BlueCross BlueShield Federal Employee Program.

FEP Medical Policy Manual

FEP 2.04.151 Genetic Biomarker Testing (Including Liquid Biopsy) for Targeted Treatment in Advanced Cancer

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Related Policies:

2.04.02 - Germline Genetic Testing for Hereditary Breast/Ovarian Cancer Syndrome and Other High-Risk Cancers (BRCA1, BRCA2, PALB2)
2.04.115 - Comprehensive Genetic Profiling for Selecting Targeted Cancer Therapies
2.04.141 - Circulating Tumor DNA and Circulating Tumor Cells for Cancer Management (Liquid Biopsy)
2.04.36 - Assays of Genetic Expression in Tumor Tissue as a Technique to Determine Prognosis in Patients with Breast Cancer
2.04.85 - BCR-ABL1 Testing in Chronic Myelogenous Leukemia and Acute Lymphoblastic Leukemia
5.21.006 - Trastuzumab
5.21.032 - Ado-Trastuzumab Emtansine (Trastuzumab-DM1) for Treatment of HER2-Positive Malignancies

Genetic Biomarker Testing (Including Liquid Biopsy) for Targeted Treatment in Advanced Cancer

Description

Description

Multiple biomarkers are being evaluated to select treatment with an FDA-approved targeted treatments for patients with unresectable, recurrent, relapsed, refractory, advanced or metastatic cancer. These include tissue-based testing as well as circulating tumor DNA (known as liquid biopsy).

PIK3CA Testing

Alterations in the protein coding gene *PIK3CA* (Phosphatidylinositol-4,5-Bisphosphate 3-Kinase Catalytic Subunit Alpha) occur in approximately 40% of patients with hormone receptor (HR)-positive, HER2-negative breast cancer. [53,]

Rearranged During Transfection

The REarranged during Transfection (RET) proto-oncogene encodes a receptor tyrosine kinase growth factor.[56,] Translocations that result in fusion genes with several partners have been reported, and occur in about 5-10% of thyroid cancer cases (primarily papillary thyroid carcinoma), 1%-2% of non-small-cell lung cancer cases [6,], and occurring in roughly 0.2% colorectal cancers.[57,] RET fusions in breast cancer, occur in less than 1% of cases.[58,]

BRAF

RAF proteins are serine/threonine kinases that are downstream of RAS in the RAS-RAF-ERK-MAPK pathway. The most common variant locus is found in codon 600 of exon 15 (V600E) of the *BRAF* gene, causing constitutive hyperactivation, proliferation, differentiation, survival, and oncogenic transformation.[1,]*BRAF* variants occur in approximately 1% of breast cancer cases.[2,]Variants in the b-raf proto-oncogene, serine/threonine kinase (*BRAF)* kinase gene are common in tumors of patients with advanced melanoma and result in constitutive activation of a key signaling pathway (rapidly accelerated fibrosarcoma [RAF]-MEK-extracellular signal-regulated kinase [ERK] pathway) that is associated with oncogenic proliferation. In general, 50% to 70% of melanoma tumors harbor a *BRAF* variant; of these, 80% are positive for the *BRAF* V600E variant, and 16% are positive for *BRAF* V600K.[3,] Thus, 45% to 60% of advanced melanoma patients may respond to a BRAF inhibitor targeted to this mutated kinase. There is considerable interest in targeted therapies that inhibit the RAF-MEK-ERK pathway, particularly in patients with high-grade and low-grade gliomas whose tumors are in locations that prevent full resection. Evidence from early-phase trials in patients with *BRAF* variant-positive melanoma with brain metastases have suggested some efficacy for brain tumor response with vemurafenib and dabrafenib indicating that these agents might be potential therapies for primary brain tumors. [4,5,] In this pathway, the *BRAF* gene is the most frequently mutated in NSCLC, in 1% to 3% of adenocarcinomas. Unlike melanoma, about 50% of the variants in NSCLC are non-V600E variants. [6,] Most *BRAF* variants occur more frequently in smokers.

ROS1

ROS1 codes for a receptor tyrosine kinase of the insulin receptor family and chromosomal rearrangements result in fusion genes. The prevalence of *ROS1* fusions in NSCLC varies from 0.9% to 3.7%. [6,] Patients with *ROS1* fusions are typically never-smokers with adenocarcinoma.

Tumor Mutational Burden

Tumor mutational burden (TMB) is a measure of gene mutations within cancer cells. Initially, assessments of TMB involved whole exome sequencing (WES). More recently, targeted next generation sequencing (NGS) panels are being adapted to estimate TMB. Currently FoundationOne CDx is the only U.S. Food and Drug Administration (FDA) approved panel for estimating TMB, but others are in development. [59,]

Tumor Protein p53

Tumor protein p53 (*TP53*) is a transcription factor protein that binds to DNA and regulates gene expression to prevent alterations of the genome. Accumulating evidence indicates that p53 is the most frequently mutated gene in human cancers and are commonly found in the ovary (47.27%), colon and rectum (44.55%), lung (40.8%), pancreas (38.53%), stomach (36.78%), urethra (35.01%), liver (29.17%), breast (26.44%), prostate (22.52%), bone (16.19%), thyroid (11.13%), hematopoietic and lymphatic (10.13%) and kidney (8.75%). [60,61,]

Circulating Tumor DNA

Normal and tumor cells release small fragments of DNA into the blood, which is referred to as cell-free DNA. Cell-free DNA from nonmalignant cells is released by apoptosis. Most cell-free tumor DNA is derived from apoptotic and/or necrotic tumor cells, either from the primary tumor, metastases, or CTCs. Unlike apoptosis, necrosis is considered a pathologic process and generates larger DNA fragments due to incomplete and random digestion of genomic DNA. The length or integrity of the circulating DNA can potentially distinguish between apoptotic and necrotic origin. Circulating tumor DNA can be used for genomic characterization of the tumor.

OBJECTIVE

The objective of this evidence review is to summarize the evidence and guidelines on genetic biomarker testing using tissue biopsy or circulating tumor DNA testing to select targeted treatment for individuals with unresectable, recurrent, relapsed, refractory, advanced, or metastatic cancer.

POLICY STATEMENT

ALK Testing

Analysis of tumor tissue for somatic rearrangement variants of the anaplastic lymphoma kinase (*ALK*) gene in tissue may be considered **medically necessary** to select treatment with an U.S. Food and Drug Administration (FDA)-approved ALK inhibitor therapy (eg, crizotinib [Xalkori], ceritinib [Zykadia], alectinib [Alecensa], brigatinib [Alunbrig], or lorlatinib [Lorbrena]) in individuals with advanced lung adenocarcinoma or in whom an adenocarcinoma component cannot be excluded, if the individual does not have any FDA-labeled contraindications to the requested agent and the agent is intended to be used consistently with the FDA-approved label.

BRAF Testing

Analysis of tumor tissue for the somatic *BRAF* V600E variant may be considered **medically necessary** to select treatment with an FDA-approved BRAF and/or MEK inhibitor therapy (eg, dabrafenib [Tafinlar] and trametinib [Mekinist]), in individuals with advanced lung adenocarcinoma, in whom an adenocarcinoma component cannot be excluded, colorectal cancer (CRC) or metastatic CRC, glioma, anaplastic thyroid cancer (ATC), unresectable or metastatic melanoma, or resected stage III melanoma, if the individual does not have any FDA-labeled contraindications to the requested agent and the agent is intended to be used consistently with the FDA-approved label.

Testing for *BRAF* V600 variants or *BRAF* fusion rearrangements (e.g., *KIAA1549::BRAF)* in individuals with relapsed or refractory pediatric low-grade glioma may be considered **medically necessary** to select individuals for targeted treatment with tovorafenib.

Testing for *BRAF* V600 variants or *BRAF* fusion rearrangements for all other individuals with glioma to select targeted treatment is considered **investigational**.

BRCA1 and BRCA2 Testing

Genetic testing for *BRCA1* or *BRCA2* germline variants may be considered **medically necessary** to select treatment with PARP inhibitors (eg, olaparib [Lynparza] and talazoparib [Talzenna]) for human epidermal receptor 2 (HER2)-negative metastatic and early stage, high-risk breast cancer, individuals with metastatic castrate-resistant prostate cancer (mCRPC), and advanced epithelial ovarian, fallopian tube, or primary peritoneal cancer.

Somatic *BRCA1/2* variant analysis using tumor tissue may be considered **medically necessary** for individuals with advanced epithelial ovarian, fallopian tube, or primary peritoneal cancer, mCRPC, and prostate cancer to select treatment with FDA-approved targeted therapies.

Claudin 18 (CLDN18) Testing

CLDN18 testing may be considered **medically necessary** to select treatment with FDA-approved targeted therapies in individuals with locally advanced unresectable or metastatic human epidermal growth factor receptor 2 (HER2)-negative gastric or gastroesophageal junction adenocarcinoma whose tumors are claudin (CLDN) 18.2 positive as determined by an FDA-approved test.

EGFR Testing

Analysis of tumor tissue for somatic variants in exons 18 through 21 (eg, G719X, L858R, T790M, S6781, L861Q) within the epidermal growth factor receptor *(EGFR)* gene, may be considered **medically necessary** to select treatment with a FDA-approved therapy (eg, erlotinib [Tarceva] alone or in combination with ramucirumab [Cyramza], gefitinib [Iressa], afatinib [Gilotrif], dacomitinib [Vizimpro], or osimertinib [Tagrisso]) in individuals with advanced lung adenocarcinoma, large cell carcinoma, advanced squamous-cell non-small-cell lung cancer (NSCLC), and NSCLC not otherwise specified, if the individual does not have any FDA-labeled contraindications to the requested agent and the agent is intended to be used consistently with the FDA-approved label.

Analysis of tumor tissue for somatic variants in exon 20 (eg, insertion mutations) within the *EGFR* gene, may be considered **medically necessary** to select treatment with an FDA-approved therapy (eg, mobocertinib [Exkivity]) in individuals with NSCLC, if the individual does not have any FDA-labeled contraindications to the requested agent and the agent is intended to be used consistently with the FDA-approved label.

Somatic *EGFR* variant analysis using tumor tissue may be considered **medically necessary** to select treatment with FDA-approved targeted therapies for individuals with metastatic colorectal cancer (CRC), if the individual does not have any FDA-labeled contraindications to the requested agent and the agent is intended to be used consistently with the FDA-approved label.

ESR1 Testing

Analysis of tissue somatic variants of the *ESR1* gene using an FDA-approved companion diagnostic tissue test to detect tumor DNA may be considered **medically necessary** as an alternative to a liquid biopsy (see Policy Guidelines) to select treatment with an FDA-approved with elacestrant (Orserdu) in individuals with estrogen receptor-positive, HER2-negative advanced or metastatic breast cancer with disease progression following at least 1 line of endocrine therapy, if the individual does not have any FDA-labeled contraindications to the requested agent and both the agent and tissue test are intended to be used consistently with their FDA-approved labels.

EZH2 Testing

EZH2 testing of tumor tissue biopsy specimens may be considered **medically necessary** to select treatment with tazemetostat (Tazverik) in individuals with relapsed or refractory follicular lymphoma whose tumors are positive for an *EZH2* variant as detected by an FDA-approved test and who have received at least 2 prior systemic therapies.

FGFR2 Testing

FGFR2 testing of tumor tissue biopsy specimens may be considered **medically necessary** to select treatment with pemigatinib (Pemazyre) in individuals with previously treated, unresectable locally advanced or metastatic cholangiocarcinoma with a fibroblast growth factor receptor 2 (FGFR2) fusion or other rearrangement as detected by an FDA-approved test.

FGFR3 Testing

FGFR3 testing of tumor tissue biopsy specimens may be considered **medically necessary** to select treatment with erdafitinib (Balversa) in individuals with locally advanced or metastatic urothelial carcinoma and progressed during or following at least one line of prior platinum-containing chemotherapy including within 12 months of neoadjuvant or adjuvant platinum-containing chemotherapy.

FLT3 Testing

Somatic testing using blood or bone marrow specimens for *FLT3*gene variants or internal tandem duplication (ITD)-positive as detected by an FDA-approved test to select treatment for acute myeloid leukemia (AML) with FDA-approved targeted therapies may be considered **medically necessary** if the individual does not have any FDA-labeled contraindications to the requested agent and the agent is intended to be used consistently with the FDA-approved label.

FOLR1 Testing

FOLR1 testing of tumor tissue biopsy specimens may be considered **medically necessary** to select treatment with FDA-approved targeted therapies for individuals with platinum-resistant epithelial ovarian, fallopian tube, or primary peritoneal cancer, who have received one to three prior systemic treatment regimens.

HER2 Testing

HER2 testing of tumor tissue biopsy specimens may be considered **medically necessary** to select treatment with FDA-approved therapies for individuals with metastatic solid tumors.

Homologous Recombination Repair (HRR) Gene Testing

Somatic testing using tissue biopsy for homologous recombination repair (HRR) gene variants (*BRCA1*, *BRCA2*, *ATM*, *BARD1*, *BRIP1*, *CDK12*, *CHEK1*, *CHEK2*, *FANCL*, *PALB2*, *RAD51B*, *RAD51C*, *RAD51D,* and *RAD54L*) to select treatment for mCRPC with FDA-approved targeted therapies may be considered **medically necessary**.

Homologous Recombination Deficiency (HRD) Gene Testing

Homologous recombination deficiency (HRD) analysis of tumor tissue may be considered **medically necessary** to select treatment with FDA-approved targeted therapies for individuals with advanced epithelial ovarian, fallopian tube, or primary peritoneal cancer.

Human Leukocyte Antigen (HLA) Testing

HLA testing of tumor tissue biopsy specimens may be considered **medically necessary** to select treatment with tebentafusp-tebn (Kimmtrak) for individuals with unresectable or metastatic uveal melanoma.

IDH1 and *IDH2* Testing

Testing for *IDH1* or *IDH2* gene variants in individuals with glioma (i.e., grade 2 astrocytoma or oligodendroglioma following surgery including biopsy, sub-total resection, or gross total resection) may be considered **medically necessary** to select individuals for targeted treatment with vorasidenib.

Testing for *IDH1* or *IDH2* gene variants in individuals with relapsed or refractory acute myeloid leukemia (AML) or individuals that are 75 years or older, or who have comorbidities that preclude use of intensive induction chemotherapy and are newly diagnosed with AML may be considered **medically necessary** to select individuals for targeted treatment with FDA-approved therapies that are consistent with the labeled indication.

Testing for *IDH1* gene variants in individuals with relapsed or refractory myelodysplastic syndromes or locally advanced or metastatic cholangiocarcinoma may be considered **medically necessary** to select individuals for targeted treatment with ivosidenib in concordance with the labeled indication.

