



Genetic Testing

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P&P # C.6.07

Policy

The Medical Management Department reviews referral requests for authorization of genetic testing.

This Medical Policy does not constitute medical advice. When deciding coverage, the enrollee's specific plan document must be referenced. The terms of an enrollee's plan document (Certificate of Coverage (COC) or Summary Plan Description (SPD)) may differ from this Medical Policy. In the event of a conflict, the enrollee's specific benefit plan document supersedes this Medical Policy. All reviewers must first identify enrollee eligibility, any federal or state regulatory requirements, and the plan benefit coverage prior to use of this Medical Policy. Other Policies and Coverage Determination Guidelines may apply. Quartz reserves the right, in its sole discretion, to modify its Policies and Guidelines as necessary.

Procedure

A. General Criteria (For genetic tests NOT listed in Section C of this policy):

1. Documentation

In order to facilitate the authorization process, referral requests **MUST** include the following:

- a. Clinical record of patient's personal and family history along with genetic counseling;
- b. Record of appropriate conventional clinical diagnostic studies/tests/interventions including results of those tests, and also results of previously completed genetic testing;
- c. Request should include name of accredited lab performing the test (e.g., College of American Pathologist/American College of Medical Genetics);
- d. An estimate of the patient's probability of having the disorders being tested;
- e. The ordering providers statement of how the patient's medical treatment plan will be directed by the requested genetic testing whether testing results are positive or negative;
- f. Genetic counseling must be performed by a qualified, appropriately trained practitioner with **ONE** of the following backgrounds:
 - i. Board certified/Board eligible (BC/BE) genetics counselor;
 - ii. BC/BE medical geneticist;
 - iii. Genetic nurse credentialed as either a genetic clinical nurse or advanced practice nurse in genetics;
 - iv. Specialist with expertise in cancer genetics to include an oncologist, surgical oncologist, or other physician or advanced practice professional with documented training and expertise in cancer genetics.
 - v. Diagnosis related specialist or advanced practice professional with experience or documented training and expertise in genetics related to the patient's condition.
 - vi. The person providing the counseling cannot be employed by a commercial genetic testing laboratory except those employed by/contracted by a laboratory that is part of an integrated health system which routinely delivers health care services beyond just the laboratory test itself

2. **General Criteria for Medical Necessity**

Genetic testing is medically necessary if **ALL** of the following criteria are met:

- a. The test is appropriate for the patient by meeting **ONE** of the following:
 - i. The patient has signs or symptoms of the disorder in question **AND** a definitive diagnosis cannot be made using conventional medical tests **AND** the test results will be used to change medical management; **OR**
 - ii. The test results will provide prognostic information **OR** predict response to treatment (pharmacogenetics) that will be used to change medical management; **OR**
 - iii. The patient's family history indicates that the patient is at risk or a carrier of a disease-causing genetic mutation/variant, or a mutation/variant that causes increased risk, **AND** the test results will be used to make decisions regarding medical management or reproductive decisions; **AND**
- b. A specific mutation, or set of mutations, has been identified, that specifically identifies the genetic disorder with a high degree of validity and reliability; **AND**
- c. The genetic test has been cleared or approved by the FDA or it will be performed in a CLIA certified laboratory; **AND**
- d. The genetic disorder cannot be identified through other types of biochemical testing; **AND**
- e. The ordered genetic test should be accompanied by genetic counseling by a qualified, appropriately trained practitioner (see Documentation section above).

B. For Specific Genetic Tests listed in Section C of this policy:

1. **Documentation**

In order to facilitate the authorization process, referral requests **MUST** include the following:

- a. Clinical record of patient's personal and family history;
- b. Record of appropriate conventional clinical diagnostic studies/tests/interventions including results of those tests, and also results of previously completed genetic testing;
- c. The ordering provider's statement of how the patient's medical treatment plan will be directed by the requested genetic testing whether testing results are positive or negative.

2. **Medical Necessity Criteria for Specific Genetic Tests listed in Section C of this policy:**

Genetic testing is medically necessary if **ALL** of the following criteria are met:

- a. The test is appropriate for the patient by meeting **ONE** of the following:
 - i. The patient has signs or symptoms of the disorder in question **AND** a definitive diagnosis cannot be made using conventional medical tests **AND** the test results will be used to change medical management; **OR**
 - ii. The test results will provide prognostic information **OR** predict response to treatment (pharmacogenetics) that will be used to change medical management; **OR**
 - iii. The patient's family history indicates that the patient is at risk or a carrier of a disease-causing genetic mutation/variant, or a mutation/variant that causes increased risk, **AND** the test results will be used to make decisions regarding medical management or reproductive decisions; **AND**
- b. A specific mutation, or set of mutations, has been identified, that specifically identifies the genetic disorder with a high degree of validity and reliability; **AND**
- c. The genetic test has been cleared or approved by the FDA or it will be performed in a CLIA certified laboratory; **AND**
- d. The genetic disorder cannot be identified through other types of biochemical testing; **AND**

- e. The ordered genetic test should be accompanied by genetic counseling by a qualified, appropriately trained practitioner (see Documentation section above).

