MEDICAL POLICY

MEDICAL POLICY DETAILS	
Medical Policy Title	**GENETIC TESTING FOR INHERITED DISORDERS**
Policy Number	**2.02.03**
Category	**Laboratory Test**
Effective Date	**10/18/01**
Revised Date	**10/18/01, 02/20/03, 04/15/04, 05/18/05, 05/18/06, 05/17/07, 06/19/08, 05/28/09, 05/27/10, 05/19/11, 05/24/12, 06/20/13, 07/17/14, 05/28/15, 0616/16, 07/20/17, 06/21/18, 06/20/19**
Product Disclaimer	• *If a product excludes coverage for a service, it is not covered, and medical policy criteria do not apply.* • *If a commercial product (including an Essential Plan product) or a Medicaid product covers a specific service, medical policy criteria apply to the benefit.* • *If a Medicare product covers a specific service, and there is no national or local Medicare coverage decision for the service, medical policy criteria apply to the benefit.*

POLICY STATEMENT

I. Based upon our criteria and review of the peer-reviewed literature, genetic testing for inheritable diseases, when offered in a setting with adequately trained health care professionals to provide appropriate pre- and post-test counseling and performed by a qualified laboratory, has been medically proven to be effective and therefore, **medically appropriate** when:
   A. There is reasonable expectation, based on family history, pedigree analysis, risk factors, and / or signs or symptoms that a genetically inherited condition exists; and
   B. The testing method is considered a proven method for the identification of a genetically-linked disease; and
   C. The test results will influence decisions concerning disease treatment or prevention.

II. Based upon our criteria and the lack of peer-reviewed literature, genetic testing for chronic fatigue or ADHD has not been proven to be medically effective and is considered **investigational**.

III. Based upon our criteria and the lack of peer-reviewed literature, genetic testing using "direct-to-the-consumer" home testing kits is considered **investigational**.

This policy is to be utilized ONLY when Health Plan medical policies do not exist for specified diseases or conditions. *Refer to the following Medical Policies for the specified diseases indicated:*

Genetic Testing for Hereditary Hemochromatosis - Policy #2.02.05,

Genetic Testing for Hereditary BRCA Mutations - Policy # 2.02.06,

Genetic Testing for Germline Mutations of the RET Proto Oncogene in Medullary Carcinoma of the Thyroid - Policy #2.02.07,

Genetic Testing for Inherited Susceptibility to Colorectal Cancer - Policy #2.02.11,

Genetic Testing for Familial Alzheimer's Disease - Policy #2.02.16,

Genetic Testing for Cystic Fibrosis – Policy #2.02.17,

Genetic Testing for Congenital Long QT Syndrome – Policy #2.02.38,

Chromosomal Microarray (CMA) for the Prenatal Evaluation and Evaluation of Patients with Developmental Delay/Intellectual Disability or Autism Spectrum Disorder – Policy #2.02.42,

Genetic Testing for Susceptibility to Hereditary Cancers – Policy #2.02.44, and

Prenatal Genetic Testing - Policy #4.01.03.

Refer to Corporate Medical Policy #11.01.03 regarding Experimental and Investigational Services.

POLICY GUIDELINES

I. The Health Plan and its employees adhere to all state and Federal laws concerning the confidentiality of genetic testing and the results of genetic testing. All records, findings and results of any genetic test performed on any person shall be deemed confidential and shall not be disclosed without the written informed consent of the person to whom such genetic test relates. This information shall not be released to any person or organization not specifically authorized by the individual subject of the test or in compliance with applicable law.

II. Laboratories performing clinical tests must be certified under the Clinical Laboratory Improvement Amendments of 1988 (CLIA).

III. The following factors should be considered when determining the medical appropriateness of a genetic test:

A. There must be reasonable expectation based on family history, pedigree analysis, risk factors, and/or symptomatology that a genetically inherited condition exists. Autosomal recessive disorders may be present without a family history.
B. The genotypes to be detected by a genetic test must be shown by scientifically valid methods to be associated with the occurrence of the disease, and the analytical and clinical validity of the test must be established.
C. The clinical utility of the test must be established (e.g., test results will influence decisions concerning disease treatment or prevention). If the genetic test is being done for knowledge only and that knowledge will not alter management or treatment of the patient then the testing is **not medically appropriate**.