KIT Testing

Testing for *KIT* gene variants in individuals with aggressive systemic mastocytosis (ASM) without the D816V c-Kit mutation or with c-Kit mutational status unknown may be considered **medically necessary** to select individuals for targeted treatment with imatinib mesylate (Gleevec).

MET Exon 14 Skipping Alteration

Analysis of tumor tissue for somatic alterations in tissue that leads to *MET* exon 14 skipping may be considered **medically necessary** to select treatment with capmatinib (Tabrecta) in individuals with metastatic NSCLC, if the individual does not have any FDA-labeled contraindications to the requested agent and the agent is intended to be used consistently with the FDA-approved label (see Policy Guidelines).

Mismatch Repair/Microsatellite Instability Testing

For individuals with unresectable or metastatic solid tumors who receive mismatch repair/microsatellite instability tumor tissue testing to select treatment may be considered **medically necessary** for FDA-approved immune checkpoint inhibitors with NCCN recommendations of 2A or higher and the individual does not have any FDA-labeled contraindications to the requested agent and the agent is intended to be used consistently with the FDA-approved label.

Neurotrophic Receptor Tyrosine Kinase (*NTRK)* Gene Fusion Testing

NTRK gene fusion testing may be considered **medically necessary** for individuals with recurrent unresectable (local or regional) or stage IV breast cancer to select individuals for treatment with FDA-approved therapies.

Analysis of tumor tissue for *NTRK* gene fusions may be considered **medically necessary** to select treatment with TRK inhibitor therapy (e.g., larotrectinib [Vitrakvi] or entrectinib [Rozlytrek]) in individuals with metastatic NSCLC, metastatic CRC, unresectable or metastatic melanoma, glioma, and individuals with advanced epithelial ovarian, fallopian tube, primary peritoneal cancer, or other solid tumors, if the individual does not have any FDA-labeled contraindications to the requested agent and the agent is intended to be used consistently with the FDA-approved label (see Policy Guidelines).

PDGFRA Testing

Analysis of tumor tissue for somatic variants of the *PDGFRA* gene (eg, D842V) may be considered **medically necessary** to select treatment with avapritinib (Ayvakit) in individuals with unresectable or metastatic gastrointestinal stromal tumor (GIST).

PDGFRB Testing

Analysis of tumor tissue for somatic gene rearrangements of the *PDGFRB* gene (eg, *FIP1L1-PDGFRα*) may be considered **medically necessary** to select treatment with imatinib mesylate (Gleevec) in individuals with myelodysplastic/myeloproliferative diseases (MDS/MPD).

PIK3CA Testing

PIK3CA testing may be considered **medically necessary** to select treatment with alpelisib (Piqray) in individuals with hormone receptor-positive, HER2-negative advanced or metastatic breast cancer who have progressed on or after an endocrine-based regimen (see Policy Guidelines).

Programmed Cell Death Ligand-1 Testing

For individuals with unresectable or metastatic solid tumors who receive programmed cell death ligand-1 (PD-L1) tumor tissue testing to select treatment may be considered **medically necessary** for FDA-approved immune checkpoint inhibitors with NCCN recommendations of 2A or higher and the individual does not have any FDA-labeled contraindications to the requested agent and the agent is intended to be used consistently with the FDA-approved label.

RAS *(KRAS and NRAS)* Testing

Analysis of tumor tissue for somatic variants of the *KRAS* gene (eg, G12C) may be considered **medically necessary** to select treatment with sotorasib (Lumakras) in individuals with advanced lung adenocarcinoma or in whom an adenocarcinoma component cannot be excluded, if the individual does not have any FDA-labeled contraindications to the requested agent and the agent is intended to be used consistently with the FDA-approved label.

KRAS and *NRAS* testing of tumor tissue biopsy specimens may be considered **medically necessary** for individuals with metastatic colorectal cancer (CRC) to select individuals for treatment with U.S. Food and Drug Administration (FDA)-approved therapies.

RET Testing

Analysis of tumor tissue for somatic alterations in the *RET* gene may be considered **medically necessary** to select treatment with RET inhibitor therapy (e.g., pralsetinib [Gavreto] or selpercatinib [Retevmo]) in individuals with advanced or metastatic NSCLC, CRC, medullary thyroid cancer, thyroid cancer, or any other solid tumors, if the individual does not have any FDA-labeled contraindications to the requested agent and the agent is intended to be used consistently with the FDA-approved label.

ROS1 Testing

Analysis of tumor tissue for somatic rearrangement variants of the *ROS1* gene may be considered **medically necessary** to select treatment with an FDA-approved *ROS1* inhibitor therapy (eg, crizotinib [Xalkori]) in individuals with advanced lung adenocarcinoma or in whom an adenocarcinoma component cannot be excluded, if the individual does not have any FDA-labeled contraindications to the requested agent and the agent is intended to be used consistently with the FDA-approved label.

TP53 Testing

Analysis of tumor tissue for a somatic deletion of chromosome 17p (*TP53* gene) may be considered **medically necessary** to select treatment with venetoclax (Venclexta) in individuals with chronic lymphocytic leukemia (CLL).

Tumor Mutational Burden Testing

For individuals with unresectable or metastatic solid tumors who receive tumor mutational burden tumor (TMB) tissue testing to select treatment may be considered **medically necessary** for FDA-approved immune checkpoint inhibitors with NCCN recommendations of 2A or higher and the individual does not have any FDA-labeled contraindications to the requested agent and the agent is intended to be used consistently with the FDA-approved label.

All other uses of genetic biomarker analysis for somatic variants to select treatment with FDA-approved targeted therapies, outlined in Table 1, for individuals with unresectable, recurrent, relapsed, refractory, advanced, or metastatic cancer are considered **investigational.**

Circulating Tumor DNA Testing (Liquid Biopsy)

Analysis of plasma for somatic rearrangement variants of the ALK gene using an FDA-approved companion diagnostic plasma test to detect ctDNA may be considered **medically necessary** as an alternative to tissue biopsy (see Policy Guidelines) to select treatment with an FDA-approved ALK inhibitor therapy in individuals with non-small cell lung cancer (NSCLC) (eg, alectinib [Alcensa]), if the individual does not have any FDA-labeled contraindications to the requested agent and both the agent and ctDNA test are intended to be used consistently with their FDA-approved labels (see Policy Guidelines).

Analysis of plasma (liquid biopsy) for the somatic BRAF V600E variants using an FDA-approved companion diagnostic plasma test to detect ctDNA may be considered **medically necessary** as an alternative to tissue biopsy (see Policy Guidelines) to select treatment with an FDA-approved therapy in

individuals with metastatic CRC and NSCLC, if the individual does not have any FDA-labeled contraindications to the requested agent and the agent is intended to be used consistently with the FDA-approved label (see Policy Guidelines).

BRCA1/2 variant analysis using circulating tumor DNA (liquid biopsy) may be considered **medically necessary** for individuals with advanced epithelial ovarian, fallopian tube, or primary peritoneal cancer to select treatment with FDA-approved targeted therapies when tissue-based analysis is not clinically feasible.

At diagnosis, analysis of plasma for somatic variants in exons 19 through 21 (eg, exon 19 deletions, L858R, T790M) within the *EGFR* gene, using an FDA-approved companion diagnostic plasma test to detect circulating tumor DNA (ctDNA) may be considered **medically necessary** as an alternative to tissue biopsy (see Policy Guidelines) to select treatment with an FDA-approved therapy in individuals with advanced lung adenocarcinoma, large cell carcinoma, advanced squamous cell NSCLC, and NSCLC not otherwise specified, if the individual does not have any FDA-labeled contraindications to the requested agent and the agent is intended to be used consistently with the FDA-approved label (see Policy Guidelines).

At progression, analysis of plasma for the EGFR T790M resistance variant for targeted therapy with osimertinib using an FDA-approved companion diagnostic plasma test to detect ctDNA may be considered **medically necessary** in individuals with advanced lung adenocarcinoma, large cell carcinoma, advanced squamous cell NSCLC, and NSCLC not otherwise specified, when tissue biopsy to obtain new tissue is not feasible (eg, in those who do not have enough tissue for standard molecular testing using formalin-fixed paraffin-embedded tissue, do not have a biopsy-amenable lesion, or cannot undergo biopsy), and when the individual does not have any FDA-labeled contraindications to osimertinib and it is intended to be used consistently with the FDA-approved label (see Policy Guidelines).

ESR1 testing using ctDNA to detect variants (liquid biopsy) may be considered **medically necessary** to predict treatment response to elacestrant (Orserdu) in individuals with estrogen receptor-positive, HER2-negative advanced or metastatic breast cancer with disease progression following at least 1 line of endocrine therapy (see Policy Guidelines).

Somatic testing using circulating tumor DNA testing (liquid biopsy) for *BRCA1*, *BRCA2*, and *ATM* variants to select treatment for mCRPC with FDA-approved targeted therapies may be considered **medically necessary**.

Analysis of plasma for somatic alteration that leads to *MET* exon 14 skipping using an FDA-approved companion diagnostic plasma test to detect ctDNA may be considered **medically necessary** as an alternative to tissue biopsy (see Policy Guidelines) to select treatment with MET inhibitor therapy (eg, capmatinib [Tabrecta]) in individuals with NSCLC, if the individual does not have any FDA-labeled contraindications to the requested agent and both the agent and ctDNA test are intended to be used consistently with their FDA-approved labels (see Policy Guidelines).

Analysis of plasma for *NTRK* gene fusions using an FDA-approved companion diagnostic plasma test to detect ctDNA may be considered **medically necessary** as an alternative to tissue biopsy (see Policy Guidelines) to select treatment with TRK inhibitor therapy (e.g., larotrectinib [Vitrakvi] or entrectinib [Rozlytrek]) in individuals with metastatic NSCLC, metastatic CRC, unresectable or metastatic melanoma, glioma, and individuals with advanced epithelial ovarian, fallopian tube, primary peritoneal cancer, or other solid tumors, if the individual does not have any FDA-labeled contraindications to the requested agent and both the agent and ctDNA test are intended to be used consistently with their FDA-approved labels (see Policy Guidelines).

PIK3CA testing using ctDNA (liquid biopsy) specimens may be considered **medically necessary** to select treatment with alpelisib (Piqray) in individuals with hormone receptor-positive, HER2 negative advanced or metastatic breast cancer who have progressed on or after an endocrine-based regimen (see Policy Guidelines).

- When tumor tissue is available, use of tissue for testing is preferred but is not required.
- When tumor tissue is available, use of tissue for testing is preferred but is not required (see Circulating Tumor DNA Testing below).

Analysis of plasma for somatic variants of the KRAS gene (eg, G12C) using an FDA-approved companion diagnostic plasma test to detect ctDNA may be considered **medically necessary** as an alternative to tissue biopsy (see Policy Guidelines) to select treatment with sotorasib (Lumakras) or adagrasib (Krazati) in individuals with locally advanced or metastatic NSCLC, if the individual does not have any FDA-labeled contraindications to the requested agent and both the agent and ctDNA test are intended to be used consistently with their FDA-approved labels (see Policy Guidelines).

Analysis of plasma for somatic alterations of the RET gene using plasma specimens to detect ctDNA is considered **investigational** as an alternative to tissue biopsy (see Policy Guidelines) to select treatment with RET inhibitor therapy (eg, selpercatinib [Retevmo], pralsetinib [Gavreto]) in individuals with advanced or metastatic NSCLC, CRC, medullary thyroid cancer, thyroid cancer, or any other solid tumors.

Analysis of plasma for somatic rearrangement variants of the *ROS1* gene to detect ctDNA may be considered **medically necessary** as an alternative to tissue biopsy (see Policy Guidelines) to select treatment with *ROS1* inhibitor therapy (eg, crizotinib [Xalkori] or entrectinib) in individuals with NSCLC.

All other uses of somatic testing using circulating tumor DNA testing (liquid biopsy) to guide cancer targeted therapy are considered **investigational**.

Plasma Testing When Tissue is Insufficient

Plasma tests for oncogenic driver variants deemed **medically necessary** on tissue biopsy may be considered **medically necessary** to select treatment with targeted therapy for individuals meeting the following criteria:

- Individual does not have sufficient tissue for standard molecular testing using formalin-fixed paraffin-embedded tissue; AND
- Follow-up tissue-based analysis is planned should no driver variant be identified via plasma testing.

Testing for other variants may become available between policy updates.

Other

Testing for other variants may become available between policy updates.

POLICY GUIDELINES

See U.S. Food and Drug Administration labels, clinical trials, and National Comprehensive Cancer Network (NCCN) guidelines for specific population descriptions. Descriptions varied slightly across sources. Plans may need to alter local coverage medical policy to conform to state law regarding coverage of biomarker testing.

This policy does not address germline testing for inherited risk of developing cancer.

For expanded panel testing, see evidence review 2.04.115. The use of circulating tumor DNA and circulating tumor cells are addressed separately in evidence review 2.04.141 and 2.04.115.

Testing for other variants may become available between policy updates.

FDA approves tests in between policy review cycles. As such, newly approved tests might need to be considered per local Plan discretion. For guidance on testing criteria between policy updates, refer to the FDA's List of Cleared or Approved Companion Diagnostic Devices (In Vitro and Imaging Tools) (https://www.fda.gov/medical-devices/in-vitro-diagnostics/list-cleared-or-approved-companion-diagnostic-devices-in-vitro-and-imaging-tools) for an updated list of FDA-approved tumor markers and consult the most current version of NCCN management algorithms.

Note: Extensive evidence review is not included for somatic tests of individual genes (not gene panels) associated with FDA-approved therapies with NCCN recommendations of 2A or higher. Additionally, while the FDA approval of companion diagnostic tests for genes might include tests that are conducted as panels, the FDA approval is for specific genes (such as driver variants) and not for all of the genes on the test panel. No evidence review is provided for somatic tests of individual genes that do not have associated FDA-approved therapies regardless of NCCN recommendations, as these off-label therapies are deemed investigational per the Blue Cross and Blue Shield Association Medical Policy Program Policies and Procedures.

This policy varies from NCCN-Pediatric CNS guidelines for pediatric gliomas, which endorse use of several off-label therapies. Plans might locally consider coverage of *BRAF* V600E testing to inform coverage of vemurafenib and *ALK* rearrangement testing to inform coverage of lorlatinib and alectinib. The NCCN guidelines for CNS cancers also endorse off-label use of ivosidenib in recurrent or progressive adult oligodendroglioma after radiotherapy and chemotherapy harboring *IDH1* variants. NCCN notes that *IDH* variant testing is required for the workup of all gliomas, as *IDH* variant status defines WHO grade 2 and 3 astrocytomas and oligodendrogliomas, and grade 4 astrocytomas. The presence of these variants distinguishes lower-grade gliomas from glioblastomas, which are *IDH* wild-type. *IDH*-mutant gliomas are considered adult-type diffuse gliomas and are addressed in the NCCN non-pediatric CNS cancer guidelines. This review does not address genetic testing for purposes of diagnosis or staging in melanoma or glioma.

