

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. In addition, testing required by a plan's pharmaceutical policies may be adjudicated by that plan's pharmaceutical guidelines.

General Coverage Criteria

Somatic tumor testing, unless separate criteria are 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 through prospective research in peer-reviewed literature to improve diagnosis, management, or clinical outcomes for the individual's tumor type and disease characteristics
- Sample type (e.g., formalin-fixed, paraffin embedded, cell-free tumor DNA, circulating tumor cells, etc.) has been proven to have clinical utility based on prospective evidence in peer-reviewed literature
- Testing methodology has been clinically validated and is the most accurate method for the actionable target unless technical limitations (e.g. poor sample quality) necessitate the need for alternate testing strategies

In addition to the above criteria, 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) and more than one target is indicated
- Identification of genes or biomarkers on the panel has been demonstrated to improve diagnosis, management, or clinical outcomes for the individual's tumor type and disease characteristics
- 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

Conditions for which testing may be medically necessary

Table 1. Solid tumor markers that are medically necessary when the above criteria is met (list may not be all inclusive):

Indication	Molecular Studies
Acute Lymphoblastic Leukemia (ALL)	Targeted multi-gene panels
Acute Lymphoblastic Leukemia (ALL) B-Cell Ph- <i>*See below for MRD testing criteria</i>	NGS Immunosequencing
Acute Myelogenous Leukemia (AML) <i>*See below for MRD testing criteria</i>	Targeted multi-gene panels
Brain/Central Nervous System Cancers	IDH1, IDH2, MGMT, 1p/19q, ATRX, TERT, H3F3A, HIST1H3B, BRAF, RELA
Breast Cancer <i>*See below for PIK3CA testing criteria</i> <i>*See below for gene expression classifier criteria</i>	PIK3CA
Chronic Lymphocytic Leukemia (CLL)	TP53, IGHV, BTK, PLCG2
Chronic Myelogenous Leukemia (CML)	BCR-ABL Targeted multi-gene panels
Colorectal Cancer Metastatic/Stage IV	BRAF, KRAS, NRAS
Endometrial Cancer	POLE
Essential Thrombocythemia or Thrombocytosis Platelet count $\geq 450 \times 10^9/L$	JAK2, CALR, MPL
Gastrointestinal Stromal Tumors (GIST)	KIT, PDGFRA, SDHB, SDHC, SDHD, NF1, BRAF
Indeterminate Thyroid Nodule Bethesda Category III (AUS/FLUS) or Bethesda Category IV (FN/SFN) <i>*FNA sample with evidence of Hurthle cell Pathology are excluded from coverage.</i>	BRAF, RAS, RET/PTC, PAX8/PPARc or ThyGeNEXT®/ThyraMIR™ or ThyroSeq® v3.0
Indeterminate Thyroid Nodule Bethesda Category III (AUS/FLUS) only <i>*FNA samples with evidence of Hurthle cell Pathology are excluded from coverage.</i>	Afirma®
Melanoma (Cutaneous) Metastatic Melanoma (Stage III or Stage IV)	BRAF, KIT

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Melanoma (Uveal)	EIF1AX, SF3B1, BAP1, PRAME, GNAQ GNA11 <i>or</i> DecisionDx - Uveal Melanoma
Metastatic Non-Small Cell Lung Cancer (NSCLC) Metastatic (Stage IIIB and above)	ALK, BRAF, EGFR, ROS1, ERBB2 (HER2), MET, RET, KRAS
Myelodysplastic Syndrome	Targeted multi-gene panels
Ovarian Cancer	BRCA1, BRCA2
Polycythemia Vera Indication Includes ONE of the following (WHO criteria 2016): <ul style="list-style-type: none"> • Hemoglobin >16.5g/dL in men, >16.0g/dL in women • Hematocrit >49% in men, >48% in women • Increased red cell mass (RCM) 	JAK2, CALR, MPL
Primary Cutaneous B-Cell Lymphoma	MYD88
Primary Myelofibrosis Pre-PMF or suspicion for PMF based on 2016 WHO criteria	JAK2, CALR, MPL Targeted multi-gene panels (<i>when JAK2, CALR, and MPL are negative</i>)
Prostate Cancer Symptomatic Cancer Screening <i>*See criteria below. Prostate cancer post-diagnosis testing is not medically necessary.</i>	ConfirmMDx® ExoDx PCA3
Solid Tumors <i>*See NTRK criteria below</i>	NTRK
T-Cell Lymphoma (Peripheral)	TET2, IDH1/IDH2, RHOA, DNMT3A, STAT3, STAT5B
Thyroid Cancer	BRAF

Conditions for which testing is not medically necessary

(list may not be all inclusive)

