## Clinical Appropriateness Guidelines

# Molecular Testing of Solid and Hematologic Tumors and Malignancies





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# Scope

This document addresses molecular testing and gene expression profiling of solid and hematologic tumors and malignancies (including cell free tumor DNA/circulating tumor cells/liquid biopsy testing) for the purpose of diagnosis, selecting chemotherapeutic agents and predicting risk, prognosis or recurrence of cancer. All tests listed in these guidelines may not require prior authorization; please refer to the health plan.

# Appropriate Use Criteria

Somatic tumor testing, unless separate criteria is stated below, is medically necessary when all of the following criteria are met:

- Identification of the specific genetic variant or gene expression profile has been demonstrated to improve diagnosis, management, or clinical outcomes for the individual's tumor type
- Individual meets specific testing criteria outlined in National Comprehensive Cancer Network® (NCCN®) algorithms with a category 1 or 2A level of evidence or supplemental criteria listed below
- Testing sample type and methodology (e.g., formalin-fixed, paraffin embedded, cell-free tumor DNA, circulating tumor cells, etc.) have been clinically validated and recommended as a companion diagnostic by the FDA or by the NCCN® as a category 1 or 2A recommendation

Somatic multi-gene panels for hematology-oncology indications are medically necessary when all of the following are met:

- Sequential testing of individual genes or biomarkers is not practical (i.e. limited tissue available, urgent treatment decisions pending)
- Identification of each or multiple genes or biomarkers on the panel has been demonstrated to improve diagnosis, management, or clinical outcomes for the individual's tumor type
- The panel is targeted and limited to genes that are associated with the specific tumor type, unless otherwise specified in tumor site-specific criteria below

Molecular testing for hematology-oncology indications is not medically necessary in the following situations:

- There are no 1 or 2A NCCN® recommendations for molecular testing for the specific tumor type
- The requested genetic variant or profile is correlated with a known therapy, but that therapy does not have clinical utility for the specific tumor type

- Topographic genotyping (e.g., PancraGen)
- Whole exome tumor sequencing
- Whole genome tumor sequencing

## National Comprehensive Cancer Network® (NCCN®) Criteria*

Somatic genetic testing for the following tumor types is medically necessary when an individual meets the testing criteria outlined in the relevant NCCN® Clinical Practice Guidelines in Oncology (NCCN Guidelines®):

- Acute Lymphoblastic Leukemia
- Acute Myeloid Leukemia
- B-Cell Lymphomas
- Central Nervous System Cancers
- Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma
- Chronic Myelogenous Leukemia
- Colon Cancer
- Hairy Cell Leukemia
- Melanoma
- Myelodysplastic Syndrome
- Non-Small Cell Lung Cancer
- Ovarian Cancer
- Primary Cutaneous B-cell Lymphomas
- Prostate Cancer Early Detection
- Rectal Cancer
- Soft Tissue Sarcoma
- T-Cell Lymphomas
- Lung Cancer
- Uveal Melanoma
- Waldenstrom Macroglobulinemia/Lymphoplasmacytic Lymphoma

See more specific criteria below for:

- Myeloproliferative neoplasms
- Breast Cancer
- Cell-Free Tumor Testing
- Cancer of Unknown Primary/Occult Neoplasm
- Prostate Cancer (confirmed, not screening)
- Thyroid Cancer and Indeterminate Thyroid Nodules
- Colorectal Cancer Screening

## Polycythemia Vera

JAK2 mutation testing is medically necessary for the diagnosis of polycythemia vera when both of the following conditions are met:

- Genetic testing impacts medical management
- ONE of the following criteria are met:
  - Hemoglobin >16.5 g/dL in men, >16.0 g/dL in women
  - Hematocrit >49% in men, >48% in women
  - Increased red cell mass (RCM) more than 25% above mean normal predicted value

## Essential Thrombocythemia or Thrombocytosis

JAK2 V617F testing is medically necessary for the diagnosis of essential thrombocythemia or thrombocytosis (ET) when both of the following conditions are met:

- Genetic testing impacts medical management
- Platelet count > or = 450 x 10^9/L

MPL common variants and CALR exon 9 mutation analysis are medically necessary for the diagnosis of essential thrombocythemia or thrombocytosis (ET) when all of the following conditions are met:

- Genetic testing impacts medical management
- Criteria for JAK2 V617F mutation is met
- JAK2 V617F mutation analysis was previously completed and was negative

## Primary Myelofibrosis

JAK2, CALR and MPL mutation testing is medically necessary for the diagnosis of primary myelofibrosis (PMF) when both of the following conditions are met:

- Genetic testing impacts medical management

- Suspicion for PMF or pre-PMF exists based on 2016 WHO diagnostic criteria

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

- Genetic testing impacts medical management
- Presence of megakaryocytic proliferation and atypia, accompanied by either reticulin and/or collagen fibrosis grades 2 or 3 OR 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

## Breast Cancer

Breast cancer assays not listed below are considered not medically necessary.

Oncotype DX® Breast Recurrence Score Test is medically necessary to assess the need for adjuvant chemotherapy in a woman with breast cancer when all of the following criteria are met:

- Breast tumor is stage 1 or stage 2
- Axillary-node status is negative or any axillary-node micro metastasis is no greater than 2.0 millimeters
- There is no evidence of distant metastatic breast cancer
- Breast tumor is estrogen and/or progesterone receptor-positive
- Breast tumor is HER2 receptor-negative
- Adjuvant chemotherapy (i.e., chemotherapy not precluded due to other factors) is being considered and this testing is being ordered specifically to guide decision making as to whether or not adjuvant chemotherapy will be utilized

Prosigna ™ PAM50 testing is medically necessary to assess the risk for recurrence in a woman when all of the following criteria are met:

- Breast tumor is stage 1 or stage 2
- Axillary-node status is negative or any axillary-node micrometastasis is no greater than 2.0 millimeters
- There is no evidence of distant metastatic breast cancer
- Breast tumor is estrogen or progesterone receptor-positive
- Breast tumor is HER2 receptor-negative
- Postmenopausal

MammaPrint® is medically necessary to assess the risk for recurrence in a woman when all of the following criteria are met:

- Breast tumor is stage 1 or stage 2
- Node negative or 1-3 positive node breast cancer
- Breast tumor is estrogen receptor positive and/or progesterone receptor positive
- Breast tumor is HER2-negative
- Patient is at high clinical risk for recurrence based on the MINDACT categorization

## Cancer of Unknown Primary/Occult Neoplasm

Molecular testing and gene expression profiling for occult neoplasms (cancers of unknown primary) is not medically necessary.