C. Medical Necessity Criteria for Specific Genetic Tests:

1. APC testing for Familial Adenomatous Polyposis

Adenosis polyposis coli (APC) genetic testing (81201, 81203) is medically necessary for **ANY** of the following:

- a. Patients with personal history of 10 or more colorectal adenomas; **OR**
- b. Personal history of a desmoid tumor, hepatoblastoma, duodenal/ampullary adenomas, cribriform-morular variant of papillary thyroid cancer, or multifocal/bilateral congenital hypertrophy of retinal pigment epithelium (CHRPE); **OR**
- c. Patients with first degree relative with familial adenomatous polyposis or known familial APC mutation (81202).

NOTE: Full sequence APC genetic testing (81201 followed by 81203 if negative) is considered medically necessary **ONLY** when it is not possible to determine the family mutation first.

2. Arrhythmogenic Right Ventricular Dysplasia/Cardiomyopathy (ARVD/C)

Genetic testing for a known DSC2, DSG2, DSP, JUP, PKP2, TMEM43 gene sequence variant for ARVD/C is considered medically necessary in:

- a. Asymptomatic patients with a first degree relative with a known familial sequence variant **AND** with International Task Force (ITF)-confirmed ARVD/C; **OR**
- b. Patients who have ARVD/C symptoms that fail to meet the ITF diagnostic criteria **AND** have a first degree relative with a known familial sequence variant **AND** with ITF-confirmed ARVD/C.

3. Catecholaminergic Polymorphic Ventricular Tachycardia (CPVT):

Cardiac ion channelopathy genomic sequence analysis panel testing (81413) followed by duplication/deletion gene analysis panel testing (81414) if sequence analysis is negative, is considered medically necessary for CPVT evaluation for **EITHER** of the following:

- a. Children or young adults (less than 40 years of age) with a first degree relative with a clinical diagnosis of CPVT, or a first or second degree relative with a defined CPVT mutation (test for specific familial mutation); **OR**
- b. Patients who display exercise or emotion induced polymorphic ventricular tachycardia or ventricular fibrillation, occurring in a structurally normal heart.

NOTE:

- Cardiac ion channelopathy genomic sequence analysis panel testing (81413) must include sequencing of at least 10 genes: ANK2, CASQ2, CAV3, KCNE1, KCNE2, KCNH2, KCNJ2, KCNQ1, RYR2, and SCN5A. Duplication/deletion gene analysis panel testing (81414) must include at least KCNH2 and KCNQ1 genes.
- Asymptomatic individuals with a known familial variant/mutation should be tested only for that specific variant. Symptomatic individuals with a known familial variant should first be tested for that specific variant and if negative, proceed to panel testing.

4. Cerebral Autosomal Dominant Arteriopathy (CADASIL):

DNA testing for CADASIL with subcortical infarcts and leukoencephalopathy (CADASIL (NOTCH3 gene) sequencing 81406), is medically necessary for **EITHER** of the following:

- a. Pre-symptomatic patients where there is a family history consistent with an autosomal dominant pattern of inheritance and there is a known mutation in an affected blood relative; **OR**
- b. Symptomatic patients who have a family history consistent with an autosomal dominant pattern of inheritance of this condition (clinical signs and symptoms of CADASIL include stroke, cognitive defects and/or dementia, migraine, and psychiatric disturbances).

5. Cytogenetic microarray (CMA):

Cytogenetic microarray (CMA) testing for copy number variation (CNV) is medically necessary for postnatal testing in the evaluation of patients with **ANY** of the following:

- a. Multiple anomalies not specific to a well-delineated genetic syndrome; **OR**
- b. Apparently non-syndromic developmental delay/intellectual disability; **OR**
- c. Autism spectrum disorders.

6. Cystic Fibrosis (CF) Diagnosis (See Policy C.6.18 for CF Carrier Screening):

Genetic testing for Cystic Fibrosis (CF) using the ACMG standard CF transmembrane regulator (CFTR) mutation panel (core panel) of 25 mutations is medically necessary for patients with **ANY** of the following:

- a. Patients who exhibit symptoms of CF and have intermediate or high sweat test results; **OR**
- b. Infants with meconium ileus or other symptoms indicative of CF who are too young to produce adequate volumes of sweat for a sweat chloride test (e.g., test is inconclusive or cannot be performed); **OR**
- c. Infants with a positive newborn screen; **OR**
- d. Persons with a family history of cystic fibrosis or a first degree relative identified as a cystic fibrosis carrier in whom the general criteria for medical necessity are met.

Genetic testing for CF is not medically necessary for **EITHER** of the following (not all-inclusive):

- a. Routine genetic mutation screening in a newborn; **OR**
- b. Testing using extended mutation panels (i.e., mutation panels that extend beyond the American College of Medical Genetics standard mutation panel).

7. Factor II Prothrombin gene mutation

Prothrombin genetic testing (Prothrombin G20210A allele variant testing, 81240) is medically necessary for patients with **ANY** of the following:

- a. Myocardial infarction in female smokers under age 50; **OR**
- b. Recurrent venous thromboembolism; **OR**
- c. Venous thromboembolism with a strong family history of thrombotic disease (e.g., two or more family members with Factor II Leiden mutation); **OR**
- d. Three or more 2nd or 3rd trimester miscarriages; **OR**

- e. Venous thromboembolism in unusual sites (e.g., hepatic, mesenteric, and cerebral veins).
- f. Pregnant women or women who are planning to become pregnant without a personal history of venous thromboembolism and with a first degree relative, (e.g., parent or sibling), with a history of venous thromboembolism who are candidates for thromboprophylaxis therapy during and after pregnancy; **OR**
- g. Pregnant women or women who are planning to become pregnant with a history of provoked venous thromboembolism, (e.g., in the setting of a surgery, fracture or prolonged immobilization but not pregnancy or estrogen related) who are not on chronic anticoagulation.

