



Genetic Testing

Last Revision/Review Date: September 15, 2021

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.

Definitions

Amsterdam II criteria:	Proposed to identify patients who should be tested for Lynch Syndrome. The patient must have at least 3 relatives with a hereditary nonpolyposis colorectal cancer (HNPCC)-related cancer (see below), and ALL of the following criteria must be met: <ol style="list-style-type: none">1. At least 1 of the relatives with colon cancer associated with HNPCC should be diagnosed before age 50 years; AND2. At least 2 successive generations must be affected; AND3. Familial adenomatous polyposis should be excluded in the colorectal cancer cases (if any); AND4. One must be a first-degree relative of the other two; AND5. Tumors should be verified whenever possible.
Close Blood Relative	Defined as a 1st, 2nd or 3rd degree blood relative. <ol style="list-style-type: none">a. First degree relatives including parents, full siblings and offspring which share approximately 50% of his/her genes.b. Second degree relatives include half-brothers/sisters, aunts/uncles, grandparents, grandchildren and nieces/nephews which share approximately 25% of his/her genes.c. Third degree relatives include first cousins, great aunts/uncles, great grandchildren and great grandparents which share approximately 12.5% of his/her genes.
Curaçao criteria:	International consensus diagnostic criteria for hereditary hemorrhagic telangiectasia (HHT, or Osler-Weber-Rendu disease). Definite is 3 or more criteria, suspected is 2 criteria, unlikely 1 criterion. <ol style="list-style-type: none">1. Spontaneous and recurrent epistaxis.2. Multiple mucocutaneous telangiectasia at characteristic sites;

	<p>3. Visceral involvement (e.g., gastrointestinal telangiectasia; pulmonary, cerebral or hepatic arteriovenous malformations);</p> <p>4. A first degree relative with HHT.</p>
Cytogenetic Studies	Describe the microscopic examination of the physical appearance of human chromosomes.
Genetic Testing	<p>Laboratory analysis of human deoxyribonucleic acid (DNA), ribonucleic acid (RNA), chromosomes, proteins, and certain metabolites in order to identify genotypes, mutations, or karyotypes to determine a predisposition to a particular health condition or to confirm a diagnosis of genetic disease. Testing may include:</p> <p>Gene: a unit of heredity composed of DNA occupying a specific location on a chromosome.</p> <p>Genome: the total chromosome genetic content of an organism.</p> <p>Exon: the protein "coding" part of the gene.</p> <p>Exome: the totality of all exons of the genome.</p> <p>Variant: a change in the genetic code. a.k.a. mutation.</p> <p>Whole exome sequencing: a type of next-generation sequencing to evaluate multiple variants at one time. Sequencing all protein-coding regions of the genome, about 1% of the entire human genome.</p> <p>Whole genome chromosome microarray: detects genetic abnormalities on all chromosomes at the same time and typically used for children with unexplained intellectual disability, congenital anomalies or autism spectrum disorder.</p> <p>Whole genome sequencing: a type of next-generation sequencing to evaluate multiple variants at one time. DNA sequencing of the entire genome, including protein coding (exon) and non-coding regions (introns). May not include mitochondrial genome.</p>
Genetic testing validity criteria	<p>Analytical validity- the test accurately and reliably detects whether a specific genetic variant is present or absent.</p> <p>Clinical validity- the genetic variant being tested is associated with a disease, outcome or a response to a treatment.</p> <p>Clinical utility – the test provides information about diagnosis, treatment management, or prevention of a disease that will be useful for the physician or patient.</p>
Hereditary nonpolyposis colorectal cancer (HNPCC-related cancers)	Include colorectal, endometrial, gastric, ovarian, pancreas, ureter and renal pelvis, biliary tract, brain (usually glioblastoma), and small intestinal cancers, as well as sebaceous gland adenomas and keratoacanthomas.
Metachronous cancers	Those occurring more than 6 months after the first primary cancer.
Molecular Cytogenetics	Involves the combination of <u>molecular biology</u> and <u>cytogenetics</u> . This includes the use of a series of techniques referred to as <u>fluorescence in situ hybridization</u> , or FISH, in which <u>DNA</u> probes are labeled with different colored fluorescent tags to visualize one

