Clinical Appropriateness Guidelines

Genetic Testing for Single-Gene and Multifactorial Conditions

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Scope

This document addresses the general principles of clinical appropriateness for genetic testing, including diagnostic testing for Mendelian disorders and susceptibility testing for multifactorial conditions. It also addresses genetic testing to predict risk of thrombosis. See separate clinical appropriateness guidelines for more specific criteria related to reproductive genetics, hereditary cancer, hereditary cardiac conditions, pharmacogenomics, somatic tumor testing, and chromosomal microarray analysis/whole exome sequencing/whole genome sequencing. All tests listed in these guidelines may not require prior authorization; please refer to the health plan.

Appropriate Use Criteria

Germline Genetic Testing

Genetic testing is medically necessary when all of the following criteria are met:

- The test is clinically reasonable:

    - Symptoms and presentation are consistent with the suspected condition

    - Results are expected to lead to a change in medical management

    - If testing guidelines exist, the clinical scenario falls within those recommendations

    - The test is customarily recognized as clinically and technically appropriate in the diagnosis and/or treatment of the suspected condition

- The clinical benefit of testing outweighs the potential risk of psychological or medical harm to the individual being tested

- The test is as targeted as possible for the clinical situation (e.g., familial pathogenic or likely pathogenic (P/LP) variant testing, common variants, genes related to phenotype)

- The clinical presentation warrants testing of multiple genes when a multi-gene panel is requested

- The testing methodology* has been clinically validated and is the most accurate method unless technical limitations (e.g., poor sample quality) necessitate the need for alternate testing strategies

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

Thrombophilia Testing

Testing for common variants in factor V (*F5*) and prothrombin (*F2*) is medically necessary for any of the following indications (*for additional genes related to thrombophilia, see germline genetic testing criteria above*):

- Pregnant woman who has a personal history of a venous thromboembolism (VTE)

- Individual who has a first-degree relative with *F5* or *F2* thrombophilia and one of the following:

    o Surgery is planned

    o Patient is pregnant

    o Females considering estrogen contraception or hormone replacement therapy if results would influence decision to use estrogen

Multifactorial (Non-Mendelian) Genetic Testing

Tests which fall into this category of testing include those which are intended to determine risk or susceptibility to conditions and are not diagnostic. A multifactorial disease is defined as a condition caused by the interaction of multiple genes and/or environmental factors, e.g., cancer, diabetes, and heart disease.

Genetic testing such as gene expression classifiers or polygenic risk scores are considered medically necessary if all of the following are met:

- Patient is at risk for the suspected condition based on personal or family history

- Presence of the genetic variant(s) is highly predictive for the development of the multifactorial condition

- Treatment exists for the multifactorial condition and has been shown to improve outcomes through published, prospective peer-reviewed studies

- Results will directly impact clinical decision-making and/or clinical outcome for the individual being tested

Testing for multifactorial conditions in the general population is not medically necessary.

HLA Histocompatibility Testing

Note: HLA typing for the purpose of matching organ and tissue transplant recipients to compatible donors may not be in scope for all health plans referencing these guidelines.

For criteria regarding HLA genotyping for disease diagnosis or susceptibility testing, please refer to general genetic testing guidelines for multifactorial diseases above. For criteria related to drug metabolism or risk of adverse reaction, see Clinical Appropriateness Guidelines for Pharmacogenomic Testing.

CPT Codes

The following codes are associated with the guidelines outlined in this document. This list is not all inclusive. Medical plans may have additional coverage policies that supersede these guidelines.

Covered when medical necessity criteria are met:

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
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
81595 (AlloMap®)	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
0268U (Versiti™ aHUS Genetic Evaluation)	Hematology (atypical hemolytic uremic syndrome [aHUS]), genomic sequence analysis of 15 genes, blood, buccal swab, or amniotic fluid
0269U (Versiti™ Autosomal Dominant Thrombocytopenia Panel)	Hematology (autosomal dominant congenital thrombocytopenia), genomic sequence analysis of 14 genes, blood, buccal swab, or amniotic fluid
0271U (Versiti™ Congenital Neutropenia Panel)	Hematology (congenital neutropenia), genomic sequence analysis of 23 genes, blood, buccal swab, or amniotic fluid
0273U (Versiti™ Fibrinolytic Disorder Panel)	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 (Versiti™ Comprehensive Platelet Disorder Panel)	Hematology (genetic platelet disorders), genomic sequence analysis of 43 genes, blood, buccal swab, or amniotic fluid
0276U (Versiti™ Inherited Thrombocytopenia Panel)	Hematology (inherited thrombocytopenia), genomic sequence analysis of 23 genes, blood, buccal swab, or amniotic fluid
0277U (Versiti™ Platelet Function Disorder Panel)	Hematology (genetic platelet function disorder), genomic sequence analysis of 31 genes, blood, buccal swab, or amniotic fluid

Considered not medically necessary:
(Proprietary tests that do not meet criteria are considered not medically necessary when submitted with their specific assigned code listed below or any less specific coding.)

