BSC_CON_2.10	Oncology: Circulating Tumor DNA and Circulating Tumor Cells (Liquid Biopsy)		
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Section:	2.0 Medicine	**Page:**	Page 1 of 25

Example Test Table

Below is a list of higher volume tests and the associated laboratories for each coverage criteria section. This list is not all inclusive.

Policy Statement Sections	Example Tests, Labs	Common CPT Codes
Molecular Profiling Panel Tests via Circulating Tumor DNA (ctDNA)		
Comprehensive Molecular Profiling Panel Tests via Circulating Tumor DNA (ctDNA)	FoundationOne® Liquid CDx (Foundation Medicine)	0239U
	Guardant360® CDx (Guardant Health)	0242U
	Guardant360® 83+ genes (Guardant Health)	0326U
	NeoLAB® Solid Tumor Liquid Biopsy (NeoGenomics Laboratories)	81445
	Tempus xF: Liquid Biopsy Panel of 105 Genes (Tempus)	81455
Lung Cancer Focused Panel Tests via Circulating Tumor DNA (ctDNA)	Resolution ctDx Lung™ (LabCorp)	0179U
	OncoBEAM™ Lung2: EGFR, KRAS, BRAF (Sysmex Inostics, Inc)	81210, 81235, 81275, 81479
	InVisionFirst®-Lung Liquid Biopsy (inivata)	81445
Colorectal Cancer Focused Panel Tests via Circulating Tumor DNA (ctDNA)	OncoBEAM™ CRC1: KRAS, NRAS, BRAF, HRAS (Sysmex Inostics, Inc)	81210, 81275, 81311, 81403, 81479
Melanoma Focused Panel Tests via Circulating Tumor DNA (ctDNA)	OncoBEAM™ Melanoma1: BRAF, NRAS (Sysmex Inostics, Inc)	81210, 81311, 81479
Single Gene Molecular Profiling Tests via Circulating Tumor DNA (ctDNA)		
EGFR Variant Analysis via ctDNA	OncoBEAM™ Lung1: EGFR (Sysmex Inostics, Inc)	81235, 81479
	EGFR T790M Mutation Detection in ctDNA (ARUP Laboratories)	81479
BRAF Variant Analysis via ctDNA	Cell-Free DNA BRAF V600 Test (Mayo Medical Laboratories)	81210
	OncoBEAM™ Melanoma2: BRAF (Sysmex Inostics, Inc)	
KRAS Variant Analysis via ctDNA	Cell-Free DNA KRAS 12, 13, 61, 146 Blood (Mayo Medical Laboratories)	81479
PIK3CA Variant Analysis via ctDNA	therascreen® PIK3CA RGQ PCR Kit (QIAGEN)	0177U
	PIK3CA Mutation CDx - Plasma (NeoGenomics Laboratories)	81309
Circulating Tumor Cell (CTC) Tests		
AR-V7 Androgen Receptor Splice Variant Analysis in Circulating Tumor Cells (CTCs)	AR-V7 Prostate Cancer (Johns Hopkins Medical Institutions - Pathology Laboratory)	81479, 81174
	OncotypeDx AR-V7 Nucleus Detect (Exact Sciences Laboratories)	

Circulating Tumor Cell (CTC) Enumeration Analysis	Circulating Tumor Cell Count (ARUP Laboratories)	86152, 86153

Policy Statement

I. Comprehensive or focused molecular profiling panel tests via circulating tumor DNA (liquid biopsy) (0239U, 0242U, 0326U, 81445) may be considered **medically necessary** at diagnosis progression or recurrence when **BOTH** of the following criteria are met:
   A. The member has a diagnosis of **ONE** of the following:
      1. Non-small cell lung cancer (e.g., adenocarcinoma, large cell carcinoma, squamous cell carcinoma, not otherwise specified) must include EGFR
      2. Locally advanced/metastatic pancreatic adenocarcinoma
      3. Gastric cancer
      4. Esophageal or esophagogastric junction cancer
      5. Metastatic prostate cancer (must include *BRCA1*, *BRCA2*, *ATM*, *BARD1*, *BRIP1*, *CDK12*, *CHEK1*, *CHEK2*, *FANCL*, *PALB2*, *RAD51B*, *RAD51C*, *RAD51D*, and *RAD54L*; 0239U meets, 0242U and 0326U do not meet)
      6. Metastatic colorectal cancer (must include *KRAS, NRAS* and *BRAF)*
      7. Advanced or metastatic breast cancer when *PIK3CA* and *ESR1* is included in the panel for hormone receptor-positive, *HER2* negative individuals
   B. At least **ONE** of the following:
      1. The member is medically unfit for invasive tissue sampling (biopsy)
      2. Biopsy was performed but material was insufficient for complete molecular analysis

II. Comprehensive or focused molecular profiling panel tests via circulating tumor DNA (liquid biopsy) (0239U, 0242U, 0326U, 81445) are considered **investigational** for all other indications.

III. Comprehensive or focused molecular profiling panel tests via circulating tumor DNA (liquid biopsy) (0239U, 0242U, 0326U, 81445) performed simultaneously with solid tumor tissue testing is considered **investigational**.

IV. *AR-V7* androgen receptor splice variant analysis (81479) in circulating tumor cells (CTCs) may be considered **medically necessary** when **BOTH** of the following criteria are met:
   A. The member has metastatic castration-resistant prostate cancer (M1 CRPC)
   B. The member has had a progression after first-line treatment with enzalutamide (Xtandi®) or abiraterone (Zytiga®).

V. *AR-V7* androgen receptor splice variant analysis (81479) in circulating tumor cells (CTCs) is considered **investigational** for all other indications.

VI. Circulating tumor cell (CTC) enumeration (86152, 86153) is considered **investigational**.

NOTE: Refer to Appendix A to see the policy statement changes (if any) from the previous version.

Policy Guidelines

Note: This policy does not address MRD testing for hematologic or solid neoplasms. See Blue Shield of California Medical Policy: Oncology: Molecular Analysis Of Solid Tumors And Hematologic Malignancies

NOTES AND DEFINITIONS

Cell-free circulating tumor DNA (ctDNA) is fragmented, tumor-derived DNA circulating in the bloodstream that is not being carried in a cell. ctDNA derives either directly from the tumor or from circulating tumor cells.
Circulating Tumor Cells (CTCs) are intact cells that have shed into the bloodstream or lymphatic system from a primary tumor or a metastasis site, and are carried around the body by blood circulation.

CLINICAL CONSIDERATIONS

Cell-free circulating tumor DNA analysis should not be used in lieu of a histologic tissue diagnosis, however there are specific clinical considerations, outlined above, where the use of ctDNA may be considered.

Cell-free circulating tumor DNA analysis should not be performed simultaneously with tissue testing of a solid tumor.

If cell-free circulating tumor DNA analysis is negative, follow-up with tissue-based analysis is recommended.

Description

Cell-free circulating tumor DNA (ctDNA) originates directly from the tumor tissue (primary or metastasis); as tumor cells die the contents are released into the bloodstream. Genetic tests performed on cell-free circulating tumor DNA (ctDNA), also referred to as a liquid biopsy, potentially offer a noninvasive alternative to tissue biopsy for detection of "driver mutations", or acquired genetic mutations that may guide targeted therapy, and may also be used to track progression of disease.

Circulating tumor cells (CTCs) are intact tumor cells that are shed from tumor cells into the bloodstream or lymphatic system. Most assays detect CTCs through the use of surface epithelial markers such as EpCAM and cytokeratins. The primary reason for detecting CTCs is prognostic rather than for guiding therapeutic choices, through quantification of circulating levels.

