Genetic Testing for Non-Cancerous Inheritable Diseases

I. Policy

University Health Alliance (UHA) will reimburse for Genetic Testing for Non-Cancerous Inheritable Diseases when determined to be medically necessary and within the medical criteria guidelines (subject to limitations and exclusions) indicated below.

This policy is based primarily on recommendations in the Final Report of the Task Force on Genetic Testing and the Secretary's Advisory Committee on Genetic Testing. The evaluation of a genetic test focuses on these main principles: Analytic validity (technical accuracy of the test in detecting a mutation that is present or in excluding a mutation that is absent); Clinical validity (diagnostic performance of the test [sensitivity, specificity, positive and negative predictive values] in detecting clinical disease); and clinical utility (how results of the diagnostic test will be used to change management of the patient and whether these changes in management lead to clinically important improvements in health outcomes).

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

Genetic testing of children to confirm current symptomatology or predict adult onset diseases is not considered medically necessary unless direct medical benefit will accrue to the child and in the case of adult onset disease, this benefit would be lost by waiting until the child has reached adulthood.

For familial assessments, unless otherwise specified, family will be considered: first-, second- and third-degree relatives on the same side of the family. The maternal and paternal sides should be considered independently. First-degree relatives refer to parents, full siblings, and offspring. Second- degree relatives are defined as grandparents, grandchildren, aunts, uncles, nephews, nieces, half-siblings and third-degree relatives are defined as great-grandparents, great-aunts, great-uncles, first cousins.

II. Criteria/Guidelines

A. Genetic testing for all the inheritable diseases listed below must meet the following general criteria (in addition to any specific criteria) in order to be covered:

   1. There must be a reasonable expectation based on family history, pedigree analysis, risk factors, and/or symptomatology that a genetically inherited condition exists.
   2. The genotypes to be detected by a genetic test must be shown by scientifically valid methods to be associated with the occurrence of the disease.
   3. The analytical validity, clinical validity, and clinical utility of the test must be established (e.g., test results will influence decisions concerning disease treatment or prevention).

B. Genetic testing is covered (subject to Limitations/Exclusions and Administrative Guidelines) if after history, physical exam, pedigree analysis, and completion of conventional diagnostic studies, a definitive diagnosis remains uncertain and a genetic linked diagnosis is suspected. These include but are not limited to:

- Achrondroplasia
- Amino acid metabolic disturbances
- Charcot-Marie Tooth disease
- Classical lissencephaly
- Congenital hydrocephalus
- Cri-du-chat
- Cystic kidney disease (including polycystic kidney, autosomal dominant)
- Dwarfism
- Fabry disease
- Factor XIII deficiency, congenital (Factor XIII beta globulin)
- Friedreich's ataxia
- Gonadal dysgenesis (Turner's, XO syndrome)
- Hereditary progressive muscular dystrophy
- Neurofibromatosis type 2
- Osteogenesis imperfecta
- Phenylketonuria
- Prader-Willi-Angelman syndrome
- Peutz-jeghers
- Thanatophoric dysplasia
- Tuberous sclerosis
- Turner syndrome
- Velo cardio facial syndrome
- Von Hippel-Lindau syndrome
- Von Willebrand's disease

C. Genetic testing for cystic fibrosis is covered (subject to Limitations and of Administrative Guidelines) using the American College of Medical Genetics (ACMG) mutation core panel (AMCG 23) for preconception or prenatal carrier testing of an individual who is pregnant or a prospective biologic parent with the capacity and desire to reproduce.

D. The following genetic tests are covered (subject to Limitations and Administrative Guidelines) with prior authorization. Note: Because of the rapidly evolving field of genetic testing, this policy does not address every genetic test available. All other genetic tests not mentioned in this policy will be reviewed based on medical necessity and the policy criteria:

    1. Complete analysis of the cystic fibrosis transmembrane conductance regulator (CFTR) gene is covered (subject to Limitations/Exclusions and Administrative Guidelines) in the following:

        a. For patients with cystic fibrosis

        b. Patients with a family history of cystic fibrosis

        c. Males with congenital bilateral absence of the vas deferens

        d. Newborns with a positive newborn screening result when mutation testing, using the standard 23-mutation panel, has a negative result

e. Cystic Fibrosis testing for Carrier status, not meeting above criteria is discussed in the UHA Genetic Testing – Carrier Screening and Preimplantation Diagnosis policy.