Targeted Therapy

Targeted therapy is a type of precision or personalized medicine that treats cancer by targeting specific features, changes, mutations (variants), or substances in or on cancer cells.

There are many kinds of targeted therapies. They are designed to stop cancer cells from growing and spreading while limiting damage to normal, healthy cells. Each type works in a specific way. For example, they might:

- Target specific biomarkers (genes and proteins that help cancer cells survive and grow).
- Change the tissue or environment that cancer cells grow in.
- Target other types of cells that help a cancer grow, like blood vessel cells.

Targeted therapy definition: treatment with drugs that interact with or block the synthesis of specific cellular components characteristic of the individual's disease to stop or interrupt the specific biochemical dysfunction involved in the progression of the disease.

Genetic therapy definition: techniques and strategies that include coding sequences and other conventional or radical means to transform or modify cells to treat or reverse disease conditions.

Paired Genetic Testing

Testing for genetic changes in tumor tissue assesses somatic changes. However, most somatic testing involves a paired blood analysis in order to distinguish whether findings in tumor tissue are acquired somatic changes or inherited germline changes. As such, simultaneous sequencing of tumor and normal tissue can recognize potential secondary germline changes that may identify risk for other cancers as well as identify risk for relatives. Thus, some laboratories offer concurrent full germline and somatic testing or paired tumor sequencing and germline sequencing, through large panels of germline and somatic variants. For paired panel testing involving germline components, see evidence review 2.04.93 - Genetic Cancer Susceptibility Panels Using Next Generation Sequencing. For paired panel testing involving somatic components, see evidence review 2.04.115 - Comprehensive Genomic Profiling for Selecting Targeted Cancer Therapies.

Repeat Genetic Testing

There may be utility in repeated testing of gene variants for determining targeted therapy or immunotherapy in individuals with NSCLC, prostate cancer, CRC, ovarian cancer, etc. as tumor molecular profiles may change with subsequent treatments and re-evaluation may be considered at time of cancer progression for treatment decision-making. For example, repeat testing (tissue or liquid based) at progression on or after targeted therapy with an FDA-approved drug may be considered to select patients for treatment with another FDA-approved therapy if an acquired resistance variant occurs that was not detected at initial diagnosis (Lin et al 2019; PMID 30425037). The American Society of Clinical Oncology (ASCO) currently suggests repeat genomic testing for individuals on targeted therapy with suspected acquired resistance, especially if choice of next-line therapy would be guided. The ASCO guidance is not tumor specific, and it cautions to consider clinical utility (Chakravarty et al, 2022; PMID 35175857).

Tissue-based Genetic Testing

Tissue biopsy testing uses tissue samples and assesses cancer DNA within the sampled tissue. The goal is to identify options for genome-informed treatment. Some providers will order a liquid biopsy test and a tissue biopsy test at the same time to hasten time to treatment. If the intent of concurrent testing is to follow an individual over time to monitor for resistance variants, then consideration could be given to doing tissue biopsy at diagnosis with the liquid biopsy to make sure that variants that are going to be followed longitudinally can be detected by the tissue biopsy.

Concurrent Somatic Liquid-Based and Tissue-Based Genetic Testing

Liquid biopsy testing uses blood samples and assesses cancer DNA and non-cancer DNA in the same blood sample. The goal is to identify options for genome-informed treatment. Some providers will order a liquid biopsy test and a tissue biopsy test at the same time to hasten time to treatment. If the intent of concurrent testing is to follow an individual over time to monitor for resistance variants, then consideration could be given to doing liquid biopsy at diagnosis with the tissue biopsy to make sure that variants that are going to be followed longitudinally can be detected by the liquid biopsy.

Recommended Testing Strategies

Individuals who meet criteria for genetic testing as outlined in the policy statements above should be tested for the variants specified.

- When tumor tissue is available, use of tissue for testing of any/all variants and biomarkers outlined in this policy is recommended, but is not required in all situations. In certain situations, circulating tumor DNA testing (liquid biopsy) may be an option.

Genetics Nomenclature Update

The Human Genome Variation Society nomenclature is used to report information on variants found in DNA and serves as an international standard in DNA diagnostics. It is being implemented for genetic testing medical evidence review updates starting in 2017 (see Table PG2). The Society's nomenclature is recommended by the Human Variome Project, the HUman Genome Organization, and by the Human Genome Variation Society itself.

The American College of Medical Genetics and Genomics and the Association for Molecular Pathology standards and guidelines for interpretation of sequence variants represent expert opinion from both organizations, in addition to the College of American Pathologists. These recommendations primarily apply to genetic tests used in clinical laboratories, including genotyping, single genes, panels, exomes, and genomes. Table PG3 shows the

recommended standard terminology- "pathogenic," "likely pathogenic," "uncertain significance," "likely benign," and "benign"- to describe variants identified that cause Mendelian disorders.

Table PG2. Nomenclature to Report on Variants Found in DNA

Previous	Updated	Definition
Mutation	Disease-associated variant	Disease-associated change in the DNA sequence
	Variant	Change in the DNA sequence
	Familial variant	Disease-associated variant identified in a proband for use in subsequent targeted genetic testing in first-degree relatives

Table PG3. ACMG-AMP Standards and Guidelines for Variant Classification

Variant Classification	Definition
Pathogenic	Disease-causing change in the DNA sequence
Likely pathogenic	Likely disease-causing change in the DNA sequence
Variant of uncertain significance	Change in DNA sequence with uncertain effects on disease
Likely benign	Likely benign change in the DNA sequence
Benign	Benign change in the DNA sequence

ACMG-AMP: American College of Medical Genetics and Genomics and the Association for Molecular Pathology.

Genetic Counseling

Genetic counseling is primarily aimed at patients who are at risk for inherited disorders, and experts recommend formal genetic counseling in most cases when genetic testing for an inherited condition is considered. The interpretation of the results of genetic tests and the understanding of risk factors can be very difficult and complex. Therefore, genetic counseling will assist individuals in understanding the possible benefits and harms of genetic testing, including the possible impact of the information on the individual"s family. Genetic counseling may alter the utilization of genetic testing substantially and may reduce inappropriate testing. Genetic counseling should be performed by an individual with experience and expertise in genetic medicine and genetic testing methods.

BENEFIT APPLICATION

Experimental or investigational procedures, treatments, drugs, or devices are not covered (See General Exclusion Section of brochure).

Some Plans may have contract or benefit exclusions for genetic testing.

FDA REGULATORY STATUS

Clinical laboratories may develop and validate tests in-house and market them as a laboratory service; laboratory-developed tests must meet the general regulatory standards of the Clinical Laboratory Improvement Amendments. Laboratories that offer laboratory-developed tests must be licensed by the Clinical Laboratory Improvement Amendments for high-complexity testing. To date, the U.S. Food and Drug Administration has chosen not to require any regulatory review of these tests.

Table 1 summarizes available targeted treatments with FDA approval for unresectable, recurrent, relapsed, refractory, advanced, and/or metastatic cancer (including immunotherapy) and the FDA cleared or approved companion diagnostic tests associated with each. The information in Table 1 was current as of November 01, 2025. An up-to-date list of FDA cleared or approved companion diagnostics is available at https://www.fda.gov/medical-devices/in-vitro-diagnostics/list-cleared-or-approved-companion-diagnostic-devices-in-vitro-and-imaging-tools. As the FDA had decided that laboratory developed tests (LDT) are no longer under their purview, this table is not all encompassing of LDT that are capable of detecting genetic biomarker variants for targeted therapy.

Table 1. Targeted Treatments for Unresectable, Recurrent, Relapsed, Refractory, Advanced, and/or Metastatic Cancer and FDA Approved Companion Diagnostic Tests

Indication - Sample Type	Diagnostic Name (Manufacturer)	Drug Trade Name (Generic) NDA / BLA	Biomarker(s)	Biomarker(s) (Details)	PMA / 510(k) /513(f)(2) / HDE (Approval / Clearance / Grant Date)	PLA Codes[a]
Acute Myelogenous Leukemia - Peripheral Blood or Bone Marrow	LeukoStrat CDx FLT3 Mutation Assay (Invivoscribe Technologies, Inc.)	Rydapt (midostaurin) NDA 207997	FLT3 (ITD/TDK)	ITD mutations and TKD mutations D835 and I836	P160040 (04/28/2017)	0023U
Acute Myelogenous Leukemia - Peripheral Blood or Bone Marrow	LeukoStrat CDx FLT3 Mutation Assay (Invivoscribe Technologies, Inc.)	Xospata (gilterinib) NDA 211349	FLT3 (ITD/TDK)	ITD mutations and TKD mutations D835 and I836	P160040/S002 (11/28/2018)	0023U
Acute Myelogenous Leukemia (AML) - Peripheral Blood or Bone Marrow	LeukoStrat CDx FLT3 Mutation Assay (Invivoscribe Technologies, Inc.)	Vanflyta (quizartinib) NDA 216993	FLT3 (ITD/TDK)	IDT mutations and TKD mutations D835 and I836	P160040/S011 (07/20/2023)	0023U
Acute Myeloid Leukemia - Peripheral Blood or Bone Marrow	Abbott RealTime IDH1 (Abbott Molecular, Inc.)	Tibsovo (ivosidenib) NDA 211192	IDH1	R132 mutations (R132C, R132H, R132G, R132S, and R132L)	P170041 (07/20/2018)	N/A
Acute Myeloid Leukemia - Peripheral Blood or Bone Marrow	Abbott RealTime IDH1 (Abbott Molecular, Inc.)	Rezlidhia (olutasidenib) NDA 215814	IDH1	R132 mutations (R132C, R132H, R132G, R132S, and R132L)	P170041/S006 (12/01/2022)	N/A
Acute Myeloid Leukemia - Peripheral Blood or Bone Marrow	Abbott RealTime IDH2 (Abbott Molecular, Inc.)	Idhifa (enasidenib) NDA 209606	IDH2	R140Q, R140L, R140G, R140W, R172K, R172M, R172G, R172S, and R172W	P170005 (08/01/2017)	N/A
Aggressive Systemic Mastocytosis - Bone Marrow	KIT D816V Assay (ARUP Laboratories, Inc.)	Gleevec (imatinib mesylate) NDA 021588	KIT	D816V	H140006 (12/18/2015)	N/A

Anaplastic Thyroid Cancer (ATC) - Tissue	Oncomine Dx Target Test (Life Technologies Corporation)	Tafinlar (dabrafenib) NDA 202806 in combination with Mekinist (trametinib) NDA 204114	BRAF	BRAF V600E mutations	P160045/S025 (09/29/2023)	0022U
Astrocytoma and Oligodendroglioma - Tissue	Oncomine Dx Target Test (Life Technologies Corporation)	VORANIGO (vorasidenib) - NDA 218784	IDH1, IDH2	IDH1 R132C, IDH1 R132G, IDH1 R132H, IDH1 R132L, IDH1 R132S, IDH2 R172M, IDH2 R172K, IDH2 R172W, IDH2 R172S, and IDH2 R172G mutations	P160045/S046 (09/18/2024)	0022U
B-cell Chronic Lymphocytic Leukemia - Peripheral Blood	Vysis CLL FISH Probe Kit (Abbott Molecular, Inc.)	Venclexta (venetoclax) NDA 208573	TP53	Deletion chromosome 17p (17p-)	P150041 (04/11/2016)	N/A
Biliary Tract Cancer (gallbladder adenocarcinoma, intrahepatic cholangiocarcinoma, and extrahepatic cholangiocarcinoma) - Tissue	PATHWAY anti-Her2/neu (4B5) Rabbit Monoclonal Primary Antibody (Ventana Medical Systems, Inc.)	Ziihera (zanidatamab-hrii) - BLA 761416	ERBB2 (HER2)	HER-2 protein overexpression	P990081/S054 (11/20/2024)	N/A
Breast Cancer - Plasma	FoundationOne Liquid CDx (Foundation Medicine, Inc.)	Piqray (alpelisib) NDA 212526	PIK3CA	C420R, E542K, E545A, E545D [1635G>T only], E545G, E545K, Q546E, Q546R, H1047L, H1047R, and H1047Y	P200006 (10/26/2020)	0239U
Breast Cancer - Plasma	FoundationOne Liquid CDx (Foundation Medicine, Inc.)	ITOVEBI (inavolisib) NDA 219249 in combination with palbociclib and fulvestrant	PIK3CA	Mutations	P190032/S023 (10/10/2024)	0239U
Breast Cancer - Plasma	Guardant360 CDx (Guardant Health, Inc.)	Orserdu (elacestrant) NDA 217639	ESR1	ESR1 missense mutations between codons 310 and 547	P200010/S010 (01/27/2023)	0326U
Breast Cancer - Tissue	Bond Oracle HER2 IHC System (Leica Biosystems)	Herceptin (trastuzumab) BLA 103792	ERBB2 (HER2)	HER-2 protein overexpression	P090015 (04/18/2012)	N/A
Breast Cancer - Tissue	FoundationOne CDx (Foundation Medicine, Inc.)	Herceptin (trastuzumab) BLA 103792	ERBB2 (HER2)	ERBB2 (HER2) amplification	P170019 (11/30/2017)	0037U
Breast Cancer - Tissue	FoundationOne CDx (Foundation Medicine, Inc.)	Perjeta (pertuzumab) BLA 125409	ERBB2 (HER2)	ERBB2 (HER2) amplification	P170019 (11/30/2017)	0037U

