Clinical Appropriateness Guidelines

Molecular Testing of Solid and Hematologic Tumors and Malignancies

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AIM SpecialtyHealth
8600 West Bryn Mawr Avenue
South Tower - Suite 800 Chicago, IL 60631
www.aimspecialtyhealth.com

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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 screening/surveillance, diagnosis, selecting therapeutic agents and predicting risk, prognosis, monitoring, 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 or polygenic risk scores not addressed in this policy, please refer to the Clinical Appropriateness Guidelines for Genetic Testing for Single Gene and Multifactorial Conditions. For germline testing, 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. 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 is medically necessary when all of the following criteria are met: (Please see below for conditions with separate specific criteria):

- 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 clinical benefit of testing outweighs the potential risk of psychological or medical harm to the individual being tested
- The test is as targeted as possible for the clinical situation (e.g., common variants, genes related to phenotype)

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

Multi-Gene Panels

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 Coverage Criteria

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. Molecular studies are medically necessary for the indications listed below when the above General Coverage Criteria or FDA Companion Diagnostics Coverage Criteria are met (list is not all inclusive) (*see criteria below for chromosomal microarray, cell-free, and minimal residual disease testing*):

Molecular Studies

Hematologic/Oncologic Testing

Targeted Genomic Sequencing Panels or Single Gene Tests

- Acute Lymphoblastic Leukemia
- Acute Myelogenous Leukemia
- B-Cell Lymphoma
- Chronic Lymphocytic Leukemia
- Chronic Myeloid Leukemia
- Myelodysplastic Syndrome
- Essential Thrombocythemia or Thrombocytosis*
- Polycythemia Vera*
- Primary Myelofibrosis, Pre-PMF, suspicion for PMF*
- T-Cell Lymphoma, Peripheral

Solid Organ Tumor Testing (*for biomarker detection to aid in therapeutic decision-making only*)

Targeted Genomic Sequencing Panels

- Cholangiocarcinoma
  - FDA CDx tests: *FoundationOne® CDx or Oncomine Dx Target Test*
- Colorectal Cancer, Metastatic/Stage IV
- Endometrial Cancer
- Gastrointestinal Stromal Tumors
- Prostate Cancer, Metastatic Castration-Resistant
  - FDA CDx tests: *FoundationOne® CDx*
- Non-Small Cell Lung Cancer, (Stage IIIB and above)
  - FDA CDx tests: *FoundationOne® CDx or Oncomine Dx Target Test*
- Tumor Agnostic/All Applicable Solid Tumors
  - FDA CDx tests: *FoundationOne® CDx for tumor mutational burden (TMB) only*

Targeted Single Gene Testing

- Breast Cancer (*PIK3CA*)
- Cutaneous Melanoma (*BRAF, KIT*)
- Non-Small Cell Lung Cancer, Resected Stage IB-IIIA (*EGFR*)
- Ovarian, Fallopian Tube, or Primary Peritoneal Cancer (*BRCA1, BRCA2*)
- Thyroid Cancer (*BRAF, RET fusions*)
- Tumor Agnostic (*MSI*, *NTRK*)

**2016 WHO Criteria must be met*

The following tests are not medically necessary

(list may not be all inclusive)

- Whole exome tumor sequencing for any indication (including other genome-wide interrogation strategies, e.g., transcriptome)

- Whole genome tumor sequencing for any indication (including other genome-wide interrogation strategies, e.g., transcriptome)

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 Gene Expression Classifiers

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:

- Patient has undergone surgery and full pathological staging prior to testing
- 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 Nottingham grade 2-3 OR nuclear grade 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 gene expression classifier (GEC) has been performed

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:

- Patient has undergone surgery and full pathological staging prior to testing
- 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

MammaPrint® (81521) is medically necessary to assess the risk for recurrence in an individual when all of the following criteria are met:

- Patient has undergone surgery and full pathological staging prior to testing
- 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

Breast GEC testing is not medically necessary to guide decision making for extended endocrine therapy.

Cell-Free Testing

Cell-free testing (e.g., cfDNA, ctDNA, liquid biopsy) in the following scenarios is medically necessary when General Coverage Criteria or FDA Companion Diagnostic Coverage Criteria above are met:

- 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
- Ovarian, Fallopian Tube, or Primary Peritoneal Cancer
    - FoundationOne® Liquid CDx is medically necessary if tumor is unavailable 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
- Advanced or Metastatic Breast Cancer
    - therascreen® PIK3CA testing is medically necessary using liquid biopsy if tumor is unavailable for advanced or metastatic breast cancer when the patient meets criteria per the FDA label for treatments for which this test has been approved as a companion diagnostic
- Locally Advanced or Metastatic Non-Small Cell Lung Cancer (NSCLC)
    - Initial Biomarker Determination
        - FDA approved companion diagnostic tests (i.e., cobas EGFR Mutation Test v2, FoundationOne® Liquid CDx, or Guardant360® CDx) or a targeted multi-gene panel (i.e., ctDx Lung™ or Target Selector™ NGS Lung Panel) are medically necessary 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
            - Targeted cell-free testing is not medically necessary when progression is on osimertinib

Cell-free testing is not medically necessary when the patient already meets criteria for treatment without the need for additional testing (e.g., patient meets criteria based on known genetic results or biomarker status is not required).