## Prostate Cancer

### *Screening*

Prostate cancer early detection assays (e.g. ConfirmMDx) are medically necessary as outlined in the criteria in the NCCN® Clinical Practice Guidelines in Oncology (NCCN Guidelines®), Prostate Cancer Early Detection.

### *Confirmed Malignancy*

Gene expression or molecular profiling assays for confirmed prostate tumors are not medically necessary.

## Thyroid Cancer

### *Confirmed or Highly-Suspected Thyroid Cancer*

BRAF V600E mutation analysis is medically necessary in cases with confirmed or highly-suspected follicular thyroid carcinoma, papillary thyroid carcinoma, medullary thyroid carcinoma, or metastatic differentiated thyroid cancer.

### *Cytologically Indeterminate Thyroid Nodule*

Gene expression classifiers (GECs), Afirma® Thyroid FNA Analysis and ThyroSeq 3.0, are medically necessary for surgical candidates with FNA Bethesda category III results (AUS/FLUS) and no additional high risk factors to help guide surgical decision making.

Mutation analysis panels that include BRAF, RAS, RET/PTC, and PAX8/PPARc, such as ThyGenX®/ThyraMIR™, are medically necessary for surgical candidates with FNA Bethesda III and IV results (AUS/FLUS and FN/SFN) to help guide surgical decision making.

GECs and/or mutation analysis are not considered medically necessary when FNA results indicate cytology consistent with Hurthle cell pathology.

### Colorectal Cancer Screening

Cologuard® is medically necessary for average-risk individuals over 49 once every 3 years as an alternative to screening colonoscopy.

# CPT Codes

The following codes are associated with the guidelines in this document. This list is not all inclusive.

Covered when medical necessity criteria are met:

| | |
|---|---|
| 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) |
| 81170 | ABL1 (ABL proto-oncogene 1, non-receptor tyrosine kinase) (eg, acquired imatinib tyrosine kinase inhibitor resistance), gene analysis, variants in the kinase domain |
| 81270 | JAK2 (Janus kinase 2) (eg, myeloproliferative disorder) gene analysis, p.Val617Phe (V617F) variant |
| 81219 | CALR (calreticulin) (eg, myeloproliferative disorders), gene analysis, common variants in exon 9 |
| 81218 | CEBPA (CCAAT/enhancer binding protein [C/EBP], alpha) (eg, acute myeloid leukemia), gene analysis, full gene sequence |
| 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) |
| 81236 | EZH2 (enhancer of zeste 2 polycomb repressive complex 2 subunit) (eg, myelodysplastic syndrome, myeloproliferative neoplasms) gene analysis, full gene sequence |
| 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) |
| 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) |

| | |
|---|---|
| 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 variant(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 (O-6-methylguanine-DNA methyltransferase) (eg, glioblastoma multiforme) promoter methylation analysis |
| 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) |
| 81320 | PLCG2 (phospholipase C gamma 2) (eg, chronic lymphocytic leukemia) gene analysis, common variants (eg, R665W, S707F, L845F) |
| 81345 | TERT (telomerase reverse transcriptase) (eg, thyroid carcinoma, glioblastoma multiforme) gene analysis, targeted sequence analysis (eg, promoter region) |
| 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 variant |
| 81450 | Targeted genomic sequence analysis panel, hematolymphoid neoplasm or disorder, DNA and RNA analysis when performed, 5-50 genes (eg, BRAF, CEBPA, DNMT3A, EZH2, FLT3, IDH1, IDH2, JAK2, KRAS, KIT, MLL, NRAS, NPM1, NOTCH1), interrogation for sequence variants, and copy number variants or rearrangements, or isoform expression or mRNA expression levels, if performed |
| 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 score |

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|---|---|
| 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 |
| 81528 | Oncology (colorectal) screening, quantitative real-time target and signal amplification of 10 DNA markers (KRAS mutations, promoter methylation of NDRG4 and BMP3) and fecal hemoglobin, utilizing stool, algorithm reported as a positive or negative result |
| 81545 | Oncology (thyroid), gene expression analysis of 142 genes, utilizing fine needle aspirate, algorithm reported as a categorical result (eg, benign or suspicious) |
| 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 |
| 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 |
| 0023U | Oncology (acute myelogenous leukemia), DNA, genotyping of internal tandem duplication, p.D835, p.I836, using mononuclear cells, reported as detection or nondetection of FLT3 mutation and indication for or against the use of midostaurin |
| 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") |
| 0040U | BCR/ABL1 (t(9;22)) (eg, chronic myelogenous leukemia) translocation analysis, major breakpoint, quantitative |

