## Clinical Appropriateness Guidelines

# Molecular Testing of Solid and Hematologic Tumors and Malignancies

**EFFECTIVE SEPTEMBER 9, 2019**

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

Appropriate.Safe.Affordable

© 2019 AIM Specialty Health

2066-0319a

# Table of Contents

Scope ..... 3
Appropriate Use Criteria ..... 3
National Comprehensive Cancer Network® (NCCN®) Criteria* ..... 4
Targeted Molecular Testing for NTRK Fusions ..... 5
Polycythemia Vera ..... 5
Essential Thrombocythemia or Thrombocytosis ..... 6
Primary Myelofibrosis ..... 6
Breast Cancer ..... 6
Cancer of Unknown Primary/Occult Neoplasm ..... 8
Pancreatic Cancer ..... 8
Prostate Cancer ..... 8
*Screening* ..... 8
*Confirmed Malignancy* ..... 8
Thyroid Cancer ..... 8
*Confirmed or Highly-Suspected Thyroid Cancer* ..... 8
*Cytologically Indeterminate Thyroid Nodule* ..... 9
Colorectal Cancer Screening ..... 9
CPT Codes ..... 9
Background ..... 15
Myeloproliferative Disorders ..... 15
*Polycythemia Vera* ..... 15
*Essential Thrombocythemia or Thrombocytosis* ..... 15
*Primary Myelofibrosis* ..... 16
Solid Tumor Testing ..... 16
*NTRK Fusion Testing* ..... 16
*Breast Cancer* ..... 16
*Lung Cancer* ..... 18
*Cell-Free Tumor Testing* ..... 19
*Cancer of Unknown Primary/Occult Neoplasm* ..... 20
*Pancreatic Cancer* ..... 20
*Prostate Cancer* ..... 21
*Thyroid Cancer* ..... 22
Cancer Screening ..... 23

PROPRIETARY

Guidelines developed by, and used with permission from, Informed Medical Decisions, Inc. © 2019 Informed Medical Decisions, Inc. All Rights Reserved.

*Indeterminate Thyroid Nodules* ..... 23
*Colorectal Cancer Screening* ..... 24
Professional Society Guidelines ..... 26
Selected References ..... 28
Revision History ..... 32

# Scope

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

# Appropriate Use Criteria

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

- Identification of the specific genetic variant or gene expression profile has been demonstrated through research in peer-reviewed literature to improve diagnosis, management, or clinical outcomes for the individual's tumor type
- Individual meets specific testing criteria outlined either in National Comprehensive Cancer Network® (NCCN®) algorithms with a category 1 or 2A level of evidence or supplemental criteria listed below
- Sample type (e.g., formalin-fixed, paraffin embedded, cell-free tumor DNA, circulating tumor cells, etc.) is recommended by NCCN® as a category 1 or 2A recommendation or has been proven to have clinical utility based on prospective evidence in peer-reviewed literature
- Testing methodology has been clinically validated and is the most accurate method for the actionable target unless technical limitations (e.g. poor sample quality) necessitate the need for alternate testing strategies when multiple targets are included

In addition to the above criteria, somatic multi-gene panels for hematology-oncology indications are medically necessary when all of the following are met:

- Sequential testing of individual genes or biomarkers is not practical (i.e. limited tissue available, urgent treatment decisions pending)
- Identification of genes or biomarkers on the panel has been demonstrated to improve diagnosis, management, or clinical outcomes for the individual's tumor type

PROPRIETARY

Guidelines developed by, and used with permission from, Informed Medical Decisions, Inc. © 2019 Informed Medical Decisions, Inc. All Rights Reserved.

- The panel is targeted and limited to genes that are associated with the specific tumor type, unless otherwise specified in tumor site-specific criteria below

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

- The tumor is included in NCCN Guidelines® without 1 or 2A NCCN® recommendations for molecular testing for the specific tumor type
- The requested genetic variant or profile is correlated with a known therapy, but that therapy does not have clinical utility for the specific tumor type
- Topographic genotyping (e.g., PancraGEN®)
- Whole exome tumor sequencing
- Whole genome tumor sequencing

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

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

- Acute Lymphoblastic Leukemia (Adult and AYA)
- Acute Myeloid Leukemia
- B-Cell Lymphomas
- Central Nervous System Cancers
- Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma
- Chronic Myelogenous Leukemia
- Colon Cancer
- Hairy Cell Leukemia
- Melanoma
- Myelodysplastic Syndrome
- Non-Small Cell Lung Cancer
- Ovarian Cancer
- Primary Cutaneous B-cell Lymphomas
- Rectal Cancer
- Soft Tissue Sarcoma

PROPRIETARY

Guidelines developed by, and used with permission from, Informed Medical Decisions, Inc. © 2019 Informed Medical Decisions, Inc. All Rights Reserved.

- T-Cell Lymphomas
- Lung Cancer
- Uveal Melanoma
- Waldenstrom Macroglobulinemia/Lymphoplasmacytic Lymphoma

See more specific criteria below for:

- NTRK Fusion Testing
- Myeloproliferative neoplasms
- Breast Cancer
- Cancer of Unknown Primary/Occult Neoplasm
- Pancreatic Cancer
- Prostate Cancer
- Thyroid Cancer and Indeterminate Thyroid Nodules
- Colorectal Cancer Screening

## Targeted Molecular Testing for NTRK Fusions

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

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

## Polycythemia Vera

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

- Genetic testing impacts medical management

PROPRIETARY

Guidelines developed by, and used with permission from, Informed Medical Decisions, Inc. © 2019 Informed Medical Decisions, Inc. All Rights Reserved.

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

## Essential Thrombocythemia or Thrombocytosis

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

- Genetic testing impacts medical management
- Platelet count ≥450 x 10^9/L

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

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

## Primary Myelofibrosis

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

- Genetic testing impacts medical management
- Suspicion for PMF or pre-PMF exists based on 2016 WHO diagnostic criteria

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

- Genetic testing impacts medical management
- Presence of megakaryocytic proliferation and atypia, accompanied by either reticulin and/or collagen fibrosis grades 2 or 3 OR megakaryocytic proliferation and atypia, without reticulin fibrosis > grade 1, accompanied by increased age-adjusted bone marrow cellularity, granulocytic proliferation, and often decreased erythropoiesis
- JAK2, CALR and MPL mutation analysis was previously completed and was negative

## Breast Cancer

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

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

- Breast tumor is anatomic stage 1 or stage 2

PROPRIETARY

Guidelines developed by, and used with permission from, Informed Medical Decisions, Inc. © 2019 Informed Medical Decisions, Inc. All Rights Reserved.

- Histologic type is ductal, lobular, mixed (ductal/lobular), or metaplastic
- Tumor size 0.6-1.0 cm and intermediate or high grade (Grade 2 or 3) OR tumor size 1.1-5.0 cm, any grade
- Axillary-node status is negative or any axillary-node micro metastasis is no greater than 2.0 millimeters
- There is no evidence of distant metastatic breast cancer
- Breast tumor is estrogen and/or progesterone receptor-positive
- Breast tumor is HER2 receptor-negative
- Patient is a candidate for chemotherapy (i.e, chemotherapy not precluded due to other factors)
- Adjuvant chemotherapy is being considered and this testing is being ordered to assess recurrence risk to guide decision making as to whether or not adjuvant chemotherapy will be utilized
- No other breast GEC has been performed on this tumor sample

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

- Breast tumor is anatomic stage 1 or stage 2
- Histologic type is ductal, lobular, mixed (ductal/lobular), or metaplastic
- Tumor size 0.6-1.0 cm and intermediate or high grade (Grade 2 or 3) OR tumor size 1.1-5.0 cm, any grade
- Axillary-node status is negative or any axillary-node micrometastasis is no greater than 2.0 millimeters
- There is no evidence of distant metastatic breast cancer
- Breast tumor is estrogen or progesterone receptor-positive
- Breast tumor is HER2 receptor-negative
- Patient is postmenopausal
- Patient is a candidate for chemotherapy (i.e, chemotherapy not precluded due to other factors)
- Adjuvant chemotherapy is being considered and this testing is being ordered to assess recurrence risk to guide decision making as to whether or not adjuvant chemotherapy will be utilized
- No other breast GEC has been performed on this tumor sample

PROPRIETARY

Guidelines developed by, and used with permission from, Informed Medical Decisions, Inc. © 2019 Informed Medical Decisions, Inc. All Rights Reserved.

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

- Breast tumor is anatomic stage 1 or stage 2
- Histologic type is ductal, lobular, mixed (ductal/lobular), or metaplastic
- Node negative or 1-3 positive node breast cancer
- Breast tumor is estrogen receptor positive and/or progesterone receptor positive
- Breast tumor is HER2-negative
- Patient is at high clinical risk for recurrence based on the MINDACT categorization
- Patient is a candidate for chemotherapy (i.e, chemotherapy not precluded due to other factors)
- Adjuvant chemotherapy is being considered and this testing is being ordered to assess recurrence risk to guide decision making as to whether or not adjuvant chemotherapy will be utilized
- No other breast GEC has been performed on this tumor sample

## Cancer of Unknown Primary/Occult Neoplasm

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

## Pancreatic Cancer

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

## Prostate Cancer

### *Screening*

Prostate cancer early detection assays (i.e. PCA3, ConfirmMDx®) are medically necessary as outlined in the criteria in the NCCN® Clinical Practice Guidelines in Oncology (NCCN Guidelines®), Prostate Cancer Early Detection.

### *Confirmed Malignancy*

Genetic testing, including single-gene, gene expression or molecular profiling assays for confirmed prostate tumors are not medically necessary.

## Thyroid Cancer

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

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

PROPRIETARY

Guidelines developed by, and used with permission from, Informed Medical Decisions, Inc. © 2019 Informed Medical Decisions, Inc. All Rights Reserved.

*Cytologically Indeterminate Thyroid Nodule*

Afirma® Genomic Sequencing Classifier is medically necessary for surgical candidates with FNA Bethesda category III results (AUS/FLUS) to help guide surgical decision making.

