Protocol

General Approach to Genetic Testing

(20491)

Medical Benefit		**Effective Date**: 01/01/17	**Next Review Date**: 11/19
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Preauthorization is required.

The following protocol contains medical necessity criteria that apply for this service. The criteria are also applicable to services provided in the local Medicare Advantage operating area for those members, unless separate Medicare Advantage criteria are indicated. If the criteria are not met, reimbursement will be denied and the patient cannot be billed. Please note that payment for covered services is subject to eligibility and the limitations noted in the patient's contract at the time the services are rendered.

Populations	Interventions	Comparators	Outcomes
Individuals: • Who are symptomatic with a suspected genetically associated disease	Interventions of interest are: • Genetic testing for a suspected genetically associated disorder	Comparators of interest are: • Standard clinical management without genetic testing	Relevant outcomes include: • Test accuracy • Test validity • Disease-specific survival • Overall survival • Change in disease status • Morbid events • Functional outcomes • Changes in reproductive decision making
Individuals: • Who are asymptomatic and have a close relative diagnosed with a genetically associated disease	Interventions of interest are: • Genetic testing for a genetically associated disorder	Comparators of interest are: • Standard clinical management without genetic testing	Relevant outcomes include: • Test accuracy • Test validity • Disease-specific survival • Overall survival • Change in disease status • Morbid events • Functional outcomes • Changes in reproductive decision making

DESCRIPTION

Commercially available genetic tests can perform a host of functions, such as providing a guided intervention in both symptomatic or asymptomatic people, identifying people at risk for future disorders, predicting the prognosis of a diagnosed disease, and predicting the appropriate treatment response. The conceptual framework provided herein offers an outline for evaluating the utility of genetic tests, by classifying the types of genetic tests into clinically relevant categories and developing criteria that can be used for evaluating tests in each category.

SUMMARY OF EVIDENCE

This conceptual framework addresses genetic testing in nonreproductive settings. Genetic testing in reproductive settings is addressed separately (e.g., the Carrier Screening for Genetic Diseases Protocol, the Invasive Prenatal (Fetal) Diagnostic Testing Protocol, and the Preimplantation Genetic Testing Protocol). For categories of genetic testing for which the benefit of testing is for the individual, criteria for medical necessity apply. When the benefit of testing is not for the individual, but for a family member, medical necessity criteria may not apply, and the criteria are developed for clinical utility.

POLICY

Genetic testing classified in one of the categories below may be considered **medically necessary** when all criteria are met for each category, as outlined in the Policy Guidelines section:

1. Testing of an affected (symptomatic) individual's germline DNA to benefit the individual (excluding reproductive testing)
    a. Diagnostic
    b. Prognostic
    c. Therapeutic
2. Testing cancer cells of an affected individual to benefit the individual
    a. Diagnostic
    b. Prognostic
    c. Therapeutic
3. Testing an asymptomatic individual to determine future risk of disease

Genetic testing that does not meet the criteria for a specific category is considered **investigational or not medically necessary**, according to the standard definitions used for these terms (see Policy Guidelines).

Genetic testing for other diseases such as but not limited to chronic fatigue, hyperhomocysteinemia, hereditary ataxia, or ADHD (attention deficit hyperactivity disorder) has not been proven to be medically effective and is considered **investigational**.

Genetic testing for variants in the MTHFR gene is considered **investigational** in all situations.

Use of home testing kits is considered **investigational**.

POLICY GUIDELINES

MEDICAL NECESSITY CRITERIA

The criteria listed below for medical necessity represent minimum criteria that must be met in each category to conclude that a test is medically necessary. Genetic testing is considered **medically necessary** for a genetic or heritable disorder when the following are met.

For ALL genetic testing, the condition being tested for must have either:

- Reduced life expectancy; OR
- At least moderate–to-severe morbidity.[3]

For the specific categories of testing, the following criteria must also be met:

