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. For gene expression classifiers and polygenic risk scores not addressed in this policy, please refer to the Clinical Appropriateness Guidelines for Genetic Testing for Hereditary Cancer Susceptibility. For genetic testing used to guide chemotherapy treatment decisions, please refer to the Clinical Appropriateness Guidelines for Pharmacogenomic Testing and Genetic Testing for Thrombotic Disorders. 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 (FFPE), 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 unless technical limitations (e.g. poor sample quality) necessitate the need for alternate testing strategies

*The testing methodology may target DNA and/or RNA.

In addition to the above criteria, somatic multi-gene panels for hematology-oncology indications are medically necessary when all of the following are met (please see additional criteria below for cell-free testing):

- 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

FDA companion diagnostics using NGS based panels may be considered medically necessary for the approved indication/medication when all of the following are met (*see Table 1. for specific approvable scenarios*):

- A more targeted test using any methodology is not available

- The patient does not otherwise meet criteria for treatment

- The patient meets criteria per the FDA label

Conditions for which testing may be medically necessary

Table 1. Solid tumor markers that are medically necessary when the above criteria are met (list may not be all inclusive) (*see criteria below for cell-free testing*):

Indication	Molecular Studies
Acute Lymphoblastic Leukemia (ALL)	Targeted multi-gene panels
Acute Lymphoblastic Leukemia (ALL) B-Cell Ph- **See below for MRD testing criteria*	NGS Immunosequencing
Acute Myelogenous Leukemia (AML) **See below for MRD testing criteria*	Targeted multi-gene panels
Brain/Central Nervous System Cancers	IDH1, IDH2, MGMT, 1p/19q, ATRX, TERT, H3F3A, HIST1H3B, BRAF, RELA, TP53

Breast Cancer
    *See below for gene expression classifier criteria
    *See below for cell-free testing criteria
	PIK3CA

Chronic Lymphocytic Leukemia (CLL)	TP53, IGHV, BTK, PLCG2
Chronic Myeloid 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 ≥450 x 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) *FNA samples with evidence of Hurthle cell* *pathology are excluded from coverage*	BRAF, RAS, RET/PTC, PAX8/PPARc *or* ThyGeNEXT®/ThyraMIR™ *or* ThyroSeq® v3.0
Indeterminate Thyroid Nodule Bethesda Category III (AUS/FLUS) only *FNA samples with evidence of Hurthle cell* *pathology are excluded from coverage*	Afirma▫
Melanoma (Cutaneous) Metastatic Melanoma (Stage III or Stage IV)	BRAF, KIT
Melanoma (Uveal)	EIF1AX, SF3B1, BAP1, PRAME, GNAQ GNA11 *or* DecisionDx - Uveal Melanoma
Metastatic Non-Small Cell Lung Cancer (NSCLC) Metastatic (Stage IIIB and above) *See below for cell-free testing criteria*	ALK, BRAF, EGFR, ROS1, ERBB2 (HER2), MET, RET, KRAS
Non-Small Cell Lung Cancer (NSCLC) Resected Stage IB - IIIA	EGFR
Multiple Myeloma	Chromosomal Microarray Analysis (CMA) when cytogenetic (karyotype) and/or FISH analysis is uninformative
Myelodysplastic Syndrome	Targeted multi-gene panels
Ovarian, Fallopian Tube, or Primary Peritoneal Cancer *See below for cell-free testing criteria*	BRCA1, BRCA2
Polycythemia Vera Indication Includes ONE of the following (WHO criteria 2016): • 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
B-Cell Lymphoma	EZH2, MYD88
Primary Myelofibrosis Pre-PMF or suspicion for PMF based on 2016 WHO criteria	JAK2, CALR, MPL Targeted multi-gene panels *(when performed on bone marrow)*
Prostate Cancer (Suspected) Symptomatic Cancer Screening *See criteria below*	ConfirmMDx® ExoDx PCA3
Prostate Cancer Metastatic Castration-Resistant Prostate Cancer *See below for cell-free testing criteria*	Targeted multi-gene panels

Tumor Agnostic/All Applicable Solid Tumors *See NTRK criteria below*	NTRK
T-Cell Lymphoma (Peripheral)	TET2, IDH1/IDH2, RHOA, DNMT3A, STAT3, STAT5B
Thyroid Cancer	BRAF, RET fusions

