal dementia (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.[20]

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 VTE at age 50 or under in association with either weak 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

Rationale: Thrombophilia testing

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.[21] 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.[22] Occult cancer is detected in approximately 5% of patients within one year of unprovoked VTE.[23]

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. Recent meta-analyses have disproven an association between the presence of these variants and venous thromboembolism and the American College of Medical Genetics and Genomics (ACMG) included the statement "do not order MTHFR genetic testing for the risk assessment of hereditary thrombophilia" as part of their contribution to the *Choosing Wisely* campaign targeting five things patients and providers should question. Other thrombophilias that are approached through other laboratory testing include the antiphospholipid syndrome (prevalence 2%), and other more rare conditions including protein C or protein S deficiency (prevalence < 0.5%) or antithrombin deficiency (prevalence 0.02%).[24]

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.[25] 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.[24, 26]

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.[27]

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:

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) organ transplant rejection is considered **not medically necessary**.

Rationale: Biomarker testing for rejection in solid organ transplantation

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.[28] 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.[29] 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.[29, 30] A wide array of biomarkers are being explored, including transcriptomic, epigenetic, proteomic, metabolomic, and cellular biomarkers[30] 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.[28]

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, 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.[31] 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.

Proof of principle of a noninvasive diagnostic method based on high-throughput screening of circulating cell-free donor-derived DNA (cfdDNA) has been demonstrated,[32] and similarly, early studies been conducted using specific sets of microRNAs to characterize antibody-mediated rejection[33, 34] or gene-expression profiling test.[35] The clinical utility of such testing is not yet clear, and guidelines from the American Heart Association and Canadian Cardiovascular Society have no recommended such testing for routine use.[36, 37]

References

1. Knob AL. Principles of genetic testing and genetic counseling for renal clinicians. Semin Nephrol. 2010;30(4):431-7. Epub 2010/09/03. PMID: 20807616
2. Patch C, Middleton A. Genetic counselling in the era of genomic medicine. Br Med Bull. 2018;126(1):27-36. Epub 2018/04/05. PMID: 29617718
3. Gray SW, Hicks-Courant K, Cronin A, et al. Physicians' attitudes about multiplex tumor genomic testing. J Clin Oncol. 2014;32(13):1317-23. Epub 2014/03/26. PMID: 24663044
4. Scheuner MT, Douglas MP, Sales P, et al. Laboratory business models and practices: implications for availability and access to germline genetic testing. Genet Med. 2021;23(9):1681-8. Epub 2021/05/08. PMID: 33958748
5. Pollard S, Sun S, Regier DA. Balancing uncertainty with patient autonomy in precision medicine. Nat Rev Genet. 2019;20(5):251-2. Epub 2019/03/16. PMID: 30872766
6. 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. Epub 2020/03/13. PMID: 32163096
7. 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. Epub 2022/04/08. PMID: 35390533
8. Isbister J, Sacilotto L, Semsarian C. Genetic Testing Panels in Inherited Cardiac Diseases-Does Size Really Matter? JAMA Cardiol. 2022. Epub 2022/08/11. PMID: 35947367
9. 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. Epub 2020/11/21. PMID: 33215938
10. 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. Epub 2019/05/24. PMID: 31117808
11. 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. Epub 2022/04/02. PMID: 35363499
12. 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. Epub 2021/07/03. PMID: 34215024
13. 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. Epub 2020/03/09. PMID: 32145862
14. Harris SL, Lubitz SA. Clinical and genetic evaluation after sudden cardiac arrest. Journal of cardiovascular electrophysiology. 2020;31(2):570-8. Epub 2020/01/08. PMID: 31909521
15. 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. Epub 2016/06/23. PMID: 27332903
16. 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. Epub 2013/08/27. PMID: 23973953
17. Fogel BL. Genetic and genomic testing for neurologic disease in clinical practice. Handb Clin Neurol. 2018;147:11-22. Epub 2018/01/13. PMID: 29325607
18. Loy CT, Schofield PR, Turner AM, et al. Genetics of dementia. Lancet. 2014;383(9919):828-40. Epub 2013/08/10. PMID: 23927914
19. Chiong W, Tsou AY, Simmons Z, et al. Ethical Considerations in Dementia Diagnosis and Care: AAN Position Statement. Neurology. 2021;97(2):80-9. Epub 2021/09/16. PMID: 34524968
20. 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. Epub 2020/12/31. PMID: 33376800
21. Kahn SR, de Wit K. Pulmonary Embolism. N Engl J Med. 2022;387(1):45-57. Epub 2022/07/07. PMID: 35793208

