PHP_2.04.151	Genetic Biomarker Testing (Including Liquid Biopsy) for Targeted Treatment in Advanced Cancer		
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Section:	2.0 Medicine	**Page:**	Page 1 of 61

State Guidelines

Applicable Medi-Cal guidelines as of the publication of this policy (this guideline supersedes the criteria in the Policy Statement section below):

I. Department of Managed Health Care (DMHC) All Plan Letter (APL) Guideline:
- N/A

II. Department of Health Care Services (DHCS) Provider Manual Guideline:
- TAR and Non-Standard Benefits List: Codes 0001M thru 0999U (tar and non cd0)
- TAR and Non-Standard Benefits List: Codes 80000 thru 89999 (tar and non cd8)
- TAR and Non-Standard Benefits List: Codes 90000 thru 99999 (tar and non cd9)
- Pathology: Surgical (path surg)
- Pathology: Molecular Pathology (path molec)

Below is an excerpt of the Molecular Pathology guideline language. Please refer to the specific Provider Manual in the link above for the complete guideline.

Biomarker and Pharmacogenetic Testing
Medi-Cal covers medically necessary biomarker and pharmacogenomic testing, as described in the manual section Proprietary Laboratory Analyses (PLA). Medi-Cal may not cover all CPT and HCPCS codes associated with a particular biomarker or pharmacogenomic test. As such, the particular biomarker or pharmacogenomic test code may be covered with an approved Treatment Authorization Request (TAR) if medical necessity is established, as described in the TAR and Non-Benefit: Introduction to List section of the Provider Manual.

Biomarker Testing
Biomarker testing is used to diagnose, treat, manage, or monitor a Medi-Cal member's disease or condition to guide treatment decisions. As defined by Section 14132.09 of the Welfare and Institutions Code, biomarker testing is the analysis of an individual's tissue, blood or other biospecimen for the presence of a biomarker. Biomarker testing includes, but is not limited to, single-analyte tests, multiplex panel tests and whole genome sequencing. Biomarkers are a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes or pharmacologic responses to a specific therapeutic intervention. A biomarker includes, but is not limited to, gene mutations or protein expression. Medically necessary biomarker testing is subject to utilization controls and evidence-based clinical practice guidelines.

When testing for biomarkers, all Medi-Cal providers must ensure that they are provided in a manner that limits disruptions to care. As with all Medi-Cal benefits, restricted or denied use of biomarker testing for the purpose of diagnosis, treatment or ongoing monitoring of any medical condition is subject to Medi-Cal's grievance, appeal and State Fair Hearing processes, as well as any additional processes established specifically for Medi-Cal managed care plans.

Pharmacogenomic Testing

Pharmacogenomic testing is defined as a laboratory genetic testing that includes, but is not limited to, a panel test to identify how a person's genetics may impact the efficacy, toxicity and safety of medications. Medically necessary pharmacogenomic testing is covered subject to utilization controls and evidence-based clinical practice guidelines.

Requirements for CPT codes 81162-81167; 81215-81217:

A TAR for CPT codes 81162-81167 or 81215-81217 requires documentation of one or more of the following numbered criteria.

1. Based on 2019 U.S. Preventive Services Task Force (USPSTF) recommendation:
   - The member has personal or family history that suggests an inherited cancer susceptibility based on any one of the following familial risk assessment tools:
     - The Ontario Family History Assessment Tool
     - Manchester Scoring System
     - Referral Screening Tool
     - Pedigree Assessment Tool
     - 7-Question Family History Screening Tool
     - International Breast Cancer Intervention Study instrument
     - Brief versions of BRCAPRO; and
   - The member is willing to talk with a health professional who is suitably trained to provide genetic counseling and interpret test results; and
   - The test results will aid in the decision-making; or
2. A member has a family member with a known deleterious BRCA mutation; or
3. Personal history of breast cancer (invasive or ductal carcinoma in situ) plus one or more of the following:
   - Diagnosed at ≤45 years of age; or
   - Diagnosed at 46 to 50 years of age with:
     - An additional breast cancer primary at any age
     - One or more close blood relatives with breast cancer at any age
     - One or more close blood relatives with prostate cancer (Gleason score ≥7)
     - An unknown or limited family history; or
   - Diagnosed at ≤60 years of age with a triple negative breast cancer; or
   - Diagnosed at any age with:
     - One or more close blood relatives with:
       - Breast cancer diagnosed at ≤50 years of age; or
       - Ovarian carcinoma; or
       - Male breast cancer; or
       - Metastatic prostate cancer; or
       - Pancreatic cancer
     - Two or more additional diagnosis of breast cancer at any age in member and/or in close blood relatives; or
   - Ashkenazi Jewish ancestry; or
4. Personal history of ovarian carcinoma (includes fallopian tube and primary peritoneal cancers); or
5. Personal history of male breast cancer; or
6. Personal history of pancreatic cancer; or
7. Personal history of metastatic prostate cancer (biopsy-proven and/or with radiographic evidence; includes distant metastasis and regional bed or nodes; not biochemical recurrence); or
8. Personal history of high-grade prostate cancer (Gleason score ≥7) at any age with:

- One or more close blood relatives (first-, second- or third-degree) with ovarian carcinoma, pancreatic cancer or metastatic prostate cancer at any age or breast cancer under 50 years of age; or
- Two or more close blood relatives (first-, second- or third-degree relatives on the same side of family) with breast or prostate cancer (any grade) at any age; or
- Ashkenazi Jewish ancestry; Or

9. BRCA1/2 pathogenic/likely pathogenic variant detected by tumor profiling on any tumor type in the absence of germline pathogenic/likely pathogenic variant analysis; or
10. For a member without history of breast or ovarian cancer, but with one or more first- or second-degree blood relative meeting any of the above criteria; or
11. For BRACAnalysis CDx testing for breast cancer, all of the following TAR criteria must be met:
    - Member has metastatic breast cancer.
    - Member is human epidermal growth factor receptor 2 (HER2)-negative.
    - Member has previously been treated with chemotherapy in the neoadjuvant, adjuvant or metastatic setting.
    - Member's additional treatment is contingent on the test results.

Requirements for CPT codes 81191-81194:
A TAR for CPT codes 81191-81194 requires documentation of the following criteria:

1. Adult and pediatric members with solid tumors with any one of the following clinical scenarios:
    - Metastatic tumor or where surgical resection is likely to result in severe morbidity, or
    - Have no satisfactory alternative treatments or have progressed following treatment

Requirements for CPT code 81212:
Requires documentation on the TAR of the following:

- A member is of an ethnicity associated with the Ashkenazi Jewish population

No additional family history may be required

Requirements for CPT code 81301:
Reimbursable for members who meet one of the following criteria: the member is diagnosed with one of the Lynch syndrome-associated cancers; or, the member is diagnosed with an unresectable or metastatic solid tumor and the treatment will be contingent on the test result.

Requirements for CPT code 81309:
A TAR/SAR for CPT code 81309 requires documentation of the following criteria:

- The member has confirmed diagnosis of breast cancer
- Treatment is contingent on the result of the test

Requirements for CPT codes 81445 and 81455:
A TAR for CPT code 81445 or 81455 requires documentation of the following criteria:

1. For Somatic Testing:
    - The member has either recurrent, relapsed, refractory, metastatic or advanced stages III or IV cancer, and
    - The member either has not been previously tested using the same Next Generation Sequencing (NGS) test for the same primary diagnosis of cancer or

repeat testing using the same NGS test only when a new primary cancer diagnosis is made by the treating physician, and
- The decision for additional cancer treatment is contingent on the test results.

2. For Germline Testing:
   - Ovarian or breast cancer, and
   - Clinical indication for germline (inherited) testing for hereditary breast or ovarian cancer (i.e., American College of Obstetrician Gynecologists' criteria for further genetic evaluation for hereditary [germline] breast and ovarian cancer), and
   - A risk factor for germline (inherited) breast or ovarian cancer, and (BRCAPRO, Myriad, Claus, Boadicea, or Tyrer Cuzick), and
   - Has not been previously tested with the same germline test using NGS for the same germline genetic content.
3. Independent of the above criteria, either Somatic or Germline testing may be approved if the test is approved by the U.S. Food and Drug Administration (FDA) as a Companion Diagnostic Device, and the decision for additional treatment is contingent on the test results.