8. Factor V Leiden:

Factor V Leiden genetic testing (Factor V Leiden mutation, 81241) is medically necessary for patients with **ANY** of the following:

- a. Myocardial infarction in female smokers under age 50; **OR**
- b. Recurrent venous thromboembolism; **OR**
- c. Venous thromboembolism with a strong family history of venous thrombotic disease (e.g., two or more family members with Factor V Leiden mutation); **OR**
- d. Three or more 2nd or 3rd trimester miscarriages; **OR**
- e. Venous thromboembolism in unusual sites (e.g., hepatic, mesenteric, retinal and cerebral veins); **OR**
- f. Pregnant women or women who are planning to become pregnant without a personal history of venous thromboembolism and who have a first degree relative, (e.g., parent or sibling), with a history of venous thromboembolism who are candidates for thromboprophylaxis therapy during and after pregnancy; **OR**
- g. Pregnant women or women who are planning to become pregnant with a history of provoked venous thromboembolism, (e.g., in the setting of a surgery, fracture or prolonged immobilization but not pregnancy or estrogen related) who are not on chronic anticoagulation; **OR**
- h. Adult patients with primary (idiopathic) osteonecrosis of hips or knees who have a family history of venous thromboembolism or first-degree relative with known Factor V Leiden mutation and are candidates for anticoagulation therapy.

9. Familial Hypocalciuric Hypercalcemia:

Genetic testing for Familial Hypocalciuric Hypercalcemia (FHH) with CASR gene sequencing followed by deletion/duplication testing if negative (81405, 81479) is medically necessary for patients with **ANY** of the following:

- a. Atypical cases where no family members are available for testing; **OR**
- b. Families with familial isolated hyperparathyroidism; **OR**
- c. Infants or children under 10 years of age with hyperparathyroidism / parathyroid hormone-dependent hypercalcemia; **OR**
- d. Patients with overlap in the calcium/creatinine (Ca/Cr) clearance ratio, namely between 0.01 and 0.02; **OR**
- e. Patients with the phenotype of FHH whose parents are both normocalcemic (e.g., FHH possibly caused by a de novo CaSR mutation).

10. Familial Nephrotic Syndrome (NPHS1 mutation):

Genetic testing for Familial Nephrotic Syndrome (NPHS1 mutation), is medically necessary for children with Congenital Nephrotic Syndrome (e.g., symptoms within the first month of life) with **EITHER** of the following:

- a. Children who are of Finnish descent; **OR**
- b. Children who have a family history of Congenital Nephrotic Syndrome.

11. Familial Nephrotic Syndrome (NPHS2 mutation):

Genetic testing for Familial Nephrotic Syndrome (NPHS2 mutation), is medically necessary for children with **EITHER** of the following:

- a. Children with Steroid Resistant Nephrotic Syndrome (SRNS); **OR**
- b. Children who have a family history of SRNS.

12. Fragile X Syndrome: (See policy C.6.18 for Fragile X carrier screening)

Genetic testing for Fragile X Syndrome (FMR1 gene analysis- 81243, 81244) is medically necessary for patients in **ANY** of the following risk categories:

- a. Patients with unexplained intellectual disability, developmental delay, autism spectrum disorder, or premature ovarian failure; **OR**
- b. Fetuses/neonates of known carrier mothers; **OR**
- c. Patients over 50 years old with progressive cerebral ataxia and/or intentional tremor.

13. Hearing Loss:

Genetic testing for the GJB2 and GJB6 (gap junction protein beta 2, a.k.a. connexin 26 (81252) & gap junction protein beta 6, a.k.a. connexin 30 (81254)) gene analysis, full gene sequencing is medically necessary for patients who meet the following criteria:

- a. Patient has non-syndromic hearing loss, i.e., patient lacks physical findings that suggests syndromic hearing loss, e.g., unusual facial appearance or asymmetry, neck, skin or ear anomalies, skeletal abnormalities; **AND**
- b. Hearing loss is not suspected to be acquired in nature, e.g., due to CMV infection, meningitis, rubella, etc., **AND**
- c. Hearing loss is bilateral, **AND**
- d. Hearing loss presented after birth or in childhood.

14. Hereditary Hemochromatosis (HFE):

Genetic testing for Hereditary Hemochromatosis (HFE) gene mutations C282Y and H63D (hemochromatosis gene analysis for common variants C282Y and H63D, 81256) is medically necessary for patients who meet **EITHER** of the following:

- a. Patient has two consecutive serum transferrin saturations performed at least one month apart of greater than or equal to 45%; **OR**
- b. Patients who have a first-degree relative that is homozygous (C282Y/C282Y) or is a compound heterozygote (C282Y/H63D) for HFE gene mutations.

Note: HFE gene testing is not considered medically necessary in patients who have a first-degree relative that is a HFE gene mutation carrier (e.g., C282Y heterozygote).