Chromosomal Microarray Analysis

Chromosomal microarray analysis is medically necessary in any of the following clinical scenarios when general coverage criteria above are met:

- To aid diagnosis when part of the initial work-up involves cytogenetic (karyotype) and/or FISH analyses and testing was uninformative or could not be performed
- For methylation analysis (e.g., brain/central nervous system cancers)

Minimal Residual Disease (MRD) Monitoring

For hematologic cancers:

NGS immunosequencing for MRD clone identification is covered when the following criteria are met:

- There is a confirmed diagnosis of B-cell acute lymphoblastic leukemia which is Philadelphia chromosome (*BCR-ABL*) negative
- Testing is performed on bone marrow

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
- Testing is performed on bone marrow

Targeted testing with prospective evidence of clinical utility for the tumor type and disease characteristics is medically necessary.

For solid tumors:

Molecular testing for MRD and/or disease monitoring is not medically necessary.

Targeted Molecular Testing for *NTRK* Fusions

Targeted molecular testing for *NTRK1*/2/3 fusions is medically necessary when General Coverage Criteria above are met 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 with positive *NTRK* IHC results or IHC is not possible for biomarker confirmation

Cancer Screening

Population Based Cancer Screening

Multi-Cancer Early Detection (MCED) testing is not medically necessary.

Prostate Cancer (symptomatic cancer screening)

ExoDx (0005U) or SelectMDx (81479) is medically necessary for men ≥50 years considering initial biopsy when there is concern for prostate cancer as evidenced by a PSA of 3.1-10.0 ng/mL and none of the following:

- Treatment for benign prostatic hyperplasia in the past six months
- Treatment using a medication which impacts serum PSA levels within the past six months

PCA3 (81313) or ConfirmMDx (81551) is medically necessary for men ≥50 years with prior negative biopsy when repeat biopsy is being considered after PSA testing (within 6 months of this test request) reveals a persistently elevated PSA of 3.1-10.0 ng/mL.

Assays not listed above are considered not medically necessary. Serial testing and/or concurrent testing with multiple assays is not medically necessary.

Indeterminate Thyroid Nodules

Targeted multi-gene panels, Afirma® Genomic Sequence Classifier, ThyGeNEXT®/ThyraMIR™, or ThyroSeq® v3 are medically necessary for Bethesda Category III (AUS/FLUS) indeterminate thyroid nodules.*

Targeted multi-gene panels, ThyGeNEXT®/ThyraMIR™, or ThyroSeq® v3 are medically necessary for Bethesda Category IV (FN/SFN) indeterminate thyroid nodules.*

*FNA samples with Hurthle cell predominance are excluded from coverage.

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)
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 (Breast Cancer Index™)	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 (Oncotype DX Breast Recurrence Score®)	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 (Prosigna™)	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 (MammaPrint®)	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 (EndoPredict®)	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 (Cologuard®)	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 (Afirma® GSC)	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 (ConfirmMDx®)	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 (DecisionDx® - UM)	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 (ExoDx™ - Prostate Test)	Oncology (prostate) gene expression profile by real-time RT-PCR of 3 genes (ERG, PCA3, and SPDEF), urine, algorithm reported as risk score
0018U (ThyraMIR®)	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 (Oncomine™ DX Target Test)	Targeted genomic sequence analysis panel, cholangiocarcinoma and non- small cell lung neoplasia, DNA and RNA analysis, 1 - 23 genes, interrogation for sequence variants and rearrangements, reported as presence/absence of variants and associated therapy(ies) to consider
0023U (Leukostrat® FLT3 Mutation Assay)	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 (ThyroSeq v3)	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 (FoundationOne® CDx)	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
0046U (AML - FLT3 ITD MRD)	FLT3 (fms-related tyrosine kinase 3) (eg, acute myeloid leukemia) internal tandem duplication (ITD) variants, quantitative
0111U (Praxis Extended RAS Panel)	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
0113U (Mi-Prostate Score)	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
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-

(therascreen FGFR RGQ RT-PCR Kit)	TACC3v1, and FGFR3-TACC3v3) utilizing formalin-fixed paraffin-embedded urothelial cancer tumor tissue, reported as FGFR gene alteration status
0155U (therascreen PIK3CA RGQ PCR Kit)	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)	Oncology (solid tumor as indicated by the label), somatic mutation analysis of BRCA1 (BRCA1, DNA repair associated), BRCA2 (BRCA2, DNA repair associated) and analysis of homologous recombination deficiency pathways, DNA, formalin-fixed paraffin-embedded tissue, algorithm quantifying tumor genomic instability score
0177U (therascreen® PIK3CA RGQ PCR Kit)	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 (Resolution ctDx Lung™)	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 (FoundationOne® Liquid CDx)	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
0242U (Guardant360® CDx)	Targeted genomic sequence analysis panel, solid organ neoplasm, cell-free circulating DNA analysis of 55-74 genes, interrogation for sequence variants, gene copy number amplifications, and gene rearrangements
0245U (ThyGeNEXT® Thyroid Oncogene Panel)	Oncology (thyroid), mutation analysis of 10 genes and 37 RNA fusions and expression of 4 mRNA markers using next-generation sequencing, fine needle aspirate, report includes associated risk of malignancy expressed as a percentage
ANY	Clonoseq®

Considered not medically necessary:
(Proprietary tests that do not meet criteria are considered not medically necessary when submitted with their specific assigned code listed below or any less specific coding.)