Breast Cancer - Tissue	FoundationOne CDx (Foundation Medicine, Inc.)	Kadcyla (ado-trastuzumab emtansine) BLA 125427	ERBB2 (HER2)	ERBB2 (HER2) amplification	P170019 (11/30/2017)	0037U
Breast Cancer - Tissue	FoundationOne CDx (Foundation Medicine, Inc.)	Piqray (alpelisib) NDA 212526	PIK3CA	C420R, E542K, E545A, E545D [1635G>T only], E545G, E545K, Q546E, Q546R, H1047L, H1047R, and H1047Y	P170019/S006 (12/03/2019)	0037U
Breast Cancer - Tissue	FoundationOne CDx (Foundation Medicine, Inc.)	TRUQAP (capivasertib) NDA218197 in combination with FASLODEX (fulvestrant) NDA021344	PIK3CA, AKT1, and PTEN	PIK3CA/AKT1/PTEN alterations	P170019/S048 (11/16/2023)	0037U
Breast Cancer - Tissue	HER2 CISH pharmDx Kit (Dako Denmark A/S)	Herceptin (trastuzumab) BLA 103792	ERBB2 (HER2)	HER-2/neu (ERBB2) gene amplification	P100024 (11/30/2011)	N/A
Breast Cancer - Tissue	HER2 FISH pharmDx Kit (Dako Denmark A/S)	Herceptin (trastuzumab) BLA 103792	ERBB2 (HER2)	HER-2/neu (ERBB2) gene amplification	P040005 (05/03/2005)	N/A
Breast Cancer - Tissue	HER2 FISH pharmDx Kit (Dako Denmark A/S)	Perjeta (pertuzumab) BLA 125409	ERBB2 (HER2)	HER-2/neu (ERBB2) gene amplification	P040005/S006 (06/08/2012)	N/A
Breast Cancer - Tissue	HER2 FISH pharmDx Kit (Dako Denmark A/S)	Kadcyla (ado-trastuzumab emtansine) BLA 125427	ERBB2 (HER2)	HER-2/neu (ERBB2) gene amplification	P040005/S009 (02/22/2013)	N/A
Breast Cancer - Tissue	HercepTest (Dako Denmark A/S)	Herceptin (trastuzumab) BLA 103792	ERBB2 (HER2)	HER-2 protein overexpression	P980018 (09/25/1998)	N/A
Breast Cancer - Tissue	HercepTest (Dako Denmark A/S)	Perjeta (pertuzumab) BLA 125409	ERBB2 (HER2)	HER-2 protein overexpression	P980018/S015 (06/08/2012)	N/A
Breast Cancer - Tissue	HercepTest (Dako Denmark A/S)	Kadcyla (ado-trastuzumab emtansine) BLA 125427	ERBB2 (HER2)	HER-2 protein overexpression	P980018/S016 (02/22/2013)	N/A
Breast Cancer - Tissue	INFORM HER-2/neu (Ventana Medical Systems, Inc.)	Herceptin (trastuzumab) BLA 103792	ERBB2 (HER2)	HER-2/neu (ERBB2) gene amplification	P940004 (12/30/1997)	N/A
Breast Cancer - Tissue	InSite Her-2/neu (CB11) Monoclonal Antibody	Herceptin (trastuzumab) BLA 103792	ERBB2 (HER2)	HER2protein overexpression	P040030 (12/22/2004)	N/A

	(Biogenex Laboratories, Inc.)					
Breast Cancer - Tissue	MI Cancer Seek (MCS) (Caris Life Sciences)	Piqray (alpelisib) - NDA 212526	PIK3CA	C420R, E542K, E545A, E545D [1635G>T only], E545G, E545K, Q546E, Q546R, H1047L, H1047R, and H1047Y	P240010 (11/05/2024)	0211U
Breast Cancer - Tissue	PathVysion HER-2 DNA Probe Kit (Abbott Molecular Inc.)	Herceptin (trastuzumab) BLA 103792	ERBB2 (HER2)	HER-2/neu (ERBB2) gene amplification	P980024 (12/11/1998)	N/A
Breast Cancer - Tissue	PATHWAY anti-Her2/neu (4B5) Rabbit Monoclonal Primary Antibody (Ventana Medical Systems, Inc.)	Herceptin (trastuzumab) BLA 103792	ERBB2 (HER2)	HER-2 protein overexpression	P990081 (11/28/2000)	N/A
Breast Cancer - Tissue	PATHWAY anti-Her2/neu (4B5) Rabbit Monoclonal Primary Antibody (Ventana Medical Systems, Inc.)	Kadcyla (ado-trastuzumab emtansine) BLA 125427	ERBB2 (HER2)	HER-2 protein overexpression	P990081/S039 (05/03/2019)	N/A
Breast Cancer - Tissue	PATHWAY anti-Her2/neu (4B5) Rabbit Monoclonal Primary Antibody (Ventana Medical Systems, Inc.)	Enhertu (fam-trastuzumab deruxtecan-nxki) BLA 761139	ERBB2 (HER2)	HER2-low expression (IHC 1+ or IHC 2+/ISH non-amplified)	P990081/S047 (09/30/2022)	N/A
Breast Cancer - Tissue	SPOT-LIGHT HER2 CISH Kit (Life Technologies Corporation)	Herceptin (trastuzumab) BLA 103792	ERBB2 (HER2)	HER-2/neu (ERBB2) gene amplification	P050040 (07/01/2008)	N/A
Breast Cancer - Tissue	Ventana HER2 Dual ISH DNA Probe Cocktail (Ventana Medical Systems, Inc.)	Herceptin (trastuzumab) BLA 103792	ERBB2 (HER2)	HER-2/neu (ERBB2) gene amplification	P190031 (07/28/2020)	N/A
Breast Cancer - Tissue or Plasma	therascreen PIK3CA RGQ PCR Kit (QIAGEN GmbH)	Piqray (alpelisib) NDA 212526	PIK3CA	C420R, E542K, E545A, E545D [1635G>T only], E545G, E545K, Q546E, Q546R, H1047L, H1047R, and H1047Y	P190001 (05/24/2019) P190004 (05/24/2019)	0155U or 0177U
Breast Cancer - Tissue	PATHWAY anti-Her2/neu (4B5)	Enhertu (fam-trastuzumab	ERBB2 (HER2)	HER2 ultralow expression (IHC 0	P990081/S055 (01/27/2025)	N/A

	Rabbit Monoclonal Primary Antibody (Ventana Medical Systems, Inc.)	deruxtecan-nxki) BLA 761139		with membrane staining)		
Breast Cancer - Whole Blood	BRACAnalysis CDx (Myriad Genetic Laboratories, Inc.)	Lynparza (olaparib) NDA 208558	BRCA1 and BRCA2	Mutations	P140020/S012 (01/12/2018)	N/A
Breast Cancer - Whole Blood	BRACAnalysis CDx (Myriad Genetic Laboratories, Inc.)	Talzenna (talazoparib) NDA 211651	BRCA1 and BRCA2	Mutations	P140020/S015 (10/16/2018)	N/A
Cervical Cancer - Tissue	PD-L1 IHC 22C3 pharmDx (Dako North America, Inc.)	Keytruda (pembrolizumab) BLA 125514	PD-L1	PD-L1 protein expression[Combined Positive Score (CPS) ≥ 1]	P150013/S009 (06/12/2018)	N/A
Cholangiocarcinoma - Tissue	FoundationOne CDx (Foundation Medicine, Inc.)	Pemazyre (pemigatinib) NDA 213736	FGFR2	FGFR2 fusions and select rearrangements	P170019/S013 (04/17/2020)	0037U
Cholangiocarcinoma - Tissue	Oncomine Dx Target Test (Life Technologies Corporation)	Tibsovo (ivosidenib) NDA 211192	IDH1	Single nucleotide variants	P160045/S028 (08/25/2021)	0022U
Chronic Myeloid Leukemia - Peripheral Blood	MRDx BCR-ABL Test (MolecularMD Corporation)	Tasigna (nilotinib) NDA 022068	t(9;21) Philadelphia chromosome	BCR-ABL fusion	K173492 (12/22/2017)	0040U
Colorectal Cancer - Tissue	cobas KRAS Mutation Test (Roche Molecular Systems, Inc.)	Erbitux (cetuximab) BLA 125084	KRAS	Mutations in codons 12 and 13 of KRAS gene	P140023 (05/07/2015)	N/A
Colorectal Cancer - Tissue	cobas KRAS Mutation Test (Roche Molecular Systems, Inc.)	Vectibix (panitumumab) BLA 125147	KRAS	Mutations in codons 12 and 13 of KRAS gene	P140023 (05/07/2015)	N/A
Colorectal Cancer - Tissue	Dako EGFR pharmDx Kit (Dako North America, Inc.)	Erbitux (cetuximab) BLA 125084	EGFR (HER1)	EGFR (HER1) protein expression	P030044 (02/12/2004)	N/A
Colorectal Cancer - Tissue	Dako EGFR pharmDx Kit (Dako North America, Inc.)	Vectibix (panitumumab) BLA 125147	EGFR (HER1)	EGFR (HER1) protein expression	P030044/S002 (09/27/2006)	N/A
Colorectal Cancer - Tissue	FoundationOne CDx (Foundation Medicine, Inc.)	Erbitux (cetuximab) BLA 125084	KRAS	KRAS wild-type (absence of mutations in codons 12 and 13)	P170019 (11/30/2017)	0037U

Colorectal Cancer - Tissue	FoundationOne CDx (Foundation Medicine, Inc.)	Vectibix (panitumumab) BLA 125147	KRAS and NRAS	KRAS wild-type (absence of mutations in exons 2, 3, and 4) and NRAS wild type (absence of mutations in exons 2, 3, and 4)	P170019 (11/30/2017)	0037U
Colorectal Cancer - Tissue	MI Cancer Seek (MCS) (Caris Life Sciences)	Vectibix (panitumumab) - BLA 125147	KRAS and NRAS	KRAS wild-type biomarkers (the absence of mutations in exons 2, 3, or 4) and NRAS wild-type biomarkers (the absence of mutations in exons 2, 3, or 4)	P240010 (11/05/2024)	0211U
Colorectal Cancer - Tissue	MI Cancer Seek (MCS) (Caris Life Sciences)	BRAFTOVI (encorafenib) NDA 210496 in combination with ERBITUX (cetuximab) BLA 125084	BRAF	V600E	P240010 (11/05/2024)	0211U
Colorectal Cancer - Tissue	ONCO/Reveal Dx Lung & Colon Cancer Assay (O/RDx-LCCA) (Pillar Biosciences, Inc.)	Erbitux (cetuximab) BLA 125084	KRAS	KRAS wild-type (absence of mutations in codons 12 and 13)	P200011 (07/30/2021)	0523U
Colorectal Cancer - Tissue	ONCO/Reveal Dx Lung & Colon Cancer Assay (O/RDx-LCCA) (Pillar Biosciences, Inc.)	Vectibix (panitumumab) BLA 125147	KRAS	KRAS wild-type (absence of mutations in codons 12 and 13)	P200011 (07/30/2021)	0523U
Colorectal Cancer - Tissue	therascreen BRAF V600E RGQ PCR Kit (QIAGEN GmbH)	Braftovi (encorafenib) NDA 210496 in combination with Erbitux (cetuximab) BLA 125084	BRAF	V600E	P190026 (04/15/2020)	N/A
Colorectal Cancer - Tissue	therascreen KRAS RGQ PCR Kit (Qiagen Manchester, Ltd.)	Vectibix (panitumumab) BLA 125147	KRAS	G12A, G12D, G12R, G12C, G12S, G12V, G13D	P110027 (05/23/2014)	N/A
Colorectal Cancer - Tissue	therascreen KRAS RGQ PCR Kit (Qiagen Manchester, Ltd.)	Erbitux (cetuximab) BLA 125084	KRAS	G12A, G12D, G12R, G12C, G12S, G12V, G13D	P110030 (07/06/2012)	N/A

Colorectal Cancer - Tissue	therascreen KRAS RGQ PCR Kit (Qiagen Manchester, Ltd.)	Erbitux (cetuximab) BLA 125084	KRAS	KRAS wild-type (absence of mutations in codons 12 and 13)	P110027/S013 (12/02/2022)	N/A
Colorectal Cancer - Tissue	therascreen KRAS RGQ PCR Kit (Qiagen Manchester, Ltd.)	Krazati (adagrasib) in combination with Erbitux (cetuximab) - NDA 216340	KRAS	KRAS G12C	P110027/S017 (06/21/2024)	N/A
Colorectal Cancer - Tissue	therascreen KRAS RGQ PCR Kit (Qiagen Manchester, Ltd.)	Lumakras (sotorasib) NDA 214665 in combination with Vectibix (panitumumab) - BLA 125147	KRAS	KRAS G12C	P110027/S018 (01/16/2025)	N/A
Colorectal Cancer (CRC) - Tissue	CRCDx RAS Mutation Detection Assay Kit (EntroGen, Inc.)	Vectibix (panitumumab) BLA 125147	KRAS and NRAS	KRAS wild-type biomarkers (the absence of mutations in exons 2, 3, or 4) and NRAS wild-type biomarkers (the absence of mutations in exons 2, 3, or 4)	P220005 (09/29/2023)	0471U
Colorectal Cancer (CRC) - Tissue	Idylla CDx MSI Test (Biocartis US, Inc.)	OPDIVO (nivolumab) alone BLA 125554 or OPDIVO (nivolumab) in combination with YERVOY (ipilimumab) BLA 125377	ACVR2A, BTBD7, DIDO1, MRE11, RYR3, SEC31A and SULF2	Microsatellite instability-High (MSI-H)	P250005 (08/15/2025)	N/A
Colorectal Cancer (CRC) - Tissue	MMR IHC Panel pharmDx (Dako Omnis) (Agilent Technologies, Inc.)	OPDIVO (nivolumab) alone BLA 125554 or OPDIVO (nivolumab) in combination with YERVOY (ipilimumab) BLA 125377	Deficient mismatch repair (dMMR) proteins	MLH1, PMS2, MSH2 and MSH6	P250004 (08/15/2025)	N/A
Colorectal Cancer (CRC) - Tissue (Matching Blood/Saliva)	xT CDx (Tempus Labs, Inc.)	Erbitux (cetuximab) BLA 125084	KRAS	KRAS wild-type (absence of mutations in codons 12 or 13)	P210011(04/28/2023)	0473U

