

MEDICAL POLICY

MEDICAL POLICY DETAILS	
Medical Policy Title	Genetic Testing for Inherited Disorders
Policy Number	2.02.03
Category	Technology Assessment
Original Effective Date	11/19/99
Committee Approval Date	12/20/01, 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, 06/16/16, 07/20/17, 06/21/18, 06/20/19, 07/16/20, 07/15/21, 12/16/21, 12/22/22, 12/21/23
Current Effective Date	12/21/23
Archived Date	N/A
Archive Review Date	N/A
Product Disclaimer	<ul style="list-style-type: none"> • 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 or Child Health Plus product), medical policy criteria apply to the benefit. • If a Medicaid product covers a specific service, and there are no New York State Medicaid guidelines (eMedNY) criteria, medical policy criteria apply to the benefit. • If a Medicare product (including Medicare HMO-Dual Special Needs Program(DSNP) 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. • If a Medicare HMO-Dual Special Needs Program (DSNP) product DOES NOT cover a specific service, please refer to the Medicaid Product coverage line.

POLICY STATEMENT

- I. Based upon our criteria and assessment 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, is considered **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 assessment of the peer-reviewed literature, testing for the specific known familial pathogenic variant (rather than full panel testing) in an individual from a family in which there is a known pathogenic variant is considered **medically necessary**.
- III. 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, therefore, is considered **investigational**.
- IV. Based upon our criteria and the lack of peer-reviewed literature, genetic testing using “direct-to-the-consumer” home testing kits is considered **investigational**.

*****NOTE***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:**

Refer to Corporate Medical Policy #2.02.16 Genetic Testing for Familial Alzheimer’s Disease

Refer to Corporate Medical Policy #2.02.17 Genetic Testing for Cystic Fibrosis

Medical Policy: GENETIC TESTING FOR INHERITED DISORDERS

Policy Number: 2.02.03

Page: 2 of 13

Refer to Corporate Medical Policy #2.02.30 Pharmacogenetics

Refer to Corporate Medical Policy #2.02.38 Genetic Testing for Cardiac Ion Channelopathies

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

Refer to Corporate Medical Policy #2.02.46 Whole Exome and Whole Genome Sequencing for Diagnosis of Genetic Disorders

Refer to Corporate Medical Policy #2.02.60 Germline Genetic Testing for Hereditary Cancer

Refer to Corporate Medical Policy #4.01.03 Prenatal Genetic Testing

Refer to Corporate Medical Policy #11.01.03 Experimental or 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. Genetic testing is appropriate only when performed by a qualified laboratory certified under the Clinical Laboratory Improvement Amendments of 1988 (CLIA) and offered in a setting with adequately trained health care professionals who are qualified to provide appropriate pre- and post-test counseling.
- III. Genetic testing is contract dependent. Coverage only applies to members with a valid contract; coverage is not provided for family members without a valid contract.

IV. Supporting documentation required:

The following factors will 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).
 - D. Genetic testing should be performed for management or treatment of the patient and not only for knowledge purposes. Documentation should demonstrate how test results will impact treatment or medical management.
 - E. When there is family history or phenotype suggestive of a specific syndrome, results of targeted testing for the mutation associated with the syndrome should be documented prior to any panel testing. If targeted testing has not been performed, rationale as to why panel testing is medically necessary should be documented.
- V. 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 considered 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:

<ul style="list-style-type: none">• Alpha-1-antitrypsin deficiency (AAT; emphysema and liver disease);• Amyotrophic lateral sclerosis (ALS; Lou Gehrig's Disease; progressive motor function loss leading to paralysis and death);	<ul style="list-style-type: none">• Hemophilia A and B (HEMA and HEMB; bleeding disorders);• Huntington's disease (HD; usually midlife onset; progressive, lethal, degenerative neurological disease);
---	---