81327	SEPT9 (Septin9) (eg, colorectal cancer) promoter methylation analysis

PROPRIETARY

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
81523 (MammaPrint® NGS)	Oncology (breast), mRNA, next-generation sequencing gene expression profiling of 70 content genes and 31 housekeeping genes, utilizing formalin-fixed paraffin-embedded tissue, algorithm reported as index related to risk to distant metastasis
81525 (OncotypeDx® Colon Cancer)	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 (DecisionDx® - Melanoma)	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 (CancerTYPE ID®)	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 (Prolaris®)	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 (Decipher® Prostate Genomic Classifier)	Oncology (prostate), mRNA, microarray gene expression profiling of 22 content genes, utilizing formalin-fixed paraffin-embedded tissue, algorithm reported as metastasis risk score
0012M (CxBladder™ Detect)	Oncology (urothelial), mRNA, gene expression profiling by real-time quantitative PCR of five genes (MDK, HOXA13, CDC2 [CDK1], IGFBP5, and XCR2), utilizing urine, algorithm reported as a risk score for having urothelial carcinoma
0013M (CxBladder™ Monitor)	Oncology (urothelial), mRNA, gene expression profiling by real-time quantitative PCR of five genes (MDK, HOXA13, CDC2 [CDK1], IGFBP5, and CXCR2), utilizing urine, algorithm reported as a risk score for having recurrent urothelial carcinoma
0045U (OncotypeDx® Breast DCIS Score)	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 (OncotypeDx Genomic Prostate Score®)	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 (MSK-IMPACT™)	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)
0089U (Pigmented Lesion Assay)	Oncology (melanoma), gene expression profiling by RTqPCR, PRAME and LINC00518, superficial collection using adhesive patch(es)
0090U (myPath melanoma)	Oncology (cutaneous melanoma), mRNA gene expression profiling by RT-PCR of 23 genes (14 content and 9 housekeeping), utilizing formalin-fixed paraffin-embedded (FFPE) tissue, algorithm reported as a categorical result (ie, benign, intermediate, malignant)
0204U (Afirma® Xpression Atlas)	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
0229U (Colvera®)	BCAT1 (Branched chain amino acid transaminase 1) or IKZF1 (IKAROS family zinc finger 1) (eg, colorectal cancer) promoter methylation analysis
0244U (Oncotype MAP™ PanCancer Tissue Test)	Oncology (solid organ), DNA, comprehensive genomic profiling, 257 genes, interrogation for single-nucleotide variants, insertions/deletions, copy number alterations, gene rearrangements, tumor-mutational burden and microsatellite instability, utilizing formalin-fixed paraffin embedded tumor tissue
0250U (PGDx elio™ tissue complete)	Oncology (solid organ neoplasm), targeted genomic sequence DNA analysis of 505 genes, interrogation for somatic alterations (SNVs [single nucleotide variant], small insertions and deletions, one amplification, and four translocations), microsatellite instability and tumor-mutation burden
0262U (OncoSignal™ 7 Pathway Signal)	Oncology (solid tumor), gene expression profiling by real-time RT-PCR of 7 gene pathways (ER, AR, PI3K, MAPK, HH, TGFB, Notch), formalin-fixed paraffin embedded (FFPE), algorithm reported as gene pathway activity score
0285U (RadTox™ cfDNA test)	Oncology, response to radiation, cell-free DNA, quantitative branched chain DNA amplification, plasma, reported as a radiation toxicity score
0287U (ThyroSeq® CRC)	Oncology (thyroid), DNA and mRNA, next generation sequencing analysis of 112 genes, fine needle aspirate or formalin fixed paraffin-embedded (FFPE) tissue, algorithmic prediction of cancer recurrence, reported as a categorical risk result (low, intermediate, high)