Related Policies

This policy document provides coverage criteria for circulating tumor DNA (ctDNA) and circulating tumor cells testing (liquid biopsy). For other oncology-related testing, please refer to:

- **Oncology: Molecular Analysis of Solid Tumors and Hematologic Malignancies** for criteria related to DNA testing of a solid tumor or a blood cancer.
- **Genetic Testing: Hereditary Cancer Susceptibility Syndromes** for criteria related to genetic testing to determine if an individual has an inherited cancer susceptibility syndrome. *(To be published)*
- **Oncology: Algorithmic (Genetic Expression) Testing** for criteria related to gene expression profiling and tumor biomarker tests with algorithmic analyses.
- **Oncology: Cancer Screening** for criteria related to the use of non-invasive fecal, urine, or blood tests for screening for cancer.
- **Genetic Testing: General Approach to Genetic Testing and Molecular Testing** for coverage criteria related to circulating tumor DNA or circulating tumor cell testing that is not specifically discussed in this or another non-general policy. *(To be published)*

Benefit Application

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

Some state or federal mandates (e.g., Federal Employee Program [FEP]) prohibits plans from denying Food and Drug Administration (FDA)-approved technologies as investigational. In these instances, plans may have to consider the coverage eligibility of FDA-approved technologies on the basis of medical necessity alone.

Regulatory Status

FDA:
Circulating Tumor DNA and Circulating Tumor Cells for Cancer Management (Liquid Biopsy)
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 (FDA) has chosen not to require any regulatory review of this test.

The FDA maintains a list of cleared or approved companion diagnostic tests at https://www.fda.gov/medical-devices/in-vitro-diagnostics/list-cleared-or-approved-companion-diagnostic-devices-in-vitro-and-imaging-tools.

Somatic (Tumor) Biomarker Testing (Including Liquid Biopsy) for Targeted Treatment and Immunotherapy in Non-Small-Cell Lung Cancer (EGFR, ALK, BRAF, ROS1, RET, MET, KRAS, HER2, PD-L1, TMB)
Table 1 summarizes the FDA-approved targeted treatments for patients with NSCLC along with the concurrently approved companion diagnostic tests. (Note this information is current as of October 17, 2022. FDA maintains a list of cleared or approved companion diagnostics at https://www.fda.gov/medical-devices/in-vitro-diagnostics/list-cleared-or-approved-companion-diagnostic-devices-in-vitro-and-imaging-tools.)

Table 1. FDA-Approved Targeted Treatments for NSCLC and Companion Diagnostic Tests

Treatment	Indication	FDA-Approved Companion Diagnostic Tests
Afatinib (Gilotrif)	• 2013: First line for patients with metastatic NSCLC whose tumors have EGFR exon 19 deletions or exon 21 (L858R) substitutions • 2016: Second line for patients with metastatic squamous NSCLC • 2018: First line for patients with nonresistant EGFR variants other than exon 19 or exon 21 NSCLC	• 2013: therascreen® EGFR Rotor-Gene Q polymerase chain reaction (RGQ PCR) kit (Qiagen) • 2017: FoundationOne CDx™ (Foundation Medicine) • 2021: ONCO/Reveal Dx Lung & Colon Cancer Assay (O/RDx-LCCA)
Alectinib (Alecensa)	• 2015: Second line for patients with ALK-positive metastatic NSCLC who have progressed on or are intolerant of crizotinib	• 2017: FoundationOne CDx™ (Foundation Medicine)

Treatment	Indication	FDA-Approved Companion Diagnostic Tests
	• 2017: Patients with ALK-positive metastatic NSCLC as detected by an FDA-approved test	• 2017: Ventana ALK (D5F3) CDx Assay • 2020: FoundationOne Liquid CDx
Amivantamab-vmjw (Rybrenant)	• 2021: adult patients with locally advanced or metastatic NSCLC with EGFR exon 20 insertion mutations, as detected by an FDA-approved test, whose disease has progressed on or after platinum-based chemotherapy	• 2021: Guardant360 CDx • 2021: Oncomine™ Dx Target Test
Atezolizumab (Tecentriq)	• 2020: First-line treatment of adult patients with metastatic NSCLC whose tumors have high PD-L1 expression (PD-L1 stained ≥ 50% of tumor cells [TC ≥ 50%] or PD-L1 stained tumor-infiltrating immune cells covering ≥ 10% of the tumor area [IC ≥ 10%]), as determined by an FDA approved test, with no EGFR or ALK genomic tumor aberrations. o in combination with bevacizumab, paclitaxel, and carboplatin, for the first line treatment of adult patients with metastatic non-squamous NSCLC with no EGFR or ALK genomic tumor aberrations o in combination with paclitaxel protein-bound and carboplatin for the first line treatment of adult patients with metastatic non-squamous NSCLC with no EGFR or ALK genomic tumor aberrations o for the treatment of adult patients with metastatic NSCLC who have disease progression during or following platinum-containing chemotherapy.	• 2020: Ventana PD-L1
Brigatinib (Alunbrig)	• 2020: Treatment of adult patients with ALK-positive metastatic NSCLC as detected by an FDA-approved test	• 2020: Vysis ALK Break Apart FISH Probe Kit
Capmatinib (Tabrecta)	• 2020: Metastatic NSCLC whose tumors have a mutation that leads to *MET* exon 14 skipping as detected by an FDA-approved test.	• 2020: FoundationOne CDx™ • 2021: FoundationOne Liquid CDx™
Cemiplimab-rwlc (Libtayo)	• 2022: First-line treatment of patients with advanced NSCLC (locally advanced who are not candidates for surgical resection or definitive chemoradiation or metastatic) whose tumors have high PD-L1 expression (Tumor Proportion Score [TPS] ≥ 50%) as determined by an FDA-approved test, with no EGFR, ALK or ROS1 aberrations	• 2021: PD-L1 IHC 22C3 pharmDx (Dako North America, Inc.)
Ceritinib (Zykadia)	• 2014: Second line for patients with ALK-positive metastatic NSCLC who have progressed on or are intolerant of crizotinib • 2017: First line for patients with ALK-positive metastatic NSCLC	• 2017: FoundationOne CDx™ (Foundation Medicine) • 2017: VENTANA ALK (D5F3) CDx Assay
Crizotinib (Xalkori)	• 2011: First line for patients with ALK -positive metastatic NSCLC	• 2011: Vysis ALK Break Apart FISH Probe Kit (Abbott Laboratories) • 2015: Ventana ALK (D5F3) CDx Assay (Ventana Medical Systems)

Treatment	Indication	FDA-Approved Companion Diagnostic Tests
		• 2017: FoundationOne CDx™ (Foundation Medicine) • 2017: Oncomine™ Dx Target Test (Thermo Fisher Scientific)
Crizotinib (Xalkori)	• 2016: Patients with ROS1-positive metastatic NSCLC	• 2017: Oncomine™ Dx Target Test (Thermo Fisher Scientific)
Dacomitinib (Vizimpro)	• 2018: First line for patients with metastatic NSCLC with EGFR exon 19 deletion or exon 21 (L858R) substitutions	• 2018: therascreen EGFR RGQ PCR Kit • 2021: ONCO/Reveal Dx Lung & Colon Cancer Assay (O/RDx-LCCA)
Dabrafenib (Tafinlar) plus trametinib (Mekinist)	• 2017: Used in combination for treatment of patients with metastatic NSCLC with BRAF V600E variant	• 2017: Oncomine™ Dx Target Test • 2017: FoundationOne CDx™ (Foundation Medicine)
Entrectinib (Rozlytrek)	• 2019: ○ Adult patients with metastatic NSCLC whose tumors are ROS1-positive ○ Adult and pediatric patients 12 years of age and older with ▪ solid tumors that have a NTRK gene fusion without a known acquired resistance mutation, ▪ are metastatic or where surgical resection is likely to result in severe morbidity, and have progressed following treatment or have no satisfactory alternative therapy	• 2022: FoundationOne CDx™ (Foundation Medicine)
Erlotinib (Tarceva)	• 2020: First-line treatment in combination with ramucirumab (Cyramza) for patients with metastatic NSCLC whose tumors have EGFR exon 19 deletions or exon 21 (L858R) substitutions • 2013: First line for patients with metastatic NSCLC whose tumors have EGFR exon 19 deletions or exon 21 (L858R) substitutions • 2010: Maintenance for patients with locally advanced or metastatic NSCLC whose disease has not progressed after 4 cycles of platinum-based chemotherapy • 2004: Second line for patients with locally advanced or metastatic NSCLC	• 2013: cobas® EGFR Mutation Test (tissue test) (Roche Diagnostics) • 2016: cobas® EGFR Mutation Test v2 (tissue or blood test) (Roche Diagnostics) • 2017: FoundationOne CDx™ (Foundation Medicine) • 2020: FoundationOne® Liquid CDx • 2021: ONCO/Reveal Dx Lung & Colon Cancer Assay (O/RDx-LCCA)
Gefitinib (Iressa)	• 2015: First line for patients with metastatic NSCLC whose tumors have EGFR exon 19 deletions or exon 21 (L858R) substitutions • 2003: Second line for patients with locally advanced or metastatic NSCLC	• 2015: therascreen® EGFR Rotor-Gene Q polymerase chain reaction (RGQ PCR) kit