Medical Policy: GENETIC TESTING FOR INHERITED DISORDERS

Policy Number: 2.02.03

Page: 3 of 13

<ul style="list-style-type: none">• Canavan Disease (cerebral degenerative diseases of infancy)	<ul style="list-style-type: none">• Myotonic dystrophy (MD; progressive muscle weakness; most common form of adult muscular dystrophy);
<ul style="list-style-type: none">• Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL);	<ul style="list-style-type: none">• Neurofibromatosis type 1 (NF1; multiple benign nervous system tumors that can be disfiguring; cancers);
<ul style="list-style-type: none">• Charcot-Marie-Tooth (CMT; loss of feeling in ends of limbs);	<ul style="list-style-type: none">• Niemann-Pick Disease (faulty lipid metabolism causes harmful amounts of lipids to accumulate in the spleen, liver, lungs, bone marrow & brain)
<ul style="list-style-type: none">• Congenital adrenal hyperplasia (CAH; hormone deficiency; ambiguous genitalia and male pseudohermaphroditism);	<ul style="list-style-type: none">• Phenylketonuria (PKU; progressive mental retardation due to missing enzyme; correctable by diet);
<ul style="list-style-type: none">• Congenital, Profound Deafness and Nonsyndromic Hearing Loss (DFNB1; GJB2 -Connexin 26 nonsyndromic, prelingual deafness)	<ul style="list-style-type: none">• Prader Willi/Angelman syndromes (PW/A; decreased motor skills, cognitive impairment, early death);
<ul style="list-style-type: none">• Duchenne muscular dystrophy/Becker muscular dystrophy (DMD; severe to mild muscle wasting, deterioration, weakness);	<ul style="list-style-type: none">• Retinoblastoma (RB1 mutation; inherited, intraocular neoplasm)
<ul style="list-style-type: none">• Dystonia (DYT; muscle rigidity, repetitive twisting movements);	<ul style="list-style-type: none">• Rett syndrome
<ul style="list-style-type: none">• Familial hypercholesterolemia (homozygous and heterozygous);	<ul style="list-style-type: none">• Sickle cell disease (SS; blood cell disorder; chronic pain and infections);
<ul style="list-style-type: none">• Fanconi anemia, group C (FA; anemia, leukemia, skeletal deformities);	<ul style="list-style-type: none">• Thalassemias (THAL; anemias - reduced red blood cell levels);
<ul style="list-style-type: none">• Fragile X syndrome (FRAX; leading cause of inherited mental retardation);	<ul style="list-style-type: none">• Tay-Sachs Disease (TS; fatal neurological disease of early childhood; seizures, paralysis)
<ul style="list-style-type: none">• Gaucher disease (GD; enlarged liver and spleen, bone degeneration);	<ul style="list-style-type: none">• Von Hippel-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).

“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 underlie 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 for Phenylketonuria (PKU);

Medical Policy: GENETIC TESTING FOR INHERITED DISORDERS

Policy Number: 2.02.03

Page: 4 of 13

- 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, pose issues related to appropriateness of test utilization, interpretation of results, and 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 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. 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, i.e., 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 personally. 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 (ACMG) (2016) expressed the view that it is critical for the public to realize that genetic testing is only one part of a complex process and has the potential for both positive and negative impact on health and well-being. The ACMG asserted that the following should be considered minimum requirements for any genetic testing protocol: (1) A knowledgeable professional should be involved in the process of ordering and interpreting a genetic test (2) The patient should be fully informed regarding what the test can and cannot say about the patient's health; (3) The scientific evidence on which a test is based should be clearly stated; and (4) The clinical

Medical Policy: GENETIC TESTING FOR INHERITED DISORDERS**Policy Number: 2.02.03****Page: 5 of 13**

testing laboratory must be accredited under the CLIA, and by the state in which it is located 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.*
- *Code Key: Experimental/Investigational = (E/I), Not medically necessary/ appropriate = (NMN).*

