# Medical Coverage Policy

**Effective Date.....11/1/2024**
**Next Review Date.....5/15/2025**
**Coverage Policy Number..... 0520**

# Molecular and Proteomic Diagnostic Testing for Hematology and Oncology Indications

## Table of Contents


Overview ..... 2
Coverage Policy..... 2
Health Equity Considerations..... 7
General Background ..... 7
Medicare Coverage Determinations ..... 17
Appendix A..... 17
Coding Information..... 19
References ..... 28
Revision Details ..... 41


## Related Coverage Resources

Genetics
Lab Management Guidelines

***INSTRUCTIONS FOR USE***

*The following Coverage Policy applies to health benefit plans administered by Cigna Companies. Certain Cigna Companies and/or lines of business only provide utilization review services to clients and do not make coverage determinations. References to standard benefit plan language and coverage determinations do not apply to those clients. Coverage Policies are intended to provide guidance in interpreting certain standard benefit plans administered by Cigna Companies. Please note, the terms of a customer's particular benefit plan document [Group Service Agreement, Evidence of Coverage, Certificate of Coverage, Summary Plan Description (SPD) or similar plan document] may differ significantly from the standard benefit plans upon which these Coverage Policies are based. For example, a customer's benefit plan document may contain a specific exclusion related to a topic addressed in a Coverage Policy. In the event of a conflict, a customer's benefit plan document always supersedes the information in the Coverage Policies. In the absence of a controlling federal or state coverage mandate, benefits are ultimately determined by the terms of the applicable benefit plan document. Coverage determinations in each specific instance require consideration of 1) the terms of the applicable benefit plan document in effect on the date of service; 2) any applicable laws/regulations; 3) any relevant collateral source materials including Coverage Policies and; 4) the specific facts of the particular situation. Each coverage request should be reviewed on its own merits. Medical directors are expected to exercise clinical judgment where appropriate and have discretion in making individual coverage determinations. Where coverage for care or services does not depend on specific circumstances, reimbursement will only be provided if a requested service(s) is submitted in accordance with the relevant criteria outlined*

*in the applicable Coverage Policy, including covered diagnosis and/or procedure code(s). Reimbursement is not allowed for services when billed for conditions or diagnoses that are not covered under this Coverage Policy (see "Coding Information" below). When billing, providers must use the most appropriate codes as of the effective date of the submission. Claims submitted for services that are not accompanied by covered code(s) under the applicable Coverage Policy will be denied as not covered. Coverage Policies relate exclusively to the administration of health benefit plans. Coverage Policies are not recommendations for treatment and should never be used as treatment guidelines. In certain markets, delegated vendor guidelines may be used to support medical necessity and other coverage determinations.*

## Overview

This Coverage Policy addresses testing for harmful or likely harmful changes in the genetic information of cells that occur after conception, for selected cancers and blood disorders. These changes, also called variants, are referred to as acquired or somatic. They are not inherited or passed down by blood relatives. The changes may occur in any cell of the human body except the egg or sperm cell. They may increase an individual's risk or tendency to have a certain disease or disorder.

Several types of testing are discussed in this Coverage Policy, including testing for a single change in a gene or part of a gene and testing for multiple changes in a gene or genes. Also discussed are tests that measure how a gene is turned on or off, which is referred to as gene expression. Test results can help determine how advanced a disease is and the chance of it coming back. Results can also help decide on a treatment and how well the disease may respond, or is responding to treatment.

## Coverage Policy

**Coverage for genetic testing varies across plans. Refer to the customer's benefit plan document for coverage details.**

**<u>General Criteria for Somatic Pathogenic or Likely Pathogenic Variant Genetic Testing</u>**

**Tumor Molecular Testing**

**Initial Evaluation (tissue- or ctDNA-based testing of the individual's tumor has never been performed)**

**General Criteria:**

**Molecular tumor biomarker or broad molecular profile panel testing is considered medically necessary when ALL of the following criteria are met:**

- the individual is a candidate for a targeted therapy associated with a specific tumor biomarker(s) or disease site
- results of testing will directly impact clinical decision-making
- the testing method is scientifically valid and proven to have clinical utility based on prospective evidence
    - the testing method may target DNA, RNA, or DNA/RNA if performed as a single assay

- no other tumor biomarker or broad molecular profile panel has been performed on the specimen for the same indication
- disease-specific criteria are not described elsewhere in this Coverage Policy

**Tissue-based testing:**

**Tissue-based testing is considered medically necessary when the general criteria above and ANY of the following criteria are met:**

- identification of the specific biomarker has been validated by the National Comprehensive Cancer Network™ (NCCN Guidelines™) as a category 1, 2A or 2B recommendation for the individual's tumor type
- identification of the specific biomarker has been demonstrated in published peer-reviewed literature to improve diagnosis, management or clinical outcomes for the individual's condition
- the "Indications and Usage" section of the US Food and Drug Administration (FDA) label requires biomarker confirmation by an FDA-approved or cleared test
- broad molecular profile panel testing for EITHER of the following:
    - advanced, metastatic solid tumors
    - ANY of the following hematologic malignancies:
        - acute myeloid leukemia
        - myelodysplastic disease
        - myeloproliferative disease
        - multiple myeloma
        - systemic mastocytosis

**Cell-free (ctDNA) DNA testing (also known as liquid biopsy):**

**Cell-free (ctDNA) DNA testing is considered medically necessary when the general criteria above are met, tissue testing is not available or contraindicated, and EITHER of the following:**

- advanced or metastatic solid tumors
- the "Indications and Usage" section of the US FDA-approved prescribing label requires biomarker confirmation by an FDA approved or cleared test prior to initiating therapy

**Concurrent tissue-based and ctDNA testing:**

**Concurrent tissue-based and ctDNA genomic sequencing (ordered within 30 days of each other) is considered medically necessary when results will directly impact clinical decision making in the following scenarios:**

- metastatic breast cancer
- metastatic non-small cell lung cancer

**Repeat or Subsequent Evaluations (tissue- or ctDNA-based genomic sequencing has been previously performed on the patient's cancer):**

**Repeat tissue-based or ctDNA-based genomic sequencing is considered medically necessary when the general criteria above and ALL of the following are met:**

- the individual has an advanced or metastatic solid tumor

- a new tissue biopsy sample or ctDNA sample is being collected on which the testing will be performed
- the individual has progressed on systemic therapy or has had clinical non-response after systemic therapy

**Molecular tumor biomarker or broad molecular profile panel testing (either tissue or ctDNA) for hematology and oncology indications is considered not medically necessary if the criteria described above are not met.**

**Testing of bone marrow samples for minimal residual disease (MRD) using high-throughput immunosequencing is considered medically necessary for ANY of the following indications or when designated by NCCN as a category 1, 2A or 2B recommendation:**

- multiple myeloma (MM)
- B-cell acute lymphoblastic leukemia (ALL)
- chronic lymphoblastic leukemia (CLL)
- peripheral and cutaneous T-cell lymphoma (TCL)

**Other testing (e.g., non-high-throughput immunosequencing) for MRD using a validated technology when recommended by NCCN Guidelines™ as a Category 1, 2A, or 2B recommendation is considered medically necessary.**

**Molecular testing for hematology and oncology indications is not covered or reimbursable if the criteria described above are not met.**

---

**Tumor Profile/Gene Expression Classifier Testing**

**Gene-Expression Classifiers (GEC)**

**Tissue-based gene expression classifier (GEC) testing is considered medically necessary when ALL of the following criteria are met:**

- the individual is a candidate for a targeted therapy associated with a specific disease site
- disease-specific criteria are not described elsewhere in the Coverage Policy
- results of testing will directly impact clinical decision making
- the testing method is scientifically valid and proven to have clinical utility based on prospective evidence
- **ANY** of the following:
  - risk assessment using a GEC has been validated by the National Comprehensive Cancer Network™ (NCCN Guidelines™) as a category 1, 2A or 2B recommendation for the individual's tumor type of disease
  - use of a GEC has been demonstrated in published peer-reviewed literature to improve diagnosis, management or clinical outcomes for the individual's condition being addressed

**Gene expression classifier testing is considered not medically necessary if the criteria described above are not met.**

---

**Proteomic Testing**

**Proteomic testing is considered medically necessary when ALL of the following criteria are met:**

- results of testing will directly impact clinical decision making
- the testing method is considered to be scientifically valid and proven to have clinical utility based on prospective evidence
- testing has been validated by the National Comprehensive Cancer Network™ (NCCN Guidelines) as a category 1, 2A or 2B recommendation for the individual's tumor type or disease
- disease-specific criteria are not described elsewhere in the Coverage Policy

**Proteomic testing is considered not medically necessary if the criteria described above are not met.**

---

**Circulating Tumor Cells Testing**

**AR-V7 testing from circulating tumor cells is considered medically necessary for a male with metastatic castrate resistant prostate cancer (mCRPC) considering second line therapy when BOTH of the following criteria are met:**

- progression on androgen receptor–signaling inhibitor (ARSi) therapy (i.e., enzalutamide (Xtandi), abiraterone (Zytiga))
- nuclear expression of AR-V7 will be assessed to guide subsequent therapeutic decision making

**Detection of circulating whole tumor cells for any other indication is considered not medically necessary.**

---

**Myeloproliferative Neoplasms**

**Polycythemia Vera (PV)**

**Genetic testing for JAK2 common variants (CPT codes 81270, 81279), MPL common variants (CPT codes 81338, 81339), and CALR exon 9 common variants (CPT code 81219) is considered medically necessary for the diagnosis of polycythemia vera (PV) when BOTH of the following criteria are met:**

- genetic testing would impact medical management of the individual being tested
- **ONE** of the following:
    - hemoglobin >16.5 g/dL in men, >16.0 g/dL in women
    - hematocrit >49% in men, >48% in women
    - increased red cell mass (RCM) more than 25% above mean normal predicted value

---

**Essential Thrombocythemia**

**Genetic testing for JAK2 common variants (CPT codes 81270, 81279), MPL common variants (CPT codes 81338, 81339), and CALR exon 9 common variants (CPT code 81219) is considered medically necessary for the diagnosis of essential thrombocythemia or thrombocytosis (ET) when BOTH of the following criteria are met:**

- results will impact medical management
- **EITHER** of the following criteria are met:
  - platelet count ≥ 450 x 10^9/L
  - bone marrow biopsy showing proliferation mainly of the megakaryocyte lineage with increased numbers of enlarged, mature megakaryocytes with hyperlobulated nuclei. No significant increase or left shift in neutrophil granulopoiesis or erythropoiesis and very rarely minor (grade 1) increase in reticulin fibers

---

**Primary Myelofibrosis (PMF)**

**Genetic testing for JAK2 common variants (CPT codes 81270, 81279), MPL common variants (CPT codes 81338, 81339), and CALR exon 9 common variants (CPT code 81219) is considered medically necessary for the diagnosis of primary myelofibrosis (PMF) when BOTH of the following criteria are met:**

- results will impact medical management
- primary myelofibrosis is suspected but not confirmed, based on results of conventional testing

**ASXL1, EZH2, TET2, IDH1/IDH2, SRSF2, and SF3B1 testing is considered medically necessary for the diagnosis of primary myelofibrosis (PMF) when ALL of the following criteria are met:**

- primary myelofibrosis is confirmed or suspected
- based on clinical findings above criteria are met
- results will impact medical management.
- bone marrow findings of megakaryocytic proliferation and atypia, without reticulin fibrosis >grade 1, accompanied by increased age-adjusted bone marrow cellularity, granulocytic proliferation, and often, decreased erythropoiesis
- testing will be completed on bone marrow sample JAK2, CALR and MPL mutation analysis was previously completed and was negative

---

**Chronic Myelogenous Leukemia (CML) and Philadelphia Chromosome Positive (PH+) Acute Lymphoblastic Leukemia (ALL)**

**BCR-ABL T315-I pathogenic variant testing (CPT codes 81401, 81170) is considered medically necessary in individuals with chronic myelogenous leukemia (CML) or Philadelphia chromosome positive (Ph+) acute lymphoblastic leukemia (ALL) when ANY of the following are met:**

- inadequate initial response to tyrosine kinase inhibitor therapy (i.e., failure to achieve complete hematological response at 3 months, minimal cytogenetic response at 6 months or major cytogenetic response at 12 months)

- loss of response to tyrosine kinase inhibitor therapy (i.e., hematologic relapse, cytogenetic relapse, loss of major molecular response [MMR])
- progression to accelerated or blast phase CML while on tyrosine kinase inhibitor therapy

---

**Experimental/Investigational/Unproven**

**mRNA gene expression profiling and algorithmic analysis (i.e., 12 genes) (CPT code 0011M) to predict high-grade prostate cancer risk score is considered experimental, investigational or unproven.**

**Not Covered or Reimbursable**

**The following tests do not meet medical necessity criteria listed above and are additionally not covered or reimbursable:**

- EpiSwitch® CiRT (CPT code 0332U)
- EpiSwitch® Prostate Screening Test (PSE) (CPT code 0433U)
- EXaCT–1 whole exome testing (CPT code 0036U)
- miR Sentinel™ Prostate Cancer Test (CPT codes 0343U, 0424U)
- MyProstateScore 2.0 (MPS2) (CPT code 0403U)
- Northstar Response® (CPT code 0486U)
- OncoAssure Prostate (CPT code 0497U)
- OptiSeq™ Colorectal Cancer NGS Panel (CPT code 0498U)
- PROphetNSCLC™ (CPT code 0436U)
- PurIST℠ (CPT code 0510U)
- Stockholm3 (CPT code 0495U)
- Tempus p-MSI (CPT code 0512U)
- Tempus p-Prostate (CPT code 0513U)

## Health Equity Considerations

Health equity is the highest level of health for all people; health inequity is the avoidable difference in health status or distribution of health resources due to the social conditions in which people are born, grow, live, work, and age.

Social determinants of health are the conditions in the environment that affect a wide range of health, functioning, and quality of life outcomes and risks. Examples include safe housing, transportation, and neighborhoods; racism, discrimination and violence; education, job opportunities and income; access to nutritious foods and physical activity opportunities; access to clean air and water; and language and literacy skills.

## General Background

**Somatic Mutation Genetic Testing**

Somatic mutations are changes in the DNA of a cell that may occur in any cell of the body except the germ cells (i.e., egg and sperm). Somatic mutations differ from germline mutations, which are passed down by blood relatives; somatic mutations are not inherited. The genetic tests described in this Coverage Policy are used to identify disease-causing somatic mutations or the biological activity of genes originating in a tumor or hematologic malignancy.

Tumor markers, also known as biomarkers, are substances that are produced by cancer cells or other cells or the body in response to cancer or certain benign (noncancerous)conditions. Tumor markers are proteins or other substances that are made at higher amounts by a cancer cell than a normal cell and may be useful in determining the extent or stage of disease or recurrence, determining the most effective treatment for a specific disease and how well the disease will respond to treatment. They can be found in the blood, urine, stool, tumor tissue, or other tissues or bodily fluids of some patients with cancer (National Cancer Institute [NCI], 2023.

Published peer-reviewed evidence and professional society/organizational consensus guidelines support testing for certain tumor markers for the screening, staging, diagnosis and management of some types of cancer. However, for other tumor markers there is insufficient evidence to establish clinical utility for informing on improvement of health outcomes.

To have clinical utility the specific gene or gene biomarker for which testing has been requested, or gene expression classifier assay should be demonstrated in the published, peer-reviewed scientific literature in the form of prospective clinical trial data to improve the diagnosis, management, or clinical outcomes for the individual's tumor type or disease when the individual is a candidate for a related therapy. The identification of the gene or biomarker should also be required to initiate a related therapy that has been validated by the NCCN as a Category 1, 2A or 2B Level of Evidence and Consensus recommendation as a standard of care. The NCCN recommendations are defined as:

- Category 1: Based upon high-level evidence there is uniform NCCN consensus that the intervention is appropriate
- Category 2A: Based upon lower-level evidence there is uniform NCCN consensus that the intervention is appropriate
- Category 2B: Based upon lower-level evidence without a uniform consensus but with no major disagreement that the intervention is appropriate
- Category 3: Based upon any level of evidence, there is major NCCN disagreement that the intervention is appropriate.

