

Clinical UM Guideline

Subject:	Genetic Testing for Inherited Diseases	Publish Date:	04/13/2022
Guideline #:	CG-GENE-13	Last Review Date:	02/17/2022
Status:	Reviewed		

Description

This document addresses testing for certain diseases with an established genetic basis. It includes testing of individual genes for individuals at risk and preconception or prenatal genetic testing of a prospective parent or parent to determine carrier status for an autosomal recessive disorder, an x-linked disorder, a disorder with variable penetrance, or to confirm the diagnosis of a disorder when genetic testing may lead to changes in clinical management for those with uncertain clinical features.

Notes:

- Genetic counseling should be a component of a decision to perform genetic testing.
- This document only addresses molecular genetic testing and does not provide criteria for karyotype analysis or biochemical testing.
- This document does not address whole exome or whole genome testing or testing of 5 or more genes as a panel.
- This document does not address panel testing. Please refer to:
 - GENE.00049 Circulating Tumor DNA Panel Testing for Cancer (Liquid Biopsy)
 - GENE.00052 Whole Genome Sequencing, Whole Exome Sequencing, Gene Panels, and Molecular Profiling
- When another document exists that addresses a specific condition or genetic test, that document supersedes this one.
- Other related documents include:
 - CG-GENE-21 Cell-Free Fetal DNA-Based Prenatal Testing
 - CG-MED-88 Preimplantation Genetic Diagnosis Testing

Clinical Indications

Medically Necessary:

Testing of individual genes for germline genetic diseases is considered **medically necessary** when **all** the criteria for the individual to be tested and for the genetic disorder being tested for (both Criteria A **and** B) are met:

A. Requirements for the individual:

Federal and State law, as well as contract language including definitions and specific coverage provisions/exclusions, and Medical Policy take precedence over Clinical UM Guidelines and must be considered first in determining eligibility for coverage. The member's contract benefits in effect on the date that services are rendered must be used. Clinical UM Guidelines, which address medical efficacy, should be considered before utilizing medical opinion in adjudication. Medical technology is constantly evolving, and we reserve the right to review and update Clinical UM Guidelines periodically. Clinical UM guidelines are used when the plan performs utilization review for the subject. Due to variances in utilization patterns, each plan may choose whether or not to adopt a particular Clinical UM Guideline. To determine if review is required for this Clinical UM Guideline, please contact the customer service number on the back of the member's card.

No part of this publication may be reproduced, stored in a retrieval system or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from the health plan.

© CPT Only – American Medical Association

Medicaid managed care administered by Amerigroup Corporation, an independent company

Genetic Testing for Inherited Diseases

The individual to be tested:

1. Is either at significant risk for a genetic disease (for example, based on family history) **or** suspected to have a known genetic disease; **and**
2. Has received genetic counseling encompassing **all** of the following components:
 - a. Interpretation of family and medical histories to assess the probability of disease occurrence or recurrence; **and**
 - b. Education about inheritance, genetic testing, disease management, prevention and resources; **and**
 - c. Counseling to promote informed choices and adaptation to the risk or presence of a genetic condition; **and**
 - d. Counseling for the psychological aspects of genetic testing.

and

B. Requirements for the genetic disorder(s) being tested for:

1. A specific mutation, or set of mutations, has been established in the scientific literature to be reliably associated with the disease; **and**
2. A biochemical or other test is identified but the results are indeterminate, or the genetic disorder cannot be identified through biochemical or other testing; **and**
3. The genetic disorder is associated with a potentially significant disability or has a lethal natural history; **and**
4. A positive or negative result of the genetic test will impact the clinical management (predictive, diagnostic, prognostic or therapeutic*) of the individual. For example, genetic test results will guide treatment decisions, surveillance recommendations or preventive strategies; **and**
5. The findings of the genetic test will likely result in improvement in net health outcomes; that is, the expected health benefits of the interventions outweigh any harmful effects (medical or psychological) of the intervention.

***Note:** See the Definitions section for information about predictive, diagnostic, prognostic and therapeutic genetic testing.

Preconception or prenatal genetic screening of a parent or prospective parent to determine carrier status of germline genetic disorders is considered **medically necessary** when criteria for family history and for the specific genetic test (both Criteria C **and** D) are met:

C. Criteria based on family history:

Genetic screening of the parent or prospective parent is considered **medically necessary** when **one** of the following criteria is met:

1. An affected child is identified with either an autosomal recessive disorder, an x-linked disorder, or an inherited disorder with variable penetrance and genetic testing is performed to determine the pattern of inheritance and to guide subsequent reproductive decisions; **or**

Federal and State law, as well as contract language including definitions and specific coverage provisions/exclusions, and Medical Policy take precedence over Clinical UM Guidelines and must be considered first in determining eligibility for coverage. The member's contract benefits in effect on the date that services are rendered must be used. Clinical UM Guidelines, which address medical efficacy, should be considered before utilizing medical opinion in adjudication. Medical technology is constantly evolving, and we reserve the right to review and update Clinical UM Guidelines periodically. Clinical UM guidelines are used when the plan performs utilization review for the subject. Due to variances in utilization patterns, each plan may choose whether or not to adopt a particular Clinical UM Guideline. To determine if review is required for this Clinical UM Guideline, please contact the customer service number on the back of the member's card.

No part of this publication may be reproduced, stored in a retrieval system or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from the health plan.

© CPT Only – American Medical Association

Medicaid managed care administered by Amerigroup Corporation, an independent company

Genetic Testing for Inherited Diseases

2. One or both parents or prospective parent(s) have a first or a second degree relative who is affected with either an autosomal recessive disorder, an x-linked disorder, or an inherited disorder with variable penetrance and genetic testing is performed to determine the pattern of inheritance and to guide subsequent reproductive decisions; **or**
3. The parent or prospective parent is at high risk for a genetic disorder with a late onset presentation, and genetic testing is performed to determine carrier status and to guide subsequent reproductive decisions; **or**
4. The parent or prospective parent is a member of an ethnic group with a high risk of a specific genetic disorder with an autosomal recessive pattern of inheritance and genetic testing is performed to determine carrier status and to guide subsequent reproductive decisions, including but not limited to Tay-Sach’s disease, Canavan disease, familial dysautonomia, mucopolipidosis IV, Niemann Pick Disease Type A, Fanconi anemia group C, Bloom syndrome or Gaucher disease.

and

D. Criteria for Specific Genetic Test:

In the parent or prospective parent who meets one of the applicable criteria above, specific genetic testing is considered **medically necessary** when **all** of the following criteria are met:

1. A specific mutation, or set of mutations, has been established in the scientific literature to be reliably associated with the disease; **and**
2. A biochemical or other test is identified but the results are indeterminate, or the genetic disorder cannot be identified through biochemical or other testing; **and**
3. The genetic disorder is associated with a potentially severe disability or has a lethal natural history; **and**
4. Genetic counseling, which encompasses **all** of the following components, has been performed:
 - a. Interpretation of family and medical histories to assess the probability of disease occurrence or recurrence; **and**
 - b. Education about inheritance, genetic testing, disease management, prevention and resources; **and**
 - c. Counseling to promote informed choices and adaptation to the risk or presence of a genetic condition; **and**
 - d. Counseling for the psychological aspects of genetic testing.

Preconception or prenatal genetic screening of a parent or prospective parent to determine carrier status for the following conditions is considered **medically necessary**:

- A. Cystic fibrosis, common variants (the current standard includes 23 of the more common gene mutations);
- B. Spinal muscular atrophy.

Not Medically Necessary:

Federal and State law, as well as contract language including definitions and specific coverage provisions/exclusions, and Medical Policy take precedence over Clinical UM Guidelines and must be considered first in determining eligibility for coverage. The member's contract benefits in effect on the date that services are rendered must be used. Clinical UM Guidelines, which address medical efficacy, should be considered before utilizing medical opinion in adjudication. Medical technology is constantly evolving, and we reserve the right to review and update Clinical UM Guidelines periodically. Clinical UM guidelines are used when the plan performs utilization review for the subject. Due to variances in utilization patterns, each plan may choose whether or not to adopt a particular Clinical UM Guideline. To determine if review is required for this Clinical UM Guideline, please contact the customer service number on the back of the member's card.

No part of this publication may be reproduced, stored in a retrieval system or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from the health plan.

© CPT Only – American Medical Association

Medicaid managed care administered by Amerigroup Corporation, an independent company

Genetic Testing for Inherited Diseases

Genetic testing of individual genes for germline genetic diseases in individuals not meeting the above criteria is considered **not medically necessary**, including, but not limited to, genetic testing for melanoma (hereditary), amyotrophic lateral sclerosis (ALS, also known as Lou Gehrig's disease) and ataxia telangiectasia.

Preconception or prenatal genetic testing of a parent or prospective parent for germline genetic medical disorders that do not meet the above criteria, including but not limited, to amyotrophic lateral sclerosis (ALS, Lou Gehrig's disease) is considered **not medically necessary**.

Preconception or prenatal genetic screening of a parent or prospective parent to determine carrier status for cystic fibrosis, using **any** of the following is considered **not medically necessary**:

- A. Complete DNA sequencing of the cystic fibrosis transmembrane conductance regulator (CFTR) gene;
- B. Gene analysis of known CFTR familial variants;
- C. Gene analysis of CFTR duplication/deletion variants.

Coding

The following codes for treatments and procedures applicable to this guideline are included below for informational purposes. Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement policy. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

Cystic fibrosis and spinal muscular atrophy testing

When services are Medically Necessary for carrier testing:

CPT

- 81220 *CFTR (cystic fibrosis transmembrane conductance regulator) (eg, cystic fibrosis) gene analysis; common variants (eg, ACMG/ACOG guidelines)*
- 81329 *SMN1 (survival of motor neuron 1, telomeric) (eg, spinal muscular atrophy) gene analysis; dosage/deletion analysis (eg, carrier testing), includes SMN2 (survival of motor neuron 2, centromeric) analysis, if performed*

ICD-10 Diagnosis

All diagnoses

When services are Not Medically Necessary for carrier testing:

CPT

- 81221 *CFTR (cystic fibrosis transmembrane conductance regulator) (eg, cystic fibrosis) gene analysis; known familial variants*
- 81222 *CFTR (cystic fibrosis transmembrane conductance regulator) (eg, cystic fibrosis) gene analysis; duplication/deletion variants*

Federal and State law, as well as contract language including definitions and specific coverage provisions/exclusions, and Medical Policy take precedence over Clinical UM Guidelines and must be considered first in determining eligibility for coverage. The member's contract benefits in effect on the date that services are rendered must be used. Clinical UM Guidelines, which address medical efficacy, should be considered before utilizing medical opinion in adjudication. Medical technology is constantly evolving, and we reserve the right to review and update Clinical UM Guidelines periodically. Clinical UM guidelines are used when the plan performs utilization review for the subject. Due to variances in utilization patterns, each plan may choose whether or not to adopt a particular Clinical UM Guideline. To determine if review is required for this Clinical UM Guideline, please contact the customer service number on the back of the member's card.

No part of this publication may be reproduced, stored in a retrieval system or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from the health plan.

© CPT Only – American Medical Association

Medicaid managed care administered by Amerigroup Corporation, an independent company

Genetic Testing for Inherited Diseases

81223 *CFTR (cystic fibrosis transmembrane conductance regulator)* (eg, cystic fibrosis) gene analysis; full gene sequence

ICD-10 Diagnosis

Z31.430 Encounter of female for testing for genetic disease carrier status for procreative management

Z31.440 Encounter of male for testing for genetic disease carrier status for procreative management

When services are Medically Necessary for other than carrier testing:

CPT

81221 *CFTR (cystic fibrosis transmembrane conductance regulator)* (eg, cystic fibrosis) gene analysis; known familial variants

81222 *CFTR (cystic fibrosis transmembrane conductance regulator)* (eg, cystic fibrosis) gene analysis; duplication/deletion variants

81223 *CFTR (cystic fibrosis transmembrane conductance regulator)* (eg, cystic fibrosis) gene analysis; full gene sequence

81224 *CFTR (cystic fibrosis transmembrane conductance regulator)* (eg, cystic fibrosis) gene analysis; intron 8 poly-T analysis (eg, male infertility)

81336 *SMN1 (survival of motor neuron 1, telomeric)* (eg, spinal muscular atrophy) gene analysis; full gene sequence

81337 *SMN1 (survival of motor neuron 1, telomeric)* (eg, spinal muscular atrophy) gene analysis; known familial sequence variant(s)

0236U *SMN1 (survival of motor neuron 1, telomeric)* and *SMN2 (survival of motor neuron 2, centromeric)* (eg, 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, Variantyx Inc

ICD-10 Diagnosis

K85.00-K85.02 Idiopathic acute pancreatitis [for CFTR 81222, 81223, 81224]

K85.80-K85.92 Other acute pancreatitis, unspecified [for CFTR 81222, 81223, 81224]

K86.1 Other chronic pancreatitis [for CFTR 81222, 81223, 81224]

All preconception/prenatal diagnoses including, but not limited to, the following:

Z31.430 Encounter of female for testing for genetic disease carrier status for procreative management

Z31.440 Encounter of male for testing for genetic disease carrier status for procreative management

Z36.0 Encounter for antenatal screening for chromosomal anomalies

Federal and State law, as well as contract language including definitions and specific coverage provisions/exclusions, and Medical Policy take precedence over Clinical UM Guidelines and must be considered first in determining eligibility for coverage. The member's contract benefits in effect on the date that services are rendered must be used. Clinical UM Guidelines, which address medical efficacy, should be considered before utilizing medical opinion in adjudication. Medical technology is constantly evolving, and we reserve the right to review and update Clinical UM Guidelines periodically. Clinical UM guidelines are used when the plan performs utilization review for the subject. Due to variances in utilization patterns, each plan may choose whether or not to adopt a particular Clinical UM Guideline. To determine if review is required for this Clinical UM Guideline, please contact the customer service number on the back of the member's card.

No part of this publication may be reproduced, stored in a retrieval system or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from the health plan.

© CPT Only – American Medical Association

Medicaid managed care administered by Amerigroup Corporation, an independent company

Genetic Testing for Inherited Diseases

Z36.8A	Encounter for antenatal screening for other genetic defects
Z84.81	Family history of carrier of genetic disease

When services may be Medically Necessary when criteria are met for other than carrier testing:

For the procedure codes listed above, for all other diagnoses.

Other gene testing for inherited diseases for all indications:

When services may be Medically Necessary when criteria are met:

CPT

81161	<i>DMD (dystrophin)</i> (eg, Duchenne/Becker muscular dystrophy) deletion analysis, and duplication analysis, if performed
81171	<i>AFF2 (AF4/FMR2 family, member 2 [FMR2])</i> (eg, fragile X mental retardation 2 [FRAXE]) gene analysis; evaluation to detect abnormal (eg, expanded) alleles
81172	<i>AFF2 (AF4/FMR2 family, member 2 [FMR2])</i> (eg, fragile X mental retardation 2 [FRAXE]) gene analysis; characterization of alleles (eg, expanded size and methylation status)
81187	<i>CNBP (CCHC-type zinc finger nucleic acid binding protein)</i> (eg, myotonic dystrophy type 2) gene analysis, evaluation to detect abnormal (eg, expanded alleles)
81205	<i>BCKDHB (branched-chain keto acid dehydrogenase E1, beta polypeptide)</i> (eg, maple syrup urine disease) gene analysis, common variants (eg, R183P, G278S, E422X)
81209	<i>BLM (Bloom syndrome, RecQ helicase-like)</i> (eg, Bloom syndrome) gene analysis, 2281del6ins7 variant
81234	<i>DMPK (DM1 protein kinase)</i> (eg, myotonic dystrophy type 1) gene analysis; evaluation to detect abnormal (expanded) alleles
81239	<i>DMPK (DM1 protein kinase)</i> (eg, myotonic dystrophy type 1) gene analysis; characterization of alleles (eg, expanded size)
81241	<i>F5 (coagulation Factor V)</i> (eg, hereditary hypercoagulability) gene analysis, Leiden variant
81242	<i>FANCC (Fanconi anemia, complementation group C)</i> (eg, Fanconi anemia, type C) gene analysis, common variant (eg, IVS4+4A>T)
81243	<i>FMRI (fragile X mental retardation 1)</i> (eg, fragile X mental retardation) gene analysis; evaluation to detect abnormal (eg, expanded) alleles
81244	<i>FMRI (fragile X mental retardation 1)</i> (eg, fragile X mental retardation) gene analysis; characterization of alleles (eg, expanded size and promoter methylation status)
81250	<i>G6PC (glucose-6-phosphatase, catalytic subunit)</i> (eg, Glycogen storage disease, Type 1a, von Gierke disease) gene analysis, common variants (eg, R83C, Q347X)
81251	<i>GBA (glucosidase, beta, acid)</i> (eg, Gaucher disease) gene analysis, common variants (eg, N370S, 84GG, L444P, IVS2+1G>A)

Federal and State law, as well as contract language including definitions and specific coverage provisions/exclusions, and Medical Policy take precedence over Clinical UM Guidelines and must be considered first in determining eligibility for coverage. The member's contract benefits in effect on the date that services are rendered must be used. Clinical UM Guidelines, which address medical efficacy, should be considered before utilizing medical opinion in adjudication. Medical technology is constantly evolving, and we reserve the right to review and update Clinical UM Guidelines periodically. Clinical UM guidelines are used when the plan performs utilization review for the subject. Due to variances in utilization patterns, each plan may choose whether or not to adopt a particular Clinical UM Guideline. To determine if review is required for this Clinical UM Guideline, please contact the customer service number on the back of the member's card.

No part of this publication may be reproduced, stored in a retrieval system or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from the health plan.

© CPT Only – American Medical Association

Medicaid managed care administered by Amerigroup Corporation, an independent company

Genetic Testing for Inherited Diseases

81256	<i>HFE (hemochromatosis)</i> (eg, hereditary hemochromatosis) gene analysis, common variants (eg, C282Y, H63D)
81257	<i>HBA1/HBA2 (alpha globin 1 and alpha globin 2)</i> (eg, alpha thalassemia, Hb Bart hydrops fetalis syndrome, HbH disease), gene analysis; common deletions or variant (eg, Southeast Asian, Thai, Filipino, Mediterranean, alpha3.7, alpha4.2, alpha20.5, and Constant Spring)
81258	<i>HBA1/HBA2 (alpha globin 1 and alpha globin 2)</i> (eg, alpha thalassemia, Hb Bart hydrops fetalis syndrome, HbH disease), gene analysis; known familial variant
81259	<i>HBA1/HBA2 (alpha globin 1 and alpha globin 2)</i> (eg, alpha thalassemia, Hb Bart hydrops fetalis syndrome, HbH disease), gene analysis; full gene sequence
81260	<i>IKBKAP (inhibitor of kappa light polypeptide gene enhancer in B-cells, kinase complex-associated protein)</i> (eg, familial dysautonomia) gene analysis, common variants (eg, 2507+6T>C, R696P)
81269	<i>HBA1/HBA2 (alpha globin 1 and alpha globin 2)</i> (eg, alpha thalassemia, Hb Bart hydrops fetalis syndrome, HbH disease), gene analysis; duplication/deletion variants
81330	<i>SMPD1 (sphingomyelin phosphodiesterase 1, acid lysosomal)</i> (eg, Niemann-Pick disease, Type A) gene analysis, common variants (eg, R496L, L302P, fsP330)
81361	<i>HBB (hemoglobin, subunit beta)</i> (eg, sickle cell anemia, beta thalassemia, hemoglobinopathy); common variant(s) (eg, HbS, HbC, HbE)
81362	<i>HBB (hemoglobin, subunit beta)</i> (eg, sickle cell anemia, beta thalassemia, hemoglobinopathy); known familial variant(s)
81363	<i>HBB (hemoglobin, subunit beta)</i> (eg, sickle cell anemia, beta thalassemia, hemoglobinopathy); duplication/deletion variant(s)
81364	<i>HBB (hemoglobin, subunit beta)</i> (eg, sickle cell anemia, beta thalassemia, hemoglobinopathy); full gene sequence
81400	Molecular pathology procedure, Level 1 (eg, identification of single germline variant [eg, SNP] by techniques such as restriction enzyme digestion or melt curve analysis) [when specified as the following]: <ul style="list-style-type: none"> • <i>ACADM (acyl-CoA dehydrogenase, C-4 to C-12 straight chain, MCAD)</i> (eg, medium chain acyl dehydrogenase deficiency), K304E variant • <i>BCKDHA (branched chain keto acid dehydrogenase E1, alpha polypeptide)</i> (eg, maple syrup urine disease, type 1A), Y438N variant • <i>F5 (coagulation factor V)</i> (eg, hereditary hypercoagulability), HR2 variant
81401	Molecular pathology procedure, Level 2 (eg, 2-10 SNPs, 1 methylated variant, or 1 somatic variant [typically using nonsequencing target variant analysis], or detection of a dynamic mutation disorder/triplet repeat) [when specified as the following]: <ul style="list-style-type: none"> • <i>ACADM (acyl-CoA dehydrogenase, C-4 to C-12 straight chain, MCAD)</i> (eg, medium chain acyl dehydrogenase deficiency), commons variants (eg, K304E, Y42H)

Federal and State law, as well as contract language including definitions and specific coverage provisions/exclusions, and Medical Policy take precedence over Clinical UM Guidelines and must be considered first in determining eligibility for coverage. The member's contract benefits in effect on the date that services are rendered must be used. Clinical UM Guidelines, which address medical efficacy, should be considered before utilizing medical opinion in adjudication. Medical technology is constantly evolving, and we reserve the right to review and update Clinical UM Guidelines periodically. Clinical UM guidelines are used when the plan performs utilization review for the subject. Due to variances in utilization patterns, each plan may choose whether or not to adopt a particular Clinical UM Guideline. To determine if review is required for this Clinical UM Guideline, please contact the customer service number on the back of the member's card.

No part of this publication may be reproduced, stored in a retrieval system or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from the health plan.

© CPT Only – American Medical Association

Medicaid managed care administered by Amerigroup Corporation, an independent company

Genetic Testing for Inherited Diseases

- 81404

 - *GALT (galactose-1-phosphate uridylyltransferase)* (eg, galactosemia), common variants (eg, Q188R, S135L, K285N, T138M, L195P, Y209C, IVS2-2A>G, P171S, del5kb, N314D, L218L/N314D)
 - *PYGM (phosphorylase, glycogen, muscle)* (eg, glycogen storage disease type V, McArdle disease), common variants (eg, R50S, G205S)

Molecular pathology procedure, Level 5 (eg, analysis of 2-5 exons by DNA sequence analysis, mutation scanning or duplication/deletion variants of 6-10 exons, or characterization of a dynamic mutation disorder/triplet repeat by Southern blot analysis) [when specified as the following]:

 - *CPT2 (carnitine palmitoyltransferase 2)* (eg, carnitine palmitoyltransferase II deficiency), full gene sequence
 - *NLGN4X (neuroligin 4, X-linked)* (eg, autism spectrum disorders), duplication/deletion analysis

 - 81405

 - *TTPA (tocopherol [alpha] transfer protein)* (eg, ataxia), full gene sequence

Molecular pathology procedure, Level 6 (eg, analysis of 6-10 exons by DNA sequence analysis, mutation scanning or duplication/deletion variants of 11-25 exons, regionally targeted cytogenomic array analysis) [when specified as the following]:

 - *ARSA (arylsulfatase A)* (eg, arylsulfatase A deficiency), full gene sequence
 - *BCKDHA (branched chain keto acid dehydrogenase E1, alpha polypeptide)* (eg, maple syrup urine disease, type 1A), full gene sequence
 - *DBT (dihydrolipoamide branched chain transacylase E2)* (eg, maple syrup urine disease type 2), duplication/deletion analysis
 - *DHCR7 (7-dehydrocholesterol reductase)* (eg, Smith-Lemli-Opitz syndrome), full gene sequence
 - *GLA (galactosidase, alpha)* (eg, Fabry disease), full gene sequence
 - *NLGN3 (neuroligin 3)* (eg, autism spectrum disorders), full gene sequence;
 - *NLGN4X (neuroligin 4, X-linked)* (eg, autism spectrum disorders), full gene sequence
 - *TGFBR1 (transforming growth factor, beta receptor 1)* (eg, Marfan syndrome), full gene sequence
 - *TGFBR2 (transforming growth factor, beta receptor 2)* (eg, Marfan syndrome), full gene sequence

 - 81406

Molecular pathology procedure, Level 7 (eg, analysis of 11-25 exons by DNA sequence analysis, mutation scanning or duplication/deletion variants of 26-50 exons, cytogenomic array analysis for neoplasia) [when specified as the following]:

 - *ATP7B (ATPase, Cu++ transporting, beta polypeptide)* (eg, Wilson disease), full gene sequence
 - *BCKDHB (branched chain keto acid dehydrogenase E1, beta polypeptide)* (eg, maple syrup urine disease, type 1B), full gene sequence
-

Federal and State law, as well as contract language including definitions and specific coverage provisions/exclusions, and Medical Policy take precedence over Clinical UM Guidelines and must be considered first in determining eligibility for coverage. The member's contract benefits in effect on the date that services are rendered must be used. Clinical UM Guidelines, which address medical efficacy, should be considered before utilizing medical opinion in adjudication. Medical technology is constantly evolving, and we reserve the right to review and update Clinical UM Guidelines periodically. Clinical UM guidelines are used when the plan performs utilization review for the subject. Due to variances in utilization patterns, each plan may choose whether or not to adopt a particular Clinical UM Guideline. To determine if review is required for this Clinical UM Guideline, please contact the customer service number on the back of the member's card.

No part of this publication may be reproduced, stored in a retrieval system or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from the health plan.

