Healthy Blue

Clinical UM Guideline

Subject:	Genetic Testing for Inherited Diseases		
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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.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-14 Gene Mutation Testing for Cancer Susceptibility and Management
  - CG-GENE-15 Genetic Testing for Lynch Syndrome, Familial Adenomatous Polyposis (FAP), Attenuated FAP and MYH-associated Polyposis
  - CG-GENE-16 BRCA Genetic Testing
  - 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:
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**
2. One or both parents or prospective parent(s) have a first or a second degree relative who is affected with (or one parent or prospective parent is a known carrier of) 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, mucolipidosis 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:

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
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
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	*DMD (dystrophin)* (eg, Duchenne/Becker muscular dystrophy) deletion analysis, and duplication analysis, if performed
81171	*AFF2 (AF4/FMR2 family, member 2 [FMR2])* (eg, fragile X mental retardation 2 [FRAXE]) gene analysis; evaluation to detect abnormal (eg, expanded) alleles
81172	*AFF2 (AF4/FMR2 family, member 2 [FMR2])* (eg, fragile X mental retardation 2 [FRAXE]) gene analysis; characterization of alleles (eg, expanded size and methylation status)
81187	*CNBP (CCHC-type zinc finger nucleic acid binding protein)* (eg, myotonic dystrophy type 2) gene analysis, evaluation to detect abnormal (eg, expanded alleles

81205	*BCKDHB (branched-chain keto acid dehydrogenase E1, beta polypeptide)* (eg, maple syrup urine disease) gene analysis, common variants (eg, R183P, G278S, E422X)
81209	*BLM (Bloom syndrome, RecQ helicase-like)* (eg, Bloom syndrome) gene analysis, 2281del6ins7 variant
81234	*DMPK (DM1 protein kinase)* (eg, myotonic dystrophy type 1) gene analysis; evaluation to detect abnormal (expanded) alleles
81239	*DMPK (DM1 protein kinase)* (eg, myotonic dystrophy type 1) gene analysis; characterization of alleles (eg, expanded size)
81241	*F5 (coagulation Factor V)* (eg, hereditary hypercoagulability) gene analysis, Leiden variant
81242	*FANCC (Fanconi anemia, complementation group C)* (eg, Fanconi anemia, type C) gene analysis, common variant (eg, IVS4+4A>T)
81243	*FMR1 (fragile X mental retardation 1)* (eg, fragile X mental retardation) gene analysis; evaluation to detect abnormal (eg, expanded) alleles
81244	*FMR1 (fragile X mental retardation 1)* (eg, fragile X mental retardation) gene analysis; characterization of alleles (eg, expanded size and promoter methylation status)
81250	*G6PC (glucose-6-phosphatase, catalytic subunit)* (eg, Glycogen storage disease, Type 1a, von Gierke disease) gene analysis, common variants (eg, R83C, Q347X)
81251	*GBA (glucosidase, beta, acid)* (eg, Gaucher disease) gene analysis, common variants (eg, N370S, 84GG, L444P, IVS2+1G>A)
81256	*HFE (hemochromatosis)* (eg, hereditary hemochromatosis) gene analysis, common variants (eg, C282Y, H63D)
81257	*HBA1/HBA2 (alpha globin 1 and alpha globin 2)* (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	*HBA1/HBA2 (alpha globin 1 and alpha globin 2)* (eg, alpha thalassemia, Hb Bart hydrops fetalis syndrome, HbH disease), gene analysis; known familial variant
81259	*HBA1/HBA2 (alpha globin 1 and alpha globin 2)* (eg, alpha thalassemia, Hb Bart hydrops fetalis syndrome, HbH disease), gene analysis; full gene sequence
81260	*IKBKAP (inhibitor of kappa light polypeptide gene enhancer in B-cells, kinase complex-associated protein)* (eg, familial dysautonomia) gene analysis, common variants (eg, 2507+6T>C, R696P)
81269	*HBA1/HBA2 (alpha globin 1 and alpha globin 2)* (eg, alpha thalassemia, Hb Bart hydrops fetalis syndrome, HbH disease), gene analysis; duplication/deletion variants
81330	*SMPD1(sphingomyelin phosphodiesterase 1, acid lysosomal)* (eg, Niemann-Pick disease, Type A) gene analysis, common variants (eg, R496L, L302P, fsP330)
81331	*SNRPN/UBE3A (small nuclear ribonucleoprotein polypeptide N and ubiquitin protein ligase E3A)* (eg, Prader-Willi syndrome and/or Angelman syndrome), methylation analysis
81361	*HBB (hemoglobin, subunit beta)* (eg, sickle cell anemia, beta thalassemia, hemoglobinopathy); common variant(s) (eg, HbS, HbC, HbE)
81362	*HBB (hemoglobin, subunit beta)* (eg, sickle cell anemia, beta thalassemia, hemoglobinopathy); known familial variant(s)
81363	*HBB (hemoglobin, subunit beta)* (eg, sickle cell anemia, beta thalassemia, hemoglobinopathy); duplication/deletion variant(s)

81364	*HBB (hemoglobin, subunit beta)* (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]: • *ACADM (acyl-CoA dehydrogenase, C-4 to C-12 straight chain, MCAD)* (eg, medium chain acyl dehydrogenase deficiency), K304E variant • *BCKDHA (branched chain keto acid dehydrogenase E1, alpha polypeptide)* (eg, maple syrup urine disease, type 1A), Y438N variant • *F5 (coagulation factor V)* (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]: • *ACADM (acyl-CoA dehydrogenase, C-4 to C-12 straight chain, MCAD)* (eg, medium chain acyl dehydrogenase deficiency), commons variants (eg, K304E, Y42H) • *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)
81404	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]: • *BTD (biotinidase)* (eg, biotinidase deficiency), full gene sequence • *CPT2 (carnitine palmitoyltransferase 2)* (eg, carnitine palmitoyltransferase II deficiency), full gene sequence • *NLGN4X (neuroligin 4, X-linked)* (eg, autism spectrum disorders), duplication/deletion analysis • *TTPA (tocopherol [alpha] transfer protein)* (eg, ataxia), full gene sequence
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]: • *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

- *OTC (ornithine carbamoyltransferase)* (eg, ornithine transcarbamylase deficiency), 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
- *DBT (dihydrolipoamide branched chain transacylase E2)* (eg, maple syrup urine disease, type 2), full gene sequence
- *DLD (dihydrolipoamide dehydrogenase)* (eg, maple syrup urine disease, type III), full gene sequence
- *GAA (glucosidase, alpha; acid)* (eg, glycogen storage disease type II [Pompe disease]), full gene sequence
- *GALT (galactose-1-phosphate uridylyltransferase)* (eg, galactosemia), full gene sequence
- *HADHA (hydroxyacyl-CoA dehydrogenase/3-ketoacyl-CoA thiolase/enoyl-CoA hydratase [trifunctional protein] alpha subunit)* (eg, long chain acyl-coenzyme A dehydrogenase deficiency), full gene sequence
- *HADHB (hydroxyacyl-CoA dehydrogenase/3-ketoacyl-CoA thiolase/enoyl-CoA hydratase [trifunctional protein] beta subunit)* (eg, trifunctional protein deficiency), full gene sequence
- *JAG1 (jagged 1)* (eg, Alagille syndrome), duplication/deletion analysis
- *PAH (phenylalanine hydroxylase)* (eg, phenylketonuria), full gene sequence
- *PYGM (phosphorylase, glycogen, muscle)* (eg, glycogen storage disease type V, McArdle disease), full gene sequence
- *RPE65 (retinal pigment epithelium-specific protein 65kDa)* (eg, retinitis pigmentosa, Leber congenital amaurosis), full gene sequence
- *SLC37A4 (solute carrier family 37 [glucose-6-phosphate transporter], member 4)* (eg, glycogen storage disease type Ib), 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]:

- *CHD7 (chromodomain helicase DNA binding protein 7)* (eg, CHARGE syndrome), full gene sequence
- *JAG1 (jagged 1)* (eg, Alagille syndrome), 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]: • *DMD (dystrophin)* (eg, Duchenne/Becker muscular dystrophy), full gene sequence • *MYH11 (myosin, heavy chain 11, smooth muscle)* (eg, thoracic aortic aneurysms and aortic dissections), full gene sequence
81479	Unlisted molecular pathology procedure [for example: *ABCB4*, *ABCB11*, *ATP8B1*, *MYO5B*, *NR1H4*, *TJP2* (eg, progressive familial intrahepatic cholestasis); *AC9DVL*, *GBE1 (1,4-alpha-glucan branching enzyme 1)* (eg. glycogen storage disease); *ELP1 (elongator complex protein 1)* (eg, familial dysautonomia); *NOTCH2 (notch receptor 2)* (eg, Alagille syndrome); *MVK; TPP1*]
81599	Unlisted multianalyte assay with algorithmic analysis
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
81182	*ATXN8OS (ataxin 8 opposite strand [non-protein coding])* (eg, spinocerebellar ataxia) gene analysis, evaluation to detect abnormal (eg, expanded) alleles
81183	*ATXN10 (ataxin 10)* (eg, spinocerebellar ataxia) gene analysis, evaluation to detect abnormal (eg, expanded) alleles
81184	*CACNA1A (calcium voltage-gated channel subunit alpha1 A)* (eg, spinocerebellar ataxia) gene analysis; evaluation to detect abnormal (eg, expanded) alleles
81185	*CACNA1A (calcium voltage-gated channel subunit alpha1 A)* (eg, spinocerebellar ataxia) gene analysis; full gene sequence
81186	*CACNA1A (calcium voltage-gated channel subunit alpha1 A)* (eg, spinocerebellar ataxia) gene analysis; known familial variant
81188	*CSTB (cystatin B)* (eg, Unverricht-Lundborg disease) gene analysis; evaluation to detect abnormal (eg, expanded) alleles
81189	*CSTB (cystatin B)* (eg, Unverricht-Lundborg disease) gene analysis; full gene sequence
81190	*CSTB (cystatin B)* (eg, Unverricht-Lundborg disease) gene analysis; known familial variant(s)
81200	*ASPA (aspartoacylase)* (eg, Canavan disease) gene analysis, common variants (eg, E285A, Y231X)
81204	*AR (androgen receptor)* (eg, spinal and bulbar muscular atrophy, Kennedy disease, X chromosome inactivation) gene analysis; characterization of alleles (eg, expanded size or methylation status)
81252	*GJB2 (gap junction protein, beta 2, 26kDa, connexin 26)* (eg, nonsyndromic hearing loss) gene analysis; full gene sequence
81253	*GJB2 (gap junction protein, beta 2, 26kDa, connexin 26)* (eg, nonsyndromic hearing loss) gene analysis; known familial variants
81254	*GJB2 (gap junction protein, beta 6, 30kDa, connexin 30)* (eg, nonsyndromic hearing loss) gene analysis, common variants (eg, 309kb [del(GJB6-D13S1830)] and 232kb [del(GJB6-D13S1854)])
81255	*HEXA (hexosaminidase A [alpha polypeptide])* (eg, Tay-Sachs disease) gene analysis, common variants (eg, 1278insTATC, 1421+1G>C, G269S)
81271	*HTT (huntingtin)* (eg, Huntington disease) gene analysis; evaluation to detect abnormal (eg, expanded) alleles
81274	*HTT (huntingtin)* (eg, Huntington disease) gene analysis; characterization of alleles (eg, expanded size)
81284	*FXN (frataxin)* (eg, Friedreich ataxia) gene analysis; evaluation to detect abnormal (expanded) alleles
81285	*FXN (frataxin)* (eg, Friedreich ataxia) gene analysis; characterization of alleles (eg, expanded size)
81286	*FXN (frataxin)* (eg, Friedreich ataxia) gene analysis; full gene sequence
81289	*FXN (frataxin)* (eg, Friedreich ataxia) gene analysis; known familial variant(s)

81290	*MCOLN1 (mucolipin 1)* (eg, Mucolipidosis, type IV) gene analysis, common variants (eg, IVS3-2A>G, del6.4kb)
81302	*MECP2 (methyl CpG binding protein 2)* (eg, Rett syndrome) gene analysis; full sequence analysis
81303	*MECP2 (methyl CpG binding protein 2)* (eg, Rett syndrome) gene analysis; known familial variant
81304	*MECP2 (methyl CpG binding protein 2)* (eg, Rett syndrome) gene analysis; duplication/deletion variants
81312	*PABPN1 (poly[A] binding protein nuclear 1)* (eg, oculopharyngeal muscular dystrophy) gene analysis, evaluation to detect abnormal (eg, expanded) alleles
81333	*TGFBI (transforming growth factor beta-induced)* (eg, corneal dystrophy) gene analysis, common variants (eg, R124H, R124C, R124L, R555W, R555Q)
81343	*PPP2R2B (protein phosphatase 2 regulatory subunit Bbeta)* (eg, spinocerebellar ataxia) gene analysis, evaluation to detect abnormal (eg, expanded) alleles
81344	*TBP (TATA box binding protein)* (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]: • 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]: • *KCNC3 (potassium voltage-gated channel, Shaw-related subfamily, member 3)* (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]: • *APTX (aprataxin)* (eg, ataxia with oculomotor apraxia 1), full gene sequence • *SIL1 (SIL1 homolog, endoplasmic reticulum chaperone [S. cerevisiae])* (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]: • *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

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) expansions, mobile element insertions, and variants in non-uniquely mappable regions
Genomic Unity® FXN Analysis, Variantyx Inc, Variantyx Inc

0234U *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
81309	*PIK3CA (phosphatidylinositol-4, 5-biphosphate 3-kinase, catalytic subunit alpha)* (eg, colorectal and breast cancer) gene analysis, targeted sequence analysis (eg, exons 7, 9, 20)
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)
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]: • *CEL (carboxyl ester lipase [bile salt-stimulated lipase])* (eg, maturity-onset diabetes of the young [MODY]), targeted sequence analysis of exon 11 (eg, c.1785delC, c.1686delT) • *PLN (phospholamban)* (eg, dilated cardiomyopathy, hypertrophic cardiomyopathy), full gene sequence
81404	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]: • *HNF1B (HNF1 homeobox B)* (eg, maturity-onset diabetes of the young [MODY]), duplication/deletion analysis

- *PDX1 (pancreatic and duodenal homeobox 1)* (eg, maturity-onset diabetes of the young [MODY]), full gene sequence
- *PRSS1 (protease, serine, 1 [trypsin 1])* (eg, hereditary pancreatitis), full gene sequence
- *SOD1 (superoxide dismutase 1, soluble*) (eg, amyotrophic lateral sclerosis), full gene sequence
- *SPINK1 (serine peptidase inhibitor, Kazal type 1)* (eg, hereditary pancreatitis), full gene sequence
- *TTR (transthyretin)* (eg, familial transthyretin amyloidosis), full gene sequence

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]:

- *ACTA2 (actin, alpha 2, smooth muscle, aorta)* (eg, thoracic aortic aneurysms and aortic dissections), full gene sequence
- *ACTC1 (actin, alpha, cardiac muscle 1)* (eg, familial hypertrophic cardiomyopathy), full gene sequence
- *CASQ2 (calsequestrin 2 [cardiac muscle])* (eg, catecholaminergic polymorphic ventricular tachycardia), full gene sequence
- *CDKL5 (cyclin-dependent kinase-like 5)* (eg, early infantile epileptic encephalopathy), duplication/deletion analysis
- *CPOX (coproporphyrinogen oxidase)* (eg, hereditary coproporphyria), full gene sequence
- *CTRC* (*chymotrypsin C*) (eg, hereditary pancreatitis), full gene sequence
- *ENG (endoglin)* (eg, hereditary hemorrhagic telangiectasia, type 1), duplication/deletion analysis
- *HNF1A (HNF1 homeobox A)* (eg, maturity-onset diabetes of the young [MODY]), full gene sequence
- *HNF1B (HNF1 homeobox B)* (eg, maturity-onset diabetes of the young [MODY]), full gene sequence
- *LDLR (low density lipoprotein receptor)* (eg, familial hypercholesterolemia), duplication/deletion analysis
- *MYL2 (myosin, light chain 2, regulatory, cardiac, slow)* (eg, familial hypertrophic cardiomyopathy), full gene sequence
- *MYL3 (myosin, light chain 3, alkali, ventricular, skeletal, slow)* (eg, familial hypertrophic cardiomyopathy), full gene sequence
- *RAI1 (retinoic acid induced 1)* (eg, Smith-Magenis syndrome), full gene sequence
- *TNNC1 (troponin C type 1 [slow])* (eg, hypertrophic cardiomyopathy or dilated cardiomyopathy), full gene sequence
- *TNNI3 (troponin I, type 3 [cardiac])* (eg, familial hypertrophic cardiomyopathy), full gene sequence
- *TPM1 (tropomyosin 1 [alpha])* (eg, familial hypertrophic cardiomyopathy), full gene sequence
- *TSC1 (tuberous sclerosis 1)* (eg, tuberous sclerosis), duplication/deletion analysis

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]:

- *CDKL5 (cyclin-dependent kinase-like 5)* (eg, early infantile epileptic encephalopathy), full gene sequence
- *DSC2 (desmocollin)* (eg, arrhythmogenic right ventricular dysplasia/cardiomyopathy 11), full gene sequence
- *DSG2 (desmoglein 2)* (eg, arrhythmogenic right ventricular dysplasia/cardiomyopathy 10), full gene sequence
- *DSP (desmoplakin)* (eg, arrhythmogenic right ventricular dysplasia/cardiomyopathy 8), full gene sequence
- *ENG (endoglin)* (eg, hereditary hemorrhagic telangiectasia, type 1), full gene sequence
- *GCK (glucokinase [hexokinase 4])* (eg, maturity-onset diabetes of the young [MODY]), full gene sequence
- *HNF4A (hepatocyte nuclear factor 4, alpha)* (eg, maturity-onset diabetes of the young [MODY]), full gene sequence
- *HMBS (hydroxymethylbilane synthase)* (eg, acute intermittent porphyria), full gene sequence
- *KCNH2 (potassium voltage-gated channel, subfamily H [eag-related], member 2)* (eg, short QT syndrome, long QT syndrome), full gene sequence [for long QT testing only]
- *KCNQ1 (potassium voltage-gated channel, KQT-like subfamily, member 1)* (eg, short QT syndrome, long QT syndrome), full gene sequence [for long QT testing only]
- *LDLR (low density lipoprotein receptor)* (eg, familial hypercholesterolemia), full gene sequence
- *LEPR (leptin receptor)* (eg, obesity with hypogonadism), full gene sequence
- *LMNA (lamin A/C)* (eg, Emery-Dreifuss muscular dystrophy [EDMD1, 2 and 3] limb-girdle muscular dystrophy [LGMD] type 1B, dilated cardiomyopathy [CMD1A], familial partial lipodystrophy [FPLD2]), full gene sequence
- *PCSK9 (proprotein convertase subtilisin/kexin type 9)* (eg, familial hypercholesterolemia), full gene sequence
- *PKP2 (plakophilin 2)* (eg, arrhythmogenic right ventricular dysplasia/ cardiomyopathy 9), full gene sequence
- *PPOX (protoporphyrinogen oxidase)* (eg, variegate porphyria), full gene sequence
- *PRKAG2 (protein kinase, AMP-activated, gamma 2 non-catalytic subunit)* (eg, familial hypertrophic cardiomyopathy with Wolff-Parkinson-White syndrome, lethal congenital glycogen storage disease of heart), full gene sequence
- *RYR1 (ryanodine receptor 1, skeletal)* (eg, malignant hyperthermia), targeted sequence analysis of exons with functionally-confirmed mutations
- *TMEM43 (transmembrane protein 43)* (eg, arrhythmogenic right ventricular cardiomyopathy), full gene sequence
- *TNNT2 (troponin T, type 2 [cardiac])* (eg, familial hypertrophic cardiomyopathy), full gene sequence
- *TSC1 (tuberous sclerosis 1)* (eg, tuberous sclerosis), full gene sequence

- *TSC2 (tuberous sclerosis 2)* (eg, tuberous sclerosis), duplication/deletion analysis

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]:
- *APOB (apolipoprotein B)* (eg, familial hypercholesterolemia type B), full gene sequence
- *MYBPC3 (myosin binding protein C, cardiac)* (eg, familial hypertrophic cardiomyopathy), full gene sequence [for HCM, DCM testing]
- *MYH7 (myosin, heavy chain 7, cardiac muscle, beta)* (eg, familial hypertrophic cardiomyopathy, Liang distal myopathy), full gene sequence [for HCM testing]
- *SCN5A (sodium channel, voltage-gated, type V, alpha subunit)* (eg, familial dilated cardiomyopathy), full gene sequence [for long QT and Brugada syndrome testing only]
- *TSC2 (tuberous sclerosis 2)* (eg, tuberous sclerosis), 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]:
- *FBN1 (fibrillin 1)* (eg, Marfan syndrome), full gene sequence
- *RYR1 (ryanodine receptor 1, skeletal)* (eg, malignant hyperthermia), full gene sequence
- *RYR2 (ryanodine receptor 2 [cardiac])* (eg, catecholaminergic polymorphic ventricular tachycardia, arrhythmogenic right ventricular dysplasia), full gene sequence or targeted sequence analysis of >50 exons [for CPVT testing only]

81414 Cardiac ion channelopathies (eg, Brugada syndrome, long QT syndrome, short QT syndrome, catecholaminergic polymorphic ventricular tachycardia); duplication/deletion gene analysis panel, must include analysis of at least 2 genes, including *KCNH2* and *KCNQ1* [when specified as testing for 4 or less genes, including KCNH2 and KCNQ1 (and SCN5A if performed) for LTQS only]

81479 Unlisted molecular pathology procedure [when specified as: *ACVRL1* (*activin A receptor like type 1)* for hereditary hemorrhagic telangiectasia type 2; *AGXT (Alanine--Glyoxylate And Serine--Pyruvate Aminotransferase)* (eg, primary hyperoxaluria type 1 [PH1]; *CACNA1S (calcium voltage-gated channel subunit alpha1 S)* for malignant hyperthermia; *COL3A1 (collagen type III alpha 1 chain)* for Ehlers-Danlos syndrome type 4; *FLNC (filamin C)* for dilated cardiomyopathy; *IL1RN (Interleukin 1 Receptor Antagonist); LDLRAP1 (low density lipoprotein receptor adaptor protein 1)* (eg. Familial hypercholesterolemia); *MAX (MYC associated factor X)* for hereditary paraganglioma-pheochromocytoma syndrome; *MOCS1 (molybdenum cofactor synthesis 1)* (eg, molybdenum cofactor deficiency); *PCSK1 (Proprotein Convertase Subtilisin/Kexin Type 1)* (obesity); *POMC (Proopiomelanocortin)* (eg, obesity); *SI (sucrase-isomaltase)* (eg, congenital sucrase-isomaltase deficiency); *SMAD3 (SMAD family member 3)* for Loeys-Dietz syndrome type 3; *TMEM127 (transmembrane protein 127)* for hereditary paraganglioma-pheochromocytoma syndrome; ***TRDN (triadin)*** (long QT Syndrome);*TTN (titin)* for DCM variants]

HCPCS

S3861	Genetic testing, sodium channel, voltage-gated, type V, alpha subunit (SCN5A) and variants for suspected Brugada syndrome
S3866	Genetic analysis for a specific gene mutation for hypertrophic cardiomyopathy (HCM) in an individual with a known HCM mutation in the family

