Quartz

# Tumor Marker Genetics

**Last Revision/Review Date: November 18, 2020** **P&P # C.6.34**

## Policy

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

**Prior authorization requests must be submitted by the staff in the Genetics Department or Clinical Experts in the medical field for which testing is requested.**

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. **1p19q codeletion molecular cytogenetic analysis (FISH, tissue)** is medically necessary for prognosis and treatment decision making in patients with astrocytomas and gliomas.

2. **Acute Lymphoblastic Leukemia (ALL)**

The following tests are considered medically necessary for the diagnosis of Acute Lymphoblastic Leukemia:

a. Conventional cytogenetics;
b. ALL FISH panel (B-ALL/B-lymphoblastic leukemia/lymphoma FISH or T-ALL FISH as indicated);
c. Ph-like B-ALL FISH panel;
d. BCR-ABL1 (usually included in FISH); including qualitative, quantitative and/or mutation profile;
e. KMT2A (MLL) rearrangement (usually included in FISH);
f. t(1;19);TCF3(E2A)-PBX1 (usually included in FISH);
g. MYC rearrangement (usually included in FISH);
h. t(9:22)(q34.1;q11.2) testing;
i. IKZF1 mutation testing;
j. ETV6-RUNX1 fusion testing;
k. Intrachromosomal amplification of chromosome 21 (iAMP21);
l. For BCR-ABL1 negative patients to evaluate for Ph-like phenotype: Gene fusion testing to include ABL1, ABL2, CRLF2, CSF1R, EPOR, FGFR, JAK1/2/3, LYN, NTRK3, PDGFRA, PDGFRB, PTK2B, TYK2, and mutation testing to include CRLF2, FLT3, IL7R, NTRKr, SH2B3, JAK1, JAK3, JAK2.

3. **Acute Myeloid Leukemia (AML)**

The following tests are considered medically necessary for the diagnosis (includes confirming remission and relapse), risk stratification, treatment and prognosis of Acute Myeloid Leukemia:

a. Conventional cytogenetics;
b. AML FISH panel;
c. t(8;21) (usually included in FISH);
d. inv(16) (usually included in FISH);
e. MLL rearrangement (usually included in FISH);
f. T(15;17) FISH (if suspicion for acute promyelocytic leukemia);
g. FLT3 mutation analysis;
h. Core binding factor translocations (CBFB-MYH11);
i. PML/RAR Alpha molecular testing;
j. AML gene panels by next generation sequencing or single gene testing to include ASXL1, CEBPA (biallelic), DNMT3A, IDH1, IDH2, KIT, c-KIT, NPM1, NRAS, FLT3-ITD, FLT3-TKD, RUNX1, TP53.
k. BCR-ABL1 mutation.

NOTE: Multiple gene panels and next generation sequencing analysis are considered medically necessary when evaluating the gene mutations listed above.

4. **ALK gene rearrangement** testing is medically necessary for **diffuse large B cell lymphoma**, **peripheral T-cell lymphoma**, and **post-transplant lymphoproliferative disorder (PTLD).**

5. **Anal Adenocarcinoma**
   KRAS mutation and BRAF testing are considered medically necessary for anal adenocarcinoma.

6. **Anaplastic Thyroid carcinoma**
   The following tests are considered medically necessary for the treatment of anaplastic thyroid carcinoma:
   a. ALK;
   b. BRAF V600E;
   c. NTRK (Neurotrophic receptor tyrosine kinase) gene fusion;
   d. RET fusion;
   e. Tumor mutational burden.

7. **APC testing for Familial Adenomatous Polyposis**
   Adenosis polyposis coli (APC) genetic testing (81479, 81201, 81203) is medically necessary for patients who meet the criteria found in *Policy C.6.07 Genetics Testing*.

8. **Aplastic anemia (AA) / Bone marrow failure**

Functional testing (described below) is considered medically necessary in patients with aplastic anemia/bone marrow failure who meet the following criteria:

a. Age < 50 **OR**
b. Personal or family history of congenital anomalies; OR
c. Family history of unexplained cytopenias; OR
d. Other clinical features worrisome for an inherited cause (e.g. lymphedema, pulmonary fibrosis, immunodeficiency, ataxia, congenital anomalies, etc.).