Targeted mutation analysis panels that include BRAF, RAS, RET/PTC, and PAX8/PPARc, ThyGeNEXT®/ThyraMIR™, and ThyroSeq® 3.0 are medically necessary for surgical candidates with FNA Bethesda III and IV results (AUS/FLUS and FN/SFN) to help guide surgical decision making.

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

### Colorectal Cancer Screening

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

# CPT Codes

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

Covered when medical necessity criteria are met:

81162 BRCA1 (BRCA1, DNA repair associated), BRCA2 (BRCA2, DNA repair associated) (eg, hereditary breast and ovarian cancer) gene analysis; full sequence analysis and full duplication/deletion analysis (ie, detection of large gene rearrangements)

81170 ABL1 (ABL proto-oncogene 1, non-receptor tyrosine kinase) (eg, acquired imatinib tyrosine kinase inhibitor resistance), gene analysis, variants in the kinase domain

81175 ASXL1 (additional sex combs like 1, transcriptional regulator) (eg, myelodysplastic syndrome, myeloproliferative neoplasms, chronic myelomonocytic leukemia), gene analysis; full gene sequence

81176 ASXL1 (additional sex combs like 1, transcriptional regulator) (eg, myelodysplastic syndrome, myeloproliferative neoplasms, chronic myelomonocytic leukemia), gene analysis; targeted sequence analysis (eg, exon 12)

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

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

81219 CALR (calreticulin) (eg, myeloproliferative disorders), gene analysis, common variants in exon 9

PROPRIETARY

Guidelines developed by, and used with permission from, Informed Medical Decisions, Inc. © 2019 Informed Medical Decisions, Inc. All Rights Reserved.

| | |
|---|---|
| 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) |

PROPRIETARY

Guidelines developed by, and used with permission from, Informed Medical Decisions, Inc. © 2019 Informed Medical Decisions, Inc. All Rights Reserved.

| | |
|---|---|
| 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 |
| 81310 | NPM1 (nucleophosmin) (eg, acute myeloid leukemia) gene analysis, exon 12 variants |
| 81311 | NRAS (neuroblastoma RAS viral [v-ras] oncogene homolog) (eg, colorectal carcinoma), gene analysis, variants in exon 2 (eg, codons 12 and 13) and exon 3 (eg, codon 61) |
| 81313 | PCA3/KLK3 (prostate cancer antigen 3 [non-protein coding]/kallikrein-related peptidase 3 [prostate specific antigen]) ratio (eg, prostate cancer) |
| 81314 | PDGFRA (platelet-derived growth factor receptor, alpha polypeptide) (eg, gastrointestinal stromal tumor [GIST]), gene analysis, targeted sequence analysis (eg, exons 12, 18) |
| 81315 | PML/RARalpha, (t(15;17)), (promyelocytic leukemia/retinoic acid receptor alpha) (eg, promyelocytic leukemia) translocation analysis; common breakpoints (eg, intron 3 and intron 6), qualitative or quantitative |
| 81316 | PML/RARalpha, (t(15;17)), (promyelocytic leukemia/retinoic acid receptor alpha) (eg, promyelocytic leukemia) translocation analysis; single breakpoint (eg, intron 3, intron 6 or exon 6), qualitative or quantitative |
| 81320 | PLCG2 (phospholipase C gamma 2) (eg, chronic lymphocytic leukemia) gene analysis, common variants (eg, R665W, S707F, L845F) |
| 81340 | TRB@ (T cell antigen receptor, beta) (eg, leukemia and lymphoma), gene rearrangement analysis to detect abnormal clonal population(s); using amplification methodology (eg, polymerase chain reaction) |
| 81341 | TRB@ (T cell antigen receptor, beta) (eg, leukemia and lymphoma), gene rearrangement analysis to detect abnormal clonal population(s); using direct probe methodology (eg, Southern blot) |
| 81342 | TRG@ (T cell antigen receptor, gamma) (eg, leukemia and lymphoma), gene rearrangement analysis, evaluation to detect abnormal clonal population(s) |
| 81345 | TERT (telomerase reverse transcriptase) (eg, thyroid carcinoma, glioblastoma multiforme) gene analysis, targeted sequence analysis (eg, promoter region) |

PROPRIETARY

Guidelines developed by, and used with permission from, Informed Medical Decisions, Inc. © 2019 Informed Medical Decisions, Inc. All Rights Reserved.

| | |
|---|---|
| 81445 | Targeted genomic sequence analysis panel, solid organ neoplasm, DNA analysis, and RNA analysis when performed, 5-50 genes (eg, ALK, BRAF, CDKN2A, EGFR, ERBB2, KIT, KRAS, NRAS, MET, PDGFRA, PDGFRB, PGR, PIK3CA, PTEN, RET), interrogation for sequence variant |
| 81450 | Targeted genomic sequence analysis panel, hematolymphoid neoplasm or disorder, DNA and RNA analysis when performed, 5-50 genes (eg, BRAF, CEBPA, DNMT3A, EZH2, FLT3, IDH1, IDH2, JAK2, KRAS, KIT, MLL, NRAS, NPM1, NOTCH1), interrogation for sequence variants, and copy number variants or rearrangements, or isoform expression or mRNA expression levels, if performed |
| 81519 | Oncology (breast), mRNA, gene expression profiling by real-time RT-PCR of 21 genes, utilizing formalin-fixed paraffin embedded tissue, algorithm reported as recurrence score |
| 81520 | Oncology (breast), mRNA gene expression profiling by hybrid capture of 58 genes (50 content and 8 housekeeping), utilizing formalin-fixed paraffin-embedded tissue, algorithm reported as a recurrence risk score |
| 81521 | Oncology (breast), mRNA, microarray gene expression profiling of 70 content genes and 465 housekeeping genes, utilizing fresh frozen or formalin-fixed paraffin-embedded tissue, algorithm reported as index related to risk of distant metastasis |
| 81528 | Oncology (colorectal) screening, quantitative real-time target and signal amplification of 10 DNA markers (KRAS mutations, promoter methylation of NDRG4 and BMP3) and fecal hemoglobin, utilizing stool, algorithm reported as a positive or negative result |
| 81545 | Oncology (thyroid), gene expression analysis of 142 genes, utilizing fine needle aspirate, algorithm reported as a categorical result (eg, benign or suspicious) |
| 81551 | Oncology (prostate), promoter methylation profiling by real-time PCR of 3 genes (GSTP1, APC, RASSF1), utilizing formalin-fixed paraffin-embedded tissue, algorithm reported as a likelihood of prostate cancer detection on repeat biopsy |
| 0018U | Oncology (thyroid), microRNA profiling by RT-PCR of 10 microRNA sequences, utilizing fine needle aspirate, algorithm reported as a positive or negative result for moderate to high risk of malignancy |
| 0022U | Targeted genomic sequence analysis panel, non-small cell lung neoplasia, DNA and RNA analysis, 23 genes, interrogation for sequence variants and rearrangements, reported as presence/absence of variants and associated therapy(ies) to consider |
| 0023U | Oncology (acute myelogenous leukemia), DNA, genotyping of internal tandem duplication, p.D835, p.I836, using mononuclear cells, reported as detection or nondetection of FLT3 mutation and indication for or against the use of midostaurin |

PROPRIETARY

Guidelines developed by, and used with permission from, Informed Medical Decisions, Inc. © 2019 Informed Medical Decisions, Inc. All Rights Reserved.

0026U Oncology (thyroid), DNA and mRNA of 112 genes, next-generation sequencing, fine needle aspirate of thyroid nodule, algorithmic analysis reported as a categorical result ("Positive, high probability of malignancy" or "Negative, low probability of malignancy")

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

0081U Oncology (uveal melanoma), mRNA, gene expression profiling by real-time RT-PCR of 15 genes (12 content and 3 housekeeping genes), utilizing fine needle aspirate or formalin-fixed paraffin embedded tissue, algorithm reported as risk of metastasis

Codes that do not meet medical necessity criteria:

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

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

81504 Oncology (tissue of origin), microarray gene expression profiling of > 2,000 genes, utilizing formalin-fixed paraffin-embedded tissue, algorithm reported as tissue similarity scores

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

81525 Oncology (colon), mRNA, gene expression profiling by real-time RT-PCR of 12 genes (7 content and 5 housekeeping), utilizing formalin-fixed paraffin-embedded tissue, algorithm reported as a recurrence score

81540 Oncology (tumor of unknown origin), mRNA, gene expression profiling by real-time RT-PCR of 92 genes (87 content and 5 housekeeping) to classify tumor into main cancer type and subtype, utilizing formalin-fixed paraffin-embedded tissue, algorithm reported

81541 Oncology (prostate), mRNA gene expression profiling by real-time RT-PCR of 46 genes (31 content and 15 housekeeping), utilizing formalin-fixed paraffin-embedded tissue, algorithm reported as a disease-specific mortality risk score

0011M Oncology, prostate cancer, mRNA expression assay of 12 genes (10 content and 2 housekeeping), RT-PCR test utilizing blood plasma and urine, algorithms to predict high-grade prostate cancer risk

PROPRIETARY

Guidelines developed by, and used with permission from, Informed Medical Decisions, Inc. © 2019 Informed Medical Decisions, Inc. All Rights Reserved.

