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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, or a disorder with variable penetrance.

Notes:

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

- CG-GENE-08 Genetic Testing for PTEN Hamartoma Tumor Syndrome
- 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~~inherited~~ 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~~inherited~~ 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 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~~inherited~~ 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~~inherited~~ 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

	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:

This Clinical UM Guideline is intended to provide assistance in interpreting Healthy Blue's standard Medicaid benefit plan. When evaluating insurance coverage for the provision of medical care, federal, state and/or contractual requirements must be referenced, since these may limit or differ from the standard benefit plan. In the event of a conflict, the federal, state and/or contractual requirements for the applicable benefit plan coverage will govern. Healthy Blue reserves the right to modify its Policies and Guidelines as necessary and in accordance with legal and contractual requirements. This Clinical UM Guideline is provided for informational purposes. It does not constitute medical advice. Healthy Blue may also use tools and criteria developed by third parties, to assist us in administering health benefits. Healthy Blue's Policies and Guidelines are intended to be used in accordance with the independent professional medical judgment of a qualified health care provider and do not constitute the practice of medicine or medical advice.

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, mytonic 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)
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]: • *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 • *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
- *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

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: *AC9DVL*, *GBE1 (1,4-alpha-glucan branching enzyme 1)* (eg. glycogen storage disease); *ELP1 (elongator complex protein 1)* (eg, familial dysautonomia), *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
81331	*SNRPN/UBE3A (small nuclear ribonucleoprotein polypeptide N and ubiquitin protein ligase E3A)* (eg, Prader-Willi syndrome and/or Angelman syndrome), methylation analysis
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
- *UBE3A* (ubiquitin protein ligase E3A) (eg, Angelman syndrome), full gene sequence

81407 Molecular pathology procedure, Level 8 (eg, analysis of 26-50 exons by DNA sequence analysis, mutation scanning or duplication/deletion variants of >50 exons, sequence analysis of multiple genes on one platform) [when specified as the following]:

- *AGL (amylo-alpha-1, 6-glucosidase, 4-alpha-glucanotransferase)* (eg, glycogen storage disease type III), full gene sequence

81408 Molecular pathology procedure, Level 9 (eg, analysis of >50 exons in a single gene by DNA sequence analysis) [when specified as the following]:

- *ITPR1 (inositol 1,4,5-triphosphate receptor, type 1)* (eg, spinocerebellar ataxia), full gene sequence

0230U *AR (androgen receptor)* (eg, spinal and bulbar muscular atrophy, Kennedy disease, X chromosome inactivation), full sequence analysis, including small sequence changes in exonic and intronic regions, deletions, duplications, short tandem repeat (STR) expansions, mobile element insertions, and variants in non-uniquely mappable regions Genomic Unity® AR Analysis, Variantyx Inc, Variantyx Inc

0231U *CACNA1A (calcium voltage-gated channel subunit alpha 1A)* (eg, spinocerebellar ataxia), full gene analysis, including small sequence changes in exonic and intronic regions, deletions, duplications, short tandem repeat (STR) gene expansions, mobile element

	insertions, and variants in non-uniquely mappable regions Genomic Unity® CACNA1A Analysis, Variantyx Inc, Variantyx Inc
0232U	*CSTB (cystatin B)* (eg, progressive myoclonic epilepsy type 1A, Unverricht-Lundborg disease), full gene analysis, including small sequence changes in exonic and intronic regions, deletions, duplications, short tandem repeat (STR) expansions, mobile element insertions, and variants in non-uniquely mappable regions Genomic Unity® CSTB Analysis, Variantyx Inc, Variantyx Inc
0233U	*FXN (frataxin)* (eg, Friedreich ataxia), gene analysis, including small sequence changes in exonic and intronic regions, deletions, duplications, short tandem repeat (STR) 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:

~~Federal and State law, as well as contract language, and Medical Policy take precedence over Clinical UM Guidelines. We reserve the right to review and update Clinical UM Guidelines periodically. Clinical guidelines approved by the Medical Policy & Technology Assessment Committee are available for general adoption by plans or lines of business for consistent review of the medical necessity of services related to the clinical guideline when the plan performs utilization review for the subject. Due to variances in utilization patterns, each plan may choose whether to implement a particular Clinical UM Guideline. To determine if review is required for this Clinical UM Guideline, please contact the customer service number on the member's card.~~

~~Alternatively, commercial or FEP plans or lines of business which determine there is not a need to adopt the guideline to review services generally across all providers delivering services to Plan's or line of business's members may instead use the clinical guideline for provider education and/or to review the medical necessity of services for any provider who has been notified that his/her/its claims will be reviewed for medical necessity due to billing practices or claims that are not consistent with other providers, in terms of frequency or in some other manner.~~

This Clinical UM Guideline is intended to provide assistance in interpreting Healthy Blue's standard Medicaid benefit plan. When evaluating insurance coverage for the provision of medical care, federal, state and/or contractual requirements must be referenced, since these may limit or differ from the standard benefit plan. In the event of a conflict, the federal, state and/or contractual requirements for the applicable benefit plan coverage will govern. Healthy Blue reserves the right to modify its Policies and Guidelines as necessary and in accordance with legal and contractual requirements. This Clinical UM Guideline is provided for informational purposes. It does not constitute medical advice. Healthy Blue may also use tools and criteria developed by third parties, to assist us in administering health benefits. Healthy Blue's Policies and Guidelines are intended to be used in accordance with the independent professional medical judgment of a qualified health care provider and do not constitute the practice of medicine or medical advice.

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

Other gene testing of individuals:
When services may be Medically Necessary when criteria are met:

CPT	
81240	*F2 (prothrombin, coagulation factor II)* (eg, hereditary hypercoagulability) gene analysis, 20210G>A variant
81332	*SERPINA1 (serpin peptidase inhibitor, clade A, alpha-1 antiproteinase, antitrypsin, member 1)* (eg, alpha-1-antitrypsin deficiency), gene analysis, common variants (eg, *S and *Z)
81401	Molecular pathology procedure, Level 2 (eg, 2-10 SNPs, 1 methylated variant, or 1 somatic variant [typically using nonsequencing target variant analysis], or detection of a dynamic mutation disorder/triplet repeat) [when specified as the following]: • *APOB (apolipoprotein B)* (eg, familial hypercholesterolemia type B), common variants (eg, R3500Q, R3500W)
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]: • *CPOX (coproporphyrinogen oxidase)* (eg, hereditary coproporphyria), full gene sequence • *LDLR (low density lipoprotein receptor)* (eg, familial hypercholesterolemia), duplication/deletion analysis • *RAI1 (retinoic acid induced 1)* (eg, Smith-Magenis 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]: • *HMBS (hydroxymethylbilane synthase)* (eg, acute intermittent porphyria), full gene sequence

- *LDLR (low density lipoprotein receptor)* (eg, familial hypercholesterolemia), full gene sequence
- *LEPR (leptin receptor)* (eg, obesity with hypogonadism), full gene sequence
- *PCSK9 (proprotein convertase subtilisin/kexin type 9)* (eg, familial hypercholesterolemia), full gene sequence
- *PPOX (protoporphyrinogen oxidase)* (eg, variegate porphyria), 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]:

- *APOB (apolipoprotein B)* (eg, familial hypercholesterolemia type B), full gene sequence

81479 Unlisted molecular pathology procedure [when specified as: *AGXT (Alanine--Glyoxylate And Serine--Pyruvate Aminotransferase)* (eg, primary hyperoxaluria type 1 [PH1], *LDLRAP1 (low density lipoprotein receptor adaptor protein 1)* (eg. familial hypercholesterolemia), *PCSK1 (Proprotein Convertase Subtilisin/Kexin Type 1)* (obesity), *POMC (Proopiomelanocortin)* (eg, obesity)]

ICD-10 Diagnosis

For all diagnoses not listed below as not medically necessary

When services are Not Medically Necessary:
For the procedure codes listed above for the following diagnoses