© CPT Only – American Medical Association

Medicaid managed care administered by Amerigroup Corporation, an independent company

Genetic Testing for Inherited Diseases

	<ul style="list-style-type: none"> • <i>DBT (dihydrolipoamide branched chain transacylase E2)</i> (eg, maple syrup urine disease, type 2), full gene sequence • <i>DLD (dihydrolipoamide dehydrogenase)</i> (eg, maple syrup urine disease, type III), full gene sequence • <i>GAA (glucosidase, alpha; acid)</i> (eg, glycogen storage disease type II [Pompe disease]), full gene sequence • <i>GALT (galactose-1-phosphate uridylyltransferase)</i> (eg, galactosemia), full gene sequence • <i>HADHA (hydroxyacyl-CoA dehydrogenase/3-ketoacyl-CoA thiolase/enoyl-CoA hydratase [trifunctional protein] alpha subunit)</i> (eg, long chain acyl-coenzyme A dehydrogenase deficiency), full gene sequence • <i>HADHB (hydroxyacyl-CoA dehydrogenase/3-ketoacyl-CoA thiolase/enoyl-CoA hydratase [trifunctional protein] beta subunit)</i> (eg, trifunctional protein deficiency), full gene sequence • <i>JAG1 (jagged 1)</i> (eg, Alagille syndrome), duplication/deletion analysis • <i>PAH (phenylalanine hydroxylase)</i> (eg, phenylketonuria), full gene sequence • <i>PYGM (phosphorylase, glycogen, muscle)</i> (eg, glycogen storage disease type V, McArdle disease), full gene sequence • <i>RPE65 (retinal pigment epithelium-specific protein 65kDa)</i> (eg, retinitis pigmentosa, Leber congenital amaurosis), full gene sequence • <i>SLC37A4 (solute carrier family 37 [glucose-6-phosphate transporter], member 4)</i> (eg, glycogen storage disease type Ib), full gene sequence
81407	<p>Molecular pathology procedure, Level 8 (eg, analysis of 26-50 exons by DNA sequence analysis, mutation scanning or duplication/deletion variants of >50 exons, sequence analysis of multiple genes on one platform) [when specified as the following]:</p> <ul style="list-style-type: none"> • <i>CHD7 (chromodomain helicase DNA binding protein 7)</i> (eg, CHARGE syndrome), full gene sequence • <i>JAG1 (jagged 1)</i> (eg, Alagille syndrome), full gene sequence
81408	<p>Molecular pathology procedure, Level 9 (eg, analysis of >50 exons in a single gene by DNA sequence analysis) [when specified as the following]:</p> <ul style="list-style-type: none"> • <i>DMD (dystrophin)</i> (eg, Duchenne/Becker muscular dystrophy), full gene sequence • <i>MYH11 (myosin, heavy chain 11, smooth muscle)</i> (eg, thoracic aortic aneurysms and aortic dissections), full gene sequence
81479	<p>Unlisted molecular pathology procedure [for example: <i>ABCB4, ABCB11, ATP8B1, MYO5B, NRIH4, TJP2</i> (eg, progressive familial intrahepatic cholestasis); <i>AC9DVL, GBE1 (1,4-alpha-glucan branching enzyme 1)</i> (eg, glycogen storage disease); <i>ELP1 (elongator complex protein 1)</i> (eg, familial dysautonomia), <i>NOTCH2 (notch receptor 2)</i> (eg, Alagille syndrome), <i>MVK, TPP1</i>]</p>
81599	<p>Unlisted multianalyte assay with algorithmic analysis</p>

Federal and State law, as well as contract language including definitions and specific coverage provisions/exclusions, and Medical Policy take precedence over Clinical UM Guidelines and must be considered first in determining eligibility for coverage. The member's contract benefits in effect on the date that services are rendered must be used. Clinical UM Guidelines, which address medical efficacy, should be considered before utilizing medical opinion in adjudication. Medical technology is constantly evolving, and we reserve the right to review and update Clinical UM Guidelines periodically. Clinical UM guidelines are used when the plan performs utilization review for the subject. Due to variances in utilization patterns, each plan may choose whether or not to adopt a particular Clinical UM Guideline. To determine if review is required for this Clinical UM Guideline, please contact the customer service number on the back of the member's card.

No part of this publication may be reproduced, stored in a retrieval system or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from the health plan.

© CPT Only – American Medical Association

Medicaid managed care administered by Amerigroup Corporation, an independent company

Genetic Testing for Inherited Diseases

- 0170U Neurology (autism spectrum disorder [ASD]), RNA, next-generation sequencing, saliva, algorithmic analysis, and results reported as predictive probability of ASD diagnosis Clarifi™, Quadrant Biosciences, Inc, Quadrant Biosciences, Inc
- 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, Variantyx Inc

HCPCS

- S3845 Genetic testing for alpha-thalassemia
- S3846 Genetic testing for hemoglobin E beta-thalassemia
- S3849 Genetic testing for Niemann-Pick diseases
- S3850 Genetic testing for sickle cell anemia
- S3853 Genetic testing for myotonic muscular dystrophy

ICD-10 Diagnosis

All diagnoses

When services are Not Medically Necessary:

For the procedure codes listed above when criteria are not met.

Other gene testing for preconception/prenatal testing

When services may be Medically Necessary when criteria are met:

CPT

- 81173 *AR (androgen receptor)* (eg, spinal and bulbar muscular atrophy, Kennedy disease, X chromosome inactivation) gene analysis; full gene sequence
- 81174 *AR (androgen receptor)* (eg, spinal and bulbar muscular atrophy, Kennedy disease, X chromosome inactivation) gene analysis; known familial variant
- 81177 *ATN1 (atrophin1)* (eg, dentatorubral-pallidoluysian atrophy) gene analysis, evaluation to detect abnormal (eg, expanded) alleles
- 81178 *ATXN1 (ataxin 1)* (eg, spinocerebellar ataxia) gene analysis, evaluation to detect abnormal (eg, expanded) alleles
- 81179 *ATXN2 (ataxin 2)* (eg, spinocerebellar ataxia) gene analysis, evaluation to detect abnormal (eg, expanded) alleles
- 81180 *ATXN3 (ataxin 3)* (eg, spinocerebellar ataxia, Machado-Joseph disease) gene analysis, evaluation to detect abnormal (eg, expanded) alleles
- 81181 *ATXN7 (ataxin 7)* (eg, spinocerebellar ataxia) gene analysis, evaluation to detect abnormal (eg, expanded) alleles

Federal and State law, as well as contract language including definitions and specific coverage provisions/exclusions, and Medical Policy take precedence over Clinical UM Guidelines and must be considered first in determining eligibility for coverage. The member's contract benefits in effect on the date that services are rendered must be used. Clinical UM Guidelines, which address medical efficacy, should be considered before utilizing medical opinion in adjudication. Medical technology is constantly evolving, and we reserve the right to review and update Clinical UM Guidelines periodically. Clinical UM guidelines are used when the plan performs utilization review for the subject. Due to variances in utilization patterns, each plan may choose whether or not to adopt a particular Clinical UM Guideline. To determine if review is required for this Clinical UM Guideline, please contact the customer service number on the back of the member's card.

No part of this publication may be reproduced, stored in a retrieval system or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from the health plan.

© CPT Only – American Medical Association

Medicaid managed care administered by Amerigroup Corporation, an independent company

Genetic Testing for Inherited Diseases

81182	<i>ATXN8OS</i> (<i>ataxin 8 opposite strand [non-protein coding]</i>) (eg, spinocerebellar ataxia) gene analysis, evaluation to detect abnormal (eg, expanded) alleles
81183	<i>ATXN10</i> (<i>ataxin 10</i>) (eg, spinocerebellar ataxia) gene analysis, evaluation to detect abnormal (eg, expanded) alleles
81184	<i>CACNA1A</i> (<i>calcium voltage-gated channel subunit alpha1 A</i>) (eg, spinocerebellar ataxia) gene analysis; evaluation to detect abnormal (eg, expanded) alleles
81185	<i>CACNA1A</i> (<i>calcium voltage-gated channel subunit alpha1 A</i>) (eg, spinocerebellar ataxia) gene analysis; full gene sequence
81186	<i>CACNA1A</i> (<i>calcium voltage-gated channel subunit alpha1 A</i>) (eg, spinocerebellar ataxia) gene analysis; known familial variant
81188	<i>CSTB</i> (<i>cystatin B</i>) (eg, Unverricht-Lundborg disease) gene analysis; evaluation to detect abnormal (eg, expanded) alleles
81189	<i>CSTB</i> (<i>cystatin B</i>) (eg, Unverricht-Lundborg disease) gene analysis; full gene sequence
81190	<i>CSTB</i> (<i>cystatin B</i>) (eg, Unverricht-Lundborg disease) gene analysis; known familial variant(s)
81200	<i>ASPA</i> (<i>aspartoacylase</i>) (eg, Canavan disease) gene analysis, common variants (eg, E285A, Y231X)
81204	<i>AR</i> (<i>androgen receptor</i>) (eg, spinal and bulbar muscular atrophy, Kennedy disease, X chromosome inactivation) gene analysis; characterization of alleles (eg, expanded size or methylation status)
81252	<i>GJB2</i> (<i>gap junction protein, beta 2, 26kDa, connexin 26</i>) (eg, nonsyndromic hearing loss) gene analysis; full gene sequence
81253	<i>GJB2</i> (<i>gap junction protein, beta 2, 26kDa, connexin 26</i>) (eg, nonsyndromic hearing loss) gene analysis; known familial variants
81254	<i>GJB2</i> (<i>gap junction protein, beta 6, 30kDa, connexin 30</i>) (eg, nonsyndromic hearing loss) gene analysis, common variants (eg, 309kb [del(GJB6-D13S1830)] and 232kb [del(GJB6-D13S1854)])
81255	<i>HEXA</i> (<i>hexosaminidase A [alpha polypeptide]</i>) (eg, Tay-Sachs disease) gene analysis, common variants (eg, 1278insTATC, 1421+1G>C, G269S)
81271	<i>HTT</i> (<i>huntingtin</i>) (eg, Huntington disease) gene analysis; evaluation to detect abnormal (eg, expanded) alleles
81274	<i>HTT</i> (<i>huntingtin</i>) (eg, Huntington disease) gene analysis; characterization of alleles (eg, expanded size)
81284	<i>FXN</i> (<i>frataxin</i>) (eg, Friedreich ataxia) gene analysis; evaluation to detect abnormal (expanded) alleles
81285	<i>FXN</i> (<i>frataxin</i>) (eg, Friedreich ataxia) gene analysis; characterization of alleles (eg, expanded size)
81286	<i>FXN</i> (<i>frataxin</i>) (eg, Friedreich ataxia) gene analysis; full gene sequence
81289	<i>FXN</i> (<i>frataxin</i>) (eg, Friedreich ataxia) gene analysis; known familial variant(s)

Federal and State law, as well as contract language including definitions and specific coverage provisions/exclusions, and Medical Policy take precedence over Clinical UM Guidelines and must be considered first in determining eligibility for coverage. The member's contract benefits in effect on the date that services are rendered must be used. Clinical UM Guidelines, which address medical efficacy, should be considered before utilizing medical opinion in adjudication. Medical technology is constantly evolving, and we reserve the right to review and update Clinical UM Guidelines periodically. Clinical UM guidelines are used when the plan performs utilization review for the subject. Due to variances in utilization patterns, each plan may choose whether or not to adopt a particular Clinical UM Guideline. To determine if review is required for this Clinical UM Guideline, please contact the customer service number on the back of the member's card.

No part of this publication may be reproduced, stored in a retrieval system or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from the health plan.

© CPT Only – American Medical Association

Medicaid managed care administered by Amerigroup Corporation, an independent company

Genetic Testing for Inherited Diseases

81290	<i>MCOLN1</i> (<i>mucolipin 1</i>) (eg, Mucopolipidosis, type IV) gene analysis, common variants (eg, IVS3-2A>G, del6.4kb)
81302	<i>MECP2</i> (<i>methyl CpG binding protein 2</i>) (eg, Rett syndrome) gene analysis; full sequence analysis
81303	<i>MECP2</i> (<i>methyl CpG binding protein 2</i>) (eg, Rett syndrome) gene analysis; known familial variant
81304	<i>MECP2</i> (<i>methyl CpG binding protein 2</i>) (eg, Rett syndrome) gene analysis; duplication/deletion variants
81312	<i>PABPN1</i> (<i>poly[A] binding protein nuclear 1</i>) (eg, oculopharyngeal muscular dystrophy) gene analysis, evaluation to detect abnormal (eg, expanded) alleles
81331	<i>SNRPN/UBE3A</i> (<i>small nuclear ribonucleoprotein polypeptide N and ubiquitin protein ligase E3A</i>) (eg, Prader-Willi syndrome and/or Angelman syndrome), methylation analysis
81333	<i>TGFBI</i> (<i>transforming growth factor beta-induced</i>) (eg, corneal dystrophy) gene analysis, common variants (eg, R124H, R124C, R124L, R555W, R555Q)
81343	<i>PPP2R2B</i> (<i>protein phosphatase 2 regulatory subunit Bbeta</i>) (eg, spinocerebellar ataxia) gene analysis, evaluation to detect abnormal (eg, expanded) alleles
81344	<i>TBP</i> (<i>TATA box binding protein</i>) (eg, spinocerebellar ataxia) gene analysis, evaluation to detect abnormal (eg, expanded) alleles
81402	Molecular pathology procedure, Level 3 (eg, > 10 SNP's 2-10 methylated variants, or 2-10 somatic variants [typically using non-sequencing target variant analysis], immunoglobulin and T-cell receptor gene rearrangements, duplication/deletion variants of 1 exon, loss of heterozygosity [LOH], uniparental disomy [UPD]) [when specified as the following]: <ul style="list-style-type: none"> • Uniparental disomy (UPD) (eg, Russell-Silver syndrome, Prader-Willi/Angelman syndrome), short tandem repeat (STR) analysis
81403	Molecular pathology procedure, Level 4 (eg, analysis of single exon by DNA sequence analysis, analysis of >10 amplicons using multiplex PCR in 2 or more independent reactions, mutation scanning or duplication/deletion variants of 2-5 exons) [when specified as the following]: <ul style="list-style-type: none"> • <i>KCNC3</i> (<i>potassium voltage-gated channel, Shaw-related subfamily, member 3</i>) (eg, spinocerebellar ataxia), targeted sequence analysis (eg, exon 2)
81405	Molecular pathology procedure, Level 6 (eg, analysis of 6-10 exons by DNA sequence analysis, mutation scanning or duplication/deletion variants of 11-25 exons, regionally targeted cytogenomic array analysis) [when specified as the following]: <ul style="list-style-type: none"> • <i>APTX</i> (<i>aprataxin</i>) (eg, ataxia with oculomotor apraxia 1), full gene sequence • <i>SIL1</i> (<i>SIL1 homolog, endoplasmic reticulum chaperone [S. cerevisiae]</i>) (eg, ataxia), full gene sequence
81406	Molecular pathology procedure, Level 7 (eg, analysis of 11-25 exons by DNA sequence analysis, mutation scanning or duplication/deletion variants of 26-50 exons, cytogenomic array analysis for neoplasia) [when specified as the following]:

Federal and State law, as well as contract language including definitions and specific coverage provisions/exclusions, and Medical Policy take precedence over Clinical UM Guidelines and must be considered first in determining eligibility for coverage. The member's contract benefits in effect on the date that services are rendered must be used. Clinical UM Guidelines, which address medical efficacy, should be considered before utilizing medical opinion in adjudication. Medical technology is constantly evolving, and we reserve the right to review and update Clinical UM Guidelines periodically. Clinical UM guidelines are used when the plan performs utilization review for the subject. Due to variances in utilization patterns, each plan may choose whether or not to adopt a particular Clinical UM Guideline. To determine if review is required for this Clinical UM Guideline, please contact the customer service number on the back of the member's card.

No part of this publication may be reproduced, stored in a retrieval system or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from the health plan.

© CPT Only – American Medical Association

Medicaid managed care administered by Amerigroup Corporation, an independent company

Genetic Testing for Inherited Diseases

- *AFG3L2 (AFG3 ATPase family gene 3-like 2 [S. cerevisiae])* (eg, spinocerebellar ataxia), full gene sequence
 - *EIF2B5 (eukaryotic translation initiation factor 2B, subunit 5 epsilon, 82kDa)* (eg, childhood ataxia with central nervous system hypomyelination/vanishing white matter), full gene sequence
 - *HEXA (hexosaminidase A, alpha polypeptide)* (eg, Tay-Sachs disease), full gene sequence
 - *NOTCH3 (notch 3)* (eg, cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy [CADASIL]), targeted sequence analysis (eg, exons 1-23)
 - *PRKCG (protein kinase C, gamma)* (eg, spinocerebellar ataxia), full gene sequence
 - *SETX (senataxin)* (eg, ataxia), full gene sequence
 - *UBE3A (ubiquitin protein ligase E3A)* (eg, Angelman syndrome), full gene sequence
- 81407 Molecular pathology procedure, Level 8 (eg, analysis of 26-50 exons by DNA sequence analysis, mutation scanning or duplication/deletion variants of >50 exons, sequence analysis of multiple genes on one platform) [when specified as the following]:
- *AGL (amylo-alpha-1, 6-glucosidase, 4-alpha-glucanotransferase)* (eg, glycogen storage disease type III), full gene sequence
- 81408 Molecular pathology procedure, Level 9 (eg, analysis of >50 exons in a single gene by DNA sequence analysis) [when specified as the following]:
- *ITPR1 (inositol 1,4,5-triphosphate receptor, type 1)* (eg, spinocerebellar ataxia), full gene sequence
- 0230U *AR (androgen receptor)* (eg, 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, Variantyx Inc
- 0231U *CACNA1A (calcium voltage-gated channel subunit alpha 1A)* (eg, 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, Variantyx Inc
- 0232U *CSTB (cystatin B)* (eg, 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, Variantyx Inc
- 0233U *FXN (frataxin)* (eg, Friedreich ataxia), gene analysis, including small sequence changes in exonic and intronic regions, deletions, duplications, short tandem repeat (STR)
-

Federal and State law, as well as contract language including definitions and specific coverage provisions/exclusions, and Medical Policy take precedence over Clinical UM Guidelines and must be considered first in determining eligibility for coverage. The member's contract benefits in effect on the date that services are rendered must be used. Clinical UM Guidelines, which address medical efficacy, should be considered before utilizing medical opinion in adjudication. Medical technology is constantly evolving, and we reserve the right to review and update Clinical UM Guidelines periodically. Clinical UM guidelines are used when the plan performs utilization review for the subject. Due to variances in utilization patterns, each plan may choose whether or not to adopt a particular Clinical UM Guideline. To determine if review is required for this Clinical UM Guideline, please contact the customer service number on the back of the member's card.

No part of this publication may be reproduced, stored in a retrieval system or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from the health plan.

© CPT Only – American Medical Association

Medicaid managed care administered by Amerigroup Corporation, an independent company

Genetic Testing for Inherited Diseases

0234U expansions, mobile element insertions, and variants in non-uniquely mappable regions
 Genomic Unity® FXN Analysis, Variantyx Inc, Variantyx Inc
 MECP2 (*methyl CpG binding protein 2*) (eg, 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, Variantyx Inc

HCPCS

S3844 DNA analysis of the connexin 26 gene (GJB2) for susceptibility to congenital, profound
 deafness

ICD-10 Diagnosis

Z31.430 Encounter of female for testing for genetic disease carrier status for procreative
 management
 Z31.440 Encounter of male for testing for genetic disease carrier status for procreative
 management
 Z36.0 Encounter for antenatal screening for chromosomal anomalies
 Z36.8A Encounter for antenatal screening for other genetic defects
 Z84.81 Family history of carrier of genetic disease

When services are Not Medically Necessary:

For the procedure and diagnosis codes listed above when criteria are not met or for all other diagnoses not listed.

Other gene testing of individuals:

When services may be Medically Necessary when criteria are met:

CPT

81240 ● *F2 (prothrombin, coagulation factor II)* (eg, hereditary hypercoagulability) gene analysis,
 20210G>A variant
 81332 *SERPINA1 (serpin peptidase inhibitor, clade A, alpha-1 antiproteinase, antitrypsin,
 member 1)* (eg, alpha-1-antitrypsin deficiency), gene analysis, common variants (eg, *S
 and *Z)
 81401 Molecular pathology procedure, Level 2 (eg, 2-10 SNPs, 1 methylated variant, or 1 somatic
 variant [typically using nonsequencing target variant analysis], or detection of a dynamic
 mutation disorder/triplet repeat) [when specified as the following]:

- *APOB (apolipoprotein B)* (eg, familial hypercholesterolemia type B), common variants
 (eg, R3500Q, R3500W)
- *PRSS1 (protease, serine, 1 [trypsin 1])* (eg, hereditary pancreatitis), common variants
 (eg, N29I, A16V, R122H)

Federal and State law, as well as contract language including definitions and specific coverage provisions/exclusions, and Medical Policy take precedence over Clinical UM Guidelines and must be considered first in determining eligibility for coverage. The member's contract benefits in effect on the date that services are rendered must be used. Clinical UM Guidelines, which address medical efficacy, should be considered before utilizing medical opinion in adjudication. Medical technology is constantly evolving, and we reserve the right to review and update Clinical UM Guidelines periodically. Clinical UM guidelines are used when the plan performs utilization review for the subject. Due to variances in utilization patterns, each plan may choose whether or not to adopt a particular Clinical UM Guideline. To determine if review is required for this Clinical UM Guideline, please contact the customer service number on the back of the member's card.

No part of this publication may be reproduced, stored in a retrieval system or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from the health plan.

© CPT Only – American Medical Association

Medicaid managed care administered by Amerigroup Corporation, an independent company

Genetic Testing for Inherited Diseases

81404	<p>Molecular pathology procedure, Level 5 (eg, analysis of 2-5 exons by DNA sequence analysis, mutation scanning or duplication/deletion variants of 6-10 exons, or characterization of a dynamic mutation disorder/triplet repeat by Southern blot analysis) [when specified as the following]:</p> <ul style="list-style-type: none"> • <i>PRSS1</i> (<i>protease, serine, 1 [trypsin 1]</i>) (eg, hereditary pancreatitis), full gene sequence • <i>SPINK1</i> (<i>serine peptidase inhibitor, Kazal type 1</i>) (eg, hereditary pancreatitis), full gene sequence
81405	<p>Molecular pathology procedure, Level 6 (eg, analysis of 6-10 exons by DNA sequence analysis, mutation scanning or duplication/deletion variants of 11-25 exons, regionally targeted cytogenomic array analysis) [when specified as the following]:</p> <ul style="list-style-type: none"> • <i>CPOX</i> (<i>coproporphyrinogen oxidase</i>) (eg, hereditary coproporphyrinuria), full gene sequence • <i>CTRC</i> (<i>chymotrypsin C</i>) (eg, hereditary pancreatitis), full gene sequence • <i>LDLR</i> (<i>low density lipoprotein receptor</i>) (eg, familial hypercholesterolemia), duplication/deletion analysis • <i>RAI1</i> (<i>retinoic acid induced 1</i>) (eg, Smith-Magenis syndrome), full gene sequence
81406	<p>Molecular pathology procedure, Level 7 (eg, analysis of 11-25 exons by DNA sequence analysis, mutation scanning or duplication/deletion variants of 26-50 exons, cytogenomic array analysis for neoplasia) [when specified as the following]:</p> <ul style="list-style-type: none"> • <i>HMBS</i> (<i>hydroxymethylbilane synthase</i>) (eg, acute intermittent porphyria), full gene sequence • <i>LDLR</i> (<i>low density lipoprotein receptor</i>) (eg, familial hypercholesterolemia), full gene sequence • <i>LEPR</i> (<i>leptin receptor</i>) (eg, obesity with hypogonadism), full gene sequence • <i>PCSK9</i> (<i>proprotein convertase subtilisin/kexin type 9</i>) (eg, familial hypercholesterolemia), full gene sequence • <i>PPOX</i> (<i>protoporphyrinogen oxidase</i>) (eg, variegate porphyria), full gene sequence
81407	<p>Molecular pathology procedure, Level 8 (eg, analysis of 26-50 exons by DNA sequence analysis, mutation scanning or duplication/deletion variants of >50 exons, sequence analysis of multiple genes on one platform) [when specified as the following]:</p> <ul style="list-style-type: none"> • <i>APOB</i> (<i>apolipoprotein B</i>) (eg, familial hypercholesterolemia type B), full gene sequence
81479	<p>Unlisted molecular pathology procedure [when specified as: <i>AGXT</i> (<i>Alanine--Glyoxylate And Serine--Pyruvate Aminotransferase</i>) (eg, primary hyperoxaluria type 1 [PH1]), <i>IL1RN</i> (<i>Interleukin 1 Receptor Antagonist</i>), <i>LDLRAP1</i> (<i>low density lipoprotein receptor adaptor protein 1</i>) (eg, familial hypercholesterolemia), <i>MOCS1</i> (<i>molybdenum cofactor synthesis 1</i>) (eg, molybdenum cofactor deficiency), <i>PCSK1</i> (<i>Proprotein Convertase Subtilisin/Kexin Type 1</i>) (obesity), <i>POMC</i> (<i>Proopiomelanocortin</i>) (eg, obesity), <i>SI</i> (<i>sucrase-isomaltase</i>) (eg, congenital sucrase-isomaltase deficiency)]</p>

Federal and State law, as well as contract language including definitions and specific coverage provisions/exclusions, and Medical Policy take precedence over Clinical UM Guidelines and must be considered first in determining eligibility for coverage. The member's contract benefits in effect on the date that services are rendered must be used. Clinical UM Guidelines, which address medical efficacy, should be considered before utilizing medical opinion in adjudication. Medical technology is constantly evolving, and we reserve the right to review and update Clinical UM Guidelines periodically. Clinical UM guidelines are used when the plan performs utilization review for the subject. Due to variances in utilization patterns, each plan may choose whether or not to adopt a particular Clinical UM Guideline. To determine if review is required for this Clinical UM Guideline, please contact the customer service number on the back of the member's card.