Treatment	Indication	FDA-Approved Companion Diagnostic Tests
		• 2017: Oncomine™ Dx Target Test • 2017: FoundationOne CDx™ (Foundation Medicine) • 2017: cobas® EGFR Mutation Test (tissue test) (Roche Diagnostics) • 2020: cobas® EGFR Mutation Test v2 (tissue or plasma) (Roche Diagnostics) • 2020: FoundationOne® Liquid CDx • 2021: ONCO/Reveal Dx Lung & Colon Cancer Assay (O/RDx-LCCA)
Larotrectinib (Vitrakvi)	• 2018: Adult and pediatric patients with solid tumors that ○ have a NTRK gene fusion without a known acquired resistance mutation, ○ are metastatic or where surgical resection is likely to result in severe morbidity, and ○ have no satisfactory alternative treatments or that have progressed following treatment	• 2020: FoundationOne CDx® (solid tumors, NTRK1/2/3 fusions)
Lorlatinib (Lorbrena)	• 2018: Patients with ALK-positive metastatic NSCLC whose disease has progressed on: ○ crizotinib and at least 1 other ALK inhibitor for metastatic disease; or ○ alectinib as the first ALK inhibitor therapy for metastatic disease; or ○ ceritinib as the first ALK inhibitor therapy for metastatic disease	• 2021: Ventana ALK (D5F3) CDx Assay
Mobocertinib (Exkivity)	• 2021: Adult patients with locally advanced or metastatic NSCLC with EGFR exon 20 insertion mutations, as detected by an FDA-approved test, whose disease has progressed on or after platinum-based chemotherapy	• 2021: Oncomine Dx Target Test
Nivolumab (Opdivo) in combination with Ipilimumab (Yervoy)	• 2020: ○ adult patients with metastatic NSCLC expressing PD-L1 (≥1%) as determined by an FDA-approved test, with no EGFR or ALK genomic tumor aberrations, as first-line treatment in combination with ipilimumab ○ adult patients with metastatic or recurrent NSCLC with no EGFR or ALK genomic tumor aberrations as first-line treatment, in combination with ipilimumab and 2 cycles of platinum-doublet chemotherapy ○ patients with metastatic NSCLC and progression on or after platinum-based chemotherapy. Patients with EGFR or ALK genomic tumor aberrations should have disease	• 2020: PD-L1 IHC 28-8 PharmDx

Treatment	Indication	FDA-Approved Companion Diagnostic Tests
	progression on FDA-approved therapy for these aberrations prior to receiving OPDIVO.	
Osimertinib (Tagrisso)	• 2015: Second line for patients with metastatic NSCLC whose tumors have EGFR T790M variants as detected by an FDA-approved test, who have not responded to EGFR-blocking therapy • 2018: First line for patients with metastatic NSCLC whose tumors have EGFR exon 19 deletions or exon 21 L858R variants • 2019: EGFR exon 19 deletion and EGFR exon 21 L858R alterations • 2020: adjuvant therapy after tumor resection in adult patients with NSCLC whose tumors have EGFR exon 19 deletions or exon 21 L858R mutations, as detected by an FDA-approved test	• 2015-2020: cobas® EGFR Mutation Test v2 (tissue or plasma • 2017-2019: FoundationOne CDx™ (Foundation Medicine) • 2020: Guardant360 CDx • 2020: FoundationOne® Liquid CDx
Pembrolizumab (Keytruda)	• 2018: Monotherapy for the treatment of patients with metastatic NSCLC whose tumors express PD-L1 (TPS ≥1%) as determined by an FDA-approved test, with disease progression on or after platinum-containing chemotherapy; patients with EGFR or ALK genomic tumor aberrations should have disease progression on FDA-approved therapy for these aberrations prior to receiving KEYTRUDA • 2020: For the treatment of adult and pediatric patients with unresectable or metastatic tumor mutational burden-high (TMB-H) [≥10 mutations/megabase (mut/Mb)] solid tumors, as determined by an FDA-approved test, that have progressed following prior treatment and who have no satisfactory alternative treatment options	• 2018: PD-L1 IHC 22C3 pharmDx • 2020: FoundationOne CDx (TMB)
Pralsetinib (Gavreto)	• 2020: Adult patients with metastatic RET fusion-positive NSCLC as detected by an FDA approved test	• 2020: Oncomine Dx Target Test
Selpercatinib (Retevmo)	• 2020: Adult patients with metastatic RET fusion-positive NSCLC	• 2022: Oncomine Dx Target Test
Sotorasib (Lumakras)	• 2021: Adult patients with KRAS G12C-mutated locally advanced or metastatic NSCLC, as determined by an FDA-approved test, who have received at least 1 prior systemic therapy	• 2021: Therascreen KRAS RGQ PCR kit • 2021: Guardant360 CDx
Tepotinib (Tepmetko)	• 2021: Adult patients with metastatic NSCLC harboring MET exon 14 skipping alterations.	• No approved companion diagnostic
Fam-trastuzumab deruxtecan-nxki (Enhertu)	• 2022: Adult patients with unresectable or metastatic NSCLC whose tumors have activating HER2 (ERBB2) mutations, as detected by an FDA-approved test, and who have received a prior systemic therapy	• 2022: Oncomine Dx Target Test • 2022: Guardant360 CDx

Sources: U.S. Food and Drug Administration (2022)[13]; U.S. Food and Drug Administration (n.d.)[14]
ALK: anaplastic lymphoma kinase; CDx: companion diagnostic; *EGFR*: epidermal growth factor receptor; ERBB2: erythroblastic oncogene B 2 receptor tyrosine kinase; FDA: U.S. Food and Drug Administration; FISH: fluorescence in situ hybridization; HER2: human epidermal growth factor receptor 2; MET: mesenchymal-epithelial transition; NSCLC: non-small-cell lung cancer; NTRK neurotrophic receptor tyrosine kinase; PCR: polymerase chain reaction.

Germline and Somatic Biomarker Testing (Including Liquid Biopsy) for Targeted Treatment and Immunotherapy in Breast Cancer

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 2 summarizes available targeted treatments with FDA approval for breast cancer (including immunotherapy) and the FDA cleared or approved companion diagnostic tests associated with each. 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.

Table 2. Targeted Treatments for Metastatic Breast Cancer and FDA Approved Companion Diagnostic Tests

Treatment	Class	Indications in Breast Cancer	Companion Diagnostic
Abemaciclib (Verzenio)	Cyclin-dependent kinase (CDK) 4/6 inhibitor	• In combination with endocrine therapy (tamoxifen or an aromatase inhibitor) for the adjuvant treatment of adult patients with HR-positive, HER2-negative, node-positive, early breast cancer at high risk of recurrence and a Ki-67 score ≥20% as determined by an FDA approved test. • In combination with an aromatase inhibitor as initial endocrine-based therapy for the treatment of postmenopausal women, and men, with HR-positive, HER2-negative advanced or metastatic breast cancer. • In combination with fulvestrant for the treatment of adult patients with HR-positive, HER2-negative advanced or metastatic breast cancer with disease progression following endocrine therapy. • As monotherapy for the treatment of adult patients with HR-positive, HER2-negative advanced or metastatic breast cancer with disease progression following endocrine therapy and prior chemotherapy in the metastatic setting.	Ki-67 IHC MIB-1 pharmDx (Dako Omnis)
Dostarlimab-gxly (Jemperli)	PD-1 blocking antibody	Adult patients with dMMR recurrent or advanced solid tumors, as determined by an FDA-approved test, that has progressed on or following prior treatment and who have no satisfactory alternative treatment options	VENTANA MMR RxDx Panel
Ado-trastuzumab emtansine (Kadcyla)	HER2-targeted antibody and microtubule inhibitor conjugate	As a single agent, for: • Treatment of patients with HER2-positive, metastatic breast cancer who previously received trastuzumab and a taxane, separately or in combination. Patients should have either: ○ received prior therapy for metastatic disease, or	FoundationOne CDx HER2 FISH pharmDx Kit HercepTest INFORM HER2 Dual ISH DNA Probe Cocktail PATHWAY anti-Her2/neu (4B5) Rabbit Monoclonal Primary Antibody