CPT Codes

Code	Description
81161	DMD (dystrophin) (e.g., Duchenne/Becker muscular dystrophy) deletion analysis, and duplication analysis, if performed
81177	ATN1 (atrophin 1) (e.g., dentatorubral-pallidoluysian atrophy) gene analysis, evaluation to detect abnormal (e.g., expanded) alleles
81178	ATXN1 (ataxin 1) (e.g., spinocerebellar ataxia) gene analysis, evaluation to detect abnormal (e.g., expanded) alleles
81179	ATXN2 (ataxin 2) (e.g., spinocerebellar ataxia) gene analysis, evaluation to detect abnormal (e.g., expanded) alleles
81180	ATXN3 (ataxin 3) (e.g., spinocerebellar ataxia, Machado-Joseph disease) gene analysis, evaluation to detect abnormal (e.g., expanded) alleles
81181	ATXN7 (ataxin 7) (e.g., spinocerebellar ataxia) gene analysis, evaluation to detect abnormal (e.g., expanded) alleles
81182	ATXN8OS (ATXN8 opposite strand [non-protein coding]) (e.g., spinocerebellar ataxia) gene analysis, evaluation to detect abnormal (e.g., expanded) alleles
81183	ATXN10 (ataxin 10) (e.g., spinocerebellar ataxia) gene analysis, evaluation to detect abnormal (e.g., expanded) alleles
81184	CACNA1A (calcium voltage-gated channel subunit alpha1 A) (e.g., spinocerebellar ataxia) gene analysis; evaluation to detect abnormal (e.g., expanded) alleles
81185	CACNA1A (calcium voltage-gated channel subunit alpha1 A) (e.g., spinocerebellar ataxia) gene analysis; full gene sequence
81186	CACNA1A (calcium voltage-gated channel subunit alpha1 A) (e.g., spinocerebellar ataxia) gene analysis; known familial variant
81187	CNBP (CCHC-type zinc finger nucleic acid binding protein) (e.g., myotonic dystrophy type 2) gene analysis, evaluation to detect abnormal (e.g., expanded) alleles
81188	CSTB (cystatin B) (e.g., Unverricht-Lundborg disease) gene analysis; evaluation to detect abnormal (e.g., expanded) alleles
81189	CSTB (cystatin B) (e.g., Unverricht-Lundborg disease) gene analysis; full gene sequence
81190	CSTB (cystatin B) (e.g., Unverricht-Lundborg disease) gene analysis; known familial variant(s)
81200	ASPA (aspartoacylase) (e.g., Canavan disease) gene analysis, common variants (e.g., E285A, Y231X)

Medical Policy: GENETIC TESTING FOR INHERITED DISORDERS**Policy Number: 2.02.03****Page: 6 of 13**

Code	Description
81205	BCKDHB (branched-chain keto acid dehydrogenase 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
81234	DMPK (DM1 protein kinase) (e.g., myotonic dystrophy type 1) gene analysis; evaluation to detect abnormal (expanded) alleles
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., expanded size and promoter 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, common deletions or variant (e.g., Southeast Asian, Thai, Filipino, Mediterranean, alpha 3.7, alpha 4.2, alpha 20.5, Constant Spring)
81260	IKBKAP (inhibitor 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 (huntingtin) (e.g., Huntington disease) gene analysis; evaluation to detect abnormal (e.g., expanded) alleles
81274	HTT (huntingtin) (e.g., Huntington disease) gene analysis; characterization of alleles (e.g., expanded size)
81284	FXN (frataxin) (e.g., Friedreich ataxia) gene analysis; evaluation to detect abnormal (expanded) alleles
81285	FXN (frataxin) (e.g., Friedreich ataxia) gene analysis; characterization of alleles (e.g., expanded size)
81286	FXN (frataxin) (e.g., Friedreich ataxia) gene analysis; full gene sequence

Medical Policy: GENETIC TESTING FOR INHERITED DISORDERS**Policy Number: 2.02.03****Page: 7 of 13**

Code	Description
81289	FXN (frataxin) (e.g., Friedreich ataxia) gene analysis; known familial variant(s)
81290	MCOLN1 (mucolipin 1) (e.g., Mucopolidosis, 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
81312	PABPN1 (poly[A] binding protein nuclear 1) (e.g., oculopharyngeal muscular dystrophy) gene analysis, evaluation to detect abnormal (e.g., expanded) alleles
81324	PMP22 (peripheral myelin protein 22) (e.g., Charcot-Marie-Tooth, hereditary neuropathy with liability to pressure palsies) gene analysis; duplication/deletion analysis
81325	PMP22 (peripheral myelin protein 22) (e.g., Charcot-Marie-Tooth, hereditary neuropathy with liability to pressure palsies) gene analysis; full sequence analysis
81326	PMP22 (peripheral myelin protein 22) (e.g., 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)
81333	TGFBI (transforming growth factor beta-induced) (e.g., corneal dystrophy) gene analysis, common variants (e.g., R124H, R124C, R124L, R555W, R555Q)
81344	TBP (TATA box binding protein) (e.g., spinocerebellar ataxia) gene analysis, evaluation to detect abnormal (e.g., expanded) alleles
81401	Molecular Pathology Procedure Level 2
81402	Molecular Pathology Procedure Level 3
81403	Molecular Pathology Procedure Level 4
81404	Molecular Pathology Procedure Level 5
81405	Molecular Pathology Procedure Level 6
81406	Molecular Pathology Procedure Level 7

Medical Policy: GENETIC TESTING FOR INHERITED DISORDERS**Policy Number: 2.02.03****Page: 8 of 13**