No part of this publication may be reproduced, stored in a retrieval system or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from the health plan.

© CPT Only – American Medical Association

Medicaid managed care administered by Amerigroup Corporation, an independent company

Genetic Testing for Inherited Diseases

ICD-10 Diagnosis

For all diagnoses not listed below as not medically necessary

When services are Not Medically Necessary:

For the procedure codes listed above for the following diagnoses

ICD-10 Diagnosis

Z31.430	Encounter of female for testing for genetic disease carrier status for procreative management
Z31.440	Encounter of male for testing for genetic disease carrier status for procreative management
Z36.0	Encounter for antenatal screening for chromosomal anomalies
Z36.8A	Encounter for antenatal screening for other genetic defects
Z84.81	Family history of carrier of genetic disease

Other testing

When services are Not Medically Necessary:

CPT

81291	<i>MTHFR (5,10-methylenetetrahydrofolate reductase)</i> (eg, hereditary hypercoagulability) gene analysis, common variants (eg, 677T, 1298C)
81400	Molecular pathology procedure, Level 1 (eg, identification of single germline variant [eg, SNP] by techniques such as restriction enzyme digestion or melt curve analysis) [when specified as the following]:
81403	<ul style="list-style-type: none"> • <i>F2 (coagulation factor 2)</i> (eg, hereditary hypercoagulability), 1199G>A variant Molecular pathology procedure, Level 4 (eg, analysis of single exon by DNA sequence analysis, analysis of >10 amplicons using multiplex PCR in 2 or more independent reactions, mutation scanning or duplication/deletion variants of 2-5 exons) [when specified as the following]:
81404	<ul style="list-style-type: none"> • <i>ANG (angiogenin, ribonuclease, RNase A family, 5)</i> (eg, amyotrophic lateral sclerosis), full gene sequence Molecular pathology procedure, Level 5 (eg, analysis of 2-5 exons by DNA sequence analysis, mutation scanning or duplication/deletion variants of 6-10 exons, or characterization of a dynamic mutation disorder/triplet repeat by Southern blot analysis) [when specified as the following]: <ul style="list-style-type: none"> • <i>CDKN2A (cyclin-dependent kinase inhibitor 2A)</i> (eg, CDKN2A-related cutaneous malignant melanoma, familial atypical mole-malignant melanoma syndrome), full gene sequence • <i>SOD1 (superoxide dismutase 1, soluble)</i> (eg, amyotrophic lateral sclerosis), full gene sequence

Federal and State law, as well as contract language including definitions and specific coverage provisions/exclusions, and Medical Policy take precedence over Clinical UM Guidelines and must be considered first in determining eligibility for coverage. The member's contract benefits in effect on the date that services are rendered must be used. Clinical UM Guidelines, which address medical efficacy, should be considered before utilizing medical opinion in adjudication. Medical technology is constantly evolving, and we reserve the right to review and update Clinical UM Guidelines periodically. Clinical UM guidelines are used when the plan performs utilization review for the subject. Due to variances in utilization patterns, each plan may choose whether or not to adopt a particular Clinical UM Guideline. To determine if review is required for this Clinical UM Guideline, please contact the customer service number on the back of the member's card.

No part of this publication may be reproduced, stored in a retrieval system or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from the health plan.

© CPT Only – American Medical Association

Medicaid managed care administered by Amerigroup Corporation, an independent company

Genetic Testing for Inherited Diseases

- 81405 Molecular pathology procedure, Level 6 (eg, analysis of 6-10 exons by DNA sequence analysis, mutation scanning or duplication/deletion variants of 11-25 exons, regionally targeted cytogenomic array analysis) [when specified as the following]:
 - *PSEN1 (presenilin 1)* (eg, Alzheimer disease), full gene sequence
 - *TARDBP (TAR DNA binding protein)* (eg, amyotrophic lateral sclerosis), full gene sequence
- 81406 Molecular pathology procedure, Level 7 (eg, analysis of 11-25 exons by DNA sequence analysis, mutation scanning or duplication/deletion variants of 26-50 exons, cytogenomic array analysis for neoplasia) [when specified as the following]:
 - *APP (amyloid beta [A4] precursor protein)* (eg, Alzheimer disease), full gene sequence
 - *FUS (fused in sarcoma)* (eg, amyotrophic lateral sclerosis), full gene sequence;
 - *OPTN (optineurin)* (eg, amyotrophic lateral sclerosis), full gene sequence
 - *PSEN2 (presenilin 2 [Alzheimer disease 4])* (eg, Alzheimer disease), full gene sequence
- 81407 Molecular pathology procedure, Level 8 (eg, analysis of 26-50 exons by DNA sequence analysis, mutation scanning or duplication/deletion variants of >50 exons, sequence analysis of multiple genes on one platform) [when specified as the following]:
 - *SPTBN2 (spectrin, beta, nono-erythrocytic 2)* (eg, spinocerebellar ataxia), full gene sequence
- 81408 Molecular pathology procedure, Level 9 (eg, analysis of >50 exons in a single gene by DNA sequence analysis) [when specified as the following]:
 - *ATM (ataxia telangiectasia mutated)* (eg, ataxia telangiectasia), full gene sequence
- 81479 Unlisted molecular pathology procedure [when specified as: *F2 (coagulation factor 2)* (eg, hereditary hypercoagulability), C20209T or Yukuhashi variants]

HCPCS

- S3800 Genetic testing for amyotrophic lateral sclerosis (ALS)
- S3852 DNA analysis for APOE epsilon 4 allele for susceptibility to Alzheimer’s disease

ICD-10 Diagnosis

All diagnoses

When services are also Not Medically Necessary:

CPT

- 81401 Molecular pathology procedure, Level 2 (eg, 2-10 SNPs, 1 methylated variant, or 1 somatic variant [typically using nonsequencing target variant analysis], or detection of a dynamic mutation disorder/triplet repeat) [when specified as the following]:

Federal and State law, as well as contract language including definitions and specific coverage provisions/exclusions, and Medical Policy take precedence over Clinical UM Guidelines and must be considered first in determining eligibility for coverage. The member’s contract benefits in effect on the date that services are rendered must be used. Clinical UM Guidelines, which address medical efficacy, should be considered before utilizing medical opinion in adjudication. Medical technology is constantly evolving, and we reserve the right to review and update Clinical UM Guidelines periodically. Clinical UM guidelines are used when the plan performs utilization review for the subject. Due to variances in utilization patterns, each plan may choose whether or not to adopt a particular Clinical UM Guideline. To determine if review is required for this Clinical UM Guideline, please contact the customer service number on the back of the member’s card.

No part of this publication may be reproduced, stored in a retrieval system or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from the health plan.

© CPT Only – American Medical Association

Medicaid managed care administered by Amerigroup Corporation, an independent company

Genetic Testing for Inherited Diseases

- *APOE (apolipoprotein E)* (eg, hyperlipoproteinemia type III, cardiovascular disease, Alzheimer disease), common variants (eg, *2, *3, *4)

ICD-10 Diagnosis

F03.90-F03.91	Unspecified dementia
G30.0-G30.9	Alzheimer's disease
G31.1	Senile degeneration of brain, not elsewhere classified
R41.0	Disorientation, unspecified
R41.3	Other amnesia (memory loss NOS)
R41.81	Age-related cognitive decline

Discussion/General Information

The phrase genetic testing can refer to the analysis of an individual’s deoxyribonucleic acid (DNA), ribonucleic acid (RNA), chromosomes, genes, or gene products, (such as enzymes and other proteins), to identify germline (inherited) or somatic (non-inherited) genetic variations associated with health or disease. This document is only concerned with the testing of individual genes at the molecular level for individuals at risk or for preconception or prenatal testing.

The use of genetic testing information is being explored as a means to:

- Guide predictive considerations and prognosis in asymptomatic individuals;
- Guide diagnosis, prognosis and treatment options, including response to therapies, in symptomatic individuals;
- Identify individuals at risk for the development of disorders in the future, (for example, susceptibility testing or population risk assessment).

Genetic tests are done for many reasons:

- Pregnancy-related genetic testing (preconception, prenatal, pre-implantation, in vitro fertilization) may be done prior to or during pregnancy to guide reproductive decisions, as part of assistive reproductive procedures, and for other reasons. This includes carrier testing to identify individuals who possess one copy of a gene variant that, when present in two copies, results in a specific genetic disorder. Having only one copy of the gene variant does not place the individual being tested at increased risk of developing the disease, but will increase the risk of the individual having an affected child who will develop the disease and may necessitate pregnancy-related genetic testing. Genetic testing for pregnancy-related conditions is addressed in this document and in the following document: CG-GENE-06 Preimplantation Genetic Diagnosis Testing.

Federal and State law, as well as contract language including definitions and specific coverage provisions/exclusions, and Medical Policy take precedence over Clinical UM Guidelines and must be considered first in determining eligibility for coverage. The member's contract benefits in effect on the date that services are rendered must be used. Clinical UM Guidelines, which address medical efficacy, should be considered before utilizing medical opinion in adjudication. Medical technology is constantly evolving, and we reserve the right to review and update Clinical UM Guidelines periodically. Clinical UM guidelines are used when the plan performs utilization review for the subject. Due to variances in utilization patterns, each plan may choose whether or not to adopt a particular Clinical UM Guideline. To determine if review is required for this Clinical UM Guideline, please contact the customer service number on the back of the member's card.

No part of this publication may be reproduced, stored in a retrieval system or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from the health plan.

© CPT Only – American Medical Association

Medicaid managed care administered by Amerigroup Corporation, an independent company

Genetic Testing for Inherited Diseases

- Somatic cell genetic testing involves the testing of tissue, (most often cancerous tissue), for variants that are not inherited. This testing is generally done for diagnostic purposes or to assist in the selection of a cancer treatment. Genetic testing for somatic cell variants is addressed more specifically in other documents.
- Predictive, diagnostic, prognostic or therapeutic (see definition section) testing is also performed. Each gene to be tested is evaluated to determine whether or not identified genetic variants reliably identify a genetic disorder and that results of the genetic test will impact the management of the individual's condition with a likelihood of improved clinical outcomes. Examples of ways a test may impact these objectives include guiding treatment decisions, formulating surveillance recommendations or guiding preventive strategies. The results of genetic testing are also expected to improve net health outcomes, which requires that the test results are actionable and that any actions taken are not outweighed by harmful effects from the intervention.

Genetic Counseling

Due to the potential impact of positive genetic test results, it is generally recommended that genetic testing only be provided in conjunction with genetic counseling. Genetic counseling should include a discussion of the potential risks for a particular genetic disorder and how identification of a genetic variant will impact treatment management. According to the National Society of Genetic Counselors (NSGC), genetic counseling is the process of assisting individuals to understand and adapt to the medical, psychological and familial ramifications of a genetic disease. This process typically includes the guidance of a specially trained professional who:

1. Integrates the interpretation of family and medical histories to assess the probability of disease occurrence or recurrence; and
2. Provides education about inheritance, genetic testing, disease management, prevention and resources; and
3. Provides counseling to promote informed choices and adaptation to the risk or presence of a genetic condition; and
4. Provides counseling for the psychological aspects of genetic testing (NSGC, 2006).

The following table lists commonly requested gene testing targets, along with an assessment of whether or not they have been shown to be useful in guiding clinical management, determining carrier status, or guiding reproductive decisions. Tests listed in the table with a check in the column for, "Individual genome testing may impact clinical management" have been shown to be useful in guiding clinical management and, in the right circumstances, findings from genetic testing may result in improved net clinical outcomes. There are many reasons why some of the tests below do not have a check mark. This may be because knowledge of the genetic status does not change the management of the condition, has not been shown to facilitate decision making around reproduction, or may be associated with genes that exhibit problematic interpretation in the context of preconception or prenatal genetic testing (for example, conditions primarily associated with late age of onset, mild phenotype, and/or incomplete penetrance).

In addition to showing that a test may be useful for guiding clinical management, determining carrier status, or guiding reproductive decisions, requests for test coverage must also document that improvements in net health outcomes are expected as a result of the testing.

Federal and State law, as well as contract language including definitions and specific coverage provisions/exclusions, and Medical Policy take precedence over Clinical UM Guidelines and must be considered first in determining eligibility for coverage. The member's contract benefits in effect on the date that services are rendered must be used. Clinical UM Guidelines, which address medical efficacy, should be considered before utilizing medical opinion in adjudication. Medical technology is constantly evolving, and we reserve the right to review and update Clinical UM Guidelines periodically. Clinical UM guidelines are used when the plan performs utilization review for the subject. Due to variances in utilization patterns, each plan may choose whether or not to adopt a particular Clinical UM Guideline. To determine if review is required for this Clinical UM Guideline, please contact the customer service number on the back of the member's card.

No part of this publication may be reproduced, stored in a retrieval system or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from the health plan.

© CPT Only – American Medical Association

Medicaid managed care administered by Amerigroup Corporation, an independent company

Genetic Testing for Inherited Diseases

Gene	Condition	Preconception or prenatal genetic testing may be useful for determining carrier status and guiding reproductive decisions	Individual genome testing may impact clinical management	Additional Information
ABCB4	Progressive familial intrahepatic cholestasis	√	√	Bylvay (odevixibat)
ABCB11	Progressive familial intrahepatic cholestasis	√	√	Bylvay (odevixibat)
ACADM	Medium-chain acyl-coenzyme A dehydrogenase (MCAD)	√	√	ACOG # 690, (2017, reaffirmed 2019)*
ACADVL	Very long-chain acylCoA dehydrogenase (VLCAD) deficiency	√	√	
AFF2	Fragile X Syndrome	√	√	
AFG3L2	Spinocerebellar ataxia Type 28 (SCA28)	√		
AGL	Glycogen Storage Disease Type III	√		
AGXT	Primary hyperoxaluria type 1 (PH1)		√	FDA label for Oxlumo (lumasiran),
ANG	Amyotrophic lateral sclerosis			
ApoB	Familial hypercholesterolemia (principally APOB3500)		√	Evkeeza (evinacumab)
APOE ε4 (apolipoprotein E epsilon 4)	Late onset Alzheimer's disease			See Discussion section
APP (amyloid precursor protein)	Early onset Alzheimer's disease			See Discussion section
APTX	Ataxia with oculomotor apraxia Type 1	√		
AR	Spinal and bulbar muscular atrophy (also known as Kennedy disease, X chromosome	√		

Federal and State law, as well as contract language including definitions and specific coverage provisions/exclusions, and Medical Policy take precedence over Clinical UM Guidelines and must be considered first in determining eligibility for coverage. The member's contract benefits in effect on the date that services are rendered must be used. Clinical UM Guidelines, which address medical efficacy, should be considered before utilizing medical opinion in adjudication. Medical technology is constantly evolving, and we reserve the right to review and update Clinical UM Guidelines periodically. Clinical UM guidelines are used when the plan performs utilization review for the subject. Due to variances in utilization patterns, each plan may choose whether or not to adopt a particular Clinical UM Guideline. To determine if review is required for this Clinical UM Guideline, please contact the customer service number on the back of the member's card.

No part of this publication may be reproduced, stored in a retrieval system or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from the health plan.

© CPT Only – American Medical Association

Medicaid managed care administered by Amerigroup Corporation, an independent company

Genetic Testing for Inherited Diseases

Gene	Condition	Preconception or prenatal genetic testing may be useful for determining carrier status and guiding reproductive decisions	Individual genome testing may impact clinical management	Additional Information
	inactivation, X-linked spinal and bulbar muscular atrophy)			
ARSA	Arylsulfatase A Deficiency	√	√	
ASPA	Canavan disease	√		ACOG # 690, (2017, reaffirmed 2019)*
ATM	Ataxia telangiectasia			
ATN1 (DRPLA)	Dentatorubral-Pallidoluysian atrophy (also known as hereditary sensory and autonomic neuropathy type 1 with dementia and hearing loss, hereditary sensory neuropathy type IE, Haw River Syndrome, and Naito-Oyanagi disease)	√		
ATP7B	Wilson disease (hepatolenticular degeneration)	√	√	
ATP8B1,	Progressive familial intraphepatic cholestasis	√	√	Bylvay (odevixibat)
ATXN1	Spinocerebellar ataxia type 1 (SCA1)	√		
ATXN10	Spinocerebellar ataxia type 10 (SCA10)	√		
ATXN2	Spinocerebellar ataxia type 2 (SCA2)	√		
ATXN3	Spinocerebellar ataxia type 3 (SCA3)	√		
ATXN7	Spinocerebellar ataxia type 7 (SCA7)	√		
ATXN8 (ATXN8OS)	Spinocerebellar ataxia type 8 (SCA8)	√		

Federal and State law, as well as contract language including definitions and specific coverage provisions/exclusions, and Medical Policy take precedence over Clinical UM Guidelines and must be considered first in determining eligibility for coverage. The member's contract benefits in effect on the date that services are rendered must be used. Clinical UM Guidelines, which address medical efficacy, should be considered before utilizing medical opinion in adjudication. Medical technology is constantly evolving, and we reserve the right to review and update Clinical UM Guidelines periodically. Clinical UM guidelines are used when the plan performs utilization review for the subject. Due to variances in utilization patterns, each plan may choose whether or not to adopt a particular Clinical UM Guideline. To determine if review is required for this Clinical UM Guideline, please contact the customer service number on the back of the member's card.

No part of this publication may be reproduced, stored in a retrieval system or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from the health plan.

© CPT Only – American Medical Association

Medicaid managed care administered by Amerigroup Corporation, an independent company

Genetic Testing for Inherited Diseases

Gene	Condition	Preconception or prenatal genetic testing may be useful for determining carrier status and guiding reproductive decisions	Individual genome testing may impact clinical management	Additional Information
BCKDHA	Maple Syrup Urine Disease type 1A	√	√	ACOG # 690, (2017, reaffirmed 2019)*
BCKDHB	Maple Syrup Urine Disease type 1B	√	√	ACOG # 690, (2017, reaffirmed 2019)*
BLM	Bloom’s syndrome	√	√	ACOG # 690, (2017, reaffirmed 2019)*
CACNA1A	Spinocerebellar ataxia type 6 (SCA6)	√		
CDKN2A	Familial malignant melanoma			
CFTR	Cystic fibrosis	√	√	ACOG # 690, (2017, reaffirmed 2019)*
CHD7	CHARGE syndrome	√	√	See Discussion section
CNBP	Myotonic dystrophy type 2	√	√	
CPOX	Hereditary coproporphyrria		√	
CPT-2	Carnitine palmitoyltransferase-2 deficiency	√	√	
CSTB	Unverricht-Lundborg disease (ULD, EPM1)	√		
CTRC	Chymotrypsin C, hereditary pancreatitis		√	In children, when testing renders additional invasive diagnostic testing unnecessary
DLD	Dihydrolipoamide dehydrogenase deficiency (E3-deficient maple syrup urine disease)	√	√	
DMD	Dystrophin (eg, Duchenne/Becker muscular dystrophy)	√	√	
DBT	Maple Syrup Urine Disease type 2	√	√	
DHCR7	Smith-Lemli-Opitz Syndrome (SLOS)	√	√	ACOG # 690, (2017, reaffirmed 2019)*
DMPK	Myotonic dystrophy type 1	√	√	

Federal and State law, as well as contract language including definitions and specific coverage provisions/exclusions, and Medical Policy take precedence over Clinical UM Guidelines and must be considered first in determining eligibility for coverage. The member’s contract benefits in effect on the date that services are rendered must be used. Clinical UM Guidelines, which address medical efficacy, should be considered before utilizing medical opinion in adjudication. Medical technology is constantly evolving, and we reserve the right to review and update Clinical UM Guidelines periodically. Clinical UM guidelines are used when the plan performs utilization review for the subject. Due to variances in utilization patterns, each plan may choose whether or not to adopt a particular Clinical UM Guideline. To determine if review is required for this Clinical UM Guideline, please contact the customer service number on the back of the member’s card.

No part of this publication may be reproduced, stored in a retrieval system or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from the health plan.

© CPT Only – American Medical Association

Medicaid managed care administered by Amerigroup Corporation, an independent company

Genetic Testing for Inherited Diseases

Gene	Condition	Preconception or prenatal genetic testing may be useful for determining carrier status and guiding reproductive decisions	Individual genome testing may impact clinical management	Additional Information
EIF2B5	Childhood ataxia with central nervous system hypomyelination/Vanishing white matter	√		
ELP1	Familial Dysautonomia	√	√	ACOG # 690, (2017, reaffirmed 2019)*
F2, G20210A	Hereditary thrombophilia		√	
F5	Factor V Leiden thrombophilia		√	
FANCC	Fanconi anemia type C	√	√	ACOG # 690, (2017, reaffirmed 2019)*
FMR1	Fragile X Syndrome	√	√	
FUS	Amyotrophic lateral sclerosis			
FXN	Friedreich ataxia (also known as Friedreich's ataxia, FRDA)	√		
G6PC	Glycogen storage disease type I (GSD I, Von Gierke disease)	√	√	
GAA Genotype	Glycogen Storage Disease Type II (GSD II, Pompe disease)	√	√	Nexviazyme (avalglucosidase alfa-ngpt)
GALT	Galactosemia	√	√	ACOG # 690, (2017, reaffirmed 2019)*
GBA	Gaucher disease	√	√	ACOG # 690, (2017, reaffirmed 2019)*
GBE1	Glycogen Storage Disease type IV	√	√	ACOG # 690, (2017, reaffirmed 2019)*
Genetic mutation amenable to exon 45 skipping	Duchenne muscular dystrophy (DMD)		√	Amondys 45 (Casimersen)
GJB2	Nonsyndromic Hearing Loss and Deafness, (DFNB1)	√		
GLA	Fabry disease	√	√	
HADHA or HADHB	Trifunctional protein (TFP) deficiency or Long-chain 3-	√	√	

Federal and State law, as well as contract language including definitions and specific coverage provisions/exclusions, and Medical Policy take precedence over Clinical UM Guidelines and must be considered first in determining eligibility for coverage. The member's contract benefits in effect on the date that services are rendered must be used. Clinical UM Guidelines, which address medical efficacy, should be considered before utilizing medical opinion in adjudication. Medical technology is constantly evolving, and we reserve the right to review and update Clinical UM Guidelines periodically. Clinical UM guidelines are used when the plan performs utilization review for the subject. Due to variances in utilization patterns, each plan may choose whether or not to adopt a particular Clinical UM Guideline. To determine if review is required for this Clinical UM Guideline, please contact the customer service number on the back of the member's card.

No part of this publication may be reproduced, stored in a retrieval system or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from the health plan.

© CPT Only – American Medical Association

Medicaid managed care administered by Amerigroup Corporation, an independent company

Genetic Testing for Inherited Diseases

Gene	Condition	Preconception or prenatal genetic testing may be useful for determining carrier status and guiding reproductive decisions	Individual genome testing may impact clinical management	Additional Information
	hydroxyacylCoA dehydrogenase (LCHAD) deficiency			
HBA1	Alpha-thalassemia	√	√	
HBA2	Alpha thalassaemia	√	√	ACOG # 690, (2017, reaffirmed 2019)*
HBB	Beta thalassemia	√	√	ACOG # 690, (2017, reaffirmed 2019)*
HBB	Sickle cell disease	√	√	ACOG # 690, (2017, reaffirmed 2019)*
HEXA	Tay-Sachs disease	√		ACOG # 690, (2017, reaffirmed 2019)*
HFE	Hemochromatosis	√	√	
HMBS	Acute intermittent porphyria		√	
HTT	Huntington disease	√		
IKBKAP	Familial dysautonomia	√	√	
IL1RN mutations	Deficiency of Interleukin-1 Receptor Antagonist (DIRA)		√	Arcalyst (riloncept) Kineret (anakinra)
ITPR1	Spinocerebellar ataxia type 15 (SCA15)	√		
JAG1/JAGGED1	Alagille syndrome	√	√	Livmarli (maralixibat)
KCNC3	Spinocerebellar ataxia type 13	√		
LDLR	Familial hypercholesterolemia (LDL) receptor (sometimes called the apoB/E receptor) homozygous		√	Evkeeza (evinacumab)
LDLRAP1 (ARH adaptor)	Familial hypercholesterolemia		√	Evkeeza (evinacumab)
MECP2	Rett syndrome	√		
MCOLN1	Mucopolidosis	√		ACOG # 690, (2017, reaffirmed 2019)*
MOCS1	Molybdenum cofactor deficiency (MoCD) type A		√	Nulibry (fosdenopterin)

Federal and State law, as well as contract language including definitions and specific coverage provisions/exclusions, and Medical Policy take precedence over Clinical UM Guidelines and must be considered first in determining eligibility for coverage. The member's contract benefits in effect on the date that services are rendered must be used. Clinical UM Guidelines, which address medical efficacy, should be considered before utilizing medical opinion in adjudication. Medical technology is constantly evolving, and we reserve the right to review and update Clinical UM Guidelines periodically. Clinical UM guidelines are used when the plan performs utilization review for the subject. Due to variances in utilization patterns, each plan may choose whether or not to adopt a particular Clinical UM Guideline. To determine if review is required for this Clinical UM Guideline, please contact the customer service number on the back of the member's card.

No part of this publication may be reproduced, stored in a retrieval system or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from the health plan.

