Medical Coverage Policy

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Tumor Profiling, Gene Expression Assays and Molecular Diagnostic Testing for Hematology/Oncology Indications

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Related Coverage Resources

Genetics
Genetic Testing Collateral File

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Overview

This Coverage Policy addresses tumor profiling, gene expression assays and molecular diagnostic testing for selected hematology/oncology indications. Somatic mutations are changes in the DNA of cells that are not inherited or passed down by blood relatives. They may occur in any cell of the body except the germ cells (i.e., egg and sperm). These tests are used to identify disease-causing somatic mutations or the biological activity of genes originating in a tumor or hematologic malignancy.

This type of testing can aid in determining the extent or stage of disease, probability of recurrence, appropriate treatment options and how well the disease may respond to treatment in certain clinical scenarios.

Coverage Policy

Many benefit plans limit coverage of genetic testing and genetic counseling services. Please refer to the applicable benefit plan language to determine benefit availability and terms, conditions and limitations of coverage for the services discussed in this Coverage Policy.

For additional information regarding coverage for specific genetic tests please refer to the Genetic Testing Collateral: Molecular Tests and Biomarkers.

General Criteria for Somatic Pathogenic or Likely Pathogenic Variant Genetic Testing

Medically Necessary

Tumor biomarker or 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 tumor biomarker or disease site
- 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
- EITHER of the following:
  - identification of the specific biomarker or risk assessment using a GEC is required in order to initiate a related therapy and the therapy 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 site
  - identification of the specific biomarker or 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

Experimental/Investigational/Unproven:

Molecular testing for hematology-oncology indications is considered experimental, investigational or unproven in the following situations:

- there is insufficient evidence to support molecular testing for the specific tumor type or disease site
- the requested gene(s) or biomarker(s) are correlated with a known therapy, but that therapy has not been validated for the specific tumor type or disease site

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Tumor Profile/Gene Expression Classifier Testing -

Medically Necessary

Tumor profile/gene expression classifier testing (GEC) is considered medically necessary when ALL of the following criteria are met:

- individual is a candidate for chemotherapy (i.e., chemotherapy not excluded due to other factors)
- adjuvant chemotherapy is being considered in a woman and this testing is being ordered to assess recurrence risk
- no other GEC has been performed on this tumor sample for the same indication

and the associated criteria are met for ANY of the following indications:

<table>
<tr><th>Test Name</th><th>Cancer Type and Indication</th></tr>
<tr><td>Breast Cancer Index (BCI) Risk of Recurrence & Extended Endocrine Benefit Test (CPT code 81518)</td><td>For a woman with recently diagnosed anatomic stage 1 or stage 2 breast cancer when ALL of the following criteria are met:
estrogen receptor (ER)positive
human epidermal growth factor receptor 2 (HER2)-negative
no evidence of distant metastasis
axillary node status is negative (micrometastasis no greater than 2.0 mm)</td></tr>
<tr><td>MammaPrint® 70-Gene Breast Cancer Recurrence Assay (CPT© Code 81521)</td><td>For a woman with anatomic stage I or stage 2 invasive breast cancer when ALL of the following criteria are met:
histologic type is ductal, lobular, mixed (ductal/lobular), or metaplastic
high clinical risk of recurrence*
estrogen receptor (ER)-positive/progesterone receptor (PR)-positive
human epidermal growth factor receptor 2 (HER2)-negative
up to three positive node
<table>
<tr><th>Tumor Grade</th><th>Nodes</th><th>Tumor Size</th></tr>
<tr><td>Well differentiated</td><td></td><td></td></tr>
<tr><td></td><td>None</td><td>3.1-5 cm</td></tr>
<tr><td></td><td>1-3</td><td>2.1-5 cm</td></tr>
<tr><td>Moderately differentiated</td><td></td><td></td></tr>
<tr><td></td><td>None</td><td>2.1-5 cm</td></tr>
<tr><td></td><td>1-3</td><td>Any size</td></tr>
<tr><td>Poorly differentiated or undifferentiated</td><td></td><td></td></tr>
<tr><td></td><td>None</td><td>1.1-5 cm</td></tr>
<tr><td></td><td>1-3</td><td>Any size</td></tr>
</table></td></tr>
<tr><td>Oncotype DX® for Early-Stage, Invasive</td><td>For recently diagnosed anatomic stage 1 or stage 2 infiltrating breast cancer when ALL of the following criteria are met:</td></tr>
</table>

Breast Cancer Assay (CPT© Code 81519)	• histologic type is ductal, lobular, mixed (ductal/lobular), or metaplastic • tumor size 0.6-1.0cm and intermediate or high grade (Grade 2 or 3) OR tumor size 1.1-5.0 cm any grade • estrogen receptor positive and/or progesterone receptor positive • HER2 receptor negative • No evidence of distant metastasis • EITHER of the following criteria: ➢ axillary node status is negative (micrometastasis is no greater than 2.0 millimeters) whether the woman is pre- or post-menopausal ➢ up to three positive axillary nodes in a post-menopausal woman
Prosigna® Breast Cancer Prognostic Gene Signature Assay (PAM50) (CPT© Code 81520) EndoPredict® Risk Score (CPT code 81599)	For recently diagnosed anatomic stage 1 or stage 2 breast cancer breast cancer when ALL of the following criteria are met: • histologic type is ductal, lobular, mixed (ductal/lobular), or metaplastic • tumor size 0.6-1.0cm and intermediate or high grade (Grade 2 or 3) OR tumor size 1.1-5.0cm any grade • estrogen receptor positive and/or progesterone receptor positive • HER2 receptor negative • postmenopausal • No evidence of distant metastasis • Axillary node status is negative (micrometastasis is no greater than 2.0 mm)
VeriStrat® serum proteomic testing (CPT© Code 81538)	For advanced non-small cell lung cancer (NSCLC) to determine second-line treatment when ALL of the following criteria are met: • EGFR variant mutation status is wild-type (i.e., no pathogenic or likely pathogenic variant detected) or unknown • individual has failed first-line systemic chemotherapy • test results will be used to decide whether to proceed with erlotinib (Tarceva®) therapy

Experimental/Investigational/Unproven

The following tumor profile or gene expression tests are considered experimental, investigational or unproven for ANY other indication than noted in the criteria listed above:

- Breast Cancer Index (BCI) Risk of Recurrence & Extended Endocrine Benefit Test
- EndoPredict® Risk Score
- MammaPrint® 70-Gene Breast Cancer Recurrence Assay
- Oncotype DX® for Early-Stage, Invasive Breast Cancer Assay
- Prosigna® Breast Cancer Prognostic Gene Signature Assay (PAM50)
- VeriStrat® serum proteomic test~~ing~~

OncotypeDx Breast DCIS Score test is considered experimental, investigational or unproven.

Circulating Tumor Cells Testing

Medically Necessary

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

Experimental, Investigational or Unproven

Detection of circulating whole tumor cells for any other indication is considered experimental, investigational or unproven.

Prostate Cancer Screening and Prognostic Tests

Medically Necessary

The following prostate cancer screening and prognostic genetic tests are considered medically necessary when the associated criteria are met:

Test Name	Cancer Type and Indication
4K score Test percent free PSA Prostate Health Index (PHI)™	For prostate cancer when results will impact medical management and the following criterion is met: • PSA >3.0 ng/mL with or without previous benign prostate biopsy
ConfirmMDx® for Prostate Cancer Progensa® PCA3 Assay	For prostate cancer when results will impact management and BOTH of the following criteria are met: • PSA >3.0 ng/mL • previous benign prostate biopsy or focal high grade prostatic intraepithelial neoplasia (PIN)

The following prostate cancer screening and prognostic tests are considered experimental, investigational or unproven for ANY other indication:

- 4K score Test
- ConfirmMDx® for Prostate Cancer
- percent free PSA
- Prostate Health Index (PHI)™
- Progensa® PCA3 Assay

Tumor Tissue-Based Molecular Assays for Prostate Cancer

Medically Necessary

The following tumor-based molecular assays for prostate cancer are considered medically necessary when the associated criteria are met:

Test Name	Cancer Type and Indication
Decipher® Prostate Cancer Classifier Assay	ANY of the following: • PSA persistence after radical prostatectomy (i.e., failure of PSA to fall to undetectable levels after radical prostatectomy) • PSA recurrence after radical prostatectomy (i.e., undetectable PSA after radical prostatectomy with a subsequent detectable PSA that increases on two or more determinations • Post-prostate biopsy for low-risk* or favorable intermediate-risk* prostate cancer when the individual is a candidate for active surveillance or definitive therapy
OncotypeDx® Genomic Prostate Score Prolaris® Prostate Cancer Test ProMark® Proteomic Prognostic Test	Post prostate biopsy for low risk* or favorable intermediate-risk* prostate cancer when the individual is a candidate for active surveillance or definitive therapy

