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 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, pharmacogenetics and thrombophilia, somatic tumor testing, and whole exome sequencing. All tests listed in these guidelines may not require prior authorization; please refer to health plan.

Appropriate Use Criteria

Genetic Testing for Germline Conditions

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

Multifactorial (Non-Mendelian) Conditions

A multifactorial disease is defined as a condition caused by the interaction of multiple genes and/or environmental factors. Genetic testing may be used to predict risk or susceptibility to multifactorial conditions but is not diagnostic.

Genetic testing for multifactorial diseases is 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
- Multiple congenital anomalies not specific to a well-delineated genetic syndrome
- Known or suspected infantile or early-onset 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

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

For reproductive indications, please see Reproductive Carrier Screening and Prenatal Diagnosis Guidelines.

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 Pharmacogenetic 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.

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

Codes that do not meet medical necessity criteria:

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

Background

Genetic Testing

The number of commercially available genetic tests is increasing rapidly, with some estimates of over 70,000 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 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 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 in 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 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 American College of Medical Genetics (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; 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 early onset epileptic encephalopathy. 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 recent 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 ASD as noted by ACMG (Schaefer and Mendelsohn 2013).

See Reproductive Carrier Screening and Prenatal Diagnosis Guidelines 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.

Professional Society Guidelines

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Revision History

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Revisions:

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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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