1. Testing of an affected (symptomatic) individual's germline to benefit the individual (excluding reproductive testing)
    a. Diagnostic
        i. an association between the marker and the disorder has been established AND
        ii. symptoms of the disease are present AND
        iii. a definitive diagnosis cannot be made based upon history, physical examination, pedigree analysis, and standard diagnostic studies/tests AND
        iv. the clinical utility of identifying the variant has been established:
            1) Leads to changes in clinical management of the condition that improve outcomes; OR
            2) Eliminates the need for further clinical workup or invasive testing; OR
            3) Leads to discontinuation of interventions that are unnecessary and/or ineffective.
    b. Prognostic
        i. An association between the marker and the natural history of the disease has been established AND
        ii. Clinical utility of identifying the variant has been established:
            1) Provides incremental prognostic information above that of standard testing; AND
            2) Reclassifies patients into clinically relevant prognostic categories for which there are different treatment strategies; AND
            3) Reclassification leads to changes in management that improve outcomes.
    c. Therapeutic
        i. Genetic testing identifies variants of a phenotype/metabolic state that relate to different pharmacokinetics, drug efficacy or adverse drug reactions; AND
        ii. Clinical utility of identifying the variant has been established:
            1) Leads to initiation of effective medication(s) OR
            2) Leads to discontinuation of medications that are ineffective or harmful OR
            3) Leads to clinical meaningful change in dosing of medication that is likely to improve outcomes.
2. Testing cancer cells of an affected individual to benefit the individual
    a. Diagnostic
        i. Genetic testing can establish the cell origin of a cancer when the origin is uncertain following standard work-up AND
        ii. Clinical utility of identifying the variant has been established:
            1) Start effective treatment; OR
            2) Discontinue ineffective or harmful treatment
    b. Prognostic
        i. An association between the marker and the natural history of the disease has been established AND

ii. Clinical utility of identifying the variant has been established:

1) Provides incremental prognostic information above that of standard testing; AND

2) Reclassifies patients into clinically relevant prognostic categories for which there are different treatment strategies; AND

3) Reclassification leads to changes in management that improve outcomes.

c. Therapeutic

i. Association between a variant and treatment response to a particular drug has been established AND

ii. Clinical utility has been established:

1) The patient is a candidate for targeted drug therapy associated with a specific variant; AND

2) There is a clinically meaningful improvement in outcomes when targeted therapy is given for the condition.

3. Testing an asymptomatic individual to determine future risk of disease

i. An association between the marker and future disorder has been established AND

ii. Clinical utility has been established

1) There is a presymptomatic phase for this disorder in which interventions or surveillance are available AND

2) Interventions in the presymptomatic phase are likely to improve outcomes:

a. Prevent/delay onset of disease OR

b. Detect disease at an earlier stage for which treatment is more effective OR

c. Discontinuation of ineffective or unnecessary interventions.

Genetic testing is considered **not medically necessary** when:

- testing is not considered standard of care, such as when the clinical diagnosis can be made without the use of a genetic test.
- testing is not clinically appropriate for the patient's condition (e.g., when it would not change diagnosis and/or management). Other situations where testing is not clinically appropriate include, but are not limited to:
  - testing performed entirely for nonmedical (e.g., social) reasons
  - testing not expected to provide a definitive diagnosis that would obviate the need for further testing.
- testing is performed primarily for the convenience of the patient, physician, or other health care provider.
- testing would result in outcomes that are equivalent to outcomes using an alternative strategy, and the genetic test is more costly.

Limitations of Genetic Testing

- The testing methods may not detect all variants that may occur in a gene.
- Genetic testing may identify variants of uncertain significance.
- Genetic testing may not necessarily determine the clinical outcome.

- Different genes can cause the same disease (genetic heterogeneity).
- A variant in a gene may cause different phenotypes (phenotypic heterogeneity).
- Some disease-causing genes may not yet be identified.
- Genetic testing is subject to laboratory error.

GENERAL PRINCIPLES OF GENETIC TESTS

A test should be cleared or approved by the U.S. Food and Drug Administration (FDA), or performed in a Clinical Laboratory Improvement Amendment (CLIA)-certified laboratory.

The accuracy and indications for the test should be derived from peer-reviewed literature that focuses on three main principles: (1) analytic validity (technical accuracy of the test in detecting a variant that is present or in excluding a variant that is absent); (2) clinical validity (diagnostic performance of the test [sensitivity, specificity, positive and negative predictive values] in detecting clinical disease); and (3) clinical utility (i.e., how results of the diagnostic test will be used to change management of the patient and whether these changes in management lead to clinically important improvements in health outcomes).