Genetic testing for HFE gene mutations TFR2, SLC40A1, HAMP and HJV is medically necessary for patients who meet **ALL** of the following:

- a. Patient has negative HFE gene mutation for C282Y and H36D; **AND**
- b. Excess iron is documented on direct assessment of patient (e.g., MRI or biopsy); **AND**

c. Other hepatic and hematologic disorders have been ruled out as the cause of iron overload.

15. Hereditary Hemorrhagic Telangiectasia (HHT, Osler-Weber-Rendu Disease):

Genetic testing for Hereditary hemorrhagic telangiectasia (ENG, ACVRL1, and SMAD4 gene mutations, sequencing followed by duplication/deletion testing if negative; 81406, 81479, 81405) is medically necessary for patients who meet **EITHER** of the following:

- a. Symptomatic individuals who meet or who do not meet definite Curaçao criteria when results are to be used for testing at-risk family members; **OR**
- b. Asymptomatic family members of a patient with HHT when results are to be used to confirm the diagnosis.

16. Hereditary Leiomyomatosis and Renal Cell Cancer (HLRCC)

Genetic testing for Hereditary leiomyomatosis and renal cell cancer telangiectasia (fumarate hydratase gene mutation; gene sequencing and duplication/deletion or CNV, 81405, 81479) is medically necessary for symptomatic patients and at-risk family members who meet **ANY** of the following criteria:

- a. Patient with > 10 cutaneous leiomyomas, one or more histologically confirmed; **OR**
- b. Patient with one or more tubulo-papillary, collecting duct, or papillary type 2 renal tumors before the age of 40; **OR**
- c. Women less than 30 years of age with large uterine leiomyomas; **OR**
- d. Family members of a person with HLRCC when results are to be used to confirm the diagnosis.

17. Hereditary Non-polyposis Colorectal Cancer (HNPCC); Also known as Lynch Syndrome:

Genetic testing for Hereditary nonpolyposis colorectal cancer/Lynch Syndrome (MLH1, MSH2, MSH6, PMS2 gene sequencing and deletion/duplication analysis **AND** Epithelial cell adhesion molecule (EPCAM) deletion analysis (MLH1 81292, 81294; MSH2 + EPCAM 81295, 81297, MSH6 81298, 81300; PMS2 81317, 81319) is medically necessary for patients who meet **ANY** of the following:

- a. Patient meets Amsterdam II criteria or revised Bethesda guidelines (see **DEFINITIONS**); **OR**
- b. Patient has a first degree relative who meets the Amsterdam II or revised Bethesda guidelines, but that individual is not available or willing to be tested themselves; **OR**
- c. Patient has a first- or second-degree relative with a disease caused by a HNPCC mutation (genes MLH1, MSH2, MSH6, PMS2, or EPCAM); **OR**
- d. Patient with colorectal cancer under the age of 70 or with colorectal cancer over the age of 70 meeting Bethesda criteria; **OR**
- e. Patients with a predicted risk for Lynch syndrome >5% on one of the following prediction models: MMRpro, PREMM5, or MMRpredict; **OR**
- f. Patient diagnosed with endometrial cancer before the age of 50.

Genetic testing for **MLH1 hypermethylation testing** (81292, 81294) is medically necessary for **colon** and **endometrial tumors** being screened for Lynch syndrome that are IHC-abnormal with loss of expression of MLH1 protein products.

18. Hereditary pancreatitis (PRSS1, SPINK1, CFTR):

Genetic testing for PRSS1 gene mutation (81404) for hereditary pancreatitis (PRSS1 mutation) is medically necessary in patients with **ANY** of the following:

- a. A known familial variant of PRSS1 gene (personal history of pancreatitis not necessary); **OR**
- b. A first episode of unexplained/idiopathic episode of documented acute pancreatitis occurring in a child with a family history of pancreatitis; **OR**
- c. Recurrent (2 or more separate, documented episodes with hyperamylasemia/hyperlipasemia) attacks of acute pancreatitis or chronic pancreatitis for which there is no explanation (e.g., anatomical anomalies, ampullary or main pancreatic strictures, trauma, viral infection, gallstones, alcohol, drugs, hyperlipidemia) in a child or adult; **OR**
- d. Known chronic pancreatitis with a family history of chronic pancreatitis in first or second-degree relatives.

Genetic testing for SPINK1 (81404) and CFTR gene mutations for hereditary pancreatitis are medically necessary in patients with the following:

- a. Meets criteria b, c or d for PRSS1 testing and PRSS1 testing is negative for mutation.

19. Huntington's disease:

Genetic testing for CAG repeat length mutation in the HTT gene for Huntington disease (81401) is considered medically necessary in asymptomatic patients who:

- a. Have a first-degree blood relative - parent or sibling - with documented Huntington disease, **OR**
- b. Have a second-degree blood relative – grandparent, aunt or uncle - with documented Huntington disease and the first-degree blood relative status is unknown, **OR**
- c. Have specific symptoms likely to be Huntington disease but without a family history of the disease.