- Proprietary Laboratory Analyses (PLA) (prop lab)

Below is an excerpt of the guideline language. Please refer to the specific Provider Manual in the link above for the complete guideline.

Requirements for PLA code 0037U:
The service requires a TAR.
A TAR requires documentation of the following criteria:
- The member has either recurrent, relapsed, refractory, metastatic or advanced stages III or IV cancer, and
- The member either has not been previously tested using the same Next Generation Sequencing (NGS) test for the same primary diagnosis of cancer or repeat testing using the same NGS test only when a new primary cancer diagnosis is made by the treating physician, and
- The decision for additional cancer treatment is contingent on the test results

Requirements for PLA code 0177U:
The service requires a TAR.
A TAR requires documentation of the following criteria:
1. The member has confirmed diagnosis of breast cancer
2. Treatment is contingent the result of the test

Requirements for PLA code 0239U:
The service requires a TAR.
A TAR requires documentation of the following criteria:
1. The member has a diagnosis of either:
   - Non-small cell lung cancer (plasma), or
   - Metastatic castrate resistant prostate cancer
2. Treatment is contingent on the test result.

Requirements for PLA code 0242U:
The service requires a TAR.
A TAR requires documentation of the following numbered criteria:
1. The member has a diagnosis of either;
   - Non-small cell lung cancer, or

- Hormone receptor-positive, Human Epidermal Growth Factor Receptor 2 (HER2)-negative breast cancer

2. Treatment is contingent on the test result.

III. Department of Health Care Services (DHCS) All Plan Letter (APL) Guideline:

- APL 22-010 – Cancer Biomarker Testing

Below is an excerpt of the guideline language. Please refer to the specific All Plan Letter in the link above for the complete guideline.

For the purposes of this APL, "Biomarker test" is defined as a diagnostic test, single or multigene, of an individual's biospecimen, such as tissue, blood, or other bodily fluids, for DNA or RNA alterations, including phenotypic characteristics of a malignancy, to identify an individual with a subtype of cancer, in order to guide treatment. Biomarkers, also called tumor markers, are substances found in higher-than-normal levels in the cancer itself, or in blood, urine, or tissues of some individuals with cancer. Biomarkers can determine the likelihood some types of cancer will spread. They can also help doctors choose the best treatment.

Medi-Cal managed care health plans (MCPs) are required to cover medically necessary biomarker testing for members with:

- Advanced or metastatic stage 3 or 4 cancer.
- Cancer progression or recurrence in the member with advanced or metastatic stage 3 or 4 cancer.

MCPs are prohibited from imposing prior authorization requirements on biomarker testing that is associated with a federal Food and Drug Administration (FDA)-approved therapy for advanced or metastatic stage 3 or 4 cancer. If the biomarker test is not associated with an FDA-approved cancer therapy for advanced or metastatic stage 3 or 4 cancer, MCPs may still require prior authorization for such testing.

Policy Statement

Any criteria that are not specifically addressed in the above APL and Provider Manuals, please refer to the criteria below.

ALK Testing

I. 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 (e.g., 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

II. 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 (e.g., 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.

III. 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.

IV. 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**

V. Genetic testing for *BRCA1* or *BRCA2* germline variants may be considered **medically necessary** to select treatment with PARP inhibitors (e.g., 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.

VI. 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**

VII. *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**

VIII. Analysis of tumor tissue for somatic variants in exons 18 through 21 (e.g., 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 (e.g., 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.

IX. Analysis of tumor tissue for somatic variants in exon 20 (e.g., insertion mutations) within the *EGFR* gene, may be considered **medically necessary** to select treatment with an FDA-approved therapy (e.g., 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.

X. 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

XI. 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 therapy (e.g., 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

XII. *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

XIII. *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

XIV. *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

XV. 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

XVI. *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

XVII. 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

XVIII. 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

XIX. 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

XX. *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

XXI. 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.

XXII. 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.

XXIII. 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

XXIV. 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

XXV. 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

XXVI. 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

XXVII. *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.

XXVIII. 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**

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

***PDGFRB* Testing**

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

***PIK3CA* Testing**

XXXI. *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).

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

Programmed Cell Death Ligand-1 Testing

XXXII. 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

XXXIII. Analysis of tumor tissue for somatic variants of the *KRAS* gene (e.g., 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.

XXXIV. *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**

XXXV. 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**

XXXVI. 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 (e.g., 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**

XXXVII. 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

XXXVIII. 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.

XXXIX. 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)

XL. 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) (e.g., 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).

XLI. 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).

XLII. *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.

XLIII. At diagnosis, analysis of plasma for somatic variants in exons 19 through 21 (e.g., 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).

XLIV. 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 (e.g., 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).

XLV. *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).

XLVI. 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**.

XLVII. 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 (e.g., 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).

XLVIII. 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).

XLIX. *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).
A. When tumor tissue is available, use of tissue for testing is preferred but is not required.

L. Analysis of plasma (liquid biopsy) for somatic variants of the *KRAS* (e.g., G12C) and *RAS* variants using an FDA-approved companion diagnostic plasma test to detect circulating tumor (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 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).

LI. Analysis of plasma for somatic variants of the KRAS gene (e.g., 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) 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 both the agent and ctDNA test are intended to be used consistently with their FDA-approved labels (see Policy Guidelines).

LII. 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 (e.g., selpercatinib [Retevmo], pralsetinib [Gavreto]) in individuals with advanced or metastatic NSCLC, CRC, medullary thyroid cancer, thyroid cancer, or any other solid tumors.

LIII. 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 (e.g., crizotinib [Xalkori] or entrectinib) in individuals with NSCLC.

LIV. 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

LV. 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 **both** of the following criteria:

A. Individual does not have sufficient tissue for standard molecular testing using formalin-fixed paraffin-embedded tissue
B. 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 Blue Shield of California Promise Medical Policy: Comprehensive Genomic Profiling for Selecting Targeted Cancer Therapies. The use of circulating tumor DNA and circulating tumor cells are addressed separately in Blue Shield of California Promise Medical Policies: Circulating Tumor DNA and Circulating Tumor Cells for Cancer Management (Liquid Biopsy) and Comprehensive Genomic Profiling for Selecting Targeted Cancer Therapies.

Testing for other variants may become available between policy updates.

The 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.

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 somatic components, see

Blue Shield of California Promise Medical Policy: 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.

Coding

See the Codes table for details.

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 and circulating tumor cell testing (known as liquid biopsy).

The objective of this evidence review is to examine whether genetic biomarker testing for *BRCA1, BRCA2*, *PIK3CA*, *ESR1,* BRAF, *EGFR, EZH2, HER2, FOLR1, FLT3, CLDN18, FGFR3, PDGFRA, TP53, KRAS, NRAS, IDH1, IDH2, HLA, KIT, MET,* homologous recombination deficiency (HDR), and homologous recombination repair (HRR) gene variants, *ALK, ROS1, RET, FGFR2, PDGFR, NTRK,* Philadelphia chromosome rearrangements or fusions, and other molecular signatures, such as, PD-L1, MSI/MMR, and TMB status, in tumor tissue, or circulating tumor DNA improves the net health outcome in patients with unresectable, recurrent, relapsed, refractory, advanced or metastatic cancer who are considering targeted therapy (Table 1).