81291	MTHFR (5,10-methylenetetrahydrofolate reductase) (eg, hereditary hypercoagulability) gene analysis, common variants (eg, 677T, 1298C)
81554 (Envisia®)	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])
0087U (Molecular Microscope® MMDx - Heart)	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 (Molecular Microscope® MMDx - Kidney)	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 (Viracor TRAC™ dd-cfDNA)	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
0270U (Versiti™ Coagulation Disorder Panel)	Hematology (congenital coagulation disorders), genomic sequence analysis of 20 genes, blood, buccal swab, or amniotic fluid
0272U (Versiti™ Comprehensive Bleeding Disorder Panel)	Hematology (genetic bleeding disorders), genomic sequence analysis of 51 genes, blood, buccal swab, or amniotic fluid, comprehensive
0278U (Versiti™ Thrombosis Panel)	Hematology (genetic thrombosis), genomic sequence analysis of 12 genes, blood, buccal swab, or amniotic fluid
0289U (MindX Blood Test™ - Memory/ Alzheimer's)	Neurology (Alzheimer disease), mRNA, gene expression profiling by RNA sequencing of 24 genes, whole blood, algorithm reported as predictive risk score
0290U (MindX Blood Test™ - Pain)	Pain management, mRNA, gene expression profiling by RNA sequencing of 36 genes, whole blood, algorithm reported as predictive risk score
0291U (MindX Blood Test™ - Mood)	Psychiatry (mood disorders), mRNA, gene expression profiling by RNA sequencing of 144 genes, whole blood, algorithm reported as predictive risk score

0292U (MindX Blood Test™ - Stress)	Psychiatry (stress disorders), mRNA, gene expression profiling by RNA sequencing of 72 genes, whole blood, algorithm reported as predictive risk score
0293U (MindX Blood Test™ - Suicidality)	Psychiatry (suicidal ideation), mRNA, gene expression profiling by RNA sequencing of 54 genes, whole blood, algorithm reported as predictive risk score
0294U (MindX Blood Test™ - Longevity)	Longevity and mortality risk, mRNA, gene expression profiling by RNA sequencing of 18 genes, whole blood, algorithm reported as predictive risk score
0318U (EpiSign Complete)	Pediatrics (congenital epigenetic disorders), whole genome methylation analysis by microarray for 50 or more genes, blood
0319U (Clarava™)	Nephrology (renal transplant), RNA expression by select transcriptome sequencing, using pre-transplant peripheral blood, algorithm reported as a risk score for early acute rejection
0320U (Tuteva™)	Nephrology (renal transplant), RNA expression by select transcriptome sequencing, using post transplant peripheral blood, algorithm reported as a risk score for acute cellular rejection
ANY	TruGraf®, Transplant Genomics™
ANY	AlloSure®, CareDx®
ANY	Prospera™, Natera™

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Background

Genetic Testing

The number of commercially available genetic tests is increasing rapidly, with over 75,000 tests on the market today (Phillips et al. 2018). Rather than individually addressing every possible test and indication, these guidelines describe our general approach to evaluating the medical necessity of genetic tests. Genetic testing may be performed for a variety of reasons, including, but not limited to: establishing a diagnosis, confirming a clinical diagnosis, predictive testing in an asymptomatic patient,

reproductive carrier screening, prenatal diagnosis and preimplantation genetic testing, drug response prediction, and clinical research.

The recommendations put forth in this document were created in consideration of national guidelines concerning the safety, clinical validity and clinical utility of genetic tests. In its narrowest definition, clinical utility refers to the demonstrated ability of a test to improve health outcomes across a large population. However, due to the rare nature of most genetic disorders, it is often difficult to meet this definition of clinical utility. Groups such as the American College of Medical Genetics and Genomics (ACMG) have urged payers to expand this narrow definition to include evaluation of psychosocial benefit, enabling testing of family members, and broader benefits to society and science. While it is true that genetic testing does not always easily fit into the traditional model of proven clinical utility, medical benefit must still be the primary factor in determining coverage. However, "improved health outcome" for genetic conditions may also include considerations such as avoiding unnecessary, unpleasant or multiple interventions and providing guidance in medical management.

The National Human Genome Research Institute Task Force on Genetic Testing ([NHGRI] 1995; Holtzman 1999) recommended the following underlying principles to ensure the safety and effectiveness of genetic tests:

- The genotypes to be detected by a genetic test must be shown by scientifically valid methods to be associated with the occurrence of a disease, independently replicated and subject to peer review.

- Analytical sensitivity and specificity of a genetic test must be determined before it is made available in clinical practice.

- Data to establish the clinical validity of genetic tests (clinical sensitivity, specificity, and predictive value) must be collected under investigative protocols. In clinical validation, the study sample must be drawn from a group of subjects representative of the population for whom the test is intended. Formal validation for each intended use of a genetic test is needed.

- Before a genetic test can be generally accepted in clinical practice, data must be collected to demonstrate the benefits and risks that accrue from both positive and negative results.

NGS Multi-Gene Panels

Multi-gene testing panels rapidly sequence several to many genes. Panels target testing to genes that have been associated with a certain phenotype, or encompass a set of genes associated with heterogeneous and overlapping phenotypes. While multi-gene panels are typically more cost-effective than stepwise testing of multiple single genes, large panels may include genes of uncertain clinical utility. Unexpected or unclear results can potentially lead to patient distress and downstream healthcare costs. A benefit of targeting testing to a smaller subset of genes is the lower risk of incidental or uncertain findings, as the genes on the panel are expected to correlate with the patient's phenotype. The risk of incidental findings is lowest with highly targeted gene testing, and increases as the number and type of genes on the panel increases.

Organ Transplant (Donor-Derived Cell-free DNA [dd-cfDNA] and RNA Gene Expression Profiles [GEP])

Organ transplant recipients are at risk for allograft rejection, even with modern immunosuppressive therapies. Traditionally, diagnosis of allograft rejection has relied on nonspecific biochemical markers and histologic examination of the grafted tissue. As this requires an invasive tissue biopsy, there is great interest among those in the field of transplantation medicine to develop a noninvasive method of detecting organ transplant rejection (Verhoeven et al. 2018). Non-invasive methods have been proposed for both rejection surveillance of stable post-transplant patients, as well as in aiding biopsy decision-making for patients experiencing symptoms of active rejection. Two general classes of molecular tests have emerged as having the potential to fill this need: donor-derived cell-free DNA (dd-cfDNA) monitoring and RNA gene expression profiles (GEP).