- Anal cancer
- Burkitt Lymphoma/diffuse noncleaved-cell lymphoma
- Cervical cancers
- Epithelioid hemangioendothelioma
- Follicular lymphoma
- Head and neck cancers

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- Hepatobiliary cancer
- Kidney cancer
- Malignant pleural mesothelioma
- Merkle cell carcinoma
- Multiple myeloma
- Neuroendocrine and adrenal tumors - including gastrointestinal and lung
- Non-epithelial ovarian cancers or borderline epithelial tumors (low malignant potential)
- Occult primary
- Pancreatic cancer
- Prostate cancer - post-diagnosis gene expression classifiers
- Skin cancer - basal and squamous cell
- Small cell lung cancer
- T-cell lymphoma: cutaneous
- Topographic genotyping (e.g., PancraGEN®)
- Whole exome tumor sequencing for any indication
- Whole genome tumor sequencing for any indication

In addition, testing of a genetic variant or profile correlated with a known therapy which does not have clinical utility for the specific tumor type and disease characteristics is not medically necessary.

Specific Coverage Criteria

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 anatomic stage 1 or stage 2
- Histologic type is ductal, lobular, mixed (ductal/lobular), or metaplastic

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- Tumor size 0.6-1.0 cm and intermediate or high grade (Grade 2 or 3) **OR** tumor size 1.1-5.0 cm, any grade
- 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
- Patient is a candidate for chemotherapy (i.e, chemotherapy not precluded due to other factors)
- Adjuvant chemotherapy is being considered and this testing is being ordered to assess recurrence risk to guide decision making as to whether or not adjuvant chemotherapy will be utilized
- No other breast GEC has been performed on this tumor sample

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

- Breast tumor is anatomic stage 1 or stage 2
- Histologic type is ductal, lobular, mixed (ductal/lobular), or metaplastic
- Tumor size 0.6-1.0 cm and intermediate or high grade (Grade 2 or 3) **OR** tumor size 1.1-5.0 cm, any grade
- 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
- Patient is postmenopausal
- Patient is a candidate for chemotherapy (i.e, chemotherapy not precluded due to other factors)
- Adjuvant chemotherapy is being considered and this testing is being ordered to assess recurrence risk to guide decision making as to whether or not adjuvant chemotherapy will be utilized
- No other breast GEC has been performed on this tumor sample

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

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- Breast tumor is anatomic stage 1 or stage 2
- Histologic type is ductal, lobular, mixed (ductal/lobular), or metaplastic
- 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
- Patient is a candidate for chemotherapy (i.e, chemotherapy not precluded due to other factors)
- Adjuvant chemotherapy is being considered and this testing is being ordered to assess recurrence risk to guide decision making as to whether or not adjuvant chemotherapy will be utilized
- No other breast GEC has been performed on this tumor sample

Cell-Free Testing

Targeted cell-free testing (e.g. cfDNA, ctDNA, liquid biopsy) is medically necessary when either of the following criteria are met:

- Stage IIIb and above non-small cell lung cancer (NSCLC) when tissue biopsy is not available/insufficient for testing or tissue biopsy testing was attempted and did not yield a result and
 - at least one of the following has an unknown status: EGFR, ALK, ROS1 and/or BRAF and
 - none of the following has a known actionable P/LP variant: EGFR, ALK, ROS1 and/or BRAF
- Stage IIIb and above NSCLC having a confirmed EGFR sensitizing P/LP variant with progression on EGFR TKI therapy (excluding osimertinib) for EGFR T790M status

Non-targeted panels without prospective evidence of clinical utility are not medically necessary.

Minimal Residual Disease (MRD) Testing

NGS immunosequencing is covered when the following criteria is met:

- There is a confirmed diagnosis of B-cell acute lymphoblastic leukemia which is Philadelphia chromosome (BCR-ABL) negative

NGS minimal residual disease (MRD) testing for Philadelphia chromosome (BCR-ABL) negative B-cell ALL is covered when all of the following criteria are met:

- Immunosequencing at the time of diagnosis identified at least one clone for MRD tracking
- Complete cytologic remission is achieved

Targeted testing with prospective evidence of clinical utility for the tumor type and disease characteristics are covered.