Codes that do not meet medical necessity criteria:

| | |
|---|---|
| 81327 | SEPT9 (Septin9) (eg, colorectal cancer) promoter methylation analysis |
| 81455 | Targeted genomic sequence analysis panel, solid organ or hematolymphoid neoplasm, DNA and RNA analysis when performed, 51 or greater genes (eg, ALK, BRAF, CDKN2A, CEBPA, DNMT3A, EGFR, ERBB2, EZH2, FLT3, IDH1, IDH2, JAK2, KIT, KRAS, MLL, NPM1, NRAS, MET, NOTCH1, PDGFRA, PDGFRB, PGR, PIK3CA, PTEN, RET), interrogation for sequence variants and copy number variants or rearrangements, if performed |

| | |
|---|---|
| 81504 | Oncology (tissue of origin), microarray gene expression profiling of > 2,000 genes, utilizing formalin-fixed paraffin-embedded tissue, algorithm reported as tissue similarity scores |
| 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 |
| 81525 | Oncology (colon), mRNA, gene expression profiling by real-time RT-PCR of 12 genes (7 content and 5 housekeeping), utilizing formalin-fixed paraffin-embedded tissue, algorithm reported as a recurrence score |
| 81540 | Oncology (tumor of unknown origin), mRNA, gene expression profiling by real-time RT-PCR of 92 genes (87 content and 5 housekeeping) to classify tumor into main cancer type and subtype, utilizing formalin-fixed paraffin-embedded tissue, algorithm reported |
| 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 |
| 0037U | Targeted genomic sequence analysis, solid organ neoplasm, DNA analysis of 324 genes, interrogation for sequence variants, gene copy number amplifications, gene rearrangements, microsatellite instability and tumor mutational burden |
| 0045U | Oncology (breast ductal carcinoma in situ), mRNA, gene expression profiling by realtime RT-PCR of 12 genes (7 content and 5 housekeeping), utilizing formalin-fixed paraffin-embedded tissue, algorithm reported as recurrence score |
| 0046U | FLT3 (fms-related tyrosine kinase 3) (eg, acute myeloid leukemia) internal tandem duplication (ITD) variants, quantitative |
| 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 |
| 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) |
| 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 |
| ANY | Guardant360® for any indication |

# Background

Somatic genetic testing for the purpose of cancer management guidance is a rapidly evolving field of molecular medicine. Genetic testing of a solid or hematologic tumor can provide important information regarding the prognosis, risk for recurrence or help predict tumor response to chemotherapeutic agents. In addition, genetic testing of tissue (e.g. blood) or stool, for evidence of a tumor is becoming an important tool in the early detection of cancer. While this is an area of rapid and ongoing research, clinical validity and utility is proven for only a subset of companion diagnostic genetic tests at this time.

## Myeloproliferative Disorders

Myeloproliferative disorders are a group of conditions that cause abnormal growth of blood cells in the bone marrow. They include polycythemia vera (PV), essential thrombocytosis (ET), pre-primary myelofibrosis (pre-PMF), primary myelofibrosis (PMF), and chronic myelogenous leukemia (CML). The World Health Organization (WHO) further classifies PV, ET, and PMF as Philadelphia chromosome-negative myeloproliferative neoplasms (MPN)s. The diagnosis of an MPN is suspected based upon clinical, laboratory, and pathological findings (i.e., bone marrow morphology). MPNs are related to, but distinct from, myelodysplastic syndromes (MDS). In general, MDS are characterized by ineffective or dysfunctional blood cells, while MPN are characterized by an increase in the number of blood cells.

Molecular testing for certain somatic mutations is included in the World Health Organization diagnostic criteria for myeloproliferative neoplasms. Specific treatments may be initiated for some individuals with a confirmed diagnosis of myeloproliferative disorder. Targeted genetic testing of the JAK2, CALR, and MPL genes may be helpful in individuals who would not otherwise meet diagnostic criteria without it. At this time, mutations in other genes associated with MPN, including mutations within ASXL1, TET2, SRSF2, U2AF1, IDH1/IDH2, TP53, DNMT3A, IKZF1, LNK, SF3B1, EZH2, CBL, and SETBP1, are recommended only in the evaluation for primary and pre-primary myelofibrosis.

### *Polycythemia Vera*

Polycythemia vera is a chronic myeloproliferative disease characterized by increased hemoglobin, hematocrit, and red blood cell mass. There is an associated increased risk for thrombosis and transformation to acute myelogenous leukemia or primary myelofibrosis; however, patients are often asymptomatic. Polycythemia vera (PV) is included among the differential for those who have negative BCR-ABL testing. The proposed revised World Health Organization (WHO) criteria for diagnosis includes presence of the somatic JAK2 V617F mutation or functionally similar exon 12 mutation. Other diagnostic criteria include elevated hemoglobin and abnormal bone marrow morphology. The JAK2 V617F mutation is present in the vast majority (greater than 90%) of cases of PV. Functionally similar mutations in JAK2 exon 12 account for most remaining cases of JAK2 V617F mutation-negative PV. These mutations lead to sustained activation of the JAK2 protein, which causes excess cell production, independent of erythropoietin levels. Together, they are identified in 98% of PV cases and lead to high diagnostic certainty. Absence of a JAK2 mutation, combined with normal or increased serum erythropoietin level, greatly decreases the likelihood of a PV diagnosis. WHO proposed revision criteria for PV do not address additional molecular markers, including CALR mutation status.

### *Essential Thrombocythemia or Thrombocytosis*

Essential thrombocythemia is a disorder of sustained increased platelet count, characterized by persistently elevated platelet count greater than 450,000/µL; megakaryocytic hyperplasia (seen in bone marrow); not meeting WHO criteria for CML, PV, PMF, MDS or other myeloid neoplasm; and the demonstration of JAK2 V617F or other clonal marker or no evidence of reactive thrombocytosis. In addition, patients can have splenomegaly and a clinical course complicated by thrombotic or hemorrhagic episodes (or both). The majority of ET patients (60%) carry a somatic JAK2 V617F mutation, while a smaller percentage (5-10%) have activating MPL mutations. Proposed criteria additionally state that 70% of patients without a JAK2 or MPL mutation carry a somatic mutation of the calreticulin (CALR) gene. Among confirmed ET cases, mutations in CALR are more common than MPL. Positive CALR mutation status is suggested as indicating a more indolent course (Klampfl et al. 2013). It is important to note that JAK2/CALR/MPL mutation screening, by itself, cannot distinguish masked PV from JAK2-mutated ET, WHO-defined ET from prefibrotic/early PMF or triple-negative ET from other causes of thrombocytosis (Barbui et al. 2015).