0288U (DetermaRx™)	Oncology (lung), mRNA, quantitative PCR analysis of 11 genes (BAG1, BRCA1, CDC6, CDK2AP1, ERBB3, FUT3, IL11, LCK, RND3, SH3BGR, WNT3A) and 3 reference genes (ESD, TBP, YAP1), formalin-fixed paraffin-embedded (FFPE) tumor tissue, algorithmic interpretation reported as a recurrence risk score
0296U (mRNA CancerDetect™)	Oncology (oral and/or oropharyngeal cancer), gene expression profiling by RNA sequencing at least 20 molecular features (eg, human and/or microbial mRNA), saliva, algorithm reported as positive or negative for signature associated with malignancy
0297U (Praxis Somatic Whole Genome Sequencing)	Oncology (pan tumor), whole genome sequencing of paired malignant and normal DNA specimens, fresh or formalin fixed paraffin-embedded (FFPE) tissue, blood or bone marrow, comparative sequence analyses and variant identification
0298U (Praxis Somatic Transcriptome)	Oncology (pan tumor), whole transcriptome sequencing of paired malignant and normal RNA specimens, fresh or formalin-fixed paraffin-embedded (FFPE) tissue, blood or bone marrow, comparative sequence analyses and expression level and chimeric transcript identification
0299U (Praxis Somatic Optical Genome Mapping)	Oncology (pan tumor), whole genome optical genome mapping of paired malignant and normal DNA specimens, fresh frozen tissue, blood, or bone marrow, comparative structural variant identification
0300U (Praxis Somatic Combined Whole Genome Sequencing and Optical Genome Mapping)	Oncology (pan tumor), whole genome sequencing and optical genome mapping of paired malignant and normal DNA specimens, fresh tissue, blood, or bone marrow, comparative sequence analyses and variant identification
0306U (Invitae PCM Tissue Profiling and MRD Baseline Assay)	Oncology (minimal residual disease [MRD]), next-generation targeted sequencing analysis, cell-free DNA, initial (baseline) assessment to determine a patient specific panel for future comparisons to evaluate for MRD (Do not report 0306U in conjunction with 0307U)
0307U (Invitae PCM MRD Monitoring)	Oncology (minimal residual disease [MRD]), next-generation targeted sequencing analysis of a patient-specific panel, cell-free DNA, subsequent assessment with comparison to previously analyzed patient specimens to evaluate for MRD (Do not report 0307U in conjunction with 0306U)
0313U (PancreaSeq® Genomic Classifier)	Oncology (pancreas), DNA and mRNA next-generation sequencing analysis of 74 genes and analysis of CEA (CEACAM5) gene expression, pancreatic cyst fluid, algorithm reported as a categorical result (ie, negative, low probability of neoplasia or positive, high probability of neoplasia)
0314U	Oncology (cutaneous melanoma), mRNA gene expression profiling by RT-PCR of 35 genes (32 content and 3 housekeeping), utilizing formalin-fixed paraffin-embedded

(DecisionDx® DiffDx™-Melanoma)	(FFPE) tissue, algorithm reported as a categorical result (ie, benign, intermediate, malignant)
0315U (DecisionDx®-SCC)	Oncology (cutaneous squamous cell carcinoma), mRNA gene expression profiling by RT-PCR of 40 genes (34 content and 6 housekeeping), utilizing formalin-fixed paraffin embedded tissue, algorithm reported as a categorical risk result (ie, Class 1, Class 2A, Class 2B)
0317U (LungLB®)	Oncology (lung cancer), four-probe FISH (3q29, 3p22.1, 10q22.3, 10cen) assay, whole blood, predictive algorithm generated evaluation reported as decreased or increased risk for lung cancer
ANY	Guardant360® LDT/Response/TissueNext or Guardant Reveal for any indication (Guardant Health, Inc.)
ANY	Galleri

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, or myeloproliferative neoplasms (MPNs), are a group of conditions that cause abnormal growth of blood cells in the bone marrow. They include polycythemia vera (PV), essential thrombocythemia or thrombocytosis, pre-primary myelofibrosis, primary myelofibrosis, chronic myelogenous leukemia, and chronic neutrophilic leukemia. The diagnosis of an MPN is suspected based upon clinical, laboratory, and pathological findings, including bone marrow morphology and certain pathogenic/likely pathogenic (P/LP) variants. Patients with MPNs may be clinically asymptomatic, but MPNs confer a risk for progression to acute myeloid leukemia, also called blast-phase MPN (Lasho et al. 2018).

JAK2, *CALR*, and *MPL* are genes involved in the growth and survival of various cell types. The presence of somatic driver mutations within these genes is part of the World Health Organization diagnostic criteria for MPNs, and molecular testing may be necessary to confirm a diagnosis. Chronic myelogenous leukemia (CML) is distinguished from the other MPNs by the presence of a *BCR-ABL*1

fusion gene. Targeted genetic testing of the *JAK2*, *CALR*, and *MPL* genes may be helpful in individuals who would not otherwise meet diagnostic criteria. There is some evidence that non-driver P/LP variants in additional genes such as *ASXL1*, *TET2*, and *TP53* can help to predict a poor prognosis for some patients with MPNs, but the utility of testing these genes is not fully established (McClure et al. 2018; Grinfeld et al. 2018). Importantly, P/LP variants in many of these genes as well as in *DNMT3A* have also been detected in older individuals with no other clinical evidence of myeloid disease, a scenario known as clonal hematopoiesis of indeterminate potential (CHIP). Therefore, genetic testing should only be performed when there is reasonable clinical suspicion of disease. At this time, variants in other genes associated with MPNs are recommended only in the evaluation for primary and pre-primary myelofibrosis.

MPNs are related to, but distinct from, myelodysplastic syndromes (MDS). In general, MDS are characterized by ineffective or dysfunctional blood cells with an increased risk of transformation to acute myeloid leukemia (AML), while MPNs are characterized by an increase in the number of blood cells. MDS typically first present as cytopenia(s) or dysplasia in one or more hematopoietic cell lines in the bone marrow. The development and transformation of MDS is driven by somatic variants in genes related to RNA splicing, epigenome regulation, myeloid transcriptional coordination, DNA damage and stress responses, and/or growth factor signaling. The WHO has developed a classification system for the diagnosis of an MDS which relies on incorporating clinical features, peripheral blood and bone marrow findings, and cytogenetic analysis. Molecular testing may be appropriate in select scenarios when a diagnosis already exists and testing will help clarify prognostic category, which can help guide the treatment pathway.

Gene Expression Classifiers

Breast Cancer Gene Expression Classifiers

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). Certain breast cancer gene expression profiling tests which identify the expression levels of defined sets of genes demonstrated utility in predicting recurrence risk and/or treatment response for some categories of breast cancer.