© CPT Only – American Medical Association

Medicaid managed care administered by Amerigroup Corporation, an independent company

Genetic Testing for Inherited Diseases

Gene	Condition	Preconception or prenatal genetic testing may be useful for determining carrier status and guiding reproductive decisions	Individual genome testing may impact clinical management	Additional Information
MTHFR C677T, A1286C and A1298C	Inherited thrombophilia			
MVK	Hyperimmunoglobulin D syndrome (HIDS)/Mevalonate kinase deficiency (MKD)	√	√	
MYH11	Marfan syndrome, Loeys-Dietz syndromes, and familial thoracic aortic aneurysms and dissections	√	√	
MYO5B	Progressive familial intrahepatic cholestasis	√	√	Bylvay (odevixibat)
NLGN3	Autism Spectrum	√	√	
NLGN4X	Autism Spectrum	√	√	
NOTCH2	Alagille syndrome	√	√	Livmarli (maralixibat)
NOTCH3	CADASIL syndrome	√		
NR1H4	Progressive familial intrahepatic cholestasis	√	√	Bylvay (odevixibat)
OPTN	Amyotrophic lateral sclerosis			
PABPN1	Oculopharyngeal muscular dystrophy (also known as OPMD)	√		
PAH	Phenylalanine hydroxylase deficiency	√	√	ACOG # 690, (2017, reaffirmed 2019)*
PCSK9	Familial hypercholesterolemia		√	Evkeeza (evinacumab)
POMC, PCSK1, LEPR deficiency;	Obesity caused by POMC, PCSK1, or LEPR deficiency		√	FDA label for Imcivree (setmelanotide)
PPOX	Variëgate porphyria		√	
PPP2R2B	Spinocerebellar ataxia type 12 (SCA12)	√		
PRKCG	Spinocerebellar ataxia type 14 (SCA14)	√		

Federal and State law, as well as contract language including definitions and specific coverage provisions/exclusions, and Medical Policy take precedence over Clinical UM Guidelines and must be considered first in determining eligibility for coverage. The member's contract benefits in effect on the date that services are rendered must be used. Clinical UM Guidelines, which address medical efficacy, should be considered before utilizing medical opinion in adjudication. Medical technology is constantly evolving, and we reserve the right to review and update Clinical UM Guidelines periodically. Clinical UM guidelines are used when the plan performs utilization review for the subject. Due to variances in utilization patterns, each plan may choose whether or not to adopt a particular Clinical UM Guideline. To determine if review is required for this Clinical UM Guideline, please contact the customer service number on the back of the member's card.

No part of this publication may be reproduced, stored in a retrieval system or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from the health plan.

© CPT Only – American Medical Association

Medicaid managed care administered by Amerigroup Corporation, an independent company

Genetic Testing for Inherited Diseases

Gene	Condition	Preconception or prenatal genetic testing may be useful for determining carrier status and guiding reproductive decisions	Individual genome testing may impact clinical management	Additional Information
PRSS1	Protease, serine, 1 (trypsin 1), hereditary pancreatitis		√	In children, when testing renders additional invasive diagnostic testing unnecessary
PSEN1 (presenilin 1)	Early onset Alzheimer’s disease			See Discussion section
PSEN2 (presenilin 2)	Early onset Alzheimer’s disease			See Discussion section
PYGM	Glycogen storage disease type V (GSD V)	√	√	
RAI1 or deletion of 17p11.2	Smith-Magenis syndrome		√	FDA label for Hetlioz (tasimelteon)
RPE65	Hereditary retinal dystrophy	√	√	Also see MED.00120 Gene Therapy for Ocular Conditions
SI	Congenital sucrase-isomaltase deficiency (CSID)		√	Sucraid (sacrosidase)
SERPINA1	Alpha-1 antitrypsin deficiency (AATD)		√	
SETX	Ataxia with Oculomotor Apraxia Type 2	√		
SIL1	Marinesco-Sjögren syndrome	√		
SLC37A4	Glycogen Storage Disease type Ib	√	√	
SMN-1	Spinal muscular atrophy	√	√	ACOG # 690, (2017, reaffirmed 2019)*
SMPD1	Acid Sphingomyelinase Deficiency (Niemann-Pick disease type B)	√	√	ACOG # 690, (2017, reaffirmed 2019)*
SNRPN	Prader-Willi syndrome	√		
SPINK1	Serine peptidase inhibitor, Kazal type 1, hereditary pancreatitis		√	In children, when testing renders additional invasive diagnostic testing unnecessary

Federal and State law, as well as contract language including definitions and specific coverage provisions/exclusions, and Medical Policy take precedence over Clinical UM Guidelines and must be considered first in determining eligibility for coverage. The member’s contract benefits in effect on the date that services are rendered must be used. Clinical UM Guidelines, which address medical efficacy, should be considered before utilizing medical opinion in adjudication. Medical technology is constantly evolving, and we reserve the right to review and update Clinical UM Guidelines periodically. Clinical UM guidelines are used when the plan performs utilization review for the subject. Due to variances in utilization patterns, each plan may choose whether or not to adopt a particular Clinical UM Guideline. To determine if review is required for this Clinical UM Guideline, please contact the customer service number on the back of the member’s card.

No part of this publication may be reproduced, stored in a retrieval system or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from the health plan.

© CPT Only – American Medical Association

Medicaid managed care administered by Amerigroup Corporation, an independent company

Genetic Testing for Inherited Diseases

Gene	Condition	Preconception or prenatal genetic testing may be useful for determining carrier status and guiding reproductive decisions	Individual genome testing may impact clinical management	Additional Information
SOD1	Amyotrophic lateral sclerosis (ALS, Lou Gehrig's disease)			
SPTBN2	Spinocerebellar ataxia type 5 (SCA5)			
TARDBP	Amyotrophic lateral sclerosis			
TBP	Spinocerebellar ataxia type 17 (SCA17)	√		
TGFBI	Corneal dystrophy	√		
TGFBR1	Marfan syndrome, Loeys-Dietz syndromes, and familial thoracic aortic aneurysms and dissections	√	√	
TGFBR2	Marfan syndrome, Loeys-Dietz syndromes, and familial thoracic aortic aneurysms and dissections	√	√	
TJP2	Progressive familial intrahepatic cholestasis	√	√	Bylvay (odevixibat)
TTPA	Ataxia with vitamin E deficiency	√	√	
TPP1	Infantile neuronal ceroid lipofuscinosis type 2	√	√	
UBE3A	Angelman syndrome	√		

*American College of Obstetricians and Gynecologists Committee on Genetics. ACOG Committee Opinion No. 690: Carrier screening in the age of genomic medicine. Obstet Gynecol. 2017(a); 129(3):e35-e40. Reaffirmed 2019.

Preconception or Prenatal Testing

Carrier testing for inherited genetic conditions is a key component of preconception and prenatal care. Carrier testing is conducted to identify an individual or a couple at risk (parent or prospective parent) for passing on genetic conditions to their offspring. Carriers are asymptomatic individuals who are typically not at risk for developing the disease, but who possess the potential to pass the gene variant to their offspring. Carrier testing is frequently performed on the parent or prospective parent before conception or during a pregnancy.

Federal and State law, as well as contract language including definitions and specific coverage provisions/exclusions, and Medical Policy take precedence over Clinical UM Guidelines and must be considered first in determining eligibility for coverage. The member's contract benefits in effect on the date that services are rendered must be used. Clinical UM Guidelines, which address medical efficacy, should be considered before utilizing medical opinion in adjudication. Medical technology is constantly evolving, and we reserve the right to review and update Clinical UM Guidelines periodically. Clinical UM guidelines are used when the plan performs utilization review for the subject. Due to variances in utilization patterns, each plan may choose whether or not to adopt a particular Clinical UM Guideline. To determine if review is required for this Clinical UM Guideline, please contact the customer service number on the back of the member's card.

No part of this publication may be reproduced, stored in a retrieval system or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from the health plan.

© CPT Only – American Medical Association

Medicaid managed care administered by Amerigroup Corporation, an independent company

Genetic Testing for Inherited Diseases

Carrier screening may be conducted for conditions that are found in the general population (panethnic), for diseases that are more common in a particular population, or based on family history. Panethnic screening (population screening) for carrier status is done for single-gene disorders that are common in the population.

Preconception or prenatal genetic testing of a parent or prospective parent is a common practice to determine carrier status. For example, the American College of Obstetrics and Gynecology (ACOG) and the American College of Medical Genetics (ACMG) recommend carrier screening for: Tay-Sach's disease, Canavan disease, mucopolysaccharidosis IV, Niemann Pick Disease Type A, Fanconi anemia group C, Bloom syndrome, Gaucher's disease and familial dysautonomia among individuals of Ashkenazi Jewish descent (ACOG, 2009; Gross, 2008). With regard to Fragile X syndrome, the ACMG has provided guidance on prenatal and preconception testing, and ACOG has published a Committee Opinion for carrier screening (Sherman, 2005; ACOG, 2009; ACOG, 2010; ACOG, 2017[b]).

Amyotrophic Lateral Sclerosis and Other Adult-onset Diseases

There has also been a growing interest in the use of genetic testing for amyotrophic lateral sclerosis (ALS, Lou Gehrig's disease). ALS is an adult-onset, progressive neurodegenerative disorder that affects nerve cells in the spinal cord and brain that eventually results in paralysis and death. The mean age of onset for ALS is 56 years in individuals without a positive family history and 46 years in individuals with more than one affected family member (familial ALS). Disease duration can vary significantly, but has been estimated to average approximately 3 years. Death usually results from respiratory failure. Alterations in several genes, including superoxide dismutase 1 (SOD1), angiogenin (ANG), TAR DNA binding protein (TARDBP), and optineurin (OPTN), have been associated with the development of ALS. Familial ALS can be inherited in an autosomal recessive, autosomal dominant, or X-linked fashion. Penetrance of familial ALS is age and variant dependent; approximately 50% of individuals with an SOD1 pathogenic variant are symptomatic by 46 years of age and 90% are symptomatic by 70 years of age. However, these percentages may be inflated due to ascertainment bias in families with high penetrance (Gene Reviews, 2015).

Neither ACOG nor ACMG recommend prenatal genetic testing for ALS. With regard to predictive genetic testing and the screening of children for adult-onset conditions, the ACMG has indicated that, "If clinical benefits will not accrue for years to decades, testing should be deferred until adulthood or should require parent or guardian permission, as well as adolescent assent." ACMG also notes that most predictive genetic testing for adult-onset conditions is predispositional, that is, testing for genes that are incompletely penetrant and may never become manifest (Ross, 2013). The ACOG Committee Opinion number 690 states, "Carrier screening panels should not include conditions primarily associated with a disease of adult onset" (ACOG, 2017[a]). The National Society of Genetic Counselors (NSGC) does not support the use of prenatal genetic testing for known adult-onset conditions if pregnancy or childhood management will not be affected (Hercher, 2016). Alpha 1 antitrypsin deficiency (incompletely associated with variants in the SERPINA1 gene) provides another example of a condition with an adult-onset phenotype where molecular testing cannot distinguish between childhood or adult onset. Likewise, preconception or prenatal genetic testing may not be appropriate for conditions, such as spinocerebellar ataxias (SCA) type 5 and familial malignant melanoma. Variants in the beta III spectrin gene (SPTBN2 gene) have been

Federal and State law, as well as contract language including definitions and specific coverage provisions/exclusions, and Medical Policy take precedence over Clinical UM Guidelines and must be considered first in determining eligibility for coverage. The member's contract benefits in effect on the date that services are rendered must be used. Clinical UM Guidelines, which address medical efficacy, should be considered before utilizing medical opinion in adjudication. Medical technology is constantly evolving, and we reserve the right to review and update Clinical UM Guidelines periodically. Clinical UM guidelines are used when the plan performs utilization review for the subject. Due to variances in utilization patterns, each plan may choose whether or not to adopt a particular Clinical UM Guideline. To determine if review is required for this Clinical UM Guideline, please contact the customer service number on the back of the member's card.

No part of this publication may be reproduced, stored in a retrieval system or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from the health plan.

© CPT Only – American Medical Association

Medicaid managed care administered by Amerigroup Corporation, an independent company

Genetic Testing for Inherited Diseases

associated with SCA type 5. This is a relatively mild disorder that typically begins between the ages of 20 and 30 and progresses slowly. CDKN2A, the most commonly identified gene variant in familial forms of melanoma (adulthood age of onset), exhibits incomplete penetrance.

Cystic Fibrosis

Cystic fibrosis (CF) is a hereditary disease that affects many organs throughout the body and most of the exocrine glands. As a result of the abnormal production of secretions, CF leads to organ and tissue damage, especially in the airways, liver, pancreas, intestines, sweat glands, and, in males, the vas deferens. While several organs and tissues are affected by CF, pulmonary disease remains the predominant cause of morbidity and mortality in individuals with CF. It has been estimated that approximately 1 in every 31 Americans is an asymptomatic carrier of the defective CF gene.

CF results when an individual inherits a gene variant in both alleles of the CF transmembrane conductance regulator (CFTR) gene, located on chromosome 7q31. The CFTR gene produces a protein that functions as a chloride channel and regulates bicarbonate and chloride transport, as well as other transport pathways. More than 1900 different variants in the CF gene have been identified. The prevalence of carrier frequencies and variant types varies among populations. Non-Hispanic whites of Northern European descent have a carrier rate of 1 in 25 with the $\Delta F508$ variant being the most common. It has been estimated that amongst individuals of Ashkenazi Jewish descent, CFTR mutation carrier frequency is 1 in 24. When considered all together, the most common variants in this population (W1282X, $\Delta F508$, G542X, 3849+10kb C>T, and N1303K) account for at least 94% of the CF cases.

The clinical severity of CF symptoms is largely determined by the specific variants that an individual carries. Any individual who screens positive for CF should receive genetic counseling. Negative screening results reduce, but do not totally eliminate, the possibility that the individual is a CF carrier. A negative screening test only indicates that the individual does not carry any of the CF variants specifically tested for during the screening.

Due to the high prevalence of carriers of CF, ACOG and ACMG recommend that DNA screening for CF be made available to all individuals seeking preconception or prenatal care regardless of personal or family history for the disease or carrier status (ACOG, 2017[a], 2017[b]). The NSGC recommends that carrier testing for CF be provided to women of reproductive age, regardless of ancestry. The NSGC also recommends that prior to conception, “CF carrier testing should also be offered to any individual with a family history of CF and to partners of mutation carriers and people with CF” (Langfelder-Schwind, 2014).

Because so many different variants in the CF gene have been identified, it is impractical to test for every known variant. In 2001, the ACMG Accreditation of Genetic Services Committee compiled a standard screening panel of 25 CF variants to screen for CF in the U.S. population (Grody et al, 2001). This 25-mutation test incorporated all CF-causing variants with an allele frequency of greater than or equal to 0.1 % in the general U.S. population. The test also included variant subsets shown to be sufficiently predominant in certain ethnic groups, such as African

Federal and State law, as well as contract language including definitions and specific coverage provisions/exclusions, and Medical Policy take precedence over Clinical UM Guidelines and must be considered first in determining eligibility for coverage. The member's contract benefits in effect on the date that services are rendered must be used. Clinical UM Guidelines, which address medical efficacy, should be considered before utilizing medical opinion in adjudication. Medical technology is constantly evolving, and we reserve the right to review and update Clinical UM Guidelines periodically. Clinical UM guidelines are used when the plan performs utilization review for the subject. Due to variances in utilization patterns, each plan may choose whether or not to adopt a particular Clinical UM Guideline. To determine if review is required for this Clinical UM Guideline, please contact the customer service number on the back of the member's card.

No part of this publication may be reproduced, stored in a retrieval system or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from the health plan.

© CPT Only – American Medical Association

Medicaid managed care administered by Amerigroup Corporation, an independent company

Genetic Testing for Inherited Diseases

Americans and Ashkenazi Jews. The ACMG recommended that this standard panel of variants be used to provide the greatest panethnic detectability that can be performed practically. In the 2004 guidelines on CF Population Carrier Screening, the ACMG recommended using a panel that contains, at a minimum, 23 of the most common CF variants (Watson, 2004).

According to the NSGC, carrier testing panels should include the variants recommended by ACOG and ACMG. For individuals of non-Northern European descent, panethnic panels that include additional variants more commonly identified in minority populations are appropriate to consider. NSGC also recommends that general population screening practices focus on, “Identifying carriers of established disease-causing CFTR mutations” (Langfelder-Schwind, 2014).

In a recent Consensus Opinion, ACOG stipulated that:

Complete analysis of the CFTR gene by DNA sequencing is not appropriate for routine carrier screening. This type of testing generally is reserved for patients with cystic fibrosis, patients with negative carrier screening result but a family history of cystic fibrosis (especially if family test results are not available), males with congenital bilateral absence of the vas deferens, or newborns with a positive newborn screening result when mutation testing (using the standard 23-mutation panel) has a negative result. Because carrier screening detects most mutations, sequence analysis should be considered only after discussion with a genetics professional to determine if it will add value to the standard screening that was performed previously (ACOG, 2017[b]).

Spinal Muscular Atrophy

Spinal muscular atrophy (SMA) is a disease characterized by muscle atrophy and weakness caused by the progressive degeneration and loss of the brain stem nuclei and the anterior horn cells in the spinal cord, (that is, the lower motor neurons). The onset of muscle weakness ranges from before birth to adolescence or young adulthood. The weakness is symmetrical and progresses from proximal to distal. Growth failure and poor weight gain, restrictive lung disease, scoliosis, joint contractures, and sleep difficulties are common complications (Prior, 2016). The age of onset of symptoms roughly correlates with the extent to which motor function is affected with the earlier the age of onset, the more profound the impact on motor function. Children who are symptomatic at birth or in infancy typically have the lowest level of function.

SMA is caused by a variant in the survival motor neuron gene (SMN1). Due to the severity of the disease and the relatively high carrier frequency, there has been interest in carrier screening for SMA in the general prenatal population. Because the genetics of SMA are complex and due to, “Limitations in the molecular diagnostic assays available, precise prediction of the phenotype in affected fetuses may not be possible” (ACOG, 2017[b]).

ACOG Committee Opinion No. 690 Carrier Screening in the Age of Genomic Medicine and No. 691 Carrier Screening for Genetic Conditions indicate that all individuals who are considering pregnancy or are already

Federal and State law, as well as contract language including definitions and specific coverage provisions/exclusions, and Medical Policy take precedence over Clinical UM Guidelines and must be considered first in determining eligibility for coverage. The member's contract benefits in effect on the date that services are rendered must be used. Clinical UM Guidelines, which address medical efficacy, should be considered before utilizing medical opinion in adjudication. Medical technology is constantly evolving, and we reserve the right to review and update Clinical UM Guidelines periodically. Clinical UM guidelines are used when the plan performs utilization review for the subject. Due to variances in utilization patterns, each plan may choose whether or not to adopt a particular Clinical UM Guideline. To determine if review is required for this Clinical UM Guideline, please contact the customer service number on the back of the member's card.

No part of this publication may be reproduced, stored in a retrieval system or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from the health plan.

© CPT Only – American Medical Association

Medicaid managed care administered by Amerigroup Corporation, an independent company

Genetic Testing for Inherited Diseases

pregnant, regardless of screening strategy and ethnicity, should be offered carrier screening for SMA (ACOG 2017[a], ACOG 2017[b]). The ACMG position statement on Carrier Screening for Spinal Muscular Atrophy also recommends panethnic screening for SMA (Prior, 2008).

Rett Syndrome

Rett syndrome is a disorder of the nervous system that leads to regression in development, especially in the areas of expressive language and hand use. In most cases, it is caused by a genetic variant on the X chromosome in the gene that contains instructions for creating methyl-CpG-binding protein 2 (MeCP2). Rett syndrome occurs almost exclusively in girls and may be misdiagnosed as autism or cerebral palsy. A child affected with Rett syndrome normally follows a standard developmental path for the first 5 months of life. After that time, development in communication skills and motor movement in the hands seems to stagnate or regress. After a short period, stereotyped hand movements, gait disturbances, and slowing of the rate of head growth become apparent. Other problems may also be associated with Rett syndrome, including seizures, disorganized breathing patterns while awake and apraxia/dyspraxia (the inability to program the body to perform motor movements). Apraxia/dyspraxia is a key symptom of Rett syndrome, and it results in significant functional impairment, interfering with body movement, including eye gaze and speech.

Duchenne Muscular Dystrophy or Becker Muscular Dystrophy

Muscular dystrophy (MD) refers to a diverse group of genetic diseases (disorders) characterized by a decrease in muscle mass over time, including progressive damage and weakness of facial, limb, breathing, and heart muscles. Some disorders within this group, referred to as dystrophinopathies, are categorized based on clinical features, (such as the age when signs are first seen), genetic (inheritance) pattern, the muscles affected, and muscle biopsy features. A major type of MD is Duchenne muscular dystrophy (DMD) which is the most common form affecting children. DMD is an x-linked genetic disorder characterized by progressive muscle atrophy. This form of muscular dystrophy primarily affects the skeletal and cardiac muscles and occurs almost exclusively in males. In this condition, muscle weakness tends to appear in early childhood and worsen rapidly. Affected children may demonstrate delayed motor skills, such as sitting, standing, walking, and are usually wheelchair-dependent by adolescence. The onset of cardiomyopathy typically begins in adolescence (Genetics Home Reference, Duchenne and Becker muscular dystrophy, 2019).

DMD is X-linked and penetrance is complete in males and can manifest in female carriers as weakness or cardiomyopathy. The gene that codes for dystrophin is the largest known human gene. A molecular confirmation of DMD is achieved by confirming the presence of a pathogenic variant in this gene by a number of available assays. A dystrophin gene alteration is implicated in a spectrum of X-linked muscle diseases, with overlapping clinical specifics and severity, resulting in a complex spectrum of dystrophinopathies. The clinical conditions within the spectrum include DMD, Becker muscular dystrophy (BMD), and DMD-associated cardiomyopathy. On December 12, 2019, the FDA cleared for marketing the first biochemical screening test to aid in newborn screening for DMD. The GSP Neonatal Creatine Kinase-MM kit works by measuring the concentration of a type of protein called CK-MM, which is part of a group of proteins called creatine kinase. Results showing elevated CK-MM should be confirmed using other testing methods, such as other laboratory tests, muscle biopsy, or genetic testing.

Federal and State law, as well as contract language including definitions and specific coverage provisions/exclusions, and Medical Policy take precedence over Clinical UM Guidelines and must be considered first in determining eligibility for coverage. The member's contract benefits in effect on the date that services are rendered must be used. Clinical UM Guidelines, which address medical efficacy, should be considered before utilizing medical opinion in adjudication. Medical technology is constantly evolving, and we reserve the right to review and update Clinical UM Guidelines periodically. Clinical UM guidelines are used when the plan performs utilization review for the subject. Due to variances in utilization patterns, each plan may choose whether or not to adopt a particular Clinical UM Guideline. To determine if review is required for this Clinical UM Guideline, please contact the customer service number on the back of the member's card.

No part of this publication may be reproduced, stored in a retrieval system or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from the health plan.

© CPT Only – American Medical Association

Medicaid managed care administered by Amerigroup Corporation, an independent company

Genetic Testing for Inherited Diseases

In 2020, the U.S. Food and Drug Administration (FDA) approved the Genomic Unity® Muscular Dystrophy Analysis by Variantyx Inc. (Framingham, MA), a test used for individuals who have been diagnosed with DMD or BMD or who exhibit symptoms of these disorders. High quality genomic DNA is isolated from whole blood and is subjected to next generation sequencing of the DMD gene.

Cerebral Autosomal Dominant Arteriopathy with Subcortical Infarcts and Leukoencephalopathy Syndrome (CADASIL)

CADASIL syndrome is considered the most common form of familial vascular dementia and familial brain small vessel arteriopathy. In addition to typical signs and symptoms of CADASIL syndrome, (for example, migraine with aura, stroke, cognitive impairment/dementias, mood disturbances), many individuals with CADASIL also develop leukoencephalopathy, which is characterized by high intensity signal lesions and areas of cystic degeneration of subcortical white matter and basal ganglia, which becomes more visible on MRI as the disease progresses. Clinical symptoms typically progress slowly with the mean onset of symptoms usually seen by age 45. By age 65, most individuals with CADASIL will exhibit cognitive deficits and dementia. There is no known cure for CADASIL syndrome and no treatment with proven efficacy for CADASIL syndrome; medical treatment is directed at relief of the presenting symptoms. Antiplatelet treatment is frequently used, but has not been proven to be effective in CADASIL. Surgery is also utilized in some cases to repair defective blood vessels, due to the degenerative effects of CADASIL, as it progresses. Additional risk factors for stroke, if present, such as hypertension, hyperlipidemia, diabetes, blood clotting disorders, and obstructive sleep apnea, should also be treated. Smoking should be discouraged in individuals at risk for CADASIL syndrome.

Genetic molecular testing, which is a method to determine the presence or absence of specific genetic variants on specific genes, has been proposed as a diagnostic aid in select individuals with moderate to high pretest likelihood of having CADASIL syndrome (based on symptoms), when other conventional diagnostic methods have yielded inconclusive or equivocal results. However, testing has no clinical utility, given that effective treatment options do not currently exist. Genetic testing for CADASIL, as part of preconceptional, preimplantation, and prenatal workups to determine carrier status and/or guide reproductive decisions when a pathologic NOTCH3 variant has been confirmed in a parent or other close relative, (that is, the proband) may be appropriate, given the pathological significance of the disease. Variants in the NOTCH3 gene have been consistently found on chromosome 19p13.2-p13.1 and have been identified as the underlying cause of CADASIL syndrome in more than 90% of confirmed cases. The NOTCH3 protein consists of 2321 amino acids, which are primarily expressed in vascular smooth muscle cells and which have a role in the control of vascular transduction. Over 170 causative NOTCH3 variants have been reported in the 33 exons of the NOTCH3 protein. All CADASIL-causing variants have been seen in exons 2 to 24, which encode the 34 epidermal growth factor-like (EGFL) repeats, with strong clustering in exons 3 and 4, which encode EGFL 2 to 5. This means that greater than 40% of NOTCH3 variants in greater than 70% of confirmed CADASIL cases have occurred in exons 2 to 24. The penetrance of sequence variants in the NOTCH3 gene is believed to be nearly 100%. Genetic testing involves targeted sequence analysis of 1 to 23 exons where known variants for CADASIL have been identified. Additional variants found on the NOTCH3 gene are of unknown significance at this time (Chabriet, 2009; Donahue, 2004; Lesnick Oberstein, 2003).