20. Hypertrophic Cardiomyopathy (HCM):

Mutation specific genetic testing for a Hypertrophic Cardiomyopathy (HCM) familial mutation is medically necessary for unaffected patients who meet a **AND** b, or c that follow:

- a. Patient has a 1st degree relative with a known pathogenic HCM gene mutation, **AND**
- b. Patient does not exhibit clinical evidence of HCM (e.g., EKG or echocardiogram), **OR**
- c. Symptomatic patients with a diagnosis of hypertrophic cardiomyopathy by echocardiography who have been recommended for genetic testing by an expert in medical genetics or hypertrophic cardiomyopathy and in whom familial testing for hypertrophic cardiomyopathy has not already been performed (this patient or an affected family member) and in whom establishing a genetic variant would impact the medical care of an unaffected and at-risk, first or second degree relative.

Notes:

- Testing of all patients with a diagnosis of hypertrophic cardiomyopathy for known familial variants is considered not medically necessary.
- HCM core genes for testing include: ACTC1, ACTN2, CSRP3, GLA, LAMP2, MYBPC3, MYH7, MYL2, MYL3, MYOZ2, PLN, PRKAG2, TNNC1, TNNI3, TNNT2, TPM1, TTR.
- Testing for alternative diagnoses in patients presenting with cardiac hypertrophy that mimics true HCM includes Fabry disease (gene: GLA), Pompe disease (GAA), Danon disease (LAMP2), AMPK-mediated glycogen storage (PRKAG2) and amyloidosis (TTR).

21. Juvenile Polyposis Syndrome (JPS)

Genetic testing for Juvenile Polyposis Syndrome (JPS) (BMP1A and SMAD4 gene mutations, sequencing followed by duplication/deletion testing if negative, 81479, 81405, 81406) is

considered medical necessary for diagnosis of JPS in persons who meet **ANY** of the following criteria:

- a. At least 3 to 5 juvenile polyps of the colon; **OR**
- b. Multiple juvenile polyps found throughout the GI tract; **OR**
- c. Any number of juvenile polyps in a person with a family history of JPS.

Genetic testing for SMAD4 is medically necessary for infants with first degree relatives with JPS due to SMAD4 gene mutation because of the additional risk of hereditary hemorrhagic telangiectasia.

22. Long QT Syndrome:

Genetic testing for long QT syndrome with the Cardiac ion channelopathy genomic sequence analysis panel testing (81413) followed by duplication/deletion gene analysis panel testing (81414) if sequence analysis is negative or serial single-gene testing (genes ANK2, CASQ2, CAV3, HERG, KCNE1, KCNE2, KCNH2, KCNQ1, RYR2, SCN5A) is medically necessary for the following:

- a. Persons with a prolonged QT interval on resting electrocardiogram (a corrected QT interval (QTc) of 470 msec in males and 480 msec in females) without an identifiable external cause for QTc prolongation (e.g., heart failure, bradycardia, electrolyte imbalances, certain medications and other medical conditions)
- b. Persons with first-degree relatives (siblings, parents, and children) with a defined LQT mutation or long QT syndrome in sudden death (1st or 2nd degree) relatives (test for the known familial variant).

23. Malignant Hyperthermia Susceptibility:

Genetic testing for RYR1 gene variants (81408, 81479) known to be causative for Malignant Hyperthermia Susceptibility is medically necessary for **ANY** of the following:

- a. First or second-degree blood relatives of patients with clinically confirmed malignant hyperthermia (clinically confirmed = positive contracture test or documented event after triggering anesthetic administered; test only for known familial variant if familial mutation known), **OR**
- b. Patient with clinically confirmed malignant hyperthermia or history suspicious for malignant hyperthermia.

Note: Genetic testing for CACNA1S gene mutation (81479) and STAC3 gene mutation (81479) is considered medically necessary for persons meeting criteria for RYR1 gene variant testing and for whom the testing is negative for a causative mutation.

24. Marfan syndrome

Genetic testing for a FBN1 gene mutation by sequence analysis followed by deletion and duplication analysis testing (81408, 81479) if negative for Marfan syndrome is considered medically necessary in **ONE** the following situations:

- a. Suspected, but not confirmed, Marfan syndrome in patients with **BOTH** of the following:
 - i. Absence of a confirmed family history of Marfan syndrome, **AND**
 - ii. Diagnosis of ectopia lentis with any aortic dilation or significant aortic dilation or dissection; **OR**

- b. Asymptomatic individual with a first-degree blood relative with Marfan Syndrome and a known genetic mutation (test for known familial mutation);

25. MUTYH Associated Polyposis

Genetic testing for MUTYH gene associated polyposis mutations (mutation testing and gene sequence analysis, 81401, 81406, 81479) is medically necessary for **ANY** of the following:

- a. Personal history of > 10 colonic adenomas; **OR**
- b. Person with a first-degree blood relative (i.e., sibling, parent, offspring) with a known familial deleterious MUTYH mutation (test only for the MUTYH pathogenic variant); **OR**
- c. A patient who meets **ONE** of the following criteria for serrated polyposis syndrome (below):
 - i. At least 5 serrated polyps proximal to the sigmoid colon with 2 or more of these being > 10 mm; **OR**
 - ii. 20 or more serrated polyps of any size, but distributed throughout the colon; **OR**
 - iii. Any number of serrated polyps proximal to the sigmoid colon in a person has a first degree relative with serrated polyposis.