Multigene panels may also provide important information regarding an individual's tumor type to direct proven therapy or support management changes for hematology-oncology indications. These tests may be clinically useful when sequential testing of individual genes or biomarkers is not feasible because of limited tissue availability, or when urgent treatment decisions are pending and sequential testing would result in a prolonged testing schedule.

There is insufficient evidence in the published, peer-reviewed scientific literature to support molecular testing when the requested gene(s) or biomarker(s) is(are) correlated with a known therapy, but that therapy has not been validated in prospective clinical trials for the specific tumor type or disease site.

**Broad Molecular Profile Testing**

Broad molecular profile tests, also known as molecular profiling and comprehensive genome profiling panels are large multigene tests which assess multiple genetic alterations simultaneously in a solid tumor. Several laboratory methods may be used to assess the tumor; however, next generation sequencing techniques are most commonly used. Broad molecular tests can identify alterations to base substitutions (substitution of an amino acid), insertions and deletions (amino acids are added or removed from DNA), copy number alterations (sections of DNA are repeated) and rearrangements (amino acids are rearranged in a different order). Broad molecular profile testing may be used with the goal of identifying mutations of interest for which drug therapy may

be available or for enrollment in a clinical trial. Limitations to testing include testing for more alterations than have been identified for a specific type of cancer and the identification of variations of unknown significance. Nonetheless, such testing is supported by published professional society guidelines, including from the NCCN as a key component of care for a number of advanced, metastatic, refractory and recurrent cancers.

**Biopsy Testing Methods**

A biopsy is used as a diagnostic and monitoring tool to identify abnormalities in tissue or blood. A traditional tissue biopsy is used to sample and analyze a solid biological specimen. Tissue biopsy remains the gold standard for the confirmation and diagnosis of disease, including various cancers. Limitations include patient risk due the invasive nature of the test and limited availability of the tissue sample.

There is increasing use of plasma cell-free DNA testing, also known as a liquid biopsy, which is used to sample and analyze nucleic acids in peripheral circulation, most commonly in plasma. At present there are no standards for analytical performance and no guidelines exist for regarding the recommended performance characteristics. Cell-free DNA testing has a high specificity rate but limitations include a compromised sensitivity with up to a 30% false-negative rate. Such testing may also identify alterations that are unrelated to a lesion of interest. Nonetheless, the use of cell-free DNA testing may be considered appropriate when a patient is medically unfit for invasive tissue sampling or there is insufficient material for analysis in advanced (III or IV), metastatic, recurrent or refractory solid cancers.

**Testing for Minimal Residual Disease**

Minimal residual disease refers to the presence of leukemic cells below the threshold of detection by conventional morphologic methods. Patients who achieve complete response by morphologic assessment alone can harbor leukemic cells in the bone marrow. Methods frequently utilized include a multiparameter (i.e., at least 6-color) flow cytometry to detect abnormal phenotypes, real-time quantitative polymerase chain reaction (RQ-PCT) assays to detect fusion genes and high-throughput next generation sequencing (NGS)-based assays to detect clonal arrangements (NCCN, 2023). An assay for minimal residual disease by high throughput sequencing methods is currently recommended as clinically useful for multiple myeloma, B-cell acute lymphoblastic leukemia, chronic lymphoblastic leukemia and peripheral and cutaneous T-cell lymphoma (NCCN, 2023).

**U.S. Food and Drug Administration (FDA)**
FDA approval is not required for the development or marketing of specific gene tumor markers profiling tests, multigene panel tests or gene classifier tests. Many high-complexity tests are laboratory-developed in a Clinical Laboratory Improvement Amendment (CLIA)-certified laboratory. However, a number of devices with reagents that are used to "qualitatively or quantitatively measure, by immunochemical techniques, tumor-associated antigens in serum, plasma, urine, or other body fluids" and intended as an aid in monitoring patients for disease progress or response to therapy or for the detection of recurrent or residual disease" are cleared by the FDA 510(k) process (FDA, 2009).

**Tumor Profile/Gene Expression Classifier Testing**

Gene expression classifier assays identify genetic alterations or biological activity of several genes in a tumor. Such tests may provide a more complete picture of a tumor's molecular signature and enable a better estimate of the risk of distant recurrence when considered along with other molecular signatures and clinical characteristics (Marrone, 2014). They have been proposed as an

adjuvant tool to assist in determining overall survival (OS), recurrence probability, appropriate treatment options and responsiveness to chemotherapy and are not advocated as stand-alone tools. Numerous gene profiling assays are currently marketed for use in the U.S.

## Proteomic Testing

Proteomics involves the quantitative and qualitative study of proteins, including the function, composition and structure and the way they interact inside cells. Protein expression may be changed by environmental conditions.

Proteomics can identify and monitor biomarkers by analyzing the proteins in body fluids such as urine, serum, exhaled breath and spinal fluid. Proteomics can also facilitate drug development by providing a comprehensive map of protein interactions associated with disease pathways. A proteomic profile may be used to find and diagnose a disease or condition and to see how well the body responds to treatment (National Cancer Institute [NCI], 2023).

To be clinically useful the testing method must be scientifically and clinically validated and proven to have clinical utility based on prospective evidence, testing must be validated by the National Comprehensive Cancer Network™ (NCCN Guidelines) as a category 1, 2A or 2B recommendation for the individual's tumor type or disease and results of testing must directly impact clinical decision making.

### Circulating Whole Tumor Cell Testing

Circulating whole tumor cells (CTCs) have been found in the peripheral blood circulation of individuals with various forms of metastatic cancer. CTCs are whole cells that have been shed by the tumor. The detection and testing of these tumor cells has been proposed as a method to stratify risk, monitor progression and monitor response to treatment.

The use of circulating whole tumor cell testing has not been proven to impact meaningful health outcomes for most cancers. There is limited evidence to establish the clinical significance of circulating whole tumor cells and how identification can improve health outcomes. Pilot studies suggest that the identification of whole tumor cells may have a role in risk stratification and monitoring responses to treatment.

However, the National Comprehensive Cancer Network® (NCCN®) (v4.2023) recommends testing for the androgen receptor splice variant 7 (AR-V7) (2022) in circulating tumor cells. Lack of response of men with metastatic castrate-resistant prostate cancer is associated with detection of this biomarker. NCCN notes that testing in circulating tumor cells can be considered to help guide selection of therapy considering second line therapy when there is progression on androgen receptor–signaling inhibitor (ARSi) therapy (2A: Based upon lower-level evidence there is uniform NCCN consensus that the intervention is appropriate).

With the exception of testing for the AR-V7 variant in metastatic castrate-resistant prostate cancer the role of this testing in patient management is not yet known. Larger longitudinal studies with standard techniques in clearly-defined populations of patients are needed to establish the role of such testing.

### Literature Review

**Breast Cancer:** Smerage et al. (2014) reported on a randomized trial of patients with persistent increase in CTCs that were tested to determine whether changing chemotherapy after one cycle of first-line chemotherapy would improve the primary outcome of overall survival (OS). Five hundred ninety-five Female patients were included with histologically confirmed breast cancer and clinical and/or radiographic evidence of metastatic disease. Patients who underwent chemotherapy had

evaluation for CTCs at baseline and then after one cycle. Women whose CTCs remained elevated after the first cycle of therapy (arm C) (n=123) were randomly assigned to either maintain the initial treatment plan (n=64) or to change of chemotherapy (n=59). Changing to an alternate regimen had no difference in OS compared with continuation of the initial regimen (median 12.5 versus 10.7 months, respectively, P= .98). The CTCs did appear to have prognostic value: the median OS for arms A, B, and C were 35 months, 23 months, and 13 months, respectively). While it appears that there is prognostic value of CTCs, the role in clinical management is has not been demonstrated.

Zhang et al. (2012) reported on a meta-analysis of published literature on the prognostic relevance of CTC, including patients with early and advanced disease. Forty-nine eligible studies with 6,825 patients were identified. The main outcomes analyzed were overall survival (OS) and disease-free survival (DFS) in early-stage breast cancer patients, as well as progression-free survival (PFS) and OS in metastatic breast cancer patients. Pooled hazard ratio (HR) and 95% confidence intervals (CIs) were calculated using the random and the fixed-effects models. The presence of CTC was significantly associated with shorter survival in the total population. The prognostic value of CTC was significant in both early (DFS: HR, 2.86; 95% CI, 2.19–3.75; OS: HR, 2.78; 95% CI, 2.22–3.48) and metastatic breast cancer (PFS: HR, 1.78; 95% CI, 1.52–2.09; OS: HR, 2.33; 95% CI, 2.09–2.60). Subgroup analyses showed that our results were stable irrespective of the CTC detection method and time point of blood withdrawal. The authors conclude that the meta-analysis indicates that the detection of CTC is a stable prognosticator in patients with early-stage and metastatic breast cancer; however further studies are required to explore the clinical utility of CTC in breast cancer.

A prospective observational study that compared serum marker levels with CTC in 267 metastatic breast cancer patients (Bidard, et al., 2012). The secondary pre-planned endpoint a study that previously reported on CTC as prognostic factor (Pierga, et al., 2011), compared prospectively the positivity rates and the value of CTC (CellSearch), of serum tumor markers (carcinoembryonic antigen (CEA), cancer antigen 15.3 (CA 15-3), CYFRA 21-1), and of serum non-tumor markers (lactate dehydrogenase (LDH), alkaline phosphatase (ALP)) at baseline and under treatment for PFS prediction, independently from the other known prognostic factors, using univariate analyses and concordance indexes. The study reported that a total of 90% of the patients had at least one elevated blood marker. The blood markers were correlated with poor performance status, high number of metastatic sites and with each other. CYFRA 21-1, a marker usually used in lung cancer, was elevated in 65% of patients. A total of 86% of patients had either CA 15-3 and/or CYFRA 21-1 elevated at baseline. Each serum marker was associated, when elevated at baseline, with a significantly shorter PFS. Serum marker changes during treatment, assessed either between baseline and the third week or between baseline and weeks six-nine, were significantly associated with PFS, as reported for CTC. Concordance indexes comparison showed no clear superiority of any of the serum marker or CTC for PFS prediction. The authors concluded that for the purpose of PFS prediction by measuring blood marker changes during treatment, currently available blood-derived markers (CTC and serum markers) had globally similar performances. There was no clear superiority found of CTC over the other serum markers.

Liu et al. (2009) conducted on a prospective study that examined the correlation of CTCs with radiographic findings for disease progression. Serial CTC levels were obtained in patients (n=68) that were starting a new treatment regimen for progressive, radiographically measurable metastatic breast cancer. Blood was collected at baseline and three to four week intervals and radiographic studies were performed in nine to twelve week intervals. Median follow-up was 13.3 months. Patients who had five or more CTCs had 6.3 times the odds of radiographic disease progression when compared with patients who had less than five CTCs. Shorter progression-fee survival was observed for patients with five or more CTCs at three to five weeks and at seven to nine weeks after the start of treatment. The CTC result was statistically significantly associated

with disease progression for all patients (p<.001). The association was noted to remain strong in patients treated with either chemotherapy or endocrine therapy. Potential limitations of the study include that the study included patients receiving various lines and types of therapy. The subgroup analysis for CTC-imaging correlation was performed by including biologic agents with either chemotherapy or endocrine therapy—it was noted that each group was too small to be analyzed alone.

Nole et al. (2007) conducted a prospective study to evaluate the prognostic significance of CTCs detection in advanced breast cancer patients. The study included 80 patients with inclusion criteria: women with histological diagnosis of breast cancer, evidence of metastatic disease from imaging studies, starting a new line of therapy and/or treated for the advanced disease with a maximum two lines of therapy. The CellSearch system was used to test for circulating tumor cell levels before starting a new treatment and after four, eight weeks and the first clinical evaluation and every two months thereafter. At baseline, 49 patients were found to have ≥ 5 CTCs. The baseline number of CTCs were associated with progression-free survival (hazard ratio [HR] 2.5; 95% confidence interval [CI] 1.2–5.4). The risk of progression for patients with CTCs ≥ 5 at the last available blood draw was five times the risk of patients with 0–4 CTCs at the same time point (HR 5.3; 95% CI 2.8–10.4). At the last available blood draw, patients with rising or persistent CTCs ≥ 5 demonstrated a statistically significant higher risk of progression with respect to patients with CTCs < 5 at both blood draws (HR 6.4; 95% CI 2.8–14.6). The authors noted that these results indicate that elevated CTCs levels measured at any time in the clinical course of a patient with metastatic breast cancer predict an imminent progression and that this analysis represents an additional step in the process of validating this method. There are still unanswered questions regarding the treatment of a patient with low or high levels of CTCs in breast cancer.

**Prostate Cancer:** Folkersma et al. (2012) reported on a prospective study that analyzed the correlation between circulating tumor cell (CTC) levels and clinicopathologic parameters (prostate-specific antigen [PSA] level, Gleason score, and TNM stage) in patients with metastatic hormone-sensitive prostate cancer (PCa) and to establish its prognostic value in overall survival (OS) and progression-free survival (PFS). The study included three arms: 30 patients with localized PCa; 30 patients with metastatic PCa; and, 30 healthy volunteers. The median follow-up was 42.9 months. A significant positive correlation was demonstrated between the CTC level and all tumor burden markers (PSA and T, N, and M stage; p<0.001), except for Gleason score (tau=0.16). A cutoff of ≥4 CTCs/7.5 mL was chosen to distinguish patients with a poor prognosis. These patients had a significantly shorter median OS and PFS (24 compared to 45 months and 7 compared to 44 months, respectively; p<0.001). As the CTC level increased, the OS and PFS were noted to decrease. The risk of mortality and progression for the patients with ≥4 CTCs was 4.1 (p=0.029) and 8.5 (p<0.001) times greater. Multivariate analyses indicated that a CTC of ≥4 was an independent prognostic factor for PFS (hazard ratio 5.9, p<0.005).

Several observational studies have been published that correlate CTC with disease status and progression in prostate cancer (Goodman, et al. 2009; Okegawa, et al., 2009; Okegawa, et al., 2008; Scher, et al., 2009; Olmos, et al., 2009; Danila, et al., 2007; and Shaffer, et al., 2007; Moreno, et al., 2005).

**Colorectal Cancer:** Groot Koerkamp et al. (2013) reported on systematic review of studies that investigated the prognostic value of tumor cells in blood (CTCs) or bone marrow (BM) (disseminated tumor cells [DTC]) of patients with resectable colorectal liver metastases or widespread metastatic colorectal cancer (CRC). A total of 16 studies with 1,491 patients were included in the review and the results of 12 studies (1,329 patients) included in the meta-analysis. Eight studies used RT-PCR methodology to detect tumor cells, nine studies applied immunocytochemistry (five with CellSearch) and one study applied both methods. The overall survival (hazard ratio [HR], 2.47; 95 % CI 1.74–3.51) and progression-free survival (PFS) (HR,

2.07; 95 % CI 1.44–2.98) were worse in patients with CTCs. The subgroup of studies with more than 35% CTC-positive patients was the only subgroup with a statistically significant worse PFS. The eight studies that had multivariable analysis identified the detection of CTCs as an independent prognostic factor for survival. Limitations of the study included a considerable degree of interstudy heterogeneity. The study does not demonstrate the clinical utility of CTC detection, or that the detection of CTCs is a predictive factor, or identify patients that may benefit from a specific treatment. Further studies are needed to investigate the clinical utility of detection of CTCs in metastatic colorectal cancer.

Sastre et al. (2012) reported on an ancillary study of 180 patients that was a subset of a phase III study (The Maintenance in Colorectal Cancer trial) that assessed maintenance therapy with single-agent bevacizumab versus bevacizumab plus chemotherapy in patients with metastatic colorectal cancer. The ancillary study was conducted to evaluate CTC count as a prognostic and/or predictive marker for efficacy endpoints. Blood samples were obtained at baseline and after three cycles. CTC enumeration was performed with CellSearch System. The study found that the median progression-free survival (PFS) interval for patients with a CTC count ≥3 at baseline was 7.8 months, as compared to 12.0 months found in patients with a CTC count <3 (p=.0002). The median overall survival (OS) time was 17.7 months for patients with a CTC count >3, compared with 25.1 months for patients with a lower count (p=.0059). After three cycles, the median PFS interval for patients with a low CTC count was 10.8 months, which was noted to be longer than the 7.5 months for patients with a high CTC count (p=.005). The median OS time for patients with a CTC count <3 was significantly longer than for patients with a CTC count ≥3, 25.1 months compared to 16.2 months, respectively (p=.0095). Further studies are needed to identify the role of CTC in treatment of metastatic colorectal cancer.