Functional testing includes:

a. Chromosome breakage analysis to rule out Fanconi anemia;
b. Lymphocyte with or without lymphocyte subset telomere length measurement via FlowFISH analysis to evaluate for a short telomere syndrome/dyskeratosis congenita.

9. **BRAF fusion and/or mutation testing** is medically necessary in central nervous system cancers.

10. **BRAF V600 mutation** is medically necessary for indeterminate thyroid nodules, anal adenocarcinoma, anaplastic thyroid carcinoma, hairy cell leukemia, gastrointestinal stromal tumors, melanoma, Lynch syndrome testing in persons meeting Lynch criteria, non-small cell lung cancer, small bowel adenocarcinoma and melanoma.

11. **B-cell lymphoma (non-Hodgkin lymphoma): Aggressive, Burkitt, Diffuse Large B-cell lymphomas**
    The following tests are considered medically necessary for the diagnosis of suspected aggressive, Burkitt, or diffuse large B-cell lymphoma:
    a. BCL2 and BCL6 rearrangements by FISH;
    b. IRF4/MUM1 by FISH;
    c. *MYC* break apart FISH;
    d. *IGH/MYC* FISH;

The following tests are considered medically necessary for the diagnosis of suspected aggressive, Burkitt, or diffuse large B-cell lymphoma in patients who are *MYC* negative:

a. ***IGK/MYC* and *IGL/MYC D-FISH*** for pediatric patients or high suspicion for Burkitt lymphoma;
b. **11q23 aberrancy and 11q24-ter deletion testing by chromosomal microarray**.

**12. Bladder cancer**

FGFR RGQ RT-PCR testing for FGFR3 and FGFR2 genetic mutations are medically necessary for Stage 3b and Stage 4 Bladder cancer.

**13. Breast Cancer Index**

The Breast Cancer Index is considered medically necessary to predict risk of late recurrence of tumor and guide the need for extended endocrine therapy decisions in women of any age with ductal, lobular, mixed, micropapillary or metaplastic breast cancer when **ALL** of the following criteria are met:

a. Patient has been taking endocrine therapy for breast cancer to prevent recurrence; AND
b. Breast tumor is hormone receptor positive (HR+) and HER2 receptor negative; **AND**
c. Patient had lymph nodes positive for cancer at diagnosis/staging, **AND**
d. No evidence of disease, i.e., recurrent or metastatic breast cancer; **AND**
e. Patient has agreed to use the results of the test for decision making about extension of length of endocrine therapy with tamoxifen past 4-5 years of endocrine therapy use.

**NOTE:** The use of more than one type of test to determine the risk of late recurrence and necessity of extended endocrine therapy in a woman with breast cancer for the same breast cancer is not medically necessary.

**14. Central Nervous System (CNS) Cancers**

The following tests are considered medically necessary for the diagnosis, treatment and prognosis of CNS cancers:

a. RELA fusion testing for diagnosis of ependymomas.
b. Multigene panel testing for glioblastoma.
c. IDH1 and IDH2 mutation testing for gliomas (i.e., astrocytomas, oligodendrogliomas and glioblastomas).
d. 1p19q testing of gliomas.
e. MGMT promoter methylation testing for high-grade gliomas.
f. ATRX, TERT, H3F3A and HIST1H3B mutation testing in gliomas.
g. BRAF fusion/ mutation testing in CNS tumors.
h. Medulloblastoma molecular subtyping including WNT, SHH, and TP53.

**15. Cholangiocarcinoma**

The following tests are considered medically necessary for the prognosis and treatment of cholangiocarcinoma:

a. MSI/MMR;
b. FGFR2 (fibroblast growth factor receptor) fusion and rearrangement.
c. IDH1 and IDH2.

**16. Chronic Lymphocytic Leukemia (CLL)/Small Lymphocytic Leukemia (SLL)**

The following tests are considered medically necessary for the diagnosis of suspected CLL/SLL and prognosis and treatment of CLL/SLL:

a. Conventional cytogenetics;
b. Chromosome analysis including CpG stimulated metaphase karyotype for complex karyotype;
c. CLL FISH panel;

d. FISH – deletion 17p13.1, TP53, +12; del(11q); del(13q); del(17p).;
e. TP53 somatic mutation (81405-TP53);
f. IGHV (immunoglobulin heavy chain variable region gene) mutation status, B-cell CLL IGHV somatic hypermutation analysis (81263-IGH);
g. ZAP-70.
h. BTK and PLCG2 mutations in patients receiving acalabrutinib and suspected of having progression.
i. BTK mutation analysis in patient with ibrutinib intolerance for whom acalabrutinib is planned.