IV. Coverage for genetic testing for specific diseases, as well as prior authorization, is contract dependent. Genetic testing done for occupation-associated risk is typically excluded from most contracts. Genetic testing as part of an organ donor search is excluded from most contracts. Please refer to your Customer (Member/Provider) Service Department for determination of contract benefits.

The following are some conditions for which there are genetics tests available from clinical genetics laboratories that are not addressed in other medical policies. Genetic testing for these conditions may be medically appropriate if after history, physical examination, pedigree analysis, genetic counseling, and completion of conventional diagnostic studies, a definitive diagnosis remains uncertain. These include, but are not limited to:

• Alpha-1-antitrypsin deficiency (AAT; emphysema and liver disease);	• Hemophilia A and B (HEMA and HEMB; bleeding disorders);
• Amyotrophic lateral sclerosis (ALS; Lou Gehrig's Disease; progressive motor function loss leading to paralysis and death);	• Huntington's disease (HD; usually midlife onset; progressive, lethal, degenerative neurological disease);
• Canavan Disease (cerebral degenerative diseases of infancy)	• Myotonic dystrophy (MD; progressive muscle weakness; most common form of adult muscular dystrophy);
• Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL);	• Neurofibromatosis type 1 (NF1; multiple benign nervous system tumors that can be disfiguring; cancers);
• Charcot-Marie-Tooth (CMT; loss of feeling in ends of limbs);	• Niemann-Pick Disease (faulty lipid metabolism causes harmful amounts of lipids to accumulate in the spleen, liver, lungs, bone marrow & brain)
• Congenital adrenal hyperplasia (CAH; hormone deficiency; ambiguous genitalia and male pseudohermaphroditism);	• Phenylketonuria (PKU; progressive mental retardation due to missing enzyme; correctable by diet);
• Congenital, Profound Deafness (DFNB1; GJB2 - Connexin 26 nonsyndromic, prelingual deafness)	• Prader Willi/Angelman syndromes (PW/A; decreased motor skills, cognitive impairment, early death);
• Duchenne muscular dystrophy/Becker muscular dystrophy (DMD; severe to mild muscle wasting, deterioration, weakness);	• Retinoblastoma (RB1 mutation; inherited, intraocular neoplasm)

• Dystonia (DYT; muscle rigidity, repetitive twisting movements);	• Sickle cell disease (SS; blood cell disorder; chronic pain and infections);
• Fanconi anemia, group C (FA; anemia, leukemia, skeletal deformities);	• Thalassemias (THAL; anemias - reduced red blood cell levels);
• Fragile X syndrome (FRAX; leading cause of inherited mental retardation);	• Tay-Sachs Disease (TS; fatal neurological disease of early childhood; seizures, paralysis)
• Gaucher disease (GD; enlarged liver and spleen, bone degeneration);	• Von Hipple-Lindau disease (hemangioblastomas of brain, spinal cord & retinas; renal cysts & carcinomas; pheochromocytomas; & endolymphatic sac tumors.)

DESCRIPTION

A genetic test is defined as "the analysis of human DNA, ribonucleic acid (RNA), chromosomes, proteins, and certain metabolites in order to detect alterations related to a heritable disorder. This can be accomplished by directly examining the DNA or RNA that makes up a gene (e.g., direct testing) looking at markers co-inherited with a disease-causing gene (e.g., linkage testing) assaying certain metabolites (e.g., biochemical testing) or examining the chromosomes (cytogenetics testing)" (Gene Tests, 2006).

Genetic disease is defined as a morbid disorder that is caused by a variation in human genetic material. In some cases, merely the presence of the variation will cause illness. It is estimated that genetic mutations are responsible for 3,000-4,000 hereditary disorders. Genetic defects find their most varied expression in disruptions of the intricate chemistry that underlies human structure and metabolism. These manifestations range from such well-known conditions as Down syndrome and Phenylketonuria (PKU) to very rare conditions. Some genetic disorders are caused by the mutation of a single gene (e.g., sickle cell anemia; cystic fibrosis; Tay-Sachs disease), while chromosomal disorders are caused by an excess or deficiency of a number of genes (e.g., Down syndrome). Other heritable conditions are considered multifactorial inheritance disorders (e.g., heart disease and many cancers), arising from a combination of genetic and environmental factors.