Table PG1. Gene Variants Found in DNA for Targeted Therapy

Biomarker	Indication
ALK rearrangements/fusions	NSCLC
ATM	Prostate
BRAF	Breast, NSCLC, metastatic CRC, Melanoma, Glioma, and ATC
BRCA1/2	Breast, Ovarian, Pancreatic, and Prostate
CLDN18	Gastric or Gastroesophageal Junction (GEJ) Adenocarcinoma

Biomarker	Indication
EGFR	NSCLC, CRC,
ERBB2 (HER2)	Breast, NSCLC, Gastric and Gastroesophageal Cancer, and Biliary Tract Cancer (gallbladder adenocarcinoma, intrahepatic cholangiocarcinoma, and extrahepatic cholangiocarcinoma)
ESR1	Breast
EZH2	Follicular Lymphoma
FGFR2	Cholangiocarcinoma
FGFR3	Urothelial Cancer
FLT3 (ITD/TDK)	Acute Myelogenous Leukemia
FOLR1	Epithelial Ovarian Cancer, Fallopian Tube Cancer, or Primary Peritoneal Cancer
HER2	NSCLC and metastatic CRC
HLA	Uveal Melanoma
HRD[a]	Ovarian
HRR (*BRCA1*, *BRCA2*, *ATM*, *BARD1*, *BRIP1*, *CDK12*, *CHEK1*, *CHEK2*, *FANCL*, *PALB2*, *RAD51B*, *RAD51C*, *RAD51D,* and *RAD54L*)	Prostate
IDH1	Melanoma, Acute Myeloid Leukemia, Myelodysplastic Syndromes, Cholangiocarcinoma, Astrocytoma, Oligodendroglioma, and Glioma
IDH2	Melanoma, Acute Myeloid Leukemia, Myelodysplastic Syndromes, Astrocytoma, Oligodendroglioma, and Glioma
KIT	Aggressive Systemic Mastocytosis
KRAS	NSCLC and metastatic CRC
MET	NSCLC
MSI (*MLH1*, *MSH2*, *MSH6*, *PMS1* and *PMS2*)/MMR (*MLH1*, *MSH2*, *PMS2*, and *MSH6*)	Solid tumors
Not MSI-H	Endometrial Carcinoma
NRAS	metastatic CRC
NTRK rearrangements/fusions	Breast, NSCLC, metastatic CRC, Ovarian, Prostate, Melanoma, Glioma, and other solid tumors
PDGFRA	Gastrointestinal Stromal Tumors
PDGFRB	Myelodysplastic Syndrome/Myeloproliferative Disease
PD-L1	Solid tumors
PIK3CA	Breast
RET rearrangements/fusions	Breast, NSCLC, metastatic CRC, Medullary Thyroid Cancer, Thyroid Cancer, and other solid tumors
ROS1 rearrangements/fusions	NSCLC
TMB	Solid tumors
TP53	B-cell Chronic Lymphocytic Leukemia

ATC: anaplastic thyroid cancer; CRC: colorectal cancer; HRD: homologous recombination deficiency; HRR: homologous recombination repair; NSCLC: non-small cell lung cancer; TMB: tumor mutational burden.
[a] Genomic instability score

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.

Additional Information
Not applicable.

Related Policies

- Assays of Genetic Expression in Tumor Tissue as a Technique to Determine Prognosis in Patients with Breast Cancer
- Circulating Tumor DNA and Circulating Tumor Cells for Cancer Management (Liquid Biopsy)
- Comprehensive Genomic Profiling for Selecting Targeted Cancer Therapies
- Germline Genetic Testing for Hereditary Breast/Ovarian Cancer Syndrome and Other High-Risk Cancers (BRCA1, BRCA2, PALB2)

Benefit Application

Blue Shield of California Promise Health Plan is contracted with L.A. Care Health Plan for Los Angeles County and the Department of Health Care Services for San Diego County to provide Medi-Cal health benefits to its Medi-Cal recipients. In order to provide the best health care services and practices, Blue Shield of California Promise Health Plan has an extensive network of Medi-Cal primary care providers and specialists. Recognizing the rich diversity of its membership, our providers are given training and educational materials to assist in understanding the health needs of their patients as it could be affected by a member's cultural heritage.

The benefit designs associated with the Blue Shield of California Promise Medi-Cal plans are described in the Member Handbook (also called Evidence of Coverage).

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	LeukoStrat CDx FLT3 Mutation Assay (Invivoscribe	Rydapt (midostaurin) NDA 207997	FLT3 (ITD/TDK)	ITD mutations and TKD mutations D835 and I836	P160040 (04/28/2017)	0023U

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]
Blood or Bone Marrow	Technologies, Inc.)					
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 Oligo-dendroglioma - 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 -	Vysis CLL FISH Probe Kit (Abbott Molecular, Inc.)	Venclexta (venetoclax) NDA 208573	TP53	Deletion chromosome 17p (17p-)	P150041 (04/11/2016)	N/A

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]
Peripheral Blood						
Biliary Tract Cancer (gallbladder adeno-carcinoma, intrahepatic cholangio-carcinoma, and extrahepatic cholangio-carcinoma) - 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,	P170019/S006 (12/03/2019)	0037U

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]
				H1047L, H1047R, and H1047Y		
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 (Biogenex Laboratories, Inc.)	Herceptin (trastuzumab) BLA 103792	ERBB2 (HER2)	HER2protein overexpression	P040030 (12/22/2004)	N/A
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

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]
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) Rabbit Monoclonal Primary	Enhertu (fam-trastuzumab deruxtecan-nxki) BLA 761139	ERBB2 (HER2)	HER2 ultralow expression (IHC 0 with membrane staining)	P990081/S055 (01/27/2025)	N/A

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]
	Antibody (Ventana Medical Systems, Inc.)					
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 (pembro-lizumab) BLA 125514	PD-L1	PD-L1 protein expression [Combined Positive Score (CPS) ≥ 1]	P150013/S009 (06/12/2018)	N/A
Cholangio-carcinoma - Tissue	FoundationOne CDx (Foundation Medicine, Inc.)	Pemazyre (pemigatinib) NDA 213736	FGFR2	FGFR2 fusions and select rearrangements	P170019/S013 (04/17/2020)	0037U
Cholangio-carcinoma - 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

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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 (panitu-mumab) – 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 (panitu-mumab) 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 (panitu-mumab) BLA 125147	KRAS	G12A, G12D, G12R, G12C, G12S, G12V, G13D	P110027 (05/23/2014)	N/A

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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 (panitu-mumab) – 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 (panitu-mumab) 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

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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 (panitu-mumab) 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 (pembro-lizumab) 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 (pembro-lizumab) 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 (mirve-tuximab 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 (pembro-lizumab) 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	Tazverik (taze-metostat) NDA 213400	EZH2	Y646N, Y646F or Y646X (Y646H, Y646S, or Y646C), A682G,	P200014 (06/18/2020)	N/A

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	Molecular Systems, Inc.)			and A692V of the EZH2 gene		
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 Gastro-esophageal Junction (GEJ) Adeno-carcinoma - Tissue	PD-L1 IHC 22C3 pharmDx (Dako North America, Inc.)	Keytruda (pembro-lizumab) BLA 125514	PD-L1	PD-L1 protein expression [Combined Positive Score (CPS) ≥ 1]	P150013/S027 (11/07/2023)	N/A
Gastric or Gastro-esophageal Junction (GEJ) Adeno-carcinoma - Tissue	VENTANA CLDN18 (43-14A) RxDx Assay (Ventana Medical Systems, Inc.)	VYLOY (zolbe-tuximab) – 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 (pembro-lizumab) 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	BRAF	V600E or V600K	P110020/S016 (11/07/2016)	N/A

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		(vemurafenib) NDA 202429				
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 (atezo-lizumab) 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 (bioMérieux Inc.)	Mekinist (trametinib) NDA 204114	BRAF	V600E or V600K	P120014 (05/29/2013)	N/A
Melanoma - Tissue	THXID BRAF Kit (bioMérieux Inc.)	Tafinlar (dabrafenib) NDA 202806	BRAF	V600E	P120014 (05/29/2013)	N/A
Melanoma - Tissue	THXID BRAF Kit (bioMérieux 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

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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 re-combination 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 / Myelo-proliferative 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

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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

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Non-Small Cell Lung Cancer (NSCLC) - Plasma	Guardant360 CDx (Guardant Health, Inc.)	Rybrevant (ami-vantamb) 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

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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 (sun-vozertinib) 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	BRAF	V600E	P160045 (06/22/2017)	0022U

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]
		with Mekinist (trametinib) NDA 204114				
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 (ami-vantamb) 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

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]
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.	Emrelis (teliso-tuzumab vedotin-tllv) BLA 761384	MET	MET protein expression (>= 50% of tumor cells exhibiting strong	P240037 (05/14/2025)	N/A

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]
	(Roche Tissue Diagnostics)			membrane and/or cytoplasmic staining 3+)		
Non-Small Cell Lung Cancer (NSCLC) - Tissue	Ventana PD-L1 (SP142) Assay (Ventana Medical Systems, Inc.)	Tecentriq (atezo-lizumab) 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-L1 (SP263) Assay (Ventana Medical Systems, Inc)	Tecentriq (atezo-lizumab) 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) -	cobas EGFR Mutation Test v2 (Roche	Iressa (gefitinib) NDA 206995	EGFR (HER1)	Exon 19 deletion or exon 21 L858R substitution mutation	P120019/S031 (10/27/2020)	N/A