**CD49d status** is medically necessary in patients with CLL/SLL who are unable to have IGHV testing performed.

**17. Chronic Myelogenous Leukemia (CML)**

The following tests are medically necessary for the diagnosis and treatment of chronic myelogenous leukemia.

a. Conventional cytogenetics;
b. Quantitative BCR-ABL1 FISH panel/qPCR;
c. BCR-ABL1 Kinase domain mutation analysis;
d. Myeloid malignancy (mutation) panel for patients with advanced phase CML .

NOTE: Once a CML diagnosis is established, quantitative BCR-ABL1 for CML treatment can be authorized for up to 12 tests in one year.

**18. Colon and Colorectal and Rectal cancer**

Limited gene panels for molecular profiling BRAF mutations including V600E (81210), KRAS (81275), NRAS (81311), HRAS (81403); PIK3CA (81309) are considered medically necessary for metastatic or unresectable colon cancer or colorectal cancer.

**19. DecisionDx-UM gene expression panel** (81552) is medically necessary for prognosis risk stratification for patients with an established diagnosis of **localized (non-metastatic) uveal melanoma**.

**20. Endometrial Carcinoma**

The following tests are medically necessary for the diagnosis, treatment and prognosis of endometrial cancer:

a. MMR/MSI and MLH1 testing;
b. POLE mutation;
c. P53 expression;
d. NTRK gene fusion (recurrent, metastatic or high-risk disease);
e. Tumor mutational burden (TMB) (recurrent, metastatic or high-risk disease).

**21. Essential Thrombocythemia Diagnosis (JAK2, CALR or MPL mutation)**

a. Genetic testing for JAK2 V617F mutation (81270-JAK2), CALR (calreticulin, 81219-CALR) and MPL (myeloproliferative leukemia virus oncogene, thrombopoietin receptor, 81403-MPL) is medically necessary for patients with suspected Essential Thrombocythemia. Testing should start with JAK2V617F mutation followed by reflex CALR and MPL testing if negative.

   NOTE: JAK2V617F, CALR and MPL can be authorized at the same time.

b. Genetic testing for SH2B3, IDH2, U2AF1, SF3B1, EZH2 and TP53 are medically necessary for prognosis assessment in Essential Thrombocytosis.

**22. Ewing Sarcoma**

The following tests are considered medically necessary for Ewing sarcoma: t(11;22) translocation (EWS-FL11 translocation) and FUS-ERG and FUS-FEV fusion transcripts.

**23. Gastric MALT Lymphoma**

The following tests are considered medically necessary for Gastric MALT lymphoma diagnosis:

a. FISH for t(11;18);
b. MALT1 translocation FISH;
c. Immunoglobulin gene rearrangement.

**24. Gastrointestinal Stromal Tumors**

**The following tests are considered medically necessary for gastrointestinal stromal tumors (GIST):**

a. KIT;
b. PDGFRA;
c. SDH.

**25. Hairy cell leukemia**

The following tests are considered medically necessary for Hairy cell leukemia:

a. BRAF V600E mutational analysis;
b. IGH somatic mutation analysis to detect IGHV4-34 rearrangement.

**26. HER2 (ERBB2)**

HER2 testing is medically necessary in patients with any of the following:

a. Metastatic esophageal or esophagogastric junction adenocarcinoma.
b. Gastric cancer with documented or suspected metastasis.
c. Breast cancer.
d. Ovarian cancer.
e. Metastatic colorectal cancer (includes rectal cancer).
f. Metastatic or unresectable salivary gland cancer.

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

Genetic testing for Hereditary nonpolyposis colorectal cancer/Lynch syndrome (MLH1, MSH2, MSH6, PMS2 sequence/deletion analysis **AND** Epithelial cell adhesion molecule (EPCAM) deletion analysis) is medically necessary for patients who meet the criteria found in *Policy C.6.07 Genetics Testing*.

Genetic testing for **MLH1 hypermethylation testing** 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.