Code	Description
81407	Molecular Pathology Procedure Level 8
81408	Molecular Pathology Procedure Level 9
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 (e.g., 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
81441	Inherited bone marrow failure syndromes (IBMFS) (e.g., Fanconi anemia, dyskeratosis congenita, Diamond-Blackfan anemia, Shwachman-Diamond syndrome, GATA2 deficiency syndrome, congenital amegakaryocytic thrombocytopenia) sequence analysis panel, must include sequencing of at least 30 genes, including BRCA2, BRIP1, DKC1, FANCA, FANCB, FANCC, FANCD2, FANCE, FANCF, FANCG, FANCI, FANCL, GATA1, GATA2, MPL, NHP2, NOP10, PALB2, RAD51C, RPL11, RPL35A, RPL5, RPS10, RPS19, RPS24, RPS26, RPS7, SBDS, TERT, and TINF2 (effective 01/01/2023)
81448	Hereditary peripheral neuropathies (e.g., Charcot-Marie-Tooth, spastic paraplegia), genomic sequence analysis panel, must include sequencing of at least 5 peripheral neuropathy-related genes (e.g., BSCL2, GJB1, MFN2, MPZ, REEP1, SPAST, SPG11, SPTLC1)
81470	X-linked intellectual disability (XLID) (e.g., syndromic and non-syndromic XLID); genomic sequence analysis panel, must include sequencing of at least 60 genes, including ARX, ATRX, CDKL5, FGD1, FMR1, HUWE1, IL1RAPL, KDM5C, L1CAM, MECP2, MED12, MID1, OCRL, RPS6KA3, AND SLC16A2
81471	X-linked intellectual disability (XLID) (e.g., syndromic and non-syndromic XLID); duplication/deletion gene analysis, must include analysis of at least 60 genes, including ARX, ATRX, CDKL5, FGD1, FMR1, HUWE1, IL1RAPL, KDM5C, L1CAM, MECP2, MED12, MID1, OCRL, RPS6KA3, and SLC16A2
81479	Unlisted molecular pathology procedure
0218U	Neurology (muscular dystrophy), DMD gene sequence analysis, including small sequence changes, deletions, duplications, and variants in non-uniquely mappable regions, blood or saliva, identification and characterization of genetic variants (Genomic Unity DMD Analysis, Variantyx Inc)

Medical Policy: GENETIC TESTING FOR INHERITED DISORDERS**Policy Number: 2.02.03****Page: 9 of 13**

Code	Description
0230U	AR (androgen receptor) (e.g., spinal and bulbar muscular atrophy, Kennedy disease, X chromosome inactivation), full sequence analysis, including small sequence changes in exonic and intronic regions, deletions, duplications, short tandem repeat (STR) expansions, mobile element insertions, and variants in non-uniquely mappable regions (Genomic Unity AR Analysis, Variantyx, Inc)
0231U	CACNA1A (calcium voltage-gated channel subunit alpha 1A) (e.g., spinocerebellar ataxia), full gene analysis, including small sequence changes in exonic and intronic regions, deletions, duplications, short tandem repeat (STR) gene expansions, mobile element insertions, and variants in non-uniquely mappable regions (Genomic Unity CACNA1A Analysis, Variantyx Inc)
0232U	CSTB (cystatin B) (e.g., progressive myoclonic epilepsy type 1A, Unverricht-Lundborg disease), full gene analysis, including small sequence changes in exonic and intronic regions, deletions, duplications, short tandem repeat (STR) expansions, mobile element insertions, and variants in non-uniquely mappable regions (Genomic Unity CSTB Analysis, Variantyx Inc)
0233U	FXN (frataxin) (e.g., Friedreich ataxia), gene analysis, including small sequence changes in exonic and intronic regions, deletions, duplications, short tandem repeat (STR) expansions, mobile element insertions, and variants in non-uniquely mappable regions (Genomic Unity FXN Analysis, Variantyx Inc)
0234U	MECP2 (methyl CpG binding protein 2) (e.g., Rett syndrome), full gene analysis, including small sequence changes in exonic and intronic regions, deletions, duplications, mobile element insertions, and variants in non-uniquely mappable regions (Genomic Unity MECP2 Analysis, Variantyx Inc)
0236U	SMN1 (survival of motor neuron 1, telomeric) and SMN2 (survival of motor neuron 2, centromeric) (e.g., spinal muscular atrophy) full gene analysis, including small sequence changes in exonic and intronic regions, duplications and deletions, and mobile element insertions (Genomic Unity SMN1/2 Analysis, Variantyx Inc)
0322U	Neurology (autism spectrum disorder [ASD]), quantitative measurements of 14 acyl carnitines and microbiome-derived metabolites, liquid chromatography with tandem mass spectrometry (LC-MS/MS), plasma, results reported as negative or positive for risk of metabolic subtypes associated with ASD (NPDX ASD Test Panel III, Stemina Biomarker Discovery d/b/a NeuroPointDX <i>(effective 04/01/2022)</i>)
0378U	RFC1 (replication factor C subunit 1), repeat expansion variant analysis by traditional and repeat-primed PCR, blood, saliva, or buccal swab <i>(effective 04/01/23)</i>

