

Clinical Appropriateness Guidelines

Genetic Testing for Single-Gene and Multifactorial Conditions

EFFECTIVE MARCH 31, 2019



8600 West Bryn Mawr Avenue
South Tower - Suite 800 Chicago, IL 60631
www.aimspecialtyhealth.com

Appropriate.Safe.Affordable
© 2019 AIM Specialty Health
2069-0319b

Table of Contents

Scope	3
Appropriate Use Criteria	3
Single-Gene Testing	3
Multi-Gene Diagnostic Panels	3
Multifactorial (Non-Mendelian) Conditions	3
Chromosomal Microarray Analysis.....	4
HLA Histocompatibility Testing.....	4
CPT Codes.....	5
Background	5
Genetic Testing	5
NGS Multi-Gene Panels	6
Microarray.....	7
Professional Society Guidelines.....	7
Selected References.....	7
Revision History.....	8

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 susceptibility, hereditary cardiac disease, 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

Single-Gene Testing

Genetic testing for a single gene 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 mutation testing, common variants)

Multi-Gene Diagnostic Panels

Genetic testing with a multi-gene panel is medically necessary when the above criteria for single-gene testing are met as well as all of the following:

- The test is as targeted as possible for the clinical situation (i.e. does not include genes or mutations that are not clinically reasonable for the specific scenario)
- Clinical presentation warrants testing of multiple genes

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

Background

Genetic Testing

The number of commercially available genetic tests is increasing rapidly, with some estimates of over 70,000 genetic 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.

PROPRIETARY

Guidelines developed by, and used with permission from, Informed Medical Decisions, Inc. © 2019 Informed Medical Decisions, Inc. All Rights Reserved.

- 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 subject's 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 or comparative genomic hybridization (CMA, CGH) detects microduplications and microdeletions in chromosomal DNA. In recent years, 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.

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 mutations 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 mutations in genes that are not clinically actionable.

Professional Society Guidelines

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.

Miller DT, Adam MP, Aradhya S, et al. Consensus statement: chromosomal microarray is a first-tier clinical diagnostic test for individuals with developmental disabilities or congenital anomalies. *Am J Hum Genet.* 2010 May 14;86(5):749-64. PubMed PMID: 20466091.

Schaefer GB, Mendelsohn NJ. Clinical genetics evaluation in identifying the etiology of autism spectrum disorders: 2013 guideline revisions. *Genet Med.* 2013 May;15(5):399-407. Epub 2013 Mar 21. PubMed PMID: 23519317.

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 Allen NM, Conroy J, Shahwan A, et al. Chromosomal microarray in unexplained severe early onset epilepsy - A single centre cohort. *Eur J Paediatr Neurol.* 2015 Jul;19(4):390-4. Epub 2015 Apr 10. PubMed PMID: 25920948.
- 3 Baris HN, Tan W-H, Kimonis VE, et al. Diagnostic utility of array-based comparative genomic hybridization in a clinical setting. *Am J Med Genet Part A* 2007;143A:2523-33. PubMed PMID: 17910064.
- 4 Beaudet AL. The utility of chromosomal microarray analysis in developmental and behavioral pediatrics. *Child Dev.* 2013 Jan-Feb;84(1):121-32. Epub 2013 Jan 11. PubMed PMID: 23311723.
- 5 Berg AT, Coryell J, Saneto RP, et al. Early-life epilepsies and the emerging role of genetic testing. *JAMA Pediatr.* 2017 Sep 1;171(9):863-71 PubMed PMID: 28759667.

PROPRIETARY

Guidelines developed by, and used with permission from, Informed Medical Decisions, Inc. © 2019 Informed Medical Decisions, Inc. All Rights Reserved.

- 6 Ellison JW, Ravnan JB, Rosenfeld JA, et al. Clinical utility of chromosomal microarray analysis. *Pediatrics*. 2012 Nov;130(5):e1085-95. Epub 2012 Oct 15. PubMed PMID: 23071206.
- 7 Epilepsy Phenome/Genome Project Epi4K Consortium. Copy number variant analysis from exome data in 349 patients with epileptic encephalopathy. *Ann Neurol*. 2015 Aug;78(2):323-8. Epub 2015 Jul 1. PubMed PMID: 26068938.
- 8 Hollenbeck D, Williams CL, Drazba K, et al. Clinical relevance of small copy-number variants in chromosomal microarray clinical testing. *Genet Med*. 2017 Apr;19(4):377-85. Epub 2016 Sep 15. PubMed PMID: 27632688.
- 9 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.
- 10 Mefford HC, Yendle SC, Hsu C, et al. Rare copy number variants are an important cause of epileptic encephalopathies. *Ann Neurol*. 2011 Dec;70(6):974-85. PubMed PMID: 22190369.
- 11 Mercimek-Mahmutoglu S, Patel J, Cordeiro D, et al. Diagnostic yield of genetic testing in epileptic encephalopathy in childhood. *Epilepsia*. 2015 May;56(5):707-16. Epub 2015 Mar 25. PubMed PMID: 25818041.
- 12 Noh GJ, Jane Tavyev Asher Y, Graham JM Jr. Clinical review of genetic epileptic encephalopathies. *Eur J Med Genet*. 2012 May;55(5):281-98. Epub 2012 Jan 25. PubMed PMID: 22342633.
- 13 Olson H, Shen Y, Avallone J, et al. Copy number variation plays an important role in clinical epilepsy. *Ann Neurol*. 2014 Jun;75(6):943-58. Epub 2014 Jun 13. PubMed PMID: 24811917.
- 14 Poduri A. When Should genetic testing be performed in epilepsy patients? *Epilepsy Curr*. 2017 Jan-Feb;17(1):16-22. PubMed PMID: 28331464.
- 15 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.
- 16 Sys M, Van den Bogaert A, Roosens B, et al. Can clinical characteristics be criteria to perform chromosomal microarray-analysis in children and adolescents with autism spectrum disorders? *Minerva Pediatr*. 2018 Jun;70(3):225-232. Epub 2016 Sep 8. PubMed PMID: 27607483.
- 17 Tumienė B, Maver A, Writzl K, Hodžić A, Čaturilo G, Kuzmanić-Šamija R, Čulić V, Peterlin B. Diagnostic exome sequencing of syndromic epilepsy patients in clinical practice. *Clin Genet*. 2018 May;93(5):1057-62. Epub 2018 Mar 23. PubMed PMID: 29286531
- 18 Wang JC, Ross L, Mahon LW, et al. Regions of homozygosity identified by oligonucleotide SNP arrays: evaluating the incidence and clinical utility. *Eur J Hum Genet*. 2015 May;23(5):663-71. Epub 2014 Aug 13. PubMed PMID 25118026.

Revision History

Medical Advisory Review Board Review:

v1.2019 11/07/2018: Reviewed

v1.2018 03/31/2018: Reviewed

Clinical Steering Committee Review:

v1.2019 10/03/2018: Approved

v1.2018 02/28/2018: Approved

v1.2017 01/25/2017: Approved

PROPRIETARY

Guidelines developed by, and used with permission from, Informed Medical Decisions, Inc. © 2019 Informed Medical Decisions, Inc. All Rights Reserved.

Revisions:

Version	Date	Editor	Description
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.

PROPRIETARY

Guidelines developed by, and used with permission from, Informed Medical Decisions, Inc. © 2019 Informed Medical Decisions, Inc. All Rights Reserved.

v1.2015	06/04/2015	Gwen Fraley, MS, CGC	Original version
---------	------------	-------------------------	------------------

Original Effective Date: 06/04/2015

Primary Author: Gwen Fraley, MS, CGC