	or more specific regions of the genome. FISH can either be performed as a direct approach to metaphase chromosomes or interphase nuclei.
Revised Bethesda criteria:	<p>Criteria were developed to identify patients with colorectal cancer who should undergo tumor testing for microsatellite instability and are also used for Lynch Syndrome screening. The patient must meet ONE OR MORE of the following:</p> <ol style="list-style-type: none"> 1. Colorectal cancer in a patient with 1 or more first-degree relatives with an HNPCC-related cancer, with one of the cancers diagnosed under age 50 years; OR 2. Colorectal cancer in a patient with two or more first- or second-degree relatives with an HNPCC-related cancer, regardless of age; OR 3. Patient has colorectal cancer diagnosed before age 50 years; OR 4. Patient has colorectal cancer with microsatellite instability-high (MSI-H) histology, where cancer is diagnosed before age 60 years; OR 5. Patient has synchronous, metachronous, colorectal or other tumor associated with HNPCC regardless of age.
Synchronous cancers	Those occurring within 6 months of the first primary cancer.
Tumor Markers	are used to assess cancers response to treatment and to check for recurrence. In some types of cancer, tumor marker levels may reflect the extent or stage of the disease and can be useful in predicting how well the disease will respond to treatment. Can be found in blood, urine or tissue.
Variants of Unknown Significance (VUS)	Gene sequencing variants that have an uncertain relationship to disease and are therefore not recommended to be used for clinical decision making (e.g., to determine further evaluation for the patient or family member or for treatment recommendations). VUS can be reclassified over time as "benign" or "likely pathogenic/pathogenic" as further information becomes available about their relationship to disease but until then, their clinical implications are unknown.

Related Documents

C.6.16 Pharmacogenetic Testing
 C.6.17 Non-Invasive Fetal Aneuploidy Testing
 C.6.18 Prenatal Preconception Genetic Testing
 C.6.21 Genetic Testing for Hereditary Breast and/or Ovarian Cancer Syndromes including BRCA
 C.6.31 Whole Exome and Whole Genome Sequencing
 C.6.34 Tumor Marker Genetics

Requirements

None.

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. Limited gene panels are provided by a vendor contracted to perform the specific genetic testing; **AND**
- e. The genetic disorder cannot be identified through other types of biochemical testing; **AND**
- f. 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. Limited gene panel tests are provided by a vendor contracted to perform the specific genetic testing; **AND**
- e. The genetic disorder cannot be identified through other types of biochemical testing; **AND**
- f. 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. AlloMap testing

AlloMap gene expression profile testing is medically necessary to assist in the diagnosis of cellular rejection and reduce the need for endomyocardial biopsy in patients with cardiac transplant who meet the following:

- a. Aged 15 or older; **AND**
- b. At least 55 days and not more than 5 years post-cardiac transplant; **AND**

- c. Based on clinical presentation the patient is suspected to have no or low rejection (0 or 1R), e.g., absence of fevers, fatigue or weakness, shortness of breath, worsening edema or weight gain, low blood pressure, rapid or irregular heart rate; **AND**
- d. Testing is done at planned intervals post-transplant at weeks, e.g., 12, 16, 20, 24, 30, 36, 42, 48, 52; at month 15, 18, 21, 24; and at year 3, 4, and 5, **AND**
- e. Testing done before 12 weeks if patient is on 20mg of prednisone or less.

Note: The initial authorization may be for 9 AlloMap tests within the first 12 months and 4 tests in the second twelve months for those patients who meet criteria a-c. A new prior authorization request will be required for continued AlloMap testing beyond the initial 12-month authorization.

2. APC testing for Familial Adenomatous Polyposis

Adenosis polyposis coli (APC) genetic testing (81479, 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 or unilateral congenital hypertrophy of retinal pigment epithelium (CHRPE); **OR**
- c. Patients with known familial APC gene mutation (81202).

NOTE: Test for the known familial mutation when available. Full sequencing and duplication/deletion APC genetic testing (81479, 81201, 81203) is considered medically necessary when the specific family mutation is not obtainable.

NOTE: Patients meeting medical necessity criteria for individual disease testing may also undergo testing using a multigene colorectal cancer panel (i.e. Prevention Genetics Colorectal Cancer panel, test code 5467).