### *Primary Myelofibrosis*

Primary myelofibrosis (PMF) is a rare disorder in which the bone marrow is replaced with fibrous tissue, leading to bone marrow failure. Clinical features are similar to ET. The approximate incidence is 1 in 100,000 individuals. Persons can be asymptomatic in the early stages of the disease. For such patients, treatment may not initially be necessary. Progression of the disease can include transformation to acute myeloid leukemia. Treatment is generally symptomatic and aimed at preventing complications.

Demonstration of a clonal marker is important for diagnosis. Somatic molecular markers in PMF patients are similar to those in patients with ET, and include JAK2 V617F, MPL, and CALR. Somatic mutations in JAK2 are identified in 55-65% of PMF cases, and MPL mutations in 10%. Mutations in CALR are less common than JAK2, but more common than MPL. When all of these are absent, testing for additional markers, such as ASXL1, EZH2, TET2, IDH1/IDH2, SRSF2 and SF3B1 can be considered. Many of these additional markers have prognostic significance for survival and progression to leukemia as well (NCCN® v.2.2018; Tefferi 2016). Identification of a clonal marker is one of the required major criteria in the diagnosis of PMF (NCCN® v.2.2018).

## Solid Tumor Testing

### *Breast Cancer*

While NGS panels are not currently recommended for use to guide chemotherapeutic treatment decisions, molecular testing may be used to predict prognosis and recurrence risk for breast cancer. The strongest prognostic factors to predict future recurrence or death from breast cancer include patient age, comorbidity, tumor size, tumor grade, number of involved axillary lymph nodes, and HER2 tumor status (NCCN® v.2.2017).

Breast cancer gene expression profiling refers to testing performed on breast cancer tumor tissue to identify expression levels of sets of genes that, taken together, may predict recurrence risk and/or treatment response. The National Comprehensive Cancer Network incorporates the Oncotype Dx Breast 21-gene assay into the treatment determination algorithm for individuals with invasive breast cancer with subtypes including ductal, lobular, mixed, and metaplastic, with no lymph node involvement or minimal lymph node involvement with micrometastasis of 2 mm or less, whose tumor is >0.5 cm (NCCN® v.2.2017). These guidelines specifically note the limitation of other multi-gene or

multi-gene expression assay systems as not yet sufficiently validated to predict response to chemotherapy.

The American Society of Clinical Oncology (ASCO 2016) recommends use of the Oncotype Dx assay to guide decisions on adjuvant chemotherapy in patients treated with tamoxifen who are node-negative and estrogen-receptor positive (Harris et al. 2016).

Sufficient data supports the use of the Oncotype Dx assay for recurrence risk prediction and determination of adjuvant chemotherapy for:

- Early stage (I or II) invasive breast cancer, AND
- Axillary lymph node negative / no evidence of distant metastatic breast cancer / any axillary-node micrometastasis is 2 mm or less, AND
- Estrogen receptor positive AND
- HER2 receptor negative AND
- Patients who are candidates for adjuvant chemotherapy

The 2016 ASCO practice guideline published in the *Journal of Clinical Oncology* supports the use of certain tumor biomarker assays beyond the Oncotype Dx Breast assay described above, in select populations to guide treatment. Importantly, these recommendations are based on review of evidence in which no true prospective trials have been performed. Specifically, ASCO supports the use of the following tests in the outlined scenarios:

- EndoPredict® for women with ER/PR-positive, HER2-negative, node-negative breast cancer to guide decisions on adjuvant systemic chemotherapy. This is an evidence-based recommendation with reported intermediate evidence quality, and a moderate strength of recommendation
- PAM50/Prosigna Breast Cancer Prognostic Gene Signature Assay for women with ER/PR-positive, HER2-negative, node-negative breast cancer to be used in conjunction with other clinicopathologic variables to guide decisions on adjuvant systemic therapy. This is an evidence-based recommendation with reported high quality evidence and a strong strength of recommendation
- Breast Cancer Index® (BCI) for women with ER/PR-positive, HER2-negative, node-negative breast cancer to guide decisions on adjuvant systemic therapy. This is an evidence-based recommendation with intermediate quality evidence, and a moderate strength of recommendation

The American Society of Clinical Oncology recently published a special addendum (Krop et al. 2017) regarding use of MammaPrint® for women with hormone receptor- positive, HER2-negative, node negative tumors based on preliminary MINDACT data. The prior recommendation for this group [women with HR+, HER2-(node positive or node-negative) breast cancer] was that the clinician should not use MammaPrint® to guide decisions on adjuvant systemic chemotherapy. The recent updated guideline separates this group into 3 categories and recommendations:

- **Recommendation 1.1.1**: MammaPrint® assay may be used for women with hormone receptor- positive, HER2-negative, node negative cancer who are considered high clinical risk per MINDACT categorization to inform decision making regarding withholding adjuvant systemic chemotherapy due to its ability to identify a good prognosis population with potentially limited chemotherapy benefit. (Evidence Quality: High and Strength of Recommendation: Strong)
- **Recommendation 1.1.2**: MammaPrint® assay should not be used for women with hormone receptor- positive, HER2-negative, node negative cancer who were considered low clinical risk per MINDACT categorization because women in the low clinical risk category had excellent outcomes and did not seem to benefit from chemotherapy even with a genomically high risk cancer. (Evidence Quality: High and Strength of Recommendation: Strong)
- **Recommendation 1.2.1**: MammaPrint® assay may be used in patients with hormone receptor- positive, HER2-negative, node positive (with 1-3 positive nodes) cancer and at high clinical risk per MINDACT categorization to inform decision making regarding withholding adjuvant systemic chemotherapy because of its ability to identify a good prognosis population with potentially limited chemotherapy benefit. Patients should be informed that benefit of chemotherapy cannot be excluded, particularly in patients with more than one involved lymph node. (Evidence Quality: High; Strength of Recommendation: Moderate)

The following tests are not supported within the ASCO practice guideline under any circumstances at this time: MammoStrat or any assays performed using circulating tumor cells or tumor-infiltrating lymphocytes.