Genetic tests are used for several reasons, including:

I. Carrier screening, which involves identifying unaffected individuals who carry one copy of a gene for a disease that requires two copies for the disease to be expressed;
II. Prenatal diagnostic testing;
III. Newborn screening such as Phenylketonuria (PKU);
IV. Presymptomatic testing for predicting adult-onset disorders such as Huntington's disease;
V. Presymptomatic testing for estimating the risk of developing adult-onset diseases; and
VI. Confirmational diagnosis of a symptomatic individual.

Direct-to-consumer marketing of genetic testing, frequently using "home testing" kits, poses issues related to appropriateness of test utilization, interpretation of results, lack of pre- and post-test counseling and follow-up.

RATIONALE

The rationale for this policy is based on the recommendations in the Final Report of the Task Force on Genetic Testing and the Secretary's Advisory Committee on Genetic Testing.

Medically appropriate genetic testing requires that there must be reasonable expectation based on family history, pedigree analysis, risk factors, and/or symptomatology that a genetically inherited condition exists. With a few limited exceptions (e.g., PKU testing and other newborn screenings), general screening of populations for diseases that can be attributed to genetic mutations is not advocated in scientific literature.

The genotypes to be detected by a genetic test must be shown by scientifically valid methods to be associated with the occurrence of the disease, and the analytical and clinical validity of the test must be established. Analytical validity is an indicator of how well a test measures the property or characteristic it is intended to measure, and it is made up of three components: analytical sensitivity, analytical specificity and reliability.

Clinical validity in genetic testing is a measurement of the accuracy with which a test identifies or predicts a clinical condition and involves the following: clinical sensitivity, clinical specificity, positive predictive value, negative predictive value, heterogeneity and penetrance.

The clinical utility of a genetic test must be established, e.g., test results will influence decisions concerning disease treatment or prevention. The development of genetic tests that can diagnose or predict disease occurrence has far outpaced the development of interventions to treat, ameliorate or prevent those same diseases. Clinical utility refers to the ability of genetic test results, either positive or negative, to provide information that is of value in the clinical setting. Specifically for positive test results, this could involve instituting treatments or surveillance measures, making decisions concerning future conception, or avoiding harmful treatments. Negative test results can have clinical utility in that unnecessary treatments or surveillance can be avoided. In the absence of such interventions, the benefits of testing are limited, and in fact, can cause psychological harm.

Information on the risks and benefits of genetic testing must be presented fully and objectively without coercion to persons contemplating genetic testing. The patient must give fully informed consent for the test with appropriate pre-test counseling. When appropriate, there should be a plan for post-test counseling.

Genetic testing of children to confirm current symptomatology or predict adult onset diseases is not considered medically necessary unless direct medical benefit would be lost by waiting until the child has reached adulthood. It is generally accepted in the published literature that unless useful medical intervention can be offered to children as a result of testing, formal testing should wait until the child is old enough to understand the consequences of testing and request it for him-or herself. Ethical concerns related to the testing of children include the breach of confidentiality that is required by revealing test results to parents, the lack of ability to counsel the child in a meaningful way regarding the risks and benefits of testing, the impact a positive test could have in terms of discrimination, and the potential psychological damage that could occur from distorting a family's perception of the child.

Direct-to-consumer genetic testing has been marketed to the public as a method of identifying the presence of or susceptibility to disease. The American College of Medical Genetics (2008) believes that it is critical for the public to realize that genetic testing is only one part of a complex process which has the potential for both positive and negative impact on health and well-being. The College believes that the following should be considered minimum requirements for any genetic testing protocol: A knowledgeable professional should be involved in the process of ordering and interpreting a genetic test. The consumer should be fully informed regarding what the test can and cannot say about his or her health. The scientific evidence on which a test is based should be clearly stated. The clinical testing laboratory must be accredited by CLIA, the State and/or other applicable accrediting agencies.

