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Corporate Medical Policy

Molecular Panel Testing of Cancers for Diagnosis, Prognosis, and Identification of Targeted Therapy AHS - M2109

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Description of Procedure or Service

Cancer is defined as the uncontrolled growth and spread of abnormal cells and is increasingly shown to be initiated, propagated, and maintained by somatic genetic events (Johnson et al., 2014). About 1,688,780 new cancer cases are expected to be diagnosed in 2017 with about 600,920 Americans expected to die of cancer (~1650 people per day) (Siegel, Miller, & Jemal, 2017).

Analyses of gene expression can be clinically useful for disease classification, diagnosis, prognosis, and tailoring treatment to underlying genetic determinants of pharmacologic response (Spira, 2017). Precision or personalized oncology refers to evidence-based, individualized medicine that uses information about a person's genes, proteins, and environment to deliver the right care to the right cancer patient at the right time and results in measurable improvements in outcomes and a reduction on health care costs (M. Kalia, 2013).

******Note: This Medical Policy is complex and technical. For questions concerning the technical language and/or specific clinical indications for its use, please consult your physician.***

Policy

BCBSNC will provide coverage for molecular panel testing of cancers for diagnosis, prognosis, and identification of targeted therapy when it is determined the medical criteria or reimbursement guidelines below are met.

Benefits Application

This medical policy relates only to the services or supplies described herein. Please refer to the Member's Benefit Booklet for availability of benefits. Member's benefits may vary according to benefit design; therefore member benefit language should be reviewed before applying the terms of this medical policy.

When Molecular Panel Testing of Cancers for Diagnosis, Prognosis, and Identification of Targeted Therapy is covered

Molecular panel testing of cancers to identify targeted therapy is considered **medically necessary** for multiplex panels of up to 50 genes that analyze for a subset of 5 or more genes considered to be standard-of-care for use with a given diagnosis, as defined in nationally recognized clinical guidelines such as those of the National Cancer Comprehensive Network (NCCN) or the American Society of Clinical Oncology (ASCO), Current genes scientifically shown to be impactful in the care of solid organ and hematolymphoid tumors are indicated in the coding table below. If less than 5 genes panel testing is needed please consult individual policies.

The covered panels must fit the American Medical Association's Current Procedural Terminology (CPT®) codes for panels comprised of 5 to 50 genes for solid organ neoplasms (CPT® 81445) or hematolymphoid neoplasms or disorders (CPT® 81450) as shown in the coding table below.

When Molecular Panel Testing of Cancers for Diagnosis, Prognosis, and Identification of Targeted Therapy is not covered

Panels containing more than 50 genes (CPT® code 81455) are **investigational.**

All other multiplex RNA panels not listed are **investigational.**

Table of Genes

Specific genes for solid organ tumors and hematolymphoid neoplasms based on current NCCN guidelines are shown in table below. See individual policies for staging of cancers in which testing is appropriate.

Tumor Type	Disease State	Genes
Solid Tumor	Bone CA (Ewing Sarcoma)	EWSR1-ERG, EWSR1-ETV1, EWSR1-ETV4, EWSR1-FEV, EWSR1-FL1, FUS-ERG, FUS-FEV,
	Breast CA	BRCA1, BRCA2, HER2, PIK3CA, NTRK, PALB2, ATM, BARD1, CHEK2, PTEN, TP53, CDH1, STK11, (NCCN, 2020e, 2020o) 21 gene expression pattern, recurrence score
Solid Tumor	Non small cell lung CA (nonsquamous)	ALK, EGFR, ERBB2, KRAS, ROS1, KRAS, MET (NCCN, 2020s)
	Central Nervous System CA	BRAF, H3F3A, HIST1H3B, RELA, ATRX, TERT, MGMT (NCCN, 2019a, 2020f)
	Cervical CA	NTRK (NCCN, 2020g)
	Colon CA	BRAF, RAS, KRAS, MLH1, MSH2, MSH6, NRAS, HER2, PMS2, APC, EPCAM, MSH6, PMS2, NTRK (NCCN, 2020)
	Cutaneous Melanoma	BRAF, KIT, BRAF/MEK, NRAS, ALK, NTRK1, NTRK2, NTRK3, ROS1, (NCCN, 2020k)
	Esophageal and Esophagogastric CA	HER2, NTRK, MLH1, MSH2, MSH6, PMS2, BLM, RECQL3, RHBDF2 (NCCN, 2020l)
	Gallbladder CA	NTRK, (NCCN, 2020p)
	Gastric CA	HER2, NTRK, CDH1 (universal) EPCAM, MLH1, MSH2, MSH6, PMS2 (Asian descent only) (NCCN, 2020f, 2020m)
	Gliomas	H3K27M (H3F3A, HIST1H3B), BRAF, TERT, ATRX, IDH, MGMT (NCCN, 2020f)
	Head and Neck Cancers	ERBB2/HER2, NTRK, AR, NTRK1, NTRK2, NTRK3 (NCCN, 2020o)