3. Aplastic Anemia (AA) / Bone Marrow Failure

Genetic testing for an inherited cause of AA/BMF/unexplained hypocellular bone marrow using a multigene inherited bone marrow failure panel approach is medically necessary in patients who meet **ANY** of the following:

- a. Age < 50; **OR**
- b. Patient with an abnormal chromosome breakage test; **OR**
- c. One or more first or second-degree relatives with one of the following **OR**:
 - i. Chronic unexplained cytopenia(s),
 - ii. AA/BMF,
 - iii. Myelodysplastic syndrome,
 - iv. Acute myeloid leukemia;
- d. Personal or family history of organ system features seen in a known inherited bone marrow failure syndrome (e.g. lymphedema, immunodeficiency, congenital anomalies, etc.).

4. 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.

5. Catecholaminergic Polymorphic Ventricular Tachycardia (CPVT):

Limited gene panel testing for catecholaminergic polymorphic ventricular tachycardia by sequence analysis panel testing (81413) followed by duplication/deletion gene analysis panel testing (81414) if sequence analysis is negative, or next generation sequencing (81479) 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, catecholamine, or emotion induced polymorphic ventricular tachycardia or ventricular fibrillation, occurring in a structurally normal heart.

NOTE:

- 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.

6. 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).

7. 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.

8. 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.

9. Diabetes (monogenic diabetes syndromes, maturity onset diabetes of the young (MODY))

Genetic testing for GCK and/or HNF1A mutations followed by HNF4A if HNF1A testing is negative as a cause of diabetes is medically necessary for patients with **ANY** of the following:

- a. Patients diagnosed with presumed Type 1 Diabetes at age 35 or younger with who have
 - i. Negative diabetes-associated autoantibodies (e.g., islet autoantibodies glutamic acid decarboxylase (GAD) 65, insulin, tyrosine phosphatases, IA-2 and IA-2 beta), **AND**
 - ii. Evidence of endogenous insulin, **AND**
 - iii. Family history of diabetes; **OR**
- b. Patients diagnosed with presumed Type 2 Diabetes at age 35 or younger who have
 - i. Strong family history of diabetes in at least two generations, **AND**
 - ii. Are non-obese.

Genetic testing using a neonatal diabetes panel to determine the cause of neonatal diabetes is medically necessary for patients with diagnosed with diabetes in the first 6 months of life.

10. (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 mutation); **OR**
- d. Venous thromboembolism in unusual sites (e.g., hepatic, mesenteric, and cerebral veins).
- e. 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**
- f. 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.

11. Factor V Leiden:

Factor V Leiden genetic testing (Factor V Leiden mutation, 81241) is medically necessary for patients with an abnormal activated protein C resistance assay **AND 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. Venous thromboembolism in unusual sites (e.g., hepatic, mesenteric, retinal and cerebral veins); **OR**
- e. VTE associated with oral contraceptives or hormone replacement therapy; **OR**
- f. VTE during pregnancy or puerperium; **OR**
- g. Pregnant women or women who are planning to become pregnant without a personal history of venous thromboembolism **AND**
 - i. 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**
 - ii. have a first-degree relative with a history of high-risk thrombophilia (e.g., antithrombin deficiency, double heterozygosity or homozygosity for FVL or prothrombin gene mutation); **OR**
- h. 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**
- i. 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.

12. 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).

13. 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.

14. 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.

15. 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.

16. 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.

17. Hereditary Diffuse Gastric Cancer

Genetic testing for Hereditary Diffuse Gastric Cancer (CDH1 mutation) is medically necessary for patients who meet **ANY** of the following criteria:

- a. 2 gastric cancer cases in a family, 1 confirmed diffuse gastric cancer (DGC) diagnosed before age 50; **OR**
- b. 3 confirmed cases of DGC in first- or second- degree relatives independent of age; **OR**
- c. DGC diagnosed before age 40 years without a family history; **OR**
- d. Personal or family history of DGC and lobular breast cancer, 1 diagnosed before the age of 50.

18. 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 **ANY** 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. Patient has excess iron documented on direct assessment, e.g., MRI scan or biopsy, AND other hepatic and hematologic disorders have been ruled out as the cause of iron overload; **OR**
- c. 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.

19. 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 either:
 - i. do not meet definite Curaçao criteria when results are to be used for testing at-risk family members or confirm a diagnosis; **OR**
 - ii. 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.