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

- Kidney cancer

- Malignant pleural mesothelioma

- Merkle cell carcinoma

- 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 the following individuals:

- Pre-menopausal women who are axillary-node negative or any axillary-node micrometastasis is no greater than 2.0 millimeters

- Post-menopausal women who are axillary-node negative or have no more than 3 positive lymph nodes

- Men who are axillary-node negative or have no more than 3 positive lymph nodes

AND 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 >0.5 cm to ≤1.0 cm plus unfavorable histological features, defined as an intermediate or high nuclear and/or histologic grade (Grade 2 or 3), or lymphovascular invasion **OR** tumor size 1.1-5.0 cm, any grade

- 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, EndoPredict®, or Breast Cancer Index testing is medically necessary to assess the risk for recurrence in an individual 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 >0.5 cm to ≤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

- Female 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 an individual 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

- 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

Cell-free testing (e.g. cfDNA, ctDNA, liquid biopsy) is medically necessary in the following scenarios when more targeted testing is not available:

- Metastatic Castrate-Resistant Prostate Cancer (mCRPC)

  - FoundationOne® Liquid CDx is medically necessary in men with metastatic castrate resistant prostate cancer (mCRPC) when the patient meets criteria per the FDA label for treatments for which this test has been approved as a companion diagnostic

    - Coverage is excluded when the patient already meets criteria without the need for additional testing (e.g. patient meets criteria based on known genetic results)

- Ovarian, Fallopian Tube, or Primary Peritoneal Cancer

  - FoundationOne® Liquid CDx is medically necessary in women with ovarian, fallopian tube, or primary peritoneal cancer when the patient meets criteria per the FDA label for treatment(s) for which this test has been approved as a companion diagnostic

    - Coverage is excluded when tissue-based testing is available

    - Coverage is excluded when the patient already meets criteria without the need for additional testing (e.g. patient meets criteria based on known genetic results)

- Advanced or Metastatic Breast Cancer

  - therascreen® PIK3CA testing is medically necessary for advanced or metastatic breast cancer, using liquid biopsy if tumor is unavailable, when the patient meets criteria per the FDA label for treatments for which this test has been approved as a companion diagnostic

- Non-Small Cell Lung Cancer (NSCLC)

  - At time of initial diagnosis

    - Targeted cell-free testing (e.g. cobas EGFR Mutation Test v2, ctDx Lung™, Guardant360® CDx) is medically necessary in patients with metastatic NSCLC when tissue-based testing cannot be performed, e.g. insufficient tissue

  - At time of progression on an EGFR tyrosine kinase inhibitor (TKI) therapy

    - Targeted cell-free testing (i.e. cobas EGFR Mutation Test v2) is medically necessary in patients with metastatic NSCLC (excluding those patients who have progressed on osimertinib)

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 is 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/PDGFRA/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 biomarker confirmation

Prostate Cancer (symptomatic cancer screening)

- ConfirmMDx or PCA3 is medically necessary for men with prior negative prostate biopsy for whom repeat biopsy is being considered due to clinical suspicion of prostate cancer (e.g. abnormal digital rectal exam, prostate specific antigen (PSA) of greater than 3)

- ExoDx is medically necessary for men for whom prostate biopsy is being considered due to clinical suspicion of prostate cancer (e.g. abnormal digital rectal exam, prostate specific antigen (PSA) of greater than 3)

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. Medical plans may have additional coverage policies that supersede these guidelines.

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)

81168   CCND1/IGH (t(11;14)) (eg, mantle cell lymphoma) translocation analysis, major breakpoint, qualitative and quantitative, if performed

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)

81191   NTRK1 (neurotrophic receptor tyrosine kinase 1) (eg, solid tumors) translocation analysis

81192   NTRK2 (neurotrophic receptor tyrosine kinase 2) (eg, solid tumors) translocation analysis

81193   NTRK3 (neurotrophic receptor tyrosine kinase 3) (eg, solid tumors) translocation analysis

81194   NTRK (neurotrophic-tropomyosin receptor tyrosine kinase 1, 2, and 3) (eg, solid tumors) translocation analysis

81206   BCR/ABL1 (t(9;22)) (eg, chronic myelogenous leukemia) translocation analysis; major breakpoint, qualitative or quantitative