Federal and State law, as well as contract language including definitions and specific coverage provisions/exclusions, and Medical Policy take precedence over Clinical UM Guidelines and must be considered first in determining eligibility for coverage. The member's contract benefits in effect on the date that services are rendered must be used. Clinical UM Guidelines, which address medical efficacy, should be considered before utilizing medical opinion in adjudication. Medical technology is constantly evolving, and we reserve the right to review and update Clinical UM Guidelines periodically. Clinical UM guidelines are used when the plan performs utilization review for the subject. Due to variances in utilization patterns, each plan may choose whether or not to adopt a particular Clinical UM Guideline. To determine if review is required for this Clinical UM Guideline, please contact the customer service number on the back of the member's card.

No part of this publication may be reproduced, stored in a retrieval system or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from the health plan.

© CPT Only – American Medical Association

Medicaid managed care administered by Amerigroup Corporation, an independent company

Prothrombin-related Thrombophilia

Thrombophilia (also known as hypercoagulability) is an inherited disorder of blood clotting that leads to the inappropriate formation of blood clots. In adults, this disorder most commonly manifests as venous thromboembolism (VTE), such as deep vein thrombosis (DVT) in the legs and pulmonary embolism (PE) in the lungs. In women, VTE may result in adverse pregnancy outcomes. It has been estimated that in the United States, approximately 300,000 to 600,000 individuals are affected by VTE annually. The predisposition to form clots may be caused by genetic factors, acquired changes in the clotting mechanism, or, more commonly, an interaction between genetic and acquired factors. Prothrombin (factor II) is a protein in blood that is essential for the formation of blood clots. In prothrombin-related thrombophilia, a specific change in the genetic code causes the body to produce an excessive amount of the prothrombin protein, which can result in excessive blood clotting. A common sequence variance of the prothrombin gene (G20210A) has been associated with elevations in plasma prothrombin levels and is a known risk factor for DVT and PE. The prothrombin G20210A variant, found almost exclusively in Caucasians, is the second most common genetic risk factor for venous thrombosis, and G20210A testing has been used as a tool to screen for, diagnose and manage prothrombin-related thrombophilia.

According to Gene Reviews for Prothrombin-Related Thrombophilia (updated 2021), “The diagnosis of prothrombin thrombophilia is established in a proband by identification of a heterozygous or homozygous 20210G>A variant (also known as c.*97G>A) in F2, the gene encoding prothrombin.”

The following information is provided by Gene Reviews:

No clinical features are specific for prothrombin thrombophilia. The diagnosis should be suspected in individuals with at least one of the following more specific findings:

- A first unprovoked venous thromboembolism (VTE) before age 50 years;
- A history of recurrent VTE;
- Venous thrombosis at certain unusual sites such as the cerebral, mesenteric, portal, or hepatic veins;
- VTE during pregnancy or the puerperium;
- VTE associated with the use of estrogen-containing oral contraceptives or hormone replacement therapy (HRT);
- An unprovoked VTE at any age in an individual with a first-degree family member with a VTE before age 50 years.

Prothrombin thrombophilia testing may be considered in individuals who have less specific findings, including the following:

- A history of unprovoked VTE considering discontinuation of anticoagulation;
- A first VTE related to use of tamoxifen or other selective estrogen receptor modulators;
- Age greater than 50 years with a first unprovoked VTE;
- Neonates and children with non-catheter related idiopathic VTE or stroke.

Federal and State law, as well as contract language including definitions and specific coverage provisions/exclusions, and Medical Policy take precedence over Clinical UM Guidelines and must be considered first in determining eligibility for coverage. The member's contract benefits in effect on the date that services are rendered must be used. Clinical UM Guidelines, which address medical efficacy, should be considered before utilizing medical opinion in adjudication. Medical technology is constantly evolving, and we reserve the right to review and update Clinical UM Guidelines periodically. Clinical UM guidelines are used when the plan performs utilization review for the subject. Due to variances in utilization patterns, each plan may choose whether or not to adopt a particular Clinical UM Guideline. To determine if review is required for this Clinical UM Guideline, please contact the customer service number on the back of the member's card.

No part of this publication may be reproduced, stored in a retrieval system or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from the health plan.

© CPT Only – American Medical Association

Medicaid managed care administered by Amerigroup Corporation, an independent company

Genetic Testing for Inherited Diseases

The range of plasma concentrations of prothrombin in heterozygotes overlaps with the normal range. Therefore, plasma prothrombin concentration is not reliable for diagnosis. Molecular genetic testing approaches can include targeted analysis for the F2 20210G>A variant or a multigene panel that includes the analysis of the F2 variant and other genes of interest. Note: The genes included and sensitivity of multigene panels vary by laboratory and are likely to change over time (Kujovich, 2021).

The 2018 American College of Obstetricians and Gynecologists (ACOG) Clinical Practice Bulletin on Inherited Thrombophilias in Pregnancy does not recommend routine thrombophilia testing. They state that, “Screening for inherited thrombophilias is useful only when results will affect management decisions, and it is not useful in situations in which treatment is indicated for other risk factors.” They recommend targeted assessment for inherited thrombophilia in the following scenarios:

- A personal history of VTE, with or without a recurrent risk factor, and no prior thrombophilia testing;
- A first-degree relative (for example, a parent or sibling) with a history of high-risk inherited thrombophilia.

Based primarily on consensus and expert opinion (Level C), ACOG also stipulates that, “Screening tests for inherited thrombophilias should include factor V Leiden mutation; prothrombin G20210A mutation; and antithrombin, protein S, and protein C deficiencies” (ACOG, 2018).

Methylenetetrahydrofolate Reductase (MTHFR) Gene Mutation Testing

Methylenetetrahydrofolate reductase (MTHFR) is an enzyme that plays a role in the processing of amino acids, the building blocks of proteins, and is important for a chemical reaction involving forms of the B-vitamin folate (folic acid or vitamin B9). The MTHFR gene provides instructions for making the MTHFR enzyme. The MTHFR enzyme is thought to have a role in homocysteine metabolism; the mutation is reported to reduce MTHFR activity, resulting in hyperhomocysteinemia. Polymorphisms or common variants (C677T and A1298C) in the MTHFR gene have been associated with an increased risk of homocysteinuria, and suggested as a possible risk factor for developing a variety of diseases and disorders. The potential associations between MTHFR genotype status and a number of medical complications have been evaluated using methodologies, such as case-control and cohort study designs, Mendelian randomization, and meta-analysis. MTHFR mutation testing is available for these disorders and has been suggested to assist in the screening, diagnosis, and management of individuals predisposed to thrombosis. Genetic testing for mutations in the MTHFR gene for inherited thrombophilia is available, however, the clinical utility has not been established in any randomized controlled trials or controlled clinical trials in which testing for thrombophilia, including hyperhomocysteinemia, was the primary intervention and recurrent VTE was the outcome measure (Cohn, 2013). There is limited evidence on the clinical utility of testing for MTHFR mutations in persons with VTE or at risk for VTE. Given the lack of available evidence, and lack of clinical utility for serum homocysteine testing in general, it is unlikely that MTHFR mutation testing would alter the management of therapy resulting in improved clinical outcomes.

Federal and State law, as well as contract language including definitions and specific coverage provisions/exclusions, and Medical Policy take precedence over Clinical UM Guidelines and must be considered first in determining eligibility for coverage. The member's contract benefits in effect on the date that services are rendered must be used. Clinical UM Guidelines, which address medical efficacy, should be considered before utilizing medical opinion in adjudication. Medical technology is constantly evolving, and we reserve the right to review and update Clinical UM Guidelines periodically. Clinical UM guidelines are used when the plan performs utilization review for the subject. Due to variances in utilization patterns, each plan may choose whether or not to adopt a particular Clinical UM Guideline. To determine if review is required for this Clinical UM Guideline, please contact the customer service number on the back of the member's card.

No part of this publication may be reproduced, stored in a retrieval system or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from the health plan.

© CPT Only – American Medical Association

Medicaid managed care administered by Amerigroup Corporation, an independent company

Genetic Testing for Inherited Diseases

At the current time, there is insufficient evidence in the peer-reviewed published medical literature and lack of support for MTHFR mutation testing from professional specialty society consensus guidelines establishing a definitive causal relationship between inherited thrombophilias and recurrent early pregnancy loss. The clinical utility of genetic testing for inherited thrombophilia disorders, including MTHFR mutation testing has not been established. The peer-reviewed published medical literature suggests MTHFR enzyme activity associated with hyperhomocysteinemia is not typically associated with pregnancy loss prior to 10 weeks gestation. Routine screening of all pregnant women is not recommended. Other evidence-based guidelines state the presence of inherited thrombophilia is an insignificant factor in determining the optimal duration of anticoagulation in individuals with VTE. It is not possible to define a clinical situation in which the benefit of MTHFR mutation testing outweighs the risks of anticoagulation given the low risk of VTE in some clinical situations. Additional studies are necessary to determine how MTHFR mutation testing impacts treatment decisions and how these treatments improve health outcomes. Evidence is lacking in the clinical utility of MTHFR testing for other conditions, including, but not limited to, cancer susceptibility, neural tube defects, Alzheimer's disease, bone loss and fracture risk, diabetes, glaucoma, behavioral health and neuropsychiatric disorders, and in guiding drug therapy for any indication.

Hereditary Pancreatitis

Hereditary pancreatitis is a type of chronic pancreatitis. It is an autosomal dominant disease that is characterized by frequent attacks of epigastric pain with nausea and vomiting. Symptoms of hereditary pancreatitis can start after birth, but onset varies, and some people won't show symptoms until adulthood.

The majority of hereditary pancreatitis cases are associated with sequence variants in the protease, serine, 1 (trypsin 1) gene (PRSS1). It is estimated that 65-80% of individuals with hereditary pancreatitis have mutations in the PRSS1 gene. When hereditary pancreatitis is caused by mutations in the PRSS1 gene, it is inherited in an autosomal dominant pattern. In some cases, an affected person inherits the PRSS1 gene mutation from one affected parent. Other cases result from new mutations in the gene and occur in people with no history of the disorder in their family. It is estimated that 20% of people who have the altered PRSS1 gene never have an episode of pancreatitis (this situation is known as reduced penetrance). It is unclear why some people with a mutated gene never develop signs and symptoms of the disease. Although rare, sequence variants in three other genes may show an increased risk for developing pancreatitis. These three genes are the serine peptidase inhibitor, Kazal type 1 gene (SPINK1), the chymotrypsin C (caldecrin) gene (CTRC), and the cystic fibrosis transmembrane conductance regulator (ATP-binding cassette sub-family C, member 7) gene (CFTR), which is more commonly associated with cystic fibrosis. Some cases are caused by mutations in other genes, some of which have not been identified.

In general, the clinical utility of genetic testing for hereditary pancreatitis has not been demonstrated as there is no evidence in the peer-reviewed published literature that treatment is changed by testing or that health outcomes are improved as a result of testing. Testing of at-risk relatives has not been shown to improve outcomes nor does it show that results of genetic testing alters the prevalence or course of the disease. The incidence of recurrent pancreatitis in children is not common. Consequently, the literature regarding genetic testing for hereditary pancreatitis in children is sparse, including small case series (Awano, 2013; Corleto, 2010; Dai, 2016; Terlizzi,

Federal and State law, as well as contract language including definitions and specific coverage provisions/exclusions, and Medical Policy take precedence over Clinical UM Guidelines and must be considered first in determining eligibility for coverage. The member's contract benefits in effect on the date that services are rendered must be used. Clinical UM Guidelines, which address medical efficacy, should be considered before utilizing medical opinion in adjudication. Medical technology is constantly evolving, and we reserve the right to review and update Clinical UM Guidelines periodically. Clinical UM guidelines are used when the plan performs utilization review for the subject. Due to variances in utilization patterns, each plan may choose whether or not to adopt a particular Clinical UM Guideline. To determine if review is required for this Clinical UM Guideline, please contact the customer service number on the back of the member's card.

No part of this publication may be reproduced, stored in a retrieval system or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from the health plan.

© CPT Only – American Medical Association

Medicaid managed care administered by Amerigroup Corporation, an independent company

Genetic Testing for Inherited Diseases

2013). While there is a paucity of evidence and literature, there is consensus opinion that, in children with recurrent episodes of pancreatitis, a positive result of this genetic testing can render other, additional invasive diagnostic testing unnecessary.

Alzheimer's disease (AD)

AD is a progressive and age-related disease caused by unrelenting neurodegeneration and brain atrophy. Behaviorally, AD is characterized by progressive memory loss and cognitive decline. Pathologically, AD is characterized by local accumulations of amyloid β ($A\beta$) peptide and neurofibrillary tangles (NFTs) comprised of tau protein in the brain. At present, a definitive diagnosis of AD requires postmortem verification of $A\beta$ deposits (plaques) and NFTs in the brain. In current clinical practice, a diagnosis of AD is based on clinical presentation, a detailed clinical history, cognitive screening tools and clinical diagnostic criteria (for example, the National Institute of Neurological and Communicative Disorders and Stroke-Alzheimer's Disease and Related Disorders Association [NINCDS-ADRDA] guidelines and the Diagnostic and Statistical Manual of Mental Disorders, 5th Edition [DSM-V]).

AD is commonly associated with a family history; 40% of individuals with AD have at least one other afflicted first-degree relative. At present, the following four genes have been associated with AD and have been investigated as a possible diagnostic test: (1) Apolipoprotein E gene, (2) Amyloid $A\beta$ precursor gene, (3) Presenilin 1 gene, and (4) Presenilin 2 gene. Genetic testing has been investigated both in individuals with probable AD and in asymptomatic family members.

Early onset AD occurs before age 65 but can occur as early as age 30 years. Some families may show an autosomal dominant pattern of inheritance. Three genes have been identified by linkage analysis of affected families: amyloid $A\beta$ precursor gene (APP), presenilin 1 gene (PSEN1), and presenilin 2 (PSEN2) genes. A variety of mutations within these genes have been associated with AD; mutations in presenilin 1 appear to be the most common. However, only 2-10% of those with AD have early onset AD, and genetic mutations have only been identified in 30-50% of those individuals. Overall, identifiable genetic mutations are rare causes of AD.

Chen and colleagues (2012) conducted a meta-analysis to evaluate the association of PSEN2 polymorphisms, rs8383 and 5'indel, with the risk of sporadic AD. Overall, the meta-analysis included six case-control studies for each polymorphism with 2186 confirmed AD cases and 2507 healthy controls in total. The analysis suggested a significant association between SNP rs8383 polymorphism and AD risk with no evidence of between-study heterogeneity or publication bias. In contrast, the authors did not find any evidence supporting the association between the 5'indel polymorphism and the risk of AD. The stratified analyses of apolipoprotein ϵ 4 status or ethnicity also failed to reveal a statistically significant association between the 5'indel polymorphism of PSEN2 and AD risk. The authors concluded that PSEN2 rs8383 polymorphism is associated with an increased risk of sporadic AD. The authors also acknowledged that larger scale studies are needed to confirm these findings and to define potential gene-gene interactions.

Federal and State law, as well as contract language including definitions and specific coverage provisions/exclusions, and Medical Policy take precedence over Clinical UM Guidelines and must be considered first in determining eligibility for coverage. The member's contract benefits in effect on the date that services are rendered must be used. Clinical UM Guidelines, which address medical efficacy, should be considered before utilizing medical opinion in adjudication. Medical technology is constantly evolving, and we reserve the right to review and update Clinical UM Guidelines periodically. Clinical UM guidelines are used when the plan performs utilization review for the subject. Due to variances in utilization patterns, each plan may choose whether or not to adopt a particular Clinical UM Guideline. To determine if review is required for this Clinical UM Guideline, please contact the customer service number on the back of the member's card.

No part of this publication may be reproduced, stored in a retrieval system or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from the health plan.

© CPT Only – American Medical Association

Medicaid managed care administered by Amerigroup Corporation, an independent company

Genetic Testing for Inherited Diseases

Based on the 2011 guidelines from the National Institute on Aging (NIA) and the Alzheimer's Association (AA), the diagnosis of AD is a clinical diagnosis, focusing on the exclusion of other causes of senile dementia. However, ancillary imaging studies, such as computed tomography [CT], magnetic resonance imaging [MRI], single-photon emission CT [SPECT], or positron emission tomography [PET]) and laboratory tests may be used. These tests help rule out other possible causes for dementia (for example, cerebrovascular disease, cobalamin [vitamin B12] deficiency, syphilis, and thyroid disease). According to the NIA-AA, the core clinical criteria for AD dementia will continue to be the foundation of the diagnosis in clinical practice, however, "Further studies are needed to prioritize biomarkers and to determine their value and validity in practice and research settings" (McKhann, 2011).

In 2018, the NIA-AA published an updated biological definition of AD that focuses on the underlying pathological activities of the disease, which can be identified either in living individuals (via biomarkers) or during autopsy. The NIA-AA framework proposes using three groups of biomarkers (β amyloid deposition, pathologic tau, and neurodegeneration) that can be measured by obtaining spinal fluid and/or special radiological imaging tests. The new definition is intended for research purposes only (to identify and stage research participants) and is meant to provide a flexible framework amenable to new (yet to be discovered) biomarker tests. The definition is not intended to be used in routine clinical care, and further investigation is required to establish the role and utility of the biomarker definition (Jack, 2018). There is inadequate data to suggest that the addition of either genetic testing or biochemical markers improves the clinical diagnosis of AD. The majority of available studies focus on those with probable AD, for whom the clinical diagnosis has a sensitivity of 85%. There is inadequate data regarding the use of these tests in individuals with possible AD where the diagnosis is less certain. Additionally, there is no data to suggest that use of the above tests would change clinical management in terms of either altering the diagnostic work-up or therapy. There are currently no published data suggesting that either biochemical or genetic testing of individuals with possible or probable AD affects the conventional diagnostic work-up, treatment or clinical outcomes.

CHARGE Syndrome

CHARGE syndrome is a rare and complex genetic condition due to the wide range of tissues/systems affected by mutations in the chromodomain helicase DNA binding protein (CHD7) gene (Hsu, 2014). It occurs in about one in every 15-17,000 births (van Ravenswaaij-Arts, 2015). CHD7 is the only gene currently known to be associated with CHARGE syndrome. In rare cases, an affected person inherits the mutation from an affected parent.

The term CHARGE comes from the first letter of some of the more common features seen in children with CHARGE syndrome which are:

- (C) = coloboma (usually retinochoroidal) and cranial nerve defects (80-90%);
- (H) = heart defects in 75-85%, especially tetralogy of Fallot;
- (A) = atresia of the choanae (blocked nasal breathing passages) (50-60%);
- (R) = retardation of growth (70-80%) and development;
- (G) = genital underdevelopment due to hypogonadotropic hypogonadism;
- (E) = ear abnormalities and sensorineural hearing loss (>90%).

Federal and State law, as well as contract language including definitions and specific coverage provisions/exclusions, and Medical Policy take precedence over Clinical UM Guidelines and must be considered first in determining eligibility for coverage. The member's contract benefits in effect on the date that services are rendered must be used. Clinical UM Guidelines, which address medical efficacy, should be considered before utilizing medical opinion in adjudication. Medical technology is constantly evolving, and we reserve the right to review and update Clinical UM Guidelines periodically. Clinical UM guidelines are used when the plan performs utilization review for the subject. Due to variances in utilization patterns, each plan may choose whether or not to adopt a particular Clinical UM Guideline. To determine if review is required for this Clinical UM Guideline, please contact the customer service number on the back of the member's card.

No part of this publication may be reproduced, stored in a retrieval system or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from the health plan.

© CPT Only – American Medical Association

Medicaid managed care administered by Amerigroup Corporation, an independent company

Genetic Testing for Inherited Diseases

Four features are almost always present in those with the CHD7 mutation found in CHARGE syndrome: external ear anomalies, cranial nerve dysfunction, semicircular canal hypoplasia, and delayed attainment of motor milestones (Bergman, 2011). The established clinical criteria can provide a diagnosis of definite CHARGE syndrome in many cases, but, due to associated variable phenotypes, some individuals may not have all the clinical features present and they are categorized as having possible or probable CHARGE syndrome.

The typical combinations of clinical features seen in CHARGE syndrome are caused by autosomal dominant mutations in the CHD7 gene, which means one copy of the altered gene in each cell is sufficient to cause the disorder. Sequence analysis of the CHD7 coding region detects mutations in many individuals with CHARGE syndrome. Penetrance in those with CHD7 mutations is 100%, meaning that all persons who are heterozygous for a CHD7 mutation have some features of CHARGE syndrome. More than 500 specific CHD7 mutations associated with CHARGE syndrome have been identified (Kim, 2014).

CHARGE syndrome is most often related to a new mutation in the CHD7 gene and occurs in persons with no family history of the disorder. In rare cases, an affected individual inherits the mutation from an affected parent. Some investigators (Hughes, 2014) have proposed that family history (any first-degree relative with at least one major feature of CHARGE) should be incorporated into the clinical diagnosis of CHARGE syndrome as a major diagnostic criterion. Most individuals diagnosed with CHARGE syndrome do not have an affected parent. In rare instances, one parent may have mild features, including more than one major characteristic, in addition to minor criteria, such as a cardiovascular malformation (Bergman, 2011). In some cases, a family history may appear negative for the syndrome because of failure to recognize mild features in family members.

The risk to siblings of the proband depends on the genetic status of the proband's parents. If a parent of the proband is affected or has a CHD7 mutation, the risk to the siblings of inheriting the mutation is 50%. If neither parent is affected, the risk to siblings of a proband is approximately 1%-2%, due to germline mosaicism. Because CHD7 mutation typically occurs as the result of a new mutation, the risk to the siblings of a proband is slight. Severely affected individuals with CHARGE syndrome do not reproduce. Each child of a mildly affected individual with CHARGE syndrome has a 50% chance of inheriting the mutation. The severity of CHARGE syndrome in a parent does not predict the severity of CHARGE syndrome in the offspring. Variable expression has been observed in familial cases.

Many cases of CHARGE syndrome can be diagnosed clinically using established criteria. However, mildly affected persons may only have one or a few of the features of CHARGE syndrome, which makes the determination of the diagnosis of CHARGE uncertain. The clinical diagnosis may also be difficult to determine if clinical features are overlapping with other syndromes. Confirming the diagnosis of CHARGE syndrome with genetic testing may lead to changes in clinical management for those with uncertain clinical features. Preimplantation, preconception or in-utero genetic testing may be helpful to assist reproductive decision making if there is a family history of a first-degree relative with CHARGE syndrome.

Federal and State law, as well as contract language including definitions and specific coverage provisions/exclusions, and Medical Policy take precedence over Clinical UM Guidelines and must be considered first in determining eligibility for coverage. The member's contract benefits in effect on the date that services are rendered must be used. Clinical UM Guidelines, which address medical efficacy, should be considered before utilizing medical opinion in adjudication. Medical technology is constantly evolving, and we reserve the right to review and update Clinical UM Guidelines periodically. Clinical UM guidelines are used when the plan performs utilization review for the subject. Due to variances in utilization patterns, each plan may choose whether or not to adopt a particular Clinical UM Guideline. To determine if review is required for this Clinical UM Guideline, please contact the customer service number on the back of the member's card.

No part of this publication may be reproduced, stored in a retrieval system or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from the health plan.

© CPT Only – American Medical Association

Medicaid managed care administered by Amerigroup Corporation, an independent company

Genetic Testing for Inherited Diseases

Genetic testing for CHARGE syndrome is a laboratory-developed test and does not require FDA approval. Clinical laboratories may develop and validate tests in-house and market them as a laboratory service. Such tests must meet the general regulatory standards of the Clinical Laboratory Improvement Act (CLIA). CHD7 is the only gene currently known to be associated with this syndrome. The clinical utility of making a definite diagnosis of CHARGE syndrome through genetic testing is high, in that confirming a diagnosis with genetic testing may lead to changes in clinical assessment, treatment recommendations and reproductive decisions. The criteria within this document for genetic testing for CHARGE syndrome are consistent with generally accepted standards of medical practice and are clinically appropriate for the indications described in the Clinical Indications section of this document.

Definitions

Acute pancreatitis: This form of pancreatitis occurs suddenly, soon after the pancreas becomes damaged or irritated.

Alzheimer’s disease (AD): A progressive neurological condition, including dementia, which primarily affects memory.

Amyloid-beta 42 (Aβ42): A protein that accumulates abnormally in the brains of individuals with AD and is the major component of amyloid plaques in the brain.

Amyotrophic lateral sclerosis (ALS, also known as Lou Gehrig's disease): A progressive neurodegenerative disorder that affects nerve cells in the spinal cord and brain, which eventually results in paralysis and death.

Analytical validity: The accuracy with which a test identifies the presence or absence of a particular gene or genetic change (mutation).

Ashkenazi Jewish: Persons related to Jewish settlers of the Rhine Valley in Germany and France in the middle ages.

Ataxia telangiectasia: A rare, progressive, neurodegenerative childhood disease that affects the brain and other body systems.

Carrier: An individual who is asymptomatic (or has only mild symptoms) of a disorder but has the potential to pass on the gene for that disorder to his or her offspring.

CHARGE syndrome: A rare genetic condition associated with multiple congenital anomalies. CHARGE is an abbreviation for several of the common features of this disorder, which are: coloboma (a gap in one of the structures of the eye), heart defects, atresia choanae (also known as choanal atresia and refers to complete blockage of one or both nasal passages), growth retardation, genital abnormalities, and ear abnormalities. The diagnosis is typically made based on clinical findings. The only gene currently known to be associated with this syndrome,

Federal and State law, as well as contract language including definitions and specific coverage provisions/exclusions, and Medical Policy take precedence over Clinical UM Guidelines and must be considered first in determining eligibility for coverage. The member's contract benefits in effect on the date that services are rendered must be used. Clinical UM Guidelines, which address medical efficacy, should be considered before utilizing medical opinion in adjudication. Medical technology is constantly evolving, and we reserve the right to review and update Clinical UM Guidelines periodically. Clinical UM guidelines are used when the plan performs utilization review for the subject. Due to variances in utilization patterns, each plan may choose whether or not to adopt a particular Clinical UM Guideline. To determine if review is required for this Clinical UM Guideline, please contact the customer service number on the back of the member's card.