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 when criteria are not met, or 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	*MTHFR (5,10-methylenetetrahydrofolate reductase)* (eg, hereditary hypercoagulability) gene analysis, common variants (eg, 677T, 1298C)
81324	*PMP22 (peripheral myelin protein 22)* (eg, Charcot-Marie-Tooth, hereditary neuropathy with liability to pressure palsies) gene analysis; duplication/deletion analysis
81325	*PMP22 (peripheral myelin protein 22)* (eg, Charcot-Marie-Tooth, hereditary neuropathy with liability to pressure palsies) gene analysis; full sequence analysis
81326	*PMP22 (peripheral myelin protein 22)* (eg, Charcot-Marie-Tooth, hereditary neuropathy with liability to pressure palsies) gene analysis; known familial variant
81328	*SLCO1B1 (solute carrier organic anion transporter family, member 1B1)* (eg, adverse drug reaction), gene analysis, common variant(s) (eg, *5)
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]: • *F2 (coagulation factor 2)* (eg, hereditary hypercoagulability), 1199G>A 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]: • *CFH/ARMS2 (complement factor H/age-related maculopathy susceptibility 2)* (eg, macular degeneration), common variants (eg, Y402H [CFH], A69S [ARMS2])
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]:
- *ANG (angiogenin, ribonuclease, RNase A family, 5)* (eg, amyotrophic lateral sclerosis), full gene sequence
- *GJB1 (gap junction protein, beta 1)* (eg, Charcot-Marie-Tooth X-linked), full gene sequence

81404 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]:
- *EGR2 (early growth response 2)* (eg, Charcot-Marie-Tooth), full gene sequence
- *HSPB1 (heat shock 27kDa protein 1)* (eg, Charcot-Marie-Tooth disease), full gene sequence
- *LITAF (lipopolysaccharide-induced TNF factor)* (eg, Charcot-Marie-Tooth), full gene sequence
- *SCN1B (sodium channel, voltage-gated, type 1, beta)* (eg, Brugada syndrome), full gene sequence

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]:
- *ANKRD1 (ankyrin repeat domain 1)* (eg, dilated cardiomyopathy), full gene sequence
- *GDAP1 (ganglioside-induced differentiation-associated protein 1)* (eg, Charcot-Marie-Tooth disease), full gene sequence
- *HTRA1 (HtrA serine peptidase 1)* (eg, macular degeneration), full gene sequence
- *MPZ (myelin protein zero)* (eg, Charcot-Marie-Tooth), full gene sequence
- *NEFL (neurofilament, light polypeptide)* (eg, Charcot-Marie-Tooth), full gene sequence
- *PRX (periaxin)* (eg, Charcot-Marie-Tooth disease), full gene sequence
- *PSEN1 (presenilin 1)* (eg, Alzheimer disease), full gene sequence
- *RAB7A (RAB7A, member RAS oncogene family)* (eg, Charcot-Marie-Tooth 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
- *CACNB2 (calcium channel, voltage-dependent, beta 2 subunit)* (eg, Brugada syndrome), full gene sequence
- *FIG4 (FIG4 homolog, SAC1 lipid phosphatase domain containing [S. cerevisiae])* (eg, Charcot-Marie-Tooth disease), full gene sequence

- *FUS (fused in sarcoma)* (eg, amyotrophic lateral sclerosis), full gene sequence
- *GARS (glycyl-tRNA synthetase)* (eg, Charcot-Marie-Tooth disease), full gene sequence
- *GRN (granulin)* (eg, frontotemporal dementia), full gene sequence
- *JUP (junction plakoglobin)* (eg, arrhythmogenic right ventricular dysplasia/ cardiomyopathy 11), full gene sequence
- *LDB3 (LIM domain binding 3)* (eg, familial dilated cardiomyopathy, myofibrillar myopathy), full gene sequence
- *MAPT (microtubule-associated protein tau)* (eg, frontotemporal dementia), full gene sequence
- *MFN2 (mitofusin 2)* (eg, Charcot-Marie-Tooth disease), full gene sequence
- *OPTN (optineurin)* (eg, amyotrophic lateral sclerosis), full gene sequence
- *PSEN2 (presenilin 2 [Alzheimer disease 4])* (eg, Alzheimer disease), full gene sequence
- *SH3TC2 (SHE domain and tetratricopeptide repeats 2)* (eg, Charcot-Marie-Tooth 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]:

- *MYH6 (myosin, heavy chain 6, cardiac muscle, alpha)* (eg, familial dilated cardiomyopathy), full gene sequence
- *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]:

- *ABCA4 (ATP-binding cassette, sub-family A [ABC1], member 4)* (eg, Stargardt disease, age-related macular degeneration), full gene sequence
- *ATM (ataxia telangiectasia mutated)* (eg, ataxia telangiectasia), full gene sequence

81479 Unlisted molecular pathology procedure [when specified as: *C2 (complement C2)* for AMD, *C3 (complement C3)* for AMD, C9orf72 PCR Fragment Analysis for frontotemporal dementia, *CFB (complement factor B)* for AMD, *F2 (coagulation factor 2)* (eg, hereditary hypercoagulability), C20209T or Yukuhashi variants, *KIF1B* (CMT2A1), *MED25* (CMT2B2), *TRPV4* (CMTC), *HSPB8* (CMT2L), *AARS* (CMT2N), *DYNC1H1* (CMT2O), or *LRSAM1* (CMT2P)]

0355U *APOL1 (apolipoprotein L1)* (eg, chronic kidney disease), risk variants (G1, G2) Apolipoprotein L1 (*APOL1*) Renal Risk Variant Genotyping, Quest Diagnostics®, Quest Diagnostics®

0378U *RFC1* (replication factor C subunit 1), repeat expansion variant analysis by traditional and repeat-primed PCR, blood, saliva, or buccal swab
UCGSL *RFC1* Repeat Expansion Test, University of Chicago Genetic Services Laboratories

HCPCS

S3800 Genetic testing for amyotrophic lateral sclerosis (ALS)

S3852	DNA analysis for APOE epsilon 4 allele for susceptibility to Alzheimer's disease
S3865	Comprehensive gene sequence analysis for hypertrophic cardiomyopathy

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]:

- *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.

- 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. The American College of Medical Genetics and Genomics

(ACMG) periodically issues a list of recommended genes for guidance in reporting secondary findings in the context of clinical exome and genome sequencing. The listed genes include associated research about utility related to specific genetic conditions. The following table contains genes from the latest ACMG listing, along with recommended usefulness for preconception/prenatal testing and testing that would impact clinical management for a particular disease or condition when applicable. For further information see: https://www.ncbi.nlm.nih.gov/clinvar/docs/acmg/. Accessed on October 19, 2022.

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
AARS	Charcot-Marie-Tooth 2N			
ABCA4	Stargardt disease, Age-related macular degeneration (AMD)			
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	√	√	
ACTA2	Aortic aneurysm, familial thoracic 6		√	
ACTC1	Familial hypertrophic cardiomyopathy (HCM) 11		√	ACMG, August 28, 2022
ACVRL1	Hereditary hemorrhagic telangiectasia type 2		√	ACMG, August 28, 2022
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			
ANKRD1	Dilated cardiomyopathy (DCM)			
ApoB	Familial hypercholesterolemia (principally APOB3500)		√	Evkeeza (evinacumab) ACMG, September 15, 2022

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
APOE ε4 (apolipoprotein E epsilon 4)	Late onset Alzheimer's disease			See Discussion section
APOL1	Chronic kidney disease			
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 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)	√	√	ACMG, Aug 12, 2022
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)	√		

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
ATXN3	Spinocerebellar ataxia type 3 (SCA3)	√		
ATXN7	Spinocerebellar ataxia type 7 (SCA7)	√		
ATXN8 (ATXN8OS)	Spinocerebellar ataxia type 8 (SCA8)	√		
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)*
BTD	Biotinidase deficiency	√	√	ACMG, Aug 12, 2022
C2	Age-related macular degeneration			
C3	Age-related macular degeneration			
CACNA1A	Spinocerebellar ataxia type 6 (SCA6)	√		
CACNA1S	Malignant hyperthermia		√	ACMG, August 28, 2022
CACNB2	Brugada syndrome			
CASQ2	Catecholaminergic polymorphic ventricular tachycardia, CPVT		√	ACMG, August 28, 2022
CDKL5	Cyclin-dependent kinase-like 5 (CDKL5) deficiency disorder (CDD)		√	FDA label for Ztalmy
CEL	Maturity-onset diabetes of the young (MODY)		√	
CFB	Age-related macular degeneration			
CFH/ARMS2	Complement factor H/age-related maculopathy susceptibility 2) (eg, macular degeneration)			
CFTR	Cystic fibrosis	√	√	ACOG # 690, (2017, reaffirmed 2019)*
CHD7	CHARGE syndrome	√	√	See Discussion section
CNBP	Myotonic dystrophy type 2	√	√	
COL3A1	Ehlers-Danlos syndrome, type 4		√	ACMG, August 28, 2022
CPOX	Hereditary coproporphyria		√	