26. Peutz-Jeghers Syndrome -STK11 gene testing (LKB1):

STK11 (LKB1) gene testing (sequencing followed by deletion/duplication testing if negative, 81404, 81405) is medically necessary for patients with a suspected or known clinical diagnosis of Peutz-Jeghers Syndrome (PJS), or a known family history of a STK11 (LKB1) mutation when **EITHER** of the following criteria are met:

- a. A relative with a known deleterious STK11 (LKB1) gene mutation; **OR**
- b. A clinical diagnosis of Peutz-Jeghers Syndrome based on at least **TWO** of the following features:
 - i. At least two Peutz-Jeghers Syndrome type hamartomatous polyps of the small intestine;
 - ii. Mucocutaneous hyperpigmentation of the mouth, lips, nose, eyes, genitalia or fingers;
 - iii. A family history of Peutz-Jeghers Syndrome.

27. Primary Dystonia (DYT1):

Genetic testing for DYT1 (81404, 81479) is medically necessary for **ANY** the following:

- a. Parents of children with an established DYT1 mutation, for purposes of family planning; **OR**
- b. Parents with onset of primary dystonia other than focal cranial-cervical dystonia after age 30 years who have an affected relative with early onset (before 30 years); **OR**
- c. Persons with primary dystonia with onset before age 30 years.

Genetic testing for DYT-1 is considered experimental and investigational for **ANY** of the following: (not all-inclusive)

- a. Asymptomatic patients (other than parents of affected children), including those with affected family members. Genetic testing for dystonia (DYT-1) is not sufficient to make a diagnosis of dystonia unless clinical features are present); **OR**
- b. Patients with onset of symptoms after age 30 years who have either focal or cranial-cervical dystonia; **OR**
- c. Patients with onset of symptoms after age 30 years who have no affected relative with early onset dystonia.

28. Phosphatase and Tensin Homolog (PTEN gene):

PTEN Gene Testing (sequencing followed by deletion/duplication testing if negative, 81321, 81323) is medically necessary in patients with a suspected or known clinical diagnosis of Cowden syndrome (CS) /PTEN Hamartoma Tumor syndrome (PHTS) or Bannayan-Riley-Ruvalcaba syndrome (BRR), or a known family history of a PTEN mutation who meets **ANY** of the following:

- a. A relative with a known deleterious PTEN gene mutation; **OR**
- b. A personal history of Bannayan Riley-Ruvalcaba syndrome; **OR**
- c. A person not meeting clinical diagnostic criteria for CS/PHTS with a personal history of **ANY** of the following:
 - i. Adult Lhermitte-Duclos disease (LDD); **OR**
 - ii. Autism-spectrum disorder and macrocephaly; **OR**
 - iii. At least two biopsy-proven trichilemmomas; **OR**
 - iv. Macrocephaly plus at least one other major criteria; **OR**
 - v. Three major criteria, without macrocephaly; **OR**
 - vi. One major and at least three minor criteria; **OR**
 - vii. Four or more minor criteria
- d. Family history of **BOTH** of the following:
 - i. At-risk relative (includes first-degree relative or more distant relatives if the first degree relative is unavailable or unwilling to be tested) with a clinical diagnosis of Cowden syndrome or Bannayan-Riley-Ruvalcaba syndrome (no previous genetic testing); **AND**
 - ii. ONE MAJOR or TWO MINOR criteria in the at-risk relative (see below). If two criteria involve the same structure/organ/tissue, both may be included as criteria.

MAJOR Criteria for PTEN genetic testing purposes are:

- a) Breast cancer;
- b) Endometrial cancer (epithelial);
- c) Follicular thyroid cancer;
- d) Multiple GI hamartomas or ganglioneuromas;
- e) Macrocephaly (e.g., 97th percentile or greater; 58 cm in adult women 60 cm in adult men);
- f) Macular pigmentation of glans penis;
- g) Mucocutaneous lesions (any of the following):
 - 1) One biopsy-proven trichilemmoma
 - 2) Multiple palmoplantar keratoses
 - 3) Multifocal or extensive oral mucosal papillomatosis
 - 4) Multiple cutaneous facial papules (often verrucous)

MINOR Criteria for PTEN genetic testing purposes are:

- a) Autism spectrum disorder;
- b) Colon cancer;
- c) Esophageal glycogenic acanthoses (>3);
- d) Lipomas
- e) Intellectual disability (i.e., IQ <75);
- f) Papillary or follicular variant of papillary thyroid cancer;
- g) Thyroid structural lesions (e.g., adenoma, nodule(s), goiter);
- h) Renal cell carcinoma;
- i) Single GI hamartoma or ganglioneuroma;

- j) Testicular lipomatosis;
- k) Vascular anomalies (including multiple intracranial developmental venous anomalies)

29. Primary Myelofibrosis Diagnosis

Genetic testing for JAK2/JAK2^{V617F}, CALR and MPL and other mutations may be medically necessary for the diagnosis of Primary Myelofibrosis in patients who meet criteria found in *Policy C.6.34 Tumor Marker Genetics*.