20. 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.

21. 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 $\geq 5\%$ on one of the following prediction models: MMRpro, PREMM5, or MMRpredict; **OR**
- f. Patient diagnosed with colon cancer or endometrial cancer and any **ONE** of the following:
 - i. Diagnosed before the age of 50; **OR**
 - ii. A synchronous or metachronous Lynch syndrome related cancer (colorectal, endometrial, gastric, ovarian, pancreas, urothelial, brain (usually glioblastoma), biliary tract, small intestinal, sebaceous adenoma, carcinoma, keratoacanthoma); **OR**
 - iii. 1 first-degree or second-degree relative with a Lynch syndrome related cancer diagnosed before the age of 50; **OR**
 - iv. ≥ 2 first degree or second-degree relatives with a Lynch syndrome cancer regardless of age; **OR**
- g. Patient diagnosed with high-risk, very high-risk, regional or metastatic prostate cancer; **OR**
- h. Patient diagnosed with ovarian cancer including fallopian tube and primary peritoneal cancers; **OR**
- i. Patient diagnosed with pancreatic adenocarcinoma; **OR**
- j. Patient with a colorectal tumor with MSI-high (MSI-H) histology or absent ≥ 1 DNA mismatch repair (dMMR) protein on IHC without MLH1 methylation; **OR**
- k. Patient with a tumor with MMR deficiency diagnosed at any age; **OR**
- l. Family history on same side of family of any **ONE** of the following:
 - i. ≥ 1 first-degree relative with colorectal or endometrial cancer diagnosed at age < 50 ;
 - ii. ≥ 1 first-degree relative with colorectal or endometrial cancer and a synchronous or metachronous Lynch syndrome related cancer (colorectal, endometrial, gastric, ovarian, pancreas, urothelial, brain (usually glioblastoma), biliary tract, small intestinal cancers, sebaceous adenoma, sebaceous carcinoma, keratoacanthoma);

- iii. ≥ 2 first-degree or second-degree relatives with Lynch syndrome related cancers (colorectal, endometrial, gastric, ovarian, pancreas, urothelial, brain (usually glioblastoma), biliary tract, small intestinal cancers, sebaceous adenoma, sebaceous carcinoma, keratoacanthoma), including ≥ 1 diagnosed before age 50;
- iv. ≥ 3 first-degree or second-degree relatives with Lynch syndrome related cancers (colorectal, endometrial, gastric, ovarian, pancreas, urothelial, brain (usually glioblastoma), biliary tract, small intestinal cancers, sebaceous adenoma, sebaceous carcinoma, keratoacanthoma) regardless of age.

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.

22. 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 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.

23. Hereditary Renal Cell Carcinoma

Genetic testing for genetic mutations associated with hereditary renal cell carcinoma using a multiple gene (see note) or single gene approach is medically necessary in patients with ANY of the following:

- a. Renal cell carcinoma diagnosed at age ≤ 46 years of age, **OR**
- b. Bilateral or multifocal tumors, **OR**
- c. 1 or more first- or second-degree relatives with renal cell carcinoma, **OR**
- d. Tumor pathology shows **ONE** of the following characteristics:
 - i. Multifocal papillary histology, **OR**
 - ii. Birt-Hogg-Dube syndrome (BHDS)-related histology (multiple chromophobe, oncocytoma, or oncocytic hydrid – test FLCN gene mutation), **OR**

- iii. Angiomyolipomas of the kidney and one additional tuberous sclerosis complex criterion in the same person (see separate tuberous sclerosis criteria -test TSC1 and TSC2 gene mutations), **OR**
- iv. Succinate dehydrogenase (SDH)-deficient renal cell histology (test SDHA/B/C/D genes).

NOTE: Patients with findings of a specific syndrome or a known family history of a specific hereditary renal cell carcinoma syndrome should be tested for that specific syndrome first before using a multiple gene panel.

NOTE: 7 syndromes have been identified: von Hippel Lindau (see also separate criteria, VHL gene), Hereditary papillary renal carcinoma (MET gene), Birt-Hogg-Dube syndrome (FLCN gene), Tuberous sclerosis complex (see also separate criteria, TSC gene, TSC1 & TSC2 gene), Hereditary leiomyomatosis and renal cell carcinoma (FH gene), BAP1 tumor predisposition syndrome (BAP1 gene) and Hereditary paraganglioma/pheochromocytoma syndrome (see also separate criteria, SDHA/B/C/D genes).