CODES

- *Eligibility for reimbursement is based upon the benefits set forth in the member's subscriber contract.*
- *CODES MAY NOT BE COVERED UNDER ALL CIRCUMSTANCES. PLEASE READ THE POLICY AND GUIDELINES STATEMENTS CAREFULLY.*
- *Codes may not be all inclusive as the AMA and CMS code updates may occur more frequently than policy updates.*

CPT Codes

Code	Description
81161	DMD (dystrophin) (eg, Duchenne/Becker muscular dystrophy) deletion analysis, and duplication analysis, if performed
81200	ASPA (aspartoacylase) (e.g., Canavan disease) gene analysis, common variants (e.g., E285A, Y231X)
81205	BCKDHB (branched-chain keto acid dehydrongenase E1, beta polypeptide) (e.g., Maple syrup urine disease) gene analysis, common variants (E.g., R183P, G278S, E422X)
81209	BLM (Bloom syndrome, recq helicase-like) (e.g., Bloom syndrome) gene analysis, 2281DEL6INS7 variant

Code	Description
81242	FANCC (Fanconi anemia, complementation group C) (e.g., Fanconi anemia, type C) gene analysis common variant (e.g., IVS4+4A>T)
81243	FMR1 (fragile X mental retardation 1 (e.g., fragile X mental retardation) gene analysis; evaluation to detect abnormal (e.g., expanded) alleles
81244	FMR1 (fragile X mental retardation 1) (e.g., fragile X mental retardation) gene analysis; characterization of alleles (e.g., expended size and methylation status)
81250	G6PC (glucose-6-phosphatase, catalytic subunit) (e.g., glycogen storage disease, type 1A, Von Gierke disease) gene analysis, common variants (e.g., R83C, Q347X)
81251	GBA (glucosidase, beta, acid) (e.g., Gaucher disease) gene analysis, common variants (e.g., N370S, 84GG, L444P, IVS2+1G>A)
81255	HEXA (hexosaminidase A [alpha polypeptide]) (e.g., Tay-Sachs disease) gene analysis, common variants (e.g., 1278INSTATC, 1421+1G>C, G269S)
81256	HFE (hemochromatosis) (e.g., hereditary hemochromatosis) gene analysis, common variants (e.g.,C282Y, H63D)
81257	HBA1/HBA2 (alpha globin 1 and alpha globin 2) (e.g., alpha thalassemia, Hb Bart hydrops fetalis syndrome, HbH disease), gene analysis, for common deletions or variant (e.g., southeast Asian, Thai, Filipino, Mediterranean, alpha 3.7, alpha 4.2, alpha 20.5, and constant spring)
81260	IKBKAP 9inhibitor of kappa light polypeptide gene enhancer in B-cells, kinase complex-associated protein) (e.g., familial dysautonomia) gene analysis, common variants (e.g., 2507+6T>C, R696P)
81271	HTT (Huntington) (eg, Huntington disease) gene analysis; evaluation to detect abnormal (eg expanded) alleles) (effective 1/1/2019)
81274	HTT (Huntington) (eg, Huntington disease) gene analysis; characterization of alleles (eg, expanded size (effective 1/1/2019)
81290	MCOLN1 (mucolipin 1) (e.g. mucolipidosis, type IV) gene analysis, common variants (e.g., IVS3 2A>G, del 6.4kb)
81302	MECP2 (methyl CPG binding protein 2) (e.g., Rett syndrome) gene analysis; full sequence analysis
81303	MECP2 (methyl CPG binding protein 2) (e.g., Rett syndrome) gene analysis; known familial variant
81304	MECP2 (methyl CPG binding protein 2) (e.g., Rett syndrome) gene analysis; duplication/deletion variants
81324	PMP22 (peripheral myelin protein 22) (eg, Charcot-Marie-Tooth, hereditary neuropathy with liability to pressure palsies) gene analysis; duplication/deletion analysis
81325	PMP22 (peripheral myelin protein 22) (eg, Charcot-Marie-Tooth, hereditary neuropathy with liability to pressure palsies) gene analysis; full sequence analysis
81326	PMP22 (peripheral myelin protein 22) (eg, Charcot-Marie-Tooth, hereditary neuropathy with liability to pressure palsies) gene analysis; known familial variant
81330	SMPD1 (sphingomyelin phosphodiesterase 1, acid lysosomal) (e.g., Neimann-Pick disease, type A) gene analysis; common variants (e.g., R496L, L302P, FSP330)
81331	SNRPN/UBE3A (small nuclear ribonucleoprotein polypeptide N and ubiquitin protein ligase E3A) (e.g., Prader-Willi syndrome and/or Angelman syndrome), methylation analysis
81332	SERPINA1 (serpin peptidase inhibitor, clade A, alpha-1 antiproteinase, antitrypsin, member 1) (e.g., alpha-1-antitrypsin deficiency), gene analysis, common variants (e.g., *S and *Z)