22. 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. Epub 2011/02/26. PMID: 21349898
23. 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. Epub 2017/08/23. PMID: 28828492
24. 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. Epub 2016/01/19. PMID: 26780744
25. Connors JM. Thrombophilia Testing and Venous Thrombosis. N Engl J Med. 2017;377(12):1177-87. Epub 2017/09/21. PMID: 28930509
26. 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. London: National Institute for Health and Care Excellence (NICE); 2020.
27. Piazza G, Morrow DA. Diagnosis, Management, and Pathophysiology of Arterial and Venous Thrombosis in COVID-19. JAMA. 2020;324(24):2548-9. Epub 2020/11/24. PMID: 33226423
28. Rogulska K, Wojciechowska-Koszko I, Dołęgowska B, et al. The Most Promising Biomarkers of Allogeneic Kidney Transplant Rejection. J Immunol Res. 2022;2022:6572338. Epub 2022/06/08. PMID: 35669103
29. Loupy A, Lefaucheur C. Antibody-Mediated Rejection of Solid-Organ Allografts. N Engl J Med. 2018;379(12):1150-60. Epub 2018/09/20. PMID: 30231232
30. Lai X, Zheng X, Mathew JM, et al. Tackling Chronic Kidney Transplant Rejection: Challenges and Promises. Front Immunol. 2021;12:661643. Epub 2021/06/08. PMID: 34093552
31. 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. Epub 2010/04/24. PMID: 20413602
32. 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. Epub 2014/06/20. PMID: 24944192
33. 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. Epub 2018/09/04. PMID: 30174164
34. 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. Epub 2014/09/02. PMID: 25176944
35. 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. Epub 2015/02/24. PMID: 25697852
36. 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. Epub 2015/04/04. PMID: 25838326
37. 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. Epub 2020/03/09. PMID: 32145863

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

81161	DMD (dystrophin) (eg, Duchenne/Becker muscular dystrophy) deletion analysis, and duplication analysis, if performed
81171	AFF2 (AF4/FMR2 family, member 2 [FMR2]) (eg, fragile X mental retardation 2 [FRAXE]) gene analysis; evaluation to detect abnormal (eg, expanded) alleles
81172	AFF2 (AF4/FMR2 family, member 2 [FMR2]) (eg, fragile X mental retardation 2 [FRAXE]) gene analysis; characterization of alleles (eg, expanded size and methylation status)