Targeted Molecular Testing for NTRK Fusions

Targeted molecular testing for NTRK1/2/3 fusions is covered for any of the following indications:

- In tumors where NTRK fusions have a frequency of ~10% or greater (e.g. infantile fibrosarcoma, cellular congenital mesoblastic nephroma, secretory breast cancer, mammary secretory carcinoma of the salivary gland, spitzoid melanoma, metastatic papillary thyroid cancer, analog pediatric high-grade glioma, or GIST when no KIT/PDGFR α /RAS pathogenic or likely pathogenic (P/LP variant) is identified)
- In solid tumors of smooth muscle, testes, or neural tissue when all of the following criteria are met:
 - Standard of care treatment options have been exhausted
 - Cancer continues to progress
 - Tumor type has been shown to respond to treatment with an FDA approved medication for this biomarker
- In solid tumors known to respond to treatment with an FDA approved medication for this biomarker with positive NTRK IHC results or IHC is not possible for molecular confirmation

Targeted Somatic Testing for PIK3CA

Targeted somatic testing for PIK3CA, using tumor tissue or liquid biopsy if tumor is unavailable, is medically necessary when all of the following criteria are met:

- Personal history of breast cancer in a post-menopausal female or in a male
- No history of any of the following:
 - Inflammatory breast cancer
 - Diabetes mellitus Type 1
 - Uncontrolled diabetes mellitus Type 2
 - Pneumonitis
- Tumor is ER/PR+ and HER2-
- Tumor is advanced or metastatic
- Patient has progressed on an endocrine-based therapy
- Treatment with Piqray (alpelisib) is being considered

Prostate Cancer (symptomatic cancer screening)

- ConfirmMDx is medically necessary for men with prior negative prostate biopsy for whom repeat biopsy is being considered due to clinical suspicion of prostate cancer
- PCA3 is medically necessary for men with a prior negative prostate biopsy for whom repeat biopsy is being considered due to clinical suspicion of prostate cancer
- ExoDx is medically necessary for men for whom prostate biopsy is being considered due to clinical suspicion of prostate cancer

Assays not listed above are considered not medically necessary.

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
- 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)
- 81210 BRAF (B-Raf proto-oncogene, serine/threonine kinase) (eg, colon cancer, melanoma), gene analysis, V600 variant(s)
- 81218 CEBPA (CCAAT/enhancer binding protein [C/EBP], alpha) (eg, acute myeloid leukemia), gene analysis, full gene sequence
- 81219 CALR (calreticulin) (eg, myeloproliferative disorders), gene analysis, common variants in exon 9
- 81233 BTK (Bruton's tyrosine kinase) (eg, chronic lymphocytic leukemia) gene analysis, common variants (eg, C481S, C481R, C481F)

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- 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)
- 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)
- 81270 JAK2 (Janus kinase 2) (eg, myeloproliferative disorder) gene analysis, p.Val617Phe (V617F) variant
- 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)
- 81277 Cytogenomic neoplasia (genome-wide) microarray analysis, interrogation of genomic regions for copy number and loss-of-heterozygosity variants for chromosomal abnormalities

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- 81287 MGMT (O-6-methylguanine-DNA methyltransferase) (eg, glioblastoma multiforme) promoter methylation analysis
- 81301 Microsatellite instability analysis (eg, hereditary non-polyposis colorectal cancer, Lynch syndrome) of markers for mismatch repair deficiency (eg, BAT25, BAT26), includes comparison of neoplastic and normal tissue, if performed
- 81305 MYD88 (myeloid differentiation primary response 88) (eg, Waldenstrom's macroglobulinemia, lymphoplasmacytic leukemia) gene analysis, p.Leu265Pro (L265P) variant
- 81309 PIK3CA (phosphatidylinositol-4, 5-biphosphate 3-kinase, catalytic subunit alpha) (eg, colorectal and breast cancer) gene analysis, targeted sequence analysis (eg, exons 7, 9, 20)
- 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)
- 81313 PCA3/KLK3 (prostate cancer antigen 3 [non-protein coding]/kallikrein-related peptidase 3 [prostate specific antigen]) ratio (eg, prostate cancer)
- 81314 PDGFRA (platelet-derived growth factor receptor, alpha polypeptide) (eg, gastrointestinal stromal tumor [GIST]), gene analysis, targeted sequence analysis (eg, exons 12, 18)
- 81315 PML/RARalpha, (t(15;17)), (promyelocytic leukemia/retinoic acid receptor alpha) (eg, promyelocytic leukemia) translocation analysis; common breakpoints (eg, intron 3 and intron 6), qualitative or quantitative
- 81316 PML/RARalpha, (t(15;17)), (promyelocytic leukemia/retinoic acid receptor alpha) (eg, promyelocytic leukemia) translocation analysis; single breakpoint (eg, intron 3, intron 6 or exon 6), qualitative or quantitative
- 81320 PLCG2 (phospholipase C gamma 2) (eg, chronic lymphocytic leukemia) gene analysis, common variants (eg, R665W, S707F, L845F)
- 81340 TRB@ (T cell antigen receptor, beta) (eg, leukemia and lymphoma), gene rearrangement analysis to detect abnormal clonal population(s); using amplification methodology (eg, polymerase chain reaction)
- 81341 TRB@ (T cell antigen receptor, beta) (eg, leukemia and lymphoma), gene rearrangement analysis to detect abnormal clonal population(s); using direct probe methodology (eg, Southern blot)
- 81342 TRG@ (T cell antigen receptor, gamma) (eg, leukemia and lymphoma), gene rearrangement analysis, evaluation to detect abnormal clonal population(s)