| | |
|---|---|
| 0037U | Targeted genomic sequence analysis, solid organ neoplasm, DNA analysis of 324 genes, interrogation for sequence variants, gene copy number amplifications, gene rearrangements, microsatellite instability and tumor mutational burden |
| 0045U | Oncology (breast ductal carcinoma in situ), mRNA, gene expression profiling by realtime RT-PCR of 12 genes (7 content and 5 housekeeping), utilizing formalin-fixed paraffin-embedded tissue, algorithm reported as recurrence score |
| 0046U | FLT3 (fms-related tyrosine kinase 3) (eg, acute myeloid leukemia) internal tandem duplication (ITD) variants, quantitative |
| 0047U | Oncology (prostate), mRNA, gene expression profiling by real-time RT-PCR of 17 genes (12 content and 5 housekeeping), utilizing formalin-fixed paraffin-embedded tissue, algorithm reported as a risk score |
| 0048U | Oncology (solid organ neoplasia), DNA, targeted sequencing of protein-coding exons of 468 cancer-associated genes, including interrogation for somatic mutations and microsatellite instability, matched with normal specimens, utilizing formalin-fixed paraffin-embedded tumor tissue, report of clinically significant mutation(s) |
| 0049U | NPM1 (nucleophosmin) (eg, acute myeloid leukemia) gene analysis, quantitative |
| 0050U | Targeted genomic sequence analysis panel, acute myelogenous leukemia, DNA analysis, 194 genes, interrogation for sequence variants, copy number variants or rearrangements |
| 0056U | Hematology (acute myelogenous leukemia), DNA, whole genome nextgeneration sequencing to detect gene rearrangement(s), blood or bone marrow, report of specific gene rearrangement(s) |
| 0057U | Oncology (solid organ neoplasia), mRNA, gene expression profiling by massively parallel sequencing for analysis of 51 genes, utilizing formalin-fixed paraffin-embedded tissue, algorithm reported as a normalized percentile rank |
| 0069U | Oncology (colorectal), microRNA, RT-PCR expression profiling of miR-31-3p, formalin-fixed paraffin-embedded tissue, algorithm reported as an expression score |
| 0089U | Oncology (melanoma), gene expression profiling by RTqPCR, PRAME and LINC00518, superficial collection using adhesive patch(es) |
| 0090U | Oncology (cutaneous melanoma), mRNA gene expression profiling by RT-PCR of 23 genes (14 content and 9 housekeeping), utilizing formalin-fixed paraffin-embedded tissue, algorithm reported as a categorical result (ie, benign, indeterminate, malignant) |
| ANY | Guardant360® for any indication (Guardant Health, Inc.) |

PROPRIETARY

Guidelines developed by, and used with permission from, Informed Medical Decisions, Inc. © 2019 Informed Medical Decisions, Inc. All Rights Reserved.

# Background

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

## Myeloproliferative Disorders

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

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

### *Polycythemia Vera*

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

### *Essential Thrombocythemia or Thrombocytosis*

Essential thrombocythemia is a disorder of sustained increased platelet count, characterized by persistently elevated platelet count greater than 450,000/μL; megakaryocytic hyperplasia (seen in bone marrow); not meeting WHO criteria for CML, PV, PMF, MDS or other myeloid neoplasm; and the

PROPRIETARY

Guidelines developed by, and used with permission from, Informed Medical Decisions, Inc. © 2019 Informed Medical Decisions, Inc. All Rights Reserved.

demonstration of JAK2 V617F or other clonal marker or no evidence of reactive thrombocytosis. In addition, patients can have splenomegaly and a clinical course complicated by thrombotic or hemorrhagic episodes (or both). The majority of ET patients (60%) carry a somatic JAK2 V617F mutation, while a smaller percentage (5-10%) have activating MPL mutations. Proposed criteria additionally state that 70% of patients without a JAK2 or MPL mutation carry a somatic mutation of the calreticulin (CALR) gene. Among confirmed ET cases, mutations in CALR are more common than MPL. Positive CALR mutation status may suggest a more indolent course (Klampfl et al. 2013). It is important to note that JAK2/CALR/MPL mutation screening, by itself, cannot distinguish masked PV from JAK2-mutated ET, WHO-defined ET from prefibrotic/early PMF or triple-negative ET from other causes of thrombocytosis (Barbui et al. 2015).

### *Primary Myelofibrosis*

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

Demonstration of a clonal marker is important for diagnosis. Somatic molecular markers in PMF patients are similar to those in patients with ET, and include JAK2 V617F, MPL, and CALR. Somatic mutations in JAK2 are identified in 55-65% of PMF cases, and MPL mutations in 10%. Mutations in CALR are less common than JAK2, but more common than MPL. When all of these are absent, testing for additional markers, such as ASXL1, EZH2, TET2, IDH1/IDH2, SRSF2 and SF3B1 can be considered. Many of these additional markers have prognostic significance for survival and progression to leukemia as well (NCCN® v.2.2019; Tefferi 2016). Identification of a clonal marker is one of the required major criteria in the diagnosis of PMF (NCCN® v.2.2019).

## Solid Tumor Testing

### *NTRK Fusion Testing*

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

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

### *Breast Cancer*

While NGS panels are not currently recommended for use to guide chemotherapeutic treatment decisions, molecular testing may be used to predict prognosis and recurrence risk for breast cancer. The strongest prognostic factors to predict future recurrence or death from breast cancer include

PROPRIETARY

Guidelines developed by, and used with permission from, Informed Medical Decisions, Inc. © 2019 Informed Medical Decisions, Inc. All Rights Reserved.

patient age, comorbidity, tumor size, tumor grade, number of involved axillary lymph nodes, and HER2 tumor status (NCCN® v.2.2019).

Breast cancer gene expression profiling refers to testing performed on breast cancer tumor tissue to identify expression levels of sets of genes that, taken together, may predict recurrence risk and/or treatment response. The National Comprehensive Cancer Network® incorporates the Oncotype Dx® Breast 21-gene assay into the treatment determination algorithm for individuals with invasive breast cancer with subtypes including ductal, lobular, mixed, and metaplastic, with no lymph node involvement or minimal lymph node involvement with micrometastasis of 2 mm or less, whose tumor is >0.5 cm (NCCN® v.2.2019). These guidelines specifically note the limitation of other multi-gene or multi-gene expression assay systems as not yet sufficiently validated to predict response to chemotherapy.

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

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

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

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

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

PROPRIETARY

Guidelines developed by, and used with permission from, Informed Medical Decisions, Inc. © 2019 Informed Medical Decisions, Inc. All Rights Reserved.

evidence-based recommendation with intermediate quality evidence, and a moderate strength of recommendation

ASCO published a special addendum (Krop et al. 2017) regarding use of MammaPrint® for women with hormone receptor- positive, HER2-negative, node negative and node positive tumors based on preliminary MINDACT data (Cardoso et al. 2016). The prior recommendation for this group [women with HR+, HER2- (node positive or node-negative) breast cancer] was that the clinician should not use MammaPrint® to guide decisions on adjuvant systemic chemotherapy. The recent updated guideline separates this group into 3 categories and recommendations:

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

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

Given the relatively lower quality evidence and moderate strength recommendation from ASCO provided for Breast Cancer Index®, this test has not yet been adequately validated for clinical use.

### *Lung Cancer*

Epidermal growth factor receptor (EGFR) mutation status has been shown to be significantly associated with tumor response to EGFR tyrosine kinase inhibitors (Lynch et al. 2004; Mok et al. 2009). This has led to the routine assessment of the presence of EGFR mutations in advanced non-small cell lung cancers (NSCLC), particularly adenocarcinomas (Keedy et al. 2011; Salto-Tellez et al. 2011). Anaplastic lymphoma kinase (ALK) gene rearrangements have been identified in a subset of patients with NSCLC

PROPRIETARY

Guidelines developed by, and used with permission from, Informed Medical Decisions, Inc. © 2019 Informed Medical Decisions, Inc. All Rights Reserved.

and represent a unique subset of patients for whom ALK inhibitors may be a very effective treatment strategy. According to NCCN® Clinical Practice Guidelines in Oncology, (NCCN Guidelines®), NSCLC (particularly adenocarcinoma), EGFR and ALK testing of tumor tissue is considered the standard of care (Ettinger et al. 2014). ROS1 gene rearrangement testing is also recommended by the most recent NCCN Guidelines® update based on data showing efficacy of treatment with crizotinib in patients with ROS1 rearrangements and recent FDA approval (NCCN® v.5.2019). PD-L1 testing is recommended as expression levels of 50% or greater are a positive test result indicating appropriateness of first-line pembrolizumab therapy (NCCN® v.5.2019). The updated ASCO Guidelines (Hanna et al. 2017) recommend that pembrolizumab be used alone as first-line treatment in patients with high PD-L1 expression in non-squamous cell carcinoma or squamous cell carcinoma (without positive markers, e.g. EGFR/ALK/ROS1). Those with low PD-L1 expression should be offered standard chemotherapy.

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

In addition, current NCCN Guidelines® recommend testing for these and other gene alterations utilizing next-generation sequencing (NGS), a technology that can detect specific mutations and gene rearrangements. The other genetic alterations more recently found to be associated with NSCLC and for which targeted therapies have been developed include: HER2 (ERBB2) mutations, BRAF mutations, RET gene rearrangements, and MET amplification. As targeted agents are available for patients with NSCLC who have these genetic alterations, the NCCN® Guidelines Panel, NSCLC recommend testing for these specific genetic alterations using NGS to ensure that patients with NSCLC receive the most appropriate treatment. The NCCN® Guidelines Panel, NSCLC also endorse broader molecular profiling (also known as precision medicine) to identify rare driver mutations in other genes with the goal of identifying patients who may be eligible for clinical trials (NCCN® v.5.2019).

While there has been some success in broad molecular profiling and targeted therapies for NSCLC, there is a lack of evidence to support tumor testing for patients diagnosed with small cell lung cancer (SCLC) (NCCN® v.1.2019). To date, there have been limited advances in the treatment of SCLC and there are specific challenges in performing genomic analysis on SCLC tumors compared to NSCLC tumors. Genomic profiling is currently being evaluated as an option, but more research is needed to demonstrate its effectiveness in this population (Umemura et al. 2015). Additionally, recent NCCN Guidelines® for SCLC do not give any recommendations to support the use of molecular profiling to aid in the treatment of SCLC.