As cell-free DNA is an indicator of dying cells, it has been hypothesized that transplant patients experiencing organ injury associated with acute rejection will have higher levels of dd-cfDNA than patients without rejection. Elevated dd-cfDNA in plasma has been associated with transplant rejection in heart, liver, lung, kidney, and bone marrow recipients (Snyder et al. 2011; Grskovic et al. 2016; Sharon et al. 2017; Jordan et al. 2018; Sayah et al. 2020). It has been proposed that these tests be used for serial monitoring in order to detect new onset injury or rejection prior to clinical symptoms, however the optimal time interval has yet to be established (Bloom et al. 2017; Knight et al. 2019). Furthermore, the ability of dd-cfDNA technology to accurately predict rejection may be different depending on the type of organ rejection; the data is more robust in the setting of antibody mediated rejection versus T-cell mediated rejection (Wijtvliet et al. 2020). In addition, dd-cfDNA testing may be able to be used to guide immunosuppressive treatment of rejection by helping to determine the minimum effective dose, although larger studies to validate this use have not been published (Oellerich et al. 2014). The evaluation of donor-derived cell free DNA has not yet been addressed by professional societies such as the American Society of Transplantation, European Society for Organ Transplantation, or the British Transplantation Society.

Gene expression profiles analyze RNA expression levels of certain genes associated with acute cellular rejection with the end goal to distinguish between rejection and the absence of rejection (Pham et al. 2010). This testing methodology has been most studied in the setting of post-cardiac transplantation monitoring, although it has been explored in other allografts (e.g., kidney). In low risk (stable) heart transplant patients, those who underwent transplant monitoring via gene expression profiling (specifically Allomap) had no worse outcomes than those who were monitored via the conventional method of endomyocardial biopsy (Pham et al. 2010). The GEP group also had six-fold fewer biopsies during the study period (Pham et al. 2010). While the current International Society of Heart and Lung Transplantation guidelines do state that GEPs (specifically Allomap) can be used to rule out the presence of acute heart rejection (grade 2R or greater) in low risk patients between 6 months and 5 years post-transplant, the use of GEPs is not universally accepted (Costanzo et al. 2010; Crespo-Leiro et al. 2017). This may be due to the test's limited sensitivity for detection of acute rejection and its inability to detect antibody-mediated rejection (Crespo-Leiro et al. 2017).

The use of noninvasive transplant monitoring methodologies to evaluate transplant rejection is a promising new development in the field of transplant medicine, however the clinical utility of these technologies has yet to be uniformly established (Knight et al. 2019; Dengu 2020). It is not clear if results of these tests will ultimately preclude the need for invasive biopsy in the majority of patients. Additional information from prospective trials as well as interventional studies are needed to

demonstrate the clinical utility (Menon et al. 2017; Crespo-Leiro et al. 2017; Verhoeven et al. 2018; Filippone and Farber 2020; Preka et al. 2020; Puliyanda et al. 2020; Jackson et al. 2021). Additionally, further research is needed to determine if these molecular biomarkers can be used as a proxy for tolerance of and adequate immunosuppression (O'Callaghan and Knight 2019).

Thrombophilia Testing

Thrombophilia describes a state of hypercoagulability that leads to an increased risk of thrombotic events. Venous thromboembolism (VTE) is a common, complex disease associated with both environmental and genetic risk factors. Risk factors for VTE include advancing age, travel, surgery, injury, family history of VTE, and certain genetic polymorphisms leading to excessive clotting. In women, pregnancy, hormonal contraceptive use, selective estrogen receptor modulators, and hormone replacement therapy are additional risk factors for VTE (Montagnana et al. 2017; Pruthi 2017).

Genetic factors that have been associated with thrombophilia include pathogenic or likely pathogenic (P/LP) variants in several genes including: *F5*, *F2*, *PROC*, *PROS1* and *SERPINC1*, as well as others.

While standard of care for work up of VTE or deep vein thrombosis (DVT) is to perform protein activity and antigen studies, factor V and prothrombin studies are easiest to perform as molecular genotyping given that these conditions are almost always caused by a common variant. There have been conflicting recommendations as to how to approach genetic testing for thrombophilias. ACMG and ACOG have recommended testing for *F2* and *F5* in certain scenarios, while the Evaluation of Genomic Applications and Prevention Working Group (EGAPP) found insufficient evidence to perform this testing for any indication. In patients with unprovoked DVT and/or PE, the American Society of Hematology (2020) suggests indefinite antithrombotic therapy over stopping anticoagulation after completion of primary treatment, rendering molecular testing unnecessary for treatment decision-making. Large NGS panels are not considered medically necessary for thrombophilia due to the frequent inclusion of additional genes with limited evidence of association and unclear management implications, such as *SERPINE1* (PAI-1) and *MTHFR* (Carroll and Piazza 2018; Franchini et al. 2016)

It has been suggested that genetic testing for inherited thrombophilias may allow for prophylactic treatment of individuals at risk for VTE or enhance the prediction of recurrence risk for patients who have already had a VTE. However, the clinical utility of such genetic testing is controversial, and testing is often ordered inappropriately in scenarios where results do not have clinical utility (Shen et al. 2016; Gavva et al. 2017; Pruthi et al. 2017; Gaddh et al. 2020).