*Low-risk: T1-T2a disease AND Gleason score ≤6/grade group 1 AND PSA <10ng/mL
Favorable intermediate-risk: T2b-T2c disease OR Gleason score 3+4=7/grade group 2 OR PSA 10-20 ng/mL AND percentage of positive biopsy cores <50%

Hematologic Cancer and Myeloproliferative and Myelodysplastic Disease

Medically Necessary

Polycythemia Vera (PV)

Genetic testing for JAK2 V617F (CPT code 81270) and JAK2 exon 12 (CPT code 81403) pathogenic or likely pathogenic variants 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

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Essential Thrombocythemia

Genetic testing for JAK2 V617F (CPT code 81270) and MPL and CALR exon 9 pathogeneic and likely pathogeneic variants (CPT code 81219) and common variants (CPT code 81402) is considered medically necessary for the diagnosis of essential thrombocythemia or thrombocytosis (ET) when BOTH of the following criteria are met:

- results will ~~would~~ 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

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Primary Myelofibrosis (PMF)

Genetic testing for JAK2 V617F pathogeneic and likely pathogeneic variants (CPT code 81270) and analysis of MPL common variants (CPT code 81402), MPL exon 10 (CPT code 81403) and CALR exon 9 (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:

- above criteria are met
- results will impact medical management.
- megakaryocytic proliferation and atypia, without reticulin fibrosis >grade 1, accompanied by increased age-adjusted bone marrow cellularity, granulocytic proliferation, and often, decreased erythropoiesis
- JAK2, CALR and MPL mutation analysis was previously completed and was negative

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

BCR-ABL T315-I mutation testing (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

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Occult Neoplasms

Medically Necessary

The following paraneoplastic (onconeural) antibodies are considered medically necessary for the evaluation of neurological symptoms when the diagnosis remains uncertain following conventional work-up and an occult neoplasm is suspected:

- anti-Hu (ANNA-1 [antineuronal nuclear autoantibodies-1])
- anti-Yo (PCA-1 [Purkinje cell antibody-1])
- anti-CV2 (CRMP5 [collapsing mediator response protein5])
- anti-Ri (ANNA-2)
- anti-MA2 (Ta)

Solid Tumor Cancers

Experimental/Investigational/Unproven

Tumor analysis or gene expression profiling for ANY of the following solid tumor types is considered experimental, investigational or unproven) unless required for management of tumor agnostic pharmacologic therapy (this list may not be all-inclusive):

Anal carcinoma	Hodgkin lymphoma
Basal cell carcinoma	Malignant mesothelioma
Bone cancer	Penile cancer
Cancer of unknown origin/unknown primary	Renal/kidney cancer
Cervical cancer	Squamous cell carcinoma of the skin
Esophageal cancer	Testicular cancer
Head and neck cancer	Tracheal cancer
Hepatobiliary cancer	

Other Tumor Profile Testing

Experimental/Investigational/Unproven

Topographic genotyping for any indication is considered experimental, investigational or unproven.

General Background

For additional information regarding specific genetic tests please refer to the Genetic Testing Collateral: Molecular Tests and Biomarkers.

General Criteria for 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 certain cells of the body in response to cancer or some noncancerous conditions. Although most tumor markers are made by normal cells as well as by cancer cells, they are produced at much higher levels in cancerous conditions. 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], 2017). Tumor marker levels 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.

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 there is NCCN consensus that the intervention is appropriate and 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.

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 approved 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 the 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.

Breast Cancer Index (BCI) Risk of Recurrence & Extended Endocrine Benefit Test
BCI (BioTheranostics, Inc, San Diego, CA) is a quantitative molecular assessment of estrogen signaling pathways. According to the manufacturer, BCI is intended for use in an individual diagnosed with estrogen receptor-positive (ER+), lymph node-negative (LN-) or lymph node positive (LN+; with 1-3 positive nodes) early-stage, invasive breast cancer, who are distant recurrence-free. BCI provides a quantitative assessment of the likelihood of both late (post-5 years) and overall (0-10 year) distant recurrence following an initial 5 years of endocrine therapy (LN- patients) or 5 years of endocrine therapy plus adjuvant chemotherapy (LN+ patients), and prediction of likelihood of benefit from extended (>5 year) endocrine therapy. BCI results require correlation with other clinical findings. The NCCN (2019) notes BCI is a prognostic assay; however, predictive value has not yet been determined (Category of Evidence 2A**).**

U.S. Food and Drug Administration (FDA)
BCI has not received U.S. Food and Drug Administration (FDA) approval.

EndoPredict Risk Score
According to the manufactuer, the EndoPredict Risk Score (Myriad Genetics Laboratory, Inc., Salt Lake City, UT), is a 12 gene next-generation breast cancer recurrence test that integrates biology and pathology to accurately predict early and late (5-15 years) recurrence with an individualized absolute chemotherapy benefit. The test is intended for use for patients diagnosed with ER+, HER2− early-stage breast cancer with either node-negative or node-positive disease (1- 3 nodes). The NCCN (2019) notes that EndoPredict is a prognostic assay for consideration for addition of adjuvant systemic chemotherapy to adjuvant endocrine therapy; however, predictive value has not yet been determined (Category of Evidence 2A). The NCCN (2019) noted EndoPredict is a prognostic assay; however, predictive vaue has not yet been determined (Category of Evidence 2A).

U.S. Food and Drug Administration (FDA)
EndoPredict has not received U.S. FDA approval.

MammaPrint® 70-Gene Breast Cancer Recurrence Assay
The MammaPrint® 70-Gene Breast Cancer Recurrence Assay (Agendia, Inc. USA, Irvine, CA) utilizes a deoxyribonucleic acid (DNA) microarray assay to perform 70-gene profiling of breast cancer tissue to assess risk of recurrence. The assay is designed to determine the expression of specific genes in a tissue sample. The result is an expression profile, or “fingerprint”, of the sample. The MammaPrint Index is calculated from fresh, frozen or formalin-fixed paraffin embedded (FFPE) breast cancer tissue and the molecular prognosis profile of the sample is determined (i.e., Low Risk, High Risk) (FDA, 2015).

The test has been validated in a woman being considered for adjuvant systemic therapy with Stage I or Stage 2 invasive breast cancer who has estrogen receptor (ER) positive/progesterone receptor (PR) positive, human epidermal growth factor receptor 2 (HER2)-negative disease, and up to three positive lymph nodes, when there is a high clinical risk of recurrence:

Tumor Grade	Nodes	Tumor Size
Well differentiated		
	None	**3.1-5 cm**
	1-3	**2.1-5 cm**
Moderately differentiated		
	None	**2.1-5 cm**
	1-3	**Any size**
Poorly differentiated or undifferentiated		
	None	**1.1-5 cm**
	1-3	**Any size**

The NCCN (2019) notes that Mammoprint is a prognostic assay for consideration for addition of adjuvant systemic chemotherapy to adjuvant endocrine therapy; however, predictive value has not yet been determined (Category of Evidence 2A). There is consensus support in the form of published guidelines by the American Society of Clinical Oncology ([ASCO], 2017) for the use of MammaPrint to inform decisions on withholding adjuvant systemic chemotherapy due to its ability to identify a good prognosis population with potentially limited chemotherapy benefit.

U.S. Food and Drug Administration (FDA)
MammaPrint® 70-Gene Breast Cancer Recurrence Assay (Agendia, Inc. USA, Irvine, CA) received a 510K approval for an individual with Stage I or Stage II lymph node negative breast cancer with a tumor size ≤ 5.0 cm. According to the FDA approval summary, MammaPrint FFPE is not indicated as a standalone test to determine the outcome of disease, nor to suggest or infer an individual's likely response to therapy. Results should be taken in the context of other relevant clinicopathological factors and standard practice of medicine (2015).

Oncotype DX® for Early-Stage, Invasive Breast Cancer Assay
According to the manufacturer (Genomic Health, Inc., Redwood City, CA), this test is recommended for use after the original breast cancer surgery and is proposed for newly diagnosed patients with node-negative or node-positive, ER-positive, HER2-negative invasive breast cancer. The purpose of the Oncotype DX Breast Cancer Assay is to quantify the likelihood of distant recurrence (i.e., within 10 years) in a woman with breast cancer, and is used as one factor in determining whether or not a patient is a candidate for chemotherapy. This assay is not proposed for or used as a test to monitor the response of a specific chemotherapy drug.