Colorectal Cancer (CRC) - Tissue (Matching Blood/Saliva)	xT CDx (Tempus Labs, Inc.)	Vectibix (panitumumab) BLA 125147	KRAS and NRAS	KRAS wild-type (absence of mutations in exons 2, 3, or 4) and NRAS wild-type (absence of mutations in exons 2, 3, or 4)	P210011 (04/28/2023)	0473U
Endometrial Carcinoma (EC) - Tissue	MI Cancer Seek (MCS) (Caris Life Sciences)	Keytruda (pembrolizumab) BLA 125514 in combination with Lenvima (lenvatinib) NDA 206947	Not MSI-High	Not Microsatellite instability-high (Not MSI-H)	P240010 (11/05/2024)	0211U
Endometrial Carcinoma (EC) - Tissue	Ventana MMR RxDx Panel (Ventana Medical Systems, Inc.)	Jemperli (dostarlimag-gxly) BLA 761174	Deficient mismatch repair (dMMR) proteins	MLH1, PMS2, MSH2 and MSH6	P200019(04/22/2021)	N/A
Endometrial Carcinoma (EC) - Tissue	Ventana MMR RxDx Panel (Ventana Medical Systems, Inc.)	Keytruda (pembrolizumab) BLA 125514 in combination with Lenvima (lenvatinib) NDA 206947	proficient mismatch repair (pMMR) proteins	MLH1, PMS2, MSH2 and MSH6	P210001/S002 (06/16/2022)	N/A
Endometrial Carcinoma (EC) - Tissue	Ventana MMR RxDx Panel (Ventana Medical Systems, Inc.)	Imfinzi (durvalumab) BLA 761069	Deficient mismatch repair (dMMR) proteins	MLH1, PMS2, MSH2 and MSH6	P210001/S013 (12/18/2024)	N/A
Epithelial Ovarian Cancer, Fallopian Tube Cancer, or Primary Peritoneal Cancer - Tissue	Ventana FOLR1 (FOLR-2.1) RxDx Assay (Ventana Medical Systems, Inc.)	Elahere (mirvetuximab soravtansine-gynx) BLA 761310	FOLR1	FOLR1 protein expression	P220006 (11/14/2022)	N/A
Esophageal Squamous Cell Carcinoma (ESCC) - Tissue	PD-L1 IHC 22C3 pharmDx (Dako North America, Inc.)	Keytruda (pembrolizumab) BLA 125514	PD-L1	PD-L1 protein expression[Combined Positive Score (CPS) ≥ 10]	P150013/S016 (07/30/2019)	N/A
Follicular Lymphoma Tumor - Tissue	cobas EZH2 Mutation Test (Roche Molecular Systems, Inc.)	Tazverik (tazemetostat) NDA 213400	EZH2	Y646N, Y646F or Y646X (Y646H, Y646S, or Y646C), A682G, and A692V of the EZH2 gene	P200014 (06/18/2020)	N/A
Gastric and Gastroesophageal Cancer - Tissue	HER2 FISH pharmDx Kit (Dako Denmark A/S)	Herceptin (trastuzumab) BLA 103792	ERBB2 (HER2)	HER-2/neu (ERBB2) gene amplification	P040005/S005 (10/20/2010)	N/A
Gastric and Gastroesophageal Cancer - Tissue	HercepTest (Dako Denmark A/S)	Herceptin (trastuzumab) BLA 103792	ERBB2 (HER2)	HER-2 protein overexpression	P980018/S010 (10/20/2010)	N/A

Gastric or Gastroesophageal Junction (GEJ) Adenocarcinoma - Tissue	PD-L1 IHC 22C3 pharmDx (Dako North America, Inc.)	Keytruda (pembrolizumab) BLA 125514	PD-L1	PD-L1 protein expression[Combined Positive Score (CPS) ≥ 1]	P150013/S027 (11/07/2023)	N/A
Gastric or Gastroesophageal Junction (GEJ) Adenocarcinoma - Tissue	VENTANA CLDN18 (43-14A) RxDx Assay (Ventana Medical Systems, Inc.)	VYLOY (zolbetuximab) - BLA 761365	Claudin 18 (CLDN18)	Claudin 18 (CLDN18) protein expression (≥75% viable tumor cells (% TC) staining)	P230018 (10/18/2024)	N/A
Gastrointestinal Stromal Tumors (GIST) - Tissue	therascreen PDGFRA RGQ PCR Kit (QIAGEN GmbH)	AYVAKIT (Avapritinib) NDA 212608	PDGFRA	D842V mutation	P210002 (06/29/2023)	N/A
Head and Neck Squamous Cell Carcinoma (HNSCC) - Tissue	PD-L1 IHC 22C3 pharmDx (Dako North America, Inc.)	Keytruda (pembrolizumab) BLA 125514	PD-L1	PD-L1 protein expression[Combined Positive Score (CPS) ≥ 1]	P150013/S014 (06/10/2019)	N/A
Low-Grade Glioma - Tissue	FoundationOne CDx (Foundation Medicine, Inc.	Ojemda (tovorafenib) - NDA 217700 and NDA 218033	BRAF	BRAF V600 mutations and BRAF fusions	P170019/S054 (01/16/2025)	0037U
Medullary Thyroid Cancer (MTC) - Tissue	Oncomine Dx Target Test (Life Technologies Corporation)	Retevmo (selpercatinib) NDA 213246	RET	RET mutations (SNVs, MNVs, and deletions)	P160045/S031 (09/21/2022)	0022U
Melanoma - Tissue	cobas 4800 BRAF V600 Mutation Test (Roche Molecular Systems, Inc.)	Zelboraf (vemurafenib) NDA 202429	BRAF	V600E	P110020 (08/17/2011)	N/A
Melanoma - Tissue	cobas 4800 BRAF V600 Mutation Test (Roche Molecular Systems, Inc.)	Cotellic (cobimetinib) NDA 206192 in combination with Zelboraf (vemurafenib) NDA 202429	BRAF	V600E or V600K	P110020/S016 (11/07/2016)	N/A
Melanoma - Tissue	FoundationOne CDx (Foundation Medicine, Inc.)	Mekinist (trametinib) NDA 204114	BRAF	V600E and V600K	P170019 (11/30/2017)	0037U
Melanoma - Tissue	FoundationOne CDx (Foundation Medicine, Inc.)	Tecentriq (atezolizumab) BLA 761034 in combination with Cotellic (cobimetinib) NDA 206192 and Zelboraf (vemurafenib) NDA 202429	BRAF	BRAF V600 mutations	P170019/S030 (01/19/2022)	0037U

Melanoma - Tissue	MI Cancer Seek (MCS) (Caris Life Sciences)	Mekinist (trametinib) NDA 204114	BRAF	V600E or V600K	P240010 (11/05/2024)	0211U
Melanoma - Tissue	THXID BRAF Kit (bioMrieux Inc.)	Mekinist (trametinib) NDA 204114	BRAF	V600E or V600K	P120014 (05/29/2013)	N/A
Melanoma - Tissue	THXID BRAF Kit (bioMrieux Inc.)	Tafinlar (dabrafenib) NDA 202806	BRAF	V600E	P120014 (05/29/2013)	N/A
Melanoma - Tissue	THXID BRAF Kit (bioMrieux Inc.)	Braftovi (encorafenib) NDA 210496 in combination with Mektovi (binimetinib) NDA 210498	BRAF	V600E or V600K	P120014/S008 (06/27/2018)	N/A
Metastatic Castrate Resistant Prostate Cancer (mCRPC) - Plasma	FoundationOne Liquid CDx (Foundation Medicine, Inc.)	Rubraca (rucaparib) NDA 209115	BRCA1 and BRCA2	BRCA1 and BRCA2 alterations	P190032 (08/26/2020)	0239U
Metastatic Castrate Resistant Prostate Cancer (mCRPC) - Plasma	FoundationOne Liquid CDx (Foundation Medicine, Inc.)	Lynparza (olaparib) NDA 208558 in combination with abiraterone	BRCA1 and BRCA2	BRCA1 and BRCA2 alterations	P190032/S016 (08/30/2024)	0239U
Metastatic Castrate Resistant Prostate Cancer (mCRPC) - Plasma	FoundationOne Liquid CDx (Foundation Medicine, Inc.)	Lynparza (Olaparib) NDA 208558	BRCA1, BRCA2 and ATM	BRCA1, BRCA2, and ATM alterations	P200016 (11/06/2020)	0239U
Metastatic Castrate Resistant Prostate Cancer (mCRPC) - plasma	FoundationOne Liquid CDx (Foundation Medicine, Inc.)	AKEEGA (niraparib +abiraterone acetate) NDA 216793	BRCA1 and BRCA2	BRCA1 and BRCA2 alterations	P190032/S014 (06/28/ 2024)	0239U
Metastatic Castrate Resistant Prostate Cancer (mCRPC) - Tissue	FoundationOne CDx (Foundation Medicine, Inc.)	Lynparza (olaparib) NDA 208558	Homologous recombination repair (HRR) genes	BRCA1, BRCA2, ATM, BARD1, BRIP1, CDK12, CHEK1, CHEK2, FANCL, PALB2, RAD51B, RAD51C, RAD51D and RAD54L alterations	P170019/S015 (05/19/2020)	0037U
Metastatic Castrate Resistant Prostate Cancer (mCRPC) - Tissue	FoundationOne CDx (Foundation Medicine, Inc.)	Lynparza (olaparib) NDA 208558 in combination with abiraterone	BRCA1 and BRCA2	BRCA1 and BRCA2 alterations	P170019/S052(08/30/2024)	0037U
Metastatic Castrate Resistant Prostate Cancer (mCRPC) - Whole Blood	BRACAnalysis CDx (Myriad Genetic Laboratories, Inc.)	Lynparza (olaparib) NDA 208558	BRCA1 and BRCA2	Mutations	P140020/S020 (05/19/2020)	0037U

Metastatic Colorectal Cancer (mCRC) - Plasma	FoundationOne Liquid CDx (Foundation Medicine, Inc.)	BRAFTOVI (encorafenib) NDA 210496 in combination with cetuximab BLA 125084	BRAF	BRAF V600E alteration	P190032/S010 (06/08/2023)	0239U
Myelodysplastic Syndrome/Myeloproliferative Disease - Bone Marrow	PDGFRB FISH Assay (ARUP Laboratories, Inc.)	Gleevec (imatinib mesylate) NDA 021588	PDGFRB	PDGFRB gene rearrangement at 5q31~33	H140005 (12/18/2015)	N/A
Myelodysplastic Syndromes (MDS) - Peripheral Blood or Bone Marrow	Abbott RealTime IDH1 (Abbott Molecular, Inc.)	Tibsovo (ivosidenib) NDA 211192	IDH1	R132 mutations (R132C, R132H, R132G, R132S, and R132L)	P170041/S007 (10/24/2023)	N/A
Non-Small Cell Lung Cancer (NSCLC) - Plasma	Agilent Resolution ctDx FIRST assay (Resolution Bioscience, Inc.)	Krazati (adagrasib) NDA 216340	KRAS	KRAS G12C	P210040 (12/12/2022)	N/A
Non-Small Cell Lung Cancer (NSCLC) - Plasma	cobas EGFR Mutation Test v2 (Roche Molecular Systems, Inc.)	Tagrisso (osimertinib) NDA 208065	EGFR (HER1)	Exon 19 deletion or exon 21 L858R substitution mutation	P120019/S018 (04/18/2018)	N/A
Non-Small Cell Lung Cancer (NSCLC) - Plasma	cobas EGFR Mutation Test v2 (Roche Molecular Systems, Inc.)	Tagrisso (osimertinib) NDA 208065	EGFR (HER1)	T790M	P150044 (09/28/2016)	N/A
Non-Small Cell Lung Cancer (NSCLC) - Plasma	cobas EGFR Mutation Test v2 (Roche Molecular Systems, Inc.)	Tarceva (erlotinib) NDA 021743	EGFR (HER1)	Exon 19 deletion or exon 21 L858R substitution mutation	P150047 (06/01/2016)	N/A
Non-Small Cell Lung Cancer (NSCLC) - Plasma	FoundationOne Liquid CDx (Foundation Medicine, Inc.)	Iressa (gefitinib) NDA 206995	EGFR (HER1)	Exon 19 deletion or exon 21 L858R substitution mutation	P190032 (08/26/2020) P190032/S008 (12/19/2022)	0239U
Non-Small Cell Lung Cancer (NSCLC) - Plasma	FoundationOne Liquid CDx (Foundation Medicine, Inc.)	Tagrisso (osimertinib) NDA 208065	EGFR (HER1)	Exon 19 deletion or exon 21 L858R substitution mutation	P190032 (08/26/2020) P190032/S008 (12/19/2022)	0239U
Non-Small Cell Lung Cancer (NSCLC) - Plasma	FoundationOne Liquid CDx (Foundation Medicine, Inc.)	Tarceva (erlotinib) NDA 021743	EGFR (HER1)	Exon 19 deletion or exon 21 L858R substitution mutation	P190032 (08/26/2020)P190032/S008 (12/19/2022)	0239U

Non-Small Cell Lung Cancer (NSCLC) - Plasma	FoundationOne Liquid CDx (Foundation Medicine, Inc.)	BRAFTOVI (encorafenib) NDA210496 in combination with MEKTOVI (binimetinib) NDA210498	BRAF	V600E	P190032/S011 (10/11/2023)	0239U
Non-Small Cell Lung Cancer (NSCLC) - Plasma	FoundationOne Liquid CDx (Foundation Medicine, Inc.)	Tabrecta (capmatinib) NDA 213591	MET	MET single nucleotide variants and indels that lead to MET exon 14 skipping	P190032/S001 (07/15/2021)	0239U
Non-Small Cell Lung Cancer (NSCLC) - Plasma	FoundationOne Liquid CDx (Foundation Medicine, Inc.)	Rozlytrek (entrectinib) NDA 212725	ROS1	ROS1 fusions	P190032/S004 (12/22/2022)	0239U
Non-Small Cell Lung Cancer (NSCLC) - Plasma	FoundationOne Liquid CDx (Foundation Medicine, Inc.)	Alecensa (alectinib) NDA 208434	ALK	ALK rearrangements	P200006 (10/26/2020)	0239U
Non-Small Cell Lung Cancer (NSCLC) - Plasma	Guardant360 CDx (Guardant Health, Inc.)	Tagrisso (osimertinib) NDA 208065	EGFR (HER1)	EGFR exon 19 deletions, EGFR exon 21 L858R, and T790M	P200010 (08/07/2020)	0326U
Non-Small Cell Lung Cancer (NSCLC) - Plasma	Guardant360 CDx (Guardant Health, Inc.)	Rybrevant (amivantamb) BLA 761210	EGFR (HER1)	EGFR exon 20 insertions	P200010/S001 (05/21/2021)	0326U
Non-Small Cell Lung Cancer (NSCLC) - Plasma	Guardant360 CDx (Guardant Health, Inc.)	Lumakras (sotorasib) NDA 214665	KRAS	G12C	P200010/S002 (05/28/2021)	0326U
Non-Small Cell Lung Cancer (NSCLC) - Plasma	Guardant360 CDx (Guardant Health, Inc.)	ENHERTU (fam-trastuzumab deruxtecan-nxki) BLA 761139	ERBB2	ERBB2 Activating Mutations (SNVs And Exon 20 Insertions)	P200010/S008 (08/11/2022)	0326U
Non-Small Cell Lung Cancer (NSCLC) - Plasma	FoundationOne Liquid CDx (Foundation Medicine, Inc.)	Tepmetko (tepotinib) - NDA 214096	MET	MET single nucleotide variants and indels that lead to MET exon 14 skipping	P190032/S015 (11/14/2024)	0239U
Non-Small Cell Lung Cancer (NSCLC) - Tissue	cobas EGFR Mutation Test v1 (Roche Molecular Systems, Inc.)	Tarceva (erlotinib) NDA 021743	EGFR (HER1)	Exon 19 deletion or exon 21 L858R substitution mutation	P120019 (07/15/2013)	N/A
Non-Small Cell Lung Cancer (NSCLC) - Tissue	cobas EGFR Mutation Test v2 (Roche Molecular Systems, Inc.)	Tagrisso (osimertinib) NDA 208065	EGFR (HER1)	T790M	P120019/S007 (11/13/2015)	N/A