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, *HER2* 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

In 2019 ASCO updated their guidelines again by incorporating data from the TAILORx trial. No changes were made to the criteria for whom should be offered OncotypeDX testing; however, adjuvant systemic treatment options were further delineated based on OncotypeDX recurrence score (Andre et al. 2019; Sparano et al. 2019).

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 (Harris et al. 2016). 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; Kalinsky et al. 2021). 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 that postmenopausal patients with 1-3 positive nodes and a low recurrence score (less than 25) can safely avoid chemotherapy and be treated with adjuvant endocrine therapy alone. The opposite is true for premenopausal women after data revealed invasive disease-free survival benefit for chemoendocrine therapy (Kalinsky et al. 2021).

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.

Of note, in 2021 ASCO released guidelines on neoadjuvant chemotherapy use; they recommended against the use of breast gene expression profiles in guiding decision-making regarding neoadjuvant chemotherapy (Korde et al. 2021).

Prostate Cancer (Post-Diagnosis Gene Expression Classifiers)

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, the ASCO statement notes that “there is a paucity of prospective studies assessing short- and long-term outcomes of patients when these markers are integrated into clinical decision making.” (Eggener et al. 2020).

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, are promising but need further evidence to confirm their clinical validity.

More recently, data from a retrospective analysis of a prospective phase 3 trial were published that showed the Decipher test as being prognostic for distant metastasis, prostate cancer-specific mortality, and overall survival (Feng et al. 2021). Additionally, a meta-analysis looking at a variety of Decipher studies has concluded sufficient clinical utility data exists for this genomic classifier to be incorporated into routine clinical practice, noting that data is most robust for intermediate risk prostate cancer and postprostatectomy decision-making (Jairath et al, 2020). These publications have added to the lively debate about the clinical utility of this class of tests, but it remains true that large, prospective, clinical trial data demonstrating clinical utility are still lacking (Broenimann et al. 2020; Eggener et al. 2020; Lin and Nelson, 2021). A number of prospective clinical trials are currently ongoing; the results of which are anticipated to help end the debate (Lin and Nelson 2021).

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 that 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).

Cancer of Unknown Primary/Occult Primary Tumors

Occult primary tumors, or cancers of unknown primary, are defined as histologically proven metastatic malignant tumors whose primary site cannot be identified by a standard diagnostic workup. 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 (GEP) 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. The European Society for Medical Oncology (ESMO) 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).

Cell-Free Tumor Testing for Biomarker Identification

Tumor testing for recommended 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). Many patients with late-stage metastatic cancer may be poor candidates for biopsy. Tumor heterogeneity is difficult to assess from localized biopsy samples (De Rubis et al. 2018). In addition, the constantly evolving nature of tumor cells presents a challenge when testing archived tumor samples, particularly if a patient has since received treatment with an agent to which the tumor may have acquired resistance (Rothwell et al. 2019).

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), positive results are generally assumed to be accurate enough to use in treatment planning (Madison et al. 2020). 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).

Cell-free tumor DNA analysis is still an active area of research and monitoring of performance data will be ongoing. Currently, there are select clinical scenarios with sufficient evidence to allow cell-free tumor DNA analysis to help guide therapeutic decision making: metastatic NSCLC, metastatic breast cancer, metastatic castrate-resistant prostate cancer or ovarian cancer. Utility has not yet been proven in other clinical scenarios including the use of methylation of the *SEPT9* gene (m*SEPT9*) for colon cancer screening. Concerns remain regarding the poor specificity of this testing methodology for colon cancer, and the USPSTF along with the American Cancer Society do not recommend the use of *SEPT9* for colorectal cancer screening in any scenarios (Rex et al. 2017; Wolf et al. 2018). Additional studies of circulating tumor DNA have not shown that this technique is able to reliably detect other colon tumor-related P/LP variants (Myint et al. 2018; Liebs et al. 2019). In general, there is also 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 in select clinical circumstances.

Minimal Residual Disease (MRD) Genetic Testing

Minimal residual disease (MRD) refers to persistence of low levels of tumor cells after a patient appears to have achieved complete remission from drug therapy or HCT. MRD may also be referred to as "measurable residual disease." Detecting MRD after apparent treatment success is of great interest to define patients at risk for relapse and to inform any necessary post-remission treatment.

Currently, recurrence and evolution of solid tumors is typically evaluated based on patient symptoms, biochemical screening, and imaging. However, there is growing interest in using cell-free tumor DNA (ctDNA) to monitor treatment response and MRD in solid tumors. This testing typically involves performing molecular profiling on a patient's primary tumor to identify its unique somatic variants. Subsequent serial monitoring of the amount of ctDNA and the type and frequency of tumor-specific variants may provide insight into disease progression and evolution. This testing is being explored in several malignancies, including colorectal, lung, and breast cancers. Guidance from the American Society of Clinical Oncology indicates additional studies are needed to include ctDNA as a high-risk feature for predicting when adjuvant chemotherapy should be considered in individuals with stage II colon cancer, but the methodology holds potential promise (Baxter et al. 2021).