Using tumor tissue, ribonucleic acid (RNA) is extracted, purified and analyzed for expression of a panel of 21 genes using quantitative reverse transcription polymerase chain reaction (RT-PCR) on formalin-fixed, paraffin-embedded (FFPE) tumor tissue. A Recurrence Score™ (RS) is calculated from the gene expression results using a proprietary Oncotype DX algorithm. The RS is based on a scale of 0–100. A score of less than 18 is considered low-risk; 18-31 is intermediate-risk; and a score over 31 is designated as high-risk. Each RS correlates with a specific likelihood of distant recurrence at 10 years. This test is recommended by the American Society of Clinical Oncology (ASCO) (2016) and NCCN (2019) for use in a select population of women with breast cancer. NCCN notes OncotypeDx is both a predictive and prognostic assay for consideration of addition of adjuvant systemic chemotherapy to adjuvant endocrine therapy for node negative disease (Category of Evidence 1). For node positive disease NCCN notes the test is prognostic but predictive value has not yet been determined (Category of Evidence 2A).

Data regarding Oncotype DX for other indications, including men with breast cancer, ductal cancer in situ and the value of repeat assays after the initial assessment are insufficient to establish clinical utility. Furthermore, professional society/organization consensus support by way of published guidelines or practice statements are lacking for these patient subsets.

US Food and Drug Administration (FDA)
Oncotype DX has not received U.S. Food and Drug Administration (FDA) approval. The assay is performed in the licensed Genomic Health laboratory where the assay was developed.

Prosigna® Breast Cancer Prognostic Gene Signature Assay: Prosigna® (NanoString Technologies, Seattle, WA) is an in vitro diagnostic assay which is performed on the NanoString nCounter® Dx Analysis System using formalin-fixed paraffin embedded (FFPE) breast tumor tissue previously diagnosed as invasive breast carcinoma. It is designed to identify intrinsic breast cancer subtypes (i.e., luminal A/B, HER2 enriched, basal like) and generate a Risk of Recurrence (ROR) score, expressed as a numerical value (0-100 scale) which correlates with the probability of distant recurrence within 10 years. The Prosigna Risk of Recurrence (ROR) score is generated by Prediction Analysis of Microarray (PAM50) proprietary algorithm (NanoString Technologies, 2014-2019).

The NCCN (2019) notes that Prosigna is a prognostic assay for consideration for addition of adjuvant systemic chemotherapy to adjuvant endocrine therapy; however, predictive value has not yet been determined (Category of Evidence 2A).

U.S. Food and Drug Administration (FDA)
Prosigna received FDA 501K approval in September, 2013. According to the FDA, the Prosigna Breast Cancer Prognostic Gene Signature Assay is indicated in female breast cancer patients who have undergone surgery in conjunction with locoregional treatment consistent with standard of care, either as:

- A prognostic indicator for distant recurrence-free survival at 10 years in postmenopausal women with Hormone Receptor-Positive (HR+), lymph node-negative, Stage I or 11 breast cancer to be treated with adjuvant endocrine therapy alone, when used in conjunction with other clinicopathological factors.
- A prognostic indicator for distant recurrence-free survival at 10 years in postmenopausal women with Hormone Receptor-Positive (HR+), lymph node-positive (1-3 positive nodes), Stage 11 breast cancer to be treated with adjuvant endocrine therapy alone, when used in conjunction with other clinicopathological factors.

Prosigna is not intended for diagnosis, to predict or detect response to therapy, or to help select the optimal therapy for patients. The device is not intended for patients with four or more positive nodes. The role of Prosigna for women with node positive disease has not yet been established.

VeriStrat® Serum Proteomic Testing
VeriStrat® (Biodesix, Boulder, CO) is not an EGFR mutation test. It is a serum protein analysis for advanced non-small cell lung cancer (NSCLC) and has been proposed as a means to identify individuals who should receive treatment with erlotinib (Tarceva®, Genentech, San Francisco, CA), an epidermal growth factor inhibitor (EGFRI). According to the Biodesix website, the test stratifies individuals who are likely to have good or poor outcomes with EGFRI treatment (2015). The analysis utilizes matrix-assisted laser desorption/ionization mass spectrometry to analyze serum for eight discriminating features. The test has an established prediction algorithm which was validated in two separate populations. Classifications based on spectra acquired at the two institutions had a concordance of 97.1%. (Taguchi, 2007). According to the manufacturer, results are predictive of outcomes, independent of ECOG performance status, PD-L1 expression, mutation status, and treatment choice.

The clinical utility of VeriStrat has been validated in both retrospective and prospective trials as a means to identify an individual who should receive treatment with erlotinib (Tarceva®, Genentech, San Francisco, CA), an epidermal growth factor inhibitor (EGFRI).

US Food and Drug Administration
VeriStrat has not received U.S. Food and Drug Administration (FDA) approval.

Literature Review
The clinical utility of VeriStrat is supported by prospective and retrospective clinical trial evidence in the published, peer-review scientific literature. The utility of VeriStrat as compared to standard KRAS and EGFR mutation analysis was performed on 102 samples by Amann et al (2010). VeriStrat classification identified 64 of 88 (73%) as predicted to have “good” and 24 of 88 (27%) predicted to have “poor” outcomes. Statistically significant correlation to VeriStrat status and clinical survival outcome was demonstrated ($p<0.001$).

Cost utility analysis of applying VeriStrat to guide treatment for NSCLC patients was compared to all patients receiving treatment with EGFRI, all patients receiving chemotherapy; and treatment determined by performance status. Patients where treatment was guided by VeriStrat showed the second best survival outcome (9.6 months) when compared to chemotherapy only (10.1 months);Performance status indicated (9.2 months) and EGFRI only (8.2 months) (Nelson, 2013).

Carbone et al. (2012) reported results of a retrospective analysis of 436 patient samples with NSCLC that were tested in patients treated with erlotinib and those on placebo. VeriStrat status was prognostic for overall survival and progression free survival, independent of clinical features ($p=0.002$); however, it was not predictive of differential survival from erlotinib over placebo ($p=0.48$). Similar results were found for progression-free survival. Data suggest a predictive effect of VeriStrat for response to erlotinib.

Subsequent studies have also sought to determine the predictive value of VeriStrat testing. Sun et al (2014) conducted a meta-analysis of current relevant publications. Eleven cohorts involving 706 patients collected from seven studies were subjected to final analysis. The statistical analysis of these articles found that the test's "good" status predicted better clinical outcome for overall and progression free survival ($p<0.001$ for both overall and progression-free survival).

A recent blinded randomized clinical trial by Gregorc et al. (2014) analyzed data collected through PROSE, a biomarker-stratified randomized phase III trial of 285 patients with stage IIIB or IV NSCLC from 14 centers across Italy. The proteomic test classification was masked for patients and investigators who gave treatments, and treatment allocation was masked for investigators who generated the proteomic classification. The primary endpoint was overall survival and the primary hypothesis was the existence of a significant interaction between the serum protein test classification and treatment. A significant interaction between treatment and proteomic classification was noted. Patients who were classified as "poor" in regards to their serum protein test status (30% of participants) were more likely to have better outcomes on chemotherapy than on erlotinib ($p=0.022$). The data suggests that this subset of patients should not receive erlotinib. This supports the use of a multivariate serum protein test in predicting overall survival for erlotinib versus chemotherapy in second-line therapy. However, there was no difference in treatment observed for patients with the classification of "good" ($p=0.714$). Although the study demonstrates which patients will not benefit from treatment with erlotinib ("poor" status), additional studies are needed to determine the best treatment option for patients with "good" status.

Professional Societies/Organizations
For a summary of professional society recommendations/guidelines regarding gene expression classifier tests please click here.

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®) recommends testing for the androgen receptor splice variant 7 (AR-V7)(2019) 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 deshydrogenase (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<.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<.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=.029) and 8.5 (P<.001) times greater. Multivariate analyses indicated that a CTC of ≥4 was an independent prognostic factor for PFS (hazard ratio 5.9, P<.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 clinico-pathologic status of patients.

Professional Societies/Organization
For a summary of professional society recommendations/guidelines regarding circulating tumor cells please click here.

Prostate Cancer Screening and Prognostic Tests

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], 2016). According to the National Comprehensive Cancer Network Guideline (NCCN Guidelines™) for Prostate Cancer Early Detection, 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) and ConfirmMDx for Prostate Cancer (MDX Health, Irvine, CA). The NCCN also notes that biomarkers that improve the specificity of detection are not recommended as firstline screening tests, rather 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.

Use of selected biomarkers (i.e., percent free PSA, 4Kscore, PCA3, PHI, ConfirmMDx) is supported by published professional society guidelines (NCCN, 2016) for the detection of prostate cancer to improve specificity. The 4Kscore, percent free PSA and Prostate Health Index (PHI) tests are considered appropriate when results of the tests will impact management and there is a PSA >3 ng/mL with or without a previous benign biopsy. PCA3 and ConfirmMDx are considered to be appropriate when results of testing will impact management, the PSA >3 ng/mL and previous biopsy results are benign or indicate focal high-grade prostatic intraepithelial neoplasia (PIN). The role of these tests for any other indication or clinical scenario has not been established.