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]
Tissue or Plasma	Molecular Systems, Inc.)					
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	Foundation Focus 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 Laboratories, Inc.)	Lynparza (olaparib) NDA 208558	BRCA1 and BRCA2	Mutations	P140020/S019 (12/27/2019)	N/A
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

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]
Solid Tumors	Ventana MMR RxDx Panel (Ventana Medical Systems, Inc.)	Keytruda (pembro-lizumab) 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 (pembro-lizumab) 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 (pembro-lizumab) 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 (pembro-lizumab) 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 Technologies Corporation)	Retevmo (selpercatinib) NDA 213246	RET	RET fusions	P160045/S031 (09/21/2022)	0022U
Triple-Negative Breast Cancer (TNBC) - Tissue	PD-L1 IHC 22C3 pharmDx (Dako North America, Inc.)	Keytruda (pembro-lizumab) BLA 125514	PD-L1	PD-L1 protein expression [Combined Positive Score (CPS) ≥ 10]	P150013/S020 (11/13/2020)	N/A

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]
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 (atezo-lizumab) 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.

Health Equity Statement

Blue Shield of California Promise Health Plan's mission is to transform its health care delivery system into one that is worthy of families and friends. Blue Shield of California Promise Health Plan seeks to advance health equity in support of achieving Blue Shield of California Promise Health Plan's mission.

Blue Shield of California Promise Health Plan ensures all Covered Services are available and accessible to all members regardless of sex, race, color, religion, ancestry, national origin, ethnic group identification, age, mental disability, physical disability, medical condition, genetic information, marital status, gender, gender identity, or sexual orientation, or identification with any other persons or groups defined in Penal Code section 422.56, and that all Covered Services are provided in a culturally and linguistically appropriate manner.

Rationale

Background

ALK Gene

ALK is a tyrosine kinase (TK) that, in NSCLC, is aberrantly activated because of a chromosomal rearrangement that leads to a fusion gene and expression of a protein with constitutive TK activity that has been demonstrated to play a role in controlling cell proliferation. The *EML4-ALK* fusion gene results from an inversion within the short arm of chromosome 2.

The *EML4-ALK* rearrangement ("*ALK*-positive") is detected in 3% to 6% of NSCLC patients, with the highest prevalence in never-smokers or light ex-smokers who have adenocarcinoma.

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.

BRCA Variant Testing

The prevalence of *BRCA* variants is approximately 0.2% to 0.3% in the general population.[7] The prevalence may be much higher for particular ethnic groups with characterized founder variants (e.g., 2.5% [1/40] in the Ashkenazi Jewish population). Family history of breast and ovarian cancer is an important risk factor for the *BRCA* variant; additionally, age and ethnicity could be independent risk factors.

Several genetic syndromes with an autosomal dominant pattern of inheritance that features breast cancer have been identified.[8] Of these, hereditary breast and ovarian cancer (HBOC) and some cases of hereditary site-specific breast cancer have in common causative variants in *BRCA* (breast cancer susceptibility) genes. Families suspected of having HBOC syndrome are characterized by an increased susceptibility to breast cancer occurring at a young age, bilateral breast cancer, male breast cancer, ovarian cancer at any age, as well as cancer of the fallopian tube and primary peritoneal cancer. Other cancers, such as prostate cancer, pancreatic cancer, gastrointestinal cancers, melanoma, and laryngeal cancer, occur more frequently in HBOC families. Hereditary site-specific breast cancer families are characterized by early-onset breast cancer with or without male cases, but without ovarian cancer. For this policy, Blue Shield of California Promise refers collectively to both as hereditary breast and/or ovarian cancer.

Germline variants in the *BRCA1* and *BRCA2* genes are responsible for the cancer susceptibility in most HBOC families, especially if ovarian cancer or male breast cancer are features.[9] However, in site-

specific cancer, BRCA variants are responsible only for a proportion of affected families. *BRCA* gene variants are inherited in an autosomal dominant fashion through maternal or paternal lineage. It is possible to test for abnormalities in *BRCA1* and *BRCA2* genes to identify the specific variant in cancer cases and to identify family members at increased cancer risk. Family members without existing cancer who are found to have *BRCA* variants can consider preventive interventions for reducing risk and mortality.

Young age of onset of breast cancer, even in the absence of family history, is a risk factor for *BRCA1* variants. Winchester (1996) estimated that hereditary breast cancers account for 36% to 85% of patients diagnosed before age 30.[10] In several studies, BRCA variants were independently predicted by early age at onset, being present in 6% to 10% of breast cancer cases diagnosed at ages younger than various premenopausal age cutoffs (age range, 35-50 years).[10,11,12,13] In cancer-prone families, the mean age of breast cancer diagnosis among women carrying *BRCA1* or *BRCA2* variants is in the 40s.[14] In the Ashkenazi Jewish population, Frank et al (2002) reported that 13% of 248 cases with no known family history and diagnosed before 50 years of age had *BRCA* variants.[11] In a similar study by Gershoni-Baruch et al (2000), 31% of Ashkenazi Jewish women, unselected for family history, diagnosed with breast cancer at younger than 42 years of age had *BRCA* variants.[15] Other studies have indicated that early age of breast cancer diagnosis is a significant predictor of BRCA variants in the absence of family history in this population.[16,17,18]

In patients with "triple-negative" breast cancer (i.e., negative for expression of estrogen, progesterone, and overexpression of human epidermal growth factor receptor 2 [HER2] receptors), there is an increased prevalence of *BRCA* variants. Pathophysiologic research has suggested that the physiologic pathway for the development of triple-negative breast cancer is similar to that for *BRCA*-associated breast cancer.[19] Young et al (2009) studied 54 women with high-grade, triple-negative breast cancer with no family history of breast or ovarian cancer, representing a group that previously was not recommended for *BRCA* testing.[20] Six BRCA variants (5 *BRCA1*, 1 *BRCA2*) were found, for a variant rate of 11%. Finally, Gonzalez-Angulo et al (2011) in a study of 77 patients with triple-negative breast cancer, reported that 15 patients (19.5%) had BRCA variants (12 in *BRCA1*, 3 in *BRCA2*).[21]

CLDN18

Claudin-18 (*CLDN18)* is a transmembrane protein that forms tight junctions between epithelial cells and regulate the flow and movement of ions across epithelial cells. Overexpression of this protein is implicated in the development of various primary malignant tumors, such as gastric cancer/gastroesophageal junction (GC/GEJ) cancer, breast cancer, colon cancer, liver cancer, head and neck cancer, bronchial cancer, and non-small-cell lung cancer.[22,23] More specifically, CLDN18.2 is an isoform that is exclusively expressed in the tight junctions of gastric mucosal cells and participates in the proliferation, differentiation and migration of tumor cells. Studies have reported that CLDN18.2 is expressed in approximately 70% of gastric cancers and up to 60% of pancreatic adenocarcinomas.[24]

EGFR

EGFR, a receptor tyrosine kinase (TK), is frequently overexpressed and activated in NSCLC. Drugs that inhibit EGFR signaling either prevent ligand binding to the extracellular domain (monoclonal antibodies) or inhibit intracellular TK activity (small-molecule tyrosine kinase inhibitors [TKIs]). These targeted therapies dampen signal transduction through pathways downstream to the EGFR, such as the RAS/RAF/MAPK cascade. RAS proteins are G proteins that cycle between active and inactive forms in response to stimulation from cell surface receptors, such as EGFR, acting as binary switches between cell surface EGFR and downstream signaling pathways. These pathways are important in cancer cell proliferation, invasion, metastasis, and stimulation of neovascularization.

Somatic variants in the TK domain of the *EGFR* gene, notably small deletions in exon 19 and a point mutation in exon 21 (L858R, indicating substitution of leucine by arginine at codon position 858) are the most commonly found *EGFR* variants associated with sensitivity to EGFR TKIs (afatinib, erlotinib,

gefitinib). These variants are referred to as sensitizing variants. Almost all patients who initially respond to an EGFR TKI experience disease progression. The most common of these secondary variants, called resistance variants, involves the substitution of methionine for threonine at position 790 (T790M) on exon 20.