81207   BCR/ABL1 (t(9;22)) (eg, chronic myelogenous leukemia) translocation analysis; minor breakpoint, qualitative or quantitative

81208   BCR/ABL1 (t(9;22)) (eg, chronic myelogenous leukemia) translocation analysis; other breakpoint, qualitative or quantitative

81210   BRAF (B-Raf proto-oncogene, serine/threonine kinase) (eg, colon cancer, melanoma), gene analysis, V600 variant(s)

81218   CEBPA (CCAAT/enhancer binding protein [C/EBP], alpha) (eg, acute myeloid leukemia), gene analysis, full gene sequence

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)

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
81278	IGH@/BCL2 (t(14;18)) (eg, follicular lymphoma) translocation analysis, major breakpoint region (MBR) and minor cluster region (mcr) breakpoints, qualitative or quantitative
81279	JAK2 (Janus kinase 2) (eg, myeloproliferative disorder) targeted sequence analysis (eg, exons 12 and 13)
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)

81338   MPL (MPL proto-oncogene, thrombopoietin receptor) (eg, myeloproliferative disorder) gene analysis; common variants (eg, W515A, W515K, W515L, W515R)

81339   MPL (MPL proto-oncogene, thrombopoietin receptor) (eg, myeloproliferative disorder) gene analysis; sequence analysis, exon 10

81340   TRB@ (T cell antigen receptor, beta) (eg, leukemia and lymphoma), gene rearrangement analysis to detect abnormal clonal population(s); using amplification methodology (eg, polymerase chain reaction)

81341   TRB@ (T cell antigen receptor, beta) (eg, leukemia and lymphoma), gene rearrangement analysis to detect abnormal clonal population(s); using direct probe methodology (eg, Southern blot)

81342   TRG@ (T cell antigen receptor, gamma) (eg, leukemia and lymphoma), gene rearrangement analysis, evaluation to detect abnormal clonal population(s)

81345   TERT (telomerase reverse transcriptase) (eg, thyroid carcinoma, glioblastoma multiforme) gene analysis, targeted sequence analysis (eg, promoter region)

81347   SF3B1 (splicing factor [3b] subunit B1) (eg, myelodysplastic syndrome/acute myeloid leukemia) gene analysis, common variants (eg, A672T, E622D, L833F, R625C, R625L)

81348   SRSF2 (serine and arginine-rich splicing factor 2) (eg, myelodysplastic syndrome, acute myeloid leukemia) gene analysis, common variants (eg, P95H, P95L)

81351   TP53 (tumor protein 53) (eg, Li-Fraumeni syndrome) gene analysis; full gene sequence

81352   TP53 (tumor protein 53) (eg, Li-Fraumeni syndrome) gene analysis; targeted sequence analysis (eg, 4 oncology)

81353   TP53 (tumor protein 53) (eg, Li-Fraumeni syndrome) gene analysis; known familial variant

81357   U2AF1 (U2 small nuclear RNA auxiliary factor 1) (eg, myelodysplastic syndrome, acute myeloid leukemia) gene analysis, common variants (eg, S34F, S34Y, Q157R, Q157P)

81360   ZRSR2 (zinc finger CCCH-type, RNA binding motif and serine/arginine-rich 2) (eg, myelodysplastic syndrome, acute myeloid leukemia) gene analysis, common variant(s) (eg, E65fs, E122fs, R448fs)

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

81479   SelectMDx

81518   Oncology (breast), mRNA, gene expression profiling by real-time RT-PCR of 11 genes (7 content and 4 housekeeping), utilizing formalin-fixed paraffin-embedded tissue, algorithms reported as percentage risk for metastatic recurrence and likelihood of benefit from extended endocrine therapy

81519   Oncology (breast), mRNA, gene expression profiling by real-time RT-PCR of 21 genes, utilizing formalin-fixed paraffin embedded tissue, algorithm reported as recurrence 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

81546   Oncology (thyroid), mRNA, gene expression analysis of 10,196 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

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")

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

0040U   BCR/ABL1 (t(9;22)) (eg, chronic myelogenous leukemia) translocation analysis, major breakpoint, quantitative

0046U   FLT3 (fms-related tyrosine kinase 3) (eg, acute myeloid leukemia) internal tandem duplication (ITD) variants, quantitative

0049U   NPM1 (nucleophosmin) (eg, acute myeloid leukemia) gene analysis, 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   Oncology (urothelial cancer), RNA, analysis by real-time RT-PCR of the 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) utilizing formalin-fixed paraffin-embedded urothelial cancer tumor tissue, reported as FGFR gene alteration status

0155U Oncology (breast cancer), DNA, PIK3CA (phosphatidylinositol-4,5-bisphosphate 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), utilizing formalin-fixed paraffin embedded breast tumor tissue, reported as PIK3CA gene mutation status

0172U myChoice® CDx (Myriad Genetics, Inc.)