Given the relatively lower quality evidence and moderate strength recommendation from ASCO provided for EndoPredict® and Breast Cancer Index®, these tests have not yet been adequately validated for clinical use. For the PAM50 Prosigna test, however, retrospective studies have suggested higher utility and ASCO's recommendation is strong.

### *Lung Cancer*

Epidermal growth factor receptor (EGFR) mutation status has been shown to be significantly associated with tumor response to EGFR tyrosine kinase inhibitors (Lynch et al. 2004; Mok et al. 2009). This has led to the routine assessment of the presence of EGFR mutations in advanced non-small cell lung cancers (NSCLC), particularly adenocarcinomas (Keedy et al. 2011; Salto-Tellez et al. 2011). The anaplastic lymphoma kinase (ALK) gene rearrangements have been identified in a subset of patients with NSCLC and represent a unique subset of patients for whom ALK inhibitors may be a very effective treatment strategy. According to NCCN® Clinical Practice Guidelines in Oncology, (NCCN Guidelines®), NSCLC (particularly adenocarcinoma), EGFR and ALK testing of tumor tissue is considered the standard of care (Ettinger et al. 2014). ROS1 gene rearrangement testing is also recommended by the most recent NCCN Guidelines® update based on data showing efficacy of treatment with crizotinib in patients with ROS1 rearrangements and recent FDA approval (v.8.2017). PD-L1 testing is recommended as expression levels are currently used to determine the most appropriate course of treatment in this rapidly evolving area of lung cancer care.

KRAS mutations are associated with primary EGFR TKI resistance, and according to the most recent NCCN Guidelines®, KRAS gene sequencing could be useful for the selection of patients as candidates for EGFR TKI therapy. Although targeted therapy for KRAS mutations is currently unavailable, KRAS testing may identify patients who may not benefit from further molecular diagnostic testing.

In addition, current NCCN Guidelines® recommend testing for these and other gene alterations utilizing next-generation sequencing (NGS), a technology that can detect specific mutations and gene rearrangements. The other genetic alterations more recently found to be associated with NSCLC and for which targeted therapies have been developed include: HER2 (ERBB2) mutations, BRAF mutations, RET gene rearrangements, and MET amplification. As targeted agents are available for patients with NSCLC who have these genetic alterations, the NCCN Guidelines® recommend testing for these specific genetic alterations using NGS to ensure that patients with NSCLC receive the most appropriate treatment. The NCCN® Guidelines Panel, NSCLC also endorses broader molecular profiling (also known as precision medicine) to identify rare driver mutations in other genes with the goal of identifying patients who may be eligible for clinical trials (v.8.2017).

While there has been some success in broad molecular profiling and targeted therapies for NSCLC, there is a lack of evidence to support tumor testing for patients diagnosed with small cell lung cancer (SCLC) (NCCN® v.1.2018). To date, there have been limited advances in the treatment of SCLC and there are specific challenges in performing genomic analysis on SCLC tumors compared to NSCLC tumors. Genomic profiling is currently being evaluated as an option, but more research is needed to demonstrate its effectiveness in this population (Umemura et al. 2015). Additionally, recent NCCN Guidelines® for SCLC do not give any recommendations to support the use of molecular profiling to aid in the treatment of SCLC.

*Cell-Free Tumor Testing*

Tumor testing for EGFR and ALK rearrangements is not always possible, primarily due to inadequate tissue sample. It is estimated that 15% of patients with NSCLC who undergo biopsy have an inadequate sample for molecular testing (Douillard et al. 2014). In addition, many patients with late-stage metastatic NSCLC may be poor candidates for biopsy.

There has been growing interest and research into alternative methodologies of assessing tumor mutation status, including cell-free plasma based tests. Primary and metastatic tumors shed circulating tumor cells (CTCs) into the bloodstream. These remain at very low concentration in the plasma and are difficult to detect. CTCs release DNA through various mechanisms. This cell-free tumor DNA or ctDNA is easier to isolate and, with the increasing capabilities of next-generation sequencing, offers an alternate opportunity to assess somatic tumor-specific mutations. While several studies have shown that ctDNA is not as sensitive or specific as direct tumor testing (Janku et al. 2016; Zhang et al. 2016), there are potential applications where ctDNA testing might be indicated (e.g., when a biopsy sample is insufficient, when repeat biopsy is overly risky, or when chemotherapy response has changed and there is a concern for intra- or inter-tumor heterogeneity). It has also been proposed that ctDNA may improve minimal residual disease monitoring. Cell-free tumor DNA analysis is an active area of ongoing research; however, few ctDNA tests have been clinically validated.

At this time, there is no testing algorithm that incorporates both plasma and tumor testing for NSCLC. Based on its inferior performance, there is insufficient evidence to recommend plasma-based testing (ctDNA) over tumor-based testing when a tumor sample is available. However, in cases of metastatic NSCLC where an inadequate tissue biopsy is available, ctDNA EGFR testing may be reasonable to aid in treatment selection.

*Cancer of Unknown Primary/Occult Neoplasm*

Occult neoplasms, or cancers of unknown primary, are defined as histologically proven metastatic malignant tumors whose primary site cannot be identified during pretreatment evaluation. These may have a wide clinical presentation and typically a poor prognosis. Several laboratories offer gene expression profiling or NGS tests to aid in the identification of the tissue of origin of a metastatic tumor. NCCN® Clinical Practice Guidelines in Oncology (NCCN Guidelines®), Occult Primary Cancer (v.2.2017) state that the literature evaluating molecular testing in the diagnosis and management of occult primaries has focused much more on establishing the tissue of origin rather than establishing whether such identification leads to better outcomes for patients. Although these results may have diagnostic benefit, there is limited evidence for clinical utility at this time. The NCCN® Guidelines panel does not recommend molecular profiling for the identification of tissue of origin as standard management in the diagnostic workup of patients with occult primary tumors (category 3).