A number of methodologies have been used to detect MRD in patients with hematologic malignancies, including flow cytometry, PCR-based assays, and next generation sequencing (NGS) tests. While achieving negative MRD in chronic lymphocytic leukemia (CLL) patients has the potential to aid in the prediction of longer progression free and overall survival, more data is needed on how to incorporate MRD information into a patient's treatment plan (Bewersdorf et al. 2020). However, evaluation for MRD in bone marrow aspirate from patients with acute lymphoblastic leukemia (ALL) has demonstrated clinical utility; MRD testing has prognostic importance in predicting relapse and can help stratify high-risk patients in whom treatment intensification would be warranted from low-risk patients in whom such treatment (e.g., hematopoietic stem cell transplantation) could be avoided (Berry et al. 2017; Heikamp and Pui 2018; Kansagra et al. 2019; Eckert et al. 2019; Shah et al. 2020). Consensus recommendations indicate MRD assessments should be done in adults with ALL on first line 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 European LeukemiaNet (ELN) working party for MRD consisting of 24 experts from Europe and the United States published a consensus document in 2018 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 acute myeloid leukemia (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. 2018).

While there is much hope that peripheral blood samples may be used for diagnosis and MRD detection in multiple myeloma (MM) in order to avoid the need for invasive biopsy, there are still many questions and technological hurdles to overcome (Soekojo et al. 2018; Romano et al. 2019; Mina et al. 2020). Intra-tumor heterogeneity adds to the complexities of detecting MRD with molecular testing. It is important to note that multiparametric flow cytometry (MFC) and NGS have not been directly compared, nor has NGS MRD testing been uniformly measured and reported in clinical trials (Bal et al. 2021). Furthermore, MRD negativity has not yet been established in the field as a surrogate endpoint in clinical trials (Holstein et al. 2021). Presently, MRD results are not incorporated in treatment change decisions, and are mainly used as a prognostic measure (Rajkumar 2020; Bal et al. 2021; Malachlan et al. 2021; Holstein et al. 2021).

Tumor Agnostic Testing

In recent years, there has been a great deal of progress in the development of targeted treatments for many types of cancer. Targeted therapies rely on the identification of the genetic variants within tumor

cells that drive the uncontrolled growth and proliferation of the cancer cells. These anticancer drugs interfere with and block the function of these specific molecular pathways. Many drugs have been incorporated into standard practice for the treatment of tumors with specific mutations. Some examples include *EGFR*-tyrosine kinase inhibitors, which are used to treat non-small cell lung cancers with *EGFR* P/LP variants, and imatinib, which targets the *BCR-ABL* fusion gene that is characteristic of chronic myelogenous leukemia. However, clinical challenges also remain as tumors can develop resistance to these therapies. Combination treatments that target multiple pathways can be a more effective treatment strategy (Morris and Kopetz 2013).

Historically, US Food and Drug Administration (FDA) approvals of cancer treatments have been specific to the anatomical site of the primary tumor development, even when different types of cancers exhibit the same somatic variants. However, given growing evidence that unrelated tumor types can have the same molecular variants driving cancer development, current research into cancer therapies has started to focus on treatment based on molecular variants rather than the location of the tumor (Flaherty, Le, and Lemery 2017). As of late 2018, the FDA has approved a small number of therapies as tumor agnostic, meaning the treatment can be administered based on specific biomarkers rather than tumor location.

Microsatellite Instability, Tumor Mutation Burden and Immune Checkpoint Inhibitors

Microsatellites are highly polymorphic DNA sequences involving repeats of one to several base pairs. They occur in both coding and non-coding regions. These regions are prone to errors during DNA replication, which are typically repaired by DNA mismatch repair (MMR) enzymes. Evidence has supported the use of MSI testing to predict the effect of immune checkpoint inhibitors such as anti-PD-L1 antibodies (Le et al. 2015). The gold standard for MSI testing is by PCR or immunohistochemistry (IHC). Many tumor types have shown dramatic responses to immune checkpoint inhibitors including undifferentiated malignancies (Devereaux et al. 2018).

Tumor mutation burden (TMB), or the total number of somatic mutations in a tumor genome, is another potential biomarker for immune checkpoint inhibitor response. High TMB (TMB-H) may lead to increased expression of tumor-specific antigens, which may be recognized by the immune system as abnormal. Tumors with a high TMB may therefore be more likely to respond to immune checkpoint inhibitors (Marabelle et al. 2020; Yarchoan et al. 2019). However, TMB alone may not adequately predict response across all tumor types, possibly due to the effects of other immune-related mechanisms; some suggest that TMB should therefore be used in combination with other predictive biomarkers (Sung et al. 2020; Strickler et al. 2021). Additionally, the standardization of TMB as a biomarker is still debated; it has yet to be uniformly established how to accurately determine TMB in a given cancer type as well as what an optimal TMB threshold may be (McGrail et al. 2021). Research suggests most MSI-H tumors are TMB-H; however, not all TMB-H tumors are MSI-H (Chalmers et al. 2017).

A retrospective analysis of cancer patients in the United States estimated that up to 44% of patients would be eligible for immune checkpoint inhibitors based on current FDA approval criteria, while only 13% would exhibit a favorable response (Haslam and Prasad 2019). Further research is ongoing to evaluate the optimal selection criteria for immune checkpoint inhibitors and additional treatment combinations for various types of cancers (Samstein et al. 2019).