2. Chromosomal microarray analysis as first line testing in initial postnatal evaluation of individuals with any of the following:
    a. Apparent nonsyndromic developmental delay/intellectual disability
    b. Autism spectrum disorder
    c. Multiple congenital anomalies not specific to a well-delineated genetic syndrome
3. Genetic testing for carrier status of spinal muscular atrophy (SMA) in high-risk individuals when ordered by a geneticist or pediatric neurologist meeting any of the following criteria:
    a. Individuals with a positive family history of SMA, limited to first- or second-degree relatives
    b. Reproductive partner of an individual with SMA or is a known SMA carrier
    c. Individuals with a first-degree relative identified as a SMA carrier
4. Genetic testing for FMR1 mutations (including fragile X syndrome) for individuals in any of the following risk categories where the results of the test will affect clinical management or reproductive decisions:
    a. Individuals with an intellectual disability, developmental delay, or autism spectrum disorder
    b. Prenatal testing of fetuses of known carrier mothers
    c. Individuals planning a pregnancy who have either of the following;
        i. A first- or second- degree relative with fragile X syndrome, or
        ii. A first- or second- degree relative with undiagnosed intellectual disability
5. Carrier screening for Ashkenazi Jewish individuals (Please also refer to the UHA Carrier Testing for Genetic Diseases policy) for:
    a. Tay-Sachs disease
    b. Canavan disease
    c. Familial Dysautomia
    d. Fanconi anemia
    e. Niemann-Pick (type A)
    f. Bloom syndrome
    g. Gaucher disease
    h. Mucolipidosis IV
6. Genetic testing for HFE gene mutations related to hereditary hemochromatosis:
    a. For diagnostic testing when the individual with symptoms consistent with hemochromatosis and serum transferrin iron saturation is greater than or equal to 45%, in the absence of confounding causes of hyperferritinemia, including but not limited to alcohol abuse, metabolic syndrome, inflammatory states or acute and chronic hepatitis.

b. In individuals with a family history of hemochromatosis in a first degree relative.

c. HFE gene mutation testing in patients with unexplained abnormal serum iron indices even in the absence of symptoms

d. When parental whole HFE gene variant status is unknown when one parent has known hereditary hemochromatosis and testing is to inform homozygosity or heterozygosity status in a child.

i. Genetic testing for HFE pathogenic variants is not medically necessary in children with at least one parent with normal HFE gene status.

ii. Genetic testing as a screening tool for hereditary hemochromatosis in the general population is not covered because it is not known to improve health outcomes.

7. Genetic testing for predisposition to hypertrophic cardiomyopathy (HCM) for individuals having one first-degree relative with established HCM when there is a known pathogenic gene mutation present in that affective relative.

8. Genetic testing for suspected congenital Long QT Syndrome (LQTS) for individuals who do not meet the clinical criteria for LQTS but have one of the following:

a. A first- or second- degree relative with a known LQTS mutation

b. A first- or second- degree relative diagnosed with LQTS by clinical means whose genetic status is unavailable

c. Signs and/or symptoms indicating a moderate to high pretest probability of LQTS, defined as a Schwartz score of 2-3 (See Appendix – Table 1)

9. Genetic testing for Factor V Leiden and/or prothrombin G20210A mutations when any of the following criteria are met:

a. Age 50 or less, any venous thrombosis

b. Age 50 or less, in patients who develop acute arterial thrombosis in the absence of other risk factors for atherosclerotic arterial occlusive disease

c. Venous thrombosis in unusual sites (such as portal hepatic, mesenteric and cerebral veins)

d. Recurrent venous thrombosis

e. Relatives of individuals with venous thrombosis under age 50

f. Venous thrombosis with a first-or second- degree relative with thrombotic disease

g. Venous thrombosis in pregnant women or women taking oral contraceptives

h. Women with recurrent pregnancy loss or unexplained severe preeclampsia, placental abruption, intrauterine fetal growth retardation or stillbirth

i. Myocardial infarction in female smokers under age 50

10. One-time genotypic or phenotypic analysis of the enzyme Thiopurine Methyltransferase (TPMT) is covered in patients beginning therapy with azathioprine (AZA), mercaptopurine (6-MP) or thioguanine (6-TG) or in patients on thiopurine therapy with abnormal complete blood count results that do not respond to dose reduction.