The European Society for Medical Oncology (ESMO) also notes the potential promise of molecular assays to assist with tissue of origin identification for cancers of unknown primary; however, the ESMO clinical practice guidelines goes on to note insufficient evidence related to further using assay-predicted tumor type to then administer primary site-specific therapy (Fizazi et al. 2015).

*Prostate Cancer*

Prostate cancer is a common malignancy in men and the worldwide burden of this disease is rising. Early detection of prostate cancer by prostate-specific antigen (PSA) screening is controversial, but changes in the PSA threshold, frequency of screening, and the use of other biomarkers have the potential to minimize the overdiagnosis associated with PSA screening. Several new biomarkers for individuals with raised PSA concentrations or those diagnosed with prostate cancer are likely to identify individuals who can be spared aggressive treatment (Cuzick et al. 2014). Multiple molecular biomarker tests for prostate cancer prognosis (e.g., Prolaris and Oncotype DX Prostate cancer) have been developed with extensive industry support, guidance, and involvement, and have been marketed under the less rigorous FDA regulatory pathway for biomarkers.

Although the intended use of most of these tests is to distinguish prostate cancer from benign prostatic conditions and many appear to have better sensitivity and specificity than PSA, many studies have shown that these tests may also be useful in the differentiation of aggressive from non-aggressive forms of prostate cancer. However, additional research is needed to fully determine the clinical utility of testing (Sartori and Chan 2014). Research is ongoing for several biomarkers that have been proposed for screening, detection, monitoring and prognosis for prostate cancer.

The NCCN Guidelines® note that men with clinically localized disease may consider the use of tumor-based molecular assays as retrospective studies have shown that molecular assays performed on biopsy or prostatectomy specimens provide prognostic information independent of NCCN® risk groups such as likelihood of death with conservative management, likelihood of biochemical progression after radical prostatectomy or external beam therapy, and likelihood of developing metastasis after radical prostatectomy or salvage radiotherapy. Naryan et al. (2017), performed an evidence-based review for biomarker assays used for prostate cancer. The group reviewed Prolaris and Oncotype DX Prostate and commented that although these tests have been incorporated into NCCN Guidelines® and may be beneficial for men with low-volume Gleason 6 disease on biopsy, these tests have not been thoroughly studied in minority populations and it is unclear how initial test results may change with repeat assessments. They recommend that these tests should be used with discretion as they add to the cost of prostate cancer care and that providers should discuss the indications and limitations thoroughly

with their patients (Narayan et al. 2017). Similarly, Lamy et al. (2017) performed a systematic review of prostate cancer biomarkers and conclude the Prostate Health Index and the 4K score have the highest level of evidence in predicting which cancers may be more aggressive. They also note that other assays, including OncotypeDx Prostate, Prolaris, and Decipher, are promising but need further evidence to confirm their clinical validity.

### *Thyroid Cancer*

Per NCCN Guidelines®, BRAF V600E testing is indicated for patients with confirmed or highly suspected thyroid cancer (FTC, MTC, PTC, or patients with metastatic differentiated thyroid carcinoma). Testing can aid in medication selection and/or surgical decisions. Aggressive BRAF-positive papillary carcinomas have been found to be associated with the overexpression of the microRNA known as miR-146b. Currently, miRs are considered independent of BRAF mutational status and may be used to assist in risk stratification for BRAF-positive cases (Ludvíková et al. 2016). RNA classifiers are not yet considered standard of care in evaluating the BRAF V600E somatic variant.

Molecular diagnostic testing to detect individual mutations (e.g., BRAF, RET/PTC, RAS, PAX8/PPAR) has been proven in the evaluation of FNA samples that are indeterminate to assist in management decisions; however, large scale, prospective studies have not been performed which demonstrate the clinical utility of such testing in patients with confirmed thyroid cancer. Further studies on the clinical utility of these tests are needed in individuals who have already been diagnosed with thyroid malignancy (NCCN® v.2.2017).

Medullary thyroid cancer (MTC) is an aggressive form of thyroid cancer that is often not definitively identified by cytology alone. About 40% of patients with MTC do not undergo central neck dissection (the recommended treatment for MTC). Molecular assays have been suggested to assist with the diagnosis of medullary thyroid carcinoma and/or aid in management. There is insufficient data at this time to support the use of genomic classifiers for this cohort (Kloos et al. 2013).

## Cancer Screening

### *Indeterminate Thyroid Nodules*

Cytological examination of fine needle aspiration (FNA) samples is currently the standard of care for classifying thyroid nodules as malignant or benign; however, approximately 25% of samples are classified as indeterminate. There is growing evidence that molecular diagnostic testing can be useful in the reclassification of these indeterminate lesions. The NCCN® Clinical Practice Guidelines in Oncology (NCCN Guidelines®), Thyroid Carcinoma (v.2.2017) states that molecular diagnostic testing to detect individual mutations (e.g., BRAF, RET/PTC, RAS, PAX8/PPAR) or pattern recognition using molecular classifiers may be useful in evaluation of FNA samples that are indeterminate to assist in management directions. Indeterminate cytology results are defined as FNA results that are suspicious for 1) follicular neoplasms, 2) atypia of undetermined significance/follicular lesion of undetermined significance (AUS/FLUS). Molecular diagnostics are not recommended for Hurthle cell neoplasms (NCCN® v.2.2017).