**28. IDH1 and IDH2 gene mutation analysis** are medically necessary for diagnosis and treatment decision-making in **acute myeloid leukemia, chondrosarcoma, cholangiocarcinoma, hepatocellular carcinoma, and gliomas & glioblastoma.**

**29. IGHV (immunoglobulin heavy chain variable region gene) mutation**

Genetic testing for IGHV mutation is medically necessary for patients with Chronic Lymphocytic Leukemia/Small lymphocytic lymphoma (CLL/SLL) and post-transplant lymphoproliferative disorder.

**30. Janus Kinase 2 (JAK2, JAK2 V617F, JAK2 Exon 12 mutation):**

Genetic testing for the Janus Kinase 2 (JAK2; JAK2 V617F (81270-JAK2)) gene mutation is medically necessary for initial diagnostic assessment of adults presenting with clinical, laboratory, or pathological findings suggesting classic forms of **ANY** of the following myeloproliferative disorders (MPD)/myeloproliferative neoplasms (MPN):

a. Any myeloproliferative disorder including polycythemia vera (PV); **OR**
b. Essential thrombocythemia (ET); **OR**
c. Primary myelofibrosis (PMF).

Genetic testing for the Janus Kinase 2 Exon 12-15 mutation is medically necessary for diagnosis of polycythemia vera. Testing should start with JAK2V617F mutation followed by reflex JAK2 Exon 12-15 mutation testing if negative.

NOTE: JAK2V617F & JAK2 Exon 12-15 mutation testing can be authorized at the same time.

Genetic testing for the Janus Kinase 2 (JAK2; JAK2 V617F) gene mutation is not medically necessary for any indication other than those outlined above, including but not limited to **EITHER** of the following:

a. Diagnostic assessment of myeloproliferative disorders (MPD)/myeloproliferative neoplasms (MPN) in children; **OR**
b. Quantitative assessment of JAK2 V617F allele burden subsequent to qualitative detection of JAK2 V617F.

**31. Lymphoblastic Lymphoma**

The following genetic tests are medically necessary for the diagnosis, treatment and prognosis of lymphoblastic lymphoma:

a. Karyotype +/- FISH for MYC, t(9;22), t(8:14);
b. BCR-ABL PCR/variants.

**32. Lymphoplasmacytic lymphoma (LPL) / Waldenstrom macroglobulinemia OR IgM Monoclonal gammopathy of undetermined significance (MGUS)**

The following genetic tests are medically necessary for the diagnosis of Lymphoplasmacytic lymphoma (LPL) / Waldenstrom macroglobulinemia OR IgM Monoclonal gammopathy of undetermined significance (MGUS):

a. MYD88 L265P somatic gene mutation;
b. CXCR4 mutation analysis.

**33. MammaPrint 70-gene breast cancer recurrence assay:**

Genetic testing of tissue for MammaPrint is medically necessary to guide the need for adjuvant chemotherapy in women of any age with recently diagnosed ductal, lobular, mixed or micropapillary breast cancer when **ALL** of the following criteria are met:

a. Lymph node-negative (pN0) or 1-3 ipsilateral lymph nodes positive, **AND**
b. Breast tumor is estrogen receptor positive (ER+); **AND**
c. Breast tumor is HER2-receptor negative; **AND**
d. No evidence of distant metastatic breast cancer; **AND**
e. Patient has high clinical risk as assessed by the modified Adjuvant! Online risk calculator (which considers ER status, HER2 status, tumor grade, node status, and tumor size, **AND**

f. Patient has agreed to use the results of the test to decision making for chemotherapy when chemotherapy is an option.

**NOTE:** The use of more than one type of test to determine the risk of early recurrence and necessity of adjuvant chemotherapy in a woman with breast cancer for the same breast cancer is not medically necessary.

**34. Mantle cell Lymphoma**

The following genetic tests are considered medically necessary for diagnosis/prognosis of Mantel cell lymphoma:

a. B-cell lymphoma FISH or CLL lymphoma FISH;
b. 17p/TP53 deletion and MYC rearrangement by FISH.

**35. Mastocytosis**

The following tests are medically necessary for the diagnosis of mastocytosis:

a. KIT D816V mutational analysis and KIT gene sequencing;
b. FIP1L1-PDGFRA;
c. Myeloid mutation panel including SRSF2, ASXL1, RUNX1.