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	Kidney Cancer	MLH1, MSH2, MSH6, PMS2 , EGFR, RET, c-KIT, FLT-3, PDGFR, VEGFR, MET, AXL, VHL (NCCN, 2020q)
	Medulloblastomas	TP53, CTNNB1, APC (NCCN, 2020f)
	Myelodysplastic Syndromes	ASXL1, EZH2, ETV6, RUNX1, SF3B1, TP53, GATA2, JAK2, MPL, CALR, PDGFRB, RUNX1, TRG, TRA, TRB, TRD
	Neuroendocrine CA	MEN1, RET
	Ovarian CA	ATM, BRCA1, BRCA2, BRIP1, PALB2, RAD51C, RAD51D, STK11, MLH1, MSH2, MSH6, PMS2, EPCAM, (NCCN, 2019d, 2020n)
	Pancreatic CA	ALK, NRG1, NTRK, BRAF, BRAC1/2, HER2, PALB2, PMS2, KRAS, TP53, CDKN2A, SMAD4, (NCCN, 2020t)
	Penile CA	n/a (NCCN, 2020u)
	Prostate CA	MLH1, MSH2, MSH6, PMS2, BRCA1, BRCA2, ATM, PALB2, FANCA, RAD51D, CHEK2, HOXB13 (NCCN, 2020w)
	Rectal CA	HER2, RAS, BRAF, MLH1, MSH2, MSH6, PMS2, NRAS, KRAS, NTRK (NCCN, 2020x)
	Small Cell Lung CA	MLH1, MSH2, MSH6, PMS2
	Soft Tissue Sarcoma	APC, ATIC-ALK, CARS-ALK, CLTC-ALK, RANBP2-ALK, TPM3-ALK, TPM4-ALK, BRAF, CSF1-ETV6-NTRK3, EWSR1-ATF1, EWSR1-CREB1, FUS-ATF1, EWSR1-DDIT3, FUS-DDIT3, EWSR1-ERG, EWSR1-ETV1, EWSR1-EWSR1-FEV, EWSR1-FLI1, EWSR1-ZSG, FUS-ERG, EWSR1-NR4A3, TAF2N, TCF12-NR4A3, TFG-NR4A3, COLIA-PDGFB, EWSR1-WT1, FUS-CREB3L1, FUS-CREB3L2, CDK4, HMGA2, MDM2, SAS, GL1, HEY1-NCOA2, KIT, MYOD1, NAB2-STAT6, NF1, CDKN2A, EED, SUZ12, PAX3-FOXO4, PAX7-FOXO1, PDGFRA, SDHB, SDHC, SDHD, SMARCB1, SS18-SSX1, SS18-SSX2, SS18-SSX4, WWTR1-CAMTA1, YAP1-TFE3, ASPL-TFE3, INI1, CTNNB1 (NCCN, 2020y)
	Squamous Cell Skin CA	EGFR (NCCN, 2020z)
	Thyroid CA	RET, MEN2A, NTRK, BRAF (NCCN, 2019f)
	Testicular CA	n/a (NCCN, 2020ab)
	Uterine CA	MLH1, MSH2, MSH6, HER2, NTRK, (NCCN, 2020ad)
	Vulvar CA	NTRK (NCCN, 2020ad)