The American Thyroid Association (ATA) issued a statement in July 2015 regarding the surgical application of molecular profiling for thyroid nodules. This statement highlights a 7-gene molecular panel including BRAF V600E, three isoforms of RAS point mutations, and translocations within PAX8/PPARy and RET/PTC genes as having been clinically validated to predict the presence of differentiated thyroid cancer with 86-94% specificity and 87-100% PPV. This test is noted to have been performed on over 1,500 indeterminate cytology specimens and correlated with histologic results to

generate a real-time algorithm for management of thyroid nodules with the ultimate goal of appropriate initial oncologic total thyroidectomy rather than lobectomy with subsequent completion thyroidectomy when total thyroidectomy is indicated. This 7-gene molecular testing panel has been demonstrated to add to the specificity of indeterminate FNA cytology and successfully refine the initial operative management of thyroid nodules and thyroid cancer. The ATA report goes on to highlight a large prospective single-center study of this 7-gene molecular test noting overall, "for thyroid lesions of indeterminate cytology, the detection of any mutation translated into a malignancy risk for AUS/FLUS, FN, and SMC of 88%, 87%, and 95% respectively, compared to 6%, 14%, and 28% in mutation-negative lesions," where AUS/FLUS refers to atypia of uncertain significance/follicular lesion of undetermined significance, FN refers to follicular neoplasm, and SMC refers to suspicious for malignant cells.

The ATA summarizes the above noted professional statement by suggesting a role exists for both molecular tumor profiling and gene expression classifier (GEC) systems in assisting with the appropriate management of cytologically indeterminate nodules; however, the type of test chosen may be dependent upon additional clinical and sonographic features. GEC is described as a "rule out" test whereas molecular profiling is described as more of a "rule in" test. An example is provided suggesting "GEC may perform better in a setting of lower cancer frequency, as well as in a cytologic category of low cancer frequency such as AUS/FLUS or FN, than it will in a setting of higher cancer frequency such as SMC or a site with a high prevalence of malignancy in a given cytologic category. Conversely, a "rule in" test such as the 7-gene MT will perform better in settings and categories of higher cancer frequency, for example if a clinician is specifically selecting "high risk" cases thereby enriching the prevalence of cancer in the examined population, or if the local malignancy rate is high at baseline" (Ferris et al. 2015).

The rate of diagnosis of a follicular variant of papillary thyroid cancer has been on the rise and is now the most common variant of PTC. In early 2017, the American Thyroid Association (Haugen et al. 2017) recommended a change in nomenclature from follicular variant of papillary thyroid carcinoma (FVPTC) to noninvasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP) in a subset of this population with certain noninvasive features. This move was based on evidence that these noninvasive tumors were indolent compared to infiltrative FVPTC and could be managed in a much less aggressive manner. Thus they emphasized that NIFTP should not be considered a carcinoma. This change in nomenclature and treatment for NIFTP impacts the performance of both GECs and mutation analyses by lowering their overall PPV. At this time, the clearest clinical utility for GECs appears to be for those with Bethesda type III cytopathology with a lower a priori risk for malignancy. A negative test result could result in a change in medical management.

Notably, the majority of RAS mutations identified are subsequently associated with an NIFTP diagnosis. Wong et al. (2016) and Hang et al. (2017) also note the majority of tumors detected by Afirma are ultimately classified as NIFTP. Hang et al. (2017) further report that from their pooled analysis the NPV for Afirma in particular is 97% for Bethesda category III and 90% for Bethesda category IV. The authors also note a significant increase in total versus partial thyroidectomy within the past 4 years and speculate it may be due to incorrectly assuming a suspicious GEC result is equivalent to a suspicious FNA result. They note concern for potential for overtreatment, particularly in the AUS group with a suspicious result from a GEC where lobectomy, instead of-total thyroidectomy, would be ideal. This would be most beneficial in patients who are ultimately diagnosed with NIFTP.

*Colorectal Cancer Screening*

Colorectal cancer is the fourth most common cancer type diagnosed in the United States (NCCN® 1.2017). Best practice guidelines are available from multiple professional organizations (e.g. NCCN®, American Cancer Society, ACOG, USPSTF, etc.) detailing recommendations for standard frequency and starting age for screening based on risk category. Underutilization of screening colonoscopy has led to the study and inclusion of stool-based testing methods in professional guidelines as well as prompting the study of plasma-based screening techniques. Screening modalities other than standard colonoscopy have been recognized by professional organizations as reasonable for individuals unable or unwilling to undergo this procedure; however, benefits and limitations of each screening method must be considered given the sensitivity for detection of not only colorectal cancer, but also polyps.

General concerns raised surrounding colorectal cancer screening via stool DNA testing and/or cell free DNA (cfDNA) testing include potential population uptake bias with those individuals with more significant comorbidities (and potentially lower or no mortality gain from screening) more likely to use these screening methods. Conversely, low-risk individuals who are considered candidates for screening colonoscopy may opt for these alternate screening options and cancers may be missed due to lower sensitivities (Parikh and Prasad 2016). The 2016 USPSTF final recommendations focus not on the level of evidence supporting each individual screening modality or which method should be used, but rather on the likelihood of screening utilization and the need for shared decision making in the selection of screening type.

The American College of Gastroenterology last published recommendations for general population colorectal cancer screening in 2017 and note colonoscopy and fecal immunochemical test (FIT) as tier 1 tests. If colonoscopy is declined, patients should be offered FIT. Second tier tests include CT colonography, FIT-fecal DNA test and flexible sigmoidoscopy (Rex et al. 2017). Similarly, a 2008 joint recommendation by the American Cancer Society, US multi-society task force on colorectal cancer, and the American College of Radiology recommend colorectal cancer prevention modalities (e.g. colonoscopy, flexible sigmoidoscopy, etc.) prior to offering colorectal cancer detection methods which are noted to include gFOBT, FIT, and stool DNA testing.