Thorsteinsson et al. (2011) conducted a review of studies of CTCs in colorectal cancer (CRC). Nine studies were included in the review. Detection rates of CTC in peripheral blood of patients with non-metastatic CRC varied from 4% to 57%. Inclusion criteria included: patients diagnosed with non-metastatic colorectal cancer; CTC detected in peripheral blood samples; pre- and/or post-operative blood samples; and, samples size of more than 99 patients. Seven studies applied RT-PCR and two studies used immunocytochemical methods. Seven studies found the presence of CTC to be a prognostic marker of poor disease-free survival. The authors concluded that the presence of CTC in peripheral blood is a potential marker of poor disease-free survival in patients with non-metastatic CRC and that the low abundance of CTC in non-metastatic CRC needs very sensitive and specific detection methods. They also noted that an international consensus on choice of detection method and markers is warranted before incorporating CTC into risk stratification in the clinical setting.

Rahbari et al. (2010) reported on a meta-analysis of studies to assess whether the detection of tumor cells in blood and bone marrow of patients diagnosed with colorectal cancer (CRC) can be used as a prognostic factor. Thirty-six studies were included in the review that examined the detection of free blood or bone marrow tumor cells with patients prognosis and included various methods of techniques (e.g., reverse transcriptase-PCR [RT-PCR]) and immunologic). The review indicated that the presence of CTCs detected in peripheral blood is of strong prognostic significance in patients with CRC. There was considerable interstudy heterogeneity noted in regards to differences in the detection methods, types and numbers of target genets or antigens, sampling site and time, and in demographic or clinicopathologic status of patients.

**Screening and Prognostic Tests for Early Detection of Prostate Cancer**

Prostate specific antigen (PSA), an organ-specific marker, is often used as a tumor marker. The higher the level of PSA at baseline, the higher is the risk for metastatic disease or subsequent disease progression. However, it is an imprecise marker of risk. Various approaches aimed at

improving the performance of PSA in early cancer detection have been tested, including the measurement of prostate biomarkers. None are clearly more accurate than total serum PSA levels (National Cancer Institute [NCI], 2023). According to the National Comprehensive Cancer Network Guideline (NCCN Guidelines™) for Prostate Cancer Early Detection (2023), tests that have been shown to increase specificity in the post-biopsy state are percent free PSA (%fPSA), 4Kscore (OPKO Health, Inc., Miami, FL), Prostate Health Index (PHI), (Beckman Coulter, Atlanta, GA) , prostate cancer gene 3 (PCA3, Progensa® PCA3, Gen-Probe, Inc., San Diego, CA), ConfirmMDx for Prostate Cancer (MDX Health, Irvine, CA), Select MDx (MDx Health, Irvine, CA) and the ExoDx (Bio-Techne, Waltham, MA) tests.

The NCCN also notes that biomarkers that improve the specificity of detection are for use in those individuals who wish to further define the probability of high-grade cancer. Improved specificity post biopsy has been demonstrated in the published-peer-reviewed scientific literature.

**Professional Societies/Organizations**
Each of these tests is specifically mentioned in the NCCN Guideline for Prostate Cancer Early Detection as a category 2A recommendation. For additional information regarding professional society recommendations please see Appendix.

**Tumor Tissue-Based Molecular and Proteomic Assays for Detection of Prostate Cancer**

The NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines™) for Prostate Cancer (v.4.2023) notes that although risk groups, life expectancy estimates and nomograms help inform treatment decisions, there remains uncertainty regarding the risk of disease progression. Several tumor tissue-based molecular assays have been included in the guideline for prostate cancer (2022). The guideline notes that men with low or favorable intermediate risk may consider the use of certain molecular tests (i.e., Decipher®, OncotypeDx Genomic Prostate Score©, Prolaris® Prostate Cancer Test, ProMark Proteomic Prostate Test), which are briefly reviewed in this section of the Coverage Policy.

Although these tests have not been validated by prospective, randomized clinical trial data, retrospective case cohort studies demonstrate that these tests provide prognostic information independent of NCCN risk groups for men with low or favorable intermediate risk disease, including likelihood of death with conservative management, likelihood of biochemical recurrence after radical prostatectomy or radiotherapy and likelihood of developing metastasis after operation or salvage radiotherapy (NCCN, 2019).

**<u>Myeloproliferative Neoplasms</u>**

**Polycythemia Vera (PV), Essential Thrombocythemia (ET) and Primary Myelofibrosis (PMF)**

Identification of the JAK2, MPL and CALR exon 9 common variants in individuals with polycythemia vera (PV), essential thrombocythemia (ET) and primary myelofibrosis (PMF) may aid in diagnosis based on diagnostic criteria for each of these diseases. For some individuals with PV, JAK2 exon 12 mutation testing may also be of benefit in disease management. Likewise genetic testing for MPL common variants and targeted mutation analysis of CALR exon 9 may be appropriate to aid in the diagnosis and management of ET and PMF. According to 2016 World Health Organization (WHO) criteria (Arber, 2016), ASXL1, EZH2, TET2, IDH1/IDH2, SRSF2 and SF3B1 mutation analysis may aid in diagnosis of PMF.

**Chronic Myelogenous Leukemia and Philadelphia Chromosome Positive (PH+) Acute Lymphoblastic Leukemia Mutation Testing**

Specific mutations in the Breakpoint Cluster Region-Abelson (BCR-ABL) gene have been shown to confer resistance to imatinib both in vitro and in vivo, by affecting the binding of the drug to the tyrosine kinase enzyme (AHRQ, 2010). Of interest is the T315-I mutation which is thought to be resistant to all current TKI therapy. The mutation frequency in imatinib resistant patients with CML ranges between 2% and 20%, with variability related to detection methods as well as patient cohort characteristics and treatment. T315I mutation frequency appears to be greater in patients with Philadelphia chromosome-positive ($Ph^{+)}$ ALL and likely increases with the continuation of TKI treatment (Nicolini, 2009). The detection of mutations of the BCR-ABL gene has been proposed with potential impact on diagnosis and management decisions (Agency for Healthcare Research and Quality [AHRQ], 2010; National Cancer Institute [NCI], 2015; Najfeld, 2012; National Institute for Clinical Excellence [NICE], 2002). Evidence in the published, peer-reviewed scientific literature also supports the usefulness of testing for BCR-ABL resistance or inhibition.

Real-time quantitative PCR (RQ-PCR) is by far the most sensitive method. It provides an accurate measure of the total leukemia cell mass and the degree to which breakpoint cluster region-Abelson (BCR-ABL) transcripts are reduced by therapy, and correlates with progression-free survival. Current international recommendations for optimal molecular monitoring of patients receiving imatinib treatment include an RQ-PCR assay expressing the BCR-ABL transcript levels, which is predictive of prognosis (Bhatia, 2012; Najfeld, 2012). Molecular responses at 12 and 18 months are also predictive of long-term outcome (Bhatia, 2012). In acute lymphocytic leukemia (ALL), because many patients have a different fusion protein from the one found in chronic myelogenous leukemia (CML), the BCR-ABL gene may be detectable only by pulsed-field gel electrophoresis or reverse-transcriptase polymerase chain reaction (RT-PCR). These tests should be performed whenever possible in patients with ALL, especially those with B-cell lineage disease (NCI, 2015a).

Although certain BCR-ABL mutations may be associated with TKI therapy resistance, sensitivity and specificity values in outcome studies are not suggestive of strong predictive ability, with the exception of the T315-I mutation. Early identification of this mutation may allow for alternative treatment regimens including increased dose scheduling and drug selection. Data in the published peer-reviewed scientific literature supports the clinical utility of testing for the presence of the T315-I mutation. The clinical utility of testing for other mutations to determine TKI resistance has not been established.

**Literature Review:** Several studies have reported associations between variations of BCR-ABL and response to drug therapy. AHRQ (2010) performed a systematic review of the published literature regarding variations of the BCR-ABL1 fusion gene and response to imatinib, dasatinib, and nilotinib in CML. Thirty-one studies were analyzed for outcomes of interest including overall survival and cancer specific survival; progression-free or event-free survival (as defined by each study); and treatment failure. Typically, treatment failure is defined as absence of hematologic, cytogenetic, or molecular response to treatment, according to various criteria. Data was analyzed for first-, second-, and third- line TKI therapy. Second-line TKI therapy studies (four publications) demonstrated sensitivity and specificity ranges of 0.35 to 0.83 and from 0.58 to 1.00, respectively, for high-dose imatinib and imatinib-based combination. These studies were small, the calculated sensitivity and specificity values have wide confidence intervals, and a range of different mutations was identified in each of them. No robust conclusions could be made. Eight studies (nine publications) pertained to dasatinib; some had overlapping populations. Sensitivities and specificities ranged from 0.27 to 0.90 and from 0.14 to 0.87, respectively. A lack of predictive ability is suggested. For nilotinib, three studies had relevant data. Sensitivity ranged from 0.56 to 0.71 and specificity ranged from 0.42 to 0.56 for all identified mutations. Only one included study reviewed overall survival (OS). No statistically significant differences in the time-to-death among patients with, versus without mutations were found. When any breakpoint cluster region- Abelson

(BCR-ABL1) mutation was considered, almost all studies reported sensitivity and specificity values that are not suggestive of strong predictive ability. The Agency for Healthcare Research and Quality (AHRQ) notes that no study explicitly reported details on changes in treatment plans before or after testing.

AHRQ determined that the presence of any BCR-ABL mutation does not appear to differentiate response to tyrosine kinase inhibitor (TKI) treatment (i.e., imatinib, dasatinib, nilotinib). AHRQ also notes that the majority of evidence pertains to the short term surrogate outcomes of hematologic, cytogenetic or molecular response. Data on overall or progression-free survival are sparse. There is consistent evidence that presence of the relatively rare T315-I mutation can predict TKI treatment failure, mainly in terms of hematologic and cytogenetic response.

Jabbour et al. (2009) studied 169 patients with chronic myelogenous leukemia (CML) after imatinib failure. The goals of the study were to investigate whether in vitro sensitivity of kinase domain mutations could be used to predict the response to therapy as well as the long-term outcome of patients receiving second-generation TKIs after imatinib failure. Treatment failure was defined as loss of a cytogenetic, or complete hematologic response (CHP), or failure to achieve a CHR or any hematologic response (for patients in accelerated phase or blast phase after 3 months of therapy, or persistence of 100% Philadelphia chromosome (Ph)–positive metaphases after 6 months of therapy, or more than or equal to 35% after 12 months). Fifty-seven patients (66%) had received prior therapy with interferon-alpha before the start of imatinib; 29 (34%) had received imatinib as their first-line therapy for CML. Mutations were detected by cDNA sequencing for mutations in the kinase domain of BCR-ABL before a change to dasatinib or nilotinib in 86 patients. Ninety-four mutations were identified in 86 patients with imatinib failure. Seven patients harbored more than 1 mutation. There was no difference in patient characteristics between those with mutations at the time of imatinib failure versus those with no mutations. Forty-one patients received dasatinib and 45 received nilotinib after developing failure to imatinib therapy. Hematologic and cytogenetic response rates were similar for patients without or with KD mutations. After a median follow-up of 23 months, 48 (58%) of patients without baseline mutations were alive compared with 52 (60%) with any mutation.

Nicolini et al. (2009) reported the results of a retrospective observational study of 222 patients with CML in chronic-phase, accelerated-phase, or blastic-phase and Philadelphia chromosome-positive ($Ph^+$) ALL patients with the BCR-ABL T315I mutation. After T315I mutation detection, second-generation TKIs were used in 56% of cases, hydroxyurea in 39%, imatinib in 35%, cytarabine in 26%, MK-0457 in 11%, stem cell transplantation in 17%, and interferon-alpha in 6% of cases. Median overall survival from T315I mutation detection was 22.4, 28.4, 4.0, and 4.9 months, and median progression-free survival was 11.5, 22.2, 1.8, and 2.5 months, respectively, for chronic phase, accelerated phase, blastic phase, and Ph(+) ALL patients. These results suggest that survival of patients harboring a T315I mutation is dependent on disease phase at the time of mutation detection.

In an earlier study by Jabbour et al. (2006) 171 patients were screened for mutations after failing TKI therapy with a median follow-up of 38 months from start of therapy. Sixty-six mutations impacting 23 amino acids in the BCR-ABL oncogene were identified in 62 (36%) patients. Factors associated with the development of mutations were older age, previous interferon therapy and accelerated or blast phase at the start of TKI therapy. By multivariate analysis, factors associated with a worse survival were development of clonal evolution and a higher percentage of peripheral blood basophils. The presence of a BCR-ABL kinase domain mutation had no impact on survival. When survival was measured from the time therapy started, non-P-loop mutations were associated with a shorter survival than P-loop mutations. The authors concluded that BCR-ABL P-loop mutations were not associated with a worse outcome. This study suggests that outcomes of individuals who fail TKI therapy may be influenced by multiple factors.

Nicolini and colleagues (2006) retrospectively analyzed the predictive impact of 94 breakpoint cluster region (BCR) - Abelson (ABL) kinase domain mutations found in 89 protein tyrosine kinase inhibitor (TKI) resistant chronic myelogenous leukemia (CML) individuals. With a median follow-up of 39 months, overall survival was worse for P-loop and another point mutation (T315-I), but not for other BCR-ABL mutations. For individuals in chronic phase only, analysis demonstrated a worse overall survival for P-loop and worse progression free survival for T315-I mutations.

## Medicare Coverage Determinations

| | Contractor | Determination Name/Number | Revision Effective Date |
|---|---|---|---|
| NCD | National | Next Generation Sequencing (NGS) (90.2) | 1/27/2020 |
| LCD | Various | Multiple LCDs for molecular diagnostic testing for hematology and oncology indications | |
| LCD | Various | Multiple LCDs for Inivata In Vision first Liquid biopsy for lung cancer | |

Note: Please review the current Medicare Policy for the most up-to-date information.
(NCD = National Coverage Determination; LCD = Local Coverage Determination)

## Appendix A

**Professional Society/Organization Recommendations/Guidelines**

**Tumor Profiling**
Sepulveda et al. (2017) published a guideline on behalf of the American Society for Clinical Pathology, College of American Pathologists, Association for Molecular Pathology, and the American Society of Clinical Oncology regarding molecular biomarkers testing for the evaluation of colorectal cancer. The guideline notes evidence supports mutational testing for genes in the EGFR signaling pathway, since they provide clinically actionable information as negative predictors of benefit to anti-EGFR monoclonal antibody therapies for targeted therapy of CRC. Mutations in several of the biomarkers have clear prognostic value.

**Gene Expression Classifier Tests**
**American Society of Clinical Oncology ([ASCO], 2016, updated 2019):** Regarding an individual who presents with a hormone receptor–positive, human epidermal growth factor receptor not overexpressed, axillary node–negative early breast cancer, ASCO notes the following updated recommendations:

- For individual's older than 50 years and whose tumors have Oncotype DX recurrence scores of less than 26, and for individual's age 50 years or younger whose tumors have Oncotype DX recurrence scores of less than 16, there is little to no benefit from chemotherapy. Clinicians may offer endocrine therapy alone (Type of recommendation: evidence based, benefits outweigh harms; Evidence quality: high; Strength of recommendation: strong).
- For individual's age 50 years or younger with Oncotype DX recurrence scores of 16 to 25, clinicians may offer chemoendocrine therapy (Type of recommendation: evidence based, benefits outweigh harms; Evidence quality: intermediate; Strength of recommendation: moderate).
- Individuals with Oncotype DX recurrence scores of greater than 30 should be considered candidates for chemoendocrine therapy (Type of recommendation: evidence based, benefits outweigh harms; Evidence quality: high; Strength of recommendation: strong).

- Based on Expert Panel consensus, oncologists may offer chemoendocrine therapy to individual's with Oncotype DX scores of 26 to 30 (Type of recommendation: informal consensus; Evidence quality: insufficient; Strength of recommendation: moderate).