ICD-10 Diagnosis	
Z31.430	Encounter of female for testing for genetic disease carrier status for procreative management
Z31.440	Encounter of male for testing for genetic disease carrier status for procreative management
Z36.0	Encounter for antenatal screening for chromosomal anomalies
Z36.8A	Encounter for antenatal screening for other genetic defects

Z84.81	Family history of carrier of genetic disease
~~Z31.430~~	~~Encounter of female for testing for genetic disease carrier status for procreative management~~

Other testing
When services are Not Medically Necessary:

CPT	
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
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
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]: • *CDKN2A (cyclin-dependent kinase inhibitor 2A)* (eg, CDKN2A-related cutaneous malignant melanoma, familial atypical mole-malignant melanoma syndrome), full gene sequence • *SOD1 (superoxide dismutase 1, soluble) (eg, amyotrophic lateral sclerosis), 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]:

	• *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]: • *FUS (fused in sarcoma)* (eg, amyotrophic lateral sclerosis), full gene sequence; • *OPTN (optineurin)* (eg, amyotrophic lateral sclerosis), full gene sequence
81407	Molecular pathology procedure, Level 8 (eg, analysis of 26-50 exons by DNA sequence analysis, mutation scanning or duplication/deletion variants of >50 exons, sequence analysis of multiple genes on one platform) [when specified as the following]: • *SPTBN2 (spectrin, beta, nono-erythrocytic 2)* (eg, spinocerebellar ataxia), full gene sequence
81408	Molecular pathology procedure, Level 9 (eg, analysis of >50 exons in a single gene by DNA sequence analysis) [when specified as the following]: • *ATM (ataxia telangiectasia mutated)* (eg, ataxia telangiectasia), full gene sequence
81479	Unlisted molecular pathology procedure [when specified as: *F2 (coagulation factor 2)* (eg, hereditary hypercoagulability), C20209T or Yukuhashi variants]

HCPCS

S3800	Genetic testing for amyotrophic lateral sclerosis (ALS)

ICD-10 Diagnosis

All diagnoses

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.

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
ACADM	Medium-chain acyl-coenzyme A dehydrogenase (MCAD)	√	√	ACOG # 690, (2017, reaffirmed 2019)*
ACADVL	Very long-chain acylCoA dehydrogenase (VLCAD) deficiency	√	√	
AFF2	Fragile X Syndrome	√	√	
AFG3L2	Spinocerebellar ataxia Type 28 (SCA28)	√		
AGL	Glycogen Storage Disease Type III	√		
AGXT	Primary hyperoxaluria type 1 (PH1)		√	FDA label for Oxlumo (lumasiran),
ANG	Amyotrophic lateral sclerosis			
ApoB	Familial hypercholesterolemia (principally APOB3500)		√	
APTX	Ataxia with oculomotor apraxia Type 1	√		

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
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)	√	√	
ATXN1	Spinocerebellar ataxia type 1 (SCA1)	√		

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
ATXN10	Spinocerebellar ataxia type 10 (SCA10)	√		
ATXN2	Spinocerebellar ataxia type 2 (SCA2)	√		
ATXN3	Spinocerebellar ataxia type 3 (SCA3)	√		
ATXN7	Spinocerebellar ataxia type 7 (SCA7)	√		
ATXN8 (ATXN8OS)	Spinocerebellar ataxia type 8 (SCA8)	√		
BCKDHA	Maple Syrup Urine Disease type 1A	√	√	ACOG # 690, (2017, reaffirmed 2019)*
BCKDHB	Maple Syrup Urine Disease type 1B	√	√	ACOG # 690, (2017, reaffirmed 2019)*
BLM	Bloom's syndrome	√	√	ACOG # 690, (2017, reaffirmed 2019)*
CACNA1A	Spinocerebellar ataxia type 6 (SCA6)	√		
CDKN2A	Familial malignant melanoma			
CFTR	Cystic fibrosis	√	√	ACOG # 690, (2017, reaffirmed 2019)*