30. RBC genotyping:

RBC genotyping is medically necessary in **ANY** of the following situations:

- a. Patient with hemoglobinopathy; **OR**
- b. Patient who are known to be alloimmunized who are:
 - i. Multiply alloimmunized, **OR**
 - ii. Alloimmunized and expected to need recurrent transfusions, **OR**
 - iii. Alloimmunized and have a co-existing autoantibody; **OR**
 - iv. Patient who is expected to receive recurrent blood transfusions for which RBC genotyping will forego the need for repeat type and crossmatching of blood to identify suitable donor blood and has one of the following conditions:
 - a) Hematologic or oncologic malignancy; **OR**
 - b) Autoimmune hemolytic anemia.

31. SHOX-Related Short Stature:

Genetic testing for SHOX-related short stature using SHOX gene sequencing analysis followed by deletion and duplication testing (81479) if negative is medically necessary for children and adolescents with **ANY** of the following features:

- a. Above-average Body Mass Index (BMI); **OR**
- b. Cubitus valgus (increased carrying angle); **OR**
- c. Dislocation of the ulna at the elbow; **OR**
- d. Increased sitting height/height ratio; **OR**
- e. Madelung deformity of the fore arm; **OR**
- f. Muscular hypertrophy; **OR**
- g. Reduced arm span/height ratio; **OR**
- h. Short or bowed forearm.

32. Spinal Muscular Atrophy (SMA):

Genetic testing for SMA by testing for deletions in SMN1 and SMN2 is medically necessary for individuals with symptoms of spinal muscular atrophy, for example, symmetrical muscle weakness, hypotonia, and abnormal (absent or decreased) deep tendon reflexes.

33. Thyroid Nodules, Indeterminate

Genetic testing is considered medically necessary to aid in thyroid nodule diagnosis for patients who meet criteria found in *Policy C.6.34 Tumor Marker Genetics*.

34. Von-Hippel Lindau (VHL) Disease

Genetic testing for Von-Hippel Lindau (VHL) disease (known mutation or sequence analysis of VHL gene followed by deletion/duplication analysis if negative, (81404, 81403)) is medically necessary for persons with **EITHER** of the following:

- a. Person with a 1st or 2nd degree blood relative diagnosed with a known or suspected VHL gene mutation (test for the specific familial mutation); **OR**
- b. Personal history of 1 or more of the following VHL-associated lesions:
 - i. Clear cell renal carcinoma;
 - ii. Hemangioblastoma;
 - iii. Pheochromocytoma or paraganglioma;
 - iv. Endolymphatic sac tumor;
 - v. Epididymal or adnexal papillary cystadenoma;
 - vi. Pancreatic serous cystadenoma;
 - vii. Pancreatic neuroendocrine tumor;
 - viii. Retinal angioma;
 - ix. Multiple renal or pancreatic cysts.

D. Genetic Testing considered Experimental, Investigational or not Medically Necessary (Not an all-inclusive list):

1. The following genetic tests:
 - a. Percepta Bronchial Genomic Classifier;
 - b. Epilepsy and Seizure disorders sequencing panels including EpiSEEK;
 - c. Inherited cardiomyopathy genomic sequence analysis panel (CPT 81439);
 - d. Hearing loss genetic panels including OtoScope, OtoGenome, OtoSeq (CPT 81430 and 81431)
2. MTHFR genetic testing for risk assessment of hereditary thrombophilia;
3. Genetic testing of NF1 for Neurofibromatosis diagnosis, treatment and management based on café au late marks;
4. Whole genome or mitochondrial sequencing;
5. Genetic Testing for the purposes of surveillance;
6. The use of a genetic Variant of Uncertain Significance (VUS) result to make decisions about further testing of a patient or family member or for clinical decision making regarding evaluation and/or treatment.
7. SERPINA1 genetic testing to diagnose alpha-1-antitrypsin deficiency (AATD) any of the following situations, 1) in children and adults with unexplained chronic liver disease, 2) in children and adults with signs and symptoms of lung disease, and 3) for diagnosis of AATD in asymptomatic first-degree relatives of individuals with known AATD.
8. Combined Cardiac Panel (GeneDx) testing.

References:

Alford RL, et al. American college of medical genetics and genomics guideline for the clinical evaluation and etiologic diagnosis of hearing loss. *Genetics in Medicine*. 2014;16:347-355.

American College of Medical Genetics (ACMG) Guidelines, Array-Based Technology and Recommendations for Utilization in Medical Genetics Practice for Detection of Chromosomal Abnormalities, 2010 Genet Med, 12:11:742-745.

American Society of Human Genetics. Uncertain results related to patient symptoms: variants of uncertain significance. Available at: <https://www.ashg.org/education/csertoolkit/uncertainresults.html> Accessed May 22, 2018.

Craufurd D, et al. Diagnostic testing for Huntington's Disease. Pract Neuro. 2015;15:80-84.

Glueck C, Wang P, Freiberg RA. 2017. Osteonecrosis and thrombophilia: pathophysiology, diagnosis and treatment. In: Sierra R (eds) Osteonecrosis of the Femoral Head. Springer, Cham. Available at: https://link.springer.com/chapter/10.1007/978-3-319-50664-7_1 Accessed November 7, 2018.

Hayes, Inc. GTE Clinical Utility.