No biomarker except for estrogen receptor, progesterone receptor, and human epidermal growth factor receptor 2 was found to guide choices of specific treatment regimens. Treatment decisions should also consider disease stage, comorbidities, and patient preferences.

**National Institute for Health and Care Excellence (NICE), United Kingdom**: A guidance document on the diagnosis and management of carcinomas of unknown primary (CUP) recommends against the use of gene-expression-based profiling to identify primary tumors in individuals with provisional CUP (2010, updated 2016).

A NICE guidance (2018) document titled Tumour Profiling Tests to Guide Adjuvant Chemotherapy Decisions in Early Breast Cancer notes that EndoPredict (EPclin score), Oncotype DX Breast Recurrence Score and Prosigna are recommended as options for guiding adjuvant chemotherapy decisions for people with oestrogen receptor (ER)-positive, human epidermal growth factor receptor 2 (HER2)-negative and lymph node (LN)-negative (including micrometastatic disease for certain populations of individuals with early breast cancer.

The guidance also notes:

- MammaPrint is not recommended for guiding adjuvant chemotherapy decisions for individual's with ER-positive, HER2-negative and LN-negative early breast cancer because it is not cost effective.

- IHC4+C is not recommended for guiding adjuvant chemotherapy decisions for individual's with ER-positive, HER2-negative and LN-negative early breast cancer because the analytical validity of the test is uncertain.

**Circulating Whole Tumor Cell Markers**

**American Society of Clinical Oncology (ASCO, 2016):** A Guideline on the Use of Biomarkers to Guide Decisions on Systemic Therapy for Women With Metastatic Breast Cancer notes for individual's already receiving systemic therapy for metastatic breast cancer, decisions on changing to a new drug or regimen or discontinuing treatment should be based on clinical evaluation, judgment of disease progression or response, and the individual's goals for care. The Guideline also notes there is no evidence at this time that changing therapy based solely on circulating biomarker results improves health outcomes, quality of life, or cost effectiveness.

**American Society of Clinical Oncologists (ASCO)/College of American Pathologists (CAP) (2018):** In collaboration with CAP, ASCO published a joint review regarding Circulating Tumor DNA Analysis in individuals with Cancer (2018). This review notes some circulating DNA (ctDNA) assays have demonstrated clinical validity and utility with certain types of advanced cancer; however, there is insufficient evidence of clinical validity and utility for the majority of ctDNA assays in advanced cancer. Evidence shows discordance between the results of ctDNA assays and genotyping tumor specimens and supports tumor tissue genotyping to confirm undetected results from ctDNA tests. There is no evidence of clinical utility and little evidence of clinical validity of ctDNA assays in early-stage cancer, treatment monitoring, or residual disease detection. There is no evidence of clinical validity and clinical utility to suggest that ctDNA assays are useful for cancer screening, outside of a clinical trial.

**National Comprehensive Cancer Network™ (NCCN™) (Prostate Cancer v.4.2023):** The NCCN guideline for Prostate Cancer notes that AR-V7 testing in circulating tumor cells can be

considered to help guide election of therapy in the post-abiraterone/enzalutamide metastatic CRPC setting.

**Prostate Cancer Screening and Prognostic Tests**

**American Urological Association (2013):** In the guideline for "Early Detection of Prostate Cancer", Carter et al. (2013) note that the literature supporting the efficacy of DRE, PSA derivatives and isoforms (e.g. free PSA, -2proPSA, prostate health index, hK2, PSA velocity or PSA doubling time) and novel urinary markers and biomarkers (e.g. PCA3) for screening with the goal of reducing prostate cancer mortality provide limited evidence to draw conclusions. While some data suggest use of these secondary screening tools may reduce unnecessary biopsies (i.e. reduce harms) while maintaining the ability to detect aggressive prostate cancer (i.e. maintain the benefits of PSA screening), more research is needed to confirm this. However, the likelihood of a future population-level screening study using these secondary screening approaches is highly unlikely at least in the near future. The authors further note that the Guideline focuses only on the efficacy of PSA screening for the early detection of prostate cancer and not secondary tests often used after screening to determine the need for a prostate biopsy or a repeat prostate biopsy (e.g., PSA isoforms, PCA3, imaging).

**National Comprehensive Cancer Network (NCCN Guidelines™):** The Guideline for Prostate Cancer Early Detection (2023) notes that PSA derivatives and other assays potentially improve the specificity of testing and may diminish the probability of unnecessary biopsies. Several biomarker tests have the goals of refining selection for biopsies, decreasing unnecessary biopsies and increasing the specificity of cancer detection, without missing a substantial number of higher-grade (Gleason ≥ 7) cancers. These tests may be especially useful in men with PSA levels between 3 and 10 ng/mL.

**BCR-ABL Mutation Analysis**

**National Cancer Institute (NCI):** Regarding BCR-ABL mutation analysis in individuals with chronic myelogenous leukemia (CML), the NCI notes "In case of treatment failure or suboptimal response, patients should undergo BCR/ABL kinase domain mutation analysis to help guide therapy with the newer tyrosine kinase inhibitors or with allogeneic transplantation." (2022)

**National Comprehensive Cancer Network™ (NCCN™):** Regarding kinase domain mutation testing, the NCCN Guideline for Chronic Myeloid Leukemia notes kinase domain mutation analysis is recommended in chronic phase CML if there is inadequate initial response at three and six months or less than complete cytogenetic response at 12-18 months, any sign of loss of response, increase in BCR-ABL transcript levels and loss of minimal molecular response (MMR), and disease progression to accelerated or blast phase (v.2.2024).

The DCIS section in the NCCN Guideline for Breast Cancer v.5.2023 does not support routine CYP2D6 genotyping in women with ductal carcinoma in situ being considered for tamoxifen therapy.

## Coding Information

**Notes:**

1. This list of codes may not be all-inclusive since the American Medical Association (AMA) and Centers for Medicare & Medicaid Services (CMS) code updates may occur more frequently than policy updates.
2. Deleted codes and codes which are not effective at the time the service is rendered may not be eligible for reimbursement.

**General Criteria for Somatic Pathogenic or Likely Pathogenic Variant Genetic Testing**

**Considered Medically Necessary when criteria in the applicable policy statements listed above are met:**

| CPT®* Codes | Description |
|---|---|
| 81120 | IDH1 (isocitrate dehydrogenase 1 [NADP+], soluble) (eg, glioma), common variants (eg, R132H, R132C) |
| 81121 | IDH2 (isocitrate dehydrogenase 2 [NADP+], mitochondrial) (eg, glioma), common variants (eg, R140W, R172M) |
| 81168 | CCND1/IGH (t(11;14)) (eg, mantle cell lymphoma) translocation analysis, major breakpoint, qualitative and quantitative, if performed |
| 81191 | NTRK1 (neurotrophic receptor tyrosine kinase 1) (eg, solid tumors) translocation analysis |
| 81192 | NTRK2 (neurotrophic receptor tyrosine kinase 2) (eg, solid tumors) translocation analysis |
| 81193 | NTRK3 (neurotrophic receptor tyrosine kinase 3) (eg, solid tumors) translocation analysis |
| 81194 | NTRK (neurotrophic receptor tyrosine kinase 1, 2, and 3) (eg, solid tumors) translocation analysis |
| 81202 | APC (adenomatous polyposis coli) (eg, familial adenomatosis polyposis [FAP], attenuated FAP) gene analysis; known familial variants |
| 81203 | APC (adenomatous polyposis coli) (eg, familial adenomatosis polyposis [FAP], attenuated FAP) gene analysis; duplication/deletion variants |
| 81206 | BCR/ABL1 (t(9;22)) (eg, chronic myelogenous leukemia) translocation analysis; major breakpoint, qualitative or quantitative |
| 81207 | BCR/ABL1 (t(9;22)) (eg, chronic myelogenous leukemia) translocation analysis; minor breakpoint, qualitative or quantitative) |
| 81208 | BCR/ABL1 (t(9;22)) (eg, chronic myelogenous leukemia) translocation analysis; other breakpoint, qualitative or quantitative |
| 81210 | BRAF (B-Raf proto-oncogene, serine/threonine kinase) (eg, colon cancer, melanoma), gene analysis, V600 variant(s) |
| 81218 | CEBPA (CCAAT/enhancer binding protein [C/EBP], alpha) (eg, acute myeloid leukemia), gene analysis, full gene sequence |
| 81229 | Cytogenomic (genome-wide) analysis for constitutional chromosomal abnormalities; interrogation of genomic regions for copy number and single nucleotide polymorphism (SNP) variants, comparative genomic hybridization (CGH) microarray analysis |
| 81232 | DPYD (dihydropyrimidine dehydrogenase) (eg, 5-fluorouracil/5-FU and capecitabine drug metabolism), gene analysis, common variant(s) (eg, *2A, *4, *5, *6) |
| 81233 | BTK (Bruton's tyrosine kinase) (eg, chronic lymphocytic leukemia) gene analysis, common variants (eg, C481S, C481R, C481F) |
| 81235 | EGFR (epidermal growth factor receptor) (eg, non-small cell lung cancer) gene analysis, common variants (eg, exon 19 LREA deletion, L858R, T790M, G719A, G719S, L861Q) |
| 81237 | EZH2 (enhancer of zeste 2 polycomb repressive complex 2 subunit) (eg, diffuse large B-cell lymphoma) gene analysis, common variant(s) (eg, codon 646) |
| 81242 | FANCC (Fanconi anemia, complementation group C) (eg, Fanconi anemia, type C) gene analysis, common variant (eg, IVS4+4A>T) |

| CPT®* Codes | Description |
|---|---|
| 81245 | FLT3 (fms-related tyrosine kinase 3) (eg, acute myeloid leukemia), gene analysis; internal tandem duplication (ITD) variants (ie, exons 14, 15) |
| 81246 | FLT3 (fms-related tyrosine kinase 3) (eg, acute myeloid leukemia), gene analysis; tyrosine kinase domain (TKD) variants (eg, D835, I836) |
| 81261 | IGH@ (Immunoglobulin heavy chain locus) (eg, leukemias and lymphomas, B-cell), gene rearrangement analysis to detect abnormal clonal population(s); amplified methodology (eg, polymerase chain reaction) |
| 81262 | IGH@ (Immunoglobulin heavy chain locus) (eg, leukemias and lymphomas, B-cell), gene rearrangement analysis to detect abnormal clonal population(s); direct probe methodology (eg, Southern blot) |
| 81263 | IGH@ (Immunoglobulin heavy chain locus) (eg, leukemia and lymphoma, B-cell), variable region somatic mutation analysis |
| 81264 | IGK@ (Immunoglobulin kappa light chain locus) (eg, leukemia and lymphoma, B-cell), gene rearrangement analysis, evaluation to detect abnormal clonal population(s) |
| 81272 | KIT (v-kit Hardy-Zuckerman 4 feline sarcoma viral oncogene homolog) (eg, gastrointestinal stromal tumor [GIST], acute myeloid leukemia, melanoma), gene analysis, targeted sequence analysis (eg, exons 8, 11, 13, 17, 18) |
| 81273 | KIT (v-kit Hardy-Zuckerman 4 feline sarcoma viral oncogene homolog) (eg, mastocytosis), gene analysis, D816 variants(s) |
| 81275 | KRAS (Kirsten rat sarcoma viral oncogene homolog) (eg, carcinoma) gene analysis; variants in exon 2 (eg, codons 12 and 13) |
| 81276 | KRAS (Kirsten rat sarcoma viral oncogene homolog) (eg, carcinoma) gene analysis; additional variant(s) (eg, codon 61, codon 146) |
| 81278 | IGH@/BCL2 (t(14;18)) (eg, follicular lymphoma) translocation analysis, major breakpoint region (MBR) and minor cluster region (mcr) breakpoints, qualitative or quantitative |
| 81287 | MGMT (0-6-methylguanine-DNA methyltransferase) (eg, glioblastoma multiforme), promoter methylation analysis |
| 81288 | MLH1 (mutL homolog 1, colon cancer, nonpolyposis type 2) (eg, hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; promoter methylation analysis |
| 81301 | Microsatellite instability analysis (eg, hereditary non-polyposis colorectal cancer, Lynch syndrome) of markers for mismatch repair deficiency (eg, BAT25, BAT26), includes comparison of neoplastic and normal tissue, if performed |
| 81305 | MYD88 (myeloid differentiation primary response 88) (eg, Waldenstrom's macroglobulinemia, lymphoplasmacytic leukemia) gene analysis, p.Leu265Pro (L265P) variant |
| 81310 | NPM1 (nucleophosmin) (eg, acute myeloid leukemia) gene analysis, exon 12 variants |
| 81311 | NRAS (neuroblastoma RAS viral [v-ras] oncogene homolog) (eg, colorectal carcinoma), gene analysis, variants in exon 2 (eg, codons 12 and 13) and exon 3 (eg, codon 61) |
| 81314 | PDGFRA (platelet-derived growth factor receptor, alpha polypeptide) (eg, gastrointestinal stromal tumor [GIST]), gene analysis, targeted sequence analysis (eg, exons 12, 18) |
| 81315 | PML/RARalpha, (t(15;17)), (promyelocytic leukemia/retinoic acid receptor alpha) (eg, promyelocytic leukemia) translocation analysis; common breakpoints (eg, intron 3 and intron 6), qualitative or quantitative |

| CPT®* Codes | Description |
|---|---|
| 81316 | PML/RARalpha, (t(15;17)), (promyelocytic leukemia/retinoic acid receptor alpha) (eg, promyelocytic leukemia) translocation analysis; single breakpoint (eg, intron 3, intron 6 or exon 6), qualitative or quantitative |
| 81320 | PLCG2 (phospholipase C gamma 2) (eg, chronic lymphocytic leukemia) gene analysis, common variants (eg, R665W, S707F, L845F) |
| 81340 | TRB@ (T cell antigen receptor, beta) (eg, leukemia and lymphoma), gene rearrangement analysis to detect abnormal clonal population(s); using amplification methodology (eg, polymerase chain reaction) |
| 81341 | TRB@ (T cell antigen receptor, beta) (eg, leukemia and lymphoma), gene rearrangement analysis to detect abnormal clonal population(s); using direct probe methodology (eg, Southern blot) |
| 81342 | TRG@ (T cell antigen receptor, gamma) (eg, leukemia and lymphoma), gene rearrangement analysis, evaluation to detect abnormal clonal population(s) |
| 81345 | TERT (telomerase reverse transcriptase) (eg, thyroid carcinoma, glioblastoma multiforme) gene analysis, targeted sequence analysis (eg, promoter region) |
| 81346 | TYMS (thymidylate synthetase) (eg, 5-fluorouracil/5-FU drug metabolism), gene analysis, common variant(s) (eg, tandem repeat variant) |
| 81351 | TP53 (tumor protein 53) (eg, Li-Fraumeni syndrome) gene analysis; full gene sequence |
| 81352 | TP53 (tumor protein 53) (eg, Li-Fraumeni syndrome) gene analysis; targeted sequence analysis (eg, 4 oncology) |
| 81353 | TP53 (tumor protein 53) (eg, Li-Fraumeni syndrome) gene analysis; known familial variant |
| 81401† | Molecular pathology procedure, Level 2 (eg, 2-10 SNPs, 1 methylated variant, or 1 somatic variant [typically using nonsequencing target variant analysis], or detection of a dynamic mutation disorder/triplet repeat) |
| 81406 | Molecular pathology procedure, Level 7 (eg, analysis of 11-25 exons by DNA sequence analysis, mutation scanning or duplication/deletion variants of 26-50 exons) |
| 81407 | Molecular pathology procedure, Level 8 (eg, analysis of 26-50 exons by DNA sequence analysis, mutation scanning or duplication/deletion variants of >50 exons, sequence analysis of multiple genes on one platform) |
| 81445†† | Targeted genomic sequence analysis panel, solid organ neoplasm, 5-50 genes (eg, ALK, BRAF, CDKN2A, EGFR, ERBB2, KIT, KRAS, 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 |
| 81500 | Oncology (ovarian), biochemical assays of two proteins (CA-125 and HE-4), utilizing serum, with menopausal status, algorithm reported as a risk score |
| 0169U | NUDT15 (nudix hydrolase 15) and TPMT (thiopurine S-methyltransferase) (eg, drug metabolism) gene analysis, common variants |