81173	AR (androgen receptor) (eg, spinal and bulbar muscular atrophy, Kennedy disease, X chromosome inactivation) gene analysis; full gene sequence
81174	AR (androgen receptor) (eg, spinal and bulbar muscular atrophy, Kennedy disease, X chromosome inactivation) gene analysis; known familial variant
81177	ATN1 (atrophin1) (eg, dentatorubral-pallidoluysian atrophy) gene analysis, evaluation to detect abnormal (eg, expanded) alleles
81178	ATXN1 (ataxin 1) (eg, spinocerebellar ataxia) gene analysis, evaluation to detect abnormal (eg, expanded) alleles
81179	ATXN2 (ataxin 2) (eg, spinocerebellar ataxia) gene analysis, evaluation to detect abnormal (eg, expanded) alleles
81180	ATXN3 (ataxin 3) (eg, spinocerebellar ataxia, Machado-Joseph disease) gene analysis, evaluation to detect abnormal (eg, expanded) alleles
81181	ATXN7 (ataxin 7) (eg, spinocerebellar ataxia) gene analysis, evaluation to detect abnormal (eg, expanded) alleles
81182	ATXN8OS (ataxin 8 opposite strand [non-protein coding]) (eg, spinocerebellar ataxia) gene analysis, evaluation to detect abnormal (eg, expanded) alleles
81183	ATXN10 (ataxin 10) (eg, spinocerebellar ataxia) gene analysis, evaluation to detect abnormal (eg, expanded) alleles
81184	CACNA1A (calcium voltage-gated channel subunit alpha1 A) (eg, spinocerebellar ataxia) gene analysis; evaluation to detect abnormal (eg, expanded) alleles
81185	CACNA1A (calcium voltage-gated channel subunit alpha1 A) (eg, spinocerebellar ataxia) gene analysis; full gene sequence
81186	CACNA1A (calcium voltage-gated channel subunit alpha1 A) (eg, spinocerebellar ataxia) gene analysis; known familial variant
81187	CNBP (CCHC-type zinc finger nucleic acid binding protein) (eg, mytonic dystrophy type 2) gene analysis, evaluation to detect abnormal (eg, expanded alleles
81188	CSTB (cystatin B) (eg, Unverricht-Lundborg disease) gene analysis; evaluation to detect abnormal (eg, expanded) alleles
81189	CSTB (cystatin B) (eg, Unverricht-Lundborg disease) gene analysis; full gene sequence
81190	CSTB (cystatin B) (eg, Unverricht-Lundborg disease) gene analysis; known familial variant(s)
81200	ASPA (aspartoacylase) (eg, Canavan disease) gene analysis, common variants (eg, E285A, Y231X)
81204	AR (androgen receptor) (eg, spinal and bulbar muscular atrophy, Kennedy disease, X chromosome inactivation) gene analysis; characterization of alleles (eg, expanded size or methylation status)
81205	BCKDHB (branched-chain keto acid dehydrogenase E1, beta polypeptide) (eg, maple syrup urine disease) gene analysis, common variants (eg, R183P, G278S, E422X)
81209	BLM (Bloom syndrome, RecQ helicase-like) (eg, Bloom syndrome) gene analysis, 2281del6ins7 variant
81220	CFTR (cystic fibrosis transmembrane conductance regulator) (eg, cystic fibrosis) gene analysis; common variants (eg, ACMG/ACOG guidelines)
81221	CFTR (cystic fibrosis transmembrane conductance regulator) (eg, cystic fibrosis) gene analysis; known familial variants
81222	CFTR (cystic fibrosis transmembrane conductance regulator) (eg, cystic fibrosis) gene analysis; duplication/deletion variants
81223	CFTR (cystic fibrosis transmembrane conductance regulator) (eg, cystic fibrosis) gene analysis; full gene sequence
81224	CFTR (cystic fibrosis transmembrane conductance regulator) (eg, cystic fibrosis) gene analysis; intron 8 poly-T analysis (eg, male infertility)
81234	DMPK (DM1 protein kinase) (eg, myotonic dystrophy type 1) gene analysis; evaluation to detect abnormal (expanded) alleles
81238	F9 (coagulation factor IX) (eg, hemophilia B), full gene sequence
81239	DMPK (DM1 protein kinase) (eg, myotonic dystrophy type 1) gene analysis; characterization of alleles (eg, expanded size)
81240	F2 (prothrombin, coagulation factor II) (eg, hereditary hypercoagulability) gene analysis, 20210G>A variant
81241	F5 (coagulation Factor V) (eg, hereditary hypercoagulability) gene analysis, Leiden variant
81242	FANCC (Fanconi anemia, complementation group C) (eg, Fanconi anemia, type C) gene analysis, common variant (eg, IVS4+4A>T)
81243	FMR1 (fragile X mental retardation 1) (eg, fragile X mental retardation) gene analysis; evaluation to detect abnormal (eg, expanded) alleles
81244	FMR1 (fragile X mental retardation 1) (eg, fragile X mental retardation) 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, Mucolipidosis, type IV) gene analysis, common variants (eg, IVS3-2A>G, del6.4kb)
81291	MTHFR (5,10-methylenetetrahydrofolate reductase) (eg, hereditary hypercoagulability) gene analysis, common variants (eg, 677T, 1298C)
81302	MECP2 (methyl CpG binding protein 2) (eg, Rett syndrome) gene analysis; full sequence analysis
81303	MECP2 (methyl CpG binding protein 2) (eg, Rett syndrome) gene analysis; known familial variant
81304	MECP2 (methyl CpG binding protein 2) (eg, Rett syndrome) gene analysis; duplication/deletion variants
81312	PABPN1 (poly[A] binding protein nuclear 1) (eg, oculopharyngeal muscular dystrophy) gene analysis, evaluation to detect abnormal (eg, expanded) alleles
81324	PMP22 (peripheral myelin protein 22) (eg, Charcot-Marie-Tooth, hereditary neuropathy with liability to pressure palsies) gene analysis; duplication/deletion analysis
81325	PMP22 (peripheral myelin protein 22) (eg, Charcot-Marie-Tooth, hereditary neuropathy with liability to pressure palsies) gene analysis; full sequence analysis
81326	PMP22 (peripheral myelin protein 22) (eg, Charcot-Marie-Tooth, hereditary neuropathy with liability to pressure palsies) gene analysis; known familial variant
81329	SMN1 (survival of motor neuron 1, telomeric) (eg, spinal muscular atrophy) gene analysis; dosage/deletion analysis (eg, carrier testing), includes SMN2 (survival of motor neuron 2, centromeric) analysis, if performed
81330	SMPD1(sphingomyelin phosphodiesterase 1, acid lysosomal) (eg, Niemann-Pick disease, Type A) gene analysis, common variants (eg, R496L, L302P, fsP330)
81331	SNRPN/UBE3A (small nuclear ribonucleoprotein polypeptide N and ubiquitin protein ligase E3A) (eg, Prader-Willi syndrome and/or Angelman syndrome), methylation analysis
81332	SERPINA1 (serpin peptidase inhibitor, clade A, alpha-1 antiproteinase, antitrypsin, member 1) (eg, alpha-1-antitrypsin deficiency), gene analysis, common variants (eg, *S and *Z)
81333	TGFBI (transforming growth factor beta-induced) (eg, corneal dystrophy) gene analysis, common variants (eg, R124H, R124C, R124L, R555W, R555Q)
81336	SMN1 (survival of motor neuron 1, telomeric) (eg, spinal muscular atrophy) gene analysis; full gene sequence
81337	SMN1 (survival of motor neuron 1, telomeric) (eg, spinal muscular atrophy) gene analysis; known familial sequence variant(s)
81343	PPP2R2B (protein phosphatase 2 regulatory subunit Bbeta) (eg, spinocerebellar ataxia) gene analysis, evaluation to detect abnormal (eg, expanded) alleles