The following hereditary conditions, *but not limited to these*, that may be **medically necessary** for genetic testing if they meet the criteria above (**Note:** additional hereditary conditions may be **medically necessary**, and those addressed in separate protocols are not included here):

- 22q11 deletion syndrome
- Achondroplasia (FGFR3)
- Albinism
- Amyotrophic lateral sclerosis (ALS)
- Angelman syndrome
- Canavan Disease
- Classical lissencephaly
- Congenital adrenal hyperplasia (CAH)
- Congenital amegakaryocytic thrombocytopenia
- Congenital profound deafness
- Crouzon syndrome
- Dentatorubral-pallidoluysian atrophy
- Dysferlin myopathy
- Dystonia
- Ehlers-Danlos syndrome
- Fabry disease
- Factor XIII deficiency, congenital
- Familial hypocalciuric hypercalcemia
- Familial Mediterranean fever
- Fanconi anemia, group C
- Friedreich's ataxia
- Gaucher disease
- Gitelman's syndrome
- Hemoglobin S and/or C
- Hemophilia A and B
- Hemophilia A/VWF (F8[factor VIII])
- Hereditary amyloidosis
- Hereditary paraganglioma
- Hereditary spastic paraplegia 3 and 4
- Huntington's disease
- Hypochondroplasia
- Jackson-Weiss syndrome
- Kallmann syndrome
- Kennedy disease
- Leber hereditary optic neuropathy
- Leigh Syndrome and NARP
- Limb girdle muscular dystrophy
- Marfan's syndrome
- McArdle disease
- Medium chain acyl coA dehydrogenase deficiency
- Medullary thyroid carcinoma
- MELAS
- Mucopolysaccharidoses type 1
- Muenke syndrome
- Multiple endocrine neoplasia type 1
- Myoclonic epilepsy
- Myotonic dystrophy
- Nephrotic syndrome, congenital
- Neurofibromatosis type 1
- Neurofibromatosis Type 1-Like Syndrome

- Neurofibromatosis type 2
- Neutropenia, congenital cyclic
- Niemann-Pick Disease
- Oculopharyngeal muscular dystrophy
- Pfeiffer syndrome
- Phenylketonuria (PKU)
- Prader Willi/Angelman syndromes
- Pyruvate kinase deficiency
- Retinoblastoma
- Saethre-Chotzen syndrome
- SHOX-related short stature
- Sickle cell disease
- Smith-Lemli-Opitz syndrome
- Spinal muscular atrophy
- Spinocerebellar ataxia
- Tay-Sacs Disease
- Thanatophoric dysplasia
- Von Hippel-Lindau disease

GENETICS NOMENCLATURE UPDATE

The Human Genome Variation Society nomenclature is used to report information on variants found in DNA and serves as an international standard in DNA diagnostics. It is being implemented for genetic testing medical protocol updates starting in 2017 (see Table PG1). The Society's nomenclature is recommended by the Human Variome Project, the HUman Genome Organization, and by the Human Genome Variation Society itself.

The American College of Medical Genetics and Genomics and the Association for Molecular Pathology standards and guidelines for interpretation of sequence variants represent expert opinion from both organizations, in addition to the College of American Pathologists. These recommendations primarily apply to genetic tests used in clinical laboratories, including genotyping, single genes, panels, exomes, and genomes. Table PG2 shows the recommended standard terminology—"pathogenic," "likely pathogenic," "uncertain significance," "likely benign," and "benign"—to describe variants identified that cause Mendelian disorders.

Table PG1. Nomenclature to Report on Variants Found in DNA

Previous	Updated	Definition
Mutation	Disease-associated variant	Disease-associated change in the DNA sequence
	Variant	Change in the DNA sequence
	Familial variant	Disease-associated variant identified in a proband for use in subsequent targeted genetic testing in first-degree relatives

Table PG2. ACMG-AMP Standards and Guidelines for Variant Classification

Variant Classification	Definition
Pathogenic	Disease-causing change in the DNA sequence
Likely pathogenic	Likely disease-causing change in the DNA sequence
Variant of uncertain significance	Change in DNA sequence with uncertain effects on disease
Likely benign	Likely benign change in the DNA sequence
Benign	Benign change in the DNA sequence

American College of Medical Genetics and Genomics; AMP: Association for Molecular Pathology.

GENETIC COUNSELING

Experts recommend formal genetic counseling for patients who are at risk for inherited disorders and who wish to undergo genetic testing. Interpreting the results of genetic tests and understanding risk factors can be difficult for some patients; genetic counseling helps individuals understand the impact of genetic testing, including the possible effects the test results could have on the individual or their family members. It should be noted that genetic counseling may alter the utilization of genetic testing substantially and may reduce inappropriate testing; further, genetic counseling should be performed by an individual with experience and expertise in genetic medicine and genetic testing methods.

MEDICARE ADVANTAGE

The above policy and policy guidelines content is applicable for Medicare Advantage for diagnostic testing, prognostic testing and testing for genetic variants that alter response to treatment or to an environmental factor which meet medically necessary criteria. Because Medicare generally only covers tests that are medically necessary for diagnosis and treatment, panels that are risk assessment testing may be considered **not medically necessary**.