Percent Free PSA (% free PSA): Serum PSA exists in both free form and complexed to a number of protease inhibitors. Assays for total PSA measure both free and complexed forms. Percent-free PSA may be related to

biologic activity of the tumor. The NCCN (2016) notes that unbound or free PSA, expressed as a ratio of total PSA is clinically useful with the potential to improve early detection, staging and monitoring of prostate cancer. According to the NCCN, this test has received widespread clinical acceptance, specifically for patients with normal digital rectal exams who have previously undergone prostate biopsy because they had a total PSA (tPSA) level within the diagnostic gray zone.

4Kscore: This test combines four prostate-specific kallikrein assay results with clinical information in an algorithm that calculates the individual patient's percent risk for aggressive prostate cancer. It also considers age, digital rectal exam results and prior biopsy status. According to the manufacturer's website, the 4Kscore is not indicated for men who have a diagnosis of prostate cancer, are taking or have taken 5-alpha reductase inhibitors within the last 6 months or have recently undergone a prostate procedure within the last 6 months. This test is a laboratory developed test and is not FDA approved. According to the NCCN Guidelines™, the test can be considered for patients prior to biopsy and for those with prior negative biopsy for those thought to be at higher risk for clinically significant prostate cancer. No cut-off threshold has been established for the 4Kscore.

Progensa® PCA3: Progensa PCA3 is an in vitro nucleic acid amplification test. The assay measures the concentration of prostate cancer gene 3 (PCA3) and prostate-specific antigen (PSA) RNA (RNA) molecules and calculates the ratio of PCA3 RNA molecules to PSA RNA molecules (PCA3 Score) in post digital rectal exam (DRE) first catch male urine specimens. U.S. Food and Drug Administration (FDA): According to the U.S. Food and Drug Administration ([FDA], 2012) it is intended for use in conjunction with other patient information to aid in the decision for repeat biopsy in men 50 years of age or older who have had one or more previous negative prostate biopsies and for whom a repeat biopsy would be recommended by a urologist based on current standard of care, before consideration of Progensa PCA3 Assay results.

Prostate Health Index (PHI)™: This test is a combination of existing tests (Access Hybritech PSA, Access Hybritech free PSA, and Access Hybritech p2PSA, Beckman Coulter, Atlanta, GA) for total PSA, free PSA and proPSA. According to the manufacturer's website, a proprietary algorithm provides a probability of prostate cancer. PHI results are intended to be used as an aid in distinguishing prostate cancer from benign prostatic conditions in men 50 years of age and older with total PSA results in the 4 – 10 ng/mL range and negative digital rectal examination (DRE) findings. The three assays that make up this test have received FDA approval with numerous supplements.

ConfirmMDx® for Prostate Cancer: This test is a tissue-based epigenetic assay which aids in the stratification of men being considered for repeat prostate biopsy. The test uses DNA methylation to assess the presence of cancer biomarkers (i.e., GSTP1, APC, RASSF1) in core biopsy tissue samples. ConfirmMDx is a laboratory developed test and is not FDA approved.

Professional Society/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 click here.

Tumor Tissue-Based Molecular Assays for Prostate Cancer

The NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines™) for Prostate Cancer (2019) 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 (2019). 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).

Decipher® Prostate Cancer Classifier Assay (GenomeDx, San Diego, CA): This test is a 22 biomarker genomic expression classifier assay which uses formalin-fixed paraffin embedded (FFPE) tissue from a radical prostatectomy specimen to predict the probability of metastasis and tumor aggressiveness. Decipher is listed as a Category 2B recommendation in the NCCN Practice Guidelines in Oncology for Prostate Cancer as an option following radical prostatectomy with PSA persistence/recurrence defined as failure of PSA to fall to undetectable levels (PSA persistence) or undetectable PSA after radical prostatectomy with a subsequent PSA that increases on two or more determinations (PSA recurrence). The Guideline also notes that Decipher may be used in men with low-risk prostate cancer, defined as T1-T2a disease, Gleason score ≤6/grade group 1 and a PSA <10ng/mL or those with favorable intermediate-risk disease, defined as T2b-Tc disease, Gleason score 3+4=7/grade group 2, PSA 10-20 ng/mL and percentage of positive biopsy cores <50%.

OncotypeDx® Genomic Prostate Score (Genomic Health©, Redwood City, CA): This test is a genomic classifier test measuring the activity of 17 genes to predict clinical risk and tumor aggressiveness. OncotypeDx Prostate uses FFPE tissue from a prostate biopsy specimen. The NCCN Practice Guidelines in Oncology for Prostate Cancer notes that men with low or favorable intermediate risk prostate cancer may consider the use of this test after prostate biopsy for low or favorable intermediate risk prostate cancer when there is a ≥ 10 years life expectancy and the individual is a candidate for active surveillance or definitive therapy.

Prolaris® Prostate Cancer Test (Myriad Genetic Laboratories, Inc., Salt Lake City, UT): This test is a gene expression classifier risk stratification tool designed to measure the expression level of 31 genes in a prostate cancer tumor biopsy tissue, in conjunction with clinical parameters such as the Gleason score and PSA. The NCCN Practice Guidelines in Oncology for Prostate Cancer notes that men with low or favorable intermediate risk prostate cancer may consider the use of this test post prostate biopsy for low or favorable intermediate risk prostate cancer when there is a ≥ 10 years life expectancy and the individual is a candidate for active surveillance or definitive therapy.

ProMark® Proteomic Prognostic Test (Metamark, Waltham, MA): This test is a prognostic assay that measures the signal intensity of eight protein biomarkers in FFPE prostate biopsy tissue. Using a proprietary algorithm the test generates a risk score indicating the likelihood of having high-risk disease. The NCCN Practice Guidelines in Oncology for Prostate Cancer notes that men with low or favorable intermediate risk prostate cancer may consider the use of this test post prostate biopsy for low or favorable intermediate risk prostate cancer when there is a ≥ 10 years life expectancy and the individual is a candidate for active surveillance or definitive therapy.

Hematologic Cancer and Myeloproliferative and Myelodysplastic Disease

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

Identification of the JAK2 V617F mutation 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.

Professional Societies/Organizations
For a summary of professional society recommendations/guidelines regarding BCR-ABL mutation analysis please click here.

Occult Neoplasms

While the supporting published evidence is limited, certain paraneoplastic/onconeural antibodies (i.e., anit-Hu, anti-Yo, anti-CV2, anti-RI, anti-MA1 and anti amphiphysin), are established markers used to aid in the diagnosis of paraneoplastic syndromes and occult neoplasms (i.e., cancers of unknown origin).

If initial diagnostic studies (e.g., laboratory, radiography, cerebral spinal fluid analysis, and/or electromyography) are negative, testing for paraneoplastic antibodies may be warranted. If the test is positive for a paraneoplastic antibody, it may help to focus the search for the neoplasm and establish the diagnosis of cancer. Continued testing (e.g., computed tomography, ultrasound) and early diagnosis for an underlying neoplasm would allow for early treatment of the cancer and could also improve the symptoms of PNS. In 90% of patients with paraneoplastic antibodies, the underlying tumor is diagnosed within the first year of PNS symptoms (Dalmau and Rosenfeld, 2008; Spiro et al., 2007; Bataller and Dalmau, 2005). The specificity of paraneoplastic antibodies reported to be greater than 90% for paraneoplastic neurologic syndromes or some types of cancer makes them useful diagnostic tools. However, not all paraneoplastic antibodies have the same sensitivity and specificity. Hu antibodies, most often associated with subacute sensory neuropathy (SSN) and small cell lung cancer, have an estimated specificity of 99% and a sensitivity of 82% (Dalmau and Rosenfeld, 2008; Honnorat and Antoine, 2007; Vedeler, et al., 2006).

Well-characterized, antibodies are reactive with molecularly defined onconeural antigens, prove the paraneoplastic etiology of the neurological syndrome, and are strongly associated with cancer. The well-characterized paraneoplastic antibodies include: anti-Hu (antineuronal nuclear autoantibodies-1 [ANNA-1]), anti-Yo (PCA-1 [Purkinje cell antibody-1]), anti-CV2 (CRMP5 [collapsing mediator response protein]), anti-Ri (ANNA-2), anti-MA2 (Ta), and anti-amphiphysin. Partially-characterized antibodies are antibodies with an unidentified target antigen and have only been found in a few patients. The partially-characterized antibodies (i.e., antibodies with an unidentified target antigen) include anti-Tr (PCA-Tr), ANNA-3, PCA-2, anti-recoverin, anti-Zic4, anti-mGluR1. The detection of partially-characterized antibodies is considered of limited diagnostic value. Antibodies that can be detected in paraneoplastic and nonparaneoplastic form and can occur with and without cancer include: anti-VGCC (voltage-gated calcium channel), anti-AchR (acetylcholine receptor), anti-nAChR (nicotine acetylcholine receptor), and anti-VGKC (volted-gated potassium channels) (Monstad, et al., 2009; De Graaf and Smitt, 2008; deBeukelaar and Smitt, 2006; Vedeler, et al., 2006; Battler and Dalmau, 2005; Karim, et al., 2005; Vincent, 2005; Graus, et al., 2004).

