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 and clinical utility validity 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 one of the following diagnoses are suspected. These include but are not limited to:
• Achondroplasia
• 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

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 Carrier Testing for Genetic Diseases policy) for:
   a. Tay-Sachs disease
   b. Canavan disease
   c. Familial Dysautonia
   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%, but the diagnosis remain uncertain after completion of conventional testing.
   b. In individuals with a family history of hemochromatosis in a first degree relative.
c. HFE gene mutation testing in patients with abnormal serum iron indices even in the absence of symptoms

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:
      A. 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.
      B. Infants who are diagnosed on newborn screening as having a hemoglobinopathy
   b. For carrier testing in either of the following situations:
A. When there is an affected first- or second-degree relative with thalassemia or sickle cell disease

B. When the patient is the reproductive partner of a known carrier (disease-causing mutation of gene HBB, HBA1, or HBA2) and the couple has the capacity and intention to reproduce

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

### 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. If a patient has been screened previously, Cystic Fibrosis screening results should be documented and the test should not be repeated.

D. Complete analysis of the Cystic fibrosis transmembrane conductance regular (CFTR) gene by DNA sequencing is NOT appropriate for routine carrier screening.

E. 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.

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

G. 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.

H. 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.
I. Home genetic testing is not a covered benefit.

J. 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).

K. 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.

L. 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 go to UHA’s website: [https://uhahealth.com/page/prior-authorization-forms](https://uhahealth.com/page/prior-authorization-forms) and submit via UHA’s online portal.

D. Applicable codes requiring prior authorization:

<table>
<thead>
<tr>
<th>CPT Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>81200</td>
<td>ASPA (aspartoacylase) (e.g., Canavan disease) gene analysis, common variants (e.g., E285A, Y231X)</td>
</tr>
<tr>
<td>81221</td>
<td>CFTR (cystic fibrosis transmembrane conductance regulator) (e.g., cystic fibrosis) gene analysis; known familial variants</td>
</tr>
<tr>
<td>81222</td>
<td>CFTR (cystic fibrosis transmembrane conductance regulator) (e.g., cystic fibrosis) gene analysis; duplication/deletion variants</td>
</tr>
<tr>
<td>81223</td>
<td>CFTR (cystic fibrosis transmembrane conductance regulator) (e.g., cystic fibrosis) gene analysis; full gene sequence</td>
</tr>
<tr>
<td>81224</td>
<td>CFTR (cystic fibrosis transmembrane conductance regulator) (e.g., cystic fibrosis) gene analysis; intron 8 poly-T analysis (e.g., male infertility)</td>
</tr>
<tr>
<td>81228</td>
<td>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)</td>
</tr>
<tr>
<td>81229</td>
<td>Cytogenomic constitutional (genome-wide) microarray analysis; interrogation of genomic regions for copy number and single nucleotide polymorphism (SNP) variants for chromosomal abnormalities</td>
</tr>
<tr>
<td>81240</td>
<td>F2 (prothrombin, coagulation factor II) (e.g., hereditary hypercoagulability) gene analysis, 20210G&gt;A variant</td>
</tr>
<tr>
<td>81241</td>
<td>F5 (coagulation factor V) (e.g., hereditary hypercoagulability) gene analysis, Leiden variant</td>
</tr>
<tr>
<td>81243</td>
<td>FMR1 (fragile X mental retardation 1) (e.g., fragile X mental retardation) gene analysis; evaluation to detect abnormal (e.g., expanded) alleles</td>
</tr>
<tr>
<td>81244</td>
<td>FMR1 (fragile X mental retardation 1) (e.g., fragile X mental retardation) gene analysis; characterization of alleles (e.g., expanded size and methylation status)</td>
</tr>
<tr>
<td>81251</td>
<td>GBA (glucosidase, beta, acid) (e.g., Gaucher disease) gene analysis, common variants (e.g., N370S, 84GG, L444P, IVS2+1G&gt;A)</td>
</tr>
<tr>
<td>81255</td>
<td>HEXA (hexosaminidase A [alpha polypeptide]) (e.g., Tay-Sachs disease) gene analysis, common variants (e.g., 1278insTATC, 1421+1G&gt;C, G269S)</td>
</tr>
<tr>
<td>81256</td>
<td>HFE (hemochromatosis) (e.g., hereditary hemochromatosis) gene analysis, common variants (e.g., C282Y, H63D)</td>
</tr>
<tr>
<td>81257</td>
<td>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)</td>
</tr>
<tr>
<td>81260</td>
<td>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&gt;C, R696P)</td>
</tr>
<tr>
<td>81412</td>
<td>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</td>
</tr>
<tr>
<td>81470</td>
<td>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, RP56KA3, and SLC16A2</td>
</tr>
</tbody>
</table>
| 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, HYUE1, IL1RAPL, KDM5C, L1CAM, MECP2, MED12, MID1, OCRL, RPS6KA3, and SLC16A2