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- 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
- 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
- 81522 Oncology (breast), mRNA, gene expression profiling by RT-PCR of 12 genes (8 content and 4 housekeeping), utilizing formalin-fixed paraffin-embedded tissue, algorithm reported as recurrence risk score
- 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
- 81552 Oncology (uveal melanoma), mRNA, gene expression profiling by real-time RT-PCR of 15 genes (12 content and 3 housekeeping), utilizing fine needle aspirate or formalin-fixed paraffin-embedded tissue, algorithm reported as risk of metastasis
- 0005U Oncology (prostate) gene expression profile by real-time RT-PCR of 3 genes (ERG, PCA3, and SPDEF), urine, algorithm reported as risk score

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- 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
- 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
- 0154U FGFR3 (fibroblast growth factor receptor 3) gene analysis (ie, p.R248C [c.742C>T], p.S249C [c.746C>G], p.G370C [c.1108G>T], p.Y373C [c.1118A>G], FGFR3-TACC3v1, and FGFR3-TACC3v3)
- 0155U PIK3CA (phosphatidylinositol-4,5- biphosphate 3-kinase, catalytic subunit alpha) (eg, breast cancer) gene analysis (ie, p.C420R, p.E542K, p.E545A, p.E545D [g.1635G>T only], p.E545G, p.E545K, p.Q546E, p.Q546R, p.H1047L, p.H1047R, p.H1047Y)
- ANY Clonoseq®

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,

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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
- 81542 Oncology (prostate), mRNA, microarray gene expression profiling of 22 content genes, utilizing formalin-fixed paraffin-embedded tissue, algorithm reported as metastasis risk score
- 0011M Oncology, prostate cancer, mRNA expression assay of 12 genes (10 content and 2 housekeeping), RT-PCR test utilizing blood plasma and urine, algorithms to predict high-grade prostate cancer risk
- 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

0056U	Hematology (acute myelogenous leukemia), DNA, whole genome nextgeneration sequencing to detect gene rearrangement(s), blood or bone marrow, report of specific gene rearrangement(s)
0057U	Oncology (solid organ neoplasia), mRNA, gene expression profiling by massively parallel sequencing for analysis of 51 genes, utilizing formalin-fixed paraffin-embedded tissue, algorithm reported as a normalized percentile rank
0069U	Oncology (colorectal), microRNA, RT-PCR expression profiling of miR-31-3p, formalin-fixed paraffin-embedded tissue, algorithm reported as an expression score
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)
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
0114U	Gastroenterology (Barrett's esophagus), VIM and CCNA1 methylation analysis, esophageal cells, algorithm reported as likelihood for Barrett's esophagus
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
0153U	Oncology (breast), mRNA, gene expression profiling by next-generation sequencing of 101 genes, utilizing formalin-fixed paraffin-embedded tissue, algorithm reported as a triple negative breast cancer clinical subtype(s) with information on immune cell involvement
ANY	Guardant360® for any indication (Guardant Health, Inc.)
ANY	FoundationOne® Liquid for any indication (Foundation Medicine, Inc.)

Background

Somatic genetic testing for the purpose of cancer management guidance is a rapidly evolving field of molecular medicine. Genetic testing of a solid tumor or hematologic neoplasm can provide important information regarding the prognosis, risk for recurrence or help predict response to chemotherapeutic agents. In addition, genetic testing of tissue (e.g. blood) or stool, for evidence of a tumor, is becoming

PROPRIETARY

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an important tool in the early detection of cancer. While this is an area of 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 MPNs are characterized by an increase in the number of blood cells.

Molecular testing for certain somatic variants 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 a 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 an identified P/LP variant. At this time, variants in other genes associated with MPNs, including P/LP variants 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 variant or functionally similar exon 12 variant. Other diagnostic criteria include elevated hemoglobin and abnormal bone marrow morphology. The JAK2 V617F variant is present in the vast majority (greater than 90%) of cases of PV. Functionally similar P/LP variants in JAK2 exon 12 account for most remaining cases of JAK2 V617F variant-negative PV. These P/LP variants 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 variant, 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 variant 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/ μ L; 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 variant, while a smaller percentage (5-10%) have activating MPL P/LP variants. Proposed criteria additionally state that 70% of patients without a JAK2 or MPL P/LP variant carry a somatic P/LP variant of the calreticulin (CALR) gene. Among confirmed ET cases, P/LP variants in CALR are more common than MPL. Positive CALR variant status may suggest a more indolent course (Klampfl et al. 2013). It is

important to note that JAK2/CALR/MPL variant 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 P/LP variants in JAK2 are identified in 55-65% of PMF cases, and MPL P/LP variants in 10%. P/LP variants 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.3.2019; Tefferi 2016). Identification of a clonal marker is one of the required major criteria in the diagnosis of PMF (NCCN® v.3.2019).