24. 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.

25. Hypertrophic Cardiomyopathy (HCM):

Mutation specific and limited gene panel 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.

26. Inherited Bone Marrow Failure / hematologic malignancy predisposition syndromes

Genetic testing for an inherited cause a hematologic malignancy, using a multigene inherited bone marrow failure panel approach is medically necessary in patients who meet **ANY** of the following:

- a. Diagnosis of myelodysplastic syndrome (MDS) or acute myeloid leukemia (AML) with myelodysplastic related changes prior to age 50; **OR**
- b. Diagnosis of chronic unexplained cytopenia(s), MDS, AML, Acute Lymphoblastic Leukemia (ALL) or a Myeloproliferative neoplasms (MPN) **AND**
 - i. First and/or second degree relative with MDS, AML, ALL, MPN or chronic unexplained cytopenia(s); **OR**
 - ii. Personal or family history of organ system features suggestive of a known inherited hematologic malignancy predisposition syndrome (e.g. lymphedema, pulmonary fibrosis, immunodeficiency, ataxia, congenital anomalies, etc.)
- c. Newly diagnosed aplastic anemia; **OR**
- d. Children and young adults with monosomy 7; **OR**
- e. Hypocellular MDS; **OR**
- f. Diagnosis of therapy-related MDS, AML or ALL after breast cancer treatment, **OR**
- g. A likely pathogenic or pathogenic variant in a gene with known hereditary potential has been identified on an acquired (non-hereditary or somatic) mutation panel performed on their hematologic malignancy at a variant allele frequency consistent with a possible hereditary state (e.g. DDX41, GATA2, RUNX1, biallelic CEBPA mutations, ANKRD26, ETV6, MBD4, MECOM/EVI1, SAMD9/SAMD9L, TERC/TERT, ATG2B, GSKIP). **NOTE:** targeted testing for the identified variant alone is warranted and panel-based germline (hereditary) testing may be warranted if the individual additionally meets a, b, or c; **OR**
- h. Three or more close blood relatives with MDS, AML, ALL, MPN, or chronic unexplained cytopenia(s), Chronic Lymphocytic Leukemia, Lymphoma or Multiple Myeloma; **OR**
- i. Close blood relative of a person with known or suspected germline (hereditary) mutation who is being evaluated as a bone marrow/stem cell donor if knowing the donor's status would impact this person's clinical management or their eligibility or safety as a donor.

NOTE: A multigene approach is warranted unless the patient meets clinical diagnostic criteria for a known syndrome with a single gene accounting for the majority of cases (e.g. Shwachman Diamond syndrome and SBDS gene) **OR** a familial variant is already known in a close relative to allow single gene sequencing plus deletion/duplication testing or familial targeted testing, respectively.

27. Juvenile Polyposis Syndrome (JPS)

Genetic testing for Juvenile Polyposis Syndrome (JPS) (BMPR1A and SMAD4 gene mutations, sequencing and duplication/deletion testing, 81479, 81405, 81406) is considered medical necessary for diagnosis of JPS in persons who meet **ANY** of the following criteria:

- a. ≥ 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.

NOTE: Patients meeting medical necessity criteria for individual disease testing may also undergo testing using a multigene colorectal cancer panel (i.e. Prevention Genetics Colorectal Cancer panel, test code 5467).

28. Li-Fraumeni Syndrome (TP53 gene mutation) – (CPT 81403, 81405)

Genetic testing for the TP53 gene mutation is medically necessary when associated with genetic counseling (see Documentation Required) and **ANY** of the following are met. (Patients with a known familial mutation must be tested for the single known mutation first. If unknown, comprehensive TP53 testing of patient or, if unaffected, the family member with the highest likelihood of mutation should be considered.)