11. Genetic testing for hemoglobinopathies (i.e., thalassemias and sickle cell disease) is covered when one of the following criteria is met (Please also refer to the Carrier Testing for Genetic Diseases policy):
    a. For confirmation of a diagnosis in either of the following situations:
        i. For individuals with clinical features suggestive of a hemoglobinopathy when test results from conventional studies (e.g., Iron deficiency test and serum electrophoresis) are inconclusive and have failed a trial of iron therapy, when indicated.
        ii. Infants who are diagnosed on newborn screening as having a hemoglobinopathy
    b. For carrier testing of hemoglobinopathies (see UHA carrier Genetic testing carrier policy.
12. Evaluation of members with recurrent pregnancy loss defined as two or more consecutive spontaneous abortions when one of the following criteria is met:
    a. Karyotype (cytogenetic analysis) of parents to detect balance chromosomal anomalies;
    b. Prenatal genetic diagnosis for all couples in which one partner has been found to have a balanced translocation or inversion;
    c. Karyotype of abortus tissue when a couple with recurrent pregnancy loss experiences a subsequent spontaneous abortion
13. Evaluation for Hereditary pancreatitis (PRSS1) in symptomatic persons with any of the following indications:
    a. A family history of pancreatitis in a 1st-degree (parent, sibling, child) or 2nd-degree (aunt, uncle, grandparent) relative; or
    b. An unexplained episode of documented pancreatitis occurring in a child that has required hospitalization, and where there is significant concern that hereditary pancreatitis should be excluded; or
    c. Recurrent (2 or more separate, documented episodes with hyper-amylasemia) attacks of acute pancreatitis for which there is no explanation (anatomical anomalies, ampullary or main pancreatic strictures, trauma, viral infection, gallstones, alcohol, drugs, hyperlipidemia, etc.); or
    d. Unexplained (idiopathic) chronic pancreatitis.

Note: Because of the rapidly evolving field of genetic testing, this policy does not address every genetic test available. All other genetic tests not mentioned in this policy will be reviewed based on medical necessity and the policy criteria.

III. Limitations/Exclusions

A. The following genetic tests are NOT covered because they have not been shown to improve health outcomes (this list is not all inclusive):
    1. Genetic testing to determine preterm labor
    2. Genetic testing to determine Warfarin sensitivity

3. Genetic testing for the diagnosis or risk assessment of Alzheimer's disease including but not limited to testing for, apolipoprotein E epsilon 4 allele, presenilin genes or amyloid precursor gene
4. Genetic testing for helicobacter pylori treatment
5. MTHFR polymorphism testing

B. Genetic testing is NOT covered in the following circumstances:
   1. Family members of subscribers, who themselves are not subscribers or dependents
   2. Members if the results of the genetic testing are for the benefit of relatives who are not subscribers or dependents

C. Except as referenced in Criteria/Guidelines, genetic screening of individuals is not covered in the absence of associated signs, symptoms or complaints. General population screening for genetic disorders is not covered except where mandated by State and Federal law.

D. Laboratories that conduct genetic testing must be CLIA certified.

E. UHA will cover pre- and post-test genetic counseling with a physician or a certified genetic counselor as medically necessary for an individual recommended for covered heritable genetic testing.

F. Genetic tests for a specific inherited disease will be covered once per lifetime unless new techniques that increase sensitivity are utilized and medical necessity criteria is met.

G. Home genetic testing is not a covered benefit.

H. For a known deleterious mutation, UHA will only cover a targeted single site analysis genetic test not a full analysis (i.e., testing for the mutation that has been identified in the family).

I. Chromosomal microarray analysis is not covered to confirm the diagnosis of a disorder or syndrome that is routinely diagnosed based on clinical evaluation alone. Such testing must have material therapeutic implications to be considered for medical necessity.

J. The following expanded prenatal panel tests are not covered because the clinical utility has not been established (This is not an all-inclusive list):
   1. Counsyl
   2. GoodStart Select
   3. Inherigen
   4. Inheritest
   5. Natera One Disease Panel
   6. Progenity CFnxt

NOTE:

This UHA payment policy is a guide to coverage, the need for prior authorization and other administrative directives. It is not meant to provide instruction in the practice of medicine and it should not deter a provider from expressing his/her judgment.