Genetic Testing for Hematologic Malignancy

Minimal Residual Disease (MRD) Genetic Testing

Acute Lymphoblastic Leukemia (ALL) is characterized by the proliferation of immature lymphoid cells in the bone marrow, peripheral blood, and other organs. It is divided into two main immunophenotypes based on cell lineage: B-cell or T-cell. B-cell is seen in about 75% of cases and T-cell in about 25%. There are a small percentage of individuals who have a mixed cell line immunophenotype. The median age at diagnosis in the United States is 14, with 60% of patients diagnosed under the age of 20. Prognosis, management, and genetic testing recommendations vary between the pediatric and adult populations.

Genetic characterization in ALL is used for risk stratification and treatment planning, which typically includes chromosome analysis, interphase fluorescence in situ hybridization (FISH) testing for major recurrent abnormalities, and reverse transcriptase-polymerase chain reaction (RT-PCR) testing for fusion genes. Fusion genes include BCR-ABL1 in B-cell ALL, and if BCR-ABL1 negative (Ph-), include other gene fusions (associated with Ph- like ALL) that activate the tyrosine kinase pathway. Testing at the time of diagnosis may be performed on either bone marrow or peripheral blood lymphoblasts. Array CGH may be considered in cases of aneuploidy or failed karyotype (NCCN® Acute Lymphoblastic Leukemia (v1.2020)). Taylor et al. (2017) provide further review of genetic testing routinely performed for B-cell and T-cell ALL.

This genetic characterization of leukemic cells is necessary to facilitate minimal residual disease (MRD) testing which can aid in therapeutic decision-making and provide essential prognostication through the identification of residual malignant cells remaining in individuals who have achieved complete remission (Pigneux et al. 2018; Short et al. 2019; Starza et al. 2019). Although many methods of detecting MRD exist including traditional standards using flow cytometric and PCR

technologies, increasingly sensitive detection tools are needed. Next generation sequencing (NGS) offers a solution through its versatility and high sensitivity while not requiring patient-specific primers (Sanchez et al. 2019). Additional evidence has also revealed a lower false-negative rate and higher analytic sensitivity for detecting MRD in pediatric B-ALL compared to flow cytometry (Wood et al. 2017).

The clinical utility for ALL is demonstrated through MRD testing's ability to identify high-risk patients to intensify treatment and low-risk patients to reduce/avoid treatment such as HSCT. Recent guidance from Short et al. (2018) provided further support for evaluation of MRD as a prognostic factor in every subtype of ALL. Consensus recommendations indicate MRD assessments should be done in adults with ALL on frontline treatment at various intervals and in relapsed or refractory ALL patients receiving salvage therapy. It is a vital component in the management of children and adults with ALL because of the association between risk for relapse and minimal residual disease (Berry et al. 2017).

Multiple NCCN® Clinical Practice Guidelines in Oncology (NCCN Guidelines®), including Pediatric Acute Lymphoblastic Leukemia (v.2.2020) and Acute Lymphoblastic Leukemia (v1.2020) address MRD testing. Currently NCCN® recommends MRD testing in both Ph+ and Ph- patients with ALL. However, MRD testing using high-throughput sequencing for Ph+ patients was largely excluded from studies assessing utility of this technology for MRD testing, and MRD testing in this population (Ph+) can be achieved by other means. For patients who are Ph-, NCCN® currently recommends MRD testing at the end of the induction phase only if a complete response is achieved. While other NCCN® Clinical Practice Guidelines in Oncology (NCCN Guidelines®) have incorporated MRD testing into its algorithms, further evidence is needed to establish the clinical utility of this testing for multiple myeloma and other tumor types.

The FDA has designated a companion diagnostic for patients with B-cell ALL in 1st or 2nd complete remission with MRD levels greater than 0.1% (Gokbuget et al. 2018).

Targeted molecular-based methods for MRD monitoring have also been found to have clinical utility in patients with certain types of cancer, such as subtypes of acute myeloid leukemia (specifically: APL, CBF AML, and NPM1-mutated AML) (Schoorhuis et al. 2019).