**36. Medullary Thyroid Carcinoma**

The following tests are medically necessary in the evaluation of medullary thyroid carcinoma:

a. Germline mutations of RET proto-oncogene (exons 10, 11, 13-16);
b. Tumor mutational burden (recurrent, persistent or metastatic disease).

**37. Melanoma (cutaneous)**

The following tests are medical necessary in the evaluation and treatment of cutaneous melanoma.

a. BRAF mutation.
b. KIT mutation in patients with metastatic disease or with clinical recurrence.

**38. Microsatellite instability (MSI) testing** and **Mismatch Repair (MMR) testing** of tumors and/or blood is considered medically necessary in patients with

a. Colorectal, or rectal cancer,
b. Small bowel adenocarcinoma,
**c.** Locally advanced, recurrent or metastatic Gastric carcinoma, esophageal adenocarcinoma, esophagogastric junction cancer, pancreatic cancer,
**d.** Unresectable or metastatic penile cancer;
**e.** Recurrent, progressive or metastatic cervical cancer;
**f.** Endometrial/uterine cancer;
**g.** Advanced prostate cancer with regional or distant metastatic disease;
h. Metastatic testicular cancer;
i. Persistent or recurrent ovarian cancer;
j. Recurrent, progressive or metastatic vulvar cancer (squamous cell carcinoma);
k. Unresectable or metastatic gallbladder cancer, cholangiocarcinoma or biliary tract cancers;
l. Unresectable or metastatic breast cancer that has progressed on treatment;
m. Unresectable or metastatic adrenocortical tumors that have progressed on treatment;
n. Persistent or recurrent primary peritoneal cancer;
o. Persistent or recurrent fallopian tube cancer;
p. Occult primary tumors;
q. Unresectable or metastatic penile cancer that has progressed on treatment;

r. Testicular cancer that has progressed on treatment;
s. Poorly differentiated neuroendocrine carcinomas/large or small cell.

**39. Multiple Myeloma**

The following genetic tests are considered medically necessary for diagnosis/prognosis of Multiple Myeloma:

a. Metaphase cytogenetics;
b. Plasma cell myeloma FISH (aka plasma cell proliferative disorder FISH);
c. Single nucleotide polymorphism array;
d. Retesting for 17p deletion, 1q gain and MYC rearrangement by FISH in subsequent bone marrows;
e. Next generation sequencing for minimal residual disease.

**40. Myelodysplastic syndromes (MDS)**

The following tests are medically necessary for the diagnosis, treatment and prognosis of myelodysplastic syndromes:

a. Conventional cytogenetics or chromosomal microarray or MDS-related FISH;
b. Myeloid malignancy panel to test for somatic (acquired) mutations, this panel may include the following genes, ASXL1, BCOR, CALR, CBL, DDX41, DNMT3A, ETV6, EZH2, FLT3, IDH1, IDH2, GATA2, JAK2, MPL, NF1, NPM1, NRAS, PHF6, PPM1D, RUNX1, SETBP1, SF3B1, SRSF2, STAG2, STAT3, TERT, TET2, TP53, U2AF1, WT1, ZRSR2;
c. TP53 mutation analysis;
d. RUNX1 and GATA2;
e. For patients with chronic myelomonocytic leukemia (CMML): and PDGFRbeta gene rearrangements at 5q32;

**41. Myeloid/Lymphoid Neoplasm with Eosinophilia and Tyrosine Kinase Fusion Genes**

The following tests are medically necessary for the diagnosis, treatment and prognosis of myeloid/lymphoid neoplasm with eosinophilia and tyrosine kinase fusion genes:

a. All tests listed for Chronic Myelogenous Leukemia diagnosis;
b. TK fusion gene rearrangements: PDGFRA, PDGFRB, FGFR1, JAK2, ABL1, FLT3;
c. IHC for typtase/CD117/CD25;
d. KIT D816V;
e. Myeloid mutation/malignancy panel.