NTRK Fusion Testing

NTRK fusions are oncogenetic drivers that stimulate tumor growth in a wide variety of solid tumors. These fusions occur in developing tumor cells, and result in constitutive activation of the *TRK* tyrosine kinase domain, which includes the *NTRK1*, *NTRK2* and *NTRK3* genes. The *ETV6-NTRK3* fusion oncogene appears to be the dominant fusion event and has been seen in multiple cancer types including secretory breast carcinoma, mammary analogue secretory carcinoma (MASC), congenital fibrosarcoma, congenital mesoblastic nephroma, and acute myeloid leukemia. *NTRK1* fusions have also been observed in lung adenocarcinoma, intrahepatic cholangiocarcinoma, spitzoid neoplasms, glioblastoma, and pontine glioma. *NTRK2* fusions appear to be the least common to date. Tumor types with the highest known incidence of *NTRK* fusions include spitzoid neoplasms, secretory breast carcinoma, MASC, papillary thyroid cancer, congenital mesoblastic nephroma, and congenital fibrosarcoma. In most tumor types, *NTRK* fusions will only represent a small percentage of patients, if any. However, limitations in current testing methodologies make the true incidence of these fusions unknown (Vaishnavi et al. 2015).

The FDA has granted accelerated approval for larotrectinib (Vitrakvi) a small-molecule inhibitor of the tropomyosin receptor kinases that are encoded by *NTRK* genes. Due to the high degree of similarity between the *NTRK* genes larotrectinib is able to target all three (Yan and Zhang 2018). In August 2019, the FDA approved a second tumor agnostic medication, entrectinib (Rozlytrek) (AACR, 2019). These drugs are indicated for adult and pediatric patients with solid tumors positive for an *NTRK* gene fusion. Per the FDA label, 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.

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, specifically the *L858R* and exon 19 del variants, 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 (Li et al. 2019). More recently, testing for *EGFR* pathogenic variants has also been shown to have clinical utility in the non-metastatic setting, specifically stages IB-IIIA (Wu et al. 2020). It is important to note that not all *EGFR* pathogenic variants have the same effect. For example, the p.T790M *EGFR* pathogenic variant is associated with relapse or resistance to TKI therapy. With the use of newer next generation sequencing assays, additional *EGFR* pathogenic variants are increasingly being identified in these patients, but there is limited data about the clinical implications of other types of *EGFR* pathogenic variants (Li et al. 2019).

While *EGFR* status, in particular *L858R* and exon 19 del variants, has been shown to have the greatest impact on predicting treatment response, a number of additional genes may provide information about treatment strategy or prognosis for patients with NSCLC, albeit with varied impact. *KRAS* P/LP variants 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 are useful to identify 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 benefit from targeted treatment (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; Hanna et al. 2020; Kalemkerian et al. 2018). Based on high quality evidence, these groups agree with a strong recommendation that testing for *ROS1*, *ALK*, and *EGFR* P/LP variants 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, with the exception of *EGFR* for resected stage IB-IIIA 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 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; Dingemans et al. 2021).

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 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. In addition, there is currently insufficient independent prospective validation of performance characteristics of gene expression classifiers in samples with predominant Hurthle cells with available data encumbered by study limitations (e.g., low numbers and/or wide confidence intervals).

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 (e.g., *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).

The American Association of Endocrine Surgeons (2020) released guidelines for surgical management of thyroid disease in adults and addressed molecular testing for indeterminate thyroid nodules stating if thyroidectomy is preferred for clinical reasons, then molecular testing is unnecessary (strong recommendation, moderate-quality evidence). The association also indicated molecular testing may be considered as an adjunct for ITNs when the need for thyroidectomy is unclear after consideration of clinical, imaging and cytologic features (strong recommendation, moderate-quality evidence). But, they also stated that the accuracy of molecular testing relies on institutional malignancy rates and should be locally examined for optimal extrapolation of results to thyroid cancer risk. (Patel et al. 2020). Concerns cited regarding molecular testing included the need for additional utility and validation studies due to limitations in the current data (Patel et al. 2020). The authors also note the difficulty in interpreting molecular test results, as well as recognizing clinical scenarios where testing is most helpful could also lead to potentially over or under treatment. A better understanding is also needed of the natural history of node negative nodules and the types of malignancies missed. The association acknowledges that changes incorporated into certain commercially available GECs may improve molecular performance in nodules characterized by Hurthle cells; however, the performance of molecular testing in Hurthle cell neoplasms has been variable to date (Patel et al. 2020).

Prostate Cancer Early Screening

Prostate cancer is a common malignancy in men, and the worldwide burden of this disease is rising. Early detection and screening for prostate cancer is a clinical challenge, given the indolent nature of many prostate tumors as well as the risks and costs associated with overdiagnosis and overtreatment of this condition. Screening with prostate-specific antigen (PSA) was originally approved by the FDA in 1994, however, this method is controversial due to its low specificity and high rates of false positive results (Alford et al. 2017; Moyer 2012; Pinksky et al. 2017). Given the limitations of PSA screening, there is a clinical need for other methods to detect high-risk prostate cancers in the general population. Changes in the PSA threshold, frequency of screening, and the use of adjuvant tests (e.g., gene expression classifiers, digital rectal exam, mpMRI) have the potential to minimize the overdiagnosis and unnecessary biopsies associated with PSA screening. However, the best use of these options has yet to be established.