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
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
C9orf72	Frontotemporal Dementia (FTD)			
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	√	√	
DSC2	Arrhythmogenic right ventricular cardiomyopathy (ARVC), type 11		√	ACMG, Aug 12, 2022
DSG2	ARVC, type 10		√	ACMG, Aug 12, 2022
DSP	ARVC, type 8		√	ACMG, Aug 12, 2022
DYNC1H1	Charcot-Marie-Tooth 2O			
EGR2	Charcot-Marie-Tooth			
EIF2B5	Childhood ataxia with central nervous system hypomyelination/Vanishing white matter	√		
ELP1	Familial Dysautonomia	√	√	ACOG # 690, (2017, reaffirmed 2019)*
ENG	Hereditary hemorrhagic telangiectasia type 1		√	ACMG, August 28, 2022
F2, G20210A	Hereditary thrombophilia		√	
F5	Factor V Leiden thrombophilia		√	
FANCC	Fanconi anemia type C	√	√	ACOG # 690, (2017, reaffirmed 2019)*
FBN1	Marfan's syndrome		√	ACMG, August 28, 2022

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
FIG4	Charcot-Marie-Tooth			
FLNC	DCM		√	ACMG, August 28, 2022
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)) ACMG, August 5, 2022
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)
GCK	MODY		√	
GDAP1	Charcot-Marie-Tooth			
GJB1	Charcot-Marie-Tooth X-linked			
GJB2	Nonsyndromic Hearing Loss and Deafness, (DFNB1)	√		
GLA	Fabry disease	√	√	ACMG, September 6 2022
GRN	FTD			
HADHA or HADHB	Trifunctional protein (TFP) deficiency or Long-chain 3-hydroxyacylCoA dehydrogenase (LCHAD) deficiency	√	√	
HBA1	Alpha-thalassemia	√	√	
HBA2	Alpha thallasemia	√	√	ACOG # 690, (2017, reaffirmed 2019)*
HBB	Beta thalassemia	√	√	ACOG # 690, (2017, reaffirmed 2019)*

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
HBB	Sickle cell disease	√	√	ACOG # 690, (2017, reaffirmed 2019)*
HEXA	Tay-Sachs disease	√		ACOG # 690, (2017, reaffirmed 2019)*
HFE	Hemachromatosis	√	√	ACMG, August 28, 2022
HMBS	Acute intermittent porphyria		√	
HNF1A	MODY		√	ACMG, August 28, 2022
HNF1B	MODY		√	
HNF4A	MODY		√	
HSPB1	Charcot-Marie-Tooth			
HSPB8	Charcot-Marie-Tooth 2L			
HTRA1	Macular degeneration			
HTT	Huntington disease	√		
IKBKAP	Familial dysautonomia	√	√	
IL1RN mutations	Deficiency of Interleukin-1 Receptor Antagonist (DIRA)		√	Arcalyst (rilonacept) Kineret (anakinra)
ITPR1	Spinocerebellar ataxia type 15 (SCA15)	√		
JAG1/JAGGED1	Alagille syndrome	√	√	Livmarli (maralixibat)
JUP	ARVC/cardiomyopathy 11			
KCNC3	Spinocerebellar ataxia type 13	√		
KCNH2	Long QT syndrome 2		√	ACMG, August 28, 2022
KCNQ1	Long QT syndrome 1		√	ACMG, August 28, 2022
KIF1B	Charcot-Marie-Tooth 2A1			
LDB3	Familial DCM, myofibrillar myopathy			
LDLR	Familial hypercholesterolemia (LDL) receptor (sometimes called the apoB/E receptor) homozygous		√	Evkeeza (evinacumab) ACMG, September 6, 2022
LDLRAP1 (ARH adaptor)	Familial hypercholesterolemia		√	Evkeeza (evinacumab)
LITAF	Charcot-Marie-Tooth			
LMNA	DCM 1A		√	ACMG, August 28, 2022
LRSAM1	Charcot-Marie-Tooth 2P			
MAPT	FTD			

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
MAX	Hereditary paraganglioma-pheochromocytoma syndrome		√	ACMG, August 28, 2022
MCOLN1	Mucolipidosis	√		ACOG # 690, (2017, reaffirmed 2019)*
MECP2	Rett syndrome	√		
MED25	Charcot-Marie-Tooth 2B2			
MFN2	Charcot-Marie-Tooth			
MOCS1	Molybdenum cofactor deficiency (MoCD) type A		√	Nulibry (fosdenopterin)
MPZ	Charcot-Marie-Tooth			
MTHFR C677T, A1286C and A1298C	Inherited thrombophilia			
MVK	Hyperimmunoglobulin D syndrome (HIDS)/Mevalonate kinase deficiency (MKD)	√	√	
MYBPC3	HCM 4, DCM 1A		√	ACMG, August 28, 2022
MYH6	Familial DCM			
MYH7	Familial HCM 1		√	ACMG, August 28, 2022
MYH11	Marfan syndrome, Loeys-Dietz syndromes, and familial thoracic aortic aneurysm 4 and dissections	√	√	ACMG, September 6, 2022
MYL2	Familial HCM 10		√	ACMG, August 28, 2022
MYL3	Familial HCM 8		√	ACMG, August 28, 2022
MYO5B	Progressive familial intrahepatic cholestasis	√	√	Bylvay (odevixibat)
NEFL	Charcot-Marie-Tooth			
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			
OTC	Ornithine carbamoyltransferase deficiency	√	√	ACMG, August 28, 2022

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
PABPN1	Oculopharyngeal muscular dystrophy (also known as OPMD)	√		
PAH	Phenylalanine hydroxylase deficiency	√	√	ACOG # 690, (2017, reaffirmed 2019)*
PCSK9	Familial hypercholesterolemia		√	Evkeeza (evinacumab) ACMG, September 10, 2022
PDX1	MODY		√	
PIK3CA	PIK3CA-Related Overgrowth Spectrum (PROS)		√	FDA label for Vijoice
PKP2	ARVC, type 9		√	ACMG, Aug 12, 2022
PLN	Familial HCM		√	
PMP22	CMT			
POMC, PCSK1, LEPR deficiency;	Obesity caused by POMC, PCSK1, or LEPR deficiency		√	FDA label for Imcivree (setmelanotide)
PPOX	Variegate porphyria		√	
PPP2R2B	Spinocerebellar ataxia type 12 (SCA12)	√		
PRKAG2	Familial HCM 6		√	ACMG, August 28, 2022
PRKCG	Spinocerebellar ataxia type 14 (SCA14)	√		
PRSS1	Protease, serine, 1 (trypsin 1), hereditary pancreatitis		√	In children, when testing renders additional invasive diagnostic testing unnecessary
PRX	Charcot-Marie-Tooth			
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)	√	√	
RAB7A	Charcot-Marie-Tooth			
RAI1 or deletion of 17p11.2	Smith-Magenis syndrome		√	FDA label for Hetlioz (tasimelteon)