0177U Oncology (breast cancer), DNA, PIK3CA (phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha) gene analysis of 11 gene variants utilizing plasma, reported as PIK3CA gene mutation status

0179U Oncology (non-small cell lung cancer), cell-free DNA, targeted sequence analysis of 23 genes (single nucleotide variations, insertions and deletions, fusions without prior knowledge of partner/breakpoint, copy number variations), with report of significant mutation(s)

0239U Targeted genomic sequence analysis panel, solid organ neoplasm, cell-free DNA, analysis of 311 or more genes, interrogation for sequence variants, including substitutions, insertions, deletions, select rearrangements, and copy number variations

ANY Guardant360® CDx (Guardant Health, Inc.)

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

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

81529 Oncology (cutaneous melanoma), mRNA, gene expression profiling by real-time RT-PCR of 31 genes (28 content and 3 housekeeping), utilizing formalin-fixed paraffin-

embedded tissue, algorithm reported as recurrence risk, including likelihood of sentinel lymph node metastasis

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

0016M   Oncology (bladder), mRNA, microarray gene expression profiling of 209 genes, utilizing formalin fixed paraffin-embedded tissue, algorithm reported as molecular subtype (luminal, luminal infiltrated, basal, basal claudin-low, neuroendocrine-like)

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

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)

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

0171U   Targeted genomic sequence analysis panel, acute myeloid leukemia, myelodysplastic syndrome, and myeloproliferative neoplasms, DNA analysis, 23 genes, interrogation for sequence variants, rearrangements and minimal residual disease, reported as presence/absence

0204U   Oncology (thyroid), mRNA, gene expression analysis of 593 genes (including BRAF, RAS, RET, PAX8, and NTRK) for sequence variants and rearrangements, utilizing fine needle aspirate, reported as detected or not detected

0208U   Oncology (medullary thyroid carcinoma), mRNA, gene expression analysis of 108 genes, utilizing fine needle aspirate, algorithm reported as positive or negative for medullary thyroid carcinoma

0211U   Oncology (pan-tumor), DNA and RNA by next-generation sequencing, utilizing formalin-fixed paraffin-embedded tissue, interpretative report for single nucleotide variants, copy number alterations, tumor mutational burden, and microsatellite instability, with therapy association

0228U	Oncology (prostate), multianalyte molecular profile by photometric detection of macromolecules adsorbed on nanosponge array slides with machine learning, utilizing first morning voided urine, algorithm reported as likelihood of prostate cancer
0229U	BCAT1 (Branched chain amino acid transaminase 1) or IKZF1 (IKAROS family zinc finger 1) (eg, colorectal cancer) promoter methylation analysis
0235U	PTEN (phosphatase and tensin homolog) (eg, Cowden syndrome, PTEN hamartoma tumor syndrome), full gene analysis, including small sequence changes in exonic and intronic regions, deletions, duplications, mobile element insertions, and variants in non-uniquely mappable regions
0238U	Oncology (Lynch syndrome), genomic DNA sequence analysis of MLH1, MSH2, MSH6, PMS2, and EPCAM, including small sequence changes in exonic and intronic regions, deletions, duplications, mobile element insertions, and variants in non-uniquely mappable regions
ANY	Guardant360® LDT for any indication (Guardant Health, 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 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/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 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. Patients can be asymptomatic in the early stages of the disease. For such individuals, 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.