1. Patient is from a family with a known TP53 mutation; **OR**
2. Classic Li-Fraumeni syndrome (LFS) including **ALL** the following:
 - a. Patient is age < 45 with a sarcoma; **AND**
 - b. A first degree relative diagnosed at age < 45 with cancer; **AND**
 - c. An additional first or second degree relative in the same lineage with cancer diagnosed at age < 45, or a sarcoma at any age; **OR**
3. Chompret criteria including **ANY** of the following:
 - a. Patient with a tumor from LFS tumor spectrum (soft tissue sarcoma, osteosarcoma, brain tumor, breast cancer, adrenocortical carcinoma, leukemia, lung bronchoalveolar cancer) at age < 46, **AND** at least one first or second degree relative with any of the aforementioned cancers (other than breast cancer if the proband has breast cancer) at age < 56 or with multiple primaries at any age; **OR**
 - b. Patient with multiple tumors (except multiple breast tumors), two of which belong to LFS tumor spectrum with the initial cancer occurring at age < 46; **OR**
 - c. Patient with adrenocortical carcinoma, choroid plexus carcinoma or rhabdomyosarcoma of embryonic anaplastic subtype, at any age of onset, regardless of the family history; **OR**.
 - d. Breast cancer diagnosed at age ≤ 30.

29. 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).

30. 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.

31. 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);

32. 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; **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, all being ≥5mm in size, with 2 or more of these being > 10 mm; **OR**
 - ii. 20 or more serrated polyps of any size, but distributed throughout the colon with ≥5 being proximal to the rectum; **OR**
 - iii. Any number of serrated polyps proximal to the sigmoid colon in a person who has a first degree relative with serrated polyposis.

NOTE: Patients meeting medical necessity criteria for individual disease testing may also undergo testing using a multigene colorectal cancer panel (i.e. Prevention Genetics Colorectal Cancer panel, test code 5467).

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

STK11 (LKB1) gene testing (sequencing and deletion/duplication testing, 81404, 81405, 81479) 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 GI tract;
 - ii. Mucocutaneous hyperpigmentation of the mouth, lips, nose, eyes, genitalia or fingers;
 - iii. A family history of Peutz-Jeghers Syndrome.

NOTE: Patients meeting medical necessity criteria for individual disease testing may also undergo testing using a multigene colorectal cancer panel (i.e. Prevention Genetics Colorectal Cancer panel, test code 5467).

34. Pheochromocytoma & Paranglioma

The following germline testing is medically necessary in patients (adults and children) with pheochromocytoma or paraganglioma:

- a. MAX, MEN1, NF1, RET, SDHA, SDHAF2, SDHB, SDHC, SDHD, VHL, TMEM127.

NOTE: for syndromic presentation, refer to Policy C.6.07 Genetic Testing and specific syndromes, i.e., Von-Hippel Lindau (VHL), RET oncogene related (MEN2 syndromes).

35. 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.

36. PTEN-associated Hamartoma Tumor Syndrome gene):

PTEN Gene Testing (sequencing and deletion/duplication testing, 81479, 81321, 81323) is medically necessary in patients with a suspected or known clinical diagnosis of Cowden syndrome (CS) /PTEN Hamartoma Tumor syndrome (PTHS) 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 meeting clinical diagnostic criteria for CS/PHTS (see criteria below under e) Must meet **ONE** of the following:
 - i. Three or more major criteria and one must include macrocephaly, Lhermitte-Duclos disease, or gastrointestinal hamartomas; **OR**
 - ii. Two major and three minor criteria. **OR**
- d. A person not meeting clinical diagnostic criteria for CS/PHTS with a personal history of **ANY** of the following:
 - i. Adult Lhermitte-Duclos disease (cerebellar tumors); **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
- e. 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** clinical diagnostic 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) Lhermitte-Duclos disease (adult)
- f) Macrocephaly (e.g., 97th percentile or greater; 58 cm in adult women 60 cm in adult men);
- g) Macular pigmentation of glans penis;
- h) Mucocutaneous lesions (any of the following):
 - 1) One biopsy-proven trichilemmoma
 - 2) Multiple (≥3) palmo/plantar/acral keratoses
 - 3) Multifocal or extensive oral mucosal papillomatosis
 - 4) Multiple (≥3) cutaneous neuromas

MINOR Criteria for PTEN genetic testing purposes are:

- a) Autism spectrum disorder;
- b) Colon cancer;
- c) Esophageal glycogenic acanthoses (≥ 3);
- d) Lipomas (≥ 3);
- e) Intellectual disability (i.e., IQ < 75);
- f) Papillary or follicular variant of papillary thyroid cancer;
- g) Thyroid structural lesions (e.g., adenoma, multinodular, goiter);
- h) Thyroid cancer (papillary or follicular variant of papillary)
- i) Renal cell carcinoma;
- j) Testicular lipomatosis;
- k) Vascular anomalies (including multiple intracranial developmental venous anomalies)

37. 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*.

