

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, NTRK, SH2B3, JAK1, JAK3, JAK2;
- m. Minimal residual disease assessment via next generation sequencing (NGS), flow cytometry, and/or Real-time quantitative (RQ)-PCR.

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;
- l. Minimal residual disease immunophenotypes assessment via real-time quantitative (RQ) PCR assays (NPM1, CBFB-MYH11, RUNX1-RUNX1T1) and multicolor flow cytometry assays.
- m. Chromosomal microarray/array CGH in cases of aneuploidy or failed karyotype.

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.
- f. MSI/MMR.

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:

- a. indeterminate thyroid nodules,
- b. anal adenocarcinoma,
- c. anaplastic thyroid carcinoma,
- d. biliary tract cancers (gall bladder and cholangiocarcinoma),
- e. hairy cell leukemia,
- f. gastrointestinal stromal tumors,
- g. Histiocytic Neoplasms: Langerhans Cell Histiocytosis & Erdheim-Chester Disease & Rosai Dorfman Disease,
- h. melanoma,
- i. Lynch syndrome testing in persons meeting Lynch criteria,
- j. non-small cell lung cancer,
- k. small bowel adenocarcinoma and
- l. 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 and PD-L1 are medically necessary for Stage 3b and Stage 4 Bladder cancer.

13. Breast Cancer Index

A. The Breast Cancer Index is considered medically necessary to predict risk of **early recurrence** of tumor and guide the need for adjuvant chemotherapy decisions in persons of any age with breast cancer when **ALL** of the following criteria are met:

- a. Breast tumor is hormone receptor positive (HR+); **AND**
- b. Breast tumor is HER2 receptor negative; **AND**
- c. No evidence of metastatic disease and node negative; **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.

B. 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 persons 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 early or late recurrence and necessity of extended endocrine therapy in a person 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.
- i. NTRK for gliomas.

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 or zanubrutinib and suspected of having progression.
- i. BTK mutation analysis in patient with ibrutinib intolerance for whom acalabrutinib or zanubrutinib is planned
- j. Minimal residual disease assessment by standardized NGS, PCR, or flow cytometry.

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), HER2 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. HER2 testing (advanced stage or recurrent serous type);
- b. MMR/MSI and MLH1 testing;
- c. POLE mutation;
- d. P53 expression;
- e. NTRK gene fusion (recurrent, metastatic or high-risk disease);
- f. Tumor mutational burden (TMB) (recurrent, metastatic or high-risk disease).

21. EndoPredict (12-gene score)

Genetic testing of tissue using EndoPredict (a.k.a. 12-gene score) is medically necessary to guide the need for adjuvant chemotherapy in persons with recently diagnosed breast cancer when **ALL** of the following criteria are met:

- a. Breast tumor is estrogen receptor positive; **AND**
- b. Breast tumor is HER2-receptor negative; **AND**
- c. No evidence of metastatic breast cancer and node negative; **AND**
- d. 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 person with breast cancer for the same breast cancer is not medically necessary.

22. 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, SRSF2, RUNX1 and TP53 are medically necessary for prognosis assessment in Essential Thrombocytosis.

23. 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 and Tumor mutational burden.

24. 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.

25. Gastrointestinal Stromal Tumors

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

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

26. 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.

27. HER2 (ERBB2)

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

- a. Endometrial carcinoma, advanced stage or recurrent serous type
- b. Locally advanced, recurrent or metastatic esophageal or esophagogastric junction adenocarcinoma.
- c. Gastric cancer with documented or suspected metastasis, locally advanced or recurrent.
- d. Breast cancer.
- e. Ovarian cancer.
- f. Metastatic colorectal cancer (includes rectal cancer).
- g. Metastatic or unresectable salivary gland cancer.

28. 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*.

29. Histiocytic Neoplasms: Langerhans Cell Histiocytosis & Erdheim-Chester Disease & Rosai Dorfman Disease

The following tests are considered medically necessary for Histiocytic neoplasms:

- a. BRAF / BRAF V600E mutational analysis;
- b. ARAF, NRAS, KRAS, MAP2K1, PIK3CA mutations;
- c. ALK and NTRK1 rearrangements.

30. 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.**

31. 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.