In all cases, the clinical utility of genetic testing for thrombophilias depends on whether test results will impact the initiation or duration of anticoagulation therapy. It is important to consider the risk of harm from inappropriate prolonged treatment with anticoagulants, as well as the fact that genetic testing does not detect all inherited risk factors for hypercoagulation. In addition, the presence of an inherited thrombophilia variant itself does not always require prophylactic treatment with anticoagulants, and other risk factors should be considered when assessing a patient's individual risk of VTE and the need for anticoagulation therapy (ACOG 2018; Carroll and Piazza 2018; Ashraf et al. 2019; Stern et al. 2019). For example, genetic test results may have direct implications for treatment in pregnant women with a previous history of VTE, thus testing in this population would be appropriate (ACOG 2018). There may also be a benefit to screening pregnant women with a family history of VTE due to a known familial variant, as those women found to have a high-risk genotype would be offered antenatal prophylactic anticoagulant therapy even in the absence of a personal history of VTE (ACOG 2018).

Factor V Leiden (F5)

The factor V Leiden (FVL) variant (1691G>A; R506Q) in the *F5* gene is the most common known inherited risk factor for thrombosis. This P/LP variant leads to reduced inactivation of clotting factor V by activated protein C (i.e., APC resistance), which causes increased thrombin generation. Heterozygous carriers of the FVL variant have an approximately 3-fold to 8-fold increased risk of VTE compared to non-carriers (Kujovich 2018). However, the absolute risk of VTE in heterozygotes remains low, with only ~5% of carriers developing a VTE by age 65 (Rodeghiero and Tosetto 1999; Heit et al. 2005). Individuals who are homozygous for the FVL variant have a much higher increased risk of VTE, approximately 9-fold to 80-fold (Rosendaal 2009, EGAPP 2011; Carroll and Piazza 2018). This increased risk corresponds to an absolute incidence of 15 VTE events/1,000 persons/year (Juul et al. 2004).

The prevalence of FVL P/LP variants varies according to population. Approximately 3-8% of the general US and European population carry a heterozygous FVL P/LP variant, while it is rarely identified in individuals from Asian and African populations (Kujovich 2018). Homozygosity of the FVL P/LP variants is seen in approximately 1/5,000 individuals in the general US and European population (Kujovich 2018).

Prothrombin (F2)

The second most common inherited risk factor for VTE is the 20210G>A (G20210A) variant in the *F2* gene, which is also called the prothrombin variant. This activating P/LP variant leads to higher circulating levels of prothrombin, which results in an increased risk for clot formation. Heterozygous carriers of the *F2* variant have a 2-fold to 5-fold increased risk of VTE compared to non-carriers (Rosendaal and Reitsma 2009; Kujovich 2021). However, the absolute risk of a VTE in heterozygotes again remains quite low: 0.19%/year to 0.41%/year in asymptomatic carriers (Lijfering et al. 2009; Kujovich 2021).

The prevalence of *F2* heterozygosity varies by population. Approximately 2-3% of the general US and European population are carriers of the *F2* variant, while individuals from African and Asian populations have a much lower prevalence (Kujovich 2021). *F2* homozygotes are very rare, approximately 1/10,000 in the general US and European population, and the increased risk associated with this genotype is not well-defined, but may be up to 7 times higher than that of the general population (Kujovich 2021; Carroll and Piazza 2018). Patients with compound heterozygosity for factor V Leiden and prothrombin mutations may have up to a 20-fold increased risk for VTE. Neither of these mutations exhibit a strongly increased risk for VTE recurrence (Carroll and Piazza 2018).

Professional Society Guidelines

American College of Medical Genetics and Genomics (ACMG)
ACMG Points to Consider Statement. DNA-Based Screening and Population Health.
Murray M, Giovanni M, Doyle D, et al. Genet Med. 2021 Jun;23(6):989-995. PubMed PMID: 33727704.

ACMG Points to Consider Statement for Individuals and Health Care Providers. DNA-Based Screening and Personal Health.

Bean L, Scheuner M, Murray M, et al. Genet Med. 2021 Jun;23(6):979-988. PubMed PMID: 33790423.

ACMG Points to Consider Statement. Incidental Detection of Acquired Variants in Germline Genetic and Genomic Testing.
Chao EC, Astbury C, Deignan JL, et al. Genet Med. 2021 Apr 16. PubMed PMID: 33864022.

ACMG Practice Guidelines. Clinical Genetics Evaluation in Identifying the Etiology of Autism Spectrum Disorders.
Schaefer GB, Mendelsohn NJ. Genet Med. 2013 May;15(5):399-407. PubMed PMID: 23519317.

ACMG Technical Standard. Next-Generation Sequencing for Constitutional Variants in the Clinical Laboratory, 2021 Revision.
Rehder C, Bean LJH, Bick D, et al. Genet Med. 2021 Apr 29. PubMed PMID: 33927380.

ACMG Clinical Practice Resource. Genetic Evaluation of Short Stature, Focused Revision.
Mintz C, Seaver L, Irons M, et al. Genet Med. 2021 Jan 29. PubMed PMID: 33514815.

International Society of Heart and Lung Transplantation (ISHLT)
ISHLT Guidelines. Care of Heart Transplant Recipients.
Costanzo MR, Dipchand A, Starling R, et al. J Heart Lung Transplant. 2010 Aug;29(8):914-956. PubMed PMID: 20643330.