Solid Tumor Testing

NTRK Fusion Testing

The FDA has granted accelerated approval for larotrectinib (Vitrakvi). The drug is indicated for adult and pediatric patients with solid tumors positive for a neurotrophic receptor tyrosine kinase (NTRK1, NTRK2, or NTRK3) gene fusion. These patients should have no known acquired resistance P/LP variant, and they must have metastatic disease or an unresectable tumor where the risk of surgery is high, and no other alternative therapeutic options exist.

The data to support the approval of larotrectinib is sparse. The FDA notes continued approval will be contingent on further evidence development. Notably, 6 of 55 (11%) patients in these studies did not respond to larotrectinib. Of these six, three had follow up tumor testing using a pan-TRK IHC assay which was negative and did not confirm evidence of the initial fusion event. It is unclear whether these cases represent false positive NGS test results or whether the gene fusion was present but not actively expressed.

PIK3CA Testing

Piqray (alpelisib) is an inhibitor of PI3K, predominantly the alpha form, PI3K α . Upregulation of PI3K α has been shown to be associated with oncogenesis in both in-vitro and in-vivo models. Gain-of-function mutations in PIK3CA are associated with upregulation of PI3K α . PI3K inhibition is associated with increased transcription of the estrogen receptor in breast cancer. It is also associated with resistance to endocrine therapy.

The FDA approved Piqray based on results from the SOLAR-I trial. SOLAR-I is a Phase III randomized double blind trial (NCT02437318). Patients were excluded if they had inflammatory breast cancer, diabetes mellitus Type 1, uncontrolled Type 2, or pneumonitis. Additional exclusions included: uncontrolled central nervous system metastases, concurrent cancer or cancer within 3 years before randomization (except for adequately treated basal-cell or squamous-cell carcinoma, non-melanomatous skin cancer, or curatively resected cervical cancer). Only 1 male was included in the PIK3CA+ treatment arm, and no men were included in the other three arms of the study.

Median progression free survival (PFS) in the treatment gene positive group was 11.0 months compared to 5.7 months in the placebo gene positive group. No PFS benefit was seen in patients without PIK3CA mutation. Overall survival data are still immature. Adverse events were greater in the treatment arm compared to the placebo arm. Patients who discontinued treatment were 25.0% on the treatment arm and 4.2% on the placebo arm largely due to hyperglycemia.

The Qiagen theascreen PIK3CA PCR RGQ PCR kit was designated by the FDA as a companion diagnostic for Piqray. All of the mutations are gain-of-function mutations. However, it is unclear if they all have the same oncogenic potential as data were not stratified by genotype. The test was approved for use in either blood or tissue. From the SOLAR-I trial, 99% of PIK3CA mutations were detected by the companion diagnostic from tissue biopsy samples. Of those with a plasma sample available for testing, only 56% had mutation detected in plasma.

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.2.2020).

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[®] strongly recommends the Oncotype Dx[®] Breast 21-gene assay into the treatment determination algorithm for individuals with invasive breast cancer with subtypes including ductal/NST, lobular, mixed, and micropapillary, 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.2.2020). 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 anatomic 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
- Prosigna[™] PAM50 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

ASCO published a special addendum (Krop et al. 2017) regarding use of MammaPrint[®] for women with hormone receptor- positive, HER2-negative, node negative and node positive tumors based on preliminary MINDACT data (Cardoso et al. 2016). 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 Breast Cancer Index®, this test has not yet been adequately validated for clinical use.

Lung Cancer

Epidermal growth factor receptor (EGFR) P/LP variant 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 P/LP variants in advanced non-small cell lung cancers (NSCLC), particularly adenocarcinomas (Keedy et al. 2011; Salto-Tellez et al. 2011). 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 NCCN Guidelines® based on data showing efficacy of treatment with an FDA approved medication in patients with ROS1 rearrangements (NCCN® v.2.2020).

KRAS P/LP variants 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 P/LP variants is currently unavailable, KRAS testing may identify patients who may not benefit from further molecular diagnostic testing.

Current NCCN Guidelines® recommend biomarker testing using validated test(s) as part of broad molecular profiling that at a minimum assesses EGFR and BRAF P/LP variants as well as ALK and ROS1 rearrangements. Rare driver P/LP variants found to be associated with NSCLC and for which targeted therapies have been developed include: NTRK gene fusions, HER2 (ERBB2) P/LP variants, RET gene rearrangements, high-level MET amplification and MET exon 14 skipping mutation. As targeted agents are available for patients with NSCLC who have these genetic alterations, the NCCN®

Guidelines Panel, NSCLC recommend testing for these specific genetic alterations and endorse broader molecular profiling to identify rare driver P/LP variants for which effective therapy may be available (NCCN® v.2.2020).

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.2.2020). 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).