Solid Tumor Cancers

Molecular testing for the following tumor markers has been proposed to direct treatment and disease management. There is insufficient evidence in the published, peer-reviewed scientific literature to demonstrate the clinical utility of tumor analysis and/or gene expression profiling for the following tumor types. However, testing of circulating tumor cells may be appropriate required for management of tumor agnostic pharmacologic therapy. Further, consensus support in the form of published professional society guidelines is lacking.

Anal carcinoma	Hodgkin lymphoma
Basal cell carcinoma	Malignant mesothelioma
Bone cancer	Penile cancer
Cancer of unknown origin/unknown primary	Renal/kidney cancer
Cervical cancer	Squamous cell carcinoma of the skin
Esophageal cancer	Testicular cancer
Head and neck cancer	Tracheal Cancer
Hepatobiliary cancer	

Professional Societies/Organizations
For a summary of professional society recommendations/guidelines regarding molecular testing for solid tumor cancers please click here.

Other Tumor Profile Testing

Topographic Genotyping

Topographic genotyping refers to a method of mutational analysis that incorporates minute tumor samples selected according to histopathologic considerations, polymerase chain reaction (PCR) amplification and direct sequencing. The mutational alterations that are found are then correlated with the histology of the tumor. It has been proposed that the results of this testing will provide predictive information that will influence the management of certain cancers.

Studies comparing topographic genotyping with established testing methods are lacking. There do not appear to be prospective studies published in the peer-reviewed medical literature that focus on the clinical validity, the clinical utility of the test or the impact of the test on clinical outcomes

Literature Review
High-quality prospective controlled studies informing the clinical validity and clinical utility of topographic genotyping tests are lacking in the published, peer-reviewed scientific literature. Studies generally focus on the association of the topographic genotyping results with tumor characteristics (Al-Haddad, et al., 2014; Al-Haddad et al., 2013; Malhotra et al, 2014; Panarelli et al., 2012; Khalid, et al., 2009).

A technology assessment and systematic review regarding topographic genotyping with PathFinderTG was commissioned by Centers for Medicare and Medicaid Services (CMS) and conducted by the Tufts Evidence-based Practice Center for the Agency for Healthcare Research and Quality (AHRQ) (Trikalinos TA, et al., 2010). The review included studies evaluating the patented technology, specifically those using loss of heterozygosity (LOH) analysis. LOH is a frequent genetic alteration that is found in many cancers. It is thought that LOH alterations may have prognostic significance. Fifteen studies were included—these pertained to: lung cancer (n=4); pancreatic and biliary tree tumors (n=4); hepatocellular carcinoma (n=4); gliomas, thyroid tumors, lacrimal gland tumors and mucinous tumors of the appendix (n=1 for each). The sample size in the studies ranged from 11 to 103. The review identified no studies regarding the analytic validity of LOH based topographic genotyping with PathFinderTG. The studies were retrospective in design and utilized available archival tissue blocks. One study, molecular profiles of gliomas and reactive gliosis were determined retrospectively and they were used prospectively on 16 diagnostically challenging cases of reactive gliosis versus glial tumors. There were no studies found that evaluated whether the use of LOH based topographic genotyping with PathFinderTG affects patient outcomes. There were no studies identified that compared LOH based topographic genotyping with PathFinderTG with conventional pathology. The review found that all studies are small, they have important methodological limitations, and they do not address patient-relevant outcomes.

Professional Societies/Organization
For a summary of professional society recommendations/guidelines regarding topographic genotyping please click here.

The American Board of Internal Medicine's (ABIM) Foundation Choosing Wisely® Initiative (2014): No relevant statements.

Use Outside of the US
For a summary of recommendations/guidelines from professional societies outside of the US please click here.

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 CLASSSIFER 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:

- 1.1.1. For patients older than 50 years and whose tumors have Oncotype DX recurrence scores of less than 26, and for patients 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).
- 1.1.2. For patients 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).
- 1.1.3. Patients 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).
- 1.1.4. Based on Expert Panel consensus, oncologists may offer chemoendocrine therapy to patients 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 Comprehensive Cancer Network™ (NCCN™)

According to assessment by the NCCN (2019), some gene expression classifier tests predict recurrence risk; others are prognostic of clinical outcome:

Test	NCCN Category of Evidence	Prognostic	Predictive
Breast Cancer Index (BCI) Risk of Recurrence & Extended Endocrine Benefit Test 1-3 positive nodes	2A	Yes	Not determined
EndoPredict® Risk Score Node negative, 1-3 positive nodes	2A	Yes	Not determined
MammaPrint test node negative, 1-3 positive nodes	1	Yes	Not determined
OncotypeDx®, for Early-Stage, Invasive Breast Cancer pN0 or node negative	1	Yes	Yes
OncotypeDx®, for Early-Stage, Invasive Breast Cancer pN+ or node positive disease	2A	Yes	Not determined
Prosigna®, Breast Cancer Prognostic Gene Signature Assay (PAM50) Node negative, 1-3 positive nodes	2A	Yes	Not determined

National Institute for Health and Clinical 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 patients 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 people 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 people with ER-positive, HER2-negative and LN-negative early breast cancer because the analytical validity of the test is uncertain.

MammaPrint® 70-Gene Breast Cancer Recurrence Assay

American Society of Clinical Oncology (ASCO, 2017): On behalf of ASCO, Krop et al. published a focused update: Use of Biomarkers to Guide Decisions on Adjuvant Systemic Therapy for Women With Early-Stage Invasive Breast Cancer which addressed the use of MammaPrint to guide decisions on the use of adjuvant systemic therapy. ASCO recommends the following:

- If a patient has ER/PgR–positive, HER2-negative, node-negative, breast cancer, the MammaPrint assay may be used in those with high clinical risk per MINDACT categorization to inform decisions on withholding adjuvant systemic chemotherapy due to its ability to identify a good prognosis population with potentially limited chemotherapy benefit (Type: evidence based; Evidence quality: high; Strength of recommendation: strong).
- If a patient has ER/PgR–positive, HER2-negative, node-negative, breast cancer, the MammaPrint assay should not be used in those with low clinical risk per MINDACT categorization to inform decisions on withholding adjuvant systemic chemotherapy, because women in the low clinical risk category had excellent outcomes and did not appear to benefit from chemotherapy even with a genomic high-risk cancer (Type: evidence based; Evidence quality: high; Strength of recommendation: strong).
- If a patient has ER/PgR–positive, HER2-negative, node-positive, breast cancer, the MammaPrint assay may be used in patients with one to three positive nodes and at high clinical risk per MINDACT categorization to inform decisions on withholding adjuvant systemic chemotherapy due to its ability to identify a good prognosis population with potentially limited chemotherapy benefit. However, such patients should be informed that a benefit of chemotherapy cannot be excluded, particularly in patients with greater than one involved lymph node (Type: evidence based; Evidence quality: high; Strength of recommendation: moderate).
- Recommendation 1.2.2: (update of 2016 recommendation 1.7): If a patient has ER/PgR–positive, HER2-negative, node-positive, breast cancer, the MammaPrint assay should not be used in patients with one to three positive nodes and at low clinical risk per MINDACT categorization to inform decisions on withholding adjuvant systemic chemotherapy. There are insufficient data on the clinical utility of MammaPrint in this specific patient population (Type: informal consensus; Evidence quality: low; Strength of recommendation: moderate).
- Recommendation 1.3: (update of 2016 recommendation 1.8): If a patient has HER2-positive breast cancer, the clinician should not use the MammaPrint assay to guide decisions on adjuvant systemic therapy. Additional studies are required to address the role of MammaPrint in patients with this tumor subtype who are also receiving HER2-targeted therapy (Type: informal consensus; Evidence quality: low; Strength of recommendation: moderate).
- Recommendation 1.4: (update of 2016 recommendation 1.9): If a patient has ER/PgR negative and HER2-negative (triple negative) breast cancer, the clinician should not use the MammaPrint assay to

guide decisions on adjuvant systemic chemotherapy (Type: informal consensus; Evidence quality: insufficient; Strength of recommendation: strong).