Treatment	Class	Indications in Breast Cancer	Companion Diagnostic
		○ developed disease recurrence during or within 6 months of completing adjuvant therapy. • Adjuvant treatment of patients with HER2-positive early breast cancer who have residual invasive disease after neoadjuvant taxane and trastuzumab-based treatment.	
Alpelisib (Piqray)	Kinase inhibitor	In combination with fulvestrant for the treatment of postmenopausal women, and men, with HR positive, HER2 -negative, PIK3CA-mutated, advanced or metastatic breast cancer as detected by an FDA approved test following progression on or after an endocrine-based regimen	FoundationOne CDx FoundationOne Liquid CDx therascreen PIK3CA RGQ PCR Kit
Entrectinib (Rozlytrek)	Kinase inhibitor	Adult and pediatric patients 12 years of age and older with solid tumors that: • have a NTRK gene fusion without a known acquired resistance mutation, • are metastatic or where surgical resection is likely to result in severe morbidity, and • have progressed following treatment or have no satisfactory alternative therapy	No FDA approved companion diagnostic test
Larotrectinib (Vitrakvi)	Kinase inhibitor	Adult and pediatric patients 12 years of age and older with solid tumors that: • have a NTRK gene fusion without a known acquired resistance mutation, • are metastatic or where surgical resection is likely to result in severe morbidity, and • have progressed following treatment or have no satisfactory alternative therapy	FoundationOne CDx
Olaparib (Lynparza)	PARP inhibitor	Adult patients with deleterious or suspected deleterious germline BRCA mutated, HER2-negative metastatic breast cancer who have been treated with chemotherapy in the neoadjuvant, adjuvant or metastatic setting. Patients with HR -positive breast cancer should have been treated with a prior endocrine therapy or be considered inappropriate for endocrine therapy. Select patients for therapy based on an FDA approved companion diagnostic for Lynparza.	BRACAnalysis CDx
Pembrolizumab (Keytruda)	PD-L1-blocking antibody	• in combination with chemotherapy, for the treatment of patients with locally recurrent unresectable or metastatic TNBC whose tumors express PD-L1 as determined by an FDA approved test	PD-L1 IHC 22C3 pharmDx
		• Adult and pediatric patients with unresectable or metastatic, microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) solid tumors that have progressed following prior treatment and who have no	No FDA approved companion diagnostic test

Treatment	Class	Indications in Breast Cancer	Companion Diagnostic
		satisfactory alternative treatment options	
		• Unresectable or metastatic tumor mutational burden-high (≥10 mutations/megabase) solid tumors, as determined by an FDA approved test, that have progressed following prior treatment and who have no satisfactory alternative treatment options.	FoundationOne CDx (Solid tumors TMB ≥ 10 mutations per megabase)
Pertuzumab (Perjeta)	HER2/neu receptor antagonist	• Use in combination with trastuzumab and docetaxel for treatment of patients with HER2-positive metastatic breast cancer who have not received prior anti-HER2 therapy or chemotherapy for metastatic disease. • Use in combination with trastuzumab and chemotherapy as ○ neoadjuvant treatment of patients with HER2-positive, locally advanced, inflammatory, or early stage breast cancer (either greater than 2 cm in diameter or node positive) as part of a complete treatment regimen for early breast cancer. ○ adjuvant treatment of patients with HER2-positive early breast cancer at high risk of recurrence	HER2 FISH pharmDx Kit HercepTest FoundationOne CDx
Talzenna (Talazoparib)	PARP inhibitor	Adult patients with deleterious or suspected deleterious germline BRCA-mutated HER2-negative locally advanced or metastatic breast cancer.	BRACAnalysis CDx
Trastuzumab (Herceptin)	HER2/neu receptor antagonist	The treatment of HER2-overexpressing breast cancer	Bond Oracle HER2 IHC System FoundationOne CDx HER2 CISH pharmDx Kit HER2 FISH pharmDx Kit HercepTest INFORM HER-2/neu INFORM HER2 Dual ISH DNA Probe Cocktail InSite Her-2/neu KIT PathVysion HER-2 DNA Probe Kit PATHWAY anti-Her2/neu (4B5) Rabbit Monoclonal Primary Antibody SPOT-LIGHT HER2 CISH Kit VENTANA HER2 Dual ISH DNA Probe Cocktail

dMMR: mismatch repair deficient; FDA: U.S. Food & Drug Administration; HER2: human epidermal growth factor receptor 2; HR: hormone receptor; MSI-H: microsatellite instability-high; NTRK: neurotrophic-tropomyosin receptor kinase; PD-1: programmed death receptor-1; D-L1: programmed death-ligand 1 ; PIK3CA: phosphatidylinositol 3-kinase catalytic alpha polypeptide; TNBC: triple-negative breast cancer
Sources: [17,18,]

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.

Germline and Somatic Biomarker Testing (Including Liquid Biopsy) for Targeted Treatment and Immunotherapy in Prostate Cancer (BRCA1/2, Homologous Recombination Repair Gene Alterations, Microsatellite Instability/Mismatch Repair, Tumor Mutational Burden)

Table 3 summarizes the targeted treatments approved by the FDA for patients with prostate cancer, along with the approved companion diagnostic tests. The information in Table 3 was current as of August 15, 2022. 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.

Table 3. Targeted Treatments for Metastatic Prostate Cancer and FDA Approved Companion Diagnostic Tests

Treatment	Indication in Prostate Cancer	Companion Diagnostic	Biomarkers
Targeted Treatment for Prostate Cancer			
Olaparib (Lynparza)	Adult patients with deleterious or suspected deleterious germline or somatic homologous recombination repair (HRR) gene-mutated metastatic castration-resistant prostate cancer (mCRPC) who have progressed following prior treatment with enzalutamide or abiraterone. Select patients for therapy based on an FDA-approved companion diagnostic for Lynparza.	BRACAnalysis CDx (Myriad Genetic Laboratories, Inc.)	*BRCA1* and *BRCA2* Mutations
		FoundationOne CDx (Foundation Medicine, Inc.)	Homologous recombination repair (HRR) genes: *BRCA1*, *BRCA2*, *ATM*, *BARD1*, *BRIP1*, *CDK12*, *CHEK1*,*CHEK2*, *FANCL*, *PALB2*, *RAD51B*, *RAD51C*,*RAD51D*, and *RAD54L* alterations
		FoundationOne Liquid CDx (Foundation Medicine, Inc.)	*BRCA1*, *BRCA2*, and *ATM* alterations
Rucaparib (Rubraca)	Adult patients with a deleterious BRCA mutation (germline and/or somatic)-associated metastatic castration-resistant prostate cancer (mCRPC) who have been treated with androgen receptor-directed therapy and a taxane-based chemotherapy. Select patients for therapy based on an FDA-approved companion diagnostic for Rubraca.	FoundationOne Liquid CDx (Foundation Medicine, Inc.)	*BRCA1* and *BRCA2* alterations
Immunotherapy for Solid Tumors			
Pembrolizumab(Keytruda)	Adult and pediatric patients with unresectable or metastatic microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) solid tumors, as determined by an FDA-approved test, that have progressed following prior treatment and who have no	FoundationOne CDx (Foundation Medicine, Inc.)	Microsatellite instability-High (MSI-H)

Treatment	Indication in Prostate Cancer	Companion Diagnostic	Biomarkers
	satisfactory alternative treatment options		
	Adult and pediatric patients with unresectable or metastatic tumor mutational burden-high (≥10 mutations/megabase) solid tumors, as determined by an FDA-approved test, that have progressed following prior treatment and who have no satisfactory alternative treatment options	FoundationOne CDx (Foundation Medicine, Inc.)	TMB ≥ 10 mutations per megabase

Sources: Food and Drug Administration (2022);[6] Drugs@FDA[7]

Laboratory-Developed Tests

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 (CLIA). Laboratories that offer laboratory-developed tests must be licensed under CLIA for high-complexity testing. To date, the FDA has chosen not to require any regulatory review of this test.