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 for assessing tumor P/LP variant 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 (ctDNA) is easier to isolate and, with the increasing capabilities of next-generation sequencing, offers an alternate opportunity to assess somatic tumor-specific P/LP variants. 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 (Levy et al. 2016). 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.2.2020) 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 guideline goes on to note insufficient evidence related to further using assay-predicted tumor type to guide primary site-specific therapy (Fizazi et al. 2015).

Pancreatic Cancer

Pancreatic cancer is relatively rare, amounting to only 3% of new cancer diagnoses, but it is the fourth most common cause of cancer death (Siegel et al. 2013). Molecular testing of pancreatic cancer has historically had limited effect on treatment choices outside of clinical trials, as there is a large number and variety of genetic P/LP variants that may be present in any individual tumor (Peters 2016; Ferguson et al. 2018). KRAS, TP53, CDKN2A, and SMAD4 P/LP variants are some of the more common driver variants identified in pancreatic adenocarcinomas. In a recent retrospective evaluation of more than 3,500 pancreatic adenocarcinomas, up to 17% of the tumors exhibited P/LP variants in genes that have specific targeted therapies available for other tumor types. However, targeted treatment of pancreatic cancer is complicated by the fact that many somatic P/LP variants in these tumors are only present in a small percentage of tumor cells, especially when the disease is advanced. Thus, P/LP variants that may be actionable for a different tumor type (e.g. RAS pathway P/LP variants that can predict response to kinase inhibitors in colon or lung cancers) are less likely to be actionable in patients with pancreatic cancer if the variant is not present in most of the tumor cells (Singhi et al. 2019). Further evidence of patient response to targeted therapies is necessary to confirm the utility of testing for low-level P/LP variants in this tumor type.

Recent FDA approvals of certain tumor agnostic treatments have changed this paradigm in some cases, as certain treatments can now be administered based on specific biomarkers present in the tumor rather than the tumor location (Flaherty et al. 2017). For example, consideration of microsatellite instability (MSI) and/or mismatch repair (MMR) protein staining may be used in individuals with pancreatic cancer to determine eligibility for treatment with pembrolizumab, which is recommended by the NCCN® as second-line therapy for locally advanced/unresectable/metastatic disease for any solid tumors that exhibit high MSI or deficient MMR proteins.

Beyond targeted treatments, a primary goal of ongoing research has been to identify gene expression patterns and molecular markers that may be useful for the early detection and prognostic prediction specifically for pancreatic adenocarcinoma (Ferguson et al. 2018; Klett et al. 2018; Root et al. 2018). There are promising research endeavors in liquid biopsy (circulating tumor DNA, circulating tumor cells, exosomes), proteomics, metabolomics and micro-RNAs that suggest development of biomarker panels may allow for earlier diagnosis in the near future (Kunovsky et al. 2018; Fischer and Wood 2018).

Testing for hereditary gene P/LP variants may also have utility for patients with pancreatic cancer. Literature suggests that patients with specific hereditary predispositions to pancreatic cancer may be sensitive to a platinum agent when combined with another chemotherapy (e.g. Gemcitabine with Cisplatin) (Ferrone 2009; Golan 2014), though data regarding patient survival is conflicting (NCCN® v1.2020). Poly(ADP-ribose) polymerases (PARP) inhibitors are another class of chemotherapeutic drugs that have shown promise in treating cancers caused by defective DNA repair pathways. Several PARP inhibitors have FDA-approval for use in patients with ovarian or breast cancer who have an inherited BRCA1 or BRCA2 P/LP variant. Early research has suggested a similar clinical benefit with this class of drugs in the treatment of pancreatic adenocarcinoma in patients with germline BRCA1 and BRCA2 P/LP variants, and further clinical trials are underway (Shroff et al. 2018). Germline testing for BRCA1 and BRCA2 and other proven genetic susceptibility genes for P/LP variants is appropriate for individuals with pancreatic cancer regardless of their treatment pathway, given the additional cancer

risks and screening recommendations that are standard of care for individuals and their family members with these gene variants (NCCN® v1.2020).

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® for 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 for this scenario (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® Clinical Practice Guidelines in Oncology (NCCN Guidelines®), Prostate Cancer (v.4.2019) note that men with low or favorable intermediate risk 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.

For men with metastatic castrate-resistant prostate cancer (mCRPC), there has been interest in the use of testing of circulating tumor cells (CTCs) for a splice site variant in the androgen receptor gene, AR-V7, to help guide therapeutic intervention, particularly in the setting of progression on androgen receptor signaling inhibitors (ARSI) such as abiraterone or enzalutamide. This potential biomarker has been extensively studied, with conflicting results (Kretschmer et al. 2017; Scher et al. 2018; Armstrong et al. 2019; Abida et al. 2019). While there is prospective evidence demonstrating men affected by mCRPC with the AR-V7 variant in CTCs have worse outcomes when treated with enzalutamide/abiraterone, there is not currently prospective evidence they do better on an alternate

therapy. More evidence is needed to show AR-V7 is a reliable biomarker to predict response to improved outcomes in this regard.