81344	TBP (TATA box binding protein) (eg, spinocerebellar ataxia) gene analysis, evaluation to detect abnormal (eg, expanded) alleles
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, cytogenomic array analysis for neoplasia)
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, TGFBR1, TGFBR2, COL3A1, MYH11, ACTA2, SLC2A10, SMAD3, and MYLK
81411	Aortic dysfunction or dilation (eg, Marfan syndrome, Loeys Dietz syndrome, Ehler Danlos syndrome type IV, arterial tortuosity syndrome); duplication/deletion analysis panel, must include analyses for TGFBR1, TGFBR2, MYH11, and COL3A1
81413	Cardiac ion channelopathies (eg, Brugada syndrome, long QT syndrome, short QT syndrome, catecholaminergic polymorphic ventricular tachycardia); genomic sequence analysis panel, must include sequencing of at least 10 genes, including ANK2, CASQ2, CAV3, KCNE1, KCNE2, KCNH2, KCNJ2, KCNQ1, RYR2, and SCN5A
81414	Cardiac ion channelopathies (eg, Brugada syndrome, long QT syndrome, catecholaminergic polymorphic ventricular tachycardia); duplication/deletion gene analysis panel, must include analysis of at least 2 genes, including KCNH2 and KCNQ1.
81419	Epilepsy genomic sequence analysis panel, must include analyses for ALDH7A1, CACNA1A, CDKL5, CHD2, GABRG2, GRIN2A, KCNQ2, MECP2, PCDH19, POLG, PRRT2, SCN1A, SCN1B, SCN2A, SCN8A, SLC2A1, SLC9A6, STXBP1, SYNGAP1, TCF4, TPP1, TSC1, TSC2, and ZEB2
81430	Hearing loss (eg, nonsyndromic hearing loss, Usher syndrome, Pendred syndrome); genomic sequence analysis panel, must include sequencing of at least 60 genes, including CDH23, CLRN1, GJB2, GPR98, MTRNR1, MYO7A, MYO15A, PCDH15, OTOF, SLC26A4, TMC1, TMPRSS3, USH1C, USH1G, USH2A, and WFS1
81431	Hearing loss (eg, nonsyndromic hearing loss, Usher syndrome, Pendred syndrome); duplication/deletion analysis panel, must include copy number analyses for STRC and DFNB1 deletions in GJB2 and GJB6 genes
81434	Hereditary retinal disorders (eg, retinitis pigmentosa, Leber congenital amaurosis, cone-rod dystrophy), genomic sequence analysis panel, must include sequencing of at least 15 genes, including ABCA4, CNGA1, CRB1, EYS, PDE6A, PDE6B, PRPF31, PRPH2, RDH12, RHO, RP1, RP2, RPE65, RPGR, and USH2A
81434	Hereditary retinal disorders (eg, retinitis pigmentosa, Leber congenital amaurosis, cone-rod dystrophy), genomic sequence analysis panel, must include sequencing of at least 15 genes, including ABCA4, CNGA1, CRB1, EYS, PDE6A, PDE6B, PRPF31, PRPH2, RDH12, RHO, RP1, RP2, RPE65, RPGR, and USH2A
81439	Hereditary cardiomyopathy (eg, hypertrophic cardiomyopathy, dilated cardiomyopathy, arrhythmogenic right ventricular cardiomyopathy), genomic sequence analysis panel, must include sequencing of at least 5 cardiomyopathy-related genes (eg, DSG2, MYBPC3, MYH7, PKP2, TTN)
81440	Nuclear encoded mitochondrial genes (eg, neurologic or myopathic phenotypes), genomic sequence panel, must include analysis of at least 100 genes, including BCS1L, C10orf2, COQ2, COX10, DGUOK, MPV17, OPA1, PDSS2, POLG, POLG2, RRM2B, SCO1, SCO2, SLC25A4, SUCLA2, SUCLG1, TAZ, TK2, and TYMP
81441	Inherited bone marrow failure syndromes (IBMFS) (eg, Fanconi anemia, dyskeratosis congenita, Diamond-Blackfan anemia, Shwachman-Diamond syndrome, GATA2 deficiency syndrome, congenital amegakaryocytic thrombocytopenia) sequence analysis panel, must include sequencing of at least 30 genes, including BRCA2, BRIP1, DKC1, FANCA, FANCB, FANCC, FANCD2, FANCE, FANCF, FANCG, FANCI, FANCL, GATA1, GATA2, MPL, NHP2, NOP10, PALB2, RAD51C, RPL11, RPL35A, RPL5, RPS10, RPS19, RPS24, RPS26, RPS7, SBDS, TERT, and TINF2