Joint Statements
Technical Standards for the Interpretation and Reporting of Constitutional Copy-Number Variants. ACMG and Clinical Genome Resource (ClinGen).
Riggs ER, Andersen EF, Cherry AM, et al.; ACMG. Genet Med. 2020 Feb;22(2):245-257. PubMed PMID: 31690835.

Standards and Guidelines for the Interpretation of Sequence Variants. ACMG and Association for Molecular Pathology (AMP). Joint Consensus Recommendation.
Richards S, Aziz N, Bale S, et al.; ACMG Laboratory Quality Assurance Committee. Genet Med. 2015 May;17(5):405-424. PubMed PMID: 25741868.

Thrombophilia Testing

American College of Medical Genetics and Genomics (ACMG)
ACMG Technical Standards. Venous Thromboembolism Laboratory Testing (Factor V Leiden and Factor II c.*97G>A)
Zhang S, Taylor A, Huang X, et al. Genet Med. 2018 Dec;20(12):1489-1498. PubMed PMID: 30297698.

American College of Obstetricians and Gynecologists (ACOG)
ACOG Practice Bulletin No. 197. Inherited Thrombophilias in Pregnancy.
Obstet Gynecol. 2018 Jul;132(1): e18-e34. PubMed PMID: 29939939.

American College of Chest Physicians (ACCP)
ACCP Guideline. VTE, Thrombophilia, Antithrombotic Therapy, and Pregnancy: Antithrombotic Therapy and Prevention of Thrombosis.
Bates SM, Greer IA, Middeldorp S, et al. Chest. 2012 Feb;141(2 Suppl): e691S-e736S. PubMed PMID: 22315276.

ACCP Guideline and Expert Panel Report. Antithrombotic Therapy for VTE Disease.

Kearon C, Akl EA, Ornelas J, et al. Chest. 2016;149(2):315-52. PubMed PMID: 26867832.

American Society of Hematology (ASH)
ASH 2020 Guidelines for Management of Venous Thromboembolism: Treatment of Deep Vein Thrombosis and Pulmonary Embolism.
Ortel T, Neumann I, Ageno W, et al. Blood Adv. 2020 Oct 13;4(19):4693-4738. PubMed PMID: 33007077.

American Society for Reproductive Medicine (ASRM)
ASRM Guideline. Combined Hormonal Contraception and the Risk of Venous Thromboembolism.
Fertil Steril. 2017 Jan;107(1):43-51. PubMed PMID: 27793376.

Selected References

1   Abdul-Rahman OA, Hudgins L. The diagnostic utility of a genetics evaluation in children with pervasive developmental disorders. Genet Med. 2006 Jan;8(1):50-4. PubMed PMID: 16418599.
2   Arnett AB, Trinh S, Bernier RA. The state of research on the genetics of autism spectrum disorder: methodological, clinical and conceptual progress. Curr Opin Psychol. 2018 July 21; 27:1-5. PubMed PMID: 30059871.
3   Bean LJH, Funke B, Carlston CM, et al. Diagnostic gene sequencing panels: from design to report- a technical standard of the American College of Medical Genetics and Genomics (ACMG). Genet Med. 2019 Nov 16. PubMed PMID: 31732716.
4   Bloom RD, Bromberg JS, Poggio ED, et al. Cell-free DNA and active rejection in kidney allografts. J Am Soc Nephrol. 2017 Jul;28(7):2221-2232. PubMed PMID: 28280140.
5   Bylstra Y, Lim WK, Kam S, et al. Family history assessment significantly enhances delivery of precision medicine in the genomics era. Genome Med. 2021 Jan 7;13(1):3. PubMed PMID: 33413596.
6   Crespo-Leiro MG, Barge-Caballero G, Couto-Mallon D. Noninvasive monitoring of acute and chronic rejection in heart transplantation. Curr Opin Cardiol. 2017 May;32(3):308-315. PubMed PMID: 28306671.
7   Dengu F. Next-generation sequencing methods to detect donor-derived cell-free DNA after transplantation. Transplant Rev (Orlando). 2020 Jul;34(3):100542. PubMed PMID: 32265093.
8   Erger F, Schaaf CP, Netzer C. Which genes to assess in the NGS diagnostics of intellectual disability? The case for a consensus database-driven and expert-curated approach. Mol Cell Probes. 2019 Jun; 45:84-88. PubMed PMID: 30914295.
9   Filippone EJ, Farber JL. The monitoring of donor-derived cell-free DNA (ddcfDNA) in kidney transplantation. Transplantation. 2020 Jul 20. Epub ahead of print. PubMed PMID: 32732615.
10 Garg N, Mandelbrot DA, Parajuli S, et al. The clinical value of donor-derived cell-free DNA measurements in kidney transplantation. Transplant Rev (Orlando). 2021 Dec;35(4):100649. PubMed PMID: 34507254.
11 Grskovic M, Hiller DJ, Eubank LA, et al. Validation of a clinical-grade assay to measure donor-derived cell-free DNA in solid organ transplant recipients. J Mol Diagn. 2016 Nov;18(6):890-902. PubMed PMID: 27727019.
12 Han JY, Jang W, Park J, et al. Diagnostic approach with genetic tests for global developmental delay and/or intellectual disability: single tertiary center experience. Ann Hum Genet. 2018 Nov 6. PubMed PMID: 30402882.
13 Holtzman NA. Promoting safe and effective genetic tests in the United States: work of the task force on genetic testing. Clin Chem. 1999 May;45(5):732-8. PubMed PMID: 10222375.
14 Jackson AM, Amato-Menker C, Bettinotti M. Cell-free DNA diagnostics in transplantation utilizing next generation sequencing. Hum Immunol. 2021 Nov;82(11):850-858. PubMed PMID: 34600770.
15 Johansen Taber KA, Dickinson BD, Wilson M. The promise and challenges of next-generation genome sequencing for clinical care. JAMA Intern Med. 2014 Feb 1;174(2):275-80. PubMed PMID: 24217348.
16 Jordan SC, Bunnapradist S, Bromberg JS, et al. Donor-derived cell-free DNA identifies antibody-mediated rejection in donor specific antibody positive kidney transplant recipients. Transplant Direct. 2018 Aug 20;4(9):e379. PubMed PMID: 30234148.
17 Kalsner L, Twachtman-Basset J, Tokarski K, et al. Genetic testing including targeted gene panel in a diverse clinical population of children with autism spectrum disorder: Findings and implications. Molecular Genetics & Genomic Medicine. 2018;6(2): 171-185. PubMed PMID: 29271092.
18 Knight SR, Thorne A, Lo Faro ML. Donor-specific cell-free DNA as a biomarker in solid organ transplantation. A systematic review. Transplantation. 2019 Feb;103(2):273-283. PubMed PMID: 30308576.
19 Medicare Contractor Palmetto GBA. Local Coverage Determination (LCD): MolDX: AlloSure Donor-Derived Cell-Free DNA Test (L37266). Accessed March 10, 2020. https://www.cms.gov/medicare-coverage-database/details/lcd-details.aspx?LCDId=37266.
20 Menon MC, Murphy B, Heeger PS. Moving biomarkers toward clinical implementation in kidney transplantation. J Am Soc Nephrol. 2017 Mar;28(3):735-747. PubMed PMID: 28062570.