According to WHO diagnostic criteria, identification of a clonal marker is one of the required major criteria in the diagnosis of PMF (Arber et al. 2016). 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 55-67% of PMF cases, CALR pathogenic variants are found in 15-20%, and MPL P/LP variants in 6-10% (Szuber et al. 2019). The presence or absence of somatic variants in additional genes (e.g., ASXL1, EZH2, IDH1, IDH2, TET2, TP53, and SRSF2) may have diagnostic or prognostic significance for patients with PMF and/or in treatment decision-making for individuals who are being considered for allogeneic hematopoietic cell transplantation (Vannucchi et al. 2013; Lasho et al. 2018; Wong and Pozdnyakova 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. Most cases of ALL are B-cell origin, and a smaller percentage originate in T-cells. 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/or 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. Taylor et al. (2017) provide review of genetic testing routinely performed for B-cell and T-cell ALL. Array CGH may be considered in cases of aneuploidy or failed karyotype following emerging evidence of its clinically relevant findings and utility (Mitrakos et al. 2019; Peterson et al. 2018).

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 prognostic importance in predicting relapse and ability to identify high-risk patients to intensify treatment and low-risk patients to reduce/avoid treatment such as HSCT (Berry et al. 2017; Heikamp and Pui 2018; Kansagra et al. 2019; Eckert et al. 2019; Shah et al. 2020). 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).

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).

The European LeukemiaNet (ELN) working party for MRD consisting of 24 experts from Europe and the United States published a consensus document in 2019 which provides recommendations to

standardize and improve the reporting of MRD results. This group also provided clinical recommendations that MRD monitoring be considered part of the standard of care for all AML patients, but that molecular methods only be used for patients with subtypes amenable to targeted PCR-based assays (specifically: APL, CBF AML, and NPM1-mutated AML). For others, flow cytometry is recommended (Schuurhuis 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.

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. Along with a patient's age and comorbidities, 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 (Cao 2016).

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 American Society of Clinical Oncology (ASCO) published recommendations on the management of male breast cancer (2019) that revealed high-level consensus for similar management in men and women regarding the use of gene expression profile testing to guide adjuvant treatment decision making (e.g. Oncotype DX and prognostic tests). 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) that was reaffirmed in 2019 (Henry et al. 2019). 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 2017 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 the benefit of chemotherapy cannot be excluded, particularly in patients with more than one involved lymph node. (Evidence Quality: High; Strength of Recommendation: Moderate)

While the clinical utility of the OncotypeDx Recurrence Score (RS) has been established in node negative, HR positive, HER2-negative patients with breast cancer; results from the RxPonder trial have been needed to establish its utility in node positive patients with similar breast cancer characteristics. An independent safety monitoring committee recommended reporting findings publicly prior to the final analysis after noting a surprising and clear pattern of benefit for postmenopausal women (Kalinsky et al. 2020). A significant association between recurrence score and chemotherapy benefit was found with menopausal status (p=0.004). While patients will still be followed for 15 years, the current data suggest adjuvant therapy can be ET alone in postmenopausal patients with 1-3 positive nodes and a RS ≤25. The opposite is true for premenopausal women after data revealed invasive disease-free survival (IDFS) benefit for chemoendocrine therapy (CET) (Kalinsky et al. 2020).

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.

Lung Cancer

A number of genetic changes within NSCLC tumors have been associated with improved response to various therapies, and best practice guidelines recommend molecular testing of advanced stage lung tumors, especially NSCLC adenocarcinomas, in order to help guide therapeutic decision-making. 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; Li et al. 2019).

Beyond EGFR, a number of additional genes may provide information about ideal treatment strategy or prognosis for patients with NSCLC. KRAS mutations have been associated with primary EGFR TKI resistance as well as poor survival. Anaplastic lymphoma kinase (ALK) and ROS1 gene rearrangements have been identified in a subset of patients with NSCLC and represent a unique subset of patients for whom ALK or ROS1 inhibitors may be a very effective treatment strategy.

A number of other genetic alterations have been identified in individuals with NSCLC for which targeted therapies have already been developed for other tumor types, including: BRAF V600 P/LP variants, HER2 (ERBB2) P/LP variants, RET gene rearrangements, and MET amplification (Gregg et al. 2019). Multi-gene panel testing that includes these additional genes should be considered to identify patients who may be eligible for clinical trials or off-label treatments (Lindeman et al. 2018).