Non-Small Cell Lung Cancer (NSCLC) - Tissue	cobas EGFR Mutation Test v2 (Roche Molecular Systems, Inc.)	Tagrisso (osimertinib) NDA 208065	EGFR (HER1)	Exon 19 deletion or exon 21 L858R substitution mutation	P120019/S016 (04/18/2018)	N/A
Non-Small Cell Lung Cancer (NSCLC) - Tissue	FoundationOne CDx (Foundation Medicine, Inc.)	Gilotrif (afatinib) NDA 201292	EGFR (HER1)	Exon 19 deletion or exon 21 L858R substitution mutation	P170019 (11/30/2017)	0037U
Non-Small Cell Lung Cancer (NSCLC) - Tissue	FoundationOne CDx (Foundation Medicine, Inc.)	Iressa (gefitinib) NDA 206995	EGFR (HER1)	Exon 19 deletion or exon 21 L858R substitution mutation	P170019 (11/30/2017)	0037U
Non-Small Cell Lung Cancer (NSCLC) - Tissue	FoundationOne CDx (Foundation Medicine, Inc.)	Tarceva (erlotinib) NDA 021743	EGFR (HER1)	Exon 19 deletion or exon 21 L858R substitution mutation	P170019 (11/30/2017)	0037U
Non-Small Cell Lung Cancer (NSCLC) - Tissue	FoundationOne CDx (Foundation Medicine, Inc.)	Tagrisso (osimertinib) NDA 208065	EGFR (HER1)	T790M	P170019 (11/30/2017)	0037U
Non-Small Cell Lung Cancer (NSCLC) - Tissue	FoundationOne CDx (Foundation Medicine, Inc.)	Alecensa (alectinib) NDA 208434	ALK	ALK rearrangements	P170019 (11/30/2017)	0037U
Non-Small Cell Lung Cancer (NSCLC) - Tissue	FoundationOne CDx (Foundation Medicine, Inc.)	Xalkori (crizotinib) NDA 202570	ALK	ALK rearrangements	P170019 (11/30/2017)	0037U
Non-Small Cell Lung Cancer (NSCLC) - Tissue	FoundationOne CDx (Foundation Medicine, Inc.)	Zykadia (ceritinib) NDA 211225	ALK	ALK rearrangements	P170019 (11/30/2017)	0037U
Non-Small Cell Lung Cancer (NSCLC) - Tissue	FoundationOne CDx (Foundation Medicine, Inc.)	Tafinlar (dabrafenib) NDA 202806 in combination with Mekinist (trametinib) NDA 204114	BRAF	V600E	P170019 (11/30/2017)	0037U
Non-Small Cell Lung Cancer (NSCLC) - Tissue	FoundationOne CDx (Foundation Medicine, Inc.)	Tagrisso (osimertinib) NDA 208065	EGFR (HER1)	Exon 19 deletion or exon 21 L858R substitution mutation	P170019/S008 (07/01/2019)	0037U
Non-Small Cell Lung Cancer (NSCLC) - Tissue	FoundationOne CDx (Foundation Medicine, Inc.)	Tabrecta (capmatinib) NDA 213591	MET	MET single nucleotide variants and indels that lead to MET exon 14 skipping	P170019/S011 (05/06/2020)	0037U
Non-Small Cell Lung Cancer (NSCLC) - Tissue	FoundationOne CDx (Foundation Medicine, Inc.)	BRAFTOVI (encorafenib) NDA210496 in combination with MEKTOVI (binimetinib) NDA210498	BRAF	V600E	P170019/S039 (10/11/2023)	0037U

Non-Small Cell Lung Cancer (NSCLC) - Tissue	FoundationOne CDx (Foundation Medicine, Inc.)	Rozlytrek (entrectinib) NDA 212725	ROS1	ROS1 fusions	P170019/S014 (06/07/2022)	0037U
Non-Small Cell Lung Cancer (NSCLC) - Tissue	ONCO/Reveal Dx Lung & Colon Cancer Assay (O/RDx-LCCA) (Pillar Biosciences, Inc.)	A tyrosine kinase inhibitor approved by FDA for that indication	EGFR (HER1)	Exon 19 deletion or exon 21 L858R substitution mutation	P200011 (07/30/2021)	0523U
Non-Small Cell Lung Cancer (NSCLC) - Tissue	Oncomine Dx Express Test (Life Technologies Corporation)	Zegfrovy (sunvozertinib) NDA 219839	EGFR	Exon 20 insertion mutations	P240040 (07/02/2025)	0022U
Non-Small Cell Lung Cancer (NSCLC) - Tissue	Oncomine Dx Target Test (Life Technologies Corporation)	Tafinlar (dabrafenib) NDA 202806 in combination with Mekinist (trametinib) NDA 204114	BRAF	V600E	P160045 (06/22/2017)	0022U
Non-Small Cell Lung Cancer (NSCLC) - Tissue	Oncomine Dx Target Test (Life Technologies Corporation)	Xalkori (crizotinib) NDA 202570	ROS1	ROS1 fusions	P160045 (06/22/2017)	0022U
Non-Small Cell Lung Cancer (NSCLC) - Tissue	Oncomine Dx Target Test (Life Technologies Corporation)	Iressa (gefitinib) NDA 206995	EGFR (HER1)	Exon 19 deletion or exon 21 L858R substitution mutation	P160045 (06/22/2017)	0022U
Non-Small Cell Lung Cancer (NSCLC) - Tissue	Oncomine Dx Target Test (Life Technologies Corporation)	Gavreto (pralsetinib) NDA 213721	RET	RET fusions	P160045/S019 (09/04/2020)	0022U
Non-Small Cell Lung Cancer (NSCLC) - Tissue	Oncomine Dx Target Test (Life Technologies Corporation)	Rybrevant (amivantamb) BLA 761210	EGFR (HER1)	Exon 20 insertion mutations	P160045/S027 (12/01/2021)	0022U
Non-Small Cell Lung Cancer (NSCLC) - Tissue	Oncomine Dx Target Test (Life Technologies Corporation)	ENHERTU (fam-trastuzumab deruxtecan-nxki) BLA 761139	ERBB2	ERBB2 Activating Mutations (SNVs And Exon 20 Insertions)	P160045/S035 (08/11/2022)	0022U
Non-Small Cell Lung Cancer (NSCLC) - Tissue	Oncomine Dx Target Test (Life Technologies Corporation)	Retevmo (selpercatinib) NDA 213246	RET	RET fusions	P160045/S031 (09/21/2022)	0022U
Non-Small Cell Lung cancer (NSCLC) - Tissue	Oncomine Dx Target Test (Life Technologies Corporation)	HERNEXEOS (zongertinib) NDA 219042	ERBB2 (HER2)	Activating mutations in the tyrosine kinase domain (SNVs in exons 18-21 and exon 20 insertions)	P160045/S049 (08/08/2025)	0022U

Non-Small Cell Lung Cancer (NSCLC) - Tissue	PD-L1 IHC 22C3 pharmDx (Dako North America, Inc.)	Keytruda (pembrolizumab) BLA 125514	PD-L1	PD-L1 protein expression[Tumor Proportion Score (TPS) ≥ 1%]	P150013 (10/02/2015); updated P150013/S012 (04/16/2019)	N/A
Non-Small Cell Lung Cancer (NSCLC) - Tissue	PD-L1 IHC 22C3 pharmDx (Dako North America, Inc.)	Libtayo (cemiplimab-rwlc) BLA 761097	PD-L1	PD-L1 protein expression [Tumor Proportion Score (TPS) ≥ 50%]	P150013/S021 (02/22/2021)	N/A
Non-small cell lung cancer (NSCLC) - Tissue	PD-L1 IHC 28-8 pharmDx (Dako North America, Inc.)	Opdivo (nivolumab) BLA 125554 in combination with Yervoy (ipilimumab) BLA 125377	PD-L1	PD-L1 protein expression (tumor cell staining ≥1%)	P150025/S013 (05/15/2020)	N/A
Non-Small Cell Lung Cancer (NSCLC) - Tissue	therascreen EGFR RGQ PCR Kit (Qiagen Manchester, Ltd.)	Gilotrif (afatinib) NDA 201292	EGFR (HER1)	Exon 19 deletion or exon 21 L858R substitution mutation	P120022 (07/12/2013)	N/A
Non-Small Cell Lung Cancer (NSCLC) - Tissue	therascreen EGFR RGQ PCR Kit (Qiagen Manchester, Ltd.)	Iressa (gefitinib) NDA 206995	EGFR (HER1)	Exon 19 deletion or exon 21 L858R substitution mutation	P120022/S001 (07/10/2015)	N/A
Non-Small Cell Lung Cancer (NSCLC) - Tissue	therascreen EGFR RGQ PCR Kit (Qiagen Manchester, Ltd.)	Gilotrif (afatinib) NDA 201292	EGFR (HER1)	L861Q, G719X and S7681	P120022/S016 (01/12/2016)	N/A
Non-Small Cell Lung Cancer (NSCLC) - Tissue	therascreen EGFR RGQ PCR Kit (Qiagen Manchester, Ltd.)	Vizimpro (dacomitinib) NDA 211288	EGFR (HER1)	Exon 19 deletion or exon 21 L858R substitution mutation	P120022/S018 (09/27/2018)	N/A
Non-Small Cell Lung Cancer (NSCLC) - Tissue	therascreen KRAS RGQ PCR Kit (Qiagen Manchester, Ltd.)	Lumakras (sotorasib) NDA 214665	KRAS	G12C	P110027/S012 (05/28/2021)	N/A
Non-Small Cell Lung Cancer (NSCLC) - Tissue	therascreen KRAS RGQ PCR Kit (Qiagen Manchester, Ltd.)	Krazati (adagrasib) NDA 216340	KRAS	KRAS G12C	P110027/S013 (12/02/2022)	N/A
Non-Small Cell Lung Cancer (NSCLC) - Tissue	Ventana ALK (D5F3) CDx Assay (Ventana Medical Systems, Inc.)	Xalkori (crizotinib) NDA 202570	ALK	ALK protein expression	P140025 (06/12/2015)	N/A
Non-Small Cell Lung Cancer (NSCLC) - Tissue	Ventana ALK (D5F3) CDx Assay (Ventana Medical Systems, Inc.)	Zykadia (ceritinib) NDA 211225	ALK	ALK protein expression	P140025/S005 (05/26/2017)	N/A

Non-Small Cell Lung Cancer (NSCLC) - Tissue	Ventana ALK (D5F3) CDx Assay (Ventana Medical Systems, Inc.)	Alecensa (alectinib) NDA 208434	ALK	ALK protein expression	P140025/S006 (11/06/2017)	N/A
Non-Small Cell Lung Cancer (NSCLC) - Tissue	Ventana ALK (D5F3) CDx Assay (Ventana Medical Systems, Inc.)	Lorbrena (lorlatinib) NDA 210868	ALK	ALK protein expression	P140025/S014 (03/03/2021)	N/A
Non-Small Cell Lung Cancer (NSCLC) - Tissue	Ventana MET (SP44) RxDx Assay (Ventana Medical Systems, Inc. (Roche Tissue Diagnostics)	Emrelis (telisotuzumab vedotin-tllv) BLA 761384	MET	MET protein expression (>= 50% of tumor cells exhibiting strong membrane and/or cytoplasmic staining 3+)	P240037 (05/14/2025)	N/A
Non-Small Cell Lung Cancer (NSCLC) - Tissue	Ventana PD-L1 (SP142) Assay (Ventana Medical Systems, Inc.)	Tecentriq (atezolizumab) BLA 761034	PD-L1	PD-L1 protein expression (PD-L1 stained ≥ 50% of tumor cells [TC ≥ 50%] or PD-L1 stained tumor-infiltrating immune cells [IC] covering ≥ 10% of the tumor area [IC ≥ 10%])	P160002/S006 (07/02/2018)	N/A
Non-Small Cell Lung Cancer (NSCLC) - Tissue	Ventana PD-LI (SP263) Assay (Ventana Medical Systems, Inc)	Tecentriq (atezolizumab) BLA 761034	PD-L1	PD-L1 protein expression(PD-L1 stained ≥ 1% of tumor cells [TC ≥ 1%])	P160046/S010 (10/15/2021)	N/A
Non-Small Cell Lung Cancer (NSCLC) - Tissue	Vysis ALK Break Apart FISH Probe Kit (Abbott Molecular Inc.)	Xalkori (crizotinib) NDA 202570	ALK	ALK gene rearrangements	P110012 (08/26/2011)	N/A
Non-Small Cell Lung Cancer (NSCLC) - Tissue	Vysis ALK Break Apart FISH Probe Kit (Abbott Molecular Inc.)	Alunbrig (brigatinib) NDA 208772	ALK	ALK gene rearrangements	P110012/S020 (05/22/2020)	N/A
Non-Small Cell Lung Cancer (NSCLC) - Tissue	Vysis ALK Break Apart FISH Probe Kit (Abbott Molecular Inc.)	ENSACOVE (ensartinib) NDA 218171	ALK	ALK gene rearrangements	P1100212/S022 (08/05/2025)	N/A
Non-Small Cell Lung Cancer (NSCLC) - Tissue	TruSight Oncology Comprehensive (Illumina, Inc.)	Retevmo (selpercatinib) NDA 213246	RET	RET fusions	P230011 (08/21/2024)	0543U
Non-Small Cell Lung Cancer (NSCLC) - Tissue	Ventana PD-L1 (SP263) Assay (Ventana Medical Systems, Inc.)	Libtayo (cemiplimab-rwlc) - BLA 761097	PD-L1	PD-L1 protein expression (PD-L1 stained ≥ 50% of tumor cells [TC ≥ 50%])	P160046/S013 (03/01/2023)	N/A