21 Neri G, Schwartz CE, Lubs HA, et al. X-linked intellectual disability update 2017. Am J Med Genet A. 2018 Jun;176(6): 1375-1388. PubMed PMID: 29696803.

22 O'Callaghan JM, Knight SR. Noninvasive biomarkers in monitoring kidney allograft health. Curr Opin Organ Transplant. 2019 Aug;24(4):411-415. PubMed PMID: 31145158.

23 Oellerich M, Schütz E, Kanzow P, et al. Use of graft-derived cell-free DNA as an organ integrity biomarker to reexamine effective tacrolimus trough concentrations after liver transplantation. Ther Drug Monit. 2014 Apr;36(2):136-40. PubMed PMID: 24452066.

24 Pham MX, Teuteberg JJ, Kfoury AG, et al. Gene-expression profiling for rejection surveillance after cardiac transplantation. N Engl J Med. 2010 May 20;362(20):1890-900. PubMed PMID: 20413602.

25 Phillips KA, Deverka PA, Hooker GW, et al. Genetic test availability and spending: where are we now? Where are we going? Health Aff (Millwood). 2018 May;37(5):710-716. PubMed PMID: 29733704.

26 Preka E, Ellershaw D, Chandler N, et al. Cell-free DNA in pediatric solid organ transplantation using a new detection method of separating donor-derived from recipient cell-free DNA. Clin Chem. 2020 Oct 1;66(10):1300-1309. PubMed PMID: 32882007.

27 Puliyanda DP, Swinford R, Pizzo H, et al. Donor-derived cell-free DNA (dd-cfDNA) for detection of allograft rejection in pediatric kidney transplants. Pediatr Transplant. 2020 Nov 20: e13850. Epub ahead of print. PubMed PMID: 33217125.

28 Sayah D, Weigt SS, Ramsey A, et al. Plasma donor-derived cell-free DNA levels are increased during acute cellular rejection after lung transplant: pilot data. Transplant Direct. 2020 Sep 24;6(10): e608. PubMed PMID: 33062841.

29 Sharon E, Shi H, Kharbanda S, et al. Quantification of transplant-derived circulating cell-free DNA in absence of a donor genotype. PLoS Comput Biol. 2017 Aug 3;13(8): e1005629. PubMed PMID: 28771616.

30 Shashi V, McConkie-Rosell A, Rosell B, et al. The utility of the traditional medical genetics diagnostic evaluation in the context of next-generation sequencing for undiagnosed genetic disorders. Genet Med. 2014 Feb;16(2):176-82. Epub 2013 Aug 29. PubMed PMID: 23928913.

31 Snyder TM, Khush KK, Valantine HA, et al. Universal noninvasive detection of solid organ transplant rejection. Proc Natl Acad Sci U S A. 2011 Apr 12;108(15):6229-6234. PubMed PMID: 21444804.

32 Verhoeven JGHP, Boer K, Van Schaik RHN, et al. Liquid biopsies to monitor solid organ transplant function: a review of new biomarkers. Ther Drug Monit. 2018 Oct;40(5):515-525. PubMed PMID: 29957668.

33 Wijtvliet VPWM, Plaeke P, Abrams S, et al. Donor-derived cell-free DNA as a biomarker for rejection after kidney transplantation: a systematic review and meta-analysis. Transpl Int. 2020 Dec;33(12):1626-1642. PubMed PMID: 32981117.

Thrombophilias

1 Ageno W, Gallus AS, Wittkowsky A, et al. Oral anticoagulant therapy: antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest. 2012 Feb;141(2 Suppl):e44S-e88S. PubMed PMID: 22315269.

2 Ashraf N, Visweshwar N, Jaglal M, et al. Evolving paradigm in thrombophilia screening. Blood Coagul Fibrinolysis. 2019 Jul;30(5):249-252. PubMed PMID: 31145103.

3 Bushnell C, McCullough LD, Awad IA, et al. Guidelines for the prevention of stroke in women: a statement for healthcare professionals from the American Heart Association/American Stroke Association. Stroke. 2014 May;45(5):1545-88. Epub 2014 Feb 6. PubMed PMID: 24503673.