38. 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; **OR**
- c. Patient currently receiving or planned to receive anti-CD38 monoclonal antibody treatment.

39. RET Oncogene

Testing for the RET oncogene is medically necessary for evaluation and treatment of patients including children at a very early age, with **ANY** of the following:

- a. Medullary thyroid carcinoma (MTC), **OR**
- b. Primary C-cell hyperplasia, **OR**
- c. Clinical diagnosis of MEN 2 syndrome in patient or patient's first degree relative with (MEN2A = 2 or more: MTC, pheochromocytoma or hyperparathyroidism; MEN2B = syndrome with MTC, pheochromocytoma, mucosal neuromas of the lips and tongue, medullated corneal nerve fibers, distinctive facies with enlarged lips, Marfanoid habitus or inability to cry tears).

40. 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:

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

41. 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.

42. Thyroid Nodules, Indeterminate

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

43. Tuberous Sclerosis Complex

Genetic testing for tuberous sclerosis (TSC or TSC1 and TSC2 genes) is considering medically necessary for patients who **ONE** meet the following:

- a. 2 or more MAJOR criteria
- b. At least 1 MAJOR and 1 MINOR criteria

MAJOR Criteria

- i. Renal angiomyolipoma,
- ii. Cardiac rhabdomyoma,
- iii. Cortical dysplasia, including tubers and cerebral white matter migration lines,
- iv. Angiofibromas (3 or more) or fibrous cephalic plaque,
- v. Hypomelanotic macules (>3mm in diameter),
- vi. Lymphangioleiomyomatosis (LAM),
- vii. Multiple retinal nodular hamartomas,
- viii. Shagreen patch,
- ix. Subependymal nodules,
- x. Ungual fibromas.

MINOR Criteria

- i. Multiple renal cysts,
- ii. Confetti skin lesions (numerous 1-3 mm hypopigmented macules scattered over regions of the body such as arms and legs),
- iii. Dental enamel pits (>3),
- iv. Nonrenal hamartomas,
- v. Retinal achromic patch.

44. Uveal Melanoma

The following germline testing for is medically necessary to evaluate for a hereditary syndrome in patients with uveal melanoma:

- a. BAP1,
- b. BRCA,
- c. PALB2.

45. Von-Hippel Lindau (VHL) Disease

Genetic testing for Von-Hippel Lindau (VHL) disease (known mutation testing or of VHL gene sequencing and deletion/duplication analysis, (81479, 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 (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);
 - e. +RNAinsight (concurrent DNA & RNA testing), Ambry Genetics.
 - f. AlloSure testing for transplant rejection in patients with heart or kidney transplants. NOTE: HeartCare testing is the combination of AlloMap and AlloSure testing – see criteria above for AlloMap testing which does not include AlloSure testing.
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 lait 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. *Genet Med*. 2010;12:11:742-745.

American College of Obstetricians and Gynecologists, Society for Maternal-Fetal Medicine. Management of Stillbirth: Obstetric Care Consensus No. 10. *Obstet Gynecol*. 2020;135(3):e110.

American Diabetes Association. 2. Classification and Diagnosis of Diabetes: Standards of Medical Care in Diabetes-2020. *Diabetes Care*. 2020;43(S1):S14-31.

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

Deignan JL, Astbury C, Cutting GR, et al. CFTR variant testing: a technical standard of the American College of Medical Genetics and Genomics (ACMG). *Genet Med*. 2020;22:1288–1295.

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).

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.

Hayes, Inc. Clinical Utility Evaluation.