†**Note: Considered Not Medically Necessary when used to report:**

- **LINC00518 (long intergenic non-protein coding RNA 518) (eg, melanoma), expression analysis**
- **PRAME (preferentially expressed antigen in melanoma) (eg, melanoma), expression analysis**

††**Note: Considered Medically Necessary when used to report ThyGeNext®**

**Considered Not Medically Necessary:**

| CPT®* Codes | Description |
|---|---|
| 81525 | Oncology (colon), mRNA, gene expression profiling by real-time RT-PCR of 12 genes (7 content and 5 housekeeping), utilizing formalin-fixed paraffin-embedded tissue, algorithm reported as a recurrence score |
| 81540 | Oncology (tumor of unknown origin), mRNA, gene expression profiling by real-time RT-PCR of 92 genes (87 content and 5 housekeeping) to classify tumor into main cancer type and subtype, utilizing formalin-fixed paraffin-embedded tissue, algorithm reported as a probability of predicted main cancer type and subtype |
| 0012M | Oncology (urothelial), mRNA, gene expression profiling by real-time quantitative PCR of five genes (MDK, HOXA13, CDC2 [CDK1], IGFBP5, and CXCR2), utilizing urine, algorithm reported as a risk score for having urothelial carcinoma |
| 0080U | Oncology (lung), mass spectrometric analysis of galectin-3-binding protein and scavenger receptor cysteine-rich type 1 protein M130, with five clinical risk factors (age, smoking status, nodule diameter, nodule-spiculation status and nodule location), utilizing plasma, algorithm reported as a categorical probability of malignancy |
| 0360U | Oncology (lung), enzyme-linked immunosorbent assay (ELISA) of 7 autoantibodies (p53, NY-ESO-1, CAGE, GBU4-5, SOX2, MAGE A4, and HuD), plasma, algorithm reported as a categorical result for risk of malignancy |
| 0363U | Oncology (urothelial), mRNA, gene-expression profiling by real-time quantitative PCR of 5 genes (MDK, HOXA13, CDC2 [CDK1], IGFBP5, and CXCR2), utilizing urine, algorithm incorporates age, sex, smoking history, and macrohematuria frequency, reported as a risk score for having urothelial carcinoma |
| 0391U | Oncology (solid tumor), DNA and RNA by next-generation sequencing, utilizing formalin-fixed paraffin-embedded (FFPE) tissue, 437 genes, interpretive report for single nucleotide variants, splice-site variants, insertions/deletions, copy number alterations, gene fusions, tumor mutational burden, and microsatellite instability, with algorithm quantifying immunotherapy response score |

**Not Covered or Reimbursable:**

| CPT®* Codes | Description |
|---|---|
| 81327 | SEPT9 (Septin9) (eg, colorectal cancer) promoter methylation analysis |
| 81350 | UGT1A1 (UDP glucuronosyltransferase 1 family, polypeptide A1) (eg, drug metabolism, hereditary unconjugated hyperbilirubinemia [Gilbert syndrome], gene analysis, common variants (eg, *28, *36, *37) |
| 81404† | Molecular pathology procedure, Level 5 (eg, analysis of 2-5 exons by DNA sequence analysis, mutation scanning or duplication/deletion variants of 6-10 exons, or characterization of a dynamic mutation disorder/triplet repeat by Southern blot analysis) |
| 0015M | Adrenal cortical tumor, biochemical assay of 25 steroid markers, utilizing 24-hour urine specimen and clinical parameters, prognostic algorithm reported as a clinical risk and integrated clinical steroid risk for adrenal cortical carcinoma, adenoma, or other adrenal malignancy |
| 0333U | Oncology (liver), surveillance for hepatocellular carcinoma (HCC) in high-risk patients, analysis of methylation patterns on circulating cell-free DNA (cfDNA) plus measurement of serum of AFP/AFP-L3 and oncoprotein des-gamma-carboxy-prothrombin (DCP), algorithm reported as normal or abnormal result |

| CPT®* Codes | Description |
|---|---|
| 0334U | Oncology (solid organ), targeted genomic sequence analysis, formalin-fixed paraffin-embedded (FFPE) tumor tissue, DNA analysis, 84 or more genes, interrogation for sequence variants, gene copy number amplifications, gene rearrangements, microsatellite instability and tumor mutational burden |
| 0368U | Oncology (colorectal cancer), evaluation for mutations of APC, BRAF, CTNNB1, KRAS, NRAS, PIK3CA, SMAD4, and TP53, and methylation markers (MYO1G, KCNQ5, C9ORF50, FLI1, CLIP4, ZNF132 and TWIST1), multiplex quantitative polymerase chain reaction (qPCR), circulating cell-free DNA (cfDNA), plasma, report of risk score for advanced adenoma or colorectal cancer |
| 0379U | Targeted genomic sequence analysis panel, solid organ neoplasm, DNA (523 genes) and RNA (55 genes) by next-generation sequencing, interrogation for sequence variants, gene copy number amplifications, gene rearrangements, microsatellite instability, and tumor mutational burden |
| 0428U | Oncology (breast), targeted hybrid-capture genomic sequence analysis panel, circulating tumor DNA (ctDNA) analysis of 56 or more genes, interrogation for sequence variants, gene copy number amplifications, gene rearrangements, microsatellite instability, and tumor mutation burden |
| 0450U | Oncology (multiple myeloma), liquid chromatography with tandem mass spectrometry (LCMS/MS), monoclonal paraprotein sequencing analysis, serum, results reported as baseline presence or absence of detectable clonotypic peptides |
| 0451U | Oncology (multiple myeloma), LCMS/MS, peptide ion quantification, serum, results compared with baseline to determine monoclonal paraprotein abundance |
| 0470U | Oncology (oropharyngeal), detection of minimal residual disease by next-generation sequencing (NGS) based quantitative evaluation of 8 DNA targets, cell-free HPV 16 and 18 DNA from plasma |

†**Note: Considered Medically Necessary when used to report:**

- **NRAS (neuroblastoma RAS viral oncogene homolog) (eg, colorectal carcinoma), exon 1 and exon 2 sequences**
- **KIT (C-kit) (v-kit Hardy-Zuckerman 4 feline sarcoma viral oncogene homolog) (eg, GIST, acute myeloid leukemia, melanoma), targeted gene analysis (eg, exons 8, 11, 13, 17, 18)**

**Tumor Profile/Gene Expression Classifier Testing**

**Considered Not Medically Necessary:**

| CPT®* Codes | Description |
|---|---|
| 81504 | Oncology (tissue of origin), microarray gene expression profiling of > 2000 genes, utilizing formalin-fixed paraffin-embedded tissue, algorithm reported as tissue similarity scores |
| 0016M | Oncology (bladder), mRNA, microarray gene expression profiling of 219 genes, utilizing formalin fixed paraffin-embedded tissue, algorithm reported as molecular subtype (luminal, luminal infiltrated, basal, basal claudin-low, neuroendocrine-like) |

| CPT®* Codes | Description |
|---|---|
| 0017M | Oncology (diffuse large B-cell lymphoma [DLBCL]), mRNA, gene expression profiling by fluorescent probe hybridization of 20 genes, formalin-fixed paraffin-embedded tissue, algorithm reported as cell of origin |
| 0019U | Oncology, RNA, gene expression by whole transcriptome sequencing, formalin-fixed paraffin embedded tissue or fresh frozen tissue, predictive algorithm reported as potential targets for therapeutic agents |
| 0153U | Oncology (breast), mRNA, gene expression profiling by next-generation sequencing of 101 genes, utilizing formalin-fixed paraffin-embedded tissue, algorithm reported as a triple negative breast cancer clinical subtype(s) with information on immune cell involvement |
| 0362U | Oncology (papillary thyroid cancer), gene-expression profiling via targeted hybrid capture–enrichment RNA sequencing of 82 content genes and 10 housekeeping genes, formalin-fixed paraffin embedded (FFPE) tissue, algorithm reported as one of three molecular subtypes |

**Circulating Tumor Cells Testing**

**Considered Not Medically Necessary:**

| CPT®* Codes | Description |
|---|---|
| 0490U | Oncology (cutaneous or uveal melanoma), circulating tumor cell selection, morphological characterization and enumeration based on differential CD146, high molecular–weight melanoma associated antigen, CD34 and CD45 protein biomarkers, peripheral blood (Code effective 10/01/2024) |
| 0491U | Oncology (solid tumor), circulating tumor cell selection, morphological characterization and enumeration based on differential epithelial cell adhesion molecule (EpCAM), cytokeratins 8, 18, and 19, CD45 protein biomarkers, and quantification of estrogen receptor (ER) protein biomarker–expressing cells, peripheral blood (Code effective 10/01/2024) |
| 0492U | Oncology (solid tumor), circulating tumor cell selection, morphological characterization and enumeration based on differential epithelial cell adhesion molecule (EpCAM), cytokeratins 8, 18, and 19, CD45 protein biomarkers, and quantification of PD-L1 protein biomarker– expressing cells, peripheral blood (Code effective 10/01/2024) |

**Myeloproliferative Neoplasms**

**Considered Medically Necessary when criteria in the applicable policy statements listed above are met:**

| CPT®* Codes | Description |
|---|---|
| 81120 | IDH1 (isocitrate dehydrogenase 1 [NADP+], soluble) (eg, glioma), common variants (eg, R132H, R132C) |
| 81121 | IDH2 (isocitrate dehydrogenase 2 [NADP+], mitochondrial) (eg, glioma), common variants (eg, R140W, R172M) |
| 81170 | ABL1 (ABL proto-oncogene 1, non-receptor tyrosine kinase) (eg, acquired imatinib tyrosine kinase inhibitor resistance), gene analysis, variants in the kinase domain |

| CPT®* Codes | Description |
|---|---|
| 81175 | ASXL1 (additional sex combs like 1, transcriptional regulator) (eg, myelodysplastic syndrome, myeloproliferative neoplasms, chronic myelomonocytic leukemia), gene analysis; full gene sequence |
| 81176 | ASXL1 (additional sex combs like 1, transcriptional regulator) (eg, myelodysplastic syndrome, myeloproliferative neoplasms, chronic myelomonocytic leukemia), gene analysis; targeted sequence analysis (eg, exon 12) |
| 81219 | CALR (calreticulin) (eg, myeloproliferative disorders), gene analysis, common variants in exon 9 |
| 81236 | EZH2 (enhancer of zeste 2 polycomb repressive complex 2 subunit) (eg, myelodysplastic syndrome, myeloproliferative neoplasms) gene analysis, full gene sequence |
| 81270 | JAK2 (Janus kinase 2) (eg, myeloproliferative disorder) gene analysis, p.Val617Phe (V617F) variant |
| 81279 | JAK2 (Janus kinase 2) (eg, myeloproliferative disorder) targeted sequence analysis (eg, exons 12 and 13) |
| 81334 | RUNX1 (runt related transcription factor 1) (eg, acute myeloid leukemia, familial platelet disorder with associated myeloid malignancy), gene analysis, targeted sequence analysis (eg, exons 3-8) |
| 81338 | MPL (MPL proto-oncogene, thrombopoietin receptor) (eg, myeloproliferative disorder) gene analysis; common variants (eg, W515A, W515K, W515L, W515R) |
| 81339 | MPL (MPL proto-oncogene, thrombopoietin receptor) (eg, myeloproliferative disorder) gene analysis; sequence analysis, exon 10 |
| 81347 | SF3B1 (splicing factor [3b] subunit B1) (eg, myelodysplastic syndrome/acute myeloid leukemia) gene analysis, common variants (eg, A672T, E622D, L833F, R625C, R625L) |
| 81348 | SRSF2 (serine and arginine-rich splicing factor 2) (eg, myelodysplastic syndrome, acute myeloid leukemia) gene analysis, common variants (eg, P95H, P95L) |
| 81357 | U2AF1 (U2 small nuclear RNA auxiliary factor 1) (eg, myelodysplastic syndrome, acute myeloid leukemia) gene analysis, common variants (eg, S34F, S34Y, Q157R, Q157P) |
| 81360 | ZRSR2 (zinc finger CCCH-type, RNA binding motif and serine/arginine-rich 2) (eg, myelodysplastic syndrome, acute myeloid leukemia) gene analysis, common variant(s) (eg, E65fs, E122fs, R448fs) |
| 81401 | Molecular pathology procedure, Level 2 (eg, 2-10 SNPs, 1 methylated variant, or 1 somatic variant [typically using nonsequencing target variant analysis], or detection of a dynamic mutation disorder/triplet repeat) |
| 81402 | Molecular pathology procedure, Level 3 (eg, >10 SNPs, 2-10 methylated variants, or 2-10 somatic variants [typically using non-sequencing target variant analysis], immunoglobulin and T-cell receptor gene rearrangements, duplication/deletion variants of 1 exon, loss of heterozygosity [LOH], uniparental disomy [UPD]) |
| 81403 | Molecular pathology procedure, Level 4 (eg, 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) |
| 0017U | Oncology (hematolymphoid neoplasia), JAK2 mutation, DNA, PCR amplification of exons 12-14 and sequence analysis, blood or bone marrow, report of JAK2 mutation not detected or detected |

| CPT®* Codes | Description |
|---|---|
| 0027U | JAK2 (Janus kinase 2) (eg, myeloproliferative disorder) gene analysis, targeted sequence analysis exons 12-15 |
| 0040U | BCR/ABL1 (t(9;22)) (eg, chronic myelogenous leukemia) translocation analysis, major breakpoint, quantitative |

**Considered Experimental/Investigational/Unproven:**

| CPT®* Codes | Description |
|---|---|
| 0011M | Oncology, prostate cancer, mRNA expression assay of 12 genes (10 content and 2 housekeeping), RT-PCR test utilizing blood plasma and/or urine, algorithms to predict high-grade prostate cancer risk |

**Not Covered or Reimbursable:**

| CPT®* Codes | Description |
|---|---|
| 0036U | Exome (ie, somatic mutations), paired formalin-fixed paraffin-embedded tumor tissue and normal specimen, sequence analyses |
| 0332U | Oncology (pan-tumor), genetic profiling of 8 DNA-regulatory (epigenetic) markers by quantitative polymerase chain reaction (qPCR), whole blood, reported as a high or low probability of responding to immune checkpoint-inhibitor therapy |
| 0343U | Oncology (prostate), exosome-based analysis of 442 small noncoding RNAs (sncRNAs) by quantitative reverse transcription polymerase chain reaction (RT-qPCR), urine, reported as molecular evidence of no-, low-, intermediate- or high-risk of prostate cancer |
| 0403U | Oncology (prostate), mRNA, gene expression profiling of 18 genes, first-catch, algorithm reported as percentage of likelihood of detecting clinically significant prostate cancer |
| 0424U | Oncology (prostate), exosome based analysis of 53 small noncoding RNAs (sncRNAs) by quantitative reverse transcription polymerase chain reaction (RTqPCR), urine, reported as no molecular evidence, low-, moderate- or elevated-risk of prostate cancer |
| 0433U | Oncology (prostate), 5 DNA regulatory markers by quantitative PCR, whole blood, algorithm, including prostate-specific antigen, reported as likelihood of cancer |
| 0436U | Oncology (lung), plasma analysis of 388 proteins, using aptamer-based proteomics technology, predictive algorithm reported as clinical benefit from immune checkpoint inhibitor therapy |
| 0486U | Oncology (pan-solid tumor), next generation sequencing analysis of tumor methylation markers present in cell-free circulating tumor DNA, algorithm reported as quantitative measurement of methylation as a correlate of tumor fraction (Code effective 10/01/2024) |
| 0495U | Oncology (prostate), analysis of circulating plasma proteins (tPSA, fPSA, KLK2, PSP94, and GDF15), germline polygenic risk score (60 variants), clinical information (age, family history of prostate cancer, prior negative prostate biopsy), algorithm reported as risk of likelihood of detecting clinically significant prostate cancer (Code effective 10/01/2024) |
| 0497U | Oncology (prostate), mRNA gene expression profiling by real-time RT-PCR of 6 genes (FOXM1, MCM3, MTUS1, TTC21B, ALAS1, and PPP2CA), utilizing formalin |

| CPT®* Codes | Description |
|---|---|
| | fixed paraffin-embedded (FFPE) tissue, algorithm reported as a risk score for prostate cancer (Code effective 10/01/2024) |
| 0498U | Oncology (colorectal), next generation sequencing for mutation detection in 43 genes and methylation pattern in 45 genes, blood, and formalin-fixed paraffin-embedded (FFPE) tissue, report of variants and methylation pattern with interpretation (Code effective 10/01/2024) |
| 0510U | Oncology (pancreatic cancer), augmentative algorithmic analysis of 16 genes from previously sequenced RNA whole transcriptome data, reported as probability of predicted molecular subtype (Code effective 10/01/2024) |
| 0512U | Oncology (prostate), augmentative algorithmic analysis of digitized whole-slide imaging of histologic features for microsatellite instability (MSI) status, formalin-fixed paraffin embedded (FFPE) tissue, reported as increased or decreased probability of MSI-high (MSI-H) (Code effective 10/01/2024) |
| 0513U | Oncology (prostate), augmentative algorithmic analysis of digitized whole-slide imaging of histologic features for microsatellite instability (MSI) and homologous recombination deficiency (HRD) status, formalin fixed paraffin-embedded (FFPE) tissue, reported as increased or decreased probability of each biomarker (Code effective 10/01/2024) |



## References

1. Iams WT, Mackay M, Ben-Shachar R, et al. Concurrent Tissue and Circulating Tumor DNA Molecular Profiling to Detect Guideline-Based Targeted Mutations in a Multicancer Cohort. JAMA Netw Open. 2024 Jan 2;7(1):e2351700.