4 Carroll BJ, Piazza G. Hypercoagulable states in arterial and venous thrombosis: when, how and who to test? Vasc Med. 2018 Aug;23(4):388-399. PubMed PMID: 30045685.

5 Croles FN, Nasserinejad K, Duvekot JJ, et al. Pregnancy, thrombophilia, and the risk of a first venous thrombosis: systematic review and Bayesian meta-analysis. BMJ. 2017 Oct 26; 359: j4452. PubMed PMID: 29074563.

6 Duhl AJ, Paidas MJ, Ural SH, et al. Antithrombotic therapy and pregnancy: consensus report and recommendations for prevention and treatment of venous thromboembolism and adverse pregnancy outcomes. Am J Obstet Gynecol. 2007;197:457. PubMed PMID: 17980177.

7 Franchini M, Martinelli I, Mannucci PM. Uncertain thrombophilia markers. Thromb Haemost. 2016 Jan; 115(1):25-30. PubMed PMID: 26271270.

8 Gaddh M, Cheng E, Elsebaie MAT, et al. Clinical utilization and cost of thrombophilia testing in patients with venous thromboembolism. TH Open. 2020 Aug 9;4(3):e153-e162. PubMed PMID: 32803121.

9 Gavva C, Sarode R, Zia A. A clinical audit of thrombophilia testing in pediatric patients with acute thromboembolic events: impact on management. Blood Adv. 2017 Nov 22;1(25):2386-2391. PubMed PMID: 29296888.

10 Gupta A, Sarode R, Nagalla S. Thrombophilia testing in provoked venous thromboembolism: a teachable moment. JAMA Intern Med. 2017 Aug;177(8):1195-6. PubMed PMID: 28586816.

11 Heit JA, Sobell JL, Li H, et al. The incidence of venous thromboembolism among Factor V Leiden carriers: a community-based cohort study. J Thromb Haemost. 2005 Feb;3(2):305-11. PubMed PMID: 15670037.

12 Holbrook A, Schulman S, Witt DM, et al. Evidence-based management of anticoagulant therapy: antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest. 2012 Feb;141(2 Suppl):e152S-e184S. PubMed PMID: 22315259.

13 Juul K, Tybjaerg-Hansen A, Schnohr P, et al. Factor V Leiden and the risk for venous thromboembolism in the adult Danish population. Ann Intern Med. 2004 Mar 2;140(5):330-7. PubMed PMID: 14996674.

14 Kujovich JL. Factor V Leiden thrombophilia. 1999 May 14 [Updated 2018 Jan 4]. In: Adam MP, Ardinger HH, Pagon RA, et al., editors. GeneReviews [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2018. Available from: https://www.ncbi.nlm.nih.gov/books/NBK1368/

15 Kujovich JL. Prothrombin thrombophilia. 2006 Jul 25 [Updated 2021 Feb 4]. In: Pagon RA, Adam MP, Ardinger HH, et al., editors. GeneReviews [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2015. Available from: http://www.ncbi.nlm.nih.gov/books/NBK1148/

16   Li X, Liu Y, Zhang R, et al. Meta-analysis of the association between plasminogen activator inhibitor-1 4G/5G polymorphism and recurrent pregnancy loss. Med Sci Monit. 2015 Apr 11; 21:1051-6. PubMed PMID: 25862335.

17   Lijfering WM, Brouwer JL, Veeger NJ, et al. Selective testing for thrombophilia in patients with first venous thrombosis: results from a retrospective family cohort study on absolute thrombotic risk for currently known thrombophilic defects in 2479 relatives. Blood. 2009 May 21;113(21):5314-22. PubMed PMID: 19139080.

18   MacCallum P, Bowles L, Keeling D. Diagnosis and management of heritable thrombophilias. BMJ. 2014 Jul 17;349. PubMed PMID: 25035247.

19   Montagnana M, Lippi G, Danese E. An overview of thrombophilia and associated laboratory testing. Methods Mol Biol. 2017; 1646:113-35. PubMed PMID: 28804823.

20   Pruthi RK. Optimal utilization of thrombophilia testing. Int J Lab Hematol. 2017 May;39 Suppl 1:104-110. PubMed PMID: 28447412.

21   Rodeghiero F, Tosetto A. Activated protein C resistance and factor V Leiden mutation are independent risk factors for venous thromboembolism. Ann Intern Med. 1999 Apr 20;130(8):643-50. PubMed PMID: 10215560.

22   Rosendaal FR, Reitsma PH. Genetics of venous thrombosis. J Thromb Haemost. 2009 Jul;7 Suppl 1:301-4. PubMed PMID: 19630821.

23   Rühle F, Stoll M. Advances in predicting venous thromboembolism risk in children. Br J Haematol. 2018 Mar;180(5):654-665. Epub 2017 Dec 19. PubMed PMID: 29265336.

24   Said JM, Tsui R, Borg AJ, et al. The PAI-1 4G/5G polymorphism is not associated with an increased risk of adverse pregnancy outcome in asymptomatic nulliparous women. J Thromb Haemost. 2012 May;10(5):881-6. PubMed PMID: 2243640.

25   Shen Y-M, Tsai J, Taiwo E, et al. Analysis of thrombophilia test ordering practices at an academic center: a proposal for appropriate testing to reduce harm and cost. PLoS One. 2016 May 13;11(5): e0155326. PubMed PMID: 27176603.