Fang et al (2013) reported *EGFR* variants (all L858R) in 3 (2%) of 146 consecutively treated Chinese patients with early-stage squamous cell carcinoma (SCC).[25] In a separate cohort of 63 Chinese patients with SCC who received erlotinib or gefitinib as second- or third-line treatment (63% never-smokers, 21% women), *EGFR* variant prevalence (all exon 19 deletion or L858R) was 23.8%. In a comprehensive analysis of 14 studies involving 2880 patients, Mitsudomi et al (2006) reported *EGFR* variants in 10% of men, 7% of non-Asian patients, 7% of current or former smokers, and 2% of patients with nonadenocarcinoma histologies.[26] Eberhard et al (2005)[27] observed *EGFR* variants in 6.4% of patients with SCC and Rosell et al (2009)[28] observed *EGFR* variants in 11.5% of patients with large cell carcinomas. Both studies had small sample sizes. In 2 other studies, the acquired *EGFR* T790M variant has been estimated to be present in 50% to 60% of TKI-resistant cases in approximately 200 patients.[29,30]

ESR1

Variants in estrogen receptor 1 (*ESR1)*, which occur in approximately 10-20% of patients with metastatic estrogen receptor-positive breast cancer, confer resistance to endocrine therapy via constitutive activation of estrogen receptor-mediated growth activity.[31,32]

EZH2

Enhancer of zeste homolog 2 (*EZH2*) is a histone-lysine N-methyltrasnferase responsible for generating epigenetic markers that regulate gene function with the most common being trimethylation of Lys-27 in histone 3 (H3K27me3).[33] *EZH2* is overexpressed in numerous tumor types including melanoma, ovarian, breast, endometrial, bladder, renal cell, lung, and liver cancer, and is associated with aggressive disease, leading to its classification as an oncogene. It is commonly overexpressed or harbors gain-of-function mutations that enhance the catalytic activity within 25 percent of follicular lymphomas.[34]

FGFR2 and *FGFR3*

The fibroblast growth factor receptor (*FGFR*) family is an integral signaling pathway for cellular activities, including proliferation, tissue repair, regeneration, chemotaxis, angiogenesis, differentiation, and survival.[35] Thus, dysregulation of this pathway with alterations of these genes has been implicated in numerous cancers, including uroepithelial carcinoma (32–14.8%), colorectal carcinoma (31%), breast carcinoma (12.6–18%), gastric carcinoma (16.8–25.6%), endometrial carcinoma (13%), squamous lung carcinoma (6.8–13%), esophageal carcinoma (12.7%), ovarian carcinoma (9%), and lung adenocarcinoma (1.3%). Most of these abnormalities were gene amplifications (53.7–66%), followed by mutations (26–38.8%), and rearrangements/fusions (5.6–8%). The frequencies of aberration for *FGFR*2 and *FGFR*3 were 14.2–19% and 17.7–26%, respectively.[36,37]

FLT3 (ITD/TDK)

Internal tandem duplications (ITDs) of the FMS-like tyrosine kinase 3 (*FLT3*) gene occur in ~25% to 30% of acute myeloid leukemia (AML) cases and results is more severe outcomes, including higher relapse rates and reduced overall survival, after standard of care treatment.[38,39,40] Variants in *FLT3* were found in 30 % of newly diagnosed AML patients, with *FLT3*-ITD variants occurring with a frequency of 24% and variants within the activation loop (FLT3-TKD mutations) occurring at a frequency of 7%.

FOLR1

Folate receptor alpha (FRα), encoded by the *FOLR1* gene, is an attractive target for cancer therapeutics due to its high expression in several cancer types including lung, breast, and epithelial ovarian cancer (EOC) with overexpression in approximately 80% of EOCs.[41]

Homologous Recombination Deficiency and Homologous Recombination Repair

DNA damage happens daily, and most are repaired to allow normal cell functioning. Double strand breaks (DSB) in the DNA are particularly damaging. Repair of DSB utilizes the homologous recombination repair (HRR) pathway. Many types of cancer, however, are unable to repair DNA damage. This leads to the accumulation of genetic errors, such as loss of DNA, rearrangements in the DNA, and loss of entire genes. The consequence of these errors is genomic instability. The loss of the HRR and associated genomic instability is called homologous recombination deficiency (HRD). HRD is associated with several types of cancer including ovarian cancer.[42,43] HRD is associated with several types of cancer including prostate cancer, where estimates as high as 30% of metastatic castrate-resistant prostate cancer (mCRPC) tumors have genetic changes that result in the loss of DNA repair capacity.[43] Specific to prostate cancer, the National Comprehensive Cancer Network (NCCN) prostate cancer guideline gives examples of HRR genes (*BRCA1*, *BRCA2*, *ATM*, *BARD1*, *BRIP1*, *CDK12*, *CHEK1*, *CHEK2*, *FANCL*, *PALB2*, *RAD51B*, *RAD51C*, *RAD51D,* and *RAD54L).*[44] Poly adenosine diphosphate-ribose polymerase (PARP) inhibitors are used to target tumor cells with alterations in the HRR genes *BRCA1* and *BRCA2.*

In ovarian cancer targeted therapies, HRD-positive status is generally defined by either a deleterious or suspected deleterious BRCA mutation, and/or genomic instability. Myriad MyChoice® is an FDA-approved companion diagnostic for the assessment of tumor genomic instability score (GIS) and the detection and classification of variants in the BRCA1 and BRCA2 genes, for the selection of patients who are eligible for targeted treatment. A patient's Myriad HRD status is determined by detecting single nucleotide variants (SNVs), variants in homopolymer stretches, insertions and deletions (indels), and large rearrangements (LRs) in the BRCA1 and BRCA2 genes, and determining a genomic instability score (GIS) using DNA obtained from ovarian tumor tissue. A positive Myriad HRD Status result is due to either the presence of a pathogenic variant in BRCA1 and/or BRCA2 and/or a GIS above a defined threshold.[45] Approximately 41% to 50% of epithelial ovarian cancers are estimated to exhibit HRD. Germline alterations in BRCA1 and BRCA2 genes have been identified in up to 17% of individuals diagnosed with epithelial ovarian cancer, and somatic mutations are found in an additional 7%.[46]

Human Epidermal Growth Factor Receptor 2 Amplification/Overexpression

Human epidermal growth factor receptor 2 (HER2) is a member of the HER (EGFR) family of tyrosine kinase receptors and has no specific ligand. When activated, it forms dimers with other EGFR family members. Amplification of HER2 is detected in approximately 4% of patients with CRC, with higher prevalence in *RAS/BRAF*-wild type tumors (5% to 14%).[47] In addition to its role as a predictive marker for HER2-targeted therapy, HER2 amplification/overexpression is being investigated as a predictor of resistance to EGFR-targeting monoclonal antibodies.

Human Leukocyte Antigen

The human leukocyte antigen (*HLA*) is a complex system of genes in humans that encode cell-surface proteins responsible for the regulation of the immune system. HLA molecular pathways present tumor antigens to T-cells to facilitate the recognition of tumor cells by the immune system. *HLA* genes are highly polymorphic allowing them to fine-tune the immune response through multiple unique combinations. *HLA* variants are crucial for targeted therapy as these drugs are engineered to bind to specific *HLA* constructs to evoke an immune response against tumor cells.[48]

IDH1 and *IDH2*

Mutations in isocitrate dehydrogenase-1 (IDH1) or -2 (IDH2) genes lead to aberrant accumulated production of D-2-hydroxyglutarate, disrupting gene expression and cellular differentiation. WHO grade 2 and 3 astrocytomas and oligodendrogliomas are defined by IDH mutations, distinguishing lower-grade gliomas from glioblastomas. IDH1 and IDH2 mutations are generally associated with a more favorable prognosis, and have been important biomarkers for stratification in clinical trials. IDH mutations are detected in over 50% of gliomas in patients aged 55 or older.[49]

KIT

KIT, also known as c-KIT, is a tyrosine kinase expressed on the surface of cells and plays a significant role in cell survival, proliferation, and differentiation via signaling pathways. For instance, KIT signaling is required for melanocyte survival, and is involved in hematopoiesis and gametogenesis. Gain-of-function variants within this gene are highly associated with cancer as it is implicated in numerous signaling pathways, such as *RAS-MAPK* and *PI-3K*. *KIT* variants are present in 85% to 95% of gastrointestinal stromal tumors (GIST) and systemic mastocytosis cancers.[50]

MET

MET alteration is one of the critical events for acquired resistance in *EGFR*-mutated adenocarcinomas refractory to EGFR TKIs.[6]

Mismatch Repair Deficiency/Microsatellite Instability

Mismatch repair deficiency (dMMR) and high levels of microsatellite instability (MSI-H) describe cells that have alterations in certain genes involved in correcting errors made when DNA is replicated. dMMR tumors are characterized by a high tumor mutational load and potential responsiveness to anti-programmed cell death ligand-1 (PD-L1)-immunotherapy. Mismatch repair (MMR) deficiency is most common in colorectal cancer, other types of gastrointestinal cancer, and endometrial cancer, but it may also be found in other cancers including breast cancer.