2. Xie J, Yao W, Chen L, et al. Plasma ctDNA increases tissue NGS-based detection of therapeutically targetable mutations in lung cancers. BMC Cancer. 2023 Mar 31;23(1):294. doi: 10.1186/s12885-023-10674-z. PMID: 37004022; PMCID: PMC10063947.

3. Abida W, Cyrta J, Heller G, Prandi D, Armenia J, Coleman I, et al. Genomic correlates of clinical outcome in advanced prostate cancer. Proc Natl Acad Sci U S A. 2019 Jun 4;116(23):11428-11436.

4. Abraham JE, Maranian MJ, Driver KE, Platte R, Kalmyrzaev B, Baynes C, Luccarini C, Earl HM, Dunning AM, Pharoah PD, Caldas C. CYP2D6 gene variants and their association with breast cancer susceptibility. Cancer Epidemiol Biomarkers Prev. 2011 Jun;20(6):1255-8.

5. Agency for Healthcare Research and Quality (AHRQ). Molecular pathology testing for the estimation of prognosis for common cancers. 2014. Accessed Oct 12, 2020. Available at URL address: http://www.ahrq.gov/research/findings/ta/index.html#archive

6. Al-Amrani S, Al-Jabri Z, Al-Zaabi A, Alshekaili J, Al-Khabori M. Proteomics: Concepts and applications in human medicine. World J Biol Chem. 2021 27 Sep: 12(5):57-69.

7. Alberts SR1, Yu TM, Behrens RJ, Renfro LA, Srivastava G, Soori GS, Dakhil SR, Mowat RB, Kuebler JP, Kim GP, Mazurczak MA, Hornberger J. Comparative Economics of a 12-Gene

Assay for Predicting Risk of Recurrence in Stage II Colon Cancer. Pharmacoeconomics. 2014 Aug 26. [Epub ahead of print].

8. Alexander EK, Kennedy GC, Baloch ZW, Cibas ES, Chudova D,Diggans J, et al. Preoperative Diagnosis of Benign Thyroid Nodules with Indeterminate Cytology. N Engl J Med. 2012;367:705-715.

9. Alexander EK, Schorr M, Klopper J, Kim C, Sipos J, Nabhan F, Parker C, Steward DL, Mandel SJ,Haugen BR. Multicenter Clinical Experience with the Afirma Gene Expression Classifier. Clin Endocrinol Metab. 2013 Oct 23.

10. Allingham-Hawkins D, Lea A, Levine S. DecisionDx-GBM Gene Expression Assay for Prognostic Testing in Glioblastoma Multiform. PLoS Curr. 2010 Oct 12;2:RRN1186.

11. Alshalalfa M, Schliekelman M, Shin H, Erho N, Davicioni E. Evolving transcriptomic fingerprint based on genome-wide data as prognostic tools in prostate cancer. Biol Cell. 2015 Jul;107(7):232-44.

12. Amann JM, Lee JW, Roder H, Brahmer J, Gonzalez A, Schiller JH, Carbone DP. Genetic and proteomic features associated with survival after treatment with erlotinib in first-line therapy of non-small cell lung cancer in Eastern Cooperative Oncology Group 3503. J Thorac Oncol. 2010 Feb;5(2):16978.

13. American Academy of Dermatology Ad Hoc Task Force for the ABCDEs of Melanoma, Tsao H, Olazagasti JM, Cordoro KM, Brewer JD, Taylor SC, Bordeaux JS, Chren MM, Sober AJ, Tegeler C, Bhushan R, Begolka WS. Early detection of melanoma: reviewing the ABCDEs. J Am Acad Dermatol. 2015

14. American Association for Clinical Chemistry (AACC). ©2001-2019 by American Association of Clinical Chemistry. Tumor Markers. Accessed Sep 9, 2019. Available at URL address: https://labtestsonline.org/tests/tumor-markers

15. American Association of Clinical Endocrinologists. American Association of Clinical Endocrinologists, Associazione Medici Endocrinologi, and European Thyroid Association Medical Guidelines for Clinical Practice for the Diagnosis and Management of Thyroid Nodules. 2010, updated 2016. Accessed Sep 9, 2019. Available at URL address: https://www.aace.com/publications/guidelines

16. American College of Obstetricians and Gynecologists (ACOG). Evauation and management of adnexal masses. Practice Bulletin 174. November 2016. Accesed Sep 9, 2019. Available at URL address: https://www.acog.org/Clinical-Guidance-and-Publications/Practice-Bulletins-List

17. American Society of Clinical Oncology. Practice and Guidelines. Clinical Practice Guidelines: American Society of Clinical Oncology Clinical Practice Guideline. Accessed Oct 12, 2020. Available at URL address: https://www.asco.org/practice-guidelines/quality-guidelines/guidelines

18. American Society of Clinical Oncology (ASCO). Clinical practice guideline. Follow-up care, surveillance protocol, and secondary prevention measures for survivors of colorectal cancer: American Society of Clinical Oncology Clinical Practice Guideline Endorsement. Nov 2013. Accessed Sep 9, 2019. Available at URL address: http://jco.ascopubs.org/content/early/2013/11/04/JCO.2013.50.7442.full.pdf+html

19. American Society of Clinical Oncology (ASCO). Clinical practice guideline. Systemic Therapy for Stage IV Non–Small-Cell Lung Cancer: American Society of Clinical Oncology Clinical Practice Guideline Update. Oct 19, 2015. Accessed Sep 9, 2019. Available at URL address: http://ascopubs.org/pdf/doi/10.1200/JCO.2017.74.6065

20. American Society of Clinical Oncology (ASCO). Clinical practice guideline. Uses of serum tumor markers in adult males with germ cell tumors. Jul, 2010. Accessed Sep 9, 2019. Available at URL address: http://www.asco.org/guidelines/Genitourinary-Cancer

21. American Society of Clinical Oncology (ASCO). Circulating Tumor DNA Analysis in Patients With Cancer: American Society of Clinical Oncology and College of American Pathologists Joint Review. Accessed Sep 9, 2019. Available at URL address: http://ascopubs.org/doi/pdf/10.1200/JCO.2017.76.8671

22. American Society of Clinical Oncology-College of American Pathologists. Recommendations for human epidermal growth factor receptor 2 testing in breast cancer guideline update. 2013. Accessed Jan 14, 2022. Available at URL address: https://ascopubs.org/doi/pdf/10.1200/jco.2006.09.2775

23. American Society of Clinical Oncology (ASCO). Molecular Biomarkers for the Evaluation of Colorectal Cancer: Guideline From the American Society for Clinical Pathology, College of American Pathologists, Association for Molecular Pathology, and the American Society of Clinical Oncology. 2017. Accessed Jan 14, 2022. Available at URL address: http://ascopubs.org/doi/pdf/10.1200/JCO.2016.71.9807

24. American Urological Association. Prostate-specific antigen best practice statement: 2013 update. Accessed Jan 14, 2022. Available at URL address: https://www.auanet.org/guidelines/prostate-specific-antigen-(2009-amended-2013)

25. Andre F, Ismaila N, Henry NL, Somerfield MR, Bast RC, Barlow W, et al. , Use of biomarkers to guide decisions on adjuvant systemic therapy for women with early-stage invasive breast cancer: ASCO Clinical Practice Guideline Update—Integration of results from TAILORx. J Clin Oncol 37:1956-1964.

26. Antonarakis ES, Lu C, Wang H, Luber B, Nakazawa M, Roeser JC, et al. AR-V7 and resistance to enzalutamide and abiraterone in prostate cancer. N Engl J Med. 2014 Sep 11;371(11):1028-38.

27. Antonarakis ES, Lu C, Luber B, Wang H, Chen Y, Nakazawa M, t al. Androgen Receptor Splice Variant 7 and Efficacy of Taxane Chemotherapy in Patients With Metastatic Castration-Resistant Prostate Cancer. JAMA Oncol. 2015 Aug;1(5):582-91.

28. Arber DA, Orazi A, Hasserjian R et al. The 2016 revision to the World Health Organization classification of myeloid neoplasms and acute leukemia. Blood. 2016 May 19;127(20):2391-405.

29. Arpino G, Generali D, Sapino A, Del Mastro L, Frassoldati A, de Laurentis M, et al. Gene expression profiling in breast cancer: a clinical perspective. Breast. 2013 Apr;22(2):109-20.

30. Azim HA Jr, Michiels S, Zagouri F, Delaloge S, Filipits M, Namer M, et al. Symmans WF, Thompson A, André F, Loi S, Swanton C. Utility of prognostic genomic tests in breast

cancer practice: The IMPAKT 2012 Working Group Consensus Statement. Ann Oncol. 2013 Mar;24(3):647-54. doi: 10.1093/annonc/mds645. Epub 2013 Jan 20. Accessed Jan 14, 2022. Available at URL address: https://www.annalsofoncology.org/article/S0923-7534(19)37154-6/fulltext

31. Azueta A, Maiques O, Velasco A, Santacana M, Pallares J, Novell A, Llombart-Cussac A, Gonzalez-Tallada X, Mozos A, Prat J, Pillai R, Mata M, Matias-Guiu X. Gene expression microarray-based assay to determine tumor site of origin in a series of metastatic tumors to the ovary and peritoneal carcinomatosis of suspected gynecologic origin. Hum Pathol. 2012 Aug 30. [Epub ahead of print]

32. Badani K, Thompson DJ, Buerki C, Davicioni E, Garrison J, Ghadessi M, Mitra AP, Wood PJ, Hornberger J. Impact of a genomic classifier of metastatic risk on postoperative treatment recommendations for prostate cancer patients: a report from the DECIDE study group. Oncotarget. 2013 Apr;4(4):600-9.

33. Badani KK, Thompson DJ, Brown G, Holmes D, Kella N, Albala D, Singh A, Buerki C, Davicioni E, Hornberger J. Effect of a genomic classifier test on clinical practice decisions for patients with high-risk prostate cancer after surgery. BJU Int. 2015 Mar;115(3):419-29.

34. Beck AH, Rodriguez-Paris J, Zehnder J, Schrijver I. Evaluation of a gene expression microarray-based assay to determine tissue type of origin on a diverse set of 49 malignancies. Am J Surg Pathol. 2011 Jul;35(7):1030-7.

35. Bishoff JT, Freedland SJ, Gerber L, Tennstedt P, Reid J, Welbourn W et al. Prognostic utility of the cell cycle progression score generated from biopsy in men treated with prostatectomy. J Urol. 2014 Aug;192(2):409-14.

36. Blok EJ, Bastiaannet E, van den Hout WB, Liefers GJ, Smit VTHBM, et al. Systematic review of the clinical and economic value of gene expression profiles for invasive early breast cancer available in Europe. Cancer Treat Rev. 2018 Jan;62:74-90.

37. BlueCross BlueShield Association (BCBSA). Gene expression analysis for prostate cancer management. TEC Assessment. Chicago, IL: BCBSA; January 2015; Vol 29 No 9.

38. Blue Cross Blue Shield Center of Clinical Excellence. Gene Expression Profiling in Women With Lymph Node–Negative Breast Cancer to Select Adjuvant Chemotherapy. 2014. Vol 29 No 3.

39. Blue Cross Blue Shield Technology Evaluation Center (TEC). Special Report: companion diagnostics—example of BRAF gene mutation testing to select patients with melanoma for treatment with BRAF kinase inhibitors. 2011 November. Volume 26 No 7.

40. Boyle P, Chapman CJ, Holdenrieder S, Murray A, Robertson C, Wood WC, Maddison P, Healey G, Fairley GH, Barnes AC, Robertson JF. Clinical validation of an autoantibody test for lung cancer. Ann Oncol. 2011 Feb;22(2):383-9.

41. Bristow RE, Hodeib M, Smith A, Chan DW, Zhang Z, Fung ET, Tewari KS, Munroe DG, Ueland FR. Impact of a multivariate index assay on referral patterns for surgical management of an adnexal mass. Am J Obstet Gynecol. 2013 Aug 11. pii: S0002-9378(13)00835-1.]

42. Bristow RE, Smith A, Zhang Z, Chan DW, Crutcher G, Fung ET, Munroe DG. Ovarian malignancy risk stratification of the adnexal mass using a multivariate index assay. Gynecol Oncol. 2013 Feb;128(2):252-9.

43. Buyse M, Loi S, van't Veer L, Viale G, Delorenzi M, Glas AM, et al., Validation and clinical utility of a 70-gene prognostic signature for women with node-negative breast cancer. J Natl Cancer Inst. 2006 Sep 98(17):1183-92. Accessed Jan 14, 2022. Available at URL address: https://academic.oup.com/jnci/article-lookup/doi/10.1093/jnci/djj329

44. Cantara S, Capezzone M, Marchisotta S, Capuano S, Busonero G, Toti P, Di Santo A, Caruso G, Carli AF, Brilli L, Montanaro A, Pacini F. Impact of proto-oncogene mutation detection in cytological specimens from thyroid nodules improves the diagnostic accuracy of cytology. J Clin Endocrinol Metab. 2010 Mar;95(3):1365-9.

45. Carbone DP, Ding K, Roder H, Grigorieva J, Roder J, Tsao MS, Seymour L, Shepherd FA. Prognostic and predictive role of the VeriStrat plasma test in patients with advanced nonsmall cell lung cancer treated with erlotinib or placebo in the NCIC Clinical Trials Group BR.21 trial. J Thorac Oncol. 2012 Nov;7(11):165360.

46. Cardoso F, van't Veer LJ, Bogaerts J, Slaets L, Viale G, Delaloge S, et al. 70-Gene Signature as an Aid to Treatment Decisions in Early-Stage Breast Cancer. N Engl J Med. 2016 Aug 25;375(8):717-29.

47. Carvajal RD, Antonescu CR, Wolchok JD, Chapman PB, Roman RA, Teitcher J, Panageas KS, Busam KJ, Chmielowski B, Lutzky J, Pavlick AC, Fusco A, Cane L, Takebe N, Vemula S, Bouvier N, Bastian BC, Schwartz GK. KIT as a therapeutic target in metastatic melanoma. JAMA. 2011 Jun 8;305(22):2327-34.

48. Centers for Medicare and Medicaid Services (CMS) National Coverage Determination (NCD) and Local Coverage Determination (LCD). Available at URL address: https://www.cms.gov/medicare-coverage-database/search.aspx

49. Chang MC, Souter LH, Kamel-Reid S, Rutherford M, Bedard P, Trudeau M, et al. Molecular Oncology Advisory Committee. Clinical utility of multigene profiling assays in early-stage breast cancer. Curr Oncol. 2017 Oct;24(5):e403-e422.

50. Chapman CJ, Healey GF, Murray A, Boyle P, Robertson C, Peek LJ, Allen J, Thorpe AJ, Hamilton-Fairley G, Parsy-Kowalska CB, MacDonald IK, Jewell W, Maddison P, Robertson JF. EarlyCDT®-Lung test: improved clinical utility through additional autoantibody assays. Tumour Biol. 2012 Oct;33(5):1319-26.