Germline and Somatic Biomarker Testing (Including Liquid Biopsy) for Targeted Treatment and Immunotherapy in Ovarian Cancer (BRCA1, BRCA2, Homologous Recombination Deficiency, Tumor Mutational Burden, Microsatellite Instability/Mismatch Repair)

Table 4 summarizes the targeted treatments approved by the FDA for patients with ovarian cancer, along with the approved companion diagnostic tests. The information in Table 4 was current as of August 27, 2022. 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.

The table does not include NTRK testing.

Several companion diagnostic tests for rucaparib in ovarian cancer have been FDA approved. However, as of June 2022, BRCA testing is no longer required for this indication.[4]

Table 4. Targeted Treatments for Ovarian Cancer and FDA-Approved Companion Diagnostic Tests

Treatment	Indication in Ovarian Cancer	Companion Diagnostic	Biomarkers
Targeted Treatment for Ovarian Cancer			
Niraparib (Zejula)	Maintenance treatment of adult patients with deleterious or suspected deleterious germline or somatic BRCA-mutated advanced epithelial ovarian, fallopian tube or primary peritoneal cancer who are in complete or partial response to first-line platinum-based chemotherapy. Maintenance treatment of adult patients with recurrent epithelial ovarian, fallopian tube or primary peritoneal cancer who are in complete or partial response to first-line platinum-based chemotherapy. Treatment of	Myriad myChoice CDx (Myriad Genetic Laboratories, Inc.)	*BRCA1* and *BRCA2* genes and/or positive Genomic Instability Score

Treatment	Indication in Ovarian Cancer	Companion Diagnostic	Biomarkers
	advanced ovarian, fallopian tube, or primary peritoneal cancer who have been treated with 3 or more prior chemotherapy regimens and whose cancer is associated with homologous reproductive recombination deficiency (HRD) positive status defined by either: a deleterious or suspected deleterious BRCA mutation, or • genomic instability and who have progressed more than 6 months after response to the last platinum-based chemotherapy		
Olaparib (Lynparza®)	Maintenance treatment of adult patients with deleterious or suspected deleterious germline or somatic *BRCA*-mutated advanced epithelial ovarian, fallopian tube or primary peritoneal cancer who are in complete or partial response to first-line platinum-based chemotherapy. In combination with bevacizumab for the maintenance treatment of adult patients with advanced epithelial ovarian, fallopian tube or primary peritoneal cancer who are in complete or partial response to first-line platinum-based chemotherapy and whose cancer is associated with HRD-positive status defined by either: • a deleterious or suspected deleterious BRCA mutation, and/or • genomic instability	BRACAnalysis CDx® (Myriad Genetic Laboratories, Inc.)	*BRCA1* and *BRCA2* mutations
		FoundationOne CDx (Foundation Medicine, Inc.)	*BRCA1* and *BRCA2* alterations
		Myriad myChoice CDx (Myriad Genetic Laboratories, Inc)	*BRCA1* and *BRCA2* mutations and/or positive Genomic Instability Score
Rucaparib (Rubraca®)[1]	Maintenance treatment of adult patients with recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in a complete or partial response to platinum-based chemotherapy.	BRACAnalysis CDx (Myriad Genetic Laboratories, Inc.)	*BRCA1* and *BRCA2* mutations
		FoundationFocus CDxBRCA Assay (Foundation Medicine, Inc.)	*BRCA1* and *BRCA2* alterations
		FoundationOne CDx (Foundation Medicine, Inc.)	*BRCA1* and *BRCA2* alterations
		FoundationOne Liquid CDx (Foundation Medicine, Inc.)	*BRCA1* and *BRCA2* alterations
Immunotherapy for Solid Tumors			
Pembrolizumab (Keytruda®)	Adult and pediatric patients with unresectable or metastatic microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) solid tumors, as determined by an FDA-approved test, that have progressed following prior treatment and who have no satisfactory alternative treatment options	FoundationOne CDx (Foundation Medicine, Inc.)	Microsatellite instability-High (MSI-H)

Treatment	Indication in Ovarian Cancer	Companion Diagnostic	Biomarkers
	Adult and pediatric patients with unresectable or metastatic tumor mutational burden-high (≥10 mutations/megabase) solid tumors, as determined by an FDA-approved test, that have progressed following prior treatment and who have no satisfactory alternative treatment options	FoundationOne CDx (Foundation Medicine, Inc.)	TMB ≥ 10 mutations per megabase

[1] As of June 2022, *BRCA* testing is not required for rucaparib treatment in ovarian cancer.
Sources: Food and Drug Administration (2022)[5]; Drugs@FDA[6]

Laboratory-Developed Tests
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 (CLIA). Laboratories that offer laboratory-developed tests must be licensed under CLIA for high-complexity testing. To date, the FDA has chosen not to require any regulatory review of this test.

State:
Starting on July 1, 2022 (per CA law SB 535) for commercial plans regulated by the California Department of Managed Healthcare and California Department of Insurance (PPO and HMO), health care service plans and insurers shall not require prior authorization for biomarker testing, including biomarker testing for cancer progression and recurrence, if a member has stage 3 or 4 cancer. Health care service plans and insurers can still do a medical necessity review of a biomarker test and possibly deny coverage after biomarker testing has been completed and a claim is submitted (post service review).

Rationale

Comprehensive Molecular Profiling Panel Tests via Circulating Tumor DNA (ctDNA)
National Comprehensive Cancer Network (NCCN)
NCCN Prostate Cancer guidelines (1.2023) strongly advocates evaluating tumor for alterations in homologous recombination DNA repair genes in individuals with metastatic prostate cancer and states that ctDNA assay is an option when biopsy for histologic and molecular evaluation is not possible (p. PROS-C 3 of 3).

NCCN Gastric Cancer guidelines (2.2022) recognize the use of liquid biopsy in patients with advanced disease who are unable to have a clinical biopsy for disease surveillance or management, and that the DNA shed from gastric carcinomas can identify targetable alterations or the evolution of clone with altered treatment response profiles. NCCN also cautions the interpretation of negative results, as it does not exclude the presence of tumor mutation or amplifications that are clinically relevant (p. GAST-B 5 of 6)

NCCN Pancreatic Adenocarcinoma guidelines (1.2022) state that while testing of tumor tissue is preferred, cell-free DNA testing can be considered if tumor tissue testing is not feasible. This testing should be performed for patients with locally advanced or metastatic disease who are candidates for anti-cancer therapy (p. PANC-1A).

NCCN Esophageal and Esophagogastric Junction Cancers guidelines (5.2022) recognize the use of liquid biopsy in patients with advanced disease who are unable to have a clinical biopsy for disease surveillance or management, and that the DNA shed from esophageal and EGJ carcinomas can identify targetable alterations or the evolution of clone with altered treatment response profiles.

NCCN also cautions the interpretation of negative results, as it does not exclude the presence of tumor mutation or amplifications that are clinically relevant (p. ESOPH-B 5 of 6).

NCCN Colon Cancer guidelines (2.2022) state that *RAS and BRAF mutation analysis* and HER2 amplification can be tested by individual genes or as part of a next generation sequencing panel, and either by tissue or blood-based assay (p. COL-4)

NCCN Non-Small Cell Lung Cancer guidelines (6.2022) support the use of cell-free circulating tumor DNA (ctDNA) testing if a patient is either not medically fit for invasive tissue sampling, or if there is insufficient tissue for molecular analysis, or if the available tissue is unable to undergo all recommended genetic testing due to tissue sufficiency or available testing methodologies. If ctDNA testing is negative, there should be follow-up with tissue-based analysis. NCCN recognizes that studies have shown generally high sensitivity, but a significantly compromised sensitivity with up to 30% false-negative rate and does not support the use of ctDNA testing in lieu of a histologic tissue diagnosis, if it is possible and feasible (p. NSCL-H 7 of 7).