Thyroid Cancer

Per NCCN® Clinical Practice Guidelines in Oncology (NCCN Guidelines®), Thyroid Carcinoma (v.2.2019), BRAF V600E testing is indicated for patients with confirmed or highly suspected thyroid cancer (FTC, follicular thyroid carcinoma; MTC, medullary thyroid carcinoma; PTC, papillary thyroid carcinoma; 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 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 P/LP variants (e.g., BRAF, RET/PTC, RAS, PAX8/PPAR) has been proven in the evaluation of fine needle aspiration (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. Molecular testing may be beneficial as certain mutations have potential prognostic importance and testing may aid in decisions regarding targeted therapy, i.e. drug therapies, or participation in clinical trials (NCCN® v.2.2019).

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 are 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 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.2.2019) states that molecular diagnostic testing to detect individual P/LP variants (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 or Hurthle cell neoplasms and 2) atypia of undetermined significance/follicular lesion of undetermined significance (AUS/FLUS). Molecular diagnostics may not perform well for Hurthle cell neoplasms (NCCN® v.2.2019).

The American Thyroid Association (ATA) issued a statement regarding the surgical application of molecular profiling for thyroid nodules (Ferris et al. 2015). 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 panel 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 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 (Haugen et al. 2017). 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 P/LP variant 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 P/LP variants 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.

Results from The Role of NGS-based ThyroSeq® Panel in Cancer Diagnosis in Thyroid Nodules (NCT02352766) have been published (Steward et al. 2018). This is a prospective, double-blind,

comparison of the outcomes of ITNs between pathology and molecular studies using ThyroSeq® 3.0. Overall, ThyroSeq® 3.0 demonstrated an NPV of 97-98% (93-99% CI; 89-100% CI) and a PPV of 64-68% (50-77% CI; 54-80% CI) when considering Bethesda III and IV nodules. The main goal of testing, as stated by Steward et al. (2018), was to correctly identify benign nodules to avoid the need for surgery. In this light, it is important to remember that the long term clinical utility in this regard is not established. Still unknown is the risk for progression and cancer development for those with ITNs determined to be at low risk for malignancy who choose active surveillance.

Colorectal Cancer Screening

Colorectal cancer is the fourth most common cancer type diagnosed in the United States (NCCN® Clinical Practice Guidelines in Oncology (NCCN Guidelines®), Colorectal Cancer Screening (v.2.2019). 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.

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 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. Fifty-three 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." While this test is FDA approved, it is not recommended for routine use by NCCN®, Colorectal Cancer Screening (v2.2019).

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Revision History

Medical Advisory Board Review:

v1.2020 11/04/2019: Approved

v3.2019 09/10/2019: Approved

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Revisions:

Version	Date	Editor	Description
v1.2020	10/02/2019	Heather Dorsey, MS, CGC	Clarification of cell free testing. Reformatted coverage criteria. Coverage criteria expansion for MPN to allow testing for JAK2, CALR, and MPL as well as criteria for targeted somatic testing of PIK3CA. Updated CPT codes, background, professional society guidelines and references.
	2/5/2020	Carrie Langbo, MS, CGC	NCCN Guidelines® were accessed for inclusion of the most recent published version. Minor revisions to text were incorporated based on updated Guidelines but did not impact coverage criteria/necessitate MAB/CSC review.
v3.2019	9/09/2019	Heather Dorsey, MS, CGC	Interim update. Minimal Residual Disease (MRD) testing criteria was added and coverage criteria for NTRK fusion testing was expanded to cover approved FDA medications. CPT codes, background, professional society guidelines and references were updated.
v2.2019	4/03/2019	Emily Higuchi, MS, CGC	Semi-annual review. Revised umbrella coverage criteria section. Added NTRK fusion criteria. Revised Oncotype DX®, Prosigna PAM50™ and MammaPrint® criteria. Added Endopredict criteria. Updated background, professional society/NCCN® guidelines and references. Renumbered to v2.2019.

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	7/25/2019	Carrie Langbo, MS, CGC	NCCN Guidelines® were accessed for inclusion of the most recent published version. Minor revisions to text were incorporated based on updated Guidelines but did not impact coverage criteria/necessitate MAB/CSC review.
v1.2019	03/04/2019	Gwen Fraley, MS, CGC	Urgent Interim review. Expand coverage of ThyroSeq3.0 for indeterminate thyroid nodules and revision to reflect current testing platforms.
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.
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

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			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.
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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