Guidelines and recommendations regarding molecular testing in NSCLC tumor have been published by multiple societies including the American Society of Clinical Oncologists (ASCO), College of American

Pathologists (CAP), the International Association for the Study of Lung Cancer (IASLC), and the Association for Molecular Pathology (AMP) (Lindeman et al. 2018; Hanna et al. 2017; Kalemkerian et al. 2018). Based on high quality evidence, these groups agree with a strong recommendation that testing for ROS1, ALK, and EGFR mutations should be performed for all patients with advanced-stage (stages III B and above) lung adenocarcinoma. There is also agreement that testing for other genes, including BRAF, RET, ERBB2 (HER2), KRAS, MET, NTRK fusions, and PD-L1 amplification are also appropriate to aid in treatment decision-making in NSCLC, including tumors with histologies other than adenocarcinoma such as large cell or squamous cell carcinomas. In general, next generation sequencing panels are preferred, given the ability to analyze multiple genes from a single sample type, and to detect gene fusions/rearrangements and copy number alterations. Testing for P/LP variants within genes beyond those described above have not been incorporated into standard practice. Molecular testing for early-stage tumors is not included in these recommendations, given that these patients may be surgically cured with no need for molecularly targeted therapies (Lindeman et al. 2018; Hanna et al. 2017; Kalemkerian et al. 2018). Evaluation of tumor mutational burden has been proposed as an emerging biomarker to assess treatment response, however, there is no current consensus on how to measure this (Cyriac and Gandhi 2018).

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) (Byers and Rudin 2015). Attempts to identify common driver P/LP variants in SCLC have revealed significant genetic heterogeneity across patients. The TP53 and RB1 genes are almost universally inactive in SCLC tumors, but targeted therapies for these genetic alterations are not yet available (Zaman and Bivona 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; Zaman and Bivona 2018).

Cell-Free Tumor Testing

Tumor testing for the recommended molecular markers is not always possible, primarily due to an 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 cancer may be poor candidates for biopsy.

There has been growing interest and research into alternative blood-based methodologies for assessing tumor P/LP variant status, including cell-free plasma-based tests. An example is cell-free tumor DNA (ctDNA) testing which is commonly employed because ctDNA is easier to isolate and, with the increasing capabilities of next-generation sequencing, it 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) to provide information about the molecular status of a tumor (Rolfo et al. 2018). It has also been proposed that ctDNA may improve minimal residual disease monitoring (Levy et al. 2016).

Cell-free tumor DNA analysis is still an active area of research and monitoring of performance data will be ongoing. In the interim, there are select clinical scenarios with sufficient evidence to allow cell-free tumor DNA analysis: metastatic NSCLC, metastatic breast cancer, metastatic castrate-resistant

prostate cancer, or ovarian cancer. Utility has not yet been proven in other clinical scenarios. In addition, there is insufficient evidence to recommend coverage of plasma-based testing (ctDNA) over tumor-based testing when an appropriate tumor sample is available (Rolfo et al. 2020). ctDNA testing may be reasonable to aid treatment selection at the time of diagnosis or to guide treatment decision making when progression occurs.

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 (Binder et al. 2018). It has been proposed that more intensive diagnostic studies aimed at identifying the primary cancer site is important to guide disease-oriented therapy. Several laboratories offer gene expression profiling or NGS tests to aid in the identification of the tissue of origin of a metastatic tumor (Binder et al. 2018). The current 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 that management changes based on results impact patient survival. A randomized phase II trial found no improvement in 1-year survival between patients who were treated with site-specific therapies based on GEP results and patients who were treated with empirical chemotherapy (Hayashi et al. 2019).

Multiple professional societies have commented on the limited evidence of clinical utility for molecular testing to identify the origin of occult primary cancers. A 2013 AHRQ Technology Assessment found insufficient evidence to assess the effect of molecular tests on treatment decision and outcomes for cancers of unknown primary (Meleth et al. 2013). 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.

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, a 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 (Feguson 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 (Colucci et al. 2010; Bao et al. 2016). 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 (Holter 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. Many clinical tests that use gene expression analysis of prostate tumor tissue have been developed in recent years to help improve the accuracy of this risk assessment with the goal of identifying individuals who can be spared aggressive treatment (Cuzick et al. 2014). These assays (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, results from gene expression profiles should not be interpreted as either positive or negative- instead, risk scores should be considered in the context of other tumor features (Cucchiara et al. 2018). Although genomic assays show promising results, further studies with large cohorts are needed to quantify the actual benefit of these technologies and how they should be

optimally implemented in routine practice (Herlemann et al. 2017; Kretschmer et al. 2017; Cucchiara et al. 2018).

