

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. See separate clinical appropriateness guidelines for more specific criteria for testing related to reproductive genetics, hereditary cancer, hereditary cardiac conditions, pharmacogenomics and thrombophilia, somatic tumor testing, and 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.

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.

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Genetic testing such as gene expression classifiers or polygenic risk scores are considered medically necessary when 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.

Chromosomal Microarray Analysis

Chromosomal microarray analysis (CMA) is medically necessary for any of the following indications:

- Non-syndromic autism spectrum disorder
- Non-syndromic global developmental delay or intellectual disability
- Individual with multiple major structural or functional congenital anomalies affecting unrelated organ systems (including major metabolic disorders)*
- Known or suspected developmental and epileptic encephalopathy (onset before three years of age) for which likely non-genetic causes of epilepsy (e.g., environmental exposures; brain injury secondary to complications of extreme prematurity, infection, trauma) have been excluded*

*CMA is intended for use in the detection of chromosomal duplications and deletions only and is therefore indicated when the possibility of microdeletion or microduplication syndromes/conditions are suspected. It cannot detect other common variant types (e.g., sequence variants). If sequence variants are high on the differential diagnosis, please see Clinical Appropriateness Guidelines for Whole Exome and Whole Genome Sequencing for coverage criteria.

For oncologic indications, please see Clinical Appropriateness Guidelines for Molecular Testing of Solid and Hematologic Tumors and Malignancies.

For reproductive indications, please see Clinical Appropriateness Guidelines for Genetic Testing for Reproductive Carrier Screening and Prenatal Diagnosis.

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

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metabolism or risk of adverse reaction, see Clinical Appropriateness Guidelines for Pharmacogenomic Testing and Genetic Testing for Thrombotic Disorders.

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 constitutional (genome-wide) microarray analysis; interrogation of genomic regions for copy number variants (eg, Bacterial Artificial Chromosome [BAC] or oligo-based comparative genomic hybridization [CGH] microarray analysis)
- 81229 Cytogenomic constitutional (genome-wide) microarray analysis; interrogation of genomic regions for copy number and single nucleotide polymorphism (SNP) variants for chromosomal abnormalities
- 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

Codes that do not meet medical necessity criteria:

- 81443 Genetic testing for severe inherited conditions (eg, cystic fibrosis, Ashkenazi Jewish-associated disorders [eg, Bloom syndrome, Canavan disease, Fanconi anemia type C, mucopolipidosis 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)

Policy Interpretation: This test is performed for the genomic analysis of at least 15 genes for carrier screening of individuals with inherited conditions. Specimen type varies. Methodology is a multiplex PCR-based assay.

- 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])
- 0055U Cardiology (heart transplant), cell-free DNA, PCR assay of 96 DNA target sequences (94 single nucleotide polymorphism targets and two control targets), plasma

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0087U	Tissue rejection (allograft organ heart), mRNA gene expression analysis of 1,283 genes utilizing microarray, measuring mRNA transcript levels in transplant heart biopsy tissue, with allograft rejection and injury algorithm reported as a probability score
0088U	Tissue rejection (allograft organ kidney), mRNA gene expression analysis of 1,494 genes utilizing microarray, measuring mRNA transcript levels in transplant kidney biopsy tissue, with allograft rejection and injury algorithm reported as a probability score
0118U	Transplantation medicine, quantification of donor-derived cell-free DNA using whole genome next-generation sequencing, plasma, reported as percentage of donor derived cell-free DNA in the total cell-free DNA
0209U	Cytogenomic constitutional (genome-wide) analysis, interrogation of genomic regions for copy number, structural changes and areas of homozygosity for chromosomal abnormalities
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 some estimates of approximately 75,000 tests on the market today. 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

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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.

Microarray

Chromosomal microarray (CMA) or comparative genomic hybridization (CGH) detects microduplications and microdeletions of chromosomal DNA. Many studies have validated this technology as a more sensitive alternative to traditional cytogenetic karyotyping. CMA is now recommended as a first-tier test in place of karyotyping for multiple indications, although the technology cannot detect balanced rearrangements (e.g., balanced reciprocal translocations). SNP arrays are a specific type of oligonucleotide array that target alternative alleles at SNPs within the genome. SNP array offers the

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ability to analyze a sample at a higher resolution than metaphase cytogenetics for DNA copy number alterations (duplications and deletions), copy number polymorphisms, and loss of heterozygosity (LOH).