**42. Neurotrophic receptor tyrosine kinase (NTRK) gene fusion**

Genetic testing for NTRK gene fusion is medically necessary in patients with metastatic cancer or cancer whereby surgical resection is likely to result in severe morbidity or who have no satisfactory alternative treatments or have progressed following treatment, especially anaplastic thyroid cancer, biliary tract cancer, brain tumors, breast cancer, cervical cancer, endometrial cancer, esophageal and esophagogastric junction cancers, follicular or Hurthle cell thyroid carcinoma, gallbladder cancer, gastric cancer, hepatocellular cancer, non-small cell lung cancer, papillary thyroid cancer, rectal cancer, salivary gland cancer, soft tissue sarcoma, and uterine sarcoma, vulvar cancer.

**43. Non-Small Cell Lung Cancer**

Limited gene panels for molecular profiling EGFR gene mutation, ALK gene rearrangements and fusions, ROS1 gene rearrangements and fusions, KRAS, BRAF point mutations including V600E, PD-L1, high-level MET amplification and MET exon 14 skipping mutation, HER2 (ERBB2) mutation, RET rearrangements and gene fusions, NTRK gene fusion, tumor mutational burden (TMB) are considered medically necessary for non-small cell lung cancer that is metastatic, advanced, or that has recurred despite adequate resection.

**44. Oncotype DX Breast Recurrence Score (21-gene RT-PCR assay):**

Genetic testing of tissue for Oncotype DX is medically necessary to guide the need for adjuvant chemotherapy in women with recently diagnosed ductal, lobular, mixed or micropapillary breast cancer when **ALL** of the following criteria are met:

a. Newly diagnosed breast tumor stage pT1, pT2 **OR** pT3; **AND**
b. Axillary node-negative (pN0) and tumor >0.5cm, **or** has axillary-node micrometastasis no greater than 2.0 millimeters (pN1mi); **or** has one to three (1-3) involved ipsilateral axillary lymph nodes; **AND**
c. Breast tumor is estrogen receptor positive; **AND**
d. Breast tumor is HER2-receptor negative; **AND**
e. No evidence of distant metastatic breast cancer; **AND**
f. Patient has agreed to use the results of the test to decision making for chemotherapy when chemotherapy is an option.

**NOTE:**

- Oncotype DX genetic testing is not covered for any other clinical evaluation. Other assays of genetic expression in tumor tissue (e.g., Breast Cancer Gene Expression Ratio, HERmark® Breast Cancer Assay, Rotterdam Signature 76-Panel, EndoPredict, Breast Cancer Assay, and Prosigna) are not covered because each is considered experimental, investigational or unproven.
- Repeat Oncotype Dx Breast Recurrence Score testing of same tumor is not medically necessary.
- Oncotype Dx Breast Recurrence Score testing of multiple tumor sites is not medically necessary unless the tumors are histologically distinct and separately meet above criteria.
- The OncoGeneDx panel should not be confused with the Oncotype DX Breast Recurrence Score panel – these are different tests.
- The use of more than one type of test to determine the risk of early recurrence and necessity of adjuvant chemotherapy in a woman with breast cancer for the same breast cancer is not medically necessary.

**45. Ovarian Cancer**

Genetic testing for BRCA1, BRCA2, homologous recombination deficiency, MSI (microsatellite instability) & MMR (DNA mismatch repair) are medically necessary in patients with persistent or recurrent ovarian cancer.

**46. Pancreatic Cancer**

Genetic testing for ATM, BRCA1, BRCA2, CDKN2A, PALB2, STK11, TP53, MSI (microsatellite instability) & MMR (DNA mismatch repair), and Lynch syndrome including MLH1, MSH2, MSH6, PMS2 sequence/deletion analysis and Epithelial cell adhesion molecule (EPCAM) deletion analysis are medically necessary for patients with pancreatic cancer.

The fifty-gene limited panel or multigene for molecular profiling is considered medically necessary for metastatic pancreatic cancer progressing despite usual regimen and tumor debulking. Testing may include: fusions (ALK, NRG1, NTRK, ROS1), mutations (BRAF, BRCA1/2, HER2, KRAS, PALB2), and mismatch repair (MMR) deficiency on tumor.