Non-Small Cell Lung Cancer (NSCLC) - Tissue or Plasma	cobas EGFR Mutation Test v2 (Roche Molecular Systems, Inc.)	Iressa (gefitinib) NDA 206995	EGFR (HER1)	Exon 19 deletion or exon 21 L858R substitution mutation	P120019/S019 (08/22/0218)	N/A
Non-Small Cell Lung Cancer (NSCLC) - Tissue or Plasma	cobas EGFR Mutation Test v2 (Roche Molecular Systems, Inc.)	Iressa (gefitinib) NDA 206995	EGFR (HER1)	Exon 19 deletion or exon 21 L858R substitution mutation	P120019/S031 (10/27/2020)	N/A
Non-Small Cell Lung Cancer (NSCLC) - Tissue or Plasma	cobas EGFR Mutation Test v2 (Roche Molecular Systems, Inc.)	Tarceva (erlotinib) NDA 021743	EGFR (HER1)	Exon 19 deletion or exon 21 L858R substitution mutation	P120019/S031 (10/27/2020)	N/A
Non-Small Cell Lung Cancer (NSCLC) - Tissue or Plasma	cobas EGFR Mutation Test v2 (Roche Molecular Systems, Inc.)	Gilotrif (afatinib) NDA 201292	EGFR (HER1)	Exon 19 deletion or exon 21 L858R substitution mutation	P120019/S031 (10/27/2020)	N/A
Non-Small Cell Lung Cancer (NSCLC) - Tissue or Plasma	cobas EGFR Mutation Test v2 (Roche Molecular Systems, Inc.)	Tagrisso (osimertinib) NDA 208065	EGFR (HER1)	Exon 19 deletion or exon 21 L858R substitution mutation	P120019/S031 (10/27/2020)	N/A
Ovarian Cancer - Tissue	FoundationFocus CDxBRCA Assay (Foundation Medicine, Inc.)	Rubraca (rucaparib) NDA 209115	BRCA1 and BRCA2	BRCA1 and BRCA2 alterations	P160018 (12/19/2016)	N/A
Ovarian Cancer - Tissue	FoundationOne CDx (Foundation Medicine, Inc.)	Lynparza (olaparib) NDA 208558	BRCA1 and BRCA2	BRCA1 and BRCA2 alterations	P170019/S004 (07/01/2019)	0037U
Ovarian Cancer - Tissue	Myriad myChoice CDx (Myriad Genetic Laboratories, Inc.)	Lynparza (olaparib) NDA 208558	Myriad HRD	Deleterious or suspected deleterious mutations in BRCA1 and BRCA2 genes and/or positive Genomic Instability Score)	P190014/S003 (05/08/2020)	0172U
Ovarian Cancer - Whole Blood	BRACAnalysis CDx (Myriad Genetic Laboratories, Inc.)	Lynparza (olaparib) NDA 208558	BRCA1 and BRCA2	Mutations	P140020 (12/19/2014)	N/A
Ovarian Cancer - Whole Blood	BRACAnalysis CDx (Myriad Genetic Laboratories, Inc.)	Rubraca (rucaparib) NDA 209115	BRCA1 and BRCA2	Mutations	P140020/S016 (10/16/2018)	N/A
Pancreatic Cancer - Whole Blood	BRACAnalysis CDx (Myriad Genetic	Lynparza (olaparib) NDA 208558	BRCA1 and BRCA2	Mutations	P140020/S019 (12/27/2019)	N/A

	Laboratories, Inc.)					
Prostate Cancer - Tissue	FoundationOne CDx (Foundation Medicine, Inc.)	AKEEGA (niraparib + abiraterone acetate) NDA 216793	BRCA1 and BRCA2	BRCA1 and BRCA2 alterations	P170019/S042 (08/11/2023)	0037U
Solid Tumors	Ventana MMR RxDx Panel (Ventana Medical Systems, Inc.)	Keytruda (pembrolizumab) BLA 125514	deficient mismatch repair (dMMR) proteins	MLH1, PMS2, MSH2 and MSH6	P210001/S001 (03/21/2022)	N/A
Solid Tumors	Ventana MMR RxDx Panel (Ventana Medical Systems, Inc.)	Jemperli (dostarlimag-gxly) BLA 761174	Deficient mismatch repair (dMMR) proteins	MLH1, PMS2, MSH2, and MSH6	P210001 (08/17/2021)	N/A
Solid Tumors - Plasma	FoundationOne Liquid CDx (Foundation Medicine, Inc.)	Rozlytrek (entrectinib) NDA 212725	NTRK1, NTRK2, and NTRK3 fusions	NTRK1/2/3 fusions	P190032/S004 (12/22/2022)	0239U
Solid Tumors - Tissue	FoundationOne CDx (Foundation Medicine, Inc.)	Keytruda (pembrolizumab) BLA 125514	TMB	TMB ≥ 10 mutations per megabase	P170019/S016 (06/16/2020)	0037U
Solid Tumors - Tissue	FoundationOne CDx (Foundation Medicine, Inc.)	Vitrakvi (larotrectinib) NDA 210861	NTRK1, NTRK2 and NTRK3	NTRK1, NTRK2 and NTRK3 fusions	P170019/S017 (10/23/2020)	0037U
Solid Tumors - Tissue	FoundationOne CDx (Foundation Medicine, Inc.)	Keytruda (pembrolizumab) BLA 125514	MSI-High	Microsatellite instability-High (MSI-H)	P170019/S029 (02/18/2022)	0037U
Solid Tumors - Tissue	FoundationOne CDx (Foundation Medicine, Inc.)	RETEVMO (selpercatinib) NDA214246	RET	RET fusions	P170019/S043 (10/06/2023)	0037U
Solid Tumors - Tissue	MI Cancer Seek (MCS) (Caris Life Sciences)	Keytruda (pembrolizumab) BLA 125514	MSI-High	Microsatellite instability - High (MSI-H)	P240010 (11/05/2024)	0211U
Solid Tumors - Tissue	MI Cancer Seek (MCS) (Caris Life Sciences)	Jemperli (dostarlimab-gxly) - BLA 761223	MSI-High	Microsatellite instability - High (MSI-H)	P240010 (11/05/2024)	0211U
Solid Tumors - Tissue	TruSight Oncology Comprehensive (Illumina, Inc.)	Vitrakvi (larotrectinib) NDA 210861	NTRK1, NTRK2, and NTRK3 fusions	NTRK1/2/3 fusions	P230011 (08/21/2024)	0543U
Solid Tumors - Tissue	FoundationOne CDx (Foundation Medicine, Inc.)	Rozlytrek (entrectinib) NDA 212725	NTRK1, NTRK2 and NTRK3	NTRK1, NTRK2 and NTRK3 fusions	P170019/S014 (06/07/2022)	0037U
Thyroid Cancer (TC) - Tissue	Oncomine Dx Target Test (Life	Retevmo (selpercatinib) NDA 213246	RET	RET fusions	P160045/S031 (09/21/2022)	0022U

	Technologies Corporation)					
Triple-Negative Breast Cancer (TNBC) - Tissue	PD-L1 IHC 22C3 pharmDx (Dako North America, Inc.)	Keytruda (pembrolizumab) BLA 125514	PD-L1	PD-L1 protein expression [Combined Positive Score (CPS) ≥ 10]	P150013/S020 (11/13/2020)	N/A
Urothelial Cancer - Tissue	therascreen FGFR RGQ RT-PCR Kit (QIAGEN Manchester Ltd.)	Balversa (erdafitinib) NDA 212018	FGFR3	Exon 7: R248C (c.742C>T), S249C (c.746C>G); exon 10: G370C (c.1108G>T) and Y373C (c.1118A>G); and fusions (FGFR3-TACC3v1 and FGFR3-TACC3v3)	P180043 (04/12/2019)	0154U
Urothelial Carcinoma - Tissue	Ventana PD-L1 (SP142) Assay (Ventana Medical Systems, Inc.)	Tecentriq (atezolizumab) BLA 761034	PD-L1	PD-L1 protein expression (PD-L1 stained tumor-infiltrating immune cells [IC] covering ≥ 5% of the tumor area)	P160002 (05/18/2016)	N/A
Uveal Melanoma - Whole Blood	SeCore CDx HLA Sequencing System (One Lambda Inc.)	Kimmtrak (tebentafusp-tebn) BLA 761228	HLA	HLA-A*02:01	BR220737 (11/28/2022)	N/A

BLA: biologics license application; dMMR: mismatch repair deficient; FDA: U.S. Food & Drug Administration; MSI-H: microsatellite instability-high; N/A: not applicable; NCCN: National Comprehensive Cancer Network; NDA: new drug application; TMB: tumor mutational burden
Source: [62,] and [63,]

[a] PLA codes are for the diagnostic test only. CPT codes for genes will be listed in the coding table.

In August 2021, Genentech voluntarily withdrew accelerated approval of atezolizumab (Tecentriq) for use in patients with PD-L1 positive, triple-negative breast cancer following FDA assessment of confirmatory trial results.

RATIONALE

Summary of Evidence

For individuals with unresectable, recurrent, relapsed, refractory, advanced, or metastatic cancer who are being considered for targeted therapy with an FDA-approved drug consistent with the labeled indication , the evidence includes FDA-approved therapeutics with National Comprehensive Cancer Network (NCCN) recommendations of 2A or higher and was not extensively evaluated. The evidence includes the pivotal studies leading to the FDA and National Comprehensive Cancer Network (NCCN) recommendations.

For individuals with unresectable, recurrent, relapsed, refractory, advanced, or metastatic cancer who receive genetic biomarker testing of tumor tissue or circulating tumor DNA and are being considered for targeted therapy with an FDA-approved drug consistent with the labeled indication , the evidence includes FDA-approved therapeutics with National Comprehensive Cancer Network (NCCN) recommendations of 2A or higher and was not extensively evaluated. The evidence includes the pivotal studies leading to the FDA and National Comprehensive Cancer Network (NCCN) recommendations.

For individuals with unresectable, recurrent, relapsed, refractory, advanced, or metastatic cancer who are being considered for targeted therapy with an FDA-approved drug consistent with the labeled indication , the evidence includes FDA-approved therapeutics with National Comprehensive Cancer Network (NCCN) recommendations of 2A or higher and was not extensively evaluated. The evidence includes the pivotal studies leading to the FDA and National Comprehensive Cancer Network (NCCN) recommendations.

SUPPLEMENTAL INFORMATION

Practice Guidelines and Position Statements

Guidelines or position statements will be considered for inclusion in 'Supplemental Information' if they were issued by, or jointly by, a US professional society, an international society with US representation, or National Institute for Health and Care Excellence (NICE). Priority will be given to guidelines that are informed by a systematic review, include strength of evidence ratings, and include a description of management of conflict of interest.

American College of Chest Physicians Guidelines

In 2013, the American College of Chest Physicians updated its evidence-based practice guidelines on the treatment of stage IV non-small-cell lung cancer (NSCLC).[66,] Based on a review of the literature, improved response rates, progression-free survival, and toxicity profiles with first-line erlotinib or gefitinib compared with first-line platinum-based therapy in patients with *EGFR* variants, especially exon 19 deletion and L858R were reported. They recommended, "testing patients with NSCLC for *EGFR* mutations at the time of diagnosis whenever feasible, and treating with first-line EGFR TKIs [tyrosine kinase inhibitors] if mutation-positive."

American Society of Clinical Oncology

In 2017, the American Society of Clinical Oncology along with American Society for Clinical Pathology, College of American Pathologists, and Association for Molecular Pathology published guidelines on molecular biomarkers for the evaluation of colorectal cancer. [67,] Table 2 summarizes the relevant guidelines.

Table 2. Summary of Recommendations

Guidelines	Type	SOE	QOE
Colorectal carcinoma patients being considered for anti-EGFR therapy must receive RAS mutational testing. Mutational analysis should include *KRAS* and *NRAS* codons 12, 13 of exon 2; 59, 61 of exon 3; and 117 and 146 of exon 4 ("expanded" or "extended" RAS)	Recommendation	Convincing/adequate, benefits outweigh harms	High/intermediate
BRAF p.V600 (BRAF c. 1799 [p.V600]) mutational analysis should be performed in colorectal cancer tissue in patients with colorectal carcinoma for prognostic stratification	Recommendation	Adequate/inadequate, balance of benefits and harms	Intermediate/low
BRAF p.V600 mutational analysis should be performed in deficient MMR tumors with loss of *MLH1* to evaluate for Lynch Syndrome risk. Presence of a *BRAF* mutation strongly favors sporadic pathogenesis. The absence of *BRAF* mutation does not exclude risk of Lynch syndrome	Recommendation	Adequate/inadequate, balance of benefits and harms	Intermediate/low
Clinicians should order mismatch repair status testing in patients with colorectal cancers for the identification of patients at high-risk for Lynch syndrome and/or prognostic stratification	Recommendation	Adequate/inadequate, balance of benefits and harms	Intermediate/low
There is insufficient evidence to recommend *BRAF* c.1799 (p.V600) mutational status as a predictive molecular biomarker for response to anti-EGFR inhibitors	No recommendation	Insufficient, benefits/harms balance unknown	Insufficient

EGFR: epidermal growth factor receptor; MLH1: mutL homolog 1;MMR: mismatch repair; QOE: quality of evidence; SOE: strength of evidence.

In 2021, the American Society of Clinical Oncology (ASCO) and Ontario Health published updated guidelines on therapy for stage IV NSCLC with driver alterations. [68,] The updated recommendations were based on a systematic review of randomized controlled trials from December 2015 to January 2020 and meeting abstracts from ASCO 2020. The recommendations include the following:

- All patients with nonsquamous NSCLC should have the results of testing for potentially targetable mutations (alterations) before implementing therapy for advanced lung cancer, regardless of smoking status, when possible.
- Targeted therapies against *ROS1* fusions, *BRAF* V600E mutations, *RET* fusions, *MET* exon 14 skipping mutations, and *NTRK* fusions should be offered to patients, either as initial or second-line therapy when not given in the first-line setting.
- Chemotherapy is still an option at most stages.

The above guidelines were updated in 2023 to add amivantamab monotherapy and mobocertinib monotherapy for second-line treatment in advanced NSCLC with an *EGFR* exon 20 insertion, and sotorasib monotherapy for second-line treatment in advanced NSCLC with a *KRAS*-G12C mutation. [69,]

In 2022, the ASCO published a guideline on the management of stage III NSCLC.[Daly ME, Singh N, Ismaila N, et al. Management of.... (12): 1356-1384. PMID 34936470] The recommendations were based on a literature search of systematic reviews, meta-analyses, and randomized controlled trials published from 1990 through 2021. Relevant recommendations include the following:

- Presence of oncogenic driver alterations, available therapies, and patient characteristics should be taken into account.
- Patients with resected stage III NSCLC with *EGFR* exon 19 deletion or exon 21 L858R mutation may be offered adjuvant osimertinib after platinum-based chemotherapy.