Copyright © 2023 American Medical Association, Chicago, IL

HCPCS Codes

Code	Description
S3800	Genetic testing for amyotrophic lateral sclerosis (ALS)
S3841	Genetic testing for retinoblastoma
S3842	Genetic testing for von Hippel-Lindau disease
S3844	DNA analysis of the connexin 26 gene (GJB2) for susceptibility to congenital, profound deafness

Medical Policy: GENETIC TESTING FOR INHERITED DISORDERS

Policy Number: 2.02.03

Page: 10 of 13

Code	Description
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

REFERENCES

- *American Academy of Pediatrics. Ethical Issues with Genetic Testing in Pediatrics. Jun 6, 2001. Reaffirmed May 1, 2005 [<http://pediatrics.aappublications.org/content/107/6/1451.full.pdf+html?sid=37ba53f6-bd21-4482-bf25-ad1d4c8c37e8>] accessed 10/02/23.
- *American College of Obstetrics and Gynecology (ACOG) Committee on Genetics. Opinion Number 318, Oct 2005. Screening for Tay-Sachs disease. *Obstet Gynecol* 2005 Oct;106(4):893-4.
- *American College of Medical Genetics. Policy Statement on Direct-to-Consumer Genetic Testing. Revised 2015 Dec 17. *Genet Med* 2016 Feb;18(2):207-208.
- *American College of Obstetricians and Gynecologists (ACOG). Patient testing: Ethical issues in selection and counseling. ACOG Committee Opinion No. 363. American College of Obstetricians and Gynecologists. *Obstet Gynecol* 2007;109:1021-3.
- *American Society of Clinical Oncology. Policy statement update: Genetic and Genomic Testing for Cancer Susceptibility. *J Clin Oncol* 2015 Nov 1;33(31):3660-7.
- Barbosa-Gouveia S, et al. Rapid molecular diagnosis of genetically inherited neuromuscular disorders using next-generation sequencing technologies. *J Clin Med* 2022 May 12;11(10):2750. Doi: 10.3390/jcm11102750. PMID: 35628876; PMCID: PMC9143479.
- Bender MA, et al. Sickle cell disease. *Gene Reviews* Initial Posting: Sep 2003, updated 2022 Nov 17. Funded by the NIH [<https://www.ncbi.nlm.nih.gov/books/NBK1377>] accessed 10/02/23.
- Bird TD. Myotonic dystrophy type 1. *Gene Reviews* Funded by the NIH. Initial posting: 2019 Oct. Last update: 2021 Mar 25 [<http://www.ncbi.nlm.nih.gov/books/NBK1165>] accessed 10/02/23.
- Cappola A, et al. Diagnostic implications of genetic copy number variation in epilepsy plus. *Epilepsia* 2019 April: 60(4): 689-706.
- Christian S, et al. Diagnostic validity and clinical utility of genetic testing for hypertrophic cardiomyopathy: a systematic review and meta-analysis. *Open Heart* 2022 Apr;9(1):e001815.
- *Dong Y, et al. Yield of screening for CADASIL mutations in lacunar stroke and leukoaraiosis. *Stroke* 2003 Jan;34(1):203-5.
- Emdin CA, et al. Genome-wide polygenic score and cardiovascular outcomes with Evacetrapib in patients with high-risk vascular disease: a nested case-control study. *Circ Genom Precis Med* 2020 Feb; 13 (1): e002767.
- Frantzen C, et al. Von Hippel-Lindau syndrome. Seattle, WA: *GeneReviews* University of Washington; 2015 Aug 6. Update 2023 Sep 21 [<http://www.ncbi.nlm.nih.gov/books/NBK1463>] accessed 10/02/23.

Medical Policy: GENETIC TESTING FOR INHERITED DISORDERS

Policy Number: 2.02.03

Page: 11 of 13

*Frayling TM, et al. A genome-wide scan in families with maturity-onset diabetes of the young. Diabetes 2003 Mar;52(3):872-81.