Testing for dMMR and MSI is used to identify individuals most likely to respond to anti-PD-L1 therapy. Either MMR testing or MSI testing can be used to screen for MMR functional defects. MMR testing is performed using IHC for 4 MMR proteins (*MLH1*, *MSH2*, *PMS2*, and *MSH6*). Microsatellite instability testing is generally performed using polymerase chain reaction (PCR) for 5 biomarkers (*MLH1*, *MSH2*, *MSH6*, *PMS1* and *PMS2*). High MSI is defined as 2 or more of the 5 biomarkers showing instability or more than 30% of the tested biomarkers showing instability depending on what panel is used.[51]

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

The presence of *NTRK* gene fusion can be detected by multiple methods including next-generation sequencing, reverse transcription-polymerase chain reaction, fluorescence in situ hybridization and immunohistochemistry.[52] Next-generation sequencing provides the most comprehensive view of a large number of genes and may identify *NTRK* gene fusions as well as other actionable alterations, with minimal tissue needed. The fluorescence in situ hybridization using break-apart probes can detect gene rearrangements in DNA that may generate a fusion transcript. The immunohistochemistry techniques have generally been used in the research setting. Reverse transcription-polymerase chain reaction is designed to identify only known translocation partners and breakpoints and cannot identify novel breakpoints or novel fusion partners.

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]

Platelet-Derived Growth Factor Receptor Alpha and Beta

Platelet-derived growth factor receptors (PDGF-R) are cell surface tyrosine kinase receptors and are members of the platelet-derived growth factor (PDGF) family. PDGF subunits α and β play important roles in regulating cell proliferation, cellular differentiation, cell growth and development with alterations in these genes being heavily implicated in oncogenesis. *PDGFRA* variants occur in approximately 10–15% of GISTs[54], however, *PDGFRB* rearrangements are rare with approximately 2% of myeloproliferative neoplasms containing these fusions.[55]

Programmed Cell Death Ligand Protein-1

Programmed cell death ligand-1 is a transmembrane protein expressed on the surface of multiple tissue types, including many tumor cells. Blocking the PD-L1 protein may prevent cancer cells from inactivating T cells.

FDA-approved PD-L1 immune checkpoint inhibitors include atezolizumab, avelumab, durvalumab, nivolumab, and pembrolizumab.

RAS (*KRAS* and *NRAS*)

Cetuximab (Erbitux®; ImClone Systems) and panitumumab (Vectibix®; Amgen) are monoclonal antibodies that bind to the epidermal growth factor receptor (EGFR), preventing intrinsic ligand binding and activation of downstream signaling pathways vital for cancer cell proliferation, invasion, metastasis, and stimulation of neovascularization. The RAS-RAF-MAP kinase pathway is activated in the EGFR cascade. The RAS proteins are G proteins that cycle between active (RAS guanosine triphosphate) and inactive (RAS guanosine diphosphate) forms in response to stimulation from a cell surface receptor, such as EGFR, and they act as a binary switch between the cell surface EGFR and downstream signaling pathways. The *KRAS* gene can harbor oncogenic variants that result in a constitutively activated protein, independent of EGFR ligand binding, rendering antibodies to the upstream EGFR ineffective. Approximately 40% of colorectal cancers (CRCs) have *KRAS* variants in codons 12 and 13 in exon 2. Another proto-oncogene that acts downstream from *KRAS-NRAS* harbors oncogenic variants in codons 12, 13, or 61 that result in constitutive activation of the EGFR-mediated pathway. These variants are less common compared with *KRAS,* detected in 2% to 7% of CRC specimens. It is unclear whether *NRAS* variants predict poor response due to anti-EGFR monoclonal antibody therapy or are prognostic of poor CRC outcomes in general.

The *KRAS* gene (which encodes RAS proteins) can harbor oncogenic variants that result in a constitutively activated protein, independent of signaling from the EGFR, possibly rendering a tumor resistant to therapies that target the EGFR. Variants in the *KRAS* gene, mainly codons 12 and 13, have been reported in 20% to 30% of NSCLC, and occur most often in adenocarcinomas in heavy smokers. *KRAS* variants can be detected by direct sequencing, polymerase chain reaction technologies, or next-generation sequencing. *EGFR*, *ALK*, *ROS1*, and *KRAS* driver mutations are considered to be mutually exclusive.

A large body of literature has shown that metastatic CRC tumors with a variant in exon 2 (codon 12 or 13) of the *KRAS* gene do not respond to cetuximab or panitumumab therapy. More recent evidence has shown that variants in *KRAS* outside exon 2 (i.e., in exons 3 [codons 59 and 61] and exon 4 [codons 117 and 146]) and variants in *NRAS* exon 2 (codons 12 and 13), exon 3 (codons 59 and 61), and exon 4 (codons 117 and 146) also predict a lack of response to these monoclonal antibodies. Variant testing of these exons outside the *KRAS* exon 2 is referred to as extended *RAS* testing.

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]

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.

Literature Review

Evidence reviews assess whether a medical test is clinically useful. A useful test provides information to make a clinical management decision that improves the net health outcome. That is, the balance of benefits and harms is better when the test is used to manage the condition than when another test or no test is used to manage the condition.

The first step in assessing a medical test is to formulate the clinical context and purpose of the test. The test must be technically reliable, clinically valid, and clinically useful for that purpose. Evidence reviews assess the evidence on whether a test is clinically valid and clinically useful. Technical reliability is outside the scope of these reviews, and credible information on technical reliability is available from other sources.

Biomarker Testing Using Tissue Biopsy to Select Targeted Treatment

Clinical Context and Test Purpose

Breast cancer treatment selection is informed by tumor type, grade, stage, patient performance status and preference, prior treatments, and the molecular characteristics of the tumor such as the presence of driver variants. One purpose of biomarker testing of individuals who have advanced cancer is to inform a decision regarding treatment selection (e.g., whether to select a targeted treatment or standard treatment).

The following PICO was used to select literature to inform this review.

Populations

The relevant population of interest is individuals with unresectable, recurrent, relapsed, refractory, advanced, or metastatic cancer for whom the selection of treatment depends on the molecular characterization of the tumor.

Interventions

The technology being considered is genetic testing for biomarkers using tissue or liquid biopsy.

Comparators
Decisions about treatment in unresectable, recurrent, relapsed, refractory, advanced, or metastatic cancer are based on clinical characteristics.

Outcomes
The general outcomes of interest in oncology are overall survival, disease-specific survival, quality of life (QOL), treatment-related mortality and morbidity.

Beneficial outcomes resulting from a true-positive test result are prolonged survival, reduced toxicity, and improved QOL associated with receiving a more effective targeted therapy. Beneficial outcomes from a true negative result are prolonged survival associated with receiving chemotherapy in those without driver variants.

Harmful outcomes resulting from a false-negative test result include shorter survival from receiving less effective and more cytotoxic chemotherapy in those with driver variants; possible harmful outcomes resulting from a false-positive test result are a shorter survival from receiving potentially ineffective targeted treatment and delay in initiation of chemotherapy in those without driver variants.

The overall response rate (ORR) may be used as a surrogate endpoint reasonably likely to predict clinical benefit in individuals with refractory solid tumors. ORR can be measured by the proportion of individuals with best overall confirmed response of complete response) or partial response by the Response Evaluation Criteria in Solid Tumors, version 1.1 (RECIST 1.1),[64] or Response Assessment in Neuro-Oncology criteria,[65] as appropriate by a blinded and independent adjudication committee.