51. Chen RC, Rumble RB, Loblaw DA, Finelli A, Ehdaie B, Cooperberg MR, et al. Active Surveillance for the Management of Localized Prostate Cancer (Cancer Care Ontario Guideline): American Society of Clinical Oncology Clinical Practice Guideline Endorsement. J Clin Oncol. 2016 Jun 20;34(18):2182-90.

52. Chen X, Ba Y, Ma L, et al. Characterization of microRNAs in serum: a novel class of biomarkers for diagnosis of cancer and other diseases. Cell Res. 2008;18(10):997-1006.

53. Chia SKL. Clinical application and utility of genomic assays in early-stage breast cancer: key lessons learned to date. Curr Oncol. 2018 Jun;25(Suppl 1):S125-S130.

54. Chua TC, Merrett ND. Clinicopathologic factors associated with HER2-Positive gastric cancer and its impact on survival outcomes - a systematic review. Int J Cancer. 2011 Jul 21. doi: 10.1002/ijc.26292.

55. Chudova D, Wilde JI, Wang ET, Wang H, Rabbee N, Egidio CM, Reynolds J, Tom E, Pagan M, Rigl CT, Friedman L, Wang CC, Lanman RB, Zeiger M, Kebebew E, Rosai J, Fellegara G, LiVolsi VA, Kennedy GC. Molecular classification of thyroid nodules using high-dimensionality genomic data. J Clin Endocrinol Metab. 2010 Dec;95(12):5296-304.

56. Chung C, Christianson M. Predictive and prognostic biomarkers with therapeutic targets in breast, colorectal, and non-small cell lung cancers: a systemic review of current development, evidence, and recommendation. J Oncol Pharm Pract. 2014 Feb;20(1):11-28.

57. Clark-Langone KM, Sangli C, Krishnakumar J, Watson D. Translating tumor biology into personalized treatment planning: analytical performance characteristics of the Oncotype DX Colon Cancer Assay. BMC Cancer. 2010 Dec 23;10:691.

58. Coates AS, Winer EP, Goldhirsch A, Gelber RD, Gnant M, Piccart-Gebhart M, et al., Tailoring therapies--improving the management of early breast cancer: St Gallen International Expert Consensus on the Primary Therapy of Early Breast Cancer 2015. Ann Oncol. 2015 Aug;26(8):1533-46

59. Colman H, Zhang L, Sulman EP, McDonald JM, Shooshtari NL, Rivera A, Popoff S, Nutt CL, Louis DN, Cairncross JG, Gilbert MR, Phillips HS, Mehta MP, Chakravarti A, Pelloski CE, Bhat K, Feuerstein BG, Jenkins RB, Aldape K. A multigene predictor of outcome in glioblastoma. Neuro Oncol. 2010 Jan;12(1):49-57.

60. Cullen J, Rosner IL, Brand TC, Zhang N, Tsiatis AC, Moncur J et al. A Biopsy-based 17-gene Genomic Prostate Score Predicts Recurrence After Radical Prostatectomy and Adverse Surgical Pathology in a Racially Diverse Population of Men with Clinically Low- and Intermediate-risk Prostate Cancer. Eur Urol. 2015 Jul;68(1):123-31.

61. Curigliano G, Burstein HJ, Winer EP, Gnant M, Dubsky P, Loibl S, et al. De-escalating and escalating treatments for early-stage breast cancer: the St. Gallen International Expert Consensus Conference on the Primary Therapy of Early Breast Cancer 2017. Ann Oncol. 2017 Aug 1;28(8):1700-1712. doi: 10.1093/annonc/mdx308. Erratum in: Ann Oncol. 2018 Oct 1;29(10):2153. Ann Oncol. 2019 Jan 9.

62. Cuzick J, Swanson GP, Fisher G, Brothman AR, Berney DM, Reid JE, Mesher D,Speights VO, Stankiewicz E, Foster CS, Møller H, Scardino P, Warren JD, Park J,Younus A, Flake DD 2nd, Wagner S, Gutin A, Lanchbury JS, Stone S; Transatlantic Prostate Group. Prognostic value of an RNA expression signature derived from cell cycle proliferation genes in patients with prostate cancer: a retrospective study. Lancet Oncol. 2011 Mar;12(3):245-55.

63. Cuzick J, Berney DM, Fisher G, Mesher D, Møller H, Reid JE, Perry M, Park J,Younus A, Gutin A, Foster CS, Scardino P, Lanchbury JS, Stone S; Transatlantic Prostate Group. Prognostic value of a cell cycle progression signature for prostate cancer death in a conservatively managed needle biopsy cohort. Br J Cancer. 2012 Mar 13;106(6):1095-9.

64. Cwik G, Wallner G, Skoczylas T, Ciechanski A, Zinkiewicz K. Cancer antigens 19-9 and 125 in the differential diagnosis of pancreatic mass lesions. Arch Surg. 2006 Oct;141(10):968-

73; discussion 974.Cooper, D, Doherty, G, Haugen, B, Kloos, R, Lee, S, Mandel, S, Mazzaferri, E, Mclver, B, Pacini, F, Schlumberger, M, Sherman, S, Steward, D, Tuttle, M. Revised American Thyroid Association Management Guidelines for Patients with Thyroid Nodules and Differentiated Thyroid Cancer. The American Thyroid Association (ATA) Guidelines Taskforce on Thyroid Nodules and Differentiated Thyroid Cancer. THYROID. Volume 19, Number 11, 2009

65. Den RB, Yousefi K, Trabulsi EJ, Abdollah F, Choeurng V, Feng FY, Dicker AP,Lallas CD, Gomella LG, Davicioni E, Karnes RJ. Genomic classifier identifies men with adverse pathology after radical prostatectomy who benefit from adjuvant radiation therapy. J Clin Oncol. 2015 Mar 10;33(8):944-51. Epub 2015 Feb 9. Erratum in: J Clin Oncol. 2015 Apr 20;33(12):1416.

66. DermNet NZ. Fitzpatrick skin phototype. Accessed Jul 12, 2021. Available at URL address: https://dermnetnz.org/topics/skin-phototype/

67. Devitt, B, Liu, W, Salemi, R, Wolfe, R, Kelly, J, Tzen, CY, Dobrovic, A, and McArthur, G. Clinical outcome and pathological features associated with NRAS mutation in cutaneous melanoma. Pigment Cell Melanoma Res. 2011; 24: 666–672.

68. Dezentje VO, Guchelaar HJ, Nortier JW, van de Velde CJ, Gelderblom H. Clinical implications of CYP2D6 genotyping in tamoxifen treatment for breast cancer. Clin Cancer res. 2009 Jan1;15(1):15-21.

69. Dhillon, et al. Gene expression profile signature (DecisionDx-Melanoma) to predict visceral metastatic risk in patients with Stage I and Stage II cutaneous melanoma. J Clin Oncol 2012;30(suppl; abstr 8543).

70. Drukker CA, Bueno-de-Mesquita JM, Retèl VP, van Harten WH, van Tinteren H, Wesseling J, et al. A prospective evaluation of a breast cancer prognosis signature in the observational RASTER study. Int J Cancer. 2013 Aug 15;133(4):929-36.

71. Duffy MJ, Harbeck N, Nap M, Molina R, Nicolini A, Senkus E, et al. Clinical use of biomarkers in breast cancer: Updated guidelines from the European Group on Tumor Markers (EGTM). Eur J Cancer. 2017 Apr;75:284-298.

72. Duick, D, Klopper, J, Diggans, J, Friedman, L, Kennedy, G, Lanman, R, and Mclver, B. The Impact of benign gene expression classifier test results on the endocrinologist–patient decision to operate on patients with thyroid nodules with indeterminate fine-needle aspiration cytopathology. Thyroid. Oct 2012; 22(10): 996–1001.

73. Ellery B, Parsons J, Merlin T. Molecular testing for prostate cancer prognosis. Technology Brief. Herston, QLD: Department of Health, Queensland; November 2014.

74. Engelman JA, Chen L, Tan X, et al. .Effective use of PI3K and MEK inhibitors to treat mutant Kras G12D and PIK3CA H1047R murine lung cancers. Nat Med. 2008 Dec;14(12):1351-6.

75. Erho N, Crisan A, Vergara IA, Mitra AP, Ghadessi M, Buerki C, et al. Discovery and validation of a prostate cancer genomic classifier that predicts early metastasis following radical prostatectomy. PLoS One. 2013 Jun 24;8(6):e66855.

76. Ernst T, Hoffmann J, Erben P, Hanfstein B, Leitner A, Hehlmann R, et al. ABL single nucleotide polymorphisms may masquerade as BCR-ABL mutations associated with resistance to tyrosine kinase in patients with chronic myeloid leukemia. Haematologica. 2008b Sep;93(9):1389-93.

77. Falzarano SM, Ferro M, Bollito E, Klein EA, Carrieri G, Magi-Galluzzi C. Novel biomarkers and genomic tests in prostate cancer: a critical analysis. Minerva Urol Nefrol. 2015 Sep;67(3):211-31.

78. Ferris LK, Jansen B, Ho J, Busam KJ, Gross K, Hansen DD et al. Utility of a Noninvasive 2-Gene Molecular Assay for Cutaneous Melanoma and Effect on the Decision to Biopsy. JAMA Dermatol. 2017 Jul 1;153(7):675-680.

79. Ferris LK, Rigel DS, Siegel DM, Skelsey MK, Peck GL, Hren C, Gorman C, Frumento T, Jansen B, Yao Z, Rock J, Knezevich SR, Cockerell CJ. Impact on clinical practice of a non-invasive gene expression melanoma rule-out test: 12-month follow-up of negative test results and utility data from a large US registry study. Dermatol Online J. 2019 May 15;25(5):13030/qt61w6h7mn. Erratum in: Dermatol Online J. 2019 Jun 06;25(6): PMID: 31220892.

80. Ferris RL, Baloch Z, Bernet V, et al. American Thyroid Association statement on surgical application of molecular profiling for thyroid nodules: current impact on perioperative decision making. Thyroid. 2015 Jul;25(7):760-8.

81. Ferraz, C, Eszlinger, M, and Paschke, R. Current state and future perspective of molecular diagnosis of fine-needle aspiration biopsy of thyroid nodules. J Clin Endocrinol Metab. 2011.

82. Fiala O, Pesek M, Finek J, Benesova L, Bortlicek Z, Minarik M. Gene Mutations in Squamous Cell NSCLC: Insignificance of EGFR, KRAS and PIK3CA Mutations in Prediction of EGFR-TKI Treatment Efficacy.Anticancer Res. 2013 Apr;33(4):1705-11.

83. Fidler MJ, Morrison LE, Basu S, et al. PTEN and PIK3CA gene copy numbers and poor outcomes in non-small cell lung cancer patients with gefitinib therapy Br J Cancer. 2011 December 6; 105(12): 1920–1926.

84. Filipits M, Nielsen TO, Rudas M, Greil R, Stöger H, Jakesz R, et al. The PAM50 risk-of-recurrence score predicts risk for late distant recurrence after endocrine therapy in postmenopausal women with endocrine-responsive early breast cancer. Clin Cancer Res. 2014 Mar 1;20(5):1298-305. Accessed Jan 14, 2022. Available at URL address: http://clincancerres.aacrjournals.org/content/20/5/1298.

85. Filipits M, Rudas M, Jakesz R, Dubsky P, Fitzal F, Singer CF, et al. A new molecular predictor of distant recurrence in ER-positive, HER2-negative breast cancer adds independent information to conventional clinical risk factors. Clin Cancer Res. 2011 Sep 15;17(18):6012-20.

86. Fleeman N, Martin Saborido C, Payne K, Boland A, Dickson R, Dundar Y, et al. The clinical effectiveness and cost-effectiveness of genotyping for CYP2D6 for management of women with breast cancer treated with tamoxifen: a systematic review. Health Technol Assess. 2011 Sep;15(33):1-102.

87. Frampton GM1, Fichtenholtz A, Otto GA, Wang K, Downing SR, He J, et al. Development and validation of a clinical cancer genomic profiling test based on massively parallel DNA sequencing. Nat Biotechnol. 2013 Nov;31(11):1023-31.

88. Freedland SJ, Gerber L, Reid J, Welbourn W, Tikishvili E, Park J, et al. Prognostic utility of cell cycle progression score in men with prostate cancer after primary external beam radiation therapy. Int J Radiat Oncol Biol Phys. 2013 Aug 1;86(5):848-53.

89. Gautschi et al. A patient with BRAF V600E lung adenocarcinoma responding to vemurafenib. J Thorac Oncol. 2012 Oct;7(10):e23-4.

90. Glass AG, Leo MC, Haddad Z, Yousefi K, du Plessis M, Chen C, et al. Validation of a Genomic Classifier for Predicting Post-Prostatectomy Recurrence in a Community Based Health Care Setting. J Urol. 2016 Jun;195(6):1748-53.

91. Gnant M, Filipits M, Greil R, Stoeger H, Rudas M, Bago-Horvath Z, et al. Predicting distant recurrence in receptor-positive breast cancer patients with limited clinicopathological risk: using the PAM50 Risk of Recurrence score in 1478 postmenopausal patients of the ABCSG-8 trial treated with adjuvant endocrine therapy alone. Ann Oncol. 2014 Feb;25(2):339-45.

92. Goetz MP, Sun JX, Suman VJ, Silva GO, Perou CM, Nakamura Y, et al. Loss of heterozygosity at the CYP2D6 locus in breast cancer: implications for germline pharmacogenetic studies. J Natl Cancer Inst. 2014 Dec 8;107(2).

93. Gregorc V, Novello S, Lazzari C, Barni S, Aieta M, Mencoboni M, et al. Predictive value of a proteomic signature in patients with non-small-cell lung cancer treated with second-line erlotinib or chemotherapy

94. (PROSE): a biomarker-stratified, randomised phase 3 trial. Lancet Oncol. 2014 Jun;15(7):713-21.

95. Harnan S, Tappenden P, Cooper K, Stevens J, Bessey A, Rafia R, Ward S, Wong R, Stein RC, Brown J. Tumour profiling tests to guide adjuvant chemotherapy decisions in early breast cancer: a systematic review and economic analysis. Health Technol Assess. 2019 Jun;23(30):1-328.

96. Higgins MJ, Stearns V. CYP2D6 polymorphisms and tamoxifen metabolism: clinical relevance. Curr Oncol Rep. 2010 Jan;12(1):7-15.

97. Huang Y, Chen Y, Mei Q, et al. Combined inhibition of the EGFR and mTOR pathways in EGFR wild-type non-small cell lung cancer cell lines with different genetic backgrounds. Oncol Rep. 2013 Jun;29(6):2486-92.

98. Jabbour E, Cortez J, Kantarjian HM. Nilotinib for the treatment of chronic myelogenous leukemia: an evidence-based review. Core Evid. 2010 June 15;4:207-13.

99. Jansen B, Hansen D, Moy R, Hanhan M, Yao Z. Gene Expression Analysis Differentiates Melanomas from Spitz Nevi. J Drugs Dermatol. 2018 May 1;17(5):574-576.

100. Klein EA, Cooperberg MR, Magi-Galluzzi C, Simko JP, Falzarano SM, Maddala T,Chan JM, et al. A 17-gene assay to predict prostate cancer aggressiveness in the context of Gleason grade heterogeneity, tumor multifocality, and biopsy undersampling. Eur Urol. 2014 Sep;66(3):550-60. doi: 10.1016/j.eururo.2014.05.004. Epub 2014 May 16.

101. Kloos RT, Reynolds JD, Walsh PS, Wilde JI, Tom EY, Pagan M, et al. Does addition of BRAF V600E mutation testing modify sensitivity or specificity of the Afirma Gene Expression Classifier in cytologically indeterminate thyroid nodules? J Clin Endocrinol Metab. 2013 Apr;98(4):E761-8. doi: 10.1210/jc.2012-3762. Epub 2013 Mar 8.

102. Knauer M, Mook S, Rutgers EJ, Bender RA, Hauptmann M, van de Vijver MJ, et al. The predictive value of the 70-gene signature for adjuvant chemotherapy in early breast cancer. Breast. Cancer Res Treat. 2010 Apr;120(3):655-61.