No part of this publication may be reproduced, stored in a retrieval system or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from the health plan.

© CPT Only – American Medical Association

Medicaid managed care administered by Amerigroup Corporation, an independent company

Genetic Testing for Inherited Diseases

chromodomain helicase DNA binding protein (CHD7), is present in most individuals with the condition. Clinical findings may be variable; however, the phenotype cannot be predicted from the genotype.

Chronic pancreatitis: This form of pancreatitis occurs when an individual has a permanently damaged or scarred pancreas. It is a slowly progressive form of pancreatitis which may take years to develop.

Clinical utility: Measures the ability of the test to improve clinical outcomes.

Clinical validity: The extent to which a test identifies or predicts an individual's clinical status.

Cystic fibrosis (CF): An inherited disease that affects the mucus and sweat glands of the body; thick mucus is formed in the breathing passages of the lungs that predisposes the person to chronic lung infections.

Deep vein thrombosis (DVT): A blood clot in one of the deep veins of the body.

Deletion/Duplication Analysis: Laboratory testing that identifies the absence of a segment of DNA (deletion) and/or the presence of an extra segment of DNA (duplication).

DNA: (deoxyribonucleic acid): A type of molecule that contains the code for genetic information.

Ethnicity: Coming from a large group that shares racial, national, language or cultural characteristics.

Exome: All the exons in a genome.

Exon: The portion of the genome that predominantly encodes protein.

Expanded panels: This term is defined by the ACMG as panels that use NGS (next-generation sequencing) to screen for variants in many genes, as opposed to gene-by-gene screening (for example, ethnic-specific screening or panethnic testing for cystic fibrosis).

Please note: For panel testing of 5 or more genes or gene variants, refer to GENE.00052 Whole Genome Sequencing, Whole Exome Sequencing, Gene Panels, and Molecular Profiling.

First-degree relative: Any relative who is a parent, sibling, or offspring of an individual.

Frontotemporal dementia: A broad term for a group of brain disorders that primarily affect the frontal and temporal lobes of the brain.

Genetic molecular testing: A type of test that studies single genes or short lengths of DNA to determine the presence or absence of a specific gene variant or set of genetic variants to help diagnose a disease, screen for specific health conditions, and for other purposes.

Federal and State law, as well as contract language including definitions and specific coverage provisions/exclusions, and Medical Policy take precedence over Clinical UM Guidelines and must be considered first in determining eligibility for coverage. The member's contract benefits in effect on the date that services are rendered must be used. Clinical UM Guidelines, which address medical efficacy, should be considered before utilizing medical opinion in adjudication. Medical technology is constantly evolving, and we reserve the right to review and update Clinical UM Guidelines periodically. Clinical UM guidelines are used when the plan performs utilization review for the subject. Due to variances in utilization patterns, each plan may choose whether or not to adopt a particular Clinical UM Guideline. To determine if review is required for this Clinical UM Guideline, please contact the customer service number on the back of the member's card.

No part of this publication may be reproduced, stored in a retrieval system or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from the health plan.

© CPT Only – American Medical Association

Medicaid managed care administered by Amerigroup Corporation, an independent company

Genetic Testing for Inherited Diseases

Genetic testing is done for predictive, diagnostic, prognostic or therapeutic indications as follows:

- Predictive genetic testing involves use of a genetic test in an asymptomatic person to predict future risk of developing a certain disease. One of the limitations of predictive genetic testing is the challenge in interpreting positive test results, because some individuals who test positive for a disease-associated variant may never develop the disease. Predictive testing can identify variants that increase a person's risk of developing disorders with a genetic basis, such as certain types of cancer. Targeted pre-symptomatic genetic testing can determine whether a person will develop a genetic disorder, such as hereditary hemochromatosis (an iron overload disorder), before any signs or symptoms appear. In order to be useful in the clinical setting, the results of predictive genetic testing should have a high positive predictive value, and evidence should demonstrate that such results improve either disease prevention or management, as compared with routine medical care without results of genetic testing.
- Diagnostic genetic testing is used to identify or rule out a specific genetic or chromosomal condition. In many cases, genetic testing is used to confirm a diagnosis when a particular condition is suspected based on physical signs and symptoms. Diagnostic testing can be performed before birth or at any time during a person's life, but is not available for all genes or all genetic conditions. The results of a diagnostic genetic test can influence a person's choices about health care and the management of the disorder.
- Prognostic genetic testing is used to assess the risk of progression and course in an asymptomatic individual not yet diagnosed with a disease, and as a means to forecast whether an individual diagnosed with a disease will have a serious or benign course (prognostic). For example, prognostic genetic testing, when performed in persons with confirmed chronic lymphocytic leukemia (CLL), helps to inform optimal disease management and also predicts survival and disease progression.
- Therapeutic genetic testing (including, but not limited to, pharmacotherapeutics) involves the identification of a genetic variant that affects the way an individual responds to a therapeutic intervention. This application is often seen in the area of pharmacogenetic testing where genetic test results are used to inform treatment decisions with regards to how an individual is expected to respond to a particular drug therapy.

Genome: An organism's entire set of DNA.

Genotype: The genetic structure (constitution) of an organism or cell.

Homocysteine: A naturally occurring amino acid that, if present at a high level in the blood, can produce an increased risk of blood clots. This condition is known as hyperhomocysteinemia. It is believed that high blood levels of homocysteine can damage the lining of blood vessels. This damage is what can lead to blood clots.

Hyperhomocysteinemia: A condition where an individual may get blood clots in either the veins (for example, DVT and pulmonary embolism) or arteries (for example, stroke and heart attack). In addition to making people prone to blood clots, hyperhomocysteinemia may also increase the risk of specific birth defects and other disorders.

Federal and State law, as well as contract language including definitions and specific coverage provisions/exclusions, and Medical Policy take precedence over Clinical UM Guidelines and must be considered first in determining eligibility for coverage. The member's contract benefits in effect on the date that services are rendered must be used. Clinical UM Guidelines, which address medical efficacy, should be considered before utilizing medical opinion in adjudication. Medical technology is constantly evolving, and we reserve the right to review and update Clinical UM Guidelines periodically. Clinical UM guidelines are used when the plan performs utilization review for the subject. Due to variances in utilization patterns, each plan may choose whether or not to adopt a particular Clinical UM Guideline. To determine if review is required for this Clinical UM Guideline, please contact the customer service number on the back of the member's card.

No part of this publication may be reproduced, stored in a retrieval system or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from the health plan.

© CPT Only – American Medical Association

Medicaid managed care administered by Amerigroup Corporation, an independent company

Genetic Testing for Inherited Diseases

Common causes of hyperhomocysteinemia include kidney disease, lack of B vitamins (such as folate, vitamin B12, and vitamin B6) in the diet, hypothyroidism, alcoholism, and certain medications.

Methylenetetrahydrofolate reductase (MTHFR): An enzyme (protein) that breaks down homocysteine. Deficiency of the MTHFR enzyme may cause hyperhomocysteinemia.

Mutation (or variant): A permanent change in the DNA code.

Mutation Scanning: A process by which a segment of DNA is screened via one of a variety of methods to identify variant gene region(s). Variant regions are further analyzed (by sequence analysis or mutation analysis) to identify the sequence alteration.

Next-generation sequencing: Any of the technologies that allow rapid sequencing of large numbers of segments of DNA, up to and including entire genomes.

Pancreatitis: An inflammation of the pancreas.

Panel testing: Involves the analysis of multiple genes for multiple variants simultaneously.

Panethnic screening: A screening approach that is done for single-gene disorders based on ethnicity, race, or both.

Penetrance: The likelihood that a person carrying a particular variation of a gene will also have an associated trait. This term refers to the proportion of persons with a mutation causing a particular disorder who display clinical symptoms of that disorder.

Phenotype: The observable physical or biochemical characteristics of an organism, as determined by both genetic makeup and environmental influences.

Polymorphism: A DNA sequence common in a population.

Positive predictive value: Percentage of individuals with positive test results who are accurately diagnosed.

Proband: A term used in medical genetics to refer to the first affected family member with a known pathogenic genetic mutation.

Prothrombin: A blood clotting protein; also referred to as coagulation factor II, factor II or F2.

Pulmonary embolism (PE): A clot that travels via the bloodstream and lodges in the lungs.

Federal and State law, as well as contract language including definitions and specific coverage provisions/exclusions, and Medical Policy take precedence over Clinical UM Guidelines and must be considered first in determining eligibility for coverage. The member's contract benefits in effect on the date that services are rendered must be used. Clinical UM Guidelines, which address medical efficacy, should be considered before utilizing medical opinion in adjudication. Medical technology is constantly evolving, and we reserve the right to review and update Clinical UM Guidelines periodically. Clinical UM guidelines are used when the plan performs utilization review for the subject. Due to variances in utilization patterns, each plan may choose whether or not to adopt a particular Clinical UM Guideline. To determine if review is required for this Clinical UM Guideline, please contact the customer service number on the back of the member's card.

No part of this publication may be reproduced, stored in a retrieval system or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from the health plan.

© CPT Only – American Medical Association

Medicaid managed care administered by Amerigroup Corporation, an independent company

Rett syndrome: A developmental disorder that affects the parts of the brain that control social interaction, communications, and motor function.

Sequence Analysis: Process by which the nucleotide sequence for a particular gene is determined for a segment of DNA.

Single-nucleotide polymorphisms (SNPs): DNA sequence variations that occur when a single nucleotide in the genome sequence is altered.

Subcortical Lacunar Lesions (SLLs): Linearly arranged groups of rounded, circumscribed lesions at the junction of the grey and white matter with a signal intensity that is identical to that of cerebrospinal fluid. SLLs are found in approximately two thirds of affected individuals and may be a specific marker for CADASIL

Thrombophilia: A blood coagulation abnormality that increases the risk of thrombosis; also known as hypercoagulability.

Thrombosis: The presence of blood clots in the blood vessels.

Venous thromboembolism (VTE): The formation of a blood clot in the veins.

References

Peer Reviewed Publications:

1. Aragon-Martin JA, Ritch R, Liebmann J, et al. Evaluation of LOXL1 gene polymorphisms in exfoliation syndrome and exfoliation glaucoma. *Mol Vis*. 2008; 17(14):533-541.
2. Awano H, Lee T, Yagi M, et al. Childhood-onset hereditary pancreatitis with mutations in the CT gene and SPINK1 gene. *Pediatr Int*. 2013; 55(5):646-649.
3. Axilbund JE, Wiley EA. Genetic testing by cancer site: pancreas. *Cancer J*. 2012; 18(4):350-354.
4. Bergman JE, Janssen N, Hoefsloot LH, et al. CHD7 mutations and CHARGE syndrome: the clinical implications of an expanding phenotype. *J Med Genet*. 2011; 48(5):334-342.
5. Cauchi S, El Achhab Y, Choquet H, et al. TCF7L2 is reproducibly associated with type 2 diabetes in various ethnic groups: a global meta-analysis. *J Mol Med*. 2007; 85(7):777-782.
6. Cauchi S, Meyre D, Choquet H, et al.; DESIR Study Group. TCF7L2 variation predicts hyperglycemia incidence in a French general population: the data from an epidemiological study on the Insulin Resistance Syndrome (DESIR) study. *Diabetes*. 2006; 55(11):3189-3192.
7. Chabriat H, Joutel A, Dichgans M, et al. Cadasil. *Lancet Neurol*. 2009; 8(7):643-653.
8. Chakrabarti S, Rao KN, Kaur I, et al. The LOXL1 gene variations are not associated with primary open-angle and primary angle-closure glaucomas. *Invest Ophthalmol Vis Sci*. 2008; 49(6):2343-2347.

Federal and State law, as well as contract language including definitions and specific coverage provisions/exclusions, and Medical Policy take precedence over Clinical UM Guidelines and must be considered first in determining eligibility for coverage. The member's contract benefits in effect on the date that services are rendered must be used. Clinical UM Guidelines, which address medical efficacy, should be considered before utilizing medical opinion in adjudication. Medical technology is constantly evolving, and we reserve the right to review and update Clinical UM Guidelines periodically. Clinical UM guidelines are used when the plan performs utilization review for the subject. Due to variances in utilization patterns, each plan may choose whether or not to adopt a particular Clinical UM Guideline. To determine if review is required for this Clinical UM Guideline, please contact the customer service number on the back of the member's card.

No part of this publication may be reproduced, stored in a retrieval system or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from the health plan.

© CPT Only – American Medical Association

Medicaid managed care administered by Amerigroup Corporation, an independent company

Genetic Testing for Inherited Diseases

9. Challa P, Schmidt S, Liu Y, et al. Analysis of LOXL1 polymorphisms in a United States population with pseudoexfoliation glaucoma. *Mol Vis*. 2008; 14:146-149.
 10. Checa MA, Alonso-Coello P, Solà I, et al. IVF/ICSI with or without preimplantation genetic screening for aneuploidy in couples without genetic disorders: A systematic review and meta-analysis. *J Assist Reprod Genet*. 2009 ;26(5):273-283.
 11. Chen C, Zhou Z, Li M, et al. Presenilin-2 polymorphisms and risk of sporadic AD: evidence from a meta-analysis. *Gene*. 2012; 503(2):194-199.
 12. Clément K, van den Akker E, Argente J, et al. Efficacy and safety of setmelanotide, an MC4R agonist, in individuals with severe obesity due to LEPR or POMC deficiency: single-arm, open-label, multicenter, phase 3 trials. *Lancet Diabetes Endocrinol*. 2020; 8(12):960-970.
 13. Cochat P, Hulton SA, Acquaviva C, et al. Primary hyperoxaluria Type 1: indications for screening and guidance for diagnosis and treatment. *Nephrol Dial Transplant*. 2012; 27(5):1729-1736.
 14. Corleto VD, Gambardella S, Gullotta F, et al. New PRSS1 and common CFTR mutations in a child with acute recurrent pancreatitis, could be considered a "Hereditary" form of pancreatitis? *BMC Gastroenterol*. 2010; 10:119.
 15. Dai LN, Chen YW, Yan WH, et al. Hereditary pancreatitis of 3 Chinese children: case report and literature review. *Medicine (Baltimore)*. 2016; 95(36):e4604.
 16. den Heijer M, Lewington S, Clarke R. Homocysteine, MTHFR and risk of venous thrombosis: a meta-analysis of published epidemiological studies. *J Thromb Haemost*. 2005; 3(2):292-299.
 17. den Heijer M, Willems HP, Blom HJ, et al. Homocysteine lowering by B vitamins and the secondary prevention of deep vein thrombosis and pulmonary embolism: a randomized, placebo-controlled, double-blind trial. *Blood*. 2007; 109(1):139-144.
 18. De Silva NM, Steele A, Shields B, et al. The transcription factor 7-like 2 (TCF7L2) gene is associated with Type 2 diabetes in UK community-based cases, but the risk allele frequency is reduced compared with UK cases selected for genetic studies. *Diabet Med*. 2007; 24(10):1067-1072.
 19. Dichgans M, Markus HS, Salloway S, et al. Donepezil in patients with subcortical vascular cognitive impairment: a randomized double-blind trial in CADASIL. *Lancet Neurol*. 2008; 7:310-318.
 20. Ding XP, Feng L, Ma L. MTHFR C677T polymorphism and ovarian cancer risk: a meta-analysis. *Asian Pac J Cancer Prev*. 2012; 13(8):3937-3942.
 21. Donahue CP, Kosik KS. Distribution pattern of Notch3 mutations suggests a gain-of-function mechanism for CADASIL. *Genomics*. 2004; 83(1):59-65.
 22. Elashoff MR, Nuttall R, Beineke P, et al. Identification of factors contributing to variability in a blood-based gene expression test. *PLoS One*. 2012; 7(7):e40068.
 23. Elbein SC. Evaluation of polymorphisms known to contribute to risk for diabetes in African and African-American populations. *Curr Opin Clin Nutr Metab Care*. 2007; 10(4):415-419.
 24. Evans JP, Skrzynia C, Burke W. The complexities of predictive genetic testing. *BMJ*. 2001; 322(7293):1052-1056.
 25. Fan BJ, Pasquale L, Grosskreutz CL, et al. DNA sequence variants in the LOXL1 gene are associated with pseudoexfoliation glaucoma in a U.S. clinic-based population with broad ethnic diversity. *BMC Med Genet*. 2008; 6(9):5.
-

Federal and State law, as well as contract language including definitions and specific coverage provisions/exclusions, and Medical Policy take precedence over Clinical UM Guidelines and must be considered first in determining eligibility for coverage. The member's contract benefits in effect on the date that services are rendered must be used. Clinical UM Guidelines, which address medical efficacy, should be considered before utilizing medical opinion in adjudication. Medical technology is constantly evolving, and we reserve the right to review and update Clinical UM Guidelines periodically. Clinical UM guidelines are used when the plan performs utilization review for the subject. Due to variances in utilization patterns, each plan may choose whether or not to adopt a particular Clinical UM Guideline. To determine if review is required for this Clinical UM Guideline, please contact the customer service number on the back of the member's card.

No part of this publication may be reproduced, stored in a retrieval system or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from the health plan.

© CPT Only – American Medical Association

Medicaid managed care administered by Amerigroup Corporation, an independent company

Genetic Testing for Inherited Diseases

26. Fisher MC, Cronstein BN. Metaanalysis of methylenetetrahydrofolate reductase (MTHFR) polymorphisms affecting methotrexate toxicity. *J Rheumatol*. 2009; 36(3):539-545.
 27. Florez JC, Jablonski KA, Bayley N, et al. TCF7L2 polymorphisms and progression to diabetes in the Diabetes Prevention Program. *N Engl J Med*. 2006; 355(3):241-250.
 28. Florez JC. The new type 2 diabetes gene TCF7L2. *Curr Opin Clin Nutr Metab Care*. 2007; 10(4):391-396.
 29. Frayling TM. A new era in finding Type 2 diabetes genes-the unusual suspects. *Diabet Med*. 2007; 24(7):696-701.
 30. Grarup N, Andersen G. Gene-environment interactions in the pathogenesis of type 2 diabetes and metabolism. *Curr Opin Clin Nutr Metab Care*. 2007; 10(4):420-426.
 31. Grocock CJ, Rebours V, Delhaye MN, et al. The variable phenotype of the p.A16V mutation of cationic trypsinogen (PRSS1) in pancreatitis families. *Gut*. 2010; 59(3):357-363.
 32. Gudbjartsson DF, Arnar DO, Helgadóttir A, et al. Variants conferring risk of atrial fibrillation on chromosome 4q25. *Nature*. 2007; 448(7151):353-357.
 33. Hsu P, Ma A, Wilson M, et al. CHARGE syndrome: A review. *J Paediatr Child Health*. 2014; 50(7):504-511.
 34. Hu C, Wen L, Deng L, et al. The differential role of human cationic trypsinogen (<i>PRSS1</i>) p.R122H mutation in hereditary and nonhereditary chronic pancreatitis: a systematic review and meta-analysis. *Gastroenterol Res Pract*. 2017; 2017:9505460.
 35. Hughes SS, Welsh HI, Safina NP, et al. Family history and clefting as major criteria for CHARGE syndrome. *Am J Med Genet A*. 2014; 164A(1):48-53.
 36. Joergensen MT, Brusgaard K, Crüger DG, et al. Genetic, epidemiological, and clinical aspects of hereditary pancreatitis: a population-based cohort study in Denmark. *Am J Gastroenterol*. 2010; 105(8):1876-1883.
 37. Keiles S, Kammesheidt A. Identification of CFTR, PRSS1, and SPINK1 mutations in 381 patients with pancreatitis. *Pancreas*. 2006; 33(3):221-227.
 38. Khandanpour N, Loke YK, Meyer FJ, et al. Homocysteine and peripheral arterial disease: systematic review and meta-analysis. *Eur J Vasc Endovasc Surg*. 2009a; 38(3):316-322.
 39. Khandanpour N, Willis G, Meyer FJ, et al. Peripheral arterial disease and methylenetetrahydrofolate reductase (MTHFR) C677T mutations: a case-control study and meta-analysis. *J Vasc Surg*. 2009b; 49(3):711-718.
 40. Kim Y, Lee HS, Yu JS, et al. Identification of a novel mutation in the CHD7 gene in a patient with CHARGE syndrome. *Korean J Pediatr*. 2014; 57(1):46-49.
 41. LaRusch J, Barmada MM, Solomon S, Whitcomb DC. Whole exome sequencing identifies multiple, complex etiologies in an idiopathic hereditary pancreatitis kindred. *JOP*. 2012; 13(3):258-262.
 42. Lazarin GA, Haque IS. Expanded carrier screening: A review of early implementation and literature. *Semin Perinatol*. 2016; 40(1):29-34.
 43. Lee H, Deignan JL, Dorrani N, et al. Clinical exome sequencing for genetic identification of rare Mendelian disorders. *JAMA*. 2014; 312(18):1880-1887.
 44. Lee RK. The molecular pathophysiology of pseudoexfoliation glaucoma. *Curr Opin Ophthalmol*. 2008; 19(2):95-101.
 45. Lee E, Illingworth P, Wilton L, Chambers GM. The clinical effectiveness of preimplantation genetic diagnosis for aneuploidy in all 24 chromosomes (PGD-A): Systematic review. *Hum Reprod*. 2015; 30(2):473-483.
-

Federal and State law, as well as contract language including definitions and specific coverage provisions/exclusions, and Medical Policy take precedence over Clinical UM Guidelines and must be considered first in determining eligibility for coverage. The member's contract benefits in effect on the date that services are rendered must be used. Clinical UM Guidelines, which address medical efficacy, should be considered before utilizing medical opinion in adjudication. Medical technology is constantly evolving, and we reserve the right to review and update Clinical UM Guidelines periodically. Clinical UM guidelines are used when the plan performs utilization review for the subject. Due to variances in utilization patterns, each plan may choose whether or not to adopt a particular Clinical UM Guideline. To determine if review is required for this Clinical UM Guideline, please contact the customer service number on the back of the member's card.

No part of this publication may be reproduced, stored in a retrieval system or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from the health plan.

© CPT Only – American Medical Association

Medicaid managed care administered by Amerigroup Corporation, an independent company

Genetic Testing for Inherited Diseases

46. Lesnik Oberstein SA, van Duinen SG, van den Boom R, et al. Evaluation of diagnostic NOTCH3 immunostaining in CADASIL. *Acta Neuropathol.* 2003; 106(2):107-111.
 47. Lettre G, Rioux JD. Autoimmune diseases: insights from genome-wide association studies. *Hum Mol Genet.* 2008; 17(R2):R116-121.
 48. Li D, Zhou M, Peng X, Sun H. Homocysteine, methylenetetrahydrofolate reductase C677T polymorphism, and risk of retinal vein occlusion: an updated meta-analysis. *BMC Ophthalmol.* 2014a; 14:147.
 49. Li P, Qin C. Methylenetetrahydrofolate reductase (MTHFR) gene polymorphisms and susceptibility to ischemic stroke: a meta-analysis. *Gene.* 2014b; 535(2):359-364.
 50. Liu Y, Schmidt S, Qin X, et al. Lack of association between LOXL1 variants and primary open-angle glaucoma in three different populations. *Invest Ophthalmol Vis Sci.* 2008. 49(8):3465-3468.
 51. Lyssenko V, Jonsson A, Almgren P, et al. Clinical risk factors, DNA variants, and the development of type 2 diabetes. *N Engl J Med.* 2008; 359(21):2220-2232.
 52. Lyssenko V, Lupi R, Marchetti P, et al. Mechanisms by which common variants in the TCF7L2 gene increase risk of type 2 diabetes. *J Clin Invest.* 2007; 117(8):2155-2163.
 53. Mahajerin A, Obasaju P, Eckert G, et al. Thrombophilia testing in children: a 7 year experience. *Pediatr Blood Cancer.* 2014; 61(3):523-527.
 54. Mailman MD, Heinz JW, Papp AC, et al. Molecular analysis of spinal muscular atrophy and modification of the phenotype by SMN2. *Genet Med.* 2002; 4(1):20-26.
 55. Mastenbroek S, Twisk M, van der Veen F, Repping S. Preimplantation genetic screening: A systematic review and meta-analysis of RCTs. *Hum Reprod Update.* 2011; 17(4):454-466.
 56. Matthews KA, Xu W, Gaglioti AH, et al. Racial and ethnic estimates of Alzheimer's disease and related dementias in the United States (2015-2060) in adults aged 65 years. *Alzheimers Dement.* 2019; 15(1):17-24.
 57. McPherson R, Pertsemlidis A, Kavaslar N, et al. A common allele on chromosome 9 associated with coronary heart disease. *Science.* 2007; 316(5830):1488-1491.
 58. Meigs JB, Shrader P, Sullivan LM, et al. Genotype score in addition to common risk factors for prediction of type 2 diabetes. *N Engl J Med.* 2008; 359(21):2208-2219.
 59. Milliner DS. The primary hyperoxalurias: an algorithm for diagnosis. *Am J Nephrol.* 2005; 25(2):154-160.
 60. Miyake K, Horikawa Y, Hara K, et al. Association of TCF7L2 polymorphisms with susceptibility to type 2 diabetes in 4,087 Japanese subjects. *J Hum Genet.* 2008; 53(2):174-180.
 61. Mossbock G, Renner W, Faschinger C, et al. Lysyl oxidase-like protein 1 (LOXL1) gene polymorphisms and exfoliation glaucoma in a Central European population. *Mol Vis.* 2008; 9(14):857-861.
 62. Nozaki H, Nishizawa M, Onodera O. Features of cerebral autosomal recessive arteriopathy with subcortical infarcts and leukoencephalopathy. *Stroke.* 2014; 45:3447-3453.
 63. Nozaki H, Sekine Y, Fukutake T, et al. Characteristic features and progression of abnormalities on MRI for CADASIL. *Neurology.* 2015; 85:459-463.
 64. Owen KR, McCarthy MI. Genetics of type 2 diabetes. *Curr Opin Genet Dev.* 2007; 17(3):239-244.
 65. Ozaki M, Lee KY, Vithana EN, et al. Association of LOXL1 gene polymorphisms with pseudoexfoliation in the Japanese. *Invest Ophthalmol Vis Sci.* 2008; 49(9):3976-3980.
 66. Palmer ND, Lehtinen AB, Langefeld CD, et al. Association of TCF7L2 gene polymorphisms with reduced acute insulin response in Hispanic Americans. *J Clin Endocrinol Metab.* 2008; 93(1):304-309.
-

Federal and State law, as well as contract language including definitions and specific coverage provisions/exclusions, and Medical Policy take precedence over Clinical UM Guidelines and must be considered first in determining eligibility for coverage. The member's contract benefits in effect on the date that services are rendered must be used. Clinical UM Guidelines, which address medical efficacy, should be considered before utilizing medical opinion in adjudication. Medical technology is constantly evolving, and we reserve the right to review and update Clinical UM Guidelines periodically. Clinical UM guidelines are used when the plan performs utilization review for the subject. Due to variances in utilization patterns, each plan may choose whether or not to adopt a particular Clinical UM Guideline. To determine if review is required for this Clinical UM Guideline, please contact the customer service number on the back of the member's card.