There are clearly defined quantitative thresholds for the follow-up of individuals in oncology trials. A general rule is a continuation of treatment until disease progression or unacceptable toxicity. Long-term follow-up outside of a study setting is conducted to determine survival status. The duration of follow-up for the outcomes of interest is 6 months and 1 year.

Study Selection Criteria
Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for randomized controlled trials (RCTs);
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
- To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- Studies with duplicative or overlapping populations were excluded.

Review of Evidence
Testing for Genetic Variants and Biomarkers for Selection of FDA-approved Targeted Therapies
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

The purpose of the following information is to provide reference material. Inclusion does not imply endorsement or alignment with the evidence review conclusions.

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 U.S. professional society, an international society with U.S. 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

Guidelines	Type	SOE	QOE
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 U.S. 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 Association/Society of Urologic Oncology

In 2023, the American Urological Association 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 (e.g., 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."

Ongoing and Unpublished Clinical Trials

Some currently unpublished trials that might influence this review are listed in Table 3.

Table 3. Summary of Key Trials

NCT No.	Trial Name	Planned Enrollment	Completion Date
Ongoing			
NCT03145961[a]	c-TRAK TN: A Randomised Trial Utilising ctDNA Mutation Tracking to Detect Minimal Residual Disease and Trigger Intervention in Patients With Moderate and High Risk Early Stage Triple Negative Breast Cancer	208	Mar 2024 (unknown status)
NCT02965755[a]	Individualized Molecular Analyses Guide Efforts in Breast Cancer - Personalized Molecular Profiling in Cancer Treatment at Johns Hopkins (IMAGE-II)	200	Jul 2026
NCT02889978[a]	The Circulating Cell-free Genome Atlas Study (CCGA)	15,254	Mar 2024 (unknown status)
NCT02568267[a]	An Open-Label, Multicenter, Global Phase 2 Basket Study of Entrectinib for the Treatment of Patients With Locally Advanced or Metastatic Solid Tumors That Harbor NTRK1/2/3, ROS1, or ALK Gene Rearrangements (STARTRK-2)	534	Apr 2025
NCT04591431	The Rome Trial - From Histology to Target: the Road to Personalize Target Therapy and Immunotherapy	400	Jun 2025 (unknown status)
NCT02693535[a]	Targeted Agent and Profiling Utilization Registry (TAPUR) Study	3791	Dec2028
NCT04526587	The Roswell Park Ciclib Study: A Prospective Study of Biomarkers and Clinical Features of Advanced/Metastatic Breast Cancer Treated With CDK4/6 Inhibitors	400	Jul 2030
NCT02306096	SCAN-B: The Sweden Cancerome Analysis Network - Breast Initiative	20000	Aug 2031

NCT No.	Trial Name	Planned Enrollment	Completion Date
NCT03225664	BATTLE-2 Program: A Biomarker-Integrated Targeted Therapy Study in Previously Treated Patients With Advanced Non-Small Cell Lung Cancer	37 (actual)	Dec 2025
NCT02622581	Clinical Research Platform into Molecular Testing, Treatment and Outcome of Non-Small Cell Lung Carcinoma Patients (CRISP)	12400	Dec 2027
NCT02465060	Molecular Analysis for Therapy Choice (MATCH)	6452	Dec 2026
NCT03199651	Beating Lung Cancer in Ohio (BLCIO) Protocol	3584	Dec 2028
NCT03178552[a]	A Phase II/III Multicenter Study Evaluating the Efficacy and Safety of Multiple Targeted Therapies as Treatments for Patients With Advanced or Metastatic Non-Small Cell Lung Cancer (NSCLC) Harboring Actionable Somatic Mutations Detected in Blood (B-FAST: Blood-First Assay Screening Trial)	1000	Aug 2028
NCT04591431	The Rome Trial - From Histology to Target: the Road to Personalize Target Therapy and Immunotherapy	400 (actual)	Jun 2025 (unknown status)
NCT06632977	PREcision Dlagnostics in Prostate Cancer Treatment (PREDICT)	474	Oct 2034
NCT02735252	Precision Oncology and Molecular Targeting in Advanced Genitourinary Cancers: Identifying Predictive Markers of Response (The "PROMOTE" Study)	156	Mar 2027
NCT03155620	NCI-COG Pediatric MATCH (Molecular Analysis for Therapy Choice) Screening Protocol	1376	May 2026
NCT05839379	Molecularly-Guided Phase II Umbrella Trial for Children, Adolescents, and Young Adults Newly Diagnosed with High-Grade Glioma, Including Diffuse Intrinsic Pontine Glioma	450	Aug 2034
NCT04264702	BESPOKE Study of ctDNA Guided Therapy in Colorectal Cancer	1788	Sep 2025
NCT05722886	DETERMINE (Determining Extended Therapeutic Indications for Existing Drugs in Rare Molecularly Defined Indications Using a National Evaluation Platform Trial): An Umbrella-Basket Platform Trial to Evaluate the Efficacy of Targeted Therapies in Rare Adult, Paediatric and Teenage/Young Adult (TYA) Cancers With Actionable Genomic Alterations, Including Common Cancers With Rare Actionable Alterations	825	Oct 2029
Unpublished			
NCT04098640	Molecular Profiling Using FoundationOne CDx in Young (<50 Years of Age) Patients With Metastatic Breast Cancer (ML41263)	200	Dec2025

NCT: national clinical trial.
[a] Denotes industry-sponsored or cosponsored trial.

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Documentation for Clinical Review

Please provide the following documentation:

- History and physical and/or consultation notes including:
  - Clinical findings (i.e., pertinent symptoms and duration)
  - Current diagnoses and status (i.e., type of cancer, stage)
  - Date of diagnosis
  - Family history, if applicable
  - Reason for test when applicable
  - Treatment plan
- Pertinent past procedural and surgical history (i.e., biopsies, resections, etc.)
- Pathology report(s)
- Pertinent past genetic tests (i.e., somatic/tumor or germline test results including but not limited to HER2, PD-L1, MSI, BRCA, etc.)

Post Service (in addition to the above, please include the following):

- Results/reports of tests performed
- Procedure report(s)

Coding

The list of codes in this Medical Policy is intended as a general reference and may not cover all codes. Inclusion or exclusion of a code(s) does not constitute or imply member coverage or provider reimbursement policy.

Type	Code	Description
CPT®	0037U	Targeted genomic sequence analysis, solid organ neoplasm, DNA analysis of 324 genes, interrogation for sequence variants, gene copy number amplifications, gene rearrangements, microsatellite instability and tumor mutational burden ***(Includes FoundationOne CDx™ (F1CDx), Foundation Medicine, Inc)***
	0048U	Oncology (solid organ neoplasia), DNA, targeted sequencing of protein-coding exons of 468 cancer-associated genes, including interrogation for somatic mutations and microsatellite instability, matched with normal specimens, utilizing formalin-fixed paraffin-embedded tumor tissue, report of clinically significant mutation(s)