Stool DNA Testing is a method of colorectal cancer screening in which stool is evaluated for specific somatic mutations known to frequently be a part of the carcinogenesis of colorectal cancer. Some stool DNA testing has gained FDA approval and has been demonstrated to have higher sensitivity over FIT for colorectal cancer and certain types of polyps. DNA-based stool testing has been incorporated into the most recent NCCN Guidelines® update and is recommended for screening average-risk individuals. However, the NCCN® discussion section notes that there is limited data about how stool DNA testing may fit into an overall screening program and how long the interval should be between screening. The NCCN® currently recommends that stool DNA testing as a primary screening modality should be individualized, particularly in high-risk individuals (1.2017). The USPSTF 2016 recommendations include FIT-DNA combination testing (FIT in addition to stool-based DNA testing) with noted limitations including insufficient evidence about appropriate longitudinal follow-up of abnormal findings after a negative diagnostic colonoscopy, in addition to potential overly intensive surveillance due to concerns from the genomic component of testing.

Circulating Tumor Marker screening is a method of cell free DNA (cfDNA) testing of plasma to identify potential tumor markers sloughed off into circulating plasma cells in order to identify colorectal cancer. The NCCN® is currently silent on this methodology. The primary marker studied to date includes methylation of the SEPT9 gene (mSEPT9). Prospective evaluation of adults >50 years of age via mSEPT9 in circulating plasma was performed via the PRESEPT study concurrent to screening

colonoscopy, including subjects in the US and Germany. 53 cases of colorectal cancer and approximately 1,500 controls were evaluated. Sensitivity of mSEPT9 for detection of colorectal cancer varied by stage: Stage I (35.0%), Stage II (63.0%), Stage III (46.0%), Stage IV (77.4%). Specificity was 91.5% for colorectal cancer, but only 11.2% for advanced adenomas. This clinical trial data published by Church et al. (2014) noted the need for improved sensitivity for early cancers and advanced adenomas for use in general population colorectal cancer screening. Other case-control study designs have demonstrated higher sensitivities for colorectal cancer ranging from 67-96% (Heichman 2014). The USPSTF 2016 recommendations include mSEPT9 as an optional screening modality. Within this publication's table for the Characteristics of Colorectal Cancer Screening Strategies, a footnote states the following: "Although a serology test to detect methylated SEPT9 DNA was included in the systematic evidence review, this screening method currently has limited evidence evaluating its use (a single published test characteristic study met inclusion criteria, which found it had a sensitivity to detect colorectal cancer of <50%). It is therefore not included in this table."

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# Revision History

**Medical Advisory Board Review:**

v1.2019 11/07/2018: Reviewed

v1.2018 03/31/2018: Reviewed

**Clinical Steering Committee Review:**

v1.2019 10/03/2018: Approved

v1.2018 02/28/2018: Approved

v5.2017 11/01/2017: Approved

v4.2017 09/20/2017: Approved

v3.2017 08/09/2017: Approved

v2.2017 05/03/2017: Approved

v1.2017 01/25/2017: Approved

**Revisions:**

| Version | Date | Editor | Description |
|---|---|---|---|
| v1.2019 | 11/01/2018 | Ashley Allenby, MS, CGC | Semi-annual review. Removed NCCN® 2B criteria recommendation from general medical necessity criteria. Added criteria for ThyroSeq3.0. Updated background, professional society/NCCN Guidelines® and references. Renumbered to 2019. Reformatted CPT code list. PMID added. |
| v1.2018 | 03/31/2018 | Gwen Fraley, MS, CGC | Semi-annual review. Added disclaimer sentence to scope section. Added uveal melanoma to list of tumor types for somatic genetic testing. Added exclusion criteria for prostate cancer tumor testing. Revised MammaPrint® criteria. Updated background, professional society/NCCN Guidelines and references. Renumbered to 2018. Submitted to CSC for approval. |

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| v5.2017 | 11/01/2017 | Gwen Fraley, MS, CGC | Revised criteria for indeterminate thyroid nodules. Updated background and references. Renumbered to v5.2017 and submitted to CSC for approval. |
| v4.2017 | 09/18/17 | Megan Czarniecki, MS, CGC | Removed specific criteria for lung cancer. Formatting changes: converted references to NLM style. Incorporated "methodological considerations" to appropriate use criteria and background. Renumbered to v4.2017 and submitted to CSC for approval. |
| v3.2017 | 08/09/2017 | Gwen Fraley, MS, CGC | Changed nomenclature of "occult primary" to "cancer of unknown primary/occult neoplasm". Changed stance on MammaPrint® to allow for coverage when criteria met. Removed separate lung cancer criteria and referred to NCCN. Updated references. Added additional codes to Coding Considerations. |
| v2.2017 | 06/30/2017 | Denise Jones, MS, CGC | Quarterly review. No criteria changes. Updated references. |
| v2.2017 | 04/25/2017 | Cheryl Thomas, MS, CGC | Quarterly review. Added changes to indeterminate thyroid nodules (removed Hurthle cell from indication per NCCN update). Added PD-L1 to NSCLC molecular targets. Updated references. |
| v1.2017 | 01/23/2017 | Gwen Fraley, MS, CGC | Quarterly review. Updated MPN criteria. Edited EGFR criteria regarding erlotinib. Updated references. Renumbered to 2017. |
| v4.2016 | 09/29/2016 | Jenna McLosky, MS, CGC | Updated background regarding occult primaries. Updated references. |
| v3.2016 | 06/30/2016 | Jenna McLosky, MS, CGC | Added EGFR Cobas cell-free test for NSCLC. Updated references. |

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| v2.2016 | 04/04/2016 | Jenna McLosky, MS, CGC | Updated and reviewed prostate cancer screening criteria. Updated references. |
| v1.2016 | 03/18/2016 | Jenna McLosky, MS, CGC | Updated and revised stance on breast cancer prognosis assays (Prosigna). Updated references. |
| v1.2015 | 09/24/2015 | Jenna McLosky, MS, CGC | Original version |

**Original Effective Date:** 09/24/2015

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