No part of this publication may be reproduced, stored in a retrieval system or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from the health plan.

© CPT Only – American Medical Association

Medicaid managed care administered by Amerigroup Corporation, an independent company

Genetic Testing for Inherited Diseases

67. Palomaki GE, Melillo S, Bradley LA. Association between 9p21 genomic markers and heart disease: a meta-analysis. *JAMA*. 2010; 303(7):648-656.
 68. Pasutto F, Krumbiegel M, Mardin CY, et al. Association of LOXL1 common sequence variants in German and Italian patients with pseudoexfoliation syndrome and pseudoexfoliation glaucoma. *Invest Ophthalmol Vis Sci*. 2008; 49(4):1459-1463.
 69. Paynter NP, Chasman DI, Buring JE, et al. Cardiovascular disease risk prediction with and without knowledge of genetic variation at chromosome 9p21.3. *Ann Intern Med*. 2009; 150(2):65-72.
 70. Prior TW, Finanger E. Spinal muscular Atrophy. 2000 [Updated 2020]. In: Pagon RA, Adam MP, Ardinger HH, et al., editors. *GeneReviews*® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2017. Last updated December 3, 2020. Available at: <https://www.ncbi.nlm.nih.gov/books/NBK1352/>. Accessed on January 26, 2022.
 71. Prior TW, Snyder PJ, Rink BD, et al. Newborn and carrier screening for spinal muscular atrophy. *Am J Med Genet A*. 2010; 152A (7):1608-1616.
 72. Rabinovici GD, Gatsonis C, Apgar C, et al. Association of amyloid positron emission tomography with subsequent change in clinical management among Medicare beneficiaries with mild cognitive impairment or dementia. *JAMA*. 2019; 321(13):1286-1294.
 73. Ramanathan G, Harichandana B, Kannan S, et al. Association between end-stage diabetic nephropathy and MTHFR (C677T and A1298C) gene polymorphisms. *Nephrology (Carlton)*. 2019; 24(2):155-159.
 74. Ramprasad VL, George R, Soumitra N, et al. Association of non-synonymous single nucleotide polymorphisms in the LOXL1 gene with pseudoexfoliation syndrome in India. *Mol Vis*. 2008; 9(14):318-322.
 75. Rätty S, Piironen A, Babu M, et al. Screening for human cationic trypsinogen (PRSS1) and trypsinogen inhibitor gene (SPINK1) mutations in a Finnish family with hereditary pancreatitis. *Scand J Gastroenterol*. 2007; 42(8):1000-1005.
 76. Rebours V, Lévy P, Ruzsniwski P. An overview of hereditary pancreatitis. *Dig Liver Dis*. 2012; 44(1):8-15.
 77. Ropers HH. New perspectives for the elucidation of genetic disorders. *Am J Hum Genet*. 2007; 81(2):199-207.
 78. Rose NC, Wick M. Current recommendations: Screening for Mendelian disorders. *Semin Perinatol*. 2016; 40(1):23-8.
 79. Russell S, Bennett J, Wellman JA, et al. Efficacy and safety of voretigene neparvovec (AAV2-hRPE65v2) in patients with RPE65-mediated inherited retinal dystrophy: a randomized, controlled, open-label, phase 3 trial. *Lancet*. 2017; 390(10097):849-860.
 80. Saitsu H, Osaka H, Sasaki M, et al. Mutations in POLR3A and POLR3B encoding RNA Polymerase III subunits cause an autosomal-recessive hypomyelinating leukoencephalopathy. *Am J Hum Genet*. 2011; 89(5):644-651.
 81. Sale MM, Smith SG, Mychaleckyj JC, et al. Variants of the transcription factor 7-like 2 (TCF7L2) gene are associated with type 2 diabetes in an African-American population enriched for nephropathy. *Diabetes*. 2007; 56(10):2638-2642.
 82. Samani NJ, Erdmann J, Hall AS, et al. Genomewide association analysis of coronary artery disease. *N Engl J Med*. 2007; 357(5):443-453.
-

Federal and State law, as well as contract language including definitions and specific coverage provisions/exclusions, and Medical Policy take precedence over Clinical UM Guidelines and must be considered first in determining eligibility for coverage. The member's contract benefits in effect on the date that services are rendered must be used. Clinical UM Guidelines, which address medical efficacy, should be considered before utilizing medical opinion in adjudication. Medical technology is constantly evolving, and we reserve the right to review and update Clinical UM Guidelines periodically. Clinical UM guidelines are used when the plan performs utilization review for the subject. Due to variances in utilization patterns, each plan may choose whether or not to adopt a particular Clinical UM Guideline. To determine if review is required for this Clinical UM Guideline, please contact the customer service number on the back of the member's card.

No part of this publication may be reproduced, stored in a retrieval system or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from the health plan.

© CPT Only – American Medical Association

Medicaid managed care administered by Amerigroup Corporation, an independent company

Genetic Testing for Inherited Diseases

83. Saxena R, Gianniny L, Burt NP, et al. Common single nucleotide polymorphisms in TCF7L2 are reproducibly associated with type 2 diabetes and reduce the insulin response to glucose in nondiabetic individuals. *Diabetes*. 2006; 55(10):2890-2895.
 84. Shayota BJ, Elsea SH. Behavior and sleep disturbance in Smith-Magenis Syndrome. *Curr Opin Psychiatry*. 2019; 32(2):73-78.
 85. Simon AL, Kiehl M, Fischer E, et al. Pregnancy outcomes from more than 1,800 in vitro fertilization cycles with the use of 24-chromosome single-nucleotide polymorphism-based preimplantation genetic testing for aneuploidy. *Fertil Steril*. 2018; 110(1):113-121.
 86. Steinthorsdottir V, Thorleifsson G, Reynisdottir I, et al. A variant in CDKAL1 influences insulin response and risk of type 2 diabetes. *Nat Genet*. 2007; 39(6):770-775.
 87. Talmud PJ, Hingorani AD, Cooper JA, et al. Utility of genetic and non-genetic risk factors in prediction of type 2 diabetes: Whitehall II prospective cohort study. *BMJ*. 2010; 340:b4838.
 88. Teer JK, Bonycastle LL, Chines PS, et al. Systematic comparison of three genomic enrichment methods for massively parallel DNA sequencing. *Genome Res*. 2010(a) 20(10):1420-1431.
 89. Teer JK, Mullikin JC. Exome sequencing: the sweet spot before whole genomes. *Hum Mol Genet*. 2010(b) 19(R2):R145-151.
 90. Terlizzi V, De Gregorio F, Sepe A, et al. Brand new SPINK1 and CFTR mutations in a child with acute recurrent pancreatitis: a case report. *Minerva Pediatr*. 2013; 65(6):669-672.
 91. Thorleifsson G, Magnusson KP, Sulem P, et al. Common sequence variants in the LOXL1 gene confer susceptibility to exfoliation glaucoma. *Science*. 2007; 317(5843):1397-1400.
 92. Torkamani A, Topol EJ, Schork NJ. Pathway analysis of seven common diseases assessed by genome-wide association. *Genomics*. 2008; 92(5):265-272.
 93. van Ravenswaaij-Arts CM, Blake K, Hoefsloot L, Verloes A. Clinical utility gene card for: CHARGE syndrome - update 2015. *Eur J Hum Genet*. 2015.
 94. Vaxillaire M, Veslot J, Dina C, et al; DESIR Study Group. Impact of common type 2 diabetes risk polymorphisms in the DESIR prospective study. *Diabetes*. 2008; 57(1):244-254.
 95. Wang G, Lin Z, Wang X, et al. The association between 5, 10 - methylenetetrahydrofolate reductase and the risk of unexplained recurrent pregnancy loss in China: a meta-analysis. *Medicine (Baltimore)*. 2021; 100(17):e25487.
 96. Weedon MN. The importance of TCF7L2. *Diabet Med*. 2007; 24(10):1062-1066.
 97. Weinstein LB. Selected genetic disorders affecting Ashkenazi Jewish families. *Fam Community Health*. 2007 30(1):50-62.
 98. Whitcomb DC, Gorry MC, Preston RA, et al. Hereditary pancreatitis is caused by a mutation in the cationic trypsinogen gene. *Nat Genet*. 1996; 14(2):141-145.
 99. Yang X, Zabriskie NA, Hau VS, et al. Genetic association of LOXL1 gene variants and exfoliation glaucoma in a Utah cohort. *Cell Cycle*. 2008; 7(4):521-524.
 100. Zacho J, Yazdanyar S, Bojesen SE, et al. Hyperhomocysteinemia, methylenetetrahydrofolate reductase c.677C>T polymorphism and risk of cancer: cross-sectional and prospective studies and meta-analyses of 75,000 cases and 93,000 controls. *Int J Cancer*. 2011; 128:644-652.
-

Federal and State law, as well as contract language including definitions and specific coverage provisions/exclusions, and Medical Policy take precedence over Clinical UM Guidelines and must be considered first in determining eligibility for coverage. The member's contract benefits in effect on the date that services are rendered must be used. Clinical UM Guidelines, which address medical efficacy, should be considered before utilizing medical opinion in adjudication. Medical technology is constantly evolving, and we reserve the right to review and update Clinical UM Guidelines periodically. Clinical UM guidelines are used when the plan performs utilization review for the subject. Due to variances in utilization patterns, each plan may choose whether or not to adopt a particular Clinical UM Guideline. To determine if review is required for this Clinical UM Guideline, please contact the customer service number on the back of the member's card.

No part of this publication may be reproduced, stored in a retrieval system or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from the health plan.

© CPT Only – American Medical Association

Medicaid managed care administered by Amerigroup Corporation, an independent company

Genetic Testing for Inherited Diseases

101. Zhang J, Qiu LX, Wang ZH, et al. MTHFR C677T polymorphism associated with breast cancer susceptibility: a meta-analysis involving 15,260 cases and 20,411 controls. *Breast Cancer Res Treat.* 2010; 123(2):549-555.
102. Zhang R, Huo C, Wang X et al. Two common MTHFR gene polymorphisms (C677T and A1298C) and fetal congenital heart disease risk: an updated meta-analysis with trial sequential analysis. *Cell Physiol Biochem.* 2018; 45(6):2483-2496.
103. Zhao X, Zhao Y, Ping Y, et al. Association between gene polymorphism of folate metabolism and recurrent spontaneous abortion in Asia: a meta-analysis. *Medicine (Baltimore).* 2020; 99(40):e21962.

Government Agency, Medical Society, and Other Authoritative Publications:

1. American Academy of Pediatrics Section on Cardiology and Cardiac Surgery. Clinical Report: cardiovascular health supervision for individuals affected by Duchenne or Becker muscular dystrophy. *Pediatrics.* 2005; 116(6):1569-1573.
2. American College of Medical Genetics and Genomics (ACMG) Board of Directors. Points to consider in the clinical application of genomic sequencing. *Genet Med.* 2012; 14(8):759-761.
3. American College of Obstetricians and Gynecologists Committee on Genetics. ACOG Committee Opinion No. 442: Preconception and prenatal carrier screening for genetic diseases in individuals of Eastern European Jewish descent. *Obstet Gynecol.* 2009; 114(4):950-953. Reaffirmed 2014.
4. American College of Obstetricians and Gynecologists Committee on Genetics. ACOG Committee Opinion No. 469: Carrier screening for fragile X syndrome. *Obstet Gynecol.* 2010; 116(4):1008-1010.
5. American College of Obstetricians and Gynecologists Committee on Genetics. ACOG Committee Opinion No. 486: Update on carrier screening for cystic fibrosis. *Obstet Gynecol.* 2011; 117(4):1028-1031. Reaffirmed 2014.
6. American College of Obstetricians and Gynecologists Committee on Genetics. ACOG Committee Opinion No. 690: Carrier screening in the age of genomic medicine. *Obstet Gynecol.* 2017(a); 129(3):e35-e40. Reaffirmed 2019.
7. American College of Obstetricians and Gynecologists Committee on Genetics. ACOG Committee Opinion No. 691. Carrier screening for genetic conditions. *Obstet Gynecol.* 2017(b); 129(3):e41-e45.
8. American College of Obstetricians and Gynecologists. ACOG Practice Bulletin No. 197: Inherited thrombophilias in pregnancy. *Obstet Gynecol.* 2018; 132(1):e18-e34.
9. American College of Obstetricians and Gynecologists Committee on Practice Bulletins—Gynecology. ACOG Practice Bulletin No. 84: Prevention of deep vein thrombosis and pulmonary embolism. *Obstet Gynecol.* 2007; 110(2 Pt 1):429-440. Reaffirmed 2018.
10. American College of Radiology. ACR Appropriateness Criteria® dementia and movement disorders. 2015. Available at: <https://acsearch.acr.org/docs/69360/Narrative/>. Accessed on January 26, 2022.
11. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition. DSM-5. American Psychiatric Association. Washington, DC. May 2013. Available at: <http://dsm.psychiatryonline.org/doi/book/10.1176/appi.books.9780890425596>. Accessed on February 23, 2022.
12. Andersen PM, Abrahams S, Borasio GD, et al. EFNS guidelines on the clinical management of amyotrophic lateral sclerosis (MALS)-revised report of an EFNS task force. *Eur J Neurol.* 2012; 19(3):360-375.

Federal and State law, as well as contract language including definitions and specific coverage provisions/exclusions, and Medical Policy take precedence over Clinical UM Guidelines and must be considered first in determining eligibility for coverage. The member's contract benefits in effect on the date that services are rendered must be used. Clinical UM Guidelines, which address medical efficacy, should be considered before utilizing medical opinion in adjudication. Medical technology is constantly evolving, and we reserve the right to review and update Clinical UM Guidelines periodically. Clinical UM guidelines are used when the plan performs utilization review for the subject. Due to variances in utilization patterns, each plan may choose whether or not to adopt a particular Clinical UM Guideline. To determine if review is required for this Clinical UM Guideline, please contact the customer service number on the back of the member's card.

No part of this publication may be reproduced, stored in a retrieval system or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from the health plan.

© CPT Only – American Medical Association

Medicaid managed care administered by Amerigroup Corporation, an independent company

Genetic Testing for Inherited Diseases

13. Arnett DK, Baird AE, Barkley RA, et al. American Heart Association Council on Epidemiology and Prevention; American Heart Association Stroke Council; Functional Genomics and Translational Biology Interdisciplinary Working Group. Relevance of genetics and genomics for prevention and treatment of cardiovascular disease: a scientific statement from the American Heart Association Council on Epidemiology and Prevention, the Stroke Council, and the Functional Genomics and Translational Biology Interdisciplinary Working Group. *Circulation*. 2007; 115(22):2878-2901.
 14. Auger RR, Burgess HJ, Emens JS, et al. Clinical practice guideline for the treatment of intrinsic circadian rhythm sleep-wake disorders: advanced sleep-wake phase disorder (ASWPD), delayed sleep-wake phase disorder (DSWPD), non-24-hour sleepwake rhythm disorder (N24SWD), and irregular sleep-wake rhythm disorder (ISWRD). An update for 2015. *J Clin Sleep Med*. 2015; 11(10):1199–1236. Available at: <http://www.aasmnet.org/Resources/clinicalguidelines/CRSWD-intrinsic.pdf>. Accessed on January 26, 2022.
 15. Bashford MT, Hickey SE, Curry CJ, Toriello HV. Addendum: ACMG practice guideline: lack of evidence for MTHFR polymorphism testing. *Genet Med*. 2020; 22(12):2125. Available at: <https://www.nature.com/articles/s41436-020-0843-0>. Accessed on January 26, 2022.
 16. Bates SM, Greer IA, Middeldorp S, et al. VTE, thrombophilia, antithrombotic therapy, and pregnancy: antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest*. 2012; 141(2 Suppl):e691S-e736S.
 17. Blue Cross and Blue Shield Association. Sequencing for Clinical Diagnosis of Patients with Suspected Genetic Disorders. *TEC Assessment*, 2013; 28(3).
 18. Brooks BR, Miller RG, Swash M, Munsat TL. El Escorial revisited: revised criteria for the diagnosis of amyotrophic lateral sclerosis. *Amyotroph Lateral Scler Other Motor Neuron Disord*. 2000; 1:293-299.
 19. Burgunder JM, Finsterer J, Szolnoki Z, et al. European Federation of Neurological Societies (EFNS) Guidelines on the molecular diagnosis of channelopathies, epilepsies, migraine, stroke, and dementias. *Eur J Neurol*. 2010; 17(5):641-648.
 20. Burgunder JM, Schols L, Baets J, et al. EFNS Guidelines for the molecular diagnosis of neurogenetic disorders: motoneuron, peripheral nerve and muscle disorders. *Eur J Neurol*. 2011; 18(2):207-217.
 21. Committee on Genetics and the Society for Maternal-Fetal Medicine. Microarrays and Next-Generation Sequencing Technology: The Use of Advanced Genetic Diagnostic Tools in Obstetrics and Gynecology. *Obstet Gynecol*. 2016; 128(6):e262-e268.
 22. Edwards JG, Feldman G, Goldberg J, et al. Expanded carrier screening in reproductive medicine—points to consider: a joint statement of the American College of Medical Genetics and Genomics, American College of Obstetricians and Gynecologists, National Society of Genetic Counselors, Perinatal Quality Foundation, and Society for Maternal-Fetal Medicine. *Obstet Gynecol*. 2015; 125(3):653-662.
 23. European Society of Human Genetics. Genetic testing in asymptomatic minors: Recommendations of the European Society of Human Genetics. *Eur J Hum Genet*. 2009; 17(6):720-721.
 24. Genetic and Rare Diseases Information Center. Alpha-1 antitrypsin deficiency. Last updated September 26, 2018. Available at: <https://rarediseases.info.nih.gov/diseases/5784/alpha-1-antitrypsin-deficiency>. Accessed on January 26, 2022.
 25. Green RC, Berg JS, Grody WW, et al. ACMG recommendations for reporting of incidental findings in clinical exome and genome sequencing. *Genet Med*. 2013; 15(7):565-574.
-

Federal and State law, as well as contract language including definitions and specific coverage provisions/exclusions, and Medical Policy take precedence over Clinical UM Guidelines and must be considered first in determining eligibility for coverage. The member's contract benefits in effect on the date that services are rendered must be used. Clinical UM Guidelines, which address medical efficacy, should be considered before utilizing medical opinion in adjudication. Medical technology is constantly evolving, and we reserve the right to review and update Clinical UM Guidelines periodically. Clinical UM guidelines are used when the plan performs utilization review for the subject. Due to variances in utilization patterns, each plan may choose whether or not to adopt a particular Clinical UM Guideline. To determine if review is required for this Clinical UM Guideline, please contact the customer service number on the back of the member's card.

No part of this publication may be reproduced, stored in a retrieval system or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from the health plan.

© CPT Only – American Medical Association

Medicaid managed care administered by Amerigroup Corporation, an independent company

Genetic Testing for Inherited Diseases

26. Gross SJ, Pletcher BA, Monaghan KG; et al. Carrier screening in individuals of Ashkenazi Jewish descent. *Genet Med.* 2008; 10(1):54-56.
27. Grody WW, Cutting GR, Klinger KW, et al. Laboratory standards and guidelines for population-based cystic fibrosis carrier screening. *Genet Med.* 2001; 3(2):149-154.
28. Grody WW, Griffin JH, Taylor AK, et al. American College of Medical Genetics consensus statement on factor V Leiden mutation testing. *Genet Med.* 2001; 3(2):139-148.
29. Grody WW, Thompson BH, Gregg AR, et al. ACMG position statement on prenatal/preconception expanded carrier screening. *Genet Med.* 2013; 15(6):482-483.
30. Hercher L, Uhlmann WR, Hoffman EP, et al. Prenatal Testing for Adult-Onset Conditions: the Position of the National Society of Genetic Counselors. *J Genet Couns.* 2016; 25(6):1139-1145.
31. Holtzman NA, Watson MS. Promoting safe and effective genetic tests in the United States: work of the Task Force on Genetic Testing. *Clin Chem.* 1999; 45(5):732-738.
32. Jack CR, Bennett DA, Blennow K, et al. National Institute on Aging and the Alzheimer's Association (NIA-AA) Research Framework: Toward a biological definition of Alzheimer's disease. *Alzheimers Dement.* 2018; 14(4):535-562.
33. Kalia SS, Adelman K, Bale SJ, et al. Recommendations for reporting of secondary findings in clinical exome and genome sequencing, 2016 update (ACMG SF v2.0): a policy statement of the American College of Medical Genetics and Genomics. *Genet Med.* 2017; 19(2):249-255.
34. Klintworth GK. Corneal dystrophies. *Orphanet J Rare Dis.* 2009; 4:7.
35. Knopman DS, DeKosky ST, Cummings JL, et al. Practice parameter: diagnosis of dementia (an evidence-based review). Report of the Quality Standards Subcommittee of the American Academy of Neurology. *Neurology.* 2001; 56(9):1143-1153.
36. Kohne E. Hemoglobinopathies: Clinical Manifestations, Diagnosis, and Treatment. *Dtsch Arztebl Int.* 2011; 108(31-32): 532–540. Available at: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3163784/>. Accessed on January 26, 2022.
37. Kujovich JL. GeneReviews® [website]. Prothrombin-Related Thrombophilia. Last updated February 4, 2021. Available at: <http://www.ncbi.nlm.nih.gov/books/NBK1148/?report=printable>. Accessed on January 26, 2022.
38. Langfelder-Schwind E, Karczeski B, Strecker MN, et al. Molecular testing for cystic fibrosis carrier status practice guidelines: recommendations of the National Society of Genetic Counselors. *J Genet Couns.* 2014; 23(1):5-15.
39. Mancuso M, Arnold M, Bersano A, et al. Monogenic cerebral small-vessel diseases: diagnosis and therapy. Consensus recommendations of the European Academy of Neurology. *Eur J Neurol.* Mar 20 2020. Available at: <https://onlinelibrary.wiley.com/doi/pdf/10.1111/ene.14183>. Accessed on January 26, 2022.
40. McKhann GM, Knopman DS, Chertkow H, et al. The diagnosis of dementia due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association and National Institute of Neurological and Communicative Disorders and Stroke-Alzheimer's Disease and Related Disorders Association [NINCDS-ADRDA] under the auspices of Department of Health and Human Services Task Force on Alzheimer's Disease. Workgroups on diagnostic guidelines for clinical diagnosis of Alzheimer's disease. *Alzheimers Dement.* 2011; 7(3):263-269.

Federal and State law, as well as contract language including definitions and specific coverage provisions/exclusions, and Medical Policy take precedence over Clinical UM Guidelines and must be considered first in determining eligibility for coverage. The member's contract benefits in effect on the date that services are rendered must be used. Clinical UM Guidelines, which address medical efficacy, should be considered before utilizing medical opinion in adjudication. Medical technology is constantly evolving, and we reserve the right to review and update Clinical UM Guidelines periodically. Clinical UM guidelines are used when the plan performs utilization review for the subject. Due to variances in utilization patterns, each plan may choose whether or not to adopt a particular Clinical UM Guideline. To determine if review is required for this Clinical UM Guideline, please contact the customer service number on the back of the member's card.

No part of this publication may be reproduced, stored in a retrieval system or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from the health plan.