**47. PD-L1 mutation**

PD-L1 mutation testing is medically necessary in patients with any of the following:

a. Esophageal or esophagogastric junction cancers if metastatic diseases is documented or suspected.

b. Non-small cell lung cancer that is metastatic, advanced, or that has recurred despite adequate resection.
c. Gastric cancer that is recurrent, locally advanced or metastatic
d. Metastatic urothelial cell carcinoma.
e. Recurrent, progressive or metastatic Cervical cancer.
f. Triple negative breast cancer.
g. Head and neck cancer that is recurrent, non-resectable or metastatic with no surgery or radiotherapy option.
h. Advanced, recurrent/metastatic vulvar cancer (squamous cell carcinoma).
i. Locally advanced or metastatic bladder cancer.

**48. PTEN-associated Hamartoma Tumor Syndrome gene**

PTEN Gene Testing 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 meet the criteria found in *Policy C.6.07Genetics Testing*.

**49. PIK3CA**

PIK3CA (81309) testing is medically necessary in patients with the following:

a. Recurrent or metastatic breast cancer that is HR+, HER2 negative;
b. Metastatic or unresectable colon or colorectal cancer.
c. Soft tissue sarcoma.

**50. Polycythemia Vera**

The following tests are medically necessary in the diagnosis and prognosis determination in patients with polycythemia vera: JAK2 V617F, JAK2 exon 12 mutation, ASXL1, SRSF2, IDH1 & IDH2.

**51. Poorly Differentiated Neuroendocrine Carcinoma/Large or Small cell**

The following tests are medically necessary in the diagnosis and prognosis determination in patients with poorly differentiated neuroendocrine carcinoma/large or small cell:

a. MSI/MMR;
b. Tumor mutational burden (TMB).

**52. Primary Cutaneous B-Cell Lymphomas**

The following tests are medically necessary in the diagnosis, treatment and prognostic evaluation of primary cutaneous b-cell lymphomas:

a. Cytogenetics (FISH/Karyotype);
b. IgH gene rearrangement studies;
c. FOXP1 expression;
d. T-cell antigen receptor (TCR) gene rearrangements;
e. ALK, DUSP22, and TP63 gene rearrangements.

**53. Primary Myelofibrosis**

a. Genetic testing for JAK2/JAK2 V617F, CALR (calreticulin gene) and MPL (thrombopoietin receptor) mutations are medically necessary for patients with clinical, laboratory and pathologic findings suggesting a diagnosis of Primary Myelofibrosis to make a definitive diagnosis if unclear. Testing should start with JAK2V617F mutation followed by reflex CALR and MPL testing if negative.

NOTE: JAK2V617F, CALR and MPL can be authorized at the same time.

b. Genetic testing for JAK2/JAK2 V617F, CALR (calreticulin gene) and MPL (thrombopoietin receptor) mutation allele burden quantification is NOT medically necessary for treatment selection or monitoring patients with Primary Myelofibrosis.
c. Genetic testing for ASXL1, EZH2, TET2, IDH1/IDH2, SRSF2, SF3B1, TP53, U2AF1 Q157 mutations are medically necessary for patients undergoing evaluation for Primary Myelofibrosis.

**54. Prostate Cancer**

a. The following tests are medically necessary in the evaluation of regional or metastatic prostate cancer: homologous recombination gene mutations (HRRm), BRCA1, BRCA2, ATM, PALB2, FANCA, RAD51D, CHEK2, CDK12, MSI-H, and dMMR.

b. Genetic testing of tissue using the Decipher molecular assay (CPT 81542) is considered medically necessary to inform adjuvant treatment decisions in patients with prostate cancer if ALL the following criteria are met:
- **a.** Post-radical prostatectomy with lymph node dissection; **AND**
- b. Patient has one or more adverse feature:
  - i. Positive margins; **OR**
  - ii. Seminal vesicle invasion; **OR**
  - iii. Extracapsular extension; **OR**
  - iv. Rising PSA (above nadir); **AND**
- c. No lymph node metastases.

**55. Small Bowel Adenocarcinoma**

KRAS mutation, BRAF testing and Microsatellite instability (MSI)/ Mismatch Repair (MMR) testing are considered medically necessary for small bowel adenocarcinoma.

**56. Soft Tissue Sarcoma**

The following tests are medically necessary in the diagnosis, treatment and prognostic evaluation of soft tissue sarcoma:

a. Targeted sarcoma gene fusion panel;
b. NTRK gene fusions.
c. PIK3CA.