BACKGROUND

The purpose of this conceptual framework is to assist evaluation of the utility of genetic tests. In providing a framework for evaluating genetic tests, this protocol will not determine the clinical utility of genetic testing for specific disorders. Rather, it provides guidelines that can be applied to a wide range of tests.

This conceptual framework applies only if there is not a separate protocol that outlines specific criteria for testing. If a separate protocol exists, then the criteria for medical necessity in that evidence review supersede the guidelines herein.

This conceptual framework does not include cytogenetic testing (karyotyping), biochemical testing, or molecular testing for infectious disease.

This conceptual framework also does not address reproductive genetic testing. There are separate protocols for genetic testing in the reproductive setting, addressing, e.g., carrier testing for genetic diseases, invasive prenatal (fetal) diagnostic testing, and preimplantation genetic testing.

The following categories of genetic testing are addressed herein:

1. Testing of an affected (symptomatic) individual's germline to benefit the individual
    a. Diagnostic
    b. Prognostic
    c. Therapeutic
2. Testing cancer cells of an affected individual to benefit the individual
    a. Diagnostic
    b. Prognostic
    c. Therapeutic
3. Testing an asymptomatic individual to determine future risk of disease
4. Testing of an affected individual's germline to benefit family members.

Reproductive testing is not addressed herein.

DEFINITIONS

Genetic Testing

Genetic testing involves the analysis of chromosomes, DNA, RNA, genes, or gene products to detect inherited (germline) or noninherited (somatic) genetic variants related to disease or health.

Carrier Testing

A carrier of a genetic disorder has one abnormal allele for a disorder. When associated with an autosomal recessive or X-linked disorder, carriers of the causative variant are typically unaffected. When associated with an

autosomal dominant disorder, the person has one normal copy of the gene and one mutated copy of the gene; such a person may be affected with the disorder, may be unaffected but at high risk of developing the disease later in life, or may remain unaffected because of the sex-limited nature of the disease.

Carrier testing may be offered to people: (a) who have family members with a genetic condition; (b) who have family members who are identified carriers; and (c) who are members of ethnic or racial groups known to have a higher carrier rate for a particular condition.

Germline Variants

Germline variants are present in the DNA of every cell of the body, from the moment of conception. They include cells in the gonads (testes or ova) and could, therefore, be passed on to offspring.

Somatic Variants

Somatic variations occur with the passage of time and are restricted to a specific cell or cells derived from it. If these variants are limited to cells that are not in the gonads, they will not be passed on to offspring.

Pharmacogenomics

Pharmacogenomics studies how a person's genetic makeup affects his or her body's response to drugs.

REGULATORY STATUS

Clinical laboratories may develop and validate tests in-house and market them as a laboratory service; laboratory-developed tests (LDTs) must meet the general regulatory standards of the Clinical Laboratory Improvement Amendments (CLIA). Most genetic tests are lab tests available under the auspices of the CLIA. Laboratories that offer LDTs must be licensed by the CLIA for high-complexity testing. To date, the U.S. Food and Drug Administration has chosen not to require any regulatory review of this test.

RELATED PROTOCOLS

Carrier Screening for Genetic Diseases

General Approach to Evaluating the Utility of Genetic Panels

Invasive Prenatal (Fetal) Diagnostic Testing

Preimplantation Genetic Testing

Services that are the subject of a clinical trial do not meet our Technology Assessment Protocol criteria and are considered investigational. *For explanation of experimental and investigational, please refer to the Technology Assessment Protocol.*

It is expected that only appropriate and medically necessary services will be rendered. We reserve the right to conduct prepayment and postpayment reviews to assess the medical appropriateness of the above-referenced procedures. **Some of this protocol may not pertain to the patients you provide care to, as it may relate to products that are not available in your geographic area.**

REFERENCES

We are not responsible for the continuing viability of web site addresses that may be listed in any references below.

1. ACMG Board of Directors. Clinical utility of genetic and genomic services: a position statement of the American College of Medical Genetics and Genomics. Genet Med. Jun 2015;17(6):505-507. PMID 25764213
2. Teutsch SM, Bradley LA, Palomaki GE, et al. The Evaluation of Genomic Applications in Practice and Prevention (EGAPP) Initiative: methods of the EGAPP Working Group. Genet Med. Jan 2009;11(1):3-14. PMID 18813139
3. Beltran-Sanchez H, Razak F, Subramanian SV. Going beyond the disability-based morbidity definition in the compression of morbidity framework. Glob Health Action. Sep 2014;7:24766. PMID 25261699