Oncotype DX® Assay

Evaluation of Genomic Applications in Practice and Prevention (EGAPP) Working Group (2016): A published recommendation for the EGAPP notes there is insufficient evidence to recommend for or against the use of Oncotype DX testing to guide chemotherapy treatment decisions in women with hormone receptor–positive, lymph node–negative, or lymph node–positive early breast cancer who are receiving endocrine therapy. Regarding clinical utility, the EGAPP notes there is evidence from prospective retrospective studies that the test predicts benefit from chemotherapy, and there was adequate evidence that the use of Oncotype DX gene expression profiling in clinical practice changes treatment decisions regarding chemotherapy. However, no direct evidence was found that the use of Oncotype DX testing leads to improved clinical outcomes.

Spanish Society of Pathology (SEAP) and the Spanish Society of Medical Oncology (SEOM): In a joint guideline for biomarker testing in colon cancer published by Garcia-Alfonso on behalf of SEAP/SEOM, the authors noted although Oncotype DX gene expression signature has been shown to have prognostic value, no consensus yet exists on its use in clinical practice. The authors noted that the clinical usefulness of the test was compromised because the predictive value of Oncotype DX could not be validated (2012).

Prediction Analysis of Microarray 50 (PAM50) Prosigna® Breast Cancer Prognostic Gene Signature Assay

American Society of Clinical Oncology ([ASCO], 2016): On behalf of ASCO, Harris et al. published recommendations titled Use of Biomarkers to Guide Decisions on Adjuvant Systemic Therapy for Women With Early-Stage Invasive Breast Cancer: American Society of Clinical Oncology Clinical Practice Guideline Summary. Regarding the PAM50 risk of recurrence score, ASCO notes that if a patient has ER/PgR-positive, HER2 negative node negative breast cancer a clinician may use this assay in conjunction with other clinicopathologic variables to guide decisions on adjuvant systemic therapy. (High Quality Evidence; Strong Recommendation)

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 patients 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 patient'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 Patients 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™) (2019): 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 (V1.2019) 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.

Under indications for biopsy: Percent free PSA, 4KScore or PHI are noted as second line tests for a PSA >3 ng/mL. In a corresponding footnote the NCCN notes that biomarkers that improve specificity of detection are not recommended as firstline screening tests. However, some may wish to further define the probability of high-risk cancer. A percent free PSA <10%, PHI>35 or 4KScore are potentially informative in patient who have never undergone biopsy or after a negative biopsy; a PCA3 score >35 is potentially informative after a negative biopsy.

Regarding the management of biopsy results, NCCN recommends that percent free PSA, 4KScore, PHI, PCA3 or ConfirmMDx be considered for men with focal high-grade prostatic intraepithelial neoplasia (PIN) and those with a benign biopsy result. In a corresponding footnote NCCN notes that it is well known that a negative biopsy does not preclude a diagnosis of prostate cancer on subsequent biopsy. Tests that improve specificity in the post-biopsy state-including 4KScore, PHI, percent free PSA, PCA3 and ConfirmMDx-should be considered in patients thought to be higher risk despite a negative biopsy.

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 (2016)

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 pf loss of response, increase in BCR-ABL transcript levels and loss of minimal molecular response (MMR), and disease progression to accelerated or blast phase (V1.2017).

The NCCN Guideline for Ductal Carcinoma in Situ does not support routine CYP2D6 genotype testing for women being considered for tamoxifen therapy (V2.2017).

TUMOR MARKERS FOR SOLID TUMOR CANCERS

American Association of Clinical Endocrinologist (AACE): In the update of 2010 guidelines for the management of thyroid nodules (2016) the AACE stated that molecular testing should be considered to complement, not replace cytologic evaluation when the results are expected to influence clinical management. As a general rule molecular testing is not recommended in nodules with established benign or malignant cytologic characteristics. Regarding testing of indeterminate nodules the AACE notes because of the insufficient evidence and the limited follow-up, we do not recommend either in favor of or against the use of gene expression classifiers (GECs) for cytologically indeterminate nodules. Regarding use of mutation testing to guide to determine the extent of surgery the AACE notes with the exception of mutations such as BRAFV600E that have a PPV approaching 100% for papillary thyroid carcinoma (PTC), evidence is insufficient to recommend in favor of or against its use.

American Association for Endocrine Surgeons: In a summary statement on the utility of molecular marker testing in thyroid cancer, Yip, et al. stated that the use of molecular markers into clinical algorithms is still evolving and studies are needed to identify how routine molecular testing can best complement cytology and ultrasound and better understand the prognostic significance of a positive test (2010).

American Cancer Society ([ACS], 2017): In a discussion of bladder cancer and tumor markers, the ACS stated that NMP22 BladderChek®, bladder tumor-associated antigen (BTA), Immunocyt™ and Urovysion™ are new tests that look for substances in the urine that might indicate bladder cancer. At this time the tests are used mainly to look for bladder cancer in people who already have signs or symptoms of cancer, or in people who have had a bladder cancer removed to check for cancer recurrence. Further research is needed before these or other newer tests are proven useful as screening tests.

American College of Obstetricians and Gynecologists (2016): A Practice Bulletin on Evaluation and Management of Adnexal Masses notes that serum biomarker panels may be used as an alternative to CA 125 level alone in determining the need for a referral or consultation with a gynecologist oncologist when an adnexal mass requires surgery. (Level C recommendation, based primarily on consensus and expert opinion).

American Society of Colon & Rectal Surgeons (ASCRS): In practice parameters for anal squamous neoplasms, ASCRS (2012) noted that biomarkers such as tumor suppressor genes P53 and P21 have shown promise but they have a limited role in follow-up of these patients.

American Thyroid Association (ATA): The Clinical Affairs Committee (Hodak and Rosenthal, 2013) published an official statement to provide direction for clinicians and patients regarding the current state of thyroid molecular diagnosis including Afirma, miRInform and Cleveland Clinic TSHR mRNA Assay. ATA stated that the commercial and noncommercial use of BRAF, RAS, RET/PTC, and PAX8/PPARγ testing have promising roles, but experience with these tests is limited and ”no test has perfect sensitivity and specificity”. ATA stated that until expert consensus review of existing data is completed, no evidence-based recommendation for or against the use of these tests can be made. They advised clinicians to use caution and to remain cognizant of the limited available data. “Until evidence-based recommendations are available, determining whether or not the limited data available support the use of these methods should be considered on a case-by-case basis”.

Ferris et al. (2015) published a statement on behalf of the ATA regarding “Surgical Application of Molecular Profiling for Thyroid Nodules: Current Impact on Perioperative Decision Making”. The ATA notes the current gene expression classifier application is to enhance the accuracy of the cytologically indeterminate categories of atypia of uncertain significance/follicular lesion of undetermined significance (AUS/FLUS and follicular neoplasm/suspicious for follicular neoplasm (FN). A benign gene expression classifier (GEC) result may be used to recommend observation and avoid a diagnostic lobectomy, especially in the absence of clinical or sonographic suspicion of malignancy. In the presence of clinical or sonographic suspicion for malignancy, and/or when the local prevalence of malignancy exceeds the 25% reported, diagnostic lobectomy is still warranted. Standard application of the GEC for all indeterminate thyroid nodules would result in only a 7.2% decrease in thyroidectomy volume.

Australia and New Zealand Horizon Scanning Networks (ANZHSN)/Health Policy Advisory Committee on Technology (HealthPACT): A HealthPACT technology summary on diagnostic tests for ovarian cancer (2010) stated that OvPlex™ (HealthLinx Ltd, Australia) is a test available directly to the consumer for the proposed purpose of providing early detection of ovarian cancer. OvPlex includes five biomarkers including CA-125, C-reactive protein (CRP), serum amyloid A (SAA), interleukin 6 (IL-6) and interleukin 8 (IL-8) and uses an algorithm to analyze the concentration of the biomarkers. The test is similar in concept to the OVA1 in the US. The authors noted that the available studies for OvPlex were in the “proof of concept state” because the sensitivity and specificity have been calculated on a high risk population. Health PACT concluded that “based on the poor quality of evidence of studies conducted in inappropriate populations, and in light of ethical concerns and the potential to do harm associated with this direct-to-consumer test, it is recommended that this summary be disseminated to CTEPC, consumer health groups, the College of General Practitioners and the National Breast and Ovarian Cancer Centre”.