In 2022, the American Society of Clinical Oncology published an updated guideline on biomarker testing to guide systemic therapy in patients with metastatic breast cancer.[70,] The guideline recommended the following biomarker tests:

- PIK3CA (Type of recommendation: evidence-based; Evidence quality: high; Strength of recommendation: strong)
- Germline BRCA1 and BRCA2 (Type of recommendation: evidence-based; Evidence quality: high; Strength of recommendation: strong)
- PD-L1 (Type of recommendation: evidence-based; Evidence quality: intermediate; Strength of recommendation: strong)
- MSI-H/dMMR (Type of recommendation: informal consensus-based; Evidence quality: low; Strength of recommendation: moderate)
- TMB (Type of recommendation: informal consensus-based; Evidence quality: low; Strength of recommendation: moderate)
- NTRK fusions (Type of recommendation: informal consensus-based; Evidence quality: low; Strength of recommendation: moderate)

The following biomarker tests were not recommended by ASCO: PALB2, TROP2 expression, circulating tumor DNA, circulating tumor cell.

Detailed recommendations are as follows:

- Patients with locally recurrent unresectable or metastatic hormone receptor-positive and human epidermal growth factor receptor 2 (HER2)-negative breast cancer who are candidates for a treatment regimen that includes a phosphatidylinositol 3-kinase inhibitor and a hormonal therapy should undergo testing for PIK3CA mutations using next-generation sequencing of tumor tissue or circulating tumor DNA (ctDNA) in plasma to determine their eligibility for treatment with the phosphatidylinositol 3-kinase inhibitor alpelisib plus fulvestrant. If no mutation is found in ctDNA, testing in tumor tissue, if available, should be used as this will detect a small number of additional patients with PIK3CA mutations (Type of recommendation: evidence-based, benefits outweigh harms; Evidence quality: high; Strength of recommendation: strong)
- Patients with metastatic HER2-negative breast cancer who are candidates for treatment with a poly (ADP-ribose) polymerase (PARP) inhibitor should undergo testing for germline BRCA1 and BRCA2 pathogenic or likely pathogenic mutations to determine their eligibility for treatment with the PARP inhibitors olaparib or talazoparib (Type of recommendation: evidence-based, benefits outweigh harms; Evidence quality: high; Strength of recommendation: strong).
- There is insufficient evidence to support a recommendation either for or against testing for a germline PALB2 pathogenic variant for the purpose of determining eligibility for treatment with PARP inhibitor therapy in the metastatic setting. This recommendation is independent of the indication for testing to assess cancer risk (Type: informal consensus; Evidence quality: low; Strength of recommendation: moderate).
    - Small single-arm studies show that oral PARP inhibitor therapy demonstrates high response rates in MBC encoding DNA repair defects, such as germline PALB2 pathogenic variants and somatic BRCA1/2 mutations. It should also be noted that the randomized PARP inhibitor trials made no direct comparison with taxanes, anthracyclines, or platinums; comparative efficacy against these compounds is unknown. There are insufficient data at present to recommend routine testing of tumors for homologous recombination deficiency to guide therapy for MBC (Type: informal consensus; Evidence quality: low; Strength of recommendation: moderate).

- Patients with locally recurrent unresectable or metastatic hormone receptor-negative and HER2-negative breast cancer who are candidates for a treatment regimen that includes an immune checkpoint inhibitor (ICI) should undergo testing for expression of programmed cell death ligand-1 in the tumor and immune cells with a US Food and Drug Administration - approved test to determine eligibility for treatment with the ICI pembrolizumab plus chemotherapy (Type of recommendation: evidence based, benefits outweigh harms; Evidence quality: intermediate; Strength of recommendation: strong).
- Patients with metastatic cancer who are candidates for a treatment regimen that includes an ICI should undergo testing for deficient mismatch repair/microsatellite instability-high to determine eligibility for dostarlimab-gxly or pembrolizumab (Type of recommendation: informal consensus; Evidence quality: low; Strength of recommendation: moderate).
- Patients with metastatic cancer who are candidates for treatment with an ICI should undergo testing for tumor mutational burden to determine eligibility for pembrolizumab monotherapy (Type of recommendation: informal consensus; Evidence quality: low; Strength of recommendation: moderate).
- Clinicians may test for NTRK fusions in patients with metastatic cancer who are candidates for a treatment regimen that includes a TRK inhibitor to determine eligibility for larotrectinib or entrectinib (Type of recommendation: informal consensus; Evidence quality: low; Strength of recommendation: moderate).
- There are insufficient data to recommend routine testing of tumors for TROP2 expression to guide therapy with an anti-TROP2 antibody-drug conjugate for hormone receptor-negative, HER2-negative MBC (Type of recommendation: informal consensus; Evidence quality: low; Strength of recommendation: moderate).
- There are insufficient data to recommend routine use of ctDNA to monitor response to therapy among patients with MBC (Type of recommendation: informal consensus; Evidence quality: low; Strength of recommendation: moderate).
- There are insufficient data to recommend routine use of circulating tumor cells to monitor response to therapy among patients with MBC (Type of recommendation: informal consensus; Evidence quality: low; Strength of recommendation: moderate).

In 2022, the American Society of Clinical Oncology published a provisional clinical opinion on the appropriate use of tumor genomic testing in patients with metastatic or advanced solid tumors. [71,]

Provisional Clinical Opinion

Informal consensus is based on the review of existing approved testing and therapy combinations, available marker prevalence data, and expert opinion. As no formal systematic review of the clinical trial evidence was conducted for this provisional clinical opinion (PCO), and all the recommendations are based on the informal consensus of the expert panel, no recommendation-by-recommendation
statement of evidence quality is provided.

Section 1: Framework for decision making on multigene panel - based genomic sequencing with disease-specific approved markers.

1. PCO 1.1. Genomic testing should be performed for patients with metastatic or advanced solid tumors with adequate performance status in the following two clinical scenarios:
    1. When there are genomic biomarker - linked therapies approved by regulatory agencies for their cancer.
    2. When considering a treatment for which there are specific genomic biomarker - based contraindications or exclusions (strength of recommendation: strong).

Section 3: Testing for gene fusions and exon skipping variants

1. PCO 3.1. In patients with metastatic or advanced solid tumors, fusion testing should be performed if there are fusion-targeted therapies with regulatory approval for that specific disease (strength of recommendation: strong).
2. PCO 3.2.1. *NTRK* fusion testing should be performed in patients with metastatic or advanced solid tumors who may be candidates for TRK-inhibitor therapy, considering the prevalence of *NTRK* fusions in individual tumor types (strength of recommendation: strong).
3. PCO 3.2.2. Testing for other fusions is recommended in patients with metastatic or advanced solid tumors if no oncogenic driver alterations are identified on large panel DNA sequencing (strength of recommendation: moderate).

Section 4: Framework for decision making on panel tests with no approved disease-specific markers.

1. PCO 4.1. Genomic testing should be considered to determine candidacy for tumor-agnostic therapies in patients with metastatic or advanced solid tumors without approved genomic biomarker - linked therapies (strength of recommendation: moderate).
2. PCO 4.2. For tumors with actionable genomic alterations without approved genomic biomarker - linked targeted therapies, patient participation in clinical trials is encouraged after considering the expected efficacy of available standard-of-care options (strength of recommendation: strong).

3. PCO 4.3. Off-label and off-study use of genomic biomarker - linked therapies approved in other diseases is not recommended when a clinical trial is available or without clinical evidence of meaningful efficacy (strength of recommendation: strong).

A rapid update to the ASCO guideline was published in March 2023 to address *ESR1* testing (which was not recommended in the previous version).[72,] The guideline recommended routine testing for *ESR1* mutations at the time of disease recurrence or progression while receiving endocrine therapy, with or without a concomitant CDK4/6 inhibitor, in patients with estrogen receptor-positive, HER2-negative metastatic breast cancer (Type of recommendation: evidence-based; Evidence quality: high; Strength of recommendation: strong). Testing should be performed with blood or tissue obtained at the time of progression, as *ESR1* alterations develop via selective pressure from treatment and are unlikely to be detected in the primary tumor. Blood-based ctDNA is preferred due to greater sensitivity.

American Urological Assocation/Society of Urologic Oncology

In 2023, the American Urological Assocation and the Society of Urologic Oncology published amended guidelines on advanced prostate cancer. [73,] The guidelines included the following relevant recommendation (level of evidence) on the treatment of mCRPC:

- In patients with mCRPC, clinicians should offer germline (if not already performed) and somatic genetic testing to identify DNA repair deficiency, microsatellite instability (MSI) status, tumor mutational burden, and other potential mutations that may inform prognosis and familial cancer risk, as well as direct potential targeted therapies.(Clinical Principle)

College of American Pathology

In 2013, the College of American Pathologists, the International Association for the Study of Lung Cancer, and the Association for Molecular Pathology published evidence-based guidelines for molecular testing to select patients with lung cancer for treatment with EGFR and ALK TKI therapy. [74,] Based on excellent quality evidence (category A), the guidelines recommended *EGFR* variant and *ALK* rearrangement testing in patients with lung adenocarcinoma regardless of clinical characteristics (eg, smoking history).

In 2018, updated guidelines were published and added new *EGFR* and *ALK* recommendations. [75,]*ROS1* testing is recommended for all patients with lung adenocarcinoma irrespective of clinical characteristics (strong recommendation). *BRAF*, *RET*, *HER2*, *KRAS*, and *MET* testing are not recommended as routine stand-alone tests, but may be considered as part of a larger testing panel or if *EGFR*, *ALK*, and *ROS1* are negative (expert consensus opinion).

The 2018 guidelines issued jointly by the College of American Pathologists, International Association for the Study of Lung Cancer, and Association for Molecular Pathology have recommended the following:

"One set of genes must be offered by all laboratories that test lung cancers, as an absolute minimum: *EGFR*, *ALK*, and *ROS1*. A second group of genes should be included in any expanded panel that is offered for lung cancer patients: *BRAF*, *MET*, *RET*, *ERBB2* (HER2), and *KRAS*, if adequate material is available. *KRAS* testing may also be offered as a single-gene test to exclude patients from expanded panel testing. All other genes are considered investigational at the time of publication."

U.S. Preventive Services Task Force Recommendations

Not applicable.

Medicare National Coverage

In January 2020, the Centers for Medicare and Medicaid Services (CMS) determined that next-generation sequencing (NGS) is covered for patients with breast or ovarian cancer when the diagnostic test is performed in a Clinical Laboratory Improvement Amendments (CLIA)-certified laboratory AND the test has approval or clearance by the U.S. Food and Drug Administration (CAG-00450R).[76,]

CMS states that local Medicare carriers may determine coverage of NGS for management of the patient for any cancer diagnosis with a clinical indication and risk factor for germline testing of hereditary cancers when performed in a CLIA-certified laboratory.

The Centers for Medicare & Medicaid Services (CMS) National Coverage Determination on Next Generation Sequencing (90.2) states [77,]:

"Effective for services performed on or after March 16, 2018, [CMS] has determined that Next Generation Sequencing (NGS) as a diagnostic laboratory test is reasonable and necessary and covered nationally, when performed in a Clinical Laboratory Improvement Amendments (CLIA)-certified laboratory, when ordered by a treating physician, and when all of the following requirements are met:

a. Patient has:

i. either recurrent, relapsed, refractory, metastatic, or advanced stage III or IV cancer; and

ii. not been previously tested with the same test using NGS for the same cancer genetic content; and

iii. decided to seek further cancer treatment (e.g., therapeutic chemotherapy).

b. The diagnostic laboratory test using NGS must have:

i. Food & Drug Administration (FDA) approval or clearance as a companion in vitro diagnostic; and,

ii. an FDA-approved or -cleared indication for use in that patient"s cancer; and,

iii. results provided to the treating physician for management of the patient using a report template to specify treatment options."

Regarding liquid biopsies, the memo states, "The NCD does not limit coverage to how to prepare a sample for performing a diagnostic laboratory test using NGS. Commenters submitted published articles on liquid biopsies (also referred to as circulating tumor DNA (ctDNA) or plasma cell-free DNA (cfDNA) tests). We reviewed and included in the evidence and analysis of 4 studies on liquid biopsies. At this time, liquid-based multi-gene sequencing panel tests are left to contractor discretion if certain patient criteria are met."

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POLICY HISTORY - THIS POLICY WAS APPROVED BY THE FEP® PHARMACY AND MEDICAL POLICY COMMITTEE ACCORDING TO THE HISTORY BELOW:

Date	Action	Description
March 2021	New policy	Policy created with literature review on November 20, 2020. Policy statements included for: testing for PIK3CA, NTRK Gene Fusions, PD-L1, MSI-H/dMMR, Tumor Mutational Burden, Circulating Tumor DNA, and Circulating Tumor Cells.
March 2022	Replace policy	Policy updated with literature review through November 8, 2021; references added. Investigational policy statements added for MSI-H/dMMR testing for dostarlimab-gxly, and PD-L1 testing for atezolizumab. Medically necessary policy statements and rationale for BRCA1/2 testing to predict treatment response to PARP inhibitors were migrated into this policy from evidence review 2.04.02. Medically necessary policy statement added for Ki-67 testing for abemaciclib to correlate with FEP pharmacy policy 5.20.104. Policy title updated to reflect both germline and somatic biomarker testing.
March 2023	Replace policy	Policy updated with literature review through October 24, 2022; references added. Evidence on the use of atezolizumab in individuals with triple negative PD-L1 positive breast cancer removed from policy, as in 2021 Genentech voluntarily withdrew accelerated approval of atezolizumab for use in these individuals.
March 2024	Replace policy	Policy updated with literature review through October 25, 2023; references added. Evidence review extensively pruned. Evidence on PD-L1, MSI-H/dMMR, and tumor mutational burden testing for immunotherapy removed as it is covered in evidence review 2.04.157. Pivotal studies and NCCN recommendations added to Table 1. Minor editorial change to PIK3CA policy statement; intent unchanged. Liquid biopsy testing for ESR1 incorporated into circulating tumor DNA indication, with corresponding updates to policy statements and guidelines. Other policy statements unchanged. Language added to policy guidelines to clarify that HER2 testing is not addressed in this review. Policy title and objective updated to reflect that only testing for targeted therapy is reviewed.
March 2025	Replace policy	Policy updated with literature review through November 1, 2024; references added. Title changed to include NTRK. Medically necessary policy statement added for NTRK gene fusion testing for individuals with recurrent unresectable (local or regional) or stage IV breast cancer to select individuals for treatment with FDA-approved therapies. Investigational policy statement added for NTRK gene fusion testing in all other situations. All other policy statements unchanged.
March 2026	Replace policy €“ correction only	Removed reference to 'circulating tumor cells' from Evidence Summary, Description and Objectives sections. Removed the medical necessary policy statement regarding the use of plasma testing for KRAS/RAS variants in colorectal cancer as the Tempus xT CDx test that is approved for matched blood/salvia samples is intended to only be used for subtracting germline variants from tumor sequencing results. Editorial revisions were made to the policy statement regarding plasma testing for KRAS/NRAS variants to align more closely with the FDA label for the targeted therapies of relevance.