The ACMG recommends CMA as a first-tier test in the initial postnatal evaluation of individuals with multiple anomalies not specific to a well-delineated genetic syndrome, apparently non-syndromic developmental delay/intellectual disability, and autism spectrum disorders (Manning et al. 2010; *reaffirmed* Manning et al. 2020; South et al. 2013).

In addition, if a specific syndrome is not readily identified, then chromosomal microarray would be a reasonable first line diagnostic measure for those with developmental and epileptic encephalopathies. Chromosomal microarray has been found to have diagnostic yields in the approximately 5–30% range in various studies in epilepsy (Noh et al. 2012). Specific to epileptic encephalopathies, array comparative hybridization (aCGH) has been reported to identify copy number variants in ~4-13% with further confirmed de novo and pathogenic variants in 2.9-13% (Epilepsy Phenome/Genome Project & Epi4K Consortium 2015; Mercimek-Mahmutoglu et al. 2015). Another study found that in patients presenting with early life epilepsies 32/188 (17%) had diagnostic/pathogenic findings on CMA (Berg et al. 2017). Other groups have found similar yields (Allen et al. 2015; Poduri 2017; Mefford et al. 2011; Olson et al. 2014; Tumiene et al. 2018). This rate is similar to diagnostic rates for autism spectrum disorders as noted by ACMG (Schaefer and Mendelsohn 2013).

See the Clinical Appropriateness Guidelines for Genetic Testing for Reproductive Carrier Screening and Prenatal Diagnosis for use of microarray in the reproductive setting.

Evaluation of Regions of Homozygosity (ROH)

In addition to identifying copy number variants, SNP arrays can identify areas of the genome with allelic homozygosity. These regions of homozygosity are identified in approximately 6% of individuals undergoing SNP array for clinical reasons (Wang et al. 2015). Most of these are caused by consanguinity, others are caused by uniparental disomy or ancestral homozygosity. With ROH, there is a concern for pathology caused by imprinting, such as Angelman or Prader Willi syndromes, or for recessive conditions as there is a higher likelihood of having homozygous P/LP variants in genes found within the ROH. No guidelines exist for how to approach further evaluation of ROH after they have been identified. If the ROH is found within a region known to be imprinted, UPD studies should be considered. To evaluate for recessive conditions, the preferred approach would be to search genes in the region associated with disease and identify candidate genes based on clinical symptoms. Sequencing of the entire region may be considered in select cases if no candidate gene is identified, but increases the chance of identifying a variant of uncertain significance or P/LP variants in genes that are not clinically actionable.

Understanding the Clinical Relevance of Copy Number Variants

Inter-laboratory interpretation of copy number variants across technologies, e.g., CMA or NGS platforms, is complex and evolving but must be consistent. The American College of Medical Genetics and Genomics (ACMG) and the Clinical Genome Resource (ClinGen) recommend a uniform five-tier CNV variant classification system outlined in the ACMG/AMP sequence variant interpretation guidelines (Richards et al. 2015; Riggs et al. 2020). Utilizing evidence at a given point in time supporting or refuting a particular variant's pathogenicity, regardless of patient-specific factors, will produce necessary consistency and clarity in establishing potential clinical impact (Riggs et al. 2020).

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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).

Cell-free DNA is an indicator of dying cells, therefore it has been hypothesized that transplant patients experiencing organ injury associated with acute rejection will have higher levels of donor-derived cell free DNA (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 (Synder 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

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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; Puliyaanda et al. 2020). 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).

Professional Society Guidelines

American College of Medical Genetics and Genomics (ACMG)

ACMG Clinical Practice Resource. Array-Based Technology and Recommendations for Utilization in Medical Genetics Practice for Detection of Chromosomal Abnormalities.

Manning M, Hudgins L. 2020 Dec;22(12):2126. PubMed PMID: 32514088.

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.

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South S, Lee C, Lamb A, et al. Genet Med. 2013 Nov;15(11):901-9. PubMed PMID: 24071793.

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.

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Revision History

Medical Advisory Review Board Review:

- 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:

- v2.2021 02/22/2021: Approved
- v1.2021 10/13/2020: Approved

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v2.2020 04/06/2020: Approved

v1.2020 10/11/2019: Approved

v2.2019 04/03/2019: Approved

v1.2019 10/03/2018: Approved

v1.2018 02/28/2018: Approved

v1.2017 01/25/2017: Approved

Revisions:

Version	Date	Editor	Description
v2.2021 <i>GEN01-0921.1</i>	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.

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Version	Date	Editor	Description
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

Original Effective Date: 06/04/2015

Primary Author: Gwen Fraley, MS, CGC

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