81442	Noonan spectrum disorders (eg, Noonan syndrome, cardio-facio-cutaneous syndrome, Costello syndrome, LEOPARD syndrome, Noonan-like syndrome), genomic sequence analysis panel, must include sequencing of at least 12 genes, including BRAF, CBL, HRAS, KRAS, MAP2K1, MAP2K2, NRAS, PTPN11, RAF1, RIT1, SHOC2, and SOS1
81443	Genetic testing for severe inherited conditions (eg, cystic fibrosis, Ashkenazi Jewish-associated disorders [eg, Bloom syndrome, Canavan disease, Fanconi anemia type C, mucolipidosis type VI, Gaucher disease, Tay-Sachs disease], beta hemoglobinopathies, phenylketonuria, galactosemia), genomic sequence analysis panel, must include sequencing of at least 15 genes (eg, ACADM, ARSA, ASPA, ATP7B, BCKDHA, BCKDHB, BLM, CFTR, DHCR7, FANCC, G6PC, GAA, GALT, GBA, GBE1, HBB, HEXA, IKBKAP, MCOLN1, PAH)
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)
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
81554	Pulmonary disease (idiopathic pulmonary fibrosis [IPF]), mRNA, gene expression analysis of 190 genes, utilizing transbronchial biopsies, diagnostic algorithm reported as categorical result (eg, positive or negative for high probability of usual interstitial pneumonia [UIP])
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
0004M	Scoliosis, DNA analysis of 53 single nucleotide polymorphisms (SNPs), using saliva, prognostic algorithm reported as a risk score
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 donorderived cell-free DNA in the total cell-free DNA
0156U	Copy number (eg, intellectual disability, dysmorphology), sequence analysis
0170U	Neurology (autism spectrum disorder [ASD]), RNA, next-generation sequencing, saliva, algorithmic analysis, and results reported as predictive probability of ASD diagnosis
0203U	Autoimmune (inflammatory bowel disease), mRNA, gene expression profiling by quantitative RT-PCR, 17 genes (15 target and 2 reference genes), whole blood, reported as a continuous risk score and classification of inflammatory
0205U	Ophthalmology (age-related macular degeneration), analysis of 3 gene variants (2 CFH gene, 1 ARMS2 gene), using PCR and MALDI-TOF, buccal swab, reported as positive or negative for neovascular agerelated macular-degeneration risk associated with zinc supplements
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
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
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
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
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)
S3800	Genetic testing for amyotrophic lateral sclerosis (ALS)
S3841	Genetic testing for retinoblastoma
S3842	Genetic testing for Von Hippel-Lindau disease
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
S3852	DNA analysis for APOE epsilon 4 allele for susceptibility to Alzheimer's disease
S3853	Genetic testing for myotonic muscular dystrophy
S3861	Genetic testing, sodium channel, voltage-gated, type V, alpha subunit (SCN5A) and variants for suspected Brugada Syndrome
S3865	Comprehensive gene sequence analysis for hypertrophic cardiomyopathy
S3866	Genetic analysis for a specific gene mutation for hypertrophic cardiomyopathy (HCM) in an individual with a known HCM mutation in the family

History

Status	Review Date	Effective Date	Action
Created	09/21/2022	02/12/2023	Independent Multispecialty Physician Panel (IMPP) review. Original effective date.