The American Urological Association (AUA), ASTRO and the Society of Urologic Oncology (SUO) published guidelines in 2018 for risk stratification, shared decision making, and care options for clinically localized prostate cancer. It is notable that these guidelines do not include a recommendation for genomic testing of prostate tumor samples, and instead use Gleason score, PSA, and clinical stage in the risk stratification and assessment of treatment options. The authors state that no genomic tests have yet been validated as providing substantial benefit in the active surveillance population (Sanda et al. 2017; Sanda et al. 2018). The European Association of Urology recently created (and externally validated) a simple risk stratification system to help identify men at high risk for biochemical recurrence; this schema uses Gleason score and PSA levels - notably absent is the incorporation of any gene expression assays (Van den Broeck et al. 2020). The American Society of Clinical Oncologists (ASCO) recently released recommendations supporting the use of commercially available molecular biomarkers in situations in which the assay results, coupled with other routine clinical factors, would be likely to change medical management (Eggener et al. 2019). However, these guidelines were not based on any new, prospective data.

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 concluded 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® Prostate Cancer Classifier, 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. ASCO guidelines indicate that there is no evidence of clinical utility and little evidence of clinical validity of ctDNA assays in early-stage cancer, treatment monitoring, or residual disease detection (Merker et al. 2018).

Thyroid Cancer

Thyroid cancers are one of the most common endocrine malignancies. Some molecular P/LP variants can be useful to clarify the diagnosis, predict prognosis and therapy response, and identify inherited predispositions in patients with thyroid cancer. However, molecular results should be interpreted with

caution and do not replace standard risk assessment based on other clinical, radiographic, and cytologic features (D'Cruz et al. 2018).

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 (Subbiah et al. 2018). 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.

TERT, PTEN, and TP53 are other genes in which mutations have been reported with a possible role in differentiating among subtypes of thyroid cancers (Hysek et al. 2018; Romei et al. 2018), and overall mutational burden may also be correlated with prognosis in follicular thyroid cancer (Nicolson et al. 2018). However, the utility of testing for additional gene mutations beyond traditional pathologic evaluations has yet to be established. Some broader molecular diagnostic tests have been developed that specifically target genes and P/LP variants known to have a strong association with thyroid malignancy (eg, BRAF, RET/PTC, RAS, PAX8/PPAR). These tests are intended to help classify thyroid nodules that are indeterminate based on cytopathology, but the clinical utility is limited when these testing panels are used for patients who already have a confirmed diagnosis of thyroid cancer.

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

Thyroid nodules occur in 1% of men and 5% of women (Haugen et al. 2016). These nodules are typically benign, although a small subset is malignant and require surgical resection with potential additional treatment. Cytological examination of FNA samples is the current standard of care for classifying thyroid nodules as malignant (thyroid carcinoma) or benign (thyroid adenoma), but this distinction is not always straightforward. Approximately 20-25% of samples are deemed indeterminate thyroid nodules (ITN) after being classified as Bethesda category III (atypia of undetermined significance/follicular lesion of undetermined significance, AUS/FLUS) or Bethesda category IV (follicular neoplasm/suspicious for a follicular neoplasm, FN/SFN). There are caveats that add complexity to ITN classification. The first is that approximately 10% of all FNA samples contain a significant Hurthle cell population. The second caveat came in early 2017, when 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 FNA 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 by the avoidance of classifying this low-grade tumor as a carcinoma.

Traditionally, diagnostic surgery was performed for clarification and management of ITNs, but most procedures turned out to be unnecessary after data revealed up to 75% of cases were actually benign (Haugen et al. 2016). There is growing evidence that molecular diagnostic testing can alleviate the burden of surgical dependence in the reclassification of these indeterminate lesions for prognosis and treatment.

Gene expression classifiers (GECs) evaluate levels of RNA or miRNA expression to better understand gene regulation behavior. This can be important in predicting an abnormal pathological process, such as neoplastic growth. Genes included in these profiles may be proprietary and vary by laboratory. GECs used for ITN have a relatively low PPV and are generally considered "rule out" tests. An NPV of 95% is generally considered an acceptable threshold for this type of "rule out" test since the historical approach to observing nodules deemed cytologically benign left patients with a residual risk of 1-5% for malignancy (Ali et al. 2019). An abnormal result is not necessarily predictive of cancer, but if expression is normal, there is a high chance that cancer is currently not present. Long term data on the impact of conservative (observational) management for individuals with ITN and negative GEC results are still pending and are needed to fully establish clinical utility of GECs.