103. Kok M, Koornstra RH, Mook S, Hauptmann M, Fles R, Jansen MP, et al. Additional value of the 70-gene signature and levels of ER and PR for the prediction of outcome in tamoxifen-treated ER-positive breast cancer. Breast. 2012 Dec;21(6):769-78.

104. Kung JS, Lopez OA, McCoy EE, Reicher S, Eysselein VE. Fluid genetic analyses predict the biological behavior of pancreatic cysts: three-year experience. JOP. 2014 Sep 28;15(5):427-32.

105. Labourier E, Shifrin A, Busseniers AE, et al. Molecular testing for miRNA, mRNA and DNA on fine needle aspiration improves the preoperative diagnosis of thyroid nodules with indeterminate cytology. J Clin Endocrinol Metab. 2015 May;jc20151158.

106. Lash TL, Cronin-Fenton D, Ahern TP, Rosenberg CL, Lunetta KL, Silliman RA, Garne JP, Sorensen HT, Hellberg Y, Christensen M, Pedersen L, Hamilton-Dutoit S. CYP2D6 inhibition and breast cancer recurrence in a population-based study in Denmark. J Natl Cancer Inst. 2011 Mar 16;103(6):489-500.

107. Lee, JH, Choi, JW, Kim, YS. Frequencies of BRAF and NRAS mutations are different in histological types and sites of origin of cutaneous melanoma: a meta-analysis. British Association of Dermatologists. 2011;164: 776–784.

108. Lee HJ, Yousefi K, Haddad Z, Abdollah F, Lam LL, Shin H, et al. Evaluation of a genomic classifier in radical prostatectomy patients with lymph node metastasis. Res Rep Urol. 2016 Jun 28;8:77-84.

109. Leighl NB, Rekhtman N, Biermann WA, Huang J, Mino-Kenudson M, Ramalingam SS, et al. Molecular testing for selection of patients with lung cancer for epidermal growth factor receptor and anaplastic lymphoma kinase tyrosine kinase inhibitors: American Society of Clinical Oncology endorsement of the College of American Pathologists/International Association for the study of lung cancer/association for molecular pathology guideline. J Clin Oncol. 2014 Nov 10;32(32):3673-9.

110. Lindeman NI, Cagle PT, Beasley MB, Chitale DA, Dacic S, Giaccone G, et al. Molecular testing guideline for selection of lung cancer patients for EGFR and ALK tyrosine kinase inhibitors: guideline from the College of American Pathologists, International Association for the Study of Lung Cancer, and Association for Molecular Pathology. J Mol Diagn. 2013 Jul;15(4):415-53.

111. Ludovini V, Bianconi F, Pistola L, et al. Phosphoinositide-3-kinase catalytic alpha and KRAS mutations are important predictors of resistance to therapy with epidermal growth factor receptor tyrosine kinase inhibitors in patients with advanced non-small cell lung cancer. J Thorac Oncol. 2011 Apr;6(4):707-15.

112. Lynch TJ, Bell DW, Sordella R, Gurubhagavatula S, Okimoto RA, et al. (2004) Activating mutations in the epidermal growth factor receptor underlying responsiveness of non-small-cell lung cancer to gefitinib. N Engl J Med 350: 2129–2139.

113. Martin M, Brase JC, Calvo L, Krappmann K, Ruiz-Borrego M, Fisch K, et al. Clinical validation of the EndoPredict test in node-positive, chemotherapy-treated ER+/HER2- breast cancer patients: results from the GEICAM 9906 trial. Breast Cancer Res. 2014 Apr 12;16(2):R38.

114. McArthur GA, Chapman PB, Robert C, Larkin J, Haanen JB, Dummer R, et al. Safety and efficacy of vemurafenib in BRAF(V600E) and BRAF(V600K) mutation-positive melanoma (BRIM-3): extended follow-up of a phase 3, randomised, open-label study. Lancet Oncol. 2014 Mar;15(3):323-32.

115. Melanoma of the Skin. In S.B. Edge (Ed.). American Joint Committee on Cancer. New York, NY: Springer. (2010). (pp 325-344)

116. Metz CH, Scheulen M, Bornfeld N, Lohmann D, Zeschnigk M. Ultradeep sequencing detects GNAQ and GNA11 mutations in cell-free DNA from plasma of patients with uveal melanoma. Cancer Med. 2013 Apr;2(2):208-15.

117. Michalopoulos SN, Kella N, Payne R, Yohannes P, Singh A, Hettinger C, et al. Influence of a genomic classifier onpost-operative treatment decisions in high-risk prostate cancer patients: results from the PRO-ACT study. Curr Med Res Opin. 2014 Aug;30(8):1547-56.

118. Morrow PK, Serna R, Broglio K, Pusztai L, Nikoloff DM, Hillman GR, Fontecha M, Li R, Michaud L, Hortobagyi G, Gonzalez-Angulo AM. Effect of CYP2D6 polymorphisms on breast cancer recurrence. Cancer. 2012 Mar 1;118(5):1221-7.

119. National Cancer Institute. Accessed Jan 14, 2022. Available at URL address: http://www.cancer.gov/

120. National Comprehensive Cancer Network® (NCCN). NCCN GUIDELINES™ Clinical Practice Guidelines in Oncology. National Comprehensive Cancer Network. 2023. Accessed Jan 14, 2023. Available at URL address: http://www.nccn.org/

121. National Institute for Health and Care Excellence. Investigating and diagnosing metastatic malignant disease of unknown primary origin. ©NICE 2017. Updated Nov 11, 2016. Accessed Jan 14, 2022. Available at URL address: https://www.nice.org.uk/guidance/CG104

122. National Institute for Health and Care Excellence. Tumour profiling tests to guide adjuvant chemotherapy decisions in early breast cancer. Published Dec 2018. Accessed Jan 14, 2022. Available at URL address: https://www.nice.org.uk/guidance/dg34

123. Nelson RE, Stehnehjem D, Akerley W. A comparison of individualized treatment guided by VeriStrat with standard of care treatment strategies in patients receiving second-line treatment for advanced non-small cell lung cancer: A cost utility analysis. Lung Cancer. 2013 Dec;82(3):4618. Epub 2013
Sep 3.

124. Nicolini FE, Mauro MJ, Martinelli G, Kim DW, Soverini S, Muller MC, et al. Epidemiological study on survival of chronic myeloid leukemia and Ph (+) acute lymphoblastic leukemia patients with BCR-ABL T315-I mutations. Blood. 2009 Dec 17;114(26):5271-8.

125. Nielsen TO, Parker JS, Leung S, Voduc D, Ebbert M, Vickery T, et al. A comparison of PAM50 intrinsic subtyping with immunohistochemistry and clinical prognostic factors in tamoxifen-treated estrogen receptor-positive breast cancer. Clin Cancer Res. 2010 Nov 1;16(21):5222-32.

126. Nikiforov YE, Ohori NP, Hodak SP, et al. Impact of mutational testing on the diagnosis and management of patients with cytologically indeterminate thyroid nodules: a prospective analysis of 1056 FNA samples. J Clin Endocrinol Metab. 2011;96:3390–3397.

127. Park HS, Choi JY, Lee MJ, Park S, Yeo CW, Lee SS, Shin JG, Park BW. Association between genetic polymorphisms of CYP2D6 and outcomes in breast cancer patients with tamoxifen treatment. J Korean Med Sci. 2011 Aug;26(8):1007-13.

128. Partin AW, Van Neste L, Klein EA, Marks LS, Gee JR, Troyer DA, et al. Clinical validation of an epigenetic assay to predict negative histopathological results in repeat prostate biopsies. J Urol. 2014 Oct;192(4):1081-7.

129. Rae JM, Drury S, Hayes DF, Stearns V, Thibert JN, Haynes BP, et al. CYP2D6 and UGT2B7 genotype and risk of recurrence in tamoxifen-treated breast cancer patients. J Natl Cancer Inst. 2012 Mar 21;104(6):452-60.

130. Ramón Y Cajal T, Altés A, Paré L, Del Rio E, Alonso C, Barnadas A, Baiget M. Impact of CYP2D6 polymorphisms in tamoxifen adjuvant breast cancer treatment. Breast Cancer Res Treat. 2010 Jan;119(1):33-8. Epub 2009 Feb 3.

131. Robinson D, Van Allen EM, Wu YM, Schultz N, Lonigro RJ, Mosquera JM, et al. Integrative Clinical Genomics of Advanced Prostate Cancer. Cell. 2015 Jul 16;162(2):454. Epub 2015 Jul 16.

132. Ross AE, Feng FY, Ghadessi M, Erho N, Crisan A, Buerki C, et al. A genomic classifier predicting metastatic disease progression in men with biochemical recurrence after prostatectomy. ProstateCancer Prostatic Dis. 2014 Mar;17(1):64-9. doi: 10.1038/pcan.2013.49.

133. Ross AE, Johnson MH, Yousefi K, Davicioni E, Netto GJ, Marchionni L, et al. Tissue-based Genomics Augments Post-prostatectomy Risk Stratification in a Natural History Cohort of Intermediate- and High-Risk Men. Eur Urol. 2016 Jan;69(1):157-65.

134. Ruddy KJ, Desantis SD, Gelman RS, Wu AH, Punglia RS, Mayer EL, Tolaney SM, Winer EP, Partridge AH, Burstein HJ. Personalized medicine in breast cancer: tamoxifen, endoxifen, and CYP2D6 in clinical practice. Breast Cancer Res Treat. 2013 Oct;141(3):421-7

135. Sacco K, Grech G. Actionable pharmacogenetic markers for prediction and prognosis in breast cancer. EPMA J. 2015 Jul 22;6(1):15. doi: 10.1186/s13167-015-0037-z. eCollection 2015.

136. Salto-Tellez M, Tsao MS, Shih JY, Thongprasert S, Lu S, et al. (2011) Clinical and testing protocols for the analysis of epidermal growth factor receptor mutations in East Asian

patients with non-small cell lung cancer: a combined clinical-molecular pathological approach. J Thorac Oncol 6: 1663–1669.

137. Satoh T, Ura T, Yamada Y, Yamazaki K, Tsujinaka T, Munakata M, Nishina T, Okamura S, Esaki T, Sasaki Y, Koizumi W, Kakeji Y, Ishizuka N, Hyodo I, Sakata Y. Genotype-directed, dose-finding study of irinotecan in cancer patients with UGT1A1*28 and/or UGT1A1*6 polymorphisms. Cancer Sci. 2011 Oct;102(10):1868-73.

138. Sestak I, Dowsett M, Zabaglo L, Lopez-Knowles E, Ferree S, Cowens JW, Cuzick J. Factors predicting late recurrence for estrogen receptor-positive breast cancer. J Natl Cancer Inst. 2013 Oct 2;105(19):1504-11.

139. Sequist LV, Waltman BA, Dias-Santagata D, et al. Genotypic and Histological Evolution of Lung Cancers Acquiring Resistance to EGFR Inhibitors Sci Transl Med. Author manuscript; available in PMC 2011 September 23. Published in final edited form as: Sci Transl Med. 2011 March 23; 3(75): 75ra26.

140. Shulman K, Cohen I, Barnett-Griness O, Kuten A, Gruber SB, Lejbkowicz F, Rennert G. Clinical implications of UGT1A1*28 genotype testing in colorectal cancer patients. Cancer. 2011 Jul 15;117(14):3156-62.

141. Sommariva S, Tarricone R, Lazzeri M, Ricciardi W, Montorsi F. Prognostic Value of the Cell Cycle Progression Score in Patients with Prostate Cancer: A Systematic Review and Meta-analysis. Eur Urol. 2016 Jan;69(1):107-15.

142. Soverini S, Hochhaus A, Nicolini FE, Gruber F, Lange T, Saglio G, et al. BCR-ABL kinase domain mutation analysis in chronic myeloid leukemia patients treated with tyrosine kinase inhibitors: recommendations from an expert panel on behalf of European LeukemiaNet. Blood. 2011 Aug 4;118(5):1208-15.

143. Sparano JA, Gray RJ, Makower DF, Pritchard KI, Albain KS, Hayes DF, et al. Prospective Validation of a 21-Gene Expression Assay in Breast Cancer. N Engl J Med. 2015 Nov 19;373(21):2005-14.

144. Stein RC, Dunn JA, Bartlett JM, Campbell AF, Marshall A, Hall P, et al. OPTIMA prelim: a randomised feasibility study of personalised care in the treatment of women with early breast cancer. Health Technol Assess. 2016 Feb;20(10):1-202.

145. Stewart GD, Van Neste L, Delvenne P, Delrée P, Delga A, McNeill SA, et al. Clinical utility of an epigenetic assay to detect occult prostate cancer in histopathologically negative biopsies: results of the MATLOC study. J Urol. 2013 Mar;189(3):1110-6.

146. Stockman, D, Tetzlaff, MT, Al-Zaid, T, Torres-Cabala, CA, Bucheit, AD, Lazar, et al. Differential clinical associations of BRAF and NRAS mutations among histologic types of cutaneous melanomas. J Clin Oncol 2013 (suppl; abstr e20034).

147. Sun W, Hu G, Long G, et al. Predictive value of a serum based proteomic test in non-small cell lung cancer patients treated with epidermal growth factor receptor tyrosine kinase inhibitors: a metaanalysis. Curr Med Res Opin. 2014 Jul 9:17. [Epub ahead of print]

148. U.S. Department of Health and Human Service. Center for Medicare and Medicaid Services. Agency for Healthcare Research and Quality; Technology Assessment: Systematic reviews on selected pharmacogenetic tests for cancer treatment: CYP2D6 for

Tamoxifen in breast cancer, KRAS for anti-EGFR antibodies in colorectal cancer, and BCR-ABL1 for tyrosine kinase inhibitors in chronic myeloid leukemia.

149. U.S. Department of Health and Human Services. National Institutes of Health. National Cancer Institute (NCI). Accessed Jan 14, 2022. Available at URL address: https://www.cancer.gov/

150. U.S. Food and Drug Administration. PMA number: P150044. cobas EGFR MUTATION TEST v2. Accessed Jan 14, 2022. Available at URL address: https://www.accessdata.fda.gov/scripts/cdrh/devicesatfda/index.cfm?db=pma&id=320648

151. van der Bol JM, Mathijssen RH, Creemers GJ, Planting AS, Loos WJ, Wiemer EA, et al. A CYP3A4 phenotype-based dosing algorithm for individualized treatment of irinotecan. Clin Cancer Res. 2010 Jan 15;16(2):736-42.

152. Van Poznak C, Harris LN, Somerfield MR. Use of Biomarkers to Guide Decisions on Systemic Therapy for Women With Metastatic Breast Cancer: American Society of Clinical Oncology Clinical Practice Guideline. J Oncol Pract. 2015 Nov;11(6):514-6.

153. Vijayalakshmi R, Krishnamurthy A. Targetable "driver" mutations in non small cell lung cancer. Indian J Surg Oncol. 2011 Sep;2(3):178-88.

154. Villaflor VM, Salgia R. Targeted agents in non-small cell lung cancer therapy: What is there on the horizon? J Carcinog. 2013 Mar 18;12:7.

155. Ward S, Scope A, Rafia R, Pandor A, Harnan S, Evans P, et al. Gene expression profiling and expanded immunohistochemistry tests to guide the use of adjuvant chemotherapy in breast cancer management: a systematic review and cost-effectiveness analysis. Health Technol Assess, 2013;17(44).

156. Yao Z, Allen T, Oakley M, Samons C, Garrison D, Jansen B. Analytical Characteristics of a Noninvasive Gene Expression Assay for Pigmented Skin Lesions. Assay Drug Dev Technol. 2016 Aug;14(6):355-63.

## Revision Details

| Type of Revision | Summary of Changes | Date |
|---|---|---|
| Focused review | • Removed policy statements for targeted PIK3CA and NTRK fusions testing; specific gene expression testing for breast cancer; certain prostate cancer tests; occult neoplasms; topographic genotyping; and adhesive patch gene expression assay.<br>• Added policy statement for specific not covered or reimbursable tests. | 11/1/2024 |
| Annual review | • Revised general criteria for somatic pathogenic or likely pathogenic variant genetic testing.<br>• Removed policy statement for VeriStrat. | 5/15/2024 |