**57. Spitzoid Melanocytic Neoplasms**

Cytogenetic/chromosomal microarray analysis (a.k.a., comparative genomic hybridization (CGH)) is medically necessary in the evaluation of Spitzoid melanocytic neoplasms that are histologically equivalent.

**58. T-Cell Lymphomas**

The following tests are medically necessary in the diagnosis, treatment and prognostic evaluation of T-Cell lymphomas:

a. Cytogenetics (FISH/karyotype);
b. T-cell antigen receptor (TCR) gene rearrangements;
c. ALK, DUSP22, and TP63 gene rearrangements;
d. TCL1 and TRA translocations;
e. TET2, IDH1, IDH2, RHOA, DNMT3A mutations;
f. STAT3 and STAT5B mutation analysis if suspected t-cell large granular lymphocytic leukemia (LGLL) or natural killer (NK) leukemia;

g. STAT3, STAT5B, PIK3CD, SETD2, INO80, TET3, SMARCA2 gene analysis if hepatosplenic gamma-delta t-cell lymphoma.

**59. Thyroid Carcinoma, including Follicular, Hurthle cell and Papillary Carcinomas**

The following tests are considered medically necessary for the treatment of follicular, Hurthle cell and papillary thyroid carcinoma that is locally recurrent, advanced and/or metastatic disease:

a. NTRK (Neurotrophic receptor tyrosine kinase) gene fusion;
b. RET fusion.
c. Tumor mutational burden.

**60. Thyroid Nodule Testing**

Genetic testing using Afirma Thyroid FNA Analysis including the Afirma Thyroid Gene Expression Classifier or Thyroseq is considered medically necessary to aid in thyroid nodule diagnosis when the Thyroid nodule cytopathologically is classified as **ONE** of the following:

a. Bethesda 3 Diagnostic Category, aka Atypia of undetermined significance or Follicular lesion of undetermined significance (AUS/FLUS); **OR**
b. Bethesda 4 Diagnostic Category, aka Follicular or Hurthle cell neoplasm or Suspicious for a Follicular neoplasm.

**Notes:**

- Repeat testing of the same thyroid nodule is considered not medical necessary.
- Other tests for indeterminate thyroid nodule diagnosis are considered experimental/investigational/unproven including ThyGenX and ThyraMIR.
- Reference Medicare LCD 35396 Biomarkers for Oncology revision effective date 11/14/19 which provides for Afirma and ThyroSeq coverage as medically necessary.

**61. Tumor Mutational Burden**

Genetic testing for tumor mutational burden is indicated in the following conditions:

a. Anaplastic thyroid carcinoma;
b. Cervical cancer, metastatic disease.
c. Endometrial cancer, recurrent, metastatic or high risk disease;
d. Follicular or Hurthle cell thyroid carcinoma, locally recurrent, advanced and/or metastatic disease;
e. Medullary thyroid carcinoma, recurrent, persistent or metastatic disease;
f. Non-small cell lung cancer;
g. Papillary thyroid carcinoma, locally recurrent, advanced and/or metastatic disease;
h. Poorly Differentiated Neuroendocrine Carcinoma/Large or Small cell;
i. Uterine sarcoma, unresectable or metastatic;
j. Vulvar cancer, unresectable or metastatic.

**62. 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) is medically necessary for patients who meet the criteria found in *Policy C.6.07 Genetics Testing*.

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

1. The following genetic tests are considered experimental, investigational or unproven.
   a. FoundationOne CDx(F1CDx), and FoundationOne Heme;
   b. Oncotype DX Colon Cancer Assay testing;
   c. Breast Cancer Gene Expression Ratio,

d. HERmark® Breast Cancer Assay,
e. Rotterdam Signature 76-Panel;
f. EndoPredict;
g. Post-biopsy genetic testing for prostate cancer including: 4Kscore Test for prostate cancer; Oncotype DX for prostate cancer; Decipher molecular assay in prostate cancer except as outlined in criteria above; ProMark and Prolaris tests;
h. DecisionDx Melanoma for any cutaneous melanoma indication.

2. Genetic testing of NF1 for Neurofibromatosis diagnosis, treatment and management based on café au late marks;
3. Molecular testing for urothelial tumor markers in patients with history of invasive bladder cancer undergoing surveillance for recurrence.
4. Genetic testing for the purposes of surveillance;
5. 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.

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