### *Cell-Free Tumor Testing*

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

There has been growing interest and research into alternative methodologies for assessing tumor mutation status, including cell-free plasma based tests. Primary and metastatic tumors shed circulating tumor cells (CTCs) into the bloodstream. These remain at very low concentration in the plasma and are difficult to detect. CTCs release DNA through various mechanisms. This cell-free tumor DNA (ctDNA) is easier to isolate and, with the increasing capabilities of next-generation sequencing, offers an alternate opportunity to assess somatic tumor-specific mutations. While several studies have

PROPRIETARY

Guidelines developed by, and used with permission from, Informed Medical Decisions, Inc. © 2019 Informed Medical Decisions, Inc. All Rights Reserved.

shown that ctDNA is not as sensitive or specific as direct tumor testing (Janku et al. 2016; Zhang et al. 2016), there are potential applications where ctDNA testing might be indicated (e.g., when a biopsy sample is insufficient, when repeat biopsy is overly risky, or when chemotherapy response has changed and there is a concern for intra- or inter-tumor heterogeneity). It has also been proposed that ctDNA may improve minimal residual disease monitoring (Levy et al. 2016). Cell-free tumor DNA analysis is an active area of ongoing research; however, few ctDNA tests have been clinically validated.

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

### *Cancer of Unknown Primary/Occult Neoplasm*

Occult neoplasms, or cancers of unknown primary, are defined as histologically proven metastatic malignant tumors whose primary site cannot be identified during pretreatment evaluation. These may have a wide clinical presentation and typically a poor prognosis. Several laboratories offer gene expression profiling or NGS tests to aid in the identification of the tissue of origin of a metastatic tumor. NCCN® Clinical Practice Guidelines in Oncology (NCCN Guidelines®), Occult Primary Cancer (v.2.2019) state that the literature evaluating molecular testing in the diagnosis and management of occult primaries has focused much more on establishing the tissue of origin rather than establishing whether such identification leads to better outcomes for patients. Although these results may have diagnostic benefit, there is limited evidence for clinical utility at this time. The NCCN® Guidelines panel does not recommend molecular profiling for the identification of tissue of origin as standard management in the diagnostic workup of patients with occult primary tumors (category 3).

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

### *Pancreatic Cancer*

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

PROPRIETARY

Guidelines developed by, and used with permission from, Informed Medical Decisions, Inc. © 2019 Informed Medical Decisions, Inc. All Rights Reserved.

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

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

Testing for hereditary gene mutations may also have utility for patients with pancreatic cancer. Literature suggests that patients with specific hereditary predispositions to pancreatic cancer may be sensitive to a platinum agent when combined with another chemotherapy (e.g. Gemcitabine with Cisplatin) (Ferrone 2009; Golan 2014), though data regarding patient survival is conflicting (NCCN® v3.2019). Poly(ADP-ribose) polymerases (PARP) inhibitors are another class of chemotherapeutic drugs that have shown promise in treating cancers caused by defective DNA repair pathways. Several PARP inhibitors have FDA-approval for use in patients with ovarian or breast cancer who have an inherited BRCA1 or BRCA2 mutation. Early research has suggested a similar clinical benefit with this class of drugs in the treatment of pancreatic adenocarcinoma in patients with germline BRCA1 and BRCA2 mutations, and further clinical trials are underway (Shroff et al. 2018). Germline testing for BRCA1 and BRCA2 mutations is appropriate for individuals with pancreatic cancer regardless of their treatment pathway, given the additional cancer risks and screening recommendations that are standard of care for individuals and their family members with these gene mutations (NCCN® v3.2019).

### *Prostate Cancer*

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

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

The NCCN® Clinical Practice Guidelines in Oncolgoy (NCCN Guidelines®), Prostate Cancer (v.2.2019) note that men with clinically localized disease may consider the use of tumor-based molecular assays



Guidelines developed by, and used with permission from, Informed Medical Decisions, Inc. © 2019 Informed Medical Decisions, Inc. All Rights Reserved.

as retrospective studies have shown that molecular assays performed on biopsy or prostatectomy specimens provide prognostic information independent of NCCN® risk groups such as likelihood of death with conservative management, likelihood of biochemical progression after radical prostatectomy or external beam therapy, and likelihood of developing metastasis after radical prostatectomy or salvage radiotherapy. Naryan et al. (2017), performed an evidence-based review for biomarker assays used for prostate cancer. The group reviewed Prolaris® and Oncotype DX® Prostate and commented that although these tests have been incorporated into NCCN Guidelines® and may be beneficial for men with low-volume Gleason 6 disease on biopsy, these tests have not been thoroughly studied in minority populations, and it is unclear how initial test results may change with repeat assessments. They recommend that these tests should be used with discretion as they add to the cost of prostate cancer care and that providers should discuss the indications and limitations thoroughly with their patients (Narayan et al. 2017). Similarly, Lamy et al. (2017) performed a systematic review of prostate cancer biomarkers and conclude the Prostate Health Index and the 4K score have the highest level of evidence in predicting which cancers may be more aggressive. They also note that other assays, including OncotypeDx® Prostate, Prolaris®, and Decipher®, are promising but need further evidence to confirm their clinical validity.

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

*Thyroid Cancer*

Per NCCN® Clinical Practice Guidelines in Oncology (NCCN Guidelines®), Thyroid Carcinoma (v.1.2019), BRAF V600E testing is indicated for patients with confirmed or highly suspected thyroid cancer (FTC, follicular thyroid carcinoma; MTC, medullary thyroid carcinoma; PTC, papillary thyroid carcinoma; or patients with metastatic differentiated thyroid carcinoma). Testing can aid in medication selection and/or surgical decisions. Aggressive BRAF-positive papillary carcinomas have been found to be associated with the overexpression of the microRNA known as miR-146b. Currently, miRs are considered independent of BRAF mutational status and may be used to assist in risk stratification for BRAF-positive cases (Ludvíková et al. 2016). RNA classifiers are not yet considered standard of care in evaluating the BRAF V600E somatic variant.

Molecular diagnostic testing to detect individual mutations (e.g., BRAF, RET/PTC, RAS, PAX8/PPAR) has been proven in the evaluation of fine needle aspiration (FNA) samples that are indeterminate to assist in management decisions; however, large scale, prospective studies have not been performed which demonstrate the clinical utility of such testing in patients with confirmed thyroid cancer. Further studies on the clinical utility of these tests are needed in individuals who have already been diagnosed with thyroid malignancy (NCCN® v.1.2019).

Medullary thyroid cancer (MTC) is an aggressive form of thyroid cancer that is often not definitively identified by cytology alone. About 40% of patients with MTC do not undergo central neck dissection (the recommended treatment for MTC). Molecular assays have been suggested to assist with the

PROPRIETARY

Guidelines developed by, and used with permission from, Informed Medical Decisions, Inc. © 2019 Informed Medical Decisions, Inc. All Rights Reserved.

diagnosis of medullary thyroid carcinoma and/or aid in management. There are insufficient data at this time to support the use of genomic classifiers for this cohort (Kloos et al. 2013).

## Cancer Screening

### *Indeterminate Thyroid Nodules*

Cytological examination of FNA samples is currently the standard of care for classifying thyroid nodules as malignant or benign; however, approximately 25% of samples are classified as indeterminate. There is growing evidence that molecular diagnostic testing can be useful in the reclassification of these indeterminate lesions. The NCCN® Clinical Practice Guidelines in Oncology (NCCN Guidelines®), Thyroid Carcinoma (v.1.2019) states that molecular diagnostic testing to detect individual mutations (e.g., BRAF, RET/PTC, RAS, PAX8/PPAR) or pattern recognition using molecular classifiers may be useful in evaluation of FNA samples that are indeterminate to assist in management directions. Indeterminate cytology results are defined as FNA results that are suspicious for 1) follicular neoplasms, 2) atypia of undetermined significance/follicular lesion of undetermined significance (AUS/FLUS). Molecular diagnostics may not preform well for Hurthle cell neoplasms (NCCN® v.1.2019).

The American Thyroid Association (ATA) issued a statement regarding the surgical application of molecular profiling for thyroid nodules (Ferris et al. 2015). This statement highlights a 7-gene molecular panel including BRAF V600E, three isoforms of RAS point mutations, and translocations within PAX8/PPARy and RET/PTC genes as having been clinically validated to predict the presence of differentiated thyroid cancer with 86-94% specificity and 87-100% PPV. This test is noted to have been performed on over 1,500 indeterminate cytology specimens and correlated with histologic results to generate a real-time algorithm for management of thyroid nodules with the ultimate goal of appropriate initial oncologic total thyroidectomy rather than lobectomy with subsequent completion thyroidectomy when total thyroidectomy is indicated. This 7-gene molecular testing panel has been demonstrated to add to the specificity of indeterminate FNA cytology and successfully refine the initial operative management of thyroid nodules and thyroid cancer. The ATA report goes on to highlight a large prospective single-center study of this 7-gene molecular test noting overall, "for thyroid lesions of indeterminate cytology, the detection of any mutation translated into a malignancy risk for AUS/FLUS, FN, and SMC of 88%, 87%, and 95% respectively, compared to 6%, 14%, and 28% in mutation-negative lesions," where AUS/FLUS refers to atypia of uncertain significance/follicular lesion of undetermined significance, FN refers to follicular neoplasm, and SMC refers to suspicious for malignant cells.

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

PROPRIETARY

Guidelines developed by, and used with permission from, Informed Medical Decisions, Inc. © 2019 Informed Medical Decisions, Inc. All Rights Reserved.

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

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

Results from The Role of NGS-based ThyroSeq® Panel in Cancer Diagnosis in Thyroid Nodules (NCT02352766) have recently been published (Steward et al. 2018). This is a prospective, double-blind, comparison of the outcomes of ITNs between pathology and molecular studies using ThyroSeq® 3.0. Overall, ThyroSeq® 3.0 demonstrated an NPV of 97-98% (93-99% CI;89-100% CI) and a PPV of 64-68% (50-77% CI; 54-80%) when considering Bethesda III and IV nodules. The main goal of testing, as stated by Steward et al. (2018), was to correctly identify benign nodules to avoid the need for surgery. In this light, it is important to remember that the long term clinical utility in this regard is not established. Still unknown is the risk for progression and cancer development for those with ITNs determined to be at low risk for malignancy who choose active surveillance.