26   Solomon HV, Cates KW, Li KJ. Does obtaining CYP3D6 and CYP2C19 pharmacogenetic testing predict antidepressant response or adverse drug reactions? Psychiatry Res. 2019 Jan; 271:604-613. PubMed PMID: 30554109.

27   Stern RM, Al-Samkari H, Connors JM. Thrombophilia evaluation in pulmonary embolism. Curr Opin Cardiol. 2019 Nov;34(6):603-609. PubMed PMID: 31389825.

28   Stevens SM, Woller SC, Bauer KA, et al. Guidance for the evaluation and treatment of hereditary and acquired thrombophilia. J Thromb Thrombolysis. 2016 Jan;41(1):154-64. PubMed PMID: 26780744.

29   van Ommen CH, Nowak-Göttl U. Inherited thrombophilia in pediatric venous thromboembolic disease: why and who to test. Front Pediatr. 2017 Mar 14; 5:50. PubMed PMID: 28352625.

30   Witt DM, Nieuwlaat R, Clark NP, et al. American Society of Hematology 2018 guidelines for management of venous thromboembolism: optimal management of anticoagulation therapy. Blood Adv. 2018 Nov 27;2(22):3257-3291. PubMed PMID: 30482765.

31   Wu O, Robertson L, Twaddle S, et al. Screening for thrombophilia in high-risk situations: systematic review and cost-effectiveness analysis. The Thrombosis: Risk and Economic Assessment of Thrombophilia Screening (TREATS) study. Health Technol Assess. 2006 Apr;10(11):1-110. PubMed PMID: 16595080.

Revision History

Medical Advisory Review Board Review:

v2.2022 03/17/2022: Approved

v1.2022 09/20/2021: Approved

v2.2021 03/12/2021: Approved

v1.2021 11/13/2020: Approved

v2.2020 05/08/2020: Reviewed

v1.2020 11/04/2019: Reviewed

v2.2019 05/23/2019: No Criteria Changes

v1.2019 11/07/2018: Reviewed

v1.2018 03/31/2018: Reviewed

Clinical Steering Committee Review:

v2.2022 02/14/2022: Approved

v1.2022 08/23/2021: Approved

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v1.2017 01/25/2017: Approved

Revisions:

Version	Date	Editor	Description
v2.2022 *GEN01-0922.2*	2/02/2022	Stefanie Finch, MS, CGC	Semi-annual review. The criteria for F5/F2 testing in an individual with an unprovoked VTE was removed. Updated CPT codes, background, professional society guidelines and references.
v1.2022 *GEN01-0322.1*	8/16/2021	Carrie Langbo, MS, CGC	Semi-annual review. No criteria changes. Thrombophilia testing criteria was moved from the Pharmacogenomic guideline. CMA criteria and content was moved to the Whole Exome and Whole Genome Sequencing guideline. Updated CPT codes, background, professional society guidelines and references (*including the addition of applicable thrombophilia information*).

v2.2021 *GEN01-0921.1*	2/15/2021	Carrie Langbo, MS, CGC	Semi-annual review. No criteria changes. Chromosomal Microarray Analysis criteria was clarified to reflect new terminology for developmental and epileptic encephalopathies. Updated CPT codes, background, professional society guidelines and references.
v1.2021	9/11/2020	Carrie Langbo, MS, CGC	Semi-annual review. No criteria changes. Chromosomal Microarray Analysis criteria was clarified. Updated CPT codes, background, professional society guidelines and references.
v2.2020	3/13/2020	Carrie Langbo, MS, CGC	Semi-annual review. Updated text in Genetic Testing for Germline Conditions and Multi-factorial (Non-Mendelian) Genetic Testing. Updated CPT codes, background (added organ transplant and RNA gene expression profiles section) and references.
v1.2020	9/10/2019	Carrie Langbo, MS, CGC	Semi-annual review. No criteria changes. Updated background and references.
v2.2019	4/03/2019	Karen Buser, MS, CGC	Semi-annual review. No criteria changes. Reformatted single and multi-gene criteria. Updated references.
v1.2019	10/03/2018	Kate Charyk, MS, CGC	Semi-annual review. Added CMA criteria for early-onset epilepsy. Updated background. Renumbered to 2019. Reformatted CPT code list. PMID added.
v1.2018	3/31/2018	Gwen Fraley, MS, CGC	Semi-annual review. Removed criteria related to evaluation by a specialty physician for multi-gene panels. Added disclaimer sentence to Scope.
v1.2017	10/27/2017	Gwen Fraley, MS, CGC	Quarterly review. No criteria changes.

v1.2017	09/18//2017	Megan Czarniecki, MS, CGC	Formatted references to NLM style. Moved methodological considerations to appropriate use criteria and background. Updated associated CPT codes. Approved by Policy Lead.
v1.2017	07/03/2017	Gwen Fraley, MS, CGC	Quarterly review. No criteria changes. Updated references.
v1.2017	04/25/2017	Gwen Fraley, MS, CGC	Quarterly review. No criteria changes. Updated references.
v1.2017	01/23/2017	Gwen Fraley, MS, CGC	Quarterly review. No criteria changes. Added "prospective" to clarify scientific validation criteria for Multifactorial (Non-Mendelian) Conditions. Updated references. Renumbered to 2017 version.
v2.2016	10/06/2016	Gwen Fraley, MS, CGC	Added HLA and transplant criteria. Updated references.
v1.2016	06/17/2016	Gwen Fraley, MS, CGC	Revised medical necessity criteria for single gene and panel testing. Updated references.
v1.2015	06/04/2015	Gwen Fraley, MS, CGC	Original version

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Primary Author: Gwen Fraley, MS, CGC