- Clinical utility of genetic testing for primary diagnosis of autism spectrum disorder. Publication date June 29, 2018. Annual review Jul 28, 2020. Accessed June 23, 2021.
- Clinical utility of genetic testing to aid in the evaluation of syndromic or complex autism spectrum disorder. Publication date: August 22, 2018. Annual review Jul 28, 2020. Accessed June 23, 2021.
- Clinical utility of genetic testing to aid in the evaluation of idiopathic autism spectrum disorder. Publication date August 22, 2018. Annual review Jul 28, 2020. Accessed June 23, 2021
- Genetic testing for alpha-1-antitrypsin deficiency associated with chronic liver disease. Published July 31, 2018. Annual review Sep 23, 2020. Accessed June 23, 2021.
- Genetic testing for alpha-1-antitrypsin deficiency associated with lung disease. Published July 31, 2018. Annual review Sep 23, 2010. Accessed June 23, 2021.
- Genetic Testing for Hereditary Hemorrhagic Telangiectasia. Published December 22, 2016. Annual Review Oct 26, 2020. Accessed June 23, 2021.
- Genetic Testing for Hereditary leiomyomatosis and renal cell cancer. Published September 8, 2016. Annual Review Jul 28, 2020. Accessed June 23, 2021

- Genetic testing for Factor V Leiden in women with unexplained recurrent pregnancy loss. Published Dec 2018. Annual Review Nov 2020. Accessed January 6, 2021.
- Genetic testing for PTEN hamartoma tumor syndrome (PHTS). Published Feb 2, 2017. Annual Review Mar 28, 2021. Accessed June 23, 2021.

Hayes, Inc. Molecular Test Assessment.

- AlloSure Kidney (CareDx Inc.). Published May 27, 2021. Accessed June 23, 2021.
- Guardant360. Published December 11, 2018. Annual review Aug 10, 2020. Accessed August 19, 2020.

Hayes, Inc. Precision Medicine Research Brief.

- Genetic Testing of NF1 for Neurofibromatosis Diagnosis, Treatment and Management. Published June 2, 2016. Accessed August 19, 2020.
- Heart Care Comprehensive Solution (CareDx Inc.). Published April 23, 2021. Accessed June 23, 2021.

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;20:899-909.

Kujovich JL. Factor V Leiden thrombophilia. *Genet Med*. 2011;13:1-16.

Lancman G, Arinsburg S, Jhang J, et al. Blood transfusion management for patients treated with anti-cd38 monoclonal antibodies. *Front Immunol*. 2018;9:2616.

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.

- Acute Lymphoblastic Leukemia. V1.2021. Accessed May 19, 2021.
- Acute Myeloid Leukemia. V3.2021. Accessed March 21, 2021.
- Breast Cancer. V4.2021. Accessed May 14, 2021.
- Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma. V3.2021. Accessed March 31, 2021.
- Colon Cancer. V1.2021. Accessed January 6, 2021.
- Gastric Cancer. V2.2021. Accessed March 31, 2021.
- Kidney Cancer. V2.2021. Accessed March 17, 2021.
- Melanoma: Uveal. V1.2021. Accessed May 14, 2021.
- Myelodysplastic Syndromes. V2.2021. Accessed January 6, 2021.
- Myeloproliferative Neoplasms. V1.2020 Accessed January 6, 2021.
- Neuroendocrine and Adrenal Tumors. V1.2021. Accessed May 5, 2021.
- Non-Small Cell Lung Cancer. V4.2021. Accessed March 12, 2021.
- Ovarian Cancer Including Fallopian Tube Cancer and Primary Peritoneal Cancer. V1.2021. Accessed March 5, 2021.
- Pancreatic Adenocarcinoma. V1.2021. Accessed January 6, 2021.
- Thyroid Carcinoma. V1.2021. Accessed May 5, 2021.

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

- Colorectal. V1.2020. Accessed August 17, 2020.
- Breast, Ovarian, and Pancreatic. V2.2021. Accessed May 19, 2021.

Pilarski R, Burt R, Kohlman W, et al. Cowden Syndrome and the PTEN Hamartoma tumor syndrome: systematic review and revised diagnostic criteria. JNCI. 2013;105(21):1607-1616.

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.

Syngal S, Brand RE, Church JM, et al. ACG clinical guideline: Genetic testing and management of hereditary gastrointestinal cancer syndromes. Am J Gastroenterol. 2015;110(2):223-263.

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, Rohlfes 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.

Zhang S, Taylor AK, Huang X, et al. Venous thromboembolism laboratory testing (factor V Leiden and factor II c.*97G>A), 2018 update: a technical standard of the American College of Medical Genetics and Genomics (ACMG). Genet Med. 2018;20:1489–1498.