### *Colorectal Cancer Screening*

Colorectal cancer is the fourth most common cancer type diagnosed in the United States (NCCN® Clinical Practice Guidelines in Oncology (NCCN Guidelines®), Colorectal Cancer Screening (v.1.2019). Best practice guidelines are available from multiple professional organizations (e.g. NCCN®, American Cancer Society, ACOG, USPSTF, etc.) detailing recommendations for standard frequency and starting age for screening based on risk category. Underutilization of screening colonoscopy has led to the study and inclusion of stool-based testing methods in professional guidelines as well as prompting the study of plasma-based screening techniques. Screening modalities other than standard colonoscopy have been recognized by professional organizations as reasonable for individuals unable or unwilling to undergo this procedure; however, benefits and limitations of each screening method must be considered given the sensitivity for detection of not only colorectal cancer, but also polyps.

General concerns raised surrounding colorectal cancer screening via stool DNA testing and/or cell free DNA (cfDNA) testing include potential population uptake bias with those individuals with more significant comorbidities (and potentially lower or no mortality gain from screening) more likely to use these screening methods. Conversely, low-risk individuals who are considered candidates for screening colonoscopy may opt for these alternate screening options and cancers may be missed due to lower

PROPRIETARY

Guidelines developed by, and used with permission from, Informed Medical Decisions, Inc. © 2019 Informed Medical Decisions, Inc. All Rights Reserved.

sensitivities (Parikh and Prasad 2016). The 2016 USPSTF final recommendations focus not on the level of evidence supporting each individual screening modality or which method should be used, but rather on the likelihood of screening utilization and the need for shared decision making in the selection of screening type.

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

Stool DNA Testing is a method of colorectal cancer screening in which stool is evaluated for specific somatic mutations known to frequently be a part of the carcinogenesis of colorectal cancer. Some stool DNA testing has gained FDA approval and has been demonstrated to have higher sensitivity over FIT for colorectal cancer and certain types of polyps. DNA-based stool testing has been incorporated into the most recent NCCN Guidelines® update and is recommended for screening average-risk individuals. However, the NCCN® discussion section notes that there are limited data about how stool DNA testing may fit into an overall screening program and how long the interval should be between screening. The NCCN® currently recommends that stool DNA testing as a primary screening modality should be individualized, particularly in high-risk individuals (NCCN® Colorectal Cancer Screening v.1.2019). The USPSTF 2016 recommendations include FIT-DNA combination testing (FIT in addition to stool-based DNA testing) with noted limitations including insufficient evidence about appropriate longitudinal follow-up of abnormal findings after a negative diagnostic colonoscopy, in addition to potential overly intensive surveillance due to concerns from the genomic component of testing.

Circulating Tumor Marker screening is a method of cell free DNA (cfDNA) testing of plasma to identify potential tumor markers sloughed off into circulating plasma cells in order to identify colorectal cancer. The primary marker studied to date includes methylation of the SEPT9 gene (mSEPT9). Prospective evaluation of adults >50 years of age via mSEPT9 in circulating plasma was performed via the PRESEPT study concurrent to screening colonoscopy, including subjects in the US and Germany. Fifty-three cases of colorectal cancer and approximately 1,500 controls were evaluated. Sensitivity of mSEPT9 for detection of colorectal cancer varied by stage: Stage I (35.0%), Stage II (63.0%), Stage III (46.0%), Stage IV (77.4%). Specificity was 91.5% for colorectal cancer, but only 11.2% for advanced adenomas. This clinical trial data published by Church et al. (2014) noted the need for improved sensitivity for early cancers and advanced adenomas for use in general population colorectal cancer screening. Other case-control study designs have demonstrated higher sensitivities for colorectal cancer ranging from 67-96% (Heichman 2014). The USPSTF 2016 recommendations include mSEPT9 as an optional screening modality. Within this publication's table for the Characteristics of Colorectal Cancer Screening Strategies, a footnote states the following: "Although a serology test to detect methylated SEPT9 DNA was included in the systematic evidence review, this screening method currently has limited evidence evaluating its use (a single published test characteristic study met inclusion criteria, which found it had a sensitivity to detect colorectal cancer of <50%). It is therefore not included in this table." The NCCN® now includes a footnote documenting FDA approval of circulating methylated SEPT9 DNA as an option for screening for those who refuse other screening modalities but stop short of a recommendation of this testing as its ability to detect CRC and advanced

PROPRIETARY

Guidelines developed by, and used with permission from, Informed Medical Decisions, Inc. © 2019 Informed Medical Decisions, Inc. All Rights Reserved.

adenocarcinoma is inferior to other recommended screening modalities (NCCN® Colorectal Cancer Screening v1.2019).

# Professional Society Guidelines

Arber DA, Orazi A, Hasserjian R et al. The 2016 revision to the World Health Organization classification of myeloid neoplasms and acute leukemia. Blood. 2016 May 19;127(20):2391-405. Epub 2016 Apr 11. PubMed PMID: 27069254.

Febbo PG, Ladanyi M, Aldape KD, et al. NCCN® Task Force report: Evaluating the clinical utility of tumor markers in oncology. J Natl Compr Canc Netw. 2011 Nov;9 Suppl 5:S1-32. PubMed PMID: 22138009.

Ferris RL, Baloch Z, Bernet V, et al. American Thyroid Association statement on surgical application of molecular profiling for thyroid nodules: current impact on perioperative decision making. Thyroid. 2015 Jul;25(7):760-8. Epub 2015 Jun 24. PubMed PMID: 26058403.

Haddad RI, Nasr C, Bischoff L, et al. NCCN Guidelines Insights: Thyroid Carcinoma, Version 2.2018. J Natl Compr Canc Netw. 2018 Dec;16(12):1429-1440. PubMed PMID: 30545990.

Hanna N, Johnson D, Temin S, et al. Systemic Therapy for Stage IV Non-Small-Cell Lung Cancer: American Society of Clinical Oncology Clinical Practice Guideline Update. J Clin Oncol. 2017 Oct 20;35(30):3484-3515. Epub 2017 Aug 14. PubMed PMID: 28806116.

Harris LN, Ismaila N, McShane LM, et al. Use of biomarkers to guide decisions on adjuvant systemic therapy for women with early-stage invasive breast cancer: American Society of Clinical Oncology clinical practice guideline. J Clin Oncol. 2016 Apr 1;34(10):1134-50. Epub 2016 Feb 8. PubMed PMID: 26858339.

Haugen BR, Alexander EK, Bible KC, et al. 2015 American Thyroid Association management guidelines for adult patients with thyroid nodules and differentiated thyroid cancer: the American Thyroid Association Guidelines Task Force on Thyroid Nodules and Differentiated Thyroid Cancer. Thyroid. 2016 Jan;26(1):1-133. PubMed PMID: 26462967.

Haugen BR, Sawka AM, Alexander EK, Bible KC, Caturegli P, Doherty GM, Mandel SJ, Morris JC, Nassar A, Pacini F, Schlumberger M, Schuff K, Sherman SI, Somerset H, Sosa JA, Steward DL, Wartofsky L, Williams MD. American Thyroid Association Guidelines on the Management of Thyroid Nodules and Differentiated Thyroid Cancer Task Force Review and Recommendation on the Proposed Renaming of Encapsulated Follicular Variant Papillary Thyroid Carcinoma Without Invasion to Noninvasive Follicular Thyroid Neoplasm with Papillary-Like Nuclear Features.Thyroid. 2017 Apr;27(4):481-483. Epub 2017 Feb 21. PubMed PMID: 28114862.

Kalemkerian GP, Narula N, Kennedy EB, et al. Molecular Testing Guideline for the Selection of Patients with Lung Cancer for Treatment with Targeted Tyrosine Kinase Inhibitors: American Society of Clinical Oncology Endorsement of the College of American Pathologists/International Association for the Study of Lung Cancer/Association for Molecular Pathology Clinical Practice Guideline Update. J Clin Oncol. 2018 Mar 20;36(9):911-919. PubMed PMID: 29401004.

PROPRIETARY

Guidelines developed by, and used with permission from, Informed Medical Decisions, Inc. © 2019 Informed Medical Decisions, Inc. All Rights Reserved.

Keedy VL, Temin S, Somerfield MR, et al. American Society of Clinical Oncology provisional clinical opinion: epidermal growth factor receptor (EGFR) mutation testing for patients with advanced non-small-cell lung cancer considering first-line EGFR tyrosine kinase inhibitor therapy. J Clin Oncol. 2011 May 20;29(15):2121-7. Epub 2011 Apr 11. PubMed PMID: 21482992.

Krop I, Ismaila N, Andre F, et al. Use of biomarkers to guide decisions on adjuvant systemic therapy for women with early-stage invasive breast cancer: American Society of Clinical Oncology clinical practice guideline focused update. J Clin Oncol. 2017 Aug 20;35(24):2838-2847. Epub 2017 Jul 10. PubMed PMID: 28692382.

NCCN® Clinical Practice Guidelines in Oncology (NCCN Guidelines®). © 2019 National Comprehensive Cancer Network, Inc. For additional information visit the NCCN® website: http://www.nccn.org/index.asp.*

- Acute Lymphoblastic Leukemia, Adult AYA (Version 2.2019) accessed July 25, 2019
- Acute Myeloid Leukemia (Version 3.2019) accessed July 25, 2019
- B-Cell Lymphomas (Version 4.2019) accessed July 25, 2019
- Breast Cancer (Version 2.2019) accessed July 25, 2019
- Central Nervous System Cancers (Version 1.2019) accessed July25, 2019
- Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma (Version 5.2019) accessed July 25, 2019
- Chronic Myeloid Leukemia (Version 1.2019) accessed July 25, 2019
- Colon Cancer (Version 2.2019) accessed July 25, 2019
- Colorectal Cancer Screening (Version 1.2019) accessed July 25, 2019
- Cutaneous Melanoma (Version 2.2019) accessed July 25, 2019
- Hairy Cell Leukemia (Version 3.2019) accessed July 25, 2019
- Myelodysplastic Syndromes (Version 2.2019) accessed July 25, 2019
- Myeloproliferative Neoplasms (Version 2.2019) accessed July 25, 2019
- Non-Small Cell Lung Cancer (Version 5.2019) accessed July 25, 2019
- Occult Primary (Version 2.2019) accessed July 25, 2019
- Ovarian Cancer (Version 1.2019) accessed July 25, 2019
- Pancreatic Adenocarcinoma (Version 3.2019) accessed July 25, 2019.
- Primary Cutaneous B-cell Lymphomas (Version 2.2019) accessed July 25, 2019
- Prostate Cancer (Version 2.2019) accessed July 25, 2019
- Prostate Cancer Early Detection (Version 2.2019) accessed July 25, 2019
- Rectal Cancer (Version 2.2019) accessed July 25, 2019
- Small Cell Lung Cancer (Version 1.2019) accessed July 25, 2019
- Soft Tissue Sarcoma (Version 2.2019) accessed July 25, 2019
- T-Cell Lymphomas (Version 2.2019) accessed July 25, 2019
- Thyroid Carcinoma (Version 1.2019) accessed July 25, 2019
- Uveal Melanoma (Version 1.2019) accessed July 25, 2019

PROPRIETARY

Guidelines developed by, and used with permission from, Informed Medical Decisions, Inc. © 2019 Informed Medical Decisions, Inc. All Rights Reserved.