Lung Cancer Focused Panel Tests via Circulating Tumor DNA (ctDNA)
National Comprehensive Cancer Network (NCCN)
The NCCN non-small cell lung cancer guidelines (6.2022) recommend biomarker testing for *EGFR* mutations (among others) for patients with advanced or metastatic disease of the following lung cancer pathologies: adenocarcinoma, large cell, squamous cell carcinoma, and non-small cell lung cancer not others specified. (page NSCL-18)

NCCN Non-Small Cell Lung Cancer guidelines (6.2022) support the use of cell-free circulating tumor DNA (ctDNA) testing if a patient is either not medically fit for invasive tissue sampling, if the tissue available is not able to undergo testing for all recommended biomarkers due to tissue quantity or available testing technologies, or if there is insufficient tissue for molecular analysis. If ctDNA testing is negative, there should be follow-up with tissue-based analysis. NCCN recognizes that studies have shown generally high sensitivity, but a significantly compromised sensitivity with up to 30% false-negative rate and does not support the use of ctDNA testing in lieu of a histologic tissue diagnosis, if it is possible and feasible (p. NSCL-H 7 of 7).

Colorectal Cancer Focused Panel Tests via Circulating Tumor DNA (ctDNA)
National Comprehensive Cancer Network (NCCN)
NCCN Colon Cancer guidelines (2.2022) state that for patients with metastatic colorectal adenocarcinoma tumor testing should be done for *RAS* (*KRAS* and *NRAS*) and *BRAF* mutations. This testing can be done as part of a panel or individually, and can be done on FFPE tissue or blood-based testing (p. COL-B 4 of 8)

Melanoma Focused Panel Tests via Circulating Tumor DNA (ctDNA)
National Comprehensive Cancer Network (NCCN)
NCCN Cutaneous Melanoma guidelines (3.2022) state that molecular testing on biopsied tissue is preferred, but can be performed on peripheral blood if tumor issue is unavailable (p. ME-C 3 of 8).

EGFR Variant Analysis via Circulating Tumor DNA (ctDNA)
National Comprehensive Cancer Network (NCCN)
The NCCN non-small cell lung cancer guidelines (6.2022) recommend biomarker testing for *EGFR* mutations (among others) for patients with advanced or metastatic disease of the following lung cancer pathologies: adenocarcinoma, large cell, squamous cell carcinoma, and non-small cell lung cancer not others specified. (page NSCL-18)

The NCCN non-small cell lung cancer guidelines (6.2022) state that the use of cfDNA tumor testing "can be considered" in specific clinical situations including: a patient is not medically fit for invasive tissue sampling, if there is not sufficient tumor material for molecular analysis and an oncogenic

driver mutation has not previously been identified, and/or if tissue-based testing is performed but did not completely assess all recommended biomarkers due to tissue quantity and/or availability of testing methodologies. (page NSCL-H 7 of 7)

College of American Pathologists, International Association for the Study of Lung Cancer, and Association for Molecular Pathology
The College of American Pathologists, the International Association for the Study of Lung Cancer, and the Association for Molecular Pathology (2018) published a guideline on molecular testing for the selection of lung cancer patients for treatment with targeted tyrosine kinase inhibitors and noted the following recommendations regarding liquid biopsy for activating *EGFR* mutations and a consensus opinion regarding liquid biopsy for the T790M resistance mutation:

- Recommendation: "In some clinical settings in which tissue is limited and/or insufficient for molecular testing, physicians may use a cfDNA assay to identify [activating] *EGFR* mutations." (Page 337)
- Expert Consensus Opinion: "Physicians may use plasma cfDNA methods to identify *EGFR* T790M mutations in lung adenocarcinoma patients with progression or secondary clinical resistance to *EGFR* targeted TKIs; testing of the tumor sample is recommended if the plasma result is negative." (Page 337)
- No recommendation: "There is currently insufficient evidence to support the use of circulating tumor cell molecular analysis for the diagnosis of primary lung adenocarcinoma, the identification of *EGFR* or other mutations, or the identification of *EGFR* T790M mutations at the time of *EGFR* TKI resistance." (Page 326)

US Food and Drug Administration (FDA)
"On June 1, 2016, the U. S. Food and Drug Administration approved cobas *EGFR* Mutation Test v2 (Roche Molecular Systems, Inc.) using plasma specimens as a companion diagnostic test for the detection of exon 19 deletions or exon 21 (L858R) substitution mutations in the epidermal growth factor receptor (*EGFR*) gene to identify patients with metastatic non-small cell lung cancer (NSCLC) eligible for treatment with Tarceva® (erlotinib). The cobas *EGFR* Mutation Test v2 is already approved for this indication using formalin-fixed paraffin-embedded (FFPE) tissue specimens. The new use is for detection of these specific mutations in circulating-free tumor DNA (cfDNA) isolated from plasma specimens, also called liquid biopsy specimens, to aid physicians in identifying patients who may be treated first with TARCEVA (erlotinib). This is the first "liquid biopsy test" approved for use by FDA. This new test may benefit patients who may be too ill or are otherwise unable to provide a tumor specimen for *EGFR* testing. Patients positive by cobas *EGFR* Mutation Test v2 using plasma specimens for the presence of *EGFR* exon 19 deletions or L858R mutations are candidates for treatment with Tarceva (erlotinib). Patients who are negative by this test should undergo routine biopsy and testing for *EGFR* mutations with the FFPE tissue sample type." (First paragraph of statement)

BRAF Variant Analysis via Circulating Tumor DNA (ctDNA)
National Comprehensive Cancer Network (NCCN)
NCCN Colon Cancer guidelines (2.2022) state that all patients with metastatic colorectal cancer should have tumor genotyped for KRAS, NRAS, and BRAF mutations. This analysis can be done either individually or as part of an NGS panel. Additionally, it is noted that molecular testing can be performed on tissue as a preferred specimen type, or blood-based assay. Finally, KRAS, NRAS and BRAF mutation analysis can be performed on either primary colorectal tumors or on metastases (p. COL-B 4 of 8).

NCCN cutaneous melanoma guidelines (3.2022) state that for patients with cutaneous melanoma of at least stage III or higher and who are being considered for adjuvant therapy or clinical trial, BRAF mutation testing is a part of the recommended workup (p. ME-4, ME-4A, ME-5A). Additionally, these guidelines state that molecular testing on tumor tissue is preferred, but may be performed on peripheral blood (liquid biopsy) if tumor tissue is not available (p. ME-C 3 of 8).

NCCN pancreatic adenocarcinoma guidelines (1.2022) state that tumor molecular profiling is recommended for patients with advanced or metastatic disease who are candidates for anti-cancer therapy. They suggest including the following genes that have known mutations that have actionable findings: BRAF, BRCA1/2, KRAS, PALB2. They indicate that tumor tissue is the preferred specimen for this testing, but cell-free DNA can be considered if testing on tissue is not feasible (p. PANC-1A).

NCCN non-small cell lung cancer guidelines (6.2022) strongly advises broad molecular profiling for advanced or metastatic disease (p. NSCL-18). They define broad molecular profiling as molecular testing for their recommended biomarkers (EGFR, KRAS, ALK rearrangements, ROS1 rearrangements, NTRK1/2/3 gene fusions, BRAF V600E, METex14 skipping, RET rearrangements, ERBB2/HER2, and PDL-1) as well as emerging biomarkers, either in a single assay or a limited number of assays (p. NSCL-18, NSCL-19). NCCN also states that in situations where tissue is minimal, peripheral blood (plasma circulating tumor DNA) can be a surrogate sample for tumor tissue (p. NSCL-H 1 of 7).

KRAS Variant Analysis via Circulating Tumor DNA (ctDNA)

National Comprehensive Cancer Network (NCCN)
NCCN Colon Cancer guidelines (2.2022) state that all patients with metastatic colorectal cancer should have tumor genotyped for KRAS, NRAS, and BRAF mutations. This analysis can be done either individually or as part of an NGS panel. Additionally, it is noted that molecular testing can be performed on tissue as a preferred specimen type, or blood-based assay. Finally, KRAS, NRAS and BRAF mutation analysis can be performed on either primary colorectal tumors or on metastases (p. COL-B 4 of 8).