Even though this payment policy may indicate that a particular service or supply is considered covered, specific provider contract terms and/or member's individual benefit plans may apply, and this policy is not a guarantee of payment UHA reserves the right to apply this payment policy to all UHA companies and subsidiaries.

UHA understands that opinions about and approaches to clinical problems may vary. Questions concerning medical necessity (see Hawaii Revised Statutes §432E-1.4) are welcome. A provider may request that UHA reconsider the application of the medical necessity criteria in light of any supporting documentation.

IV. Administrative Guidelines

A. Prior authorization for the genetic tests is required and must be submitted by a properly certified/licensed and credentialed genetic specialist (i.e., board certified neurologist (MD), board-certified medical geneticist (MD), board-certified clinical geneticist (PhD), board-certified genetic counselor (MS and/or CGC), or licensed advanced practice registered nurse in genetics (APRN)).

B. Complete UHA's Prior Authorization Request and Notification Form and include the following information:

1. Specify the condition for which the genetic test is being performed and if there are any known first- or second-degree relatives with the condition
2. Other types of biochemical testing apart from molecular genetic testing (enzyme activity assays, hemoglobin electrophoresis, blood chemistries, etc.), phenotypic findings and relevant clinical history and exam details
3. Specify how the results of the genetic test will impact the clinical management of the patient in terms of improving health outcomes

C. To request prior authorization, please submit via UHA's online portal. If a login has not been established, you may contact UHA at 808-532-4000 to establish one.

D. Applicable codes requiring prior authorization:

CPT Code	Description
81200	ASPA (aspartoacylase) (e.g., Canavan disease) gene analysis, common variants (e.g. E285A, Y231X)
81221	CFTR (cystic fibrosis transmembrane conductance regulator) (e.g., cystic fibrosis) gene analysis; known familial variants
81222	CFTR (cystic fibrosis transmembrane conductance regulator) (e.g., cystic fibrosis) gene analysis; duplication/deletion variants
81223	CFTR (cystic fibrosis transmembrane conductance regulator) (e.g., cystic fibrosis) gene analysis; full gene sequence
81224	CFTR (cystic fibrosis transmembrane conductance regulator) (e.g., cystic fibrosis) gene analysis; intron 8 poly-T analysis (e.g., male infertility)
81228	Cytogenomic constitutional (genome-wide) microarray analysis; interrogation of genomic regions for copy number variants (e.g., bacterial artificial chromosome [BAC] or oligo-based comparative genomic hybridization [CGH] microarray analysis)
81229	Cytogenomic constitutional (genome-wide) microarray analysis; interrogation of genomic regions for copy number and single nucleotide polymorphism (SNP) variants for chromosomal abnormalities
81240	F2 (prothrombin, coagulation factor II) (e.g., hereditary hypercoagulability) gene analysis, 20210G>A variant
81241	F5 (coagulation factor V) (e.g., hereditary hypercoagulability) gene analysis, Leiden variant
81243	FMR1 (fragile X mental retardation 1) (e.g., fragile X mental retardation) gene analysis; evaluation to detect abnormal (e.g., expanded) alleles
81244	FMR1 (fragile X mental retardation 1) (e.g., fragile X mental retardation) gene analysis; characterization of alleles (e.g., expanded size and methylation status)