- Waldenstrom's Macroglobulinemia/Lymphoplasmacytic Lymphoma (Version 2.2019) accessed July 25, 2019

Rex DK, Boland CR, Dominitz J. Colorectal Cancer Screening: Recommendations for Physicians and Patients from the U.S. Multi-Society Task Force on Colorectal Cancer. Am J Gastroenterol. 2017 Jul;112(7):1016-1030. Epub 2017 Jun 6. PubMed PMID: 28555630.

US Preventative Services Task Force. Screening for colorectal cancer: US Preventive Services Task Force recommendation statement. JAMA. 2016;315(23):2564-2575. PubMed PMID: 27304597.

*Referenced with permission from the NCCN® Clinical Practice Guidelines in Oncology (NCCN Guidelines®) Available at: http://www.nccn.org. Accessed November 1, 2018 ©National Comprehensive Cancer Network, 2019 To view the most recent and complete version of the NCCN Guidelines®, go online to www.nccn.org.

The NCCN Guidelines® are a work in progress that may be refined as often as new significant data becomes available.

The NCCN Guidelines® are a statement of consensus of its authors regarding their views of currently accepted approaches to treatment. Any clinician seeking to apply or consult any NCCN Guidelines® is expected to use independent medical judgment in the context of individual clinical circumstances to determine any patient's care or treatment. The National Comprehensive Cancer Network makes no warranties of any kind whatsoever regarding their content, use or application and disclaims any responsibility for their application or use in any way.

# Selected References


1 Abida W, Cyrta J, Heller G, et al. Genomic correlates of clinical outcome in advanced prostate cancer. Proc Natl Acad Sci U S A. 2019 May 6. pii: 201902651. Doi: 10.1073/pnas.1902651116. [Epub ahead of print] PubMed PMID: 31061129.

2 Albert CM, Davis JL, Federman N, et al. TRK fusion cancers in children: A clinical review and recommendations for screening. J Clin Oncol. 2019 Feb 20;37(6):513-524. PubMed PMID: 30592640.

3 Alghasham N, Alnouri Y, Abalkhil H, et al. Detection of mutations in JAK2 exons 12-15 by Sanger sequencing. Int J Lab Hematol. 2016 Feb;38(1):34-41. Epub 2015 Sep 11. PubMed PMID: 26361084.

4 Albain KS, Barlow WE, Shak S, et al. Prognostic and predictive value of the 21-gene recurrence score assay in postmenopausal women with node-positive, estrogen-receptor-positive breast cancer on chemotherapy: a retrospective analysis of a randomised trial. Lancet Oncol. 2010 Jan;11(1):55-65. Epub 2009 Dec 10. PubMed PMID: 20005174.

5 Alexander EK, Schorr M, Klopper J, et al. Multicenter clinical experience with the Afirma Gene Expression Classifier. J Clin Endocrinol Metab. 2014 Jan;99(1):119-25. Epub 2013 Dec 20. PubMed PMID: 24152684.

6 Armstrong AJ, Halabi S, Luo J, et al. Prospective multicenter validation of androgen receptor splice variant 7 and hormone therapy resistance in high-risk castration-resistant prostate cancer: The PROPHECY Study. J Clin Oncol. 2019 May 1;37(13):1120-1129. doi: 10.1200/JCO.18.01731. Epub 2019 Mar 13. PubMed PMID: 30865549.

7 Arpino G, Generali D, Sapino A, et al. Gene expression profiling in breast cancer: A clinical perspective. Breast. 2013 Apr;22(2):109-20. Epub 2013 Feb 23. PubMed PMID: 23462680.

8 Ayala de la Peña F, Andrés R, Garcia-Sáenz JA, et al. SEOM clinical guidelines in early stage breast cancer (2018). Clin Transl Oncol. 2019 Jan;21(1):18-30. PMID: 30443868.

9 Azim HA Jr, Michiels S, Zagouri F, et al. Utility of prognostic genomic tests in breast cancer practice: The IMPAKT 2012 Working Group Consensus Statement. Ann Oncol. 2013;24(3):647-54. Epub 2013 Jan 20. PubMed PMID: 23337633.

10 Barbui T, Thiele J, Vannucchi AM, et al. Rationale for revision and proposed changes of the WHO diagnostic criteria for polycythemia vera, essential thrombocythemia and primary myelofibrosis. Blood Cancer J. 2015 Aug 14;5:e337. PubMed PMID: 26832847.

11 Blok EJ, Bastiaannet E, van den Hout WB, Liefers GJ, Smit VTHBM, Kroep JR, van de Velde CJH. Systematic review of the clinical and economic value of gene expression profiles for invasive early breast cancer available in Europe. Cancer Treat Rev. 2018 Jan;62:74-90. Review. PMID: 29175678.



PROPRIETARY

Guidelines developed by, and used with permission from, Informed Medical Decisions, Inc. © 2019 Informed Medical Decisions, Inc. All Rights Reserved.

12 Buus R, Sestak I, Kronenwett R, et al. (2016) Comparison of EndoPredict and EPclin with Oncotype DX Recurrence Score for Prediction of Risk of Distant Recurrence after Endocrine Therapy; JNCI, Vol. 108, No. 11. PubMed PMID: 24700969.
13 Bombard Y, Bach PB, Offit K. Translating genomics in cancer care. J Natl Compr Canc Netw. 2013 Nov;11(11):1343-53. PubMed PMID: 24225968.
14 Brody JR, Yabar CS, Zarei M, et al. Identification of a novel metabolic-related mutation (IDH1) in metastatic pancreatic cancer. Cancer Biol Ther. 2018 Apr 3; 19(4):249-253. Epub 2018 Mar 6. PubMed PMID: 27466707.
15 Cantara S, Capezzone M, Marchisotta S, et al. Impact of proto-oncogene mutation detection in cytological specimens from thyroid nodules improves the diagnostic accuracy of cytology. J Clin Endocrinol Metab. 2010 Mar;95(3):1365-9. Epub 2010 Feb 3. PubMed PMID: 20130073.
16 Cardoso F, van't Veer LJ, Bogaerts J, et al. 70-Gene Signature as an aid to treatment decisions in early-stage breast cancer. N Engl J Med. 2016 Aug 25; 375(8):717-29. PubMed PMID: 27557300.
17 Chand S, O'Hayer K, Blanco FF, Winter JM, Brody JR. The landscape of pancreatic cancer therapeutic resistance mechanisms. Int J Biol Sci. 2016 Jan 27;12(3):273-82. PubMed PMID: 26929734.
18 Chang MC, Souter LH, Kamel-Reid S, et al; Molecular Oncology Advisory Committee. Clinical utility of multigene profiling assays in early-stage breast cancer. Current oncology (Toronto, Ont.) vol. 24,5 (2017): e403-e422.Curr Oncol. 2017 Oct;24(5):e403-e422. PubMed PMID: 29089811.
19 Chia SKL. Clinical application and utility of genomic assays in early-stage breast cancer: key lessons learned to date.. Curr Oncol. 2018 Jun;25(Suppl 1):S125-S130. Doi: 10.3747/co.25.3814. Epub 2018 Jun 13. Review. PMID: 29910655.
20 Church TR, Wandell M, Lofton-Day C, et al. Prospective evaluation of methylated SEPT9 in plasma for detection of asymptomatic colorectal cancer. Gut. 2014 Feb;63(2):317-25. Epub 2013 Feb 13. PubMed PMID: 23408352.
21 Colomer R, Aranda-López I, Albanell J, et al. Biomarkers in breast cancer: A consensus statement by the Spanish Society of Medical Oncology and the Spanish Society of Pathology. Clin Transl Oncol. 2018 Jul;20(7):815-826. PubMed PMID: 29273958.
22 Curigliano G, Burstein HJ, P Winer E, et al. De-escalating and escalating treatments for early-stage breast cancer: the St. Gallen International Expert Consensus Conference on the Primary Therapy of Early Breast Cancer 2017. Ann Oncol. 2017 Aug 1;28(8):1700-1712. PMID: 28838210.
23 Cuzick J, Thorat MA, Andriole G, et al. Prevention and early detection of prostate cancer. Lancet Oncol. 2014 Oct;15(11):e484-92. PubMed PMID: 25281467.
24 Denkert C, Kronenwett R, Schlake W, et al. Decentral gene expression analysis for ER+/Her2- breast cancer: results of a proficiency testing program for the EndoPredict assay. Virchows Arch. 2012 Mar; 460(3):251-259. PubMed PMID: 22371223.
25 Douillard JY, Ostoros G, Cobo M, et al. Gefitinib treatment in EGFR mutated caucasian NSCLC: circulating- free tumor DNA as a surrogate for determination of EGFR status. J Thorac Oncol 2014;9:1345–53. PubMed PMID: 25122430.
26 Dubsky P, Brase JC, Jakesz R, et al. The EndoPredict score provides prognostic information on late distant metastases in ER+/HER2- breast cancer patients. Br J Cancer. 2013;109(12):2959–2964. PubMed PMID: 24157828.
27 Dubsky P, Filipits M, Jakesz R, et al. EndoPredict improves the prognostic classification derived from common clinical guidelines in ER-positive, HER2-negative early breast cancer. Ann Oncol. 2013 Mar;24(3):640-647. PubMed PMID: 23035151.
28 Duffy MJ, Harbeck N, Nap M, et al. Clinical use of biomarkers in breast cancer: updated guidelines from the European Group on Tumor Markers (EGTM). Eur J Cancer. 2017 Apr;75:284-298. Epub 2017 Feb 28. PubMed PMID: 28259011.
29 Duick D, Klopper J, Diggans J, et al. The impact of benign gene expression classifier test results on the endocrinologist-patient decision to operate on patients with thyroid nodules with indeterminate fine-needle aspiration cytopathology. Thyroid. Oct 2012; 22(10): 996–1001. Epub 2012 Aug 8. PubMed PMID: 22873825.
30 Engelman JA, Chen L, Tan X, et al. Effective use of PI3K and MEK inhibitors to treat mutant Kras G12D and PIK3CA H1047R murine lung cancers. Nat Med. 2008 Dec;14(12):1351-6. Epub 2008 Nov 30. PubMed PMID: 19029981.
31 Ferguson MD, Dong L, Wan J, et al. Molecular Alterations Associated with DNA Repair in Pancreatic Adenocarcinoma Are Associated with Sites of Recurrence. J Gastrointest Cancer. 2018 Feb 10. PubMed PMID: 29427136.
32 Ferrone CR, Levine DA, Tang LH et al. BRCA germline mutations in Jewish patients with pancreatic adenocarcinoma. J Clin Oncol. 2009 Jan 20; 27(3): 433–438. PubMed PMID: 19064968.
33 Fiala O, Pesek M, Finek J, et al. Gene mutations in squamous cell NSCLC: insignificance of EGFR, KRAS and PIK3CA mutations in prediction of EGFR-TKI treatment efficacy. Anticancer Res. 2013 Apr;33(4):1705-11. PubMed PMID: 23564819.
34 Fidler MJ, Morrison LE, Basu S, et al. PTEN and PIK3CA gene copy numbers and poor outcomes in non-small cell lung cancer patients with gefitinib therapy. Br J Cancer. 2011 Dec 6;105(12):1920-6. Epub 2011 Nov 17. PubMed PMID: 22095222.
35 Filipits M, Rudas M, Jakesz R, et al. A new molecular predictor of distant recurrence in ER-positive, HER2-negative breast cancer adds independent information to conventional clinical risk factors. Clin Cancer Res 2011;17:6012-6020. PubMed PMID: 21807638.
36 Fischer CG, Wood LD. From somatic mutation to early detection: insights from molecular characterization of pancreatic cancer precursor lesions. J Pathol. 2018 Dec;246(4):395-404. doi: 10.1002/path.5154. Review. PubMed PMID: 30105857.
37 Fizazi K, Greco FA, Pavlidis N, et al. Cancers of unknown primary site: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2015 Sep;26 Suppl 5:v133-8. PubMed PMID: 26314775.
38 Flaherty KT, Le DT, Lemery S. Tissue-Agnostic Drug Development. Am Soc Clin Oncol Educ Book. 2017;37:222-230. doi: 10.14694/EDBK_173855. PubMed PMID: 28561648.
39 Golan T, Kanji ZS, Epelbaum R et al. Overall survival and clinical characteristics of pancreatic cancer in BRCA mutation carriers. Br J Cancer. 2014 Sep 9;111(6):1132-8. PubMed PMID: 25072261.
40 Gore JL, du Plessis M, Santiago-Jimenez M, et al. Decipher test impacts decision making among patients considering adjuvant and salvage treatment after radical prostatectomy: Interim results from the Multicenter Prospective PRO-IMPACT study. Cancer. 2017 Aug 1;123(15):2850-9. Epub 2017 Apr 19. PubMed PMID: 28422278.