NCCN pancreatic adenocarcinoma guidelines (1.2022) state that tumor molecular profiling is recommended for patients with advanced or metastatic disease who are candidates for anti-cancer therapy. They suggest including the following genes that have known mutations that have actionable findings: BRAF, BRCA1/2, KRAS, PALB2. They indicate that tumor tissue is the preferred specimen for this testing, but cell-free DNA can be considered if testing on tissue is not feasible (p. PANC-1A).

NCCN non-small cell lung cancer guidelines (6.2022) strongly advise broad molecular profiling for advanced or metastatic disease (p. NSCL-18). They define broad molecular profiling as molecular testing for their recommended biomarkers (EGFR, KRAS, ALK rearrangements, ROS1 rearrangements, NTRK1/2/3 gene fusions, BRAF V600E, METex14 skipping, RET rearrangements, ERBB2/HER2, and PDL-1) as well as emerging biomarkers, either in a single assay or a limited number of assays (p. NSCL-18, NSCL-19). NCCN also states that in situations where tissue is minimal, peripheral blood (plasma circulating tumor DNA) can be a surrogate sample for tumor tissue (p. NSCL-H 1 of 7).

PIK3CA Variant Analysis via Circulating Tumor DNA (ctDNA)

National Comprehensive Cancer Network (NCCN)
NCCN Breast Cancer guidelines (4.2022) states that, for patients with hormone receptor positive/HER2 negative breast cancer, *PIK3CA* mutation testing can be done on tumor tissue or ctDNA in peripheral blood (liquid biopsy) and if liquid biopsy is negative, tumor tissue testing is recommended (p. BINV-R 1 of 3).

AR-V7 Androgen Receptor Splice Variant Analysis in Circulating Tumor Cells (CTCs)

National Comprehensive Cancer Network (NCCN)
NCCN Prostate Cancer guidelines (1.2023) suggest the consideration of *AR-V7* tests to help guide selection of therapy for patients with disease progression in the post-abiraterone/enzalutamide metastatic castration resistant prostate cancer setting (p. PROS-15A).

Circulating Tumor Cells (CTC) Enumeration Analysis
National Comprehensive Cancer Network (NCCN)
NCCN Breast Cancer guidelines (4.2022) recognize that patients with metastatic breast cancer and persistently increased CTC after 3 weeks of first-line chemotherapy have a poor PFS and OS; however, while CTC count has prognostic ability, it has failed to show a predictive value at this time (p. MS-75).

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11. Cobas EGFR Mutation Test v2. U.S. Food & Drug Administration website. Published June 2, 2016. Accessed July 1, 2021. Available at: https://www.fda.gov/drugs/resources-information-approved-drugs/cobas-egfr-mutation-test-v2

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)
  - Type and stage of cancer
  - Comorbidities, activity and functional limitations or other reasons for being medically unfit for invasive tissue sampling (biopsy) if applicable

  - Documentation of a lack of tissue to complete the molecular analysis if applicable
  - Family history, if applicable
  - Reason for procedure/test/device, when applicable
  - Pertinent past procedural and surgical history
  - Pertinent past and present diagnostic testing and results
  - Pertinent prior conservative treatments, duration, and response
  - Evidence of medication resistance or cancer progression if applicable
  - Treatment plan (i.e., surgical intervention, change of medical management)
- Consultation(s) when applicable
- Radiology report(s) and interpretation (i.e., MRI, CT, bone scan)
- Laboratory results including prior genetic testing

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

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

Coding

This Policy relates only to the services or supplies described herein. Benefits may vary according to product design; therefore, contract language should be reviewed before applying the terms of the Policy.

The following codes are included below for informational purposes. Inclusion or exclusion of a code(s) does not constitute or imply member coverage or provider reimbursement policy. Policy Statements are intended to provide member coverage information and may include the use of some codes for clarity. The Policy Guidelines section may also provide additional information for how to interpret the Policy Statements and to provide coding guidance in some cases.

Type	Code	Description
CPT®	81174	AR (androgen receptor) (e.g., spinal and bulbar muscular atrophy, Kennedy disease, X chromosome inactivation) gene analysis; known familial variant
	81210	BRAF (B-Raf proto-oncogene, serine/threonine kinase) (e.g., colon cancer, melanoma), gene analysis, V600 variant(s)
	81235	EGFR (epidermal growth factor receptor) (e.g., non-small cell lung cancer) gene analysis, common variants (e.g., exon 19 LREA deletion, L858R, T790M, G719A, G719S, L861Q)
	81275	KRAS (Kirsten rat sarcoma viral oncogene homolog) (e.g., carcinoma) gene analysis; variants in exon 2 (e.g., codons 12 and 13)
	81276	KRAS (Kirsten rat sarcoma viral oncogene homolog) (e.g., carcinoma) gene analysis; additional variant(s) (e.g., codon 61, codon 146)
	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)
	81311	NRAS (neuroblastoma RAS viral [v-ras] oncogene homolog) (e.g., colorectal carcinoma), gene analysis, variants in exon 2 (e.g., codons 12 and 13) and exon 3 (e.g., codon 61)
	81403	Molecular pathology procedure, Level 4 (e.g., analysis of single exon by DNA sequence analysis, analysis of >10 amplicons using multiplex PCR in 2 or more independent reactions, mutation scanning or duplication/deletion variants of 2-5 exons)

Type	Code	Description
	81445	Targeted genomic sequence analysis panel, solid organ neoplasm, 5-50 genes (e.g., ALK, BRAF, CDKN2A, EGFR, ERBB2, KIT, KRAS, MET, NRAS, PDGFRA, PDGFRB, PGR, PIK3CA, PTEN, RET), interrogation for sequence variants and copy number variants or rearrangements, if performed; DNA analysis or combined DNA and RNA analysis
	81455	Targeted genomic sequence analysis panel, solid organ or hematolymphoid neoplasm or disorder, 51 or greater genes (e.g., ALK, BRAF, CDKN2A, CEBPA, DNMT3A, EGFR, ERBB2, EZH2, FLT3, IDH1, IDH2, JAK2, KIT, KRAS, MET, MLL, NOTCH1, NPM1, NRAS, PDGFRA, PDGFRB, PGR, PIK3CA, PTEN, RET), 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
	81462	Solid organ neoplasm, genomic sequence analysis panel, cell-free nucleic acid (e.g., plasma), interrogation for sequence variants; DNA analysis or combined DNA and RNA analysis, copy number variants and rearrangements ***(Code effective 1/1/2024)***
	81463	Solid organ neoplasm, genomic sequence analysis panel, cell-free nucleic acid (e.g., plasma), interrogation for sequence variants; DNA analysis, copy number variants, and microsatellite instability ***(Code effective 1/1/2024)***
	81464	Solid organ neoplasm, genomic sequence analysis panel, cell-free nucleic acid (e.g., plasma), interrogation for sequence variants; DNA analysis or combined DNA and RNA analysis, copy number variants, microsatellite instability, tumor mutation burden, and rearrangements ***(Code effective 1/1/2024)***
	81479	Unlisted molecular pathology procedure
	86152	Cell enumeration using immunologic selection and identification in fluid specimen (e.g., circulating tumor cells in blood);
	86153	Cell enumeration using immunologic selection and identification in fluid specimen (e.g., circulating tumor cells in blood); physician interpretation and report, when required
	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
	0179U	Oncology (non-small cell lung cancer), cell-free DNA, targeted sequence analysis of 23 genes (single nucleotide variations, insertions and deletions, fusions without prior knowledge of partner/breakpoint, copy number variations), with report of significant mutation(s)
	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
	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
	0326U	Targeted genomic sequence analysis panel, solid organ neoplasm, cell-free circulating DNA analysis of 83 or more genes, interrogation for sequence variants, gene copy number amplifications, gene rearrangements, microsatellite instability and tumor mutational burden

Type	Code	Description
	0356U	Oncology (oropharyngeal or anal), evaluation of 17 DNA biomarkers using droplet digital PCR (ddPCR), cell-free DNA, algorithm reported as a prognostic risk score for cancer recurrence ***(Code revision effective 1/1/2024)***
	0388U	Oncology (non-small cell lung cancer), next-generation sequencing with identification of single nucleotide variants, copy number variants, insertions and deletions, and structural variants in 37 cancer-related genes, plasma, with report for alteration detection ***(Code effective 7/1/2023)***
	0397U	Oncology (non-small cell lung cancer), cell-free DNA from plasma, targeted sequence analysis of at least 109 genes, including sequence variants, substitutions, insertions, deletions, select rearrangements, and copy number variations ***(Deleted code effective 10/1/2023)***
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
06/01/2023	New policy (combined policies 2.04.141 and 2.04.45).
07/01/2023	Administrative update. Coding update.
11/01/2023	Administrative update. Coding update.
03/01/2024	Coding update.