Code	Description
81410	Aortic dysfunction or dilation (e.g., Marfan Syndrome, Loeys-Dietz Syndrome, Ehler-Danlos Syndrome type IV, arterial tortuosity syndrome); genomic sequence analysis panel, must include sequencing of at least 9 genes, including FBN1, TGFBR1, TGFBR2, COL3A1, MYH11, ACTA2, SLC2A10, SMAD3, and MYLK
81411	Aortic dysfunction or dilation (e.g., Marfan Syndrome, Loeys-Dietz Syndrome, Ehler-Danlos Syndrome type IV, arterial tortuosity syndrome); duplication/deletion analysis panel, must include analyses for TGFBR1, TGFBR2, MYH11, AND COL3A1
81412	Ashkenazi Jewish associated disorders (eg, Bloom syndrome, Canavan disease, cystic fibrosis, familial dysautonomia, Fanconi anemia group C, Gaucher disease, Tay-Sachs disease), genomic sequence analysis panel, must include sequencing of at least 9 genes, including ASPA, BLM, CFTR, FANCC, GBA, HEXA, IKBKAP, MCOLN1, and SMPD1
81448	Hereditary peripheral neurophaties (eg, Charcot-Marie-Tooth, spastic paraplegia), genomic sequence analysis panel, must include sequencing of at least 5 peripheral neuropathy-related genes (eg, BSCL2, GJB1, MFN2, MPZ, REEP1, SPAST, SPG11, SPTLC1) (*effective 1/1/2018*)
81479	Unlisted molecular pathology procedure

HCPCS Codes

Code	Description
S3800	Genetic testing for amyotrophic lateral sclerosis (ALS)
S3841	Genetic testing for retinoblastoma
S3842	Genetic testing for von Hipple-Lindau disease
S3844	DNA analysis of the connexin26 gene (GJB2) for susceptibility to congenital, profound deafness
S3845	Genetic testing for alpha-thalassemia
S3846	Genetic testing for hemoglobin E beta-thalassemia
S3849	Genetic testing for Niemann-Pick disease
S3850	Genetic testing for sickle cell anemia
S3853	Genetic testing for myotonic muscular dystrophy

ICD10 Codes

Code	Description
Numerous diagnoses	

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*Key Article

KEY WORDS

Carrier screening, genetic analysis, inherited disease.

CMS COVERAGE FOR MEDICARE PRODUCT MEMBERS

There is currently a Local Coverage Determination (LCD) for Molecular Pathology Procedures. Please refer to the following LCD website for Medicare Members: https://www.cms.gov/medicare-coverage-database/details/lcd-details.aspx?LCDId=35000&ver=128&CntrctrSelected=298*1&Cntrctr=298&s=41&DocType=Active&bc=AggAAAIBAAAA&

COVERAGE FOR NYS MEDICAID MANAGED CARE/HARP PRODUCT MEMBERS

The Department of Health (DOH) has mandated testing of the Duchenne muscular dystrophy (DMD) gene in indivuduals who are being considered for treatment with Exondys 51® (eteplirsen) be carved-in to the Medicaid managed care (MMC) and Health and Recovery Plan (HARP) benefit packages.
Duchenne muscular dystrophy is a genetic disorder characterized by progressive muscle degeneration and weakness. It is one of nine types of muscular dystrophy. Exondys 51® (eteplirsen) has been identified as the first disease-modifying drug for DMD.
Effective for dates of service on or after November 1, 2019, the health plan will cover DMD gene testing. DMD gene testing is reimbursable once in a lifetime.