PROPRIETARY

Guidelines developed by, and used with permission from, Informed Medical Decisions, Inc. © 2019 Informed Medical Decisions, Inc. All Rights Reserved.

41 Hang JF, Westra WH, Cooper DS, Ali SZ. The impact of noninvasive follicular thyroid neoplasm with papillary-like nuclear features on the performance of the Afirma gene expression classifier. Cancer. 2017 Sep; 125(9):683-91. Epub 2017 May 24. PubMed PMID: 28544601.
42 Harris LN, Ismaila N, McShane LM, et al. Use of biomarkers to guide decisions on adjuvant systemic therapy for women with early-stage invasive breast cancer: American Society of Clinical Oncology clinical practice guideline. J Clin Oncol. 2016 Feb 8. Pii: JCO652289. [Epub ahead of print] PUbMed PMID: 26858339.
43 Heichman KA. Blood-based testing for colorectal cancer screening. Mol Diagn Ther. 2014 Apr;18(2):127-135. PubMed PMID: 24307563.
44 Hong DS, Bauer TM, Lee JJ, et al. Larotrectinib in adult patients with solid tumours: a multi-centre, open-label, phase I dose-escalation study. Ann Oncol. 2019 Feb 1;30(2):325-331.PubMed PMID: 30624546.
45 Janku F, Huang HJ, Claes B, et al. BRAF mutation testing in cell-free DNA from the plasma of patients with advanced cancers using a rapid, automated molecular diagnostics system. Mol Cancer Ther. 2016 Jun;15(6):1397-404. Epub 2016 May 20. PubMed PMID: 27207774.
46 Klampfl T, Gisslinger H, Harutyunyan AS, et al. Somatic mutations of calreticulin in myeloproliferative neoplasms. N Engl J Med. 2013 Dec 19; 369(25):2379-90. Epub 2013 Dec 10. PubMed PMID: 24325356.
47 Klett H, Fuellgraf H, Levit-Zerdoun E, et al. Identification and Validation of a Diagnostic and Prognostic Multi-Gene Biomarker Panel for Pancreatic Ductal Adenocarcinoma. Frontiers in Genetics. 2018;9:108. PubMed PMID: 29675033.
48 Kloos RT, Reynolds JD, Walsh PS, et al. Does addition of BRAF V600E mutation testing modify sensitivity or specificity of the Afirma Gene Expression Classifier in cytologically indeterminate thyroid nodules? J Clin Endocrinol Metab. 2013 Apr;98(4):E761-8. Epub 2013 Mar 8. PubMed PMID: 23476074.
49 Kretschmer A, Tilki D. Biomarkers in prostate cancer - Current clinical utility and future perspectives. Crit Rev Oncol Hematol. 2017 Dec;120:180-193. doi:10.1016/j.critrevonc.2017.11.007. Epub 2017 Nov 13. Review. PubMed PMID: 29198331.
50 Kronenwett R, Bohmann K, Prinzler J, et al. Decentral gene expression analysis: analytical validation of the Endopredict genomic multianalyte breast cancer prognosis test. BMC Cancer. 2012 Oct 5;12:456. PubMed PMID: 23039280.
51 Krop I, Ismaila N, Andre F, et al. Use of biomarkers to guide decisions on adjuvant systemic therapy for women with early-stage invasive breast cancer: American Society of Clinical Oncology clinical practice guideline focused update. J Clin Oncol 2017;35:2838-2847. PubMed PMID: 28692382.
52 Kunovsky L, Tesarikova P, Kala Z, Kroupa R, Kysela P, Dolina J, Trna J. The Use of Biomarkers in Early Diagnostics of Pancreatic Cancer. Can J Gastroenterol Hepatol. 2018 Aug 14;2018:5389820. PubMed PMID: 30186820.
53 Lerch MM, Mayerle J, Mahajan U, et al. Development of pancreatic cancer: targets for early detection and treatment. Dig Dis. 2016;34(5):525-31. PubMed PMID: 27332960.
54 Levy B, Hu ZI, Cordova KN, Close S, et al. Clinical Utility of Liquid Diagnostic Platforms in Non-Small Cell Lung Cancer. Oncologist. 2016 Sep;21(9):1121-30. Review.
PMID: 27388233.
55 Ludvíková M, Kalfeřt D, Kholová I. Pathobiology of microRNAs and their emerging role in thyroid fine-needle aspiration. Acta Cytol. 2015;59(6):435-44. Epub 2016 Jan 9. PubMed PMID: 26745212.
56 Lamy PJ, Allory Y, Gauchez AS, et al. Prognostic Biomarkers Used for Localised Prostate Cancer Management: A Systematic Review. Eur Urol Focus. 2017 Mar 7. pii: S2405-4569(17)30065-2. PubMed PMID: 28753865.
57 Lynch TJ, Bell DW, Sordella R, et al. Activating mutations in the epidermal growth factor receptor underlying responsiveness of non-small-cell lung cancer to gefitinib. N Engl J Med. 2004 May 20;350(21):2129-39. Epub 2004 Apr 29. PMID: 15118073.
58 Martin M, Brase JC, Calvo L, et al. Clinical validation of the EndoPredict test in node-positive, chemotherapy-treated ER+/HER2- breast cancer patients: results from the GEICAM 9906 trial. Breast Cancer Res. 2014 Apr 12;16(2):R38. PubMed PMID: 24725534.
59 McIver B, Castro MR, Morris JC, et al. An independent study of a gene expression classifier (Afirma) in the evaluation of cytologically indeterminate thyroid nodules. J Clin Endocrinol Metab. 2014 Nov;99(11):4069-77. Epub 2014 Apr 29. PubMed PMID: 24780044.
60 Mok TS, Wu YL, Thongprasert S, et al. Gefitinib or carboplatin-paclitaxel in pulmonary adenocarcinoma. N Engl J Med. 2009 Sep 3;361(10):947-57. Epub 2009 Aug 19. PubMed PMID: 19692680.
61 Müller BM, Keil E, Lehmann A, et al. The EndoPredict Gene-Expression Assay in Clinical Practice - Performance and Impact on Clinical Decisions. PLoS One. 2013 Jun 27;8(6):e68252. PubMed PMID: 23826382.
62 Narayan VM, Konety BR, Warlick C. Novel biomarkers for prostate cancer: An evidence-based review for use in clinical practice. Int J Urol. 2017 May;24(5):352-360. Epub 2017 Mar 27. PubMed PMID: 28345187.
63 Parikh RB, Prasad V. Blood-based screening for colon cancer: A disruptive innovation or simply a disruption? JAMA. 2016 Jun 21;315(23):2519-20. PubMed PMID: 27305625.
64 Peters ML, Tseng JF, Miksad RA. Genetic testing in pancreatic ductal adenocarcinoma: implications for prevention and treatment. Clin Ther. 2016 Jul;38(7):1622-35. PubMed PMID: 27041411.
65 Pinsky PF, Prorok PC, Kramer BS. Prostate cancer screening - a perspective on the current state of the evidence. N Engl J Med. 2017 Mar 30;376(13):1285-9. PubMed PMID: 28355509.
66 Ragon BK, Savona MR. The challenge of treating myelodsyplastic syndromes/myeloproliferative neoplasms. Clin Lymphoma Myeloma Leuk. 2017 Jul; 17S:S37-42. PubMed PMID: 28760301.
67 Root A, Allen P, Tempst P, Yu K. Protein Biomarkers for Early Detection of Pancreatic Ductal Adenocarcinoma: Progress and Challenges Cancers (Basel). 2018 Mar 7;10(3). PubMed PMID: 29518918.
68 Salto-Tellez M, Tsao MS, Shih JY, et al. Clinical and testing protocols for the analysis of epidermal growth factor receptor mutations in East Asian patients with non-small cell lung cancer: a combined clinical-molecular pathological approach. J Thorac Oncol. 2011 Oct;6(10):1663-9. PubMed PMID: 21869714.