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
CNBP	Myotonic dystrophy type 2	√	√	
CPOX	Hereditary coproporphyria		√	
CPT-2	Carnitine palmitoyltransferase-2 deficiency	√	√	
CSTB	Unverricht-Lundborg disease (ULD, EPM1)	√		
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	√	√	
EIF2B5	Childhood ataxia with central nervous system hypomyelination/V~~v~~anishing white matter	√		
ELP1	Familial Dysautonomia	√	√	ACOG # 690,

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
				(2017, reaffirmed 2019)*
F2, G20210A	Hereditary thrombophilia		√	
F5	Factor V Leiden thrombophilia	√	√	
FANCC	Fanconi anemia type C	√	√	ACOG # 690, (2017, reaffirmed 2019)*
FMR1	Fragile X Syndrome	√	√	
FUS	Amyotrophic lateral sclerosis			
FXN	Friedreich ataxia (also known as Friedreich's ataxia, FRDA)	√		
G6PC	Glycogen storage disease type I (GSD I, Von Gierke disease)	√	√	
GAA	Glycogen Storage Disease Type II (GSD II, Pompe disease)	√	√	
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)*
GJB2	Nonsyndromic Hearing Loss and Deafness, (DFNB1)	√		

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
GLA	Fabry disease	√	√	
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)*
HBB	Sickle cell disease	√	√	ACOG # 690, (2017, reaffirmed 2019)*
HEXA	Tay-Sachs disease	√		ACOG # 690, (2017, reaffirmed 2019)*
HFE	Hemachromatosis	√	√	
HMBS	Acute intermittent porphyria		√	
HTT	Huntington disease	√		
IKBKAP	Familial dysautonomia	√	√	
ITPR1	Spinocerebellar ataxia type 15 (SCA15)	√		
KCNC3	Spinocerebellar ataxia type 13	√		

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
LDLR	Familial hypercholesterolemia (LDL) receptor (sometimes called the apoB/E receptor)		√	
LDLRAP1	Familial hypercholesterolemia		√	
MECP2	Rett syndrome	√		
MCOLN1	Mucolipidosis	√		ACOG # 690, (2017, reaffirmed 2019)*
MVK	Hyperimmunoglobulin D syndrome (HIDS)/Mevalonate kinase deficiency (MKD)	√	√	
MYH11	Marfan syndrome, Loeys-Dietz syndromes, and familial thoracic aortic aneurysms and dissections	√	√	
NLGN3	Autism Spectrum	√	√	
NLGN4X	Autism Spectrum	√	√	
NOTCH3	CADASIL syndrome	√		
OPTN	Amyotrophic lateral sclerosis			
PABPN1	Oculopharyngeal muscular dystrophy (also known as OPMD)	√		

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
PAH	Phenylalanine hydroxylase deficiency	√	√	ACOG # 690, (2017, reaffirmed 2019)*
PCSK9	Familial hypercholesterolemia		√	
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)	√		
PRKCG	Spinocerebellar ataxia type 14 (SCA14)	√		
PYGM	Glycogen storage disease type V GSD V)	√	√	
RAI1	Smith-Magenis syndrome		√	FDA label for Hetlioz (tasimelteon)
RPE65	Hereditary retinal dystrophy	√	√	Also see MED.00120 Gene Therapy for Ocular Conditions
SERPINA1	Alpha-1 antitrypsin deficiency (AATD)		√	

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
SETX	Ataxia with Oculomotor Apraxia Type 2	√		
SIL1	Marinesco-Sjögren syndrome	√		
SLC37A4	Glycogen Storage Disease type Ib	√	√	
SMN-1	Spinal muscular atrophy	√	√	ACOG # 690, (2017, reaffirmed 2019)*
SMPD1	Acid Sphingomyelinase Deficiency (Niemann-Pick disease type B)	√	√	ACOG # 690, (2017, reaffirmed 2019)*
SNRPN	Prader-Willi syndrome	√		
SOD1	Amyotrophic lateral sclerosis (ALS, Lou Gehrig's disease)			
SPTBN2	Spinocerebellar ataxia type 5 (SCA5)			
TARDBP	Amyotrophic lateral sclerosis			
TBP	Spinocerebellar ataxia type 17 (SCA17)	√		
TGFBI	Corneal dystrophy	√		
TGFBR1	Marfan syndrome, Loeys-Dietz syndromes, and familial thoracic aortic aneurysms and dissections	√	√	