Type	Code	Description
		(Includes MSK-IMPACT (Integrated Mutation Profiling of Actionable Cancer Targets), Memorial Sloan Kettering Cancer Center)
	0155U	Oncology (breast cancer), DNA, PIK3CA (phosphatidylinositol-4,5-bisphosphate 3-kinase, catalytic subunit alpha) (e.g., breast cancer) gene analysis (i.e., p.C420R, p.E542K, p.E545A, p.E545D [g.1635G>T only], p.E545G, p.E545K, p.Q546E, p.Q546R, p.H1047L, p.H1047R, p.H1047Y), utilizing formalin-fixed paraffin-embedded breast tumor tissue, reported as PIK3CA gene mutation status ***(Includes therascreen® PIK3CA RGQ PCR Kit, QIAGEN, QIAGEN GmbH)***
	0177U	Oncology (breast cancer), DNA, PIK3CA (phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha) gene analysis of 11 gene variants utilizing plasma, reported as PIK3CA gene mutation status ***(Includes therascreen® PIK3CA RGQ PCR Kit, QIAGEN, QIAGEN GmbH)***
	0239U	Targeted genomic sequence analysis panel, solid organ neoplasm, cell-free DNA, analysis of 311 or more genes, interrogation for sequence variants, including substitutions, insertions, deletions, select rearrangements, and copy number variations ***(Includes FoundationOne® Liquid CDx, Foundation Medicine, Inc)***
	0242U	Targeted genomic sequence analysis panel, solid organ neoplasm, cell-free circulating DNA analysis of 55-74 genes, interrogation for sequence variants, gene copy number amplifications, and gene rearrangements ***(Includes Guardant360® CDx, Guardant Health Inc)***
	0338U	Oncology (solid tumor), circulating tumor cell selection, identification, morphological characterization, detection and enumeration based on differential EpCAM, cytokeratins 8, 18, and 19, and CD45 protein biomarkers, and quantification of HER2 protein biomarker-expressing cells, peripheral blood ***(Includes CELLSEARCH® HER2 Circulating Tumor Cell (CTC-HER2) Test, Menarini Silicon Biosystems, Inc, Menarini Silicon Biosystems, Inc)***
	81162	BRCA1 (BRCA1, DNA repair associated), BRCA2 (BRCA2, DNA repair associated) (e.g., hereditary breast and ovarian cancer) gene analysis; full sequence analysis and full duplication/deletion analysis (i.e., detection of large gene rearrangements)
	81163	BRCA1 (BRCA1, DNA repair associated), BRCA2 (BRCA2, DNA repair associated) (e.g., hereditary breast and ovarian cancer) gene analysis; full sequence analysis
	81164	BRCA1 (BRCA1, DNA repair associated), BRCA2 (BRCA2, DNA repair associated) (e.g., hereditary breast and ovarian cancer) gene analysis; full duplication/deletion analysis (i.e., detection of large gene rearrangements)
	81165	BRCA1 (BRCA1, DNA repair associated) (e.g., hereditary breast and ovarian cancer) gene analysis; full sequence analysis
	81166	BRCA1 (BRCA1, DNA repair associated) (e.g., hereditary breast and ovarian cancer) gene analysis; full duplication/deletion analysis (i.e., detection of large gene rearrangements)
	81167	BRCA2 (BRCA2, DNA repair associated) (e.g., hereditary breast and ovarian cancer) gene analysis; full duplication/deletion analysis (i.e., detection of large gene rearrangements)

Type	Code	Description
	81191	NTRK1 (neurotrophic receptor tyrosine kinase 1) (e.g., solid tumors) translocation analysis
	81192	NTRK2 (neurotrophic receptor tyrosine kinase 2) (e.g., solid tumors) translocation analysis
	81193	NTRK3 (neurotrophic receptor tyrosine kinase 3) (e.g., solid tumors) translocation analysis
	81194	NTRK (neurotrophic receptor tyrosine kinase 1, 2, and 3) (e.g., solid tumors) translocation analysis
	81212	BRCA1 (BRCA1, DNA repair associated), BRCA2 (BRCA2, DNA repair associated) (e.g., hereditary breast and ovarian cancer) gene analysis; 185delAG, 5385insC, 6174delT variants
	81215	BRCA1 (BRCA1, DNA repair associated) (e.g., hereditary breast and ovarian cancer) gene analysis; known familial variant
	81216	BRCA2 (BRCA2, DNA repair associated) (e.g., hereditary breast and ovarian cancer) gene analysis; full sequence analysis
	81217	BRCA2 (BRCA2, DNA repair associated) (e.g., hereditary breast and ovarian cancer) gene analysis; known familial variant
	81301	Microsatellite instability analysis (e.g., hereditary non-polyposis colorectal cancer, Lynch syndrome) of markers for mismatch repair deficiency (e.g., BAT25, BAT26), includes comparison of neoplastic and normal tissue, if performed
	81309	PIK3CA (phosphatidylinositol-4, 5-biphosphate 3-kinase, catalytic subunit alpha) (e.g., colorectal and breast cancer) gene analysis, targeted sequence analysis (e.g., exons 7, 9, 20)
	81445	Solid organ neoplasm, genomic sequence analysis panel, 5-50 genes, interrogation for sequence variants and copy number variants or rearrangements, if performed; DNA analysis or combined DNA and RNA analysis
	81455	Solid organ or hematolymphoid neoplasm or disorder, 51 or greater genes, genomic sequence analysis panel, interrogation for sequence variants and copy number variants or rearrangements, or isoform expression or mRNA expression levels, if performed; DNA analysis or combined DNA and RNA analysis
	88360	Morphometric analysis, tumor immunohistochemistry (e.g., Her-2/neu, estrogen receptor/progesterone receptor), quantitative or semiquantitative, per specimen, each single antibody stain procedure; manual
	88361	Morphometric analysis, tumor immunohistochemistry (e.g., Her-2/neu, estrogen receptor/progesterone receptor), quantitative or semiquantitative, per specimen, each single antibody stain procedure; using computer-assisted technology
	81479	Unlisted molecular pathology procedure
	96041	Medical genetics and genetic counseling services, each 30 minutes of total time provided by the genetic counselor on the date of the encounter
HCPCS	None	

Policy History

This section provides a chronological history of the activities, updates and changes that have occurred with this Medical Policy.

Effective Date	Action
03/01/2026	New policy.

Definitions of Decision Determinations

Healthcare Services: For the purpose of this Medical Policy, Healthcare Services means procedures, treatments, supplies, devices, and equipment.

Medically Necessary or **Medical Necessity** means reasonable and necessary services to protect life, to prevent significant illness or significant disability, or alleviate severe pain through the diagnosis or treatment of disease, illness, or injury, as required under W&I section 14059.5(a) and 22 CCR section 51303(a). Medically Necessary services must include services necessary to achieve age-appropriate growth and development, and attain, maintain, or regain functional capacity.

For Members less than 21 years of age, a service is Medically Necessary if it meets the Early and Periodic Screening, Diagnostic, and Treatment (EPSDT) standard of Medical Necessity set forth in 42 USC section 1396d(r)(5), as required by W&I sections 14059.5(b) and 14132(v). Without limitation, Medically Necessary services for Members less than 21 years of age include all services necessary to achieve or maintain age-appropriate growth and development, attain, regain or maintain functional capacity, or improve, support, or maintain the Member's current health condition. Contractor must determine Medical Necessity on a case-by-case basis, taking into account the individual needs of the Child.

Criteria Determining Experimental/Investigational Status
In making a determination that any procedure, treatment, therapy, drug, biological product, facility, equipment, device, or supply is "experimental or investigational" by the Plan, the Plan shall refer to evidence from the national medical community, which may include one or more of the following sources:

1. Evidence from national medical organizations, such as the National Centers of Health Service Research.
2. Peer-reviewed medical and scientific literature.
3. Publications from organizations, such as the American Medical Association (AMA).
4. Professionals, specialists, and experts.
5. Written protocols and consent forms used by the proposed treating facility or other facility administering substantially the same drug, device, or medical treatment.
6. An expert physician panel selected by one of two organizations, the Managed Care Ombudsman Program of the Medical Care Management Corporation or the Department of Managed Health Care.

Feedback

Blue Shield of California Promise Health Plan is interested in receiving feedback relative to developing, adopting, and reviewing criteria for medical policy. Any licensed practitioner who is contracted with Blue Shield of California Promise Health Plan is welcome to provide comments, suggestions, or concerns. Our internal policy committees will receive and take your comments into consideration. Our medical policies are available to view or download at www.blueshieldca.com/en/bsp/providers.

For medical policy feedback, please send comments to: MedPolicy@blueshieldca.com

Questions regarding the applicability of this policy should be directed to the Blue Shield of California Promise Health Plan Prior Authorization Department at (800) 468-9935, or the Complex Case Management Department at (855) 699-5557 (TTY 711) for San Diego County and (800) 605-2556 (TTY 711) for Los Angeles County or visit the provider portal at www.blueshieldca.com/en/bsp/providers.

Disclaimer: Blue Shield of California Promise Health Plan may consider published peer-reviewed scientific literature, national guidelines, and local standards of practice in developing its medical policy. Federal and state law, as well as member health services contract language, including definitions and specific contract provisions/exclusions, take precedence over medical policy and must be considered first in determining covered services. Member health services contracts may differ in their benefits. Blue Shield of California Promise Health Plan reserves the right to review and update policies as appropriate.