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

### E. Applicable codes that do not require prior authorization:

<table>
<thead>
<tr>
<th>CPT Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>81161</td>
<td>DMD (dystrophin) (eg, Duchenne/Becker muscular dystrophy) deletion analysis, and duplication analysis, if performed</td>
</tr>
<tr>
<td>81205</td>
<td>BCKDHB (branched-chain keto acid dehydrogenase E1, beta polypeptide) (eg, maple syrup urine disease) gene analysis, common variants (eg, R183P, G278S, E422X)</td>
</tr>
<tr>
<td>81220</td>
<td>CFTR (cystic fibrosis transmembrane conductance regulator) (eg, cystic fibrosis) gene analysis; common variants (eg, ACMG/ACOG guidelines)</td>
</tr>
<tr>
<td>81290</td>
<td>MCOLN1 (mucolipin 1) (eg, Mucolipidosis, type IV) gene analysis, common variants (eg, IVS3-2A&gt;G, del6.4kb)</td>
</tr>
<tr>
<td>81324</td>
<td>PMP22 (peripheral myelin protein 22) (eg, Charcot-Marie-Tooth, hereditary neuropathy with liability to pressure palsies) gene analysis; duplication/deletion analysis</td>
</tr>
<tr>
<td>81325</td>
<td>PMP22 (peripheral myelin protein 22) (eg, Charcot-Marie-Tooth, hereditary neuropathy with liability to pressure palsies) gene analysis; full sequence analysis</td>
</tr>
<tr>
<td>81326</td>
<td>PMP22 (peripheral myelin protein 22) (eg, Charcot-Marie-Tooth, hereditary neuropathy with liability to pressure palsies) gene analysis; known familial variant</td>
</tr>
<tr>
<td>81330</td>
<td>SMPD1 (sphingomyelin phosphodiesterase 1, acid lysosomal) (eg, Niemann-Pick disease, Type A) gene analysis, common variants (eg, R496L, L302P, fsP330)</td>
</tr>
<tr>
<td>81331</td>
<td>SNRPN/UBE3A (small nuclear ribonucleoprotein polypeptide N and ubiquitin protein ligase E3A) (eg, Prader-Willi syndrome and/or Angelman syndrome), methylation analysis</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>HCPCS Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>S3842</td>
<td>Genetic testing for Von Hippel-Lindau disease</td>
</tr>
<tr>
<td>S3849</td>
<td>Genetic testing for Niemann-Pick disease</td>
</tr>
<tr>
<td>S3853</td>
<td>Genetic testing for myotonic muscular dystrophy</td>
</tr>
</tbody>
</table>
### V. Appendix

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

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

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

**Policy Number:** MPP-0093-121120

**Current Effective Date:** 02/12/2018

**Original Document Effective Date:** 11/20/2012

**Previous Revision Dates:** 12/01/2015

**PAP Approved Date:** 11/20/2012