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
RFC1	replication factor C subunit 1; CANVAS syndrome			
RPE65	Hereditary retinal dystrophy	√	√	Also see MED.00120 Gene Therapy for Ocular Conditions ACMG, September 4, 2022
RYR1	Malignant hyperthermia		√	ACMG, August 28, 2022
RYR2	Catecholaminergic polymorphic ventricular tachycardia (CPVT)		√	ACMG, August 28, 2022
SCN1B	Brugada syndrome			
SCN5A	Brugada 1, long QT syndrome 3		√	ACMG, August 28, 2022
SI	Congenital sucrase-isomaltase deficiency (CSID)		√	Sucraid (sacrosidase)
SERPINA1	Alpha-1 antitrypsin deficiency (AATD)		√	
SETX	Ataxia with Oculomotor Apraxia Type 2	√		
SH3TC2	Charcot-Marie-Tooth			
SIL1	Marinesco-Sjögren syndrome	√		
SLC37A4	Glycogen Storage Disease type Ib	√	√	
SLCO1B1	Statin-induced myopathy			
SMAD3	Loeys-Dietz syndrome type 3		√	ACMG, August 28, 2022
SMN-1	Spinal muscular atrophy	√	√	ACOG # 690, (2017, reaffirmed 2019)*
SMPD1	Acid Sphingomyelinase Deficiency (Niemann-Pick disease type B)	√	√	ACOG # 690, (2017, reaffirmed 2019)* Olipudase alfa
SNRPN	Prader-Willi syndrome	√	√	
SPINK1	Serine peptidase inhibitor, Kazal type 1, hereditary pancreatitis		√	In children, when testing renders additional invasive diagnostic testing unnecessary
SOD1	Amyotrophic lateral sclerosis (ALS, Lou Gehrig's disease)		√	Qalsody (tofersen) injection, FDA approval April 2023
SPTBN2	Spinocerebellar ataxia type 5 (SCA5)	√		

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
TARDBP	Amyotrophic lateral sclerosis			
TBP	Spinocerebellar ataxia type 17 (SCA17)	√		
TGFBI	Corneal dystrophy	√		
TGFBR1	Marfan syndrome, Loeys-Dietz syndrome types 1A, 2A, and familial thoracic aortic aneurysms and dissections	√	√	ACMG, August 28, 2022
TGFBR2	Marfan syndrome, Loeys-Dietz syndrome types 1B, 2B, and familial thoracic aortic aneurysms and dissections	√	√	ACMG, August 28, 2022
TJP2	Progressive familial intraphepatic cholestasis	√	√	Bylvay (odevixibat)
TMEM43	ARVC type 5		√	ACMG, August 28, 2022
TMEM127	Hereditary paraganglioma-pheochromocytoma syndrome		√	ACMG, August 28, 2022
TNN13	Familial HCM 7		√	ACMG, August 28, 2022
TNNC1	HCM, DCM		√	
TPM1	Familial HCM 3		√	ACMG, August 28, 2022
TPP1	Infantile neuronal cord lipofuscinosis type 2	√	√	
TRDN	Long QT syndrome		√	ACMG, August 28, 2022
TRPV4	Charcot-Marie-Tooth C			
TSC1	Tuberous sclerosis 1		√	ACMG, August 28, 2022
TSC2	Tuberous sclerosis 2		√	ACMG, August 28, 2022
TTN	DCM, truncating variants only		√	ACMG, August 28, 2022
TTPA	Ataxia with vitamin E deficiency	√	√	
TTR	Hereditary transthyretin amyloidosis		√	Amvuttra (vutrisiran)
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 (Return to Clinical Indications)

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. In 2017, the American College of Obstetricians and Gynecologists (ACOG) Committee on Genetics issued its Committee Opinion No. 691 on carrier screening for genetic conditions, in which ACOG recommended, "If an individual is found to be a carrier for a specific condition, the patient's reproductive partner should be offered testing in order to receive informed genetic counseling about potential reproductive outcomes" (ACOG, 2017[b]).

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, ACOG and the ACMG recommend carrier screening for: Tay-Sach's disease, Canavan disease, mucolipidosis 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 (TARDP), 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 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.

> In April 2023 the FDA approved Qalsody™ (tofersen) injection (Biogen Inc., Cambridge, MA) for intrathecal use for the following indication: Qalsody is indicated for the treatment of amyotrophic lateral sclerosis (ALS) in adults who have a mutation in the superoxide dismutase 1 (SOD1) gene. This indication is approved under accelerated approval based on reduction in plasma neurofilament light chain (NfL) observed in patients treated with Qalsody. Continued approval for this indication may be contingent upon verification of clinical benefit in confirmatory trial(s).

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 ΔF508 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, ΔF508, 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 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 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 Creating 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.

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 CADSIL have been identified. Additional variants found on the NOTCH3 gene are of unknown significance at this time (Chabriat, 2009; Donahue, 2004; Lesnick Oberstein, 2003).

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.

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.

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, 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 (Aβ) peptide and neurofibrillary tangles (NFTs) comprised of tau protein in the brain. At present, a definitive diagnosis of AD requires postmortem verification of Aβ 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 Aβ 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 Aβ 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 ε4 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.

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:
I = 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%).

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.

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.

Inherited Peripheral Neuropathies
Charcot-Marie-Tooth (CMT) disease is actually a group of inherited neuropathies characterized classically by distal sensory loss and weakness, abnormal deep tendon reflexes, and skeletal abnormalities. The majority of inherited polyneuropathies are variants of CMT disease. The clinical phenotype of CMT is highly variable, ranging from minimal neurological findings to the classic picture with pes cavus and "stork legs" to a severe polyneuropathy with respiratory failure. More than 40 genes associated with CMT have been described, including autosomal dominant, autosomal recessive, X-linked dominant, and X-linked recessive forms. CMT type 1 (CMT1) is a demyelinating peripheral neuropathy characterized by progressive peripheral motor and sensory neuropathy, slow nerve conduction velocity, and enlarged nerves. CMT1 accounts for approximately 50% of all CMT. There are five genes that are currently associated with CMT1:

1. peripheral myelin protein 22 (PMP22; CMT1A [common duplication] and CMT1E [point variants]);
2. myelin protein zero (MPZ; CMT1B);
3. lipopolysaccharide-induced tumor necrosis factor-alpha factor (LITAF; CMT1C);
4. early growth response 2 (EGR2; CMT1D); and
5. neurofilament protein, light polypeptide (NEFL; CMT1F).

CMT1A accounts for 70% to 80% of CMT1, while CMT1B accounts for 5% to 10%; CMT1E and CMT1F each account for less than 5% of cases, and CMT1C and CMT1D each account for less than 2% of identified cases. Clinical genetic testing for CMT1 is available from several laboratories in the United States. The most commonly available genetic test is for the common 1.5-megabase duplication of the PMP22 gene associated with CMT1A, which is performed using fluorescence in situ hybridization (FISH) or molecular methods. Genetic testing is also available from some laboratories for PMP22 point variants (CMT1E) and variants in EGR2, LITAF, MPZ, and NEFL by direct DNA sequencing.

The American Academy of Neurology (AAN), American Association of Neuromuscular and Electrodiagnostic Medicine (AANEM), and the American Academy of Physical Medicine and Rehabilitation (AAPMR) published an evidence-based review addressing the role of laboratory and genetic tests in the evaluation of distal symmetric

polyneuropathies (England, updated 2022). This review determined that genetic testing is established as "Useful" for the accurate diagnosis and classification of hereditary polyneuropathies in individuals with a cryptogenic polyneuropathy who exhibit a classical hereditary neuropathy phenotype (Level A). This review also determined that genetic testing "May be considered" in subjects with cryptogenic polyneuropathy who exhibit a hereditary neuropathy phenotype (Level C). The guideline recommends that initial genetic testing should be guided by the clinical phenotype, inheritance pattern, and electrodiagnostic (EDX) features and should focus on the most common abnormalities which are CMT1A duplication/HNPP deletion, Cx32 (GJB1), and MFN2 mutation screening. However, the authors also concluded that there is insufficient evidence to determine the usefulness of routine genetic testing in cryptogenic polyneuropathy that does not exhibit a hereditary neuropathy phenotype (Level U) (England, 2009). The authors of this guideline did not describe how the results of the genetic tests would be used to improve patient-specific clinical outcomes. The likelihood that genetic testing for the inherited peripheral neuropathies will alter treatment management is low because the diagnosis of an inherited peripheral neuropathy can generally be made clinically, and there is no specifically designated treatment strategy based on the genetic phenotype. As such, the clinical utility of a genetic confirmation of these disorders has not been demonstrated in the peer-reviewed literature at this time.