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
TGFBR2	Marfan syndrome, Loeys-Dietz syndromes, and familial thoracic aortic aneurysms and dissections	√	√	
TTPA	Ataxia with vitamin E deficiency	√	√	
TPP1	Infantile neuronal cord lipofuscinosis type 2	√	√	
UBE3A	Angelman syndrome	√		

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

Preconception or Prenatal Testing

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

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

Preconception or prenatal genetic testing of a parent or prospective parent is a common practice to determine carrier status. For example, the American College of Obstetrics and Gynecology (ACOG) and the American College of Medical Genetics (ACMG) recommend carrier screening for: Tay-Sach's disease, Canavan disease, 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~~mutations~~ 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~~Mutations~~ in the beta III spectrin gene (SPTBN2 gene) have been associated with spinocerebellar ataxias (SCA) type 5. This is a relatively mild disorder that typically begins between the ages of 20 and 30 and progresses slowly. CDKN2A, the most commonly identified gene variant in familial forms of melanoma (adulthood age of onset), exhibits incomplete penetrance.

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

CF results when an individual inherits a gene variant in both alleles of the CF transmembrane conductance regulator (CFTR) gene, located on chromosome 7q31. The CFTR gene produces a protein that functions as a chloride channel and regulates bicarbonate and chloride transport, as well as other transport pathways. More than 1900 different variants~~mutations~~ in the CF gene have been identified. The prevalence of carrier frequencies and variant~~mutation~~ types varies among populations. Non-Hispanic whites of Northern European descent have a carrier rate of 1 in 25 with the ΔF508 variant~~mutation~~ 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 ~~National Society of Genetic Counselors (~~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~~mutations~~ 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~~mutations~~ 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~~mutations~~ (Watson, 2004).

According to the NSGC, carrier testing panels should include the variants ~~mutations~~ recommended by ACOG and ACMG. For individuals of non-Northern European descent, panethnic panels that include additional variants~~mutations~~ 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~~mutation~~ 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 Mmuscular Ddystrophy or Becker Mmuscular Ddystrophy
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~~uchenne~~ or BMD~~ecker muscular dystrophy~~ 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).

Definitions

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

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

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

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

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

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.

Genetic molecular testing: A type of test that studies single genes or short lengths of DNA ~~is used~~ to determine the presence or absence of a specific gene variant or set of genetic~~s~~ 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~~mutation~~ may never develop the disease. Predictive testing can identify variants~~mutations~~ 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.

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.

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

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

Penetrant: The likelihood that a person carrying a particular variation of a gene will also have an associated trait.

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.

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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This Clinical UM Guideline is intended to provide assistance in interpreting Healthy Blue's standard Medicaid benefit plan. When evaluating insurance coverage for the provision of medical care, federal, state and/or contractual requirements must be referenced, since these may limit or differ from the standard benefit plan. In the event of a conflict, the federal, state and/or contractual requirements for the applicable benefit plan coverage will govern. Healthy Blue reserves the right to modify its Policies and Guidelines as necessary and in accordance with legal and contractual requirements. This Clinical UM Guideline is provided for informational purposes. It does not constitute medical advice. Healthy Blue may also use tools and criteria developed by third parties, to assist us in administering health benefits. Healthy Blue's Policies and Guidelines are intended to be used in accordance with the independent professional medical judgment of a qualified health care provider and do not constitute the practice of medicine or medical advice.

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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
Revised	05/13/2021	Medical Policy & Technology Assessment Committee (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	~~Medical Policy & Technology Assessment Committee (~~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.