81251	GBA (glucosidase, beta, acid) (e.g., Gaucher disease) gene analysis, common variants (e.g., N370S, 84GG, L444P, IVS2+1G>A)
81255	HEXA (hexosaminidase A [alpha polypeptide]) (e.g., Tay-Sachs disease) gene analysis, common variants (e.g., 1278insTATC, 1421+1G>C, G269S)
81256	HFE (hemochromatosis) (e.g., hereditary hemochromatosis) gene analysis, common variants (e.g., C282Y, H63D)
81257	HBA1/HBA2 (alpha globin 1 and alpha globin 2) (e.g., alpha thalassemia, Hb Bart hydrops fetalis syndrome, HbH disease), gene analysis; common deletions or variant (e.g., Southeast Asian, Thai, Filipino, Mediterranean, alpha3.7, alpha4.2, alpha20.5, Constant Spring)
81260	IKBKAP (inhibitor of kappa light polypeptide gene enhancer in B-cells, kinase complex-associated protein) (e.g., familial dysautonomia) gene analysis, common variants (e.g., 2507+6T>C, R696P)
81412	Ashkenazi Jewish associated disorders (e.g., Bloom syndrome, Canavan disease, cystic fibrosis, familial dysautonomia, Fanconi anemia group C, Gaucher disease, Tay-Sachs disease), genomic sequence analysis panel, must include sequencing of at least 9 genes, including ASPA, BLM, CFTR, FANCC, GBA, HEXA, IKBKAP, MCOLN1, and SMPD1
81470	X-linked intellectual disability (XLID) (e.g., syndromic and non-syndromic XLID); genomic sequence analysis panel, must include sequencing of at least 60 genes, including ARX, ATRX, CDKL5, FGD1, FMR1, HUWE1, IL1RAPL, KDM5C, L1CAM, MECP2, MED12, MID1, OCRL, RPS6KA3, and SLC16A2
81471	X-linked intellectual disability (XLID) (e.g., syndromic and non-syndromic XLID); duplication/deletion gene analysis, must include analysis of at least 60 genes, including ARX, ATRX, CDKL5, FGD1, FMR1, HUWE1, IL1RAPL, KDM5C, L1CAM, MECP2, MED12, MID1, OCRL, RPS6KA3, and SLC16A2

HCPCS Code	Description
S3845	Genetic testing for alpha-thalassemia
S3846	Genetic testing for hemoglobin E beta-thalassemia
S3850	Genetic testing for sickle cell anemia
S3861	Genetic testing, sodium channel, voltage-gated, type V, alpha subunit (SCN5A) and variants for suspected Brugada Syndrome
S3865	Comprehensive gene sequence analysis for hypertrophic cardiomyopathy
S3866	Genetic analysis for a specific gene mutation for hypertrophic cardiomyopathy (HCM) in an individual with a known HCM mutation in the family
S3870	Comparative genomic hybridization (CGH) microarray test for developmental delay/ autism spectrum disorder and/or mental retardation

E. Applicable codes that do not require prior authorization:

CPT Code	Description
81161	DMD (dystrophin) (eg, Duchenne/Becker muscular dystrophy) deletion analysis, and duplication analysis, if performed
81205	BCKDHB (branched-chain keto acid dehydrogenase E1, beta polypeptide) (eg, maple syrup urine disease) gene analysis, common variants (eg, R183P, G278S, E422X)
81220	CFTR (cystic fibrosis transmembrane conductance regulator) (eg, cystic fibrosis) gene analysis; common variants (eg, ACMG/ACOG guidelines)
81290	MCOLN1 (mucolipin 1) (eg, Mucolipidosis, type IV) gene analysis, common variants (eg, IVS3-2A>G, del6.4kb)
81324	PMP22 (peripheral myelin protein 22) (eg, Charcot-Marie-Tooth, hereditary neuropathy with liability to pressure palsies) gene analysis; duplication/deletion analysis
81325	PMP22 (peripheral myelin protein 22) (eg, Charcot-Marie-Tooth, hereditary neuropathy with liability to pressure palsies) gene analysis; full sequence analysis
81326	PMP22 (peripheral myelin protein 22) (eg, Charcot-Marie-Tooth, hereditary neuropathy with liability to pressure palsies) gene analysis; known familial variant

81330	SMPD1(sphingomyelin phosphodiesterase 1, acid lysosomal) (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

HCPCS Code	Description
S3842	Genetic testing for Von Hippel-Lindau disease
S3849	Genetic testing for Niemann-Pick disease
S3853	Genetic testing for myotonic muscular dystrophy

V. Appendix

Table 1: LQTS Clinical Probability Score Card (i.e., Schwartz Score)

Finding	Points
History	
Clinical history of syncope* without stress	1
Clinical history of syncope* with stress	2
Congenital deafness	0.5
Family history of LQTS*	1
Unexplained sudden death in a first-degree family member < 30 years old*	0.5
ECG	
Corrected QT interval (QTc by Bazett's formula)	
450 ms (in males)	1
460-470 ms	2
> 480 ms	3
Torsade de pointes**	2
T-wave alternans	1
> 3 Leads with notched T-waves	1
Bradycardia (< second percentile for age)	0.5

A score < 1 = low probability; 1 to < 4 = intermediate probability; > 4 = high probability

* Cannot count the same family member for both criteria

** Syncope and torsade de pointes are mutually exclusive

VI. Policy History

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