© CPT Only – American Medical Association

Medicaid managed care administered by Amerigroup Corporation, an independent company

Genetic Testing for Inherited Diseases

41. Monaghan KG, Lyon E, Spector EB; American College of Medical Genetics and Genomics. ACMG Standards and Guidelines for fragile X testing: a revision to the disease-specific supplements to the Standards and Guidelines for Clinical Genetics Laboratories of the American College of Medical Genetics and Genomics. *Genet Med.* 2013; 15(7):575-586.
 42. Moxley RT III, Ashwal S, Pandya S, et al. Practice parameter: corticosteroid treatment of Duchenne dystrophy: report of the Quality Standards Subcommittee of the American Academy of Neurology and the Practice Committee of the Child Neurology Society. *Neurology.* 2005; 64(1):13-20.
 43. National Center for Biotechnology Information (NCBI). GeneReviews: Available at: <https://www.ncbi.nlm.nih.gov/books/NBK1116/>. Accessed on January 26, 2022.
 - Alpha-1 Antitrypsin Deficiency. Updated Jan 19, 2017.
 - Amyotrophic Lateral Sclerosis. Updated January 12, 2015.
 - Angelman Syndrome. Updated Dec 21, 2017.
 - Arylsulfatase A Deficiency. Updated Dec 14, 2017.
 - Bloom's Syndrome. Updated Apr 7, 2016.
 - Canavan Disease. Updated Sep 13, 2018.
 - Classic Galactosemia and Clinical Variant Galactosemia. Updated Mar 9, 2017.
 - Dihydrolipoamide Dehydrogenase Deficiency (DLD Deficiency). Initial posting July 17, 2014.
 - DRPLA. Updated June 9, 2016.
 - Dystrophinopathies. April 26, 2018.
 - Factor V Leiden Thrombophilia. Updated January 4, 2018.
 - Familial Dysautonomia. Updated Dec 18, 2014.
 - Fanconi Anemia. Mar 8, 2018.
 - Friedreich Ataxia. Updated June 1, 2017.
 - Gaucher Disease. Updated Jun 2018.
 - Glycogen Storage Disease Type I (Von Gierke Disease). Updated November 2018.
 - Glycogen Storage Disease Type IV. Updated Jan 3, 2013.
 - HBA1 (Alpha-Thalassemia). Updated December 29, 2016.
 - HFE Hemochromatosis. Updated December 6, 2018.
 - Hexosaminidase A Deficiency. Updated Aug 11, 2011.
 - Huntington Disease. Updated July 5, 2018.
 - Maple Syrup Urine Disease. Updated May 9, 2013.
 - MECP2-Related Disorders. Updated September 19, 2019.
 - Medium-Chain Acyl-Coenzyme A Dehydrogenase Deficiency. Updated Apr 20, 2000.
 - Myotonic Dystrophy type 1. Updated March 25, 2021.
 - Myotonic Dystrophy type 2. Updated March 19, 2020.
 - Nonsyndromic Hearing Loss and Deafness, DFNB1. Updated August 18, 2016.
 - Oculopharyngeal Muscular Dystrophy. Updated October 22, 2020.
 - Phenylalanine Hydroxylase Deficiency. Updated Jan 5, 2017.
-

Federal and State law, as well as contract language including definitions and specific coverage provisions/exclusions, and Medical Policy take precedence over Clinical UM Guidelines and must be considered first in determining eligibility for coverage. The member's contract benefits in effect on the date that services are rendered must be used. Clinical UM Guidelines, which address medical efficacy, should be considered before utilizing medical opinion in adjudication. Medical technology is constantly evolving, and we reserve the right to review and update Clinical UM Guidelines periodically. Clinical UM guidelines are used when the plan performs utilization review for the subject. Due to variances in utilization patterns, each plan may choose whether or not to adopt a particular Clinical UM Guideline. To determine if review is required for this Clinical UM Guideline, please contact the customer service number on the back of the member's card.

No part of this publication may be reproduced, stored in a retrieval system or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from the health plan.

© CPT Only – American Medical Association

Medicaid managed care administered by Amerigroup Corporation, an independent company

Genetic Testing for Inherited Diseases

- Pompe Disease. Updated May 11, 2017.
 - Prader-Willi Syndrome. Updated December 14, 2017.
 - Sickle Cell Disease. Updated Aug 17 2017.
 - Smith-Lemli-Opitz Syndrome. Updated January 30, 2020.
 - Spinal and Bulbar Muscular Atrophy. Updated January 26, 2017.
 - Spinocerebellar Ataxia Type 1. Updated June 22, 2017.
 - Spinocerebellar ataxia Type 2. Updated February 14, 2019.
 - Spinocerebellar Ataxia Type 3. Updated June 4, 2020.
 - Spinocerebellar Ataxia Type 6. Updated November 21, 2019.
 - Spinocerebellar Ataxia Type 7. Updated July 23, 2020.
 - Spinocerebellar Ataxia Type 8. Updated April 3, 2014.
 - Spinocerebellar Ataxia Type 10. Updated September 19, 2019.
 - Spinocerebellar Ataxia Type 11. Updated October 31, 2019.
 - Spinocerebellar Ataxia Type 13. Updated June 4, 2020.
 - Unverricht-Lundborg Disease. Updated November 26, 2014.
 - Wilson Disease. Updated July 29, 2016.
44. National Library of Medicine (NLM). Genetics Home Reference.
- CDKN2A gene. Cyclin dependent kinase inhibitor 2A. Reviewed August 2018. Published January 29, 2019.
 - CFTR gene. Cystic fibrosis transmembrane conductance regulator. Reviewed January 2008. Published January 22, 2019. Available at: <https://ghr.nlm.nih.gov/gene/CFTR>. Accessed on January 26, 2022.
 - FANCC gene. FA complementation group C Reviewed January 2012. Published January 22, 2019. Updated August 18, 2020. Available at: <https://ghr.nlm.nih.gov/gene/FANCC>. Accessed on January 26, 2022.
 - HBB gene. Hemoglobin subunit beta. Reviewed July 2015. Published January 29, 2019. Updated August 18, 2020. Available at: <https://ghr.nlm.nih.gov/gene/HBB>. Accessed on January 26, 2022.
 - SMN1 gene. Survival of motor neuron 1, telomeric. Reviewed October 2018. Published January 29, 2019. Updated August 18, 2020. Available at <https://ghr.nlm.nih.gov/gene/SMN1>. Accessed on January 26, 2022.
 - TGFBI gene. Transforming growth factor beta 1. Reviewed November 2017. Published January 29, 2019. Updated August 18, 2020. Available at: <https://ghr.nlm.nih.gov/gene/TGFBI>. Accessed on January 26, 2022.
45. National Organization of Rare Disorders (NORD).
- Beta thalassemia. Published 2018. Available at: <https://rarediseases.org/rare-diseases/thalassemia-major/>. Accessed on January 26, 2022.
 - Corneal dystrophies. Published 2010. Available at: <https://rarediseases.org/rare-diseases/corneal-dystrophies/>. Accessed on January 26, 2022.
 - Maple Syrup Urine Disease. Published 2017. Updated 2020. Available at: <https://rarediseases.org/rare-diseases/maple-syrup-urine-disease/>. Accessed on January 26, 2022.

Federal and State law, as well as contract language including definitions and specific coverage provisions/exclusions, and Medical Policy take precedence over Clinical UM Guidelines and must be considered first in determining eligibility for coverage. The member's contract benefits in effect on the date that services are rendered must be used. Clinical UM Guidelines, which address medical efficacy, should be considered before utilizing medical opinion in adjudication. Medical technology is constantly evolving, and we reserve the right to review and update Clinical UM Guidelines periodically. Clinical UM guidelines are used when the plan performs utilization review for the subject. Due to variances in utilization patterns, each plan may choose whether or not to adopt a particular Clinical UM Guideline. To determine if review is required for this Clinical UM Guideline, please contact the customer service number on the back of the member's card.

No part of this publication may be reproduced, stored in a retrieval system or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from the health plan.

© CPT Only – American Medical Association

Medicaid managed care administered by Amerigroup Corporation, an independent company

Genetic Testing for Inherited Diseases

- Mucopolipidosis IV. Published 2014. Available at: <https://rarediseases.org/rare-diseases/mucopolipidosis-iv/>. Accessed on January 26, 2022.
 - 46. National Society of Genetic Counselors. Genetic Counselor Scope of Practice. Available at: <https://www.nsgc.org/p/cm/ld/fid=18#scope>. Accessed on January 26, 2022.
 - 47. National Society of Genetic Counselors' Definition Task Force, Resta R, Biesecker BB, et al. A new definition of Genetic Counseling: National Society of Genetic Counselors' Task Force report. *J Genet Couns*. 2006; 5(2):77-83.
 - 48. Petersen RC, et al. Practice guideline update summary: Mild Cognitive Impairment. Report of the guideline development, dissemination, and implementation subcommittee of the American Academy of Neurology. *Neurology*. 2018; 90:126-135.
 - 49. Practice Committees of the American Society for Reproductive Medicine and the Society for Assisted Reproductive Technology. Practice Committees of the American Society for Reproductive Medicine and the Society for Assisted Reproductive Technology. The use of preimplantation genetic testing for aneuploidy (PGT-A): A committee opinion. *Fertil Steril*. 2018; 109(3):429-436.
 - 50. Prior TW; Professional Practice and Guidelines Committee. Carrier screening for spinal muscular atrophy. *Genet Med*. 2008; 10(11):840-842.
 - 51. Remco H, Rutten J, Lesnik Oberstein SA. GeneReviews [website]. CADASIL: Cerebral Autosomal Dominant Arteriopathy with Subcortical Infarcts and Leukoencephalopathy. Last updated March 14, 2019. Available at: <http://www.ncbi.nlm.nih.gov/books/NBK1500/>. Accessed on January 26, 2022.
 - 52. Ross LF, Saal HM, David KL, et al. Technical report: Ethical and policy issues in genetic testing and screening of children. *Genet Med*. 2013; 15(3):234-245.
 - 53. Shen T, Dies KA, Holm IA, et al.; Autism Consortium Clinical Genetics/DNA Diagnostics Collaboration. Clinical genetic testing for patients with autism spectrum disorders. *Pediatrics*. 2010; 125(4):e727-e735.
 - 54. Sherman S, Pletcher BA, Driscoll DA. Fragile X syndrome: diagnostic and carrier testing. *Genet Med*. 2005; 7(8):584-587.
 - 55. Sorbi S, Hort J, Erkinjuntti T, et al. European Federation of Neurological Societies/European Neurological Society (EFNS-ENS) Guidelines on the diagnosis and management of disorders associated with dementia. *Eur J Neurol*. 2012; 19(9):1159-1179. Available at: <https://onlinelibrary.wiley.com/doi/full/10.1111/j.1468-1331.2012.03784.x>. Accessed on January 26, 2022.
 - 56. Stone EM, Aldave AJ, Drack AV, et al. Recommendations for genetic testing of inherited eye diseases: report of the American Academy of Ophthalmology task force on genetic testing. *Ophthalmology*. 2012; 119(11):2408-2410.
 - 57. Tenner S, Baillie J, DeWitt J, et al. American College of Gastroenterology guideline: management of acute pancreatitis. *Am J Gastroenterol*. 2013; 108(9):1400-1415.
 - 58. 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*. 2009; 11(1):3-14.
 - 59. U. S. Food and Drug Administration (FDA). FDA Advisory Committee Briefing Document: Spark Therapeutics, Inc. LUXTURNA™ (voretigene neparvovec). October 27, 2017. Available at: <https://www.fda.gov/downloads/advisorycommittees/committeesmeetingmaterials/bloodvaccinesandotherbiologics/cellulartissueandgenetherapiesadvisorycommittee/ucm579300.pdf>. Accessed on January 26, 2022.
-

Federal and State law, as well as contract language including definitions and specific coverage provisions/exclusions, and Medical Policy take precedence over Clinical UM Guidelines and must be considered first in determining eligibility for coverage. The member's contract benefits in effect on the date that services are rendered must be used. Clinical UM Guidelines, which address medical efficacy, should be considered before utilizing medical opinion in adjudication. Medical technology is constantly evolving, and we reserve the right to review and update Clinical UM Guidelines periodically. Clinical UM guidelines are used when the plan performs utilization review for the subject. Due to variances in utilization patterns, each plan may choose whether or not to adopt a particular Clinical UM Guideline. To determine if review is required for this Clinical UM Guideline, please contact the customer service number on the back of the member's card.

No part of this publication may be reproduced, stored in a retrieval system or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from the health plan.

© CPT Only – American Medical Association

Medicaid managed care administered by Amerigroup Corporation, an independent company

Genetic Testing for Inherited Diseases

60. U.S. Food and Drug Administration (FDA). FDA News Release: FDA approves targeted treatment for rare Duchenne muscular dystrophy mutation. Updated August 12, 2020. Available at: <https://www.fda.gov/news-events/press-announcements/fda-approves-targeted-treatment-rare-duchenne-muscular-dystrophy-mutation>. Accessed on January 26, 2022.
61. U.S. Preventive Services Task Force. Screening for hemochromatosis: recommendation statement. *Ann Intern Med*. 2006; 145(3):204-208.
62. Watson MS, Cutting GR, Desnick RJ, et al. Cystic fibrosis population carrier screening: 2004 revision of American College of Medical Genetics mutation panel. *Genet Med*. 2004; 6(5):3873-91.
63. Yawn BP, John-Sowah J. Management of sickle cell disease: Recommendations from the 2014 Expert Panel Report. *Am Fam Physician*. 2015; 92(12):1069-1076. Available at: <https://www.aafp.org/afp/2015/1215/p1069.html>. Accessed on January 26, 2022.
64. Zhu Y1, Shentu X, Wang W. The TGFBI R555W mutation induces a new granular corneal dystrophy type I phenotype. *Mol Vis*. 2011; 17:225-230.

Websites for Additional Information

1. American Board of Genetic Counselors. About genetic counseling. Available at: <https://www.abgc.net/about-genetic-counseling/>. Accessed on January 26, 2022.
2. American College of Medical Genetics and Genomics (ACMG). ©2019 American College of Medical Genetics and Genomics. Available at: https://www.acmg.net/ACMG/Medical-Genetics-PracticeResources/Practice_Resources/ACMG/Medical-Genetics-Practice-Resources/Medical-GeneticsPractice-Resources.aspx?hkey=d56a0de8-cfb0-4c6e-bf1e-ffb96e5f86aa. Accessed on January 26, 2022.
3. American College of Obstetricians and Gynecologists. Frequently asked questions. FAQ165. Prenatal Genetic Screening Tests June 2020. Available at: <https://www.acog.org/womens-health/faqs/prenatal-genetic-screening-tests>. Accessed on January 26, 2022.
4. American Gastroenterological Association. Understanding pancreatitis. Available at: www.gastro.org. Accessed on January 26, 2022.
5. American Psychological Association (APA). Guidelines for the evaluation of dementia and age-related cognitive change. *Am Psychol*. 2012; 67(1):1-9. Available at: <https://www.apa.org/practice/guidelines/guidelines-dementia-age-related-cognitive-change.pdf>. Accessed on January 10, 2022.
6. Chiong W, Tsou AY, Simmons Z, et al. Ethics, Law, and Humanities Committee (a joint committee of the American Academy of Neurology, American Neurological Association, and Child Neurology Society). Ethical considerations in dementia diagnosis and care: AAN Position Statement. *Neurology*. 2021; 97(2):80-89.
7. Dubois B, Villain N, Frisoni GB, et al. Clinical diagnosis of Alzheimer's disease: recommendations of the International Working Group. *Lancet Neurol*. 2021; 20(6):484-496.
8. National Institutes of Health. National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK). Available at: <http://www.niddk.nih.gov/Pages/default.aspx>. Accessed on January 26, 2022.

Federal and State law, as well as contract language including definitions and specific coverage provisions/exclusions, and Medical Policy take precedence over Clinical UM Guidelines and must be considered first in determining eligibility for coverage. The member's contract benefits in effect on the date that services are rendered must be used. Clinical UM Guidelines, which address medical efficacy, should be considered before utilizing medical opinion in adjudication. Medical technology is constantly evolving, and we reserve the right to review and update Clinical UM Guidelines periodically. Clinical UM guidelines are used when the plan performs utilization review for the subject. Due to variances in utilization patterns, each plan may choose whether or not to adopt a particular Clinical UM Guideline. To determine if review is required for this Clinical UM Guideline, please contact the customer service number on the back of the member's card.

No part of this publication may be reproduced, stored in a retrieval system or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from the health plan.

© CPT Only – American Medical Association

Medicaid managed care administered by Amerigroup Corporation, an independent company

Genetic Testing for Inherited Diseases

9. National Library of Medicine (NLM). Genetics Home Reference. What are the uses of genetic tests? Published March 12, 2019. Updated September 22, 2020. Available at: <https://ghr.nlm.nih.gov/primer/testing/uses>. Accessed on January 26, 2022.
10. National Library of Medicine (NLM). Genetic Conditions: Ataxia-telangiectasia. Published January 29, 2019. Updated August 18, 2020. Available at: <http://ghr.nlm.nih.gov/condition/ataxia-telangiectasia>. Accessed on January 26, 2022.
11. National Library of Medicine (NLM). Genetics Home Reference. NOTCH3 gene. Updated August 18, 2020. Available at: <https://ghr.nlm.nih.gov/gene/NOTCH3#conditions>. Accessed on January 26, 2022.
12. National Society of Genetic Counselors. Position Statement on Genetic Testing of Minors for Adult-onset Disorders. Updated April 12, 2018. Available at: <https://www.nsgc.org/Policy-Research-and-Publications/Position-Statements/Position-Statements/Post/genetic-testing-of-minors-for-adult-onset-conditions>. Accessed on January 26, 2022.
13. U.S. Food and Drug Administration (FDA). Center for Devices and Radiological Health. CLIA-Clinical Laboratory Improvement Amendments. Current: Sept. 13, 2021. Available at: <http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/IVDRegulatoryAssistance/ucm124105.htm>. Accessed on January 26, 2022.

Index

Alzheimer 's disease (AD)
 Amyloid Aβ precursor gene (APP)
 ApoE
 Apolipoprotein E
 Becker muscular dystrophy
 Bloom Syndrome
 CADASIL Syndrome, Cerebral Autosomal Dominant Arteriopathy with Subcortical Infarcts and Leukoencephalopathy Syndrome
 Canavan Disease
 CHARGE syndrome
 chromodomain helicase DNA binding protein (CHD7)
 Complete CADASIL Evaluation #421
 Counsyl Family Prep Screen
 Cystic Fibrosis
 Diagnostic genetic test
 Duchenne muscular dystrophy (DMD)
 Factor II (FII, F2)
 Fanconi Anemia Group C
 Fragile X syndrome
 Gaucher's Disease
 Genetic Testing, Preconception or Prenatal

Federal and State law, as well as contract language including definitions and specific coverage provisions/exclusions, and Medical Policy take precedence over Clinical UM Guidelines and must be considered first in determining eligibility for coverage. The member's contract benefits in effect on the date that services are rendered must be used. Clinical UM Guidelines, which address medical efficacy, should be considered before utilizing medical opinion in adjudication. Medical technology is constantly evolving, and we reserve the right to review and update Clinical UM Guidelines periodically. Clinical UM guidelines are used when the plan performs utilization review for the subject. Due to variances in utilization patterns, each plan may choose whether or not to adopt a particular Clinical UM Guideline. To determine if review is required for this Clinical UM Guideline, please contact the customer service number on the back of the member's card.

No part of this publication may be reproduced, stored in a retrieval system or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from the health plan.

© CPT Only – American Medical Association

Medicaid managed care administered by Amerigroup Corporation, an independent company

Genetic Testing for Inherited Diseases

- GoodStart GeneVu
- Hereditary thrombophilia
- Inherigen
- Inheritest Carrier Screen
- Methylenetetrahydrofolate reductase (MTHFR)
- Mucopolidosis IV
- Muscular dystrophy
- Neurogenic locus notch homolog protein 3
- Niemann Pick Disease Type A
- Notch homolog 3 (Drosophila)
- NOTCH3
- Pancreatitis hereditary
- Pharmacotherapeutic genetic test
- Predictive genetic test
- Primary hyperoxaluria type 1 (PH1)
- Prognostic genetic test
- Prothrombin
- Rett syndrome
- Smith Magenis syndrome
- Tay-Sach's Disease
- Therapeutic genetic test

The use of specific product names is illustrative only. It is not intended to be a recommendation of one product over another, and is not intended to represent a complete listing of all products available.

History

Status	Date	Action
Reviewed	02/17/2022	Medical Policy & Technology Assessment Committee (MPTAC) review. Moved content of GENE.00003 Genetic Testing and Biochemical Markers for the Diagnosis of Alzheimer's Disease into this document with no revisions to criteria. Moved content of CG-GENE-09 Genetic Testing for CHARGE Syndrome into this document with no revisions to criteria. Updated table of genes to add amyloid Aβ precursor gene (APP), APOE ε4, presenilin 1 gene (PSEN1), presenilin 2 (PSEN2), CHD7, GAA, JAG1/JAGGED1, NOTCH2, ATP8B1, ABCB11, ABCB4, TJP2, NR1H4, MYO5B. Updated the Scope, Discussion, Definitions, Index and References sections. Updated Coding section, added HCPCS code S3852, and genes to Tier 2 codes and NOC code, including those previously addressed in GENE.00003 and CG-GENE-09.

Federal and State law, as well as contract language including definitions and specific coverage provisions/exclusions, and Medical Policy take precedence over Clinical UM Guidelines and must be considered first in determining eligibility for coverage. The member's contract benefits in effect on the date that services are rendered must be used. Clinical UM Guidelines, which address medical efficacy, should be considered before utilizing medical opinion in adjudication. Medical technology is constantly evolving, and we reserve the right to review and update Clinical UM Guidelines periodically. Clinical UM guidelines are used when the plan performs utilization review for the subject. Due to variances in utilization patterns, each plan may choose whether or not to adopt a particular Clinical UM Guideline. To determine if review is required for this Clinical UM Guideline, please contact the customer service number on the back of the member's card.

No part of this publication may be reproduced, stored in a retrieval system or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from the health plan.

© CPT Only – American Medical Association

Medicaid managed care administered by Amerigroup Corporation, an independent company

Genetic Testing for Inherited Diseases

Reviewed	11/11/2021	MPTAC review. Moved content of GENE.00036 Genetic Testing for Hereditary Pancreatitis into this document with no revisions to criteria. Moved content of GENE.00047 Methylenetetrahydrofolate Reductase Mutation Testing into this document with no revisions to criteria. Updated table of genes to add: PRSS1, SPINK1, CTRC. Exon 45 skipping, IL1RN, MOCS1, S1, MTHFR. The Discussion, Definitions, Index and References sections were updated. Updated Coding section; added 81291 previously addressed in GENE.00047, and Tier 2 codes for genes PRSS1, SPINK1, and CTRC previously addressed in GENE.00036.
Revised	05/13/2021	MPTAC review. Revised the language of the Statements in the Clinical Indications section to clarify that testing of individual genes is for germline genetic diseases and preconception or prenatal genetic screening of a parent or prospective parent to determine carrier status is for germline genetic disorders. Updated table of genes to add: AGXT, POMC, PCSK1, LEPR, RAI1, NOTCH3, F2, G20210A. Incorporated GENE.00042 (Genetic Testing for CADASIL) and GENE.00046 (Prothrombin [Factor II] Genetic Testing) into this document with applicable genes added to the table of MN genes. The Discussion, Definitions, References and Index sections were updated. ADMIN edits were made to Discussion section. Updated Coding section; added 81240 and genes to Tier 2 codes and 81479 NOC.
Reviewed	02/11/2021	MPTAC review. Moved content of CG-GENE-05 Genetic Testing for DMD Mutations (Duchenne or Becker Muscular Dystrophy) into this document with no revisions to criteria. Updated table of genes to add: ACADVL, CPT-2, DMD, GLA, HADHA, HADHB, MVK, TPP1. The Discussion, References and Index sections were updated. Reformatted Coding section and added CPT codes 81161, 0218U (were previously addressed in CG-GENE-05); updated Tier 2 codes with additional genes.
	12/16/2020	Updated Coding section with 01/01/2021 CPT changes; added PLA codes 0230U-0234U, 0236U.
Reviewed	05/14/2020	MPTAC review. Updated table of genes to add: ApoB, LDLR, LDLRAP1, MYH11, PCSK9, TGFBR1, TGFBR2, HMBS, CPOX, PPOX. Updated Coding section to add these genes to the appropriate Tier 2 CPT codes; removed S3841, S3842 now addressed in CG-GENE-14.
	04/01/2020	Updated Coding section with 04/01/2020 CPT changes; added 0170U.
	02/27/2020	Updated formatting in Clinical Indications section.
New	11/07/2019	MPTAC review. Initial document development. Moved the contents of GENE.00012 Preconception or Prenatal Genetic Testing of a Parent or Prospective Parent and GENE.00043 Genetic Testing of an Individual's Genome for Inherited Diseases into this new clinical UM guideline CG-GENE-13 Genetic Testing for Inherited Diseases with a new title. Removed the position

Federal and State law, as well as contract language including definitions and specific coverage provisions/exclusions, and Medical Policy take precedence over Clinical UM Guidelines and must be considered first in determining eligibility for coverage. The member's contract benefits in effect on the date that services are rendered must be used. Clinical UM Guidelines, which address medical efficacy, should be considered before utilizing medical opinion in adjudication. Medical technology is constantly evolving, and we reserve the right to review and update Clinical UM Guidelines periodically. Clinical UM guidelines are used when the plan performs utilization review for the subject. Due to variances in utilization patterns, each plan may choose whether or not to adopt a particular Clinical UM Guideline. To determine if review is required for this Clinical UM Guideline, please contact the customer service number on the back of the member's card.

No part of this publication may be reproduced, stored in a retrieval system or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from the health plan.

© CPT Only – American Medical Association

Medicaid managed care administered by Amerigroup Corporation, an independent company

statements about whole genome, whole exome and panel testing which were transitioned over to GENE.00052 Whole Genome Sequencing, Whole Exome Sequencing, Gene Panels and Molecular Profiling. Revised Coding section to remove panel test codes 81410, 81411, 81415-81417, 81416, 81417, 81425-81427, 81430, 81431, 81440, 81442, 81443, 81460, 81465, 81470, 81471, 81506, 0012U, 0094U.

Historical

Federal and State law, as well as contract language including definitions and specific coverage provisions/exclusions, and Medical Policy take precedence over Clinical UM Guidelines and must be considered first in determining eligibility for coverage. The member's contract benefits in effect on the date that services are rendered must be used. Clinical UM Guidelines, which address medical efficacy, should be considered before utilizing medical opinion in adjudication. Medical technology is constantly evolving, and we reserve the right to review and update Clinical UM Guidelines periodically. Clinical UM guidelines are used when the plan performs utilization review for the subject. Due to variances in utilization patterns, each plan may choose whether or not to adopt a particular Clinical UM Guideline. To determine if review is required for this Clinical UM Guideline, please contact the customer service number on the back of the member's card.

No part of this publication may be reproduced, stored in a retrieval system or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from the health plan.

© CPT Only – American Medical Association

Medicaid managed care administered by Amerigroup Corporation, an independent company