PROPRIETARY

Guidelines developed by, and used with permission from, Informed Medical Decisions, Inc. © 2019 Informed Medical Decisions, Inc. All Rights Reserved.

69 Samuels Y, Wang Z, Bardelli A, et al. High frequency of mutations of the PIK3CA gene in human cancers. Science. 2004 Apr 23;304(5670):554. Epub 2004 Mar 11. PubMed PMID: 15016963.
70 Sartori DA, Chan DW. Biomarkers in prostate cancer: what's new? Curr Opin Oncol. 2014 May;26(3):259-64. PubMed PMID: 24626128.
71 Scher HI, Graf RP, Schreiber NA, et al. Assessment of the validity of nuclear-localized androgen receptor splice variant 7 in circulating tumor cells as a predictive biomarker for castration-resistant prostate cancer. JAMA Oncol. 2018 Sep 1;4(9):1179-1186. doi: 10.1001/jamaoncol.2018.1621. PubMed PMID: 29955787.
72 Senkus E, Kyriakides S, Ohno S, et al. Primary breast cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2015; 26(Suppl 5):v8–v30. PubMed PMID: 26314782.
73 Sestak I, Buus R, Cuzick J, et al. Comparison of the performance of 6 prognostic signatures for estrogen receptor-positive breast cancer: A secondary analysis of a randomized clinical trial. JAMA Oncol. 2018 Apr 1;4(4):545-553. PMID: 29450494.
74 Shroff RT, Hendifar A, McWilliams RR, et al. Rucaparib Monotherapy in Patients With Pancreatic Cancer and a Known Deleterious BRCA Mutation. JCO Precision Oncology 2018 :2, 1-15. PubMed PMID: 30051098.
75 Siegel R., Naishadham D., Jemal A. (2013) Cancer statistics. CA Cancer J Clin 63: 11-30. PubMed PMID: 23335087.
76 Singhi AD, George B, Greenbowe JR, et al. Real-time Targeted Genome Profile Analysis of Pancreatic Ductal Adenocarcinomas Identifies Genetic Alterations that Might be Targeted with Existing Drugs or Used as Biomarkers. Gastroenterology. 2019 Mar 2. pii: S0016-5085(19)32505-3. doi: 10.1053/j.gastro.2019.02.037. [Epub ahead of print] PubMed PMID: 30836094.
77 Song L, Li Y. SEPT9: A specific circulating biomarker for colorectal cancer. Adv Clin Chem. 2015;72:171-204. Epub 2015 Aug 29. PubMed PMID: 26471083.
78 Sparano JA, Gray RJ, Makower DF, et al. Prospective validation of a 21-gene expression assay in breast cancer. N Engl J Med 2015;373:2005-2014. PMID: 26412349.
79 Sparano JA, Gray RJ, Makower DF, et al. Adjuvant Chemotherapy Guided by a 21-Gene Expression Assay in Breast Cancer. N Engl J Med. 2018 Jul 12;379(2):111-121. PMID: 29860917.
80 Spivak JL. Myeloproliferative neoplasms. N Engl J Med. 2017 Jun 1;376(22):2168-81. PubMed PMID: 28564565.
81 Steward DL, Carty SE, Sippel RS, et al. Performance of a multigene genomic classifier in thyroid nodules with indeterminate cytology: A prospective blinded multicenter study. JAMA Oncol. 2018 Nov 8. doi: 10.1001/jamaoncol.2018.4616. [Epub ahead of print] PubMed PMID: 30419129.
82 Tefferi A. Primary myelofibrosis: 2017 update on diagnosis, risk-stratification, and management. Am J Hematol. 2016 Dec;91(12):1262-71. PubMed PMID: 27870387.
83 Umemura S, Tsuchihara K, Goto K. Genomic profiling of small-cell lung cancer: the era of targeted therapies. Jpn J Clin Oncol. 2015 Jun;45(6):513-9. Epub 2015 Feb 10. PubMed PMID: 25670763.
84 Varga Z, Sinn P, Seidman AD. Summary of head-to-head comparisons of patient risk classifications by the 21-gene Recurrence Score® (RS) assay and other genomic assays for early breast cancer. Int J Cancer. 2019 Jan 17. PubMed PMID: 30653259.
85 Vatandoost N, Ghanbari J, Mojaver M, et al. Early detection of colorectal cancer: from conventional methods to novel biomarkers. J Cancer Res Clin Oncol. 2016 Feb;142(2):341-51. Epub 2015 Feb 17. PubMed PMID: 25687380.
86 Wong KS, Angell TE, Strickland KC, et al. Noninvasive follicular variant of papillary thyroid carcinoma and the Afirma gene-expression classifier. Thyroid. 2016 Jul; 26(7):911-5. PubMed PMID: 27219469.
87 Zhang L, Zeng J, Zeng Z, et al. MGMT in colorectal cancer: a promising component of personalized treatment. Tumour Biol. 2016 Aug;37(8):11443-56. Epub 2016 Mar 22. PubMed PMID: 27006309.

PROPRIETARY

Guidelines developed by, and used with permission from, Informed Medical Decisions, Inc. © 2019 Informed Medical Decisions, Inc. All Rights Reserved.

# Revision History

**Medical Advisory Board Review:**

v2.2019 05/23/2019: Approved

v1.2019 11/07/2018: Reviewed

v1.2018 03/31/2018: Reviewed

**Clinical Steering Committee Review:**

v2.2019 04/03/2019: Approved

v1.2019 10/03/2018: Approved

v1.2018 02/28/2018: Approved

v5.2017 11/01/2017: Approved

v4.2017 09/20/2017: Approved

v3.2017 08/09/2017: Approved

v2.2017 05/03/2017: Approved

v1.2017 01/25/2017: Approved

**Revisions:**

| Version | Date | Editor | Description |
|---|---|---|---|
| v2.2019 | 4/03/2019 | Emily Higuchi, MS, CGC | Semi-annual review. Revised umbrella coverage criteria section. Added NTRK fusion criteria. Revised Oncotype DX®, Prosigna PAM50™ and MammaPrint® criteria. Added Endopredict criteria. Updated background, professional society/NCCN® guidelines and references. Renumbered to v2.2019. |
| | 7/25/2019 | Carrie Langbo, MS, CGC | NCCN Guidelines® were accessed for inclusion of the most recent published version. Minor revisions to text were incorporated based on updated Guidelines but did not impact coverage criteria/necessitate MAB/CSC review. |

PROPRIETARY

Guidelines developed by, and used with permission from, Informed Medical Decisions, Inc. © 2019 Informed Medical Decisions, Inc. All Rights Reserved.

| | | | |
|---|---|---|---|
| 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. |

PROPRIETARY

Guidelines developed by, and used with permission from, Informed Medical Decisions, Inc. © 2019 Informed Medical Decisions, Inc. All Rights Reserved.

| | | | |
|---|---|---|---|
| v2.2017 | 06/30/2017 | Denise Jones, MS, CGC | Quarterly review. No criteria changes. Updated references. |
| v2.2017 | 04/25/2017 | Cheryl Thomas, MS, CGC | Quarterly review. Added changes to indeterminate thyroid nodules (removed Hurthle cell from indication per NCCN update). Added PD-L1 to NSCLC molecular targets. Updated references. |
| v1.2017 | 01/23/2017 | Gwen Fraley, MS, CGC | Quarterly review. Updated MPN criteria. Edited EGFR criteria regarding erlotinib. Updated references. Renumbered to 2017. |
| v4.2016 | 09/29/2016 | Jenna McLosky, MS, CGC | Updated background regarding occult primaries. Updated references. |
| v3.2016 | 06/30/2016 | Jenna McLosky, MS, CGC | Added EGFR Cobas cell-free test for NSCLC. Updated references. |
| v2.2016 | 04/04/2016 | Jenna McLosky, MS, CGC | Updated and reviewed prostate cancer screening criteria. Updated references. |
| v1.2016 | 03/18/2016 | Jenna McLosky, MS, CGC | Updated and revised stance on breast cancer prognosis assays (Prosigna). Updated references. |
| v1.2015 | 09/24/2015 | Jenna McLosky, MS, CGC | Original version |

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

**Primary Author:** Jenna McLosky, MS, CGC

PROPRIETARY

Guidelines developed by, and used with permission from, Informed Medical Decisions, Inc. © 2019 Informed Medical Decisions, Inc. All Rights Reserved.