- Clinical utility of genetic testing for primary diagnosis of autism spectrum disorder. Publication date: June 29, 2018. Accessed November 7, 2018.
- Clinical utility of genetic testing to aid in the evaluation of syndromic or complex autism spectrum disorder. Publication date: August 22, 2018. Accessed November 7, 2018.
- Clinical utility of genetic testing to aid in the evaluation of idiopathic autism spectrum disorder. Publication date: August 22, 2018. Accessed November 7, 2018.
- Genetic testing for alpha-1-antitrypsin deficiency associated with chronic liver disease. Published July 31, 2018. Accessed November 7, 2018.
- Genetic testing for alpha-1-antitrypsin deficiency associated with lung disease. Published July 31, 2018. Accessed November 7, 2018.

Hayes, Inc. GTE Indication.

- Genetic Testing for Hereditary Hemorrhagic Telangiectasia. Published December 22, 2016. Accessed November 7, 2018.
- Genetic Testing for Hereditary leiomyomatosis and renal cell cancer. Published September 8, 2016. Accessed October 16, 2017.
- Genetic testing for PTEN hamartoma tumor syndrome (PHTS). Published Feb 2, 2017. Annual Review Mar 21, 2018. Accessed November 7, 2018.

Hayes, Inc. GTE Overview.

- Cystic Fibrosis Transmembrane Regulator – (CFTR). Published May 30, 2013. Annual Review May 13, 2015. Report archived Jun 30, 2018. Accessed November 7, 2018.
- Genetic Testing of NF1 for Neurofibromatosis Diagnosis, Treatment and Management. Publication date: June 2, 2016. Accessed November 7, 2018.
- Genetic Testing for Lynch Syndrome. Published Dec 11, 2014. Report archived Sept 11, 2018. Accessed November 7, 2018.

Hayes, Inc. GTE Report.

- Afirma Thyroid FNA Analysis (Veracyte). Published October 19, 2017. Accessed November 7, 2018.
- Guardant360. Published September 15, 2016. Annual review May 8, 2018. Accessed June 25, 2018

Hershberger RE, et al. Genetic evaluation of cardiomyopathy: a clinical practice resource of the American College of Medical Genetics and Genomics (ACMG). Genetics in Medicine. 2018; Published online 14 June 2018. Available at: <https://www.acmg.net/PDFLibrary/Genetic-Evaluation-Cardiomyopathy.pdf> Accessed August 8, 2018.

Evaluation of genomic Applications in Practice and Prevention (EGAPP) Working Group, Recommendations from the EGAPP Working Group: Routine Testing for Factor V Leiden (R506Q) and prothrombin (20210G.A) mutations in adults with history of idiopathic venous thromboembolism and their adult family members, *Genetics in Medicine*. 2011;13(1).

Loupakis, F., et al, KRAS codon 61, 146, and BRAF mutations predict resistance to cetuximab and irinotecan in KRAS codon 12 and 13, wild type metastatic colorectal cancer. *BR J Cancer*, 2009. 101(4): p. 715-721.

Marcus FI, et al. Diagnosis of Arrhythmogenic Right Ventricular Cardiomyopathy/Dysplasia Proposed Modification of the Task Force Criteria. *Circulation*. 2010;121:1533-1541.

Martin AJ, Braunwald E. Hypertrophic cardiomyopathy. Genetics, pathogenesis, clinical manifestations, diagnosis and therapy. *Circ Res*. 2017;121:749-770.

National Comprehensive Cancer Network (NCCN); NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines); Available at NCCN.org.

- Breast Cancer. V2.2018-Oct, 2017; Accessed October 10, 2018.
- Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma; V2.2019-October; Accessed October 10, 2018.
- Myeloproliferative Neoplasms; V2.2018-Sept 7, 2017; NCCN.org. Accessed May 21, 2018.
- Non-Small Cell Lung Cancer. V1.2019-October; Accessed October 24, 2018.
- Thyroid Carcinoma; V1.2019-March; Accessed June 12, 2019.

National Comprehensive Cancer Network (NCCN); NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines); Genetic/Familial High-Risk Assessment:

- Colorectal; Version 3.2017-October 10, 2017; NCCN.org. Accessed October 16, 2017.
- Breast and Ovarian; V2.2019-July; Accessed October 24, 2018.

Seaver LH, Irons M. ACMG practice guideline: genetic evaluation of short stature. *Genet Med*. 2009;11(6):465-470.

Segal JB, Brotman DJ, et.al. Predictive Value of Factor V Leiden and Prothrombin G20210A in Adults with Venous Thromboembolism and in Family Members of Those with a Mutation. *JAMA*. 2009;301(23):2472-2485.

Telen M. The use of genotyping in transfusion medicine. *Hematologist*. 2014;11(6):4-5. Available at: <http://www.hematology.org/Thehematologist/Issues/5432.aspx> Accessed November 7, 2018.

Vaughn, C.P., et al, Frequency of KRAS, BRAF, and NRAS Mutations in Colorectal Cancer. *Genes, Chromosomes, and Cancer*. 2011. 501(5):307-312.

Watson MS, Cutting GR, Desnick RJ, Driscoll DA, Klinger K, Mennuti M, Palomaki GE, Popovich BW, Pratt VM, Rohlf EM, Strom CM, Richards CS, Witt DR, Grody WW. Cystic fibrosis population carrier screening: 2004 revision of American College of Medical Genetics mutation panel. *Genet Med* 2004;6:387-391.