32. 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.

33. Liquid biopsy (cell-free or circulating tumor DNA testing for genetic variants)

Genetic testing using liquid biopsy including cell-free or circulating tumor DNA testing for genetic variants (up to 50 genes), is medically necessary in one of the following circumstances:

- a. Patient has tissue diagnosis of non-small cell lung cancer **AND**
 - i. Is not medically fit for invasive tissue sampling, **OR**
 - ii. There is insufficient tissue for molecular analysis and follow-up tissue-based analysis will be done if an oncogenic driver is not identified.
- b. Patient has metastatic or advanced esophageal/esophagogastric or gastric cancer and is unable to undergo a traditional biopsy for biomarker testing.

34. 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.

35. 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.

36. MammaPrint 70-gene breast cancer recurrence assay:

Genetic testing of tissue for MammaPrint is medically necessary to guide the need for adjuvant chemotherapy in persons 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 persons with breast cancer for the same breast cancer is not medically necessary.

37. 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.

38. Mastocytosis

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

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

39. 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).

40. 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.
- c. NRAS mutation.
- d. NTRK gene fusion.

41. 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 esophageal adenocarcinoma, esophagogastric junction cancer, pancreatic cancer,
- d. Gastric cancer (all);
- e. Unresectable or metastatic penile cancer;
- f. Recurrent, progressive or metastatic cervical cancer;
- g. Endometrial/uterine cancer;
- h. Advanced prostate cancer with regional or distant metastatic disease;
- i. Metastatic testicular cancer;
- j. Persistent or recurrent ovarian cancer;
- k. Recurrent, progressive or metastatic vulvar cancer (squamous cell carcinoma);
- l. Unresectable or metastatic gallbladder cancer, cholangiocarcinoma or biliary tract cancers;
- m. Unresectable or metastatic breast cancer that has progressed on treatment;
- n. Unresectable or metastatic adrenocortical tumors that have progressed on treatment;
- o. Persistent or recurrent primary peritoneal cancer;
- p. Persistent or recurrent fallopian tube cancer;
- q. Occult primary tumors;
- r. Testicular cancer that has progressed on treatment;
- s. Poorly differentiated neuroendocrine carcinomas/large or small cell;
- t. Head and neck cancers that are non-nasopharyngeal in origin, e.g. lip, oral cavity, oropharynx, hypopharynx, glottic larynx, supraglottic pharynx, ethmoid sinus, maxillary sinus, and occult primary;
- u. Germ cell tumor, metastatic;
- v. Bone cancer that is unresectable or metastatic (e.g., osteosarcoma).
- w. Advanced, metastatic, progressive or threatening papillary, follicular or Hurthle cell thyroid carcinoma.
- x. Anaplastic thyroid carcinoma.

42. MLH1 hypermethylation

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

43. 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.

44. 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): PDGFRbeta gene rearrangements at 5q32.

45. 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.

46. 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:

- a. anaplastic thyroid cancer,
- b. biliary tract cancer,
- c. brain tumors,
- d. breast cancer,
- e. cervical cancer,
- f. cholangiocarcinoma, intra- and extrahepatic,
- g. endometrial cancer,
- h. esophageal and esophagogastric junction cancers,
- i. follicular or Hurthle cell thyroid carcinoma,
- j. gallbladder cancer,
- k. gastric cancer,
- l. gliomas,
- m. hepatocellular cancer,
- n. histiocytic neoplasms (Langerhans Cell Histiocytosis & Erdheim-Chester Disease & Rosai Dorfman Disease),
- o. melanoma (cutaneous),
- p. non-small cell lung cancer,
- q. ovarian cancer,
- r. papillary thyroid cancer,
- s. rectal cancer,
- t. salivary gland cancer,
- u. soft tissue sarcoma,

- v. small bowel adenocarcinoma,
- w. uterine sarcoma,
- x. vulvar cancer.

47. 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.

48. 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 persons 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.
- 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 person with breast cancer for the same breast cancer is not medically necessary.

49. Ovarian Cancer

The following genetic tests are medically necessary in patients with ovarian cancer.