Currently, treatment for CMT is generally symptomatic, including pain management, exercise, and orthotics or orthopedic surgery for severe foot and ankle problems. For this reason, confirming a molecular diagnosis of CMT does not affect the course of treatment for this disease.

Long QT Syndrome and other Channelopathies
Congenital long QT syndrome (LQTS) is an inherited phenotypic disorder characterized by the lengthening of the repolarization phase of the ventricular action potential (an abnormally long QT interval seen on electrocardiographic [EKG] tracings) and polymorphic ventricular tachycardia, which may lead to syncope and sudden cardiac death (SCD). Diagnostic criteria for LQTS have been established which focus on EKG findings, as well as clinical and family history. LQTS can be primary, when inherited or genetic, or secondary, when precipitated by numerous drugs, structural cardiac disease and other clinical conditions. Primary or congenital/inherited LQTS has been associated with hundreds of mutations in more than 10 genes that affect ion channels contributing to the cardiac action potential. Disorders resulting from ion channel dysfunction are known as channelopathies. Approximately 75% of individuals presenting with LQTS have an identifiable gene mutation (Ackerman, 2011). Congenital LQTS usually manifests before the age of 40 and may be suspected when there is a history of seizure, syncope, or SCD in a child or young adult with a prolonged QT interval, in the absence of structural cardiac disease. This may prompt genetic analysis to identify the presence of genetic mutations associated with cardiac channelopathies. A history of these occurrences or the confirmation of a gene mutation associated with cardiac channelopathies in a first-degree relative may prompt diagnostic scrutiny of other family members.

The European Society of Cardiology Task Force on Sudden Cardiac Death first published a guidance document in 2001 (Priori, et al) referring to genetic defects on one specific cardiac sodium channel gene (LQT3), which are associated with higher risk for SCD in LQTS. Subsequent research has identified specific sequence variants associated with LQTS. Migdalovich correlated gender-specific risks for adverse cardiac events with the specific location of mutations (pore-loop vs. non-pore-loop) on the KCNH2 gene in 490 males and 676 females with LQTS. They reported that males with pore-loop mutations had a greater risk of adverse events (hazard ratio [HR], 2.18; p=0.01) than males without pore-loop mutations but that this association was not present in females. Albert examined genetic profiles from 516 cases of LQTS included in six prospective cohort studies. The authors identified 147 sequence variations found in five specific cardiac ion channel genes and tested the association of

these variations with SCD. Two common intronic variations, one in the KCNQ1 gene and one in the SCN5A gene, were most strongly associated with SCD in individuals of European ancestry. This research suggests that combined assessments of the individual's clinical information and mutation-specific data from a known proband may be used for improved risk stratification of individuals considered at risk for life threatening cardiac events related to LQTS (Albert, 2010; Migdalovich, 2011). At least 12 types of LQTS have been identified, varying in part based on their effect on the action potential, ion channel and genotype. There are three major types of LQTS: LGT1, LGT2 and LGT3, accounting for OVER 90% of LQTS (Schwartz, 2001). Gene specific therapy recommendations have been developed and gene testing can contribute to treatment choice (Ruan, 2008).

In 2011, a Heart Failure Society of America/European Heart Rhythm Association (HRS/EHRA) Consensus Statement on the State of Genetic Testing for Channelopathies and Cardiomyopathies was issued (Ackerman, 2011) which included the following guidance:

- A Class I recommendation ("is recommended") was applied for genetic testing in index cases with a sound clinical suspicion for the presence of a channelopathy or a cardiomyopathy when the positive predictive value of a genetic test is high (likelihood of positive result > 40% and signal/noise ratio > 10 AND/OR when the genetic test result provides either diagnostic or prognostic information, or when the genetic test result influences therapeutic choices);
- Screening of family members for the mutation identified in the proband of the family is recommended as a Class I recommendation when genetic testing leads to the adoption of therapy/protective measures/lifestyle adaptations;
- Conversely, the authors have assigned a Class IIa recommendation when results of genetic testing are not associated with the use of therapeutic or protective measures but the results may be useful for reproductive counseling or instances in which genetic testing is requested by the patient who wants to know his/her mutation status.

Regarding other channelopathies, such as short QT syndrome (SQTS) and Brugada syndrome (BrS), there are molecular genetic tests available for the targeted gene variants most commonly associated with these conditions. However, the low prevalence of these rare conditions and confounding factors, such as varying penetrance, genotype-phenotypic profiles, and risk stratification have resulted in inadequate data to demonstrate the clinical utility, validity, and sensitivity of this testing, to date.

Genetic testing has been proposed to determine an individual's predisposition to hypertrophic cardiomyopathy (HCM) among those persons considered to be at risk, due to confirmed HCM in a close family member. Familial HCM is the most common hereditary cardiac condition in the U.S. and is thought to be the most common cause of sudden cardiac death (SCD) in young athletes and others 35 years of age and younger. Developments in the field of genetic testing have led to identification of specific genetic mutations that are associated with high risk for HCM. Proponents of this testing suggest that identification of these mutations in at risk individuals may lead to improved clinical outcomes.

In 2020, the ACC/AHA issued an updated Guideline for the Diagnosis and Treatment of patients with Hypertrophic Cardiomyopathy, which is considered a full guideline revision intended to replace the former Gersh, 2011 guideline. This document provides a comprehensive guide to the evaluation and management of HCM in adults and

children, which is based on the current evidence, including relevant studies and other specialty society guidelines. This document provided the following Class I recommendations for genetic testing (with Evidence Level: B):

- In patients with HCM, evaluation of familial inheritance, including a 3-generation family history, is recommended as part of the initial assessment;
- In patients with HCM, genetic testing is beneficial to elucidate the genetic basis to facilitate the identification of family members at risk for developing HCM (cascade testing);
- In patients with an atypical clinical presentation of HCM or when another genetic condition is suspected to be the cause, a work-up including genetic testing for HCM and other genetic causes of unexplained cardiac hypertrophy ("HCM phenocopies") is recommended;
- In patients with HCM who choose to undergo genetic testing, pre- and post-test genetic counseling by an expert in the genetics of cardiovascular disease is recommended so that risks, benefits, results, and their clinical significance can be reviewed and discussed with the patient in a shared decision-making process;
- When performing genetic testing in an HCM proband, the initial tier of genes tested should include genes with strong evidence to be disease-causing in HCM (which currently includes MYH7, MYBPC3, TNNI3, TNNT2, TPM1, MYL2, MYL3, and ACTC1);
- In first-degree relatives of patients with HCM, both clinical screening (ECG and 2D echocardiogram) and cascade genetic testing (when a pathogenic/likely pathogenic variant has been identified in the proband) should be offered;
- In families where a sudden unexplained death has occurred with a postmortem diagnosis of HCM, postmortem genetic testing is beneficial to facilitate cascade genetic testing and clinical screening in first-degree relatives;
- In patients with HCM who have undergone genetic testing, serial reevaluation of the clinical significance of the variant(s) identified is recommended to assess for variant reclassification, which may impact diagnosis and cascade genetic testing in family members;
- In affected families with HCM, preconception and prenatal reproductive and genetic counseling should be offered (Ommen, 2020).

The high negative predictive value of genetic testing for HCM can be used to reduce follow-up screening in individuals who have a first degree relative with clinical findings of HCM and a genetic test which has strong evidence for pathogenicity when the individual being tested has no evidence of HCM. However, even an individual with a negative test can develop clinical disease due to, as yet, unidentified gene variants and de novo variants. For this reason, genetic counseling is necessary to make sure any individual to be tested understands the implications of the test and the uncertainty that often remains after the results are known. The positive predictive value of genetic testing for HCM remains of uncertain clinical value and the diagnostic utility of a positive result remains uncertain. More comprehensive evidence across different population groups and in larger numbers of individuals will continue to inform the practice community about the role of genetic testing, particularly in the heritable cardiomyopathies (Maron, 2012).