Galanello R, Cao A. Alpha-Thalassemia. Gene Reviews Initial Posting 2005 Nov 1; Last update: 2020 Oct 1. Funded by the NIH. [<http://www.ncbi.nlm.nih.gov/books/NBK1435>] accessed 10/02/23.

*Garber KB, et al. Fragile X syndrome. Eur J Hum Genet 2008 Jun;16(6):666-72.

*Ganalez-Porras JR, et al. Risk of recurrent venous thrombosis in patients with G20210A mutation in the prothrombin gene or factor V Leiden mutation. Blood Coagul Fibrinolysis 2006 Jan;17(1):23-8.

*Glueck CJ, et al. Factor V Leiden mutation: a treatable etiology for sporadic and recurrent pregnancy loss. Fertil Steril 2008 Feb;89(2):410-6.

*Grody WW, et al. American College of Medical Genetics Consensus Statement on Factor V Leiden Mutation Testing. Mar/Apr 2001; reaffirmed 2007 May 14 [<https://www.acmg.net/PDFLibrary/Factor-V-Leiden-Mutation-Testing.pdf>] accessed 10/02/23.

Huml AM, et al. Consistency of direct to consumer genetic testing results among identical twins. Am J Med 2020 Jan; 133 (1): 143-146.

Jonas MC, et al. Physician experience with direct-to-consumer genetic testing in Karise Permanente. J Pers Med 2019 Nov 1;9(4):47.

Kaback M. Hexoaminidase A deficiency. Posted: 1999 Mar 11. Funded by the NIH. Developed at the University of Washington, Seattle. Gene Reviews Update 2020 Oct 1 [<http://www.ncbi.nlm.nih.gov/books/NBK1218>] accessed 10/02/23.

*Kaye CI; Committee on Genetics, et al. Introduction to the newborn screening fact sheets. Pediatrics 2006 Sep;118(3):1304-12.

*Kaye CI; Committee on Genetics, et al. Newborn screening fact sheets. Pediatrics 2006 Sep;118(3):e934-63.

Kujovich J. Factor V Leiden Thrombophilia. Gene Reviews Initial posting: 1999 May 04. Updated 2018 Jan 04. Funded by the NIH [<http://www.ncbi.nlm.nih.gov/books/NBK1368>] accessed 10/02/23.

*Li MM, et al; ACMG Professional Practice and Guidelines Committee. Clinical evaluation and etiologic diagnosis of hearing loss: A clinical practice resource of the American College of Medical Genetics and Genomics (ACMG). Genet Med 2022 Jul;24(7):1392-1406.

*Lindegren ML, et al. Applying public health strategies to primary immunodeficiency diseases: a potential approach to genetic disorders. MMWR Recomm Rep 2004 Jan 16;53(RR-1):1-29.

Lohmann D and Gallie B. Retinoblastoma. Gene Reviews Funded by the NIH. Developed at the University of Washington, Seattle. Initial posting: 2000 Jul 18. Last update: 2023 Sep 21. [<http://www.ncbi.nlm.nih.gov/books/NBK1452>] accessed 10/02/23.

Matalon R. Canavan disease. Gene Reviews University of Washington. Initial posting: 1999 Sep 16. Last updated 2018 Sep 13. [<http://www.ncbi.nlm.nih.gov/books/NBK1234>] accessed 10/02/23.

McKusick V. GBA gene map: Gaucher Disease. GD I, Gaucher disease, noncerebral juvenile glucocerebrosidase deficiency, acid beta-glycosidase deficiency, GBA deficiency. In Web site: OMIM. Online Mendelian inheritance in man. Johns Hopkins University. 1986. Edited 2021 Oct 08 [<https://www.omim.org/entry/230800>] accessed 10/02/23.

Nadkarni GN, et al. Effects of testing and disclosing ancestry-specific genetic risk for kidney failure on patients and health care professionals: a randomized clinical trial. JAMA Netw Open 2022 Mar;5(3):e221048.

National Cancer Institute (NCI). U.S. National Institutes of Health (NIH). Retinoblastoma (PDQ): treatment. Last modified: 2023 Apr 11 [<https://www.cancer.gov/types/retinoblastoma/hp/retinoblastoma-treatment-pdq>] accessed 10/02/23.

Medical Policy: GENETIC TESTING FOR INHERITED DISORDERS

Policy Number: 2.02.03

Page: 13 of 13

The Department of Health (DOH) has mandated testing of the Duchenne muscular dystrophy (DMD) gene in individuals 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.