- a. BRCA1, BRCA2, homologous recombination deficiency / status;
- b. MSI (microsatellite instability) & MMR (DNA mismatch repair);
- c. NTRK gene fusions;
- d. Tumor mutational burden.

50. PAM 50

Genetic testing of tissue using PAM 50 is medically necessary to guide the need for adjuvant chemotherapy in persons with recently diagnosed breast cancer when **ALL** of the following criteria are met:

- e. Breast tumor is estrogen receptor positive; **AND**
- f. Breast tumor is HER2-receptor negative; **AND**
- g. No evidence of metastatic breast cancer and node negative; **AND**
- h. 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 person with breast cancer for the same breast cancer is not medically necessary.

51. 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.

52. PD-L1 mutation

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

- a. Esophageal or esophagogastric junction cancers if locally advanced, recurrent, or 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.
- j. Gestational trophoblastic neoplasia.
- k. Advanced, relapsed and refractory Hodgkin lymphoma in pediatric or young adult patient.

53. 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*.

54. 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.
- d. Histiocytic Neoplasms: Langerhans Cell Histiocytosis & Erdheim-Chester Disease & Rosai Dorfman Disease

55. 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, U2AF1, RUNX1.

56. 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).

57. 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.

58. 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, CBL, DNMT3A, EZH2, TET2, IDH1/IDH2, SRSF2, SF3B1, TP53, U2AF1 Q157 mutations are medically necessary for patients undergoing evaluation for Primary Myelofibrosis.

59. 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.

60. Small Bowel Adenocarcinoma

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

61. 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.

62. 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.

63. Systemic Mastocytosis

The following tests are medically necessary in the diagnosis, treatment and prognostic evaluation of systemic mastocytosis:

- a. KIT D816V mutation
- b. FIP1L1-PDGFR fusion gene if KIT D816V negative
- c. Myeloid mutation panel testing.

64. 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.

65. 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, progressive, threatening and/or metastatic disease:

- a. NTRK (Neurotrophic receptor tyrosine kinase) gene fusion;
- b. RET fusion.
- c. Tumor mutational burden.
- d. MMR/MSI.
- e. ALK fusions.

66. Thyroid Nodule Testing

Genetic testing using Afirma Thyroid FNA Analysis including the Afirma Thyroid Genomic Sequencing 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 with the same test or different genetic test to aid in thyroid nodule diagnosis 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.

67. 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. cholangiocarcinoma, intra- and extrahepatic;
- d. Chondrosarcoma, metastatic;
- e. Endometrial cancer, recurrent, metastatic or high-risk disease;
- f. Esophageal and esophagogastric junction cancers, locally advanced, recurrent or metastatic;
- g. Ewing sarcoma, metastatic;
- h. Follicular or Hurthle cell thyroid carcinoma, locally recurrent, advanced and/or metastatic disease;
- i. Gall bladder cancer, unresectable;
- j. Gastric cancer, locally advanced, recurrent or metastatic;
- k. Germ cell tumor, metastatic;
- l. Medullary thyroid carcinoma, recurrent, persistent or metastatic disease;
- m. Nasopharyngeal cancer, recurrent, unresectable or metastatic disease;
- n. Non-small cell lung cancer;
- o. Occult primary, suspected metastatic;
- p. Ovarian cancer;
- q. Papillary thyroid carcinoma, locally recurrent, advanced and/or metastatic disease;
- r. Poorly Differentiated Neuroendocrine Carcinoma/Large or Small cell;

- s. Salivary gland tumors, recurrent, unresectable, or metastatic disease;
- t. Uterine sarcoma, unresectable or metastatic;
- u. Vulvar cancer, unresectable or metastatic.

68. 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 (Not an all- inclusive list):

1. The following genetic tests are considered experimental, investigational or unproven.
 - a. Oncotype DX Colon Cancer Assay testing;
 - b. Breast Cancer Gene Expression Ratio,
 - c. HERmark® Breast Cancer Assay,
 - d. Rotterdam Signature 76-Panel;
 - e. 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;
 - f. DecisionDx Melanoma for any cutaneous melanoma indication.
2. Molecular testing for urothelial tumor markers in patients with history of invasive bladder cancer undergoing surveillance for recurrence.
3. Genetic testing for the purposes of surveillance;
4. 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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