Tests that use next generation sequencing, point mutation analysis, or other targeted analyses of genes and P/LP variants known to have a strong association with thyroid malignancy (eg, BRAF, RET/PTC, RAS, PAX8/PPAR) are generally used as "rule in" tests. If a P/LP variant is identified, there is assumed to be a high likelihood that the thyroid nodule is malignant and requires surgical intervention. The prevalence of malignancy varies by the specific P/LP variant identified (Cohen et al. 2019), and the exact PPVs associated with these tests are highly variable.

Several professional societies have published guidelines regarding the use of molecular testing for indeterminate thyroid nodules and how to incorporate results into the management plan for patients with indeterminate cytology. The American Association of Clinical Endocrinologists do not recommend either in favor of or against the use of GECs for indeterminate thyroid nodules, due to insufficient evidence and limited follow-up. Molecular testing should not replace cytologic evaluation and should be considered when results are expected to influence clinical management. As a general rule molecular testing should not be considered in nodules with established benign or malignant cytologic characteristics (Gharib et al. 2016). Cytopathology expertise, patient characteristics and prevalence of malignancy within the population being tested impact NPV and PPV for molecular testing, but they do recommend it for BRAF and RET/PTC along with possibly PAX/PPARG and RAS P/LP variants if such detection is available (Gharib et al. 2016). With the exception of pathogenic variants such as BRAF V600E with PPV approaching 100% for PTC, evidence is insufficient to recommend in favor or against P/LP variant testing as a guide to determine the extent of surgery. Close follow-up is also still recommended for mutation-negative nodules or nodules classified as benign by a GEC because experience and follow-up for these is insufficient (Gharib et al. 2016).

The American Thyroid Association (ATA) issued a statement in 2015 regarding the surgical application of molecular profiling for thyroid nodules (Ferris et al. 2015). They suggest that 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. They note that GECs may perform better when the initial suspicion for cancer is low, such as when the cytologic category is Bethesda III (AUS/FLUS), and that molecular testing performs better in settings with higher cancer frequencies (Haugen et al. 2016).

Colorectal Cancer Screening

Colorectal cancer is the fourth most common cancer type diagnosed in the United States. Best practice guidelines are available from multiple professional organizations (e.g., 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, professional society guidelines have not been updated to recommend its routine use.

Professional Society Guidelines

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Revision History

Medical Advisory Board Review:

v4.2020 12/29/2020: Approved

v3.2020 11/13/2020: Approved

v2.2020 05/08/2020: Reviewed

v1.2020 11/04/2019: Approved

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Clinical Steering Committee Review:

v4.2020 12/29/2020: Approved

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v1.2017 01/25/2017: Approved

Revisions:

Version	Date	Editor	Description
v4.2020	12/29/2020	Heather Dorsey, MS, CGC	Interim Update: Coverage criteria was expanded for OncotypeDX Breast Recurrence Score test. Coverage for EGFR in NSCLC (Stage IB-IIIA) was added.

v3.2020	10/09/2020	Heather Dorsey, MS, CGC	Interim Update: Coverage criteria was added for liquid biopsy testing in patients with metastatic castrate-resistant prostate cancer, metastatic breast cancer (updated), ovarian cancer and metastatic NSCLC. General coverage criteria for multi-gene panels was updated to clarify coverage for tests designated as FDA companion diagnostics. CPT codes, background and references were updated.
v2.2020	03/13/2020	Heather Dorsey, MS, CGC	General coverage criteria for somatic multi-gene panels was updated to include criteria for an FDA companion diagnostic. Criteria was added for CMA testing for multiple myeloma. Targeted multi-gene panels were added for metastatic castration-resistant prostate cancer. Gene list was updated for B-Cell Lymphoma and RET fusions were added for thyroid cancer. Gene expression classifier testing criteria for breast cancer was expanded. Prostate Cancer (symptomatic cancer screening) was clarified. Updated CPT codes, professional society guidelines, background and references.
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.
	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 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.
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