There are a number of genomic biomarker tests (e.g., PCA3, ConfirmMDx, ExoDx, SelectMDx) that have emerged in recent years with the goal of providing a more accurate method to aid in early detection of prostate cancer. PCA3 is a non-coding prostate-specific mRNA that is highly over-expressed in prostate cancer cells (median 66-fold up-regulation compared to adjacent benign tissue). The FDA has approved the use of this test for men age 50 or older who have had one or more previous negative prostate biopsies and for whom a repeat biopsy would be recommended by a urologist based on current

standard of care (Narayan et al. 2017). The ConfirmMDx test is an epigenetic assay that evaluates the methylation status of the *GTSP1*, *APC* and *RASSF1* genes. Methylation of these three genes can lead to a "field effect" which can indicate cancer nearby even if it was not included directly in the biopsy (Narayan et al. 2017). This test is most useful for deciding on repeat biopsy if PSA is high and initial biopsy is negative. ExoDx Prostate is a gene signature assay that evaluates expression of three genes known to play a role in prostate cancer initiation and progression: *ERG*, *PCA3*, and *SPDEF*. This test is considered a “rule-out” assay, as low-risk results indicate a low risk for high-grade prostate cancer and can support the decision to forego initial biopsy (McKiernan et al. 2016; McKiernan et al. 2018). SelectMDx measures expression levels of *DLX1* and *HOXC6* mRNA. Higher levels may be associated with an increased probability that prostate cancer will be detected on biopsy and increased risk of high-grade (Gleason score greater or equal to 7) prostate cancer, thus the test is intended to identify low risk patients who can safely avoid biopsy and proceed with active surveillance. Haese et al. (2019) concluded that the assay was optimized for biopsy native patients with serum PSA less than 10 ng/ml after clinical validation in 1955 men in a multicenter study.

The intended use of most gene expression classifier tests is to distinguish prostate cancer from benign prostatic conditions when a higher chance for cancer is suspected and many appear to have better sensitivity and specificity than PSA. 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).

Population Based Cancer Screening

Multi-Cancer Early Detection (MCED) platforms are intended to provide early detection of cancer theoretically anywhere within the body in asymptomatic individuals. Many commercially available MCED tests sequence cell-free DNA from blood samples for targeted methylation analysis in order to identify both an increased risk for cancer and the likely site of the cancer. MCEDs are distinct from other commercially available liquid biopsy tests used to guide treatment in patients with a confirmed diagnosis of cancer. While well-validated MCEDs with high sensitivity and specificity hold promise for cancer detection, important questions remain including which population to test, how often to screen, what conditions to include in screening and how to follow-up a positive result. No MCED platform has been sufficiently validated for clinical use at this time.

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Revision History

Medical Advisory Board Review:

v2.2022 03/17/2022: Approved

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Revisions:

Version	Date	Editor	Description
v2.2022 *GEN04-0922.2*	02/02/2022	Heather Dorsey, MS, CGC	Semi-annual review. Table 1 was reformatted. FoundationOne® for NSCLC (stage IIIB and above) and targeted multigene panels

			for endometrial cancer were added. Cell-free testing criteria was revised for locally advanced or metastatic NSCLC. MRD testing was revised. CPT codes, professional society guidelines, background and references were updated.
v1.2022 *GEN04-0322.1*	8/16/2021	Heather Dorsey, MS, CGC	Semi-annual review. Table 1 changes included: (1) adding genes to the biomarker list for B-Cell Lymphoma; (2) substituting "targeted multigene panels" in lieu of the current list of genes for brain/CNS cancers and NSCLC; (3) updating cholangiocarcinoma to include the biomarker IDH1, Oncomine Dx Target Test and infigratinib or ivosidenib; (4) treatment considerations based on HRR gene analysis for prostate cancer was added; and (5) treatment consideration for pembrolizumab based on TMB was added for tumor agnostic/all applicable solid tumors. Cell Free Testing: FoundationOne Liquid CDx was added to the list of approved FDA CDx tests for NSCLC. Population Based Cancer Screening was listed as not medically necessary. All other revisions to coverage criteria represent formatting changes. CPT codes, professional society guidelines, background and references were updated.
v2.2021 *GEN04-0921.1*	2/15/2021	Heather Dorsey, MS, CGC	Semi-annual review. Formatting changes were made to Table 1 and T-Cell antigen receptor (TCR) was added for T-Cell Lymphoma (peripheral). Test name was corrected for ExoDx. CPT codes, professional society guidelines, background and references were updated.
v1.2021	9/11/2020	Heather Dorsey, MS, CGC	Semi-annual review. Criteria was added for cholangiocarcinoma and neuroblastoma testing. Prostate cancer and tumor agnostic criteria was revised. Breast cancer GEC, MRD testing and targeted testing for NTRK fusions criteria were updated. CPT codes, professional society guidelines, background and references were updated.

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	10/9/2020	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 2/5/2020	Heather Dorsey, MS, CGC Carrie Langbo, 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. 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 7/25/2019	Emily Higuchi, MS, CGC Carrie Langbo, 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. 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.
v1.2015	09/24/2015	Jenna McLosky, MS, CGC	Original version

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Primary Author: Jenna McLosky, MS, CGC