Definitions of Decision Determinations

Medically Necessary: Services that are Medically Necessary include only those which have been established as safe and effective, are furnished under generally accepted professional standards to treat illness, injury or medical condition, and which, as determined by Blue Shield, are: (a) consistent with Blue Shield medical policy; (b) consistent with the symptoms or diagnosis; (c) not furnished primarily for the convenience of the patient, the attending Physician or other provider; (d) furnished at the most appropriate level which can be provided safely and effectively to the patient; and (e) not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of the Member's illness, injury, or disease.

Investigational/Experimental: A treatment, procedure, or drug is investigational when it has not been recognized as safe and effective for use in treating the particular condition in accordance with generally accepted professional medical standards. This includes services where approval by the federal or state governmental is required prior to use, but has not yet been granted.

Split Evaluation: Blue Shield of California/Blue Shield of California Life & Health Insurance Company (Blue Shield) policy review can result in a split evaluation, where a treatment, procedure, or drug will be considered to be investigational for certain indications or conditions, but will be deemed safe and effective for other indications or conditions, and therefore potentially medically necessary in those instances.

Prior Authorization Requirements and Feedback (as applicable to your plan)

Within five days before the actual date of service, the provider must confirm with Blue Shield that the member's health plan coverage is still in effect. Blue Shield reserves the right to revoke an authorization prior to services being rendered based on cancellation of the member's eligibility. Final determination of benefits will be made after review of the claim for limitations or exclusions.

Questions regarding the applicability of this policy should be directed to the Prior Authorization Department at (800) 541-6652, or the Transplant Case Management Department at (800) 637-2066 ext. 3507708 or visit the provider portal at www.blueshieldca.com/provider.

We are 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 or 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.

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

Disclaimer: This medical policy is a guide in evaluating the medical necessity of a particular service or treatment. Blue Shield of California 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 contract language, including definitions and specific contract provisions/exclusions, take precedence over medical policy and must be considered first in determining covered services. Member contracts may differ in their benefits. Blue Shield reserves the right to review and update policies as appropriate.

Appendix A

POLICY STATEMENT	
BEFORE Red font: Verbiage removed	**AFTER** Blue font: Verbiage Changes/Additions
Oncology: Circulating Tumor DNA and Circulating Tumor Cells (Liquid Biopsy) BSC_CON_2.10 **Policy Statement:** **Note:** Starting on July 1, 2022 (per CA law SB 535) for commercial plans regulated by the California Department of Managed Healthcare and California Department of Insurance (PPO and HMO), health care service plans and insurers shall not require prior authorization for biomarker testing, including biomarker testing for cancer progression and recurrence, if a member has stage 3 or 4 cancer. Health care service plans and insurers can still do a medical necessity review of a biomarker test and possibly deny coverage after biomarker testing has been completed and a claim is submitted (post service review). ***(moved to Regulatory Status section)*** I. Comprehensive or focused molecular profiling panel tests via circulating tumor DNA (liquid biopsy) (0239U, 0242U, 0326U, 81445) are considered **medically necessary** at diagnosis progression or recurrence when **BOTH** of the following criteria are met: A. The member has a diagnosis of **ONE** of the following: 1. Non-small cell lung cancer (e.g., adenocarcinoma, large cell carcinoma, squamous cell carcinoma, not otherwise specified) must include EGFR 2. Locally advanced/metastatic pancreatic adenocarcinoma 3. Gastric cancer 4. Esophageal or esophagogastric junction cancer 5. Metastatic prostate cancer (must include *BRCA1*, *BRCA2*, *ATM*, *BARD1*, *BRIP1*, *CDK12*, *CHEK1*, *CHEK2*, *FANCL*, *PALB2*, *RAD51B*, *RAD51C*, *RAD51D*, and *RAD54L*; 0239U meets, 0242U and 0326U do not meet) 6. Metastatic colorectal cancer (must include *KRAS, NRAS* and *BRAF)* 7. Advanced or metastatic breast cancer when *PIK3CA* and *ESR1* is included in the panel for hormone receptor-positive, *HER2* negative individuals	**Oncology: Circulating Tumor DNA and Circulating Tumor Cells (Liquid Biopsy) BSC_CON_2.10** **Policy Statement:** I. Comprehensive or focused molecular profiling panel tests via circulating tumor DNA (liquid biopsy) (0239U, 0242U, 0326U, 81445) may be considered **medically necessary** at diagnosis progression or recurrence when **BOTH** of the following criteria are met: A. The member has a diagnosis of **ONE** of the following: 1. Non-small cell lung cancer (e.g., adenocarcinoma, large cell carcinoma, squamous cell carcinoma, not otherwise specified) must include EGFR 2. Locally advanced/metastatic pancreatic adenocarcinoma 3. Gastric cancer 4. Esophageal or esophagogastric junction cancer 5. Metastatic prostate cancer (must include *BRCA1*, *BRCA2*, *ATM*, *BARD1*, *BRIP1*, *CDK12*, *CHEK1*, *CHEK2*, *FANCL*, *PALB2*, *RAD51B*, *RAD51C*, *RAD51D*, and *RAD54L*; 0239U meets, 0242U and 0326U do not meet) 6. Metastatic colorectal cancer (must include *KRAS, NRAS* and *BRAF)* 7. Advanced or metastatic breast cancer when *PIK3CA* and *ESR1* is included in the panel for hormone receptor-positive, *HER2* negative individuals

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B. At least **ONE** of the following: 1. The member is medically unfit for invasive tissue sampling (biopsy) 2. Biopsy was performed but material was insufficient for complete molecular analysis	B. At least **ONE** of the following: 1. The member is medically unfit for invasive tissue sampling (biopsy) 2. Biopsy was performed but material was insufficient for complete molecular analysis
II. Comprehensive or focused molecular profiling panel tests via circulating tumor DNA (liquid biopsy) (0239U, 0242U, 0326U, 81445) are considered **investigational** for all other indications.	II. Comprehensive or focused molecular profiling panel tests via circulating tumor DNA (liquid biopsy) (0239U, 0242U, 0326U, 81445) are considered **investigational** for all other indications.
III. Comprehensive or focused molecular profiling panel tests via circulating tumor DNA (liquid biopsy) (0239U, 0242U, 0326U, 81445) performed simultaneously with solid tumor tissue testing is considered **investigational**.	III. Comprehensive or focused molecular profiling panel tests via circulating tumor DNA (liquid biopsy) (0239U, 0242U, 0326U, 81445) performed simultaneously with solid tumor tissue testing is considered **investigational**.
IV. *AR-V7* androgen receptor splice variant analysis (81479) in circulating tumor cells (CTCs) is considered **medically necessary** when **BOTH** of the following criteria are met: A. The member has metastatic castration-resistant prostate cancer (M1 CRPC) B. The member has had a progression after first-line treatment with enzalutamide (Xtandi®) or abiraterone (Zytiga®).	IV. *AR-V7* androgen receptor splice variant analysis (81479) in circulating tumor cells (CTCs) may be considered **medically necessary** when **BOTH** of the following criteria are met: A. The member has metastatic castration-resistant prostate cancer (M1 CRPC) B. The member has had a progression after first-line treatment with enzalutamide (Xtandi®) or abiraterone (Zytiga®).
V. *AR-V7* androgen receptor splice variant analysis (81479) in circulating tumor cells (CTCs) is considered **investigational** for all other indications.	V. *AR-V7* androgen receptor splice variant analysis (81479) in circulating tumor cells (CTCs) is considered **investigational** for all other indications.
VI. Circulating tumor cell (CTC) enumeration (86152, 86153) is considered **investigational**.	VI. Circulating tumor cell (CTC) enumeration (86152, 86153) is considered **investigational**.