College of American Pathologists, International Association for the Study of Lung Cancer, and Association for Molecular Pathology (2013): A joint guideline regarding Molecular Testing Guideline for Selection of Lung Cancer Patients for EGFR and ALK Tyrosine Kinase Inhibitors (Lindeman et al.) recommends that EGFR molecular testing should be used to select patients for EGFR-targeted and ALK-targeted TKI therapy. EGFR and ALK testing is not recommended in lung cancers that lack any adenocarcinoma component, such as pure squamous cell carcinomas, pure small cell carcinomas, or large cell carcinomas lacking any immunohistochemistry (IHC). To determine EGFR and ALK status for initial treatment selection, primary tumors or metastatic lesions are equally suitable for testing.

Ministry of Health, Singapore: A cancer screening clinical practice guideline by the Ministry of Health (MOH), Singapore (2010), stated that the use of serum markers for the screening in women at average risk for epithelial ovarian cancer is not recommended, the use of biomarkers as a screening tool for lung cancers is under investigation and there is currently no role for biomarkers other than PSA for primary screening for prostate cancer.

TOPOGRAPHIC GENOTYPING

American Gastroenterological Association Institute: A Guideline on the Diagnosis and Management of Asymptomatic Neoplastic Pancreatic Cysts notes, that molecular techniques to evaluate pancreatic cysts remain an emerging area of research and the diagnostic utility of these tests is uncertain (Vege, et al., 2015).

Coding/Billing Information

Note: 1) This list of codes may not be all-inclusive.
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)
81162	BRCA1 (BRCA1, DNA repair associated), BRCA2 (BRCA2, DNA repair associated) (eg, hereditary breast and ovarian cancer) gene analysis; full sequence analysis and full duplication/deletion analysis (ie, detection of large gene rearrangements)
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)
81211	BRCA1, BRCA2 (breast cancer 1 and 2) (eg, hereditary breast and ovarian cancer) gene analysis; full sequence analysis and common duplication/deletion variants in BRCA1 (ie, exon 13 del 3.835kb, exon 13 dup 6kb, exon 14-20 del 26kb, exon 22 del 510bp, exon 8-9 del 7.1kb) (Code deleted 12/31/2018)

81218	CEBPA (CCAAT/enhancer binding protein [C/EBP], alpha) (eg, acute myeloid leukemia), gene analysis, full gene sequence
81229	Cytogenomic constitutional (genome-wide) microarray analysis; interrogation of genomic regions for copy number and single nucleotide polymorphism (SNP) variants for chromosomal abnormalities
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)
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)
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
81292	MLH1 (mutL homolog 1, colon cancer, nonpolyposis type 2) (eg, hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; full sequence analysis
81293	MLH1 (mutL homolog 1, colon cancer, nonpolyposis type 2) (eg, hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; known familial variants
81294	MLH1 (mutL homolog 1, colon cancer, nonpolyposis type 2) (eg, hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; duplication/deletion variants
81295	MSH2 (mutS homolog 2, colon cancer, nonpolyposis type 1) (eg, hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; full sequence analysis
81298	MSH6 (mutS homolog 6 [E. coli]) (eg, hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; full sequence analysis
81299	MSH6 (mutS homolog 6 [E. coli]) (eg, hereditary nonpolyposis colorectal cancer, Lynch syndrome) gene analysis; known familial variants
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)
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
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)
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, cytogenomic array analysis for neoplasia)
81407	Molecular pathology procedure, Level 9 (eg, analysis of >50 exons in a single gene by DNA sequence analysis)
81415	Exome (eg, unexplained constitutional or heritable disorder or syndrome); sequence 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
81503	Oncology (ovarian), biochemical assays of five proteins (CA-125, apolipoprotein A1, beta-2 microglobulin, transferrin, and pre-albumin), utilizing serum, algorithm reported as a risk score
81545	Oncology (thyroid), gene expression analysis of 142 genes, utilizing fine needle aspirate, algorithm reported as a categorical result (eg, benign or suspicious)
82105	Alpha-fetoprotein (AFP); serum
82232	Beta-2 microglobulin
82308	Calcitonin
82378	Carcinoembryonic antigen (CEA)
83497	Hydroxyindolacetic acid, 5-(HIAA)
83876	Myeloperoxidase (MPO)
83950	Oncoprotein; HER-2/neu
84432	Thyroglobulin
84702	Gonadotropin, chorionic (hCG); quantitative
84703	Gonadotropin, chorionic (hCG); qualitative
84704	Gonadotropin, chorionic (hCG); free beta chain
86294	Immunoassay for tumor antigen, qualitative or semiquantitative (eg, bladder tumor antigen)
86300	Immunoassay for tumor antigen, quantitative; CA 15-3 (27.29)
86301	Immunoassay for tumor antigen, quantitative; CA 19-9
86304	Immunoassay for tumor antigen, quantitative; CA 125
86386	Nuclear Matrix Protein 22 (NMP22), qualitative

88120	Cytopathology, in situ hybridization (eg, FISH), urinary tract specimen with morphometric analysis, 3-5 molecular probes, each specimen; manual
88121	Cytopathology, in situ hybridization (eg, FISH), urinary tract specimen with morphometric analysis, 3-5 molecular probes, each specimen; using computer-assisted technology
88271	Molecular cytogenetics; DNA probe, each (eg, FISH)
88272	Molecular cytogenetics; chromosomal in situ hybridization, analyze 3-5 cells (eg, for derivatives and markers)
88273	Molecular cytogenetics; chromosomal in situ hybridization, analyze 10-30 cells (eg, for microdeletions)
88274	Molecular cytogenetics; interphase in situ hybridization, analyze 25-99 cells
88275	Molecular cytogenetics; interphase in situ hybridization, analyze 100-300 cells
88342	Immunohistochemistry or immunocytochemistry, per specimen; initial single antibody stain procedure
88360	Morphometric analysis, tumor immunohistochemistry (eg, Her-2/neu, estrogen receptor/progesterone receptor), quantitative or semiquantitative, per specimen, each single antibody stain procedure; manual
88361	Morphometric analysis, tumor immunohistochemistry (eg, Her-2/neu, estrogen receptor/progesterone receptor), quantitative or semiquantitative, per specimen, each single antibody stain procedure; using computer-assisted technology
0016U	Oncology (hematolymphoid neoplasia), RNA, BCR/ABL1 major and minor breakpoint fusion transcripts, quantitative PCR amplification, blood or bone marrow, report of fusion not detected or detected with quantitation
0018U	Oncology (thyroid), microRNA profiling by RT-PCR of 10 microRNA sequences, utilizing fine needle aspirate, algorithm reported as a positive or negative result for moderate to high risk of malignancy
0022U	Targeted genomic sequence analysis panel, non-small cell lung neoplasia, DNA and RNA analysis, 23 genes, interrogation for sequence variants and rearrangements, reported as presence/absence of variants and associated therapy(ies) to consider
0048U	Oncology (solid organ neoplasia), DNA, targeted sequencing of protein-coding exons of 468 cancer-associated genes, including interrogation for somatic mutations and microsatellite instability, matched with normal specimens, utilizing formalin-fixed paraffin-embedded tumor tissue, report of clinically significant mutation(s)
0081U	Oncology (uveal melanoma), mRNA, gene-expression profiling by real-time RT-PCR of 15 genes (12 content and 3 housekeeping genes), utilizing fine needle aspirate or formalin-fixed paraffin-embedded tissue, algorithm reported as risk of metastasis
0111U	Oncology (colon cancer), targeted KRAS (codons 12, 13, and 61) and NRAS (codons 12, 13, and 61) gene analysis utilizing formalin-fixed paraffin-embedded tissue

†**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**

Considered Not Medically Necessary:

CPT®* Codes	Description
81327	SEPT9 (Septin9) (eg, colorectal cancer) promoter methylation analysis
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)
0049U	NPM1 (nucleophosmin) (eg, acute myeloid leukemia) gene analysis, quantitative
0050U	Targeted genomic sequence analysis panel, acute myelogenous leukemia, DNA analysis, 194 genes, interrogation for sequence variants, copy number variants or rearrangements
0069U	Oncology (colorectal), microRNA, RT-PCR expression profiling of miR-31-3p, formalin fixed paraffin-embedded tissue, algorithm reported as an expression score

0120U	Oncology (B-cell lymphoma classification), mRNA, gene expression profiling by fluorescent probe hybridization of 58 genes (45 content and 13 housekeeping genes), formalin-fixed paraffin-embedded tissue, algorithm reported as likelihood for primary mediastinal B-cell lymphoma (PMBCL) and diffuse large B-cell lymphoma (DLBCL) with cell of origin subtyping in the latter

†**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)**

††**Note: Considered Medically Necessary when used for companion diagnostic testing to determine appropriate drug therapy**

Considered Experimental/Investigational/Unproven:

CPT®* Codes	Description
81445†	Targeted genomic sequence analysis panel, solid organ neoplasm, DNA analysis, and RNA analysis when performed, 5-50 genes (eg, ALK, BRAF, CDKN2A, EGFR, ERBB2, KIT, KRAS, NRAS, MET, PDGFRA, PDGFRB, PGR, PIK3CA, PTEN, RET), interrogation for sequence variants and copy number variants or rearrangements, if performed
81479††	Unlisted molecular pathology procedure
81504	Oncology (tissue of origin), microarray gene expression profiling of > 2000 genes, utilizing formalin-fixed paraffin-embedded tissue, algorithm reported as tissue similarity scores
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 parrafin-embedded tissue, algorithm reported as a probability of predicted main cancer type and subtype
81599††	Unlisted multianalyte assay with algorithmic analysis
82387	Cathepsin-D
83520††	Immunoassay for analyte other than infectious agent antibody or infectious agent antigen; quantitative, not otherwise specified
83951	Oncoprotein; des-gama-carboxy-prothrombin (DCP)
84275	Sialic acid
84999††	Unlisted chemistry procedure
88358	Morphometric analysis; tumor (eg, DNA ploidy)
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
0013M	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 recurrent urothelial carcinoma
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
0089U	Oncology (melanoma), gene expression profiling by RTqPCR, PRAME and LINC00518, superficial collection using adhesive patch(es)
0090U	Oncology (cutaneous melanoma), mRNA gene expression profiling by RT-PCR of 23 genes (14 content and 9 housekeeping), utilizing formalin-fixed paraffin-embedded tissue, algorithm reported as a categorical result (ie, benign, indeterminate, malignant)

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

††**Note: Considered Experimental/Investigational/Unproven when used to report any non- covered genetic test for somatic mutations that do not have an assigned CPT/HCPCS code**

Tumor Profile/Gene Expression Classifier Testing

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

CPT®* Codes	Description
81518	Oncology (breast), mRNA, gene expression profiling by real-time RT-PCR of 11 genes (7 content and 4 housekeeping), utilizing formalin-fixed paraffin-embedded tissue, algorithms reported as percentage risk for metastatic recurrence and likelihood of benefit from extended endocrine therapy
81519	Oncology (breast), mRNA, gene expression profiling by real-time RT-PCR of 21 genes, utilizing formalin-fixed paraffin embedded tissue, algorithm reported as recurrence risk score
81520	Oncology (breast), mRNA gene expression profiling by hybrid capture of 58 genes (50 content and 8 housekeeping), utilizing formalin-fixed paraffin-embedded tissue, algorithm reported as a recurrence risk score
81521	Oncology (breast), mRNA, microarray gene expression profiling of 70 content genes and 465 housekeeping genes, utilizing fresh frozen or formalin-fixed paraffin-embedded tissue, algorithm reported as index related to risk of distant metastasis
81538	Oncology (lung), mass spectrometric 8-protein signature, including amyloid A, utilizing serum, prognostic and predictive algorithm reported as good versus poor overall survival
81599†	Unlisted multianalyte assay with algorithmic analysis
0026U	Oncology (thyroid), DNA and mRNA of 112 genes, next-generation sequencing, fine needle aspirate of thyroid nodule, algorithmic analysis reported as a categorical result ("Positive, high probability of malignancy" or "Negative, low probability of malignancy")

†**Note: Considered Medically Necessary when used to report EndoPredict® Risk Score**

HCPCS Codes	Description
S3854	Gene expression profiling panel for use in the management of breast cancer treatment

Considered Experimental/Investigational/Unproven:

CPT®* Codes	Description
0009U	Oncology (breast cancer), ERBB2 (HER2) copy number by FISH, tumor cells from formalin fixed paraffin embedded tissue isolated using image-based dielectrophoresis (DEP) sorting, reported as ERBB2 gene amplified or non-amplified
0045U	Oncology (breast ductal carcinoma in situ), 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 recurrence score

Circulating Tumor Cells Testing

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

CPT®* Codes	Description
86152	Cell enumeration using immunologic selection and identification in fluid specimen (eg, circulating tumor cells in blood);
86153	Cell enumeration using immunologic selection and identification in fluid specimen (eg, circulating tumor cells in blood); physician interpretation and report, when required

ICD-10-CM Codes	Description
C61	Malignant neoplasm of prostate
C79.82	Secondary malignant neoplasm of genital organs
D40.0	Neoplasm of uncertain behavior of prostate

Prostate Cancer Screening and Prognostic Tests

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

CPT®* Codes	Description
81313	PCA/KLK3 (prostate cancer antigen 3 [non-protein coding]/kallikrein-related peptidase 3 [prostate specific antigen]) ratio (eg, prostate cancer)
81539	Oncology (high-grade prostate cancer), biochemical assay of four proteins (Total PSA, Free PSA, Intact PSA and human kallikrein-2 [hK2]), utilizing plasma or serum, prognostic algorithm reported as a probability score
81551	Oncology (prostate), promoter methylation profiling by real-time PCR of 3 genes (GSTP1, APC, RASSF1), utilizing formalin-fixed paraffin-embedded tissue, algorithm reported as a likelihood of prostate cancer detection on repeat biopsy

Considered Experimental/Investigational/Unproven:

CPT®* Codes	Description
0005U	Oncology (prostate) gene expression profile by real-time RT-PCR of 3 genes (ERG, PCA3, and SPDEF), urine, algorithm reported as risk score
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

Considered Not Medically Necessary:

CPT®* Codes	Description
0113U	Oncology (prostate), measurement of PCA3 and TMPRSS2-ERG in urine and PSA in serum following prostatic massage, by RNA amplification and fluorescence-based detection, algorithm reported as risk score

Tumor Tissue-Based Molecular Assays for Prostate Cancer

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

CPT®* Codes	Description
81479†	Unlisted molecular pathology procedure
81541	Oncology (prostate), mRNA gene expression profiling by real-time RT-PCR of 46 genes (31 content and 15 housekeeping), utilizing formalin-fixed paraffin-embedded tissue, algorithm reported as a disease-specific mortality risk score
0047U	Oncology (prostate), mRNA, gene expression profiling by real-time RT-PCR of 17 genes (12 content and 5 housekeeping), utilizing formalin-fixed paraffin-embedded tissue, algorithm reported as a risk score

†**Note: Considered Medically Necessary when used to report Decipher® Prostate Cancer Classifier Assay or ProMark® Proteomic Prognostic Test**

Hematologic Cancer and Myeloproliferative and Myelodysplastic Disease

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
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
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)
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)
81479†	Unlisted molecular pathology procedure
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
0023U	Oncology (acute myelogenous leukemia), DNA, genotyping of internal tandem duplication, p.D835, p.I836, using mononuclear cells, reported as detection or non-detection of FLT3 mutation and indication for or against the use of midostaurin
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

†Note: Considered Medically Necessary when used to report TET2, SRSF2, or SF3B1 gene mutation analysis testing

Considered Experimental/Investigational/Unproven:

CPT®* Codes	Description
0016U	Oncology (hematolymphoid neoplasia), RNA, BCR/ABL1 major and minor breakpoint fusion transcripts, quantitative PCR amplification, blood or bone marrow, report of fusion not detected or detected with quantitation

Occult Neoplasms

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

CPT®* Codes	Description
83516	Immunoassay for analyte other than infectious agent antibody or infectious agent antigen; qualitative or semiquantitative, multiple step method
83520†	Immunoassay for analyte other than infectious agent antibody or infectious agent antigen; quantitative, not otherwise specified
84181	Protein; Western Blot, with interpretation and report, blood or other body fluid
84182	Protein; Western Blot, with interpretation and report, blood or other body fluid, immunological probe for band identification, each
86255	Fluorescent noninfectious agent antibody; screen, each antibody
86256	Fluorescent noninfectious agent antibody; titer, each antibody

†**Note: Considered Medically Necessary when used to report anti-CV2 (CRMP5 [collapsing mediator response protein5]) or anti-MA2 (Ta)**

Solid Tumor Cancers

Considered Experimental/Investigational/Unproven unless required for the management of tumor agnostic pharmacologic therapy:

CPT®* Codes	Description
81479	Unlisted molecular pathology procedure
81599	Unlisted multianalyte assay with algorithmic analysis
84999	Unlisted chemistry test
88299	Unlisted cytogenetic study
88399	Unlisted surgical pathology procedure
89240	Unlisted miscellaneous pathology test
0003U	Oncology (ovarian) biochemical assays of five proteins (apolipoprotein A-1, CA 125 II, follicle stimulating hormone, human epididymis protein 4, transferrin), utilizing serum algorithm reported as a likelihood score

Other Tumor Profile Testing

Considered Experimental/Investigational/Unproven when used to report topographic genotyping:

CPT®* Codes	Description
81479	Unlisted molecular pathology procedure
81599	Unlisted multianalyte assay with algorithmic analysis
84999	Unlisted chemistry procedure

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