Frontotemporal Dementia (FTD)
FTD is a degenerative condition characterized by focal atrophy of the frontal and anterior temporal lobes of the brain. It differs from other causes of dementia, such as Alzheimer's, Lewy Body and Creutzfeldt Jakob's diseases. FTD, formerly known as Pick's disease, represents a clinically, neuropathologically and genetically heterogeneous

group of progressive non-Alzheimer dementias characterized by progressive atrophy of the frontal and anterior temporal lobes of the brain. These neurodegenerative changes result in behavioral and language disturbances in the presence of intact memory and visuospatial functions. Three causative genes account for more than 80% of cases of FTD in families with a strong autosomal dominant family history: (microtubule-associated-protein-tau (MAPT), progranulin (PGRN), and chromosome 9 open reading frame 72 (C9orf72). Other possible causes of FTD which are being investigated include, but are not necessarily limited to, the valosin-containing protein (VCP), TAR DNA binding protein (TDP-43), charged multivesicular body protein 2B (CHMP2B), fused in sarcoma protein (FUS), presenilin-1 (PSEN1) and leucine-rich repeat kinase (Lrrk2).

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Statin-induced Myopathy
Statin drugs are the primary pharmacologic treatment for hypercholesterolemia and coronary artery disease (CAD) worldwide. Their use is associated with an approximate 30% reduction in cardiovascular events and they are the most commonly prescribed medications in the United States. It has been reported in clinical trials that 1% to 5% of subjects develop statin-associated muscle pain (myalgia), with approximately 1 in 1000 experiencing muscle degradation (myopathy), and 1.6 in 100,000 suffering from severe muscle damage with associated acute kidney injury (rhabdomyolysis). Myositis is much less common than myalgia, with an estimated per-person incidence of 0.01%. These complications have been reported to negatively impact compliance, tolerability, and quality of life (QOL) in individuals taking statins (Harper, 2010; Ramsey, 2014; Stone, 2012).

Genetic factors appear to increase the risk of statin-induced myopathy in certain populations. Clinical studies have demonstrated a statistical association between statin-induced myopathy and specific variations in the SLCO1B1 gene. Additional studies have demonstrated that individuals who have inherited variations on the SLCO1B1 gene are significantly more likely to suffer myopathy as a side effect of statin medications. Inherited variations in the SLCO1B1 gene may result in reduced effectiveness of statin therapy and increased risk of myopathy. In particular, a genome-wide association study demonstrated that common variants of the SLCO1B1 gene significantly increased or decreased the risk of myopathy in individuals treated with simvastatin (Stewart, 2013).

The body of evidence regarding the use of genetic testing to assess the risk of statin-induced myopathy is sparse and of low quality. In particular, studies that evaluate the clinical validity and clinical utility of genetic testing for statin-induced myopathy are lacking. In 2018, the American College of Cardiology (ACC) and American Heart Association (AHA) in conjunction with several other professional organizations (Grundy, 2019) published updated clinical guidelines for the management of high blood cholesterol and related disorders. The guidelines recommended statin therapy as primary prevention for individuals with severe hypercholesterolemia and in adults

40 to 75 years of age with either diabetes mellitus or at higher atherosclerotic cardiovascular disease (ASCVD) risk. Throughout the guidelines, consistent attention is given to a clinician-patient risk discussion for making shared decisions regarding statin therapy. The guidelines do not include genotype testing as a recommendation for consideration in determining the safety and efficacy of statin-based therapy.

Definitions (Return to Clinical Indications)

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).

Arrhythmogenic right ventricular dysplasia/cardiomyopathy (ARVD/C): This is a myocardial disorder that predominantly affects the right ventricle. ARVD/C is a progressive disorder characterized by fibro-fatty replacement of the myocardium (heart muscle), which predisposes affected individuals to ventricular tachycardia and sudden death commonly in young persons and athletes. The pathology in ARVD/C may also extend to involve the left ventricle

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.

Catecholaminergic polymorphic ventricular tachycardia (CPVT): An inherited cardiac channelopathy characterized by irregular heart rhythms brought on by physical exertion or intense emotion. CPVT may cause syncope (fainting), cardiac arrest, or SCD in affected individuals, resulting from a gene mutation.

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,

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.
The National Human Genome Research Institute of the National Institutes of Health (NIH) defines the following terms in the context of potential transmission of inherited conditions associated with genetic mutations as follows:

- First-degree relative: Any relative who shares approximately 50% of an individual's genetic material, such as an individual's parent (father or mother), full sibling (brother or sister), or offspring.
- Second-degree relative: Any relative who shares approximately 25% of an individual's genetic material, such as an individual's grandparent, grandchild, uncle, aunt, niece, nephew, or half-sibling.
- Third-degree relative: Any relative who shares approximately 12.5% of an individual's genetic material, such as an individual's first cousin, great grandparent, great grandchild, great uncle, great aunt, half-uncle, half-aunt, half-niece, or half-nephew.

Frontotemporal dementia (FTD): 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.

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.

Hereditary neuropathy with liability to pressure palsies (HNPP): A neuromuscular disorder associated with deletions of the PMP22 gene.

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. 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.

Hypertrophic cardiomyopathy (HCM): This myocardial disorder is caused by mutation in one of the genes currently known to encode different components of the sarcomere. The disorder is characterized by left ventricular hypertrophy (LVH) in the absence of predisposing cardiac conditions, (for example, aortic stenosis) or cardiovascular conditions, (for example, long-standing hypertension). The clinical manifestations of HCM range from asymptomatic to progressive heart failure to sudden cardiac death and vary from individual to individual even within the same family. Common symptoms include shortness of breath (particularly with exertion), chest pain, palpitations, orthostasis, presyncope, and syncope. Most often the LVH of HCM becomes apparent during adolescence or young adulthood, although it may also develop late in life, in infancy, or in childhood.

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

Maturity-Onset Diabetes of the Young (MODY): A rare group of inherited diabetes conditions that occurs due to a primary defect in pancreatic beta cell function. It is inherited in an autosomal dominant pattern. Three genes are responsible for 90% of cases which are HNF1A, HNF4A and GCK. Symptoms usually present before the age of 25.

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.

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.

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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
	05/25/2023	Updated Discussion section and table of genes to address newly approved Qalsody and the *SOD1* gene variant. Updated Coding section for gene *SOD1* tier 2 code 81404, to be considered MN when criteria are met.
	03/29/2023	Updated Coding section with 04/01/2023 CPT changes, added 0378U; also added gene RFC1 to gene table in Discussion section.
Revised	11/10/2022	Medical Policy & Technology Assessment Committee (MPTAC) review. Additional genes have been added to the table, including those identified as medically actionable by ACMG recommendations, drug-related genes for Amvuttra (vutrisiran) and Olipudase alfa and genes associated with Maturity-Onset Diabetes of the Young (MODY). A revision was made to the medically necessary criteria for preconception or prenatal genetic screening of a parent or prospective parent Criterion C based on family history to add: "or one parent or prospective parent is a known carrier of." The Discussion, Definitions, Index and Reference sections were updated. Content of the following documents have been moved into this document with no change to stance: CG-GENE-23 Genetic Testing for Heritable Cardiac Conditions; GENE.00033 Genetic Testing for Inherited Peripheral Neuropathies; GENE.00037 Genetic Testing for Macular Degeneration (partial content); GENE.00038 Genetic Testing for Statin-induced Myopathy; GENE.00039 Genetic Testing for Frontotemporal Dementia (FTD). Updated Coding section to add codes 81324, 81325, 81326, 81328, 81414, S3861, S3865, S3866 and genes to Tier 2 codes and NOC code from the incorporated documents listed above; added additional genes to Tier 2 codes and NOC code and updated with 01/01/2023 CPT changes to add 0355U..
	10/05/2022	Updated table of genes in Discussion section to add CDKL5 and PIK3CA; updated Coding section, added 81309 and genes to Tier 2 codes 81405, 81406.
Reviewed	02/17/2022	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 codes, including those previously addressed in GENE.00003 and CG-GENE-09.

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 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.