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Hematolymphoid	ALL	ABL1, ABL2, CRLF2, CSF1R, EPOR, JAK1, JAK2, JAK3, PDGFRB, EBF1, FLT3, O:7R, NTRK3, SJ2B3, BCR-ABL1, TPMT, ETV-RUNX1, IL3-IGH, KMT2A, TCF3-PBX1 (NCCN, 2020a)
	AML	FLT3-ITD, ASXL1, BCR-ABL1, CBFB-MYH11, CEBPA, DEK-NUP214, DNMT3A, c-KIT, FLT3-TKD, IDH1, IDH2 KIT, MLL, MLLT3-MLL, NPM1, PML-RARA, RPN1-EV11, RUNX1, RUNX1-RUNX1T1, TP53, (NCCN, 2020b)
	CML	ABL1, BCR-ABL1, (NCCN, 2020i)
	CLL/SLL	BTK, TP53, IGHV, PLCG2 (NCCN, 2020h)
	Primary Cutaneous B-Cell Lymphoma	BCL2, BCL6, MYC (NCCN, 2020c)
	Extranodal NK/T-Cell Lymphoma, nasal type	STAT3 (NCCN, 2018, 2020aa)
	Peripheral T-Cell Lymphomas	ALK, DUSP22, TCR, (NCCN, 2018, 2020aa)
	Primary Cutaneous CD30+ T-Cell Lymphoproliferative Disorders	ALK, DUSP22, TCR (NCCN, 2018, 2020v)
	T-Cell Large Granular Lymphocytic Leukemia	STAT3, STAT5B, TCR (NCCN, 2018, 2020aa)
	T-Cell Prolymphocytic Leukemia	TCR, TCL1, CD52, (NCCN, 2018, 2020aa)
	Myelodysplastic Syndromes	TET2, DNMT3A, ASXL1, EZH2, SF3B1, SRSF2, U2AF1, ZRSR2, RUNX1, TP53, STAG2, NRAS, CBL, NF1, JAK2, CALR, MPL, ETV6, GATA2, DDX41, IDH1, IDH2, SETBP1, PHF6, BCOR, FLT3, WT1, NPM1, STAT3, PPM1D (NCCN, 2020r)
	Myeloproliferative Neoplasms	JAK2, MPL, CALR, TET2, ASXL1, EZH2, IDH1, IDH2, DNM3TA, SRSF2, TP53, U2AF1, SF3B1, SH2B3/LNK, CBL (NCCN, 2019c)
	Waldenstroms Macroglobulinemia/ LymMacroglobulinemia/Lymphoplasmacytic Lymphoma	MyD88 (L265P), CXCR4 (NCCN, 2020ae)

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Policy Guidelines

Advances in sequencing technology have facilitated the identification of crucial genetic alterations that drive cancer cell growth by constitutive activation of cell signaling/cell cycling pathways or by inactivation of critical negative regulators of these networks (Bos, 1989; Davies et al., 2002; Levine & Oren, 2009; Soda et al., 2007). Compared with protein biomarkers, cancer genetic markers are more reproducible and less subject to intrinsic and extrinsic stimuli (M. Kalia, 2013; Li, Kung, Mack, & Gandara, 2016). The use of this information in personalized medicine has changed the paradigms in oncology because it is now based on understanding molecular carcinogenesis, pharmacogenomics, and individual genetic differences that determine the response to chemotherapeutics (Grullich & von Kalle, 2012; Madhu Kalia, 2015; Nalejska, Maczynska, & Lewandowska, 2014).

The approach of determining therapy based on genetic abnormalities rather than tissue of origin is increasingly important. Small molecule inhibitors and antibodies have been developed that target particular oncogenic drivers (Chapman et al., 2011; Druker et al., 2001; Shaw et al., 2013; Slamon et al., 2001; Zhou et al., 2011). These targeted agents may be equivalent or even inferior to standard therapy in an unselected population but frequently induce dramatic regression in tumors harboring the target, demonstrating the value of precision medicine (Flaherty et al., 2010; Karapetis et al., 2008; Mok et al., 2009). Many agents are also now demonstrating signs of efficacy, even in previously difficult to target pathways involving activated RAS, impaired p53, and loss of cyclin-dependent kinase regulation(Ascierto et al., 2013; Dickson et al., 2013; Janne et al., 2013; Lehmann et al., 2012). Therefore, the ability to identify potentially actionable genetic alterations is imperative to exploiting the molecular vulnerabilities of cancer. (Johnson et al., 2014). For example, use of anti- epidermal growth factor receptor (*EGFR*) agents often depends on the mutation status of the Kirsten ras oncogene homolog (*KRAS*) oncogene, as activating mutations in the *KRAS* oncogene cause anti-*EGFR* resistance (Frucht, 2019). Other drugs such as pembrolizumab are being developed and approved based on molecular indications (MSI-high or MMR deficient) independent of anatomical site of cancer origin (Hulick, 2019, 2020). However, the clinical utility and cost effectiveness of multigene panels versus broader sequencing methods is still in need of further study.

Targeted next-generation sequencing (NGS) (e.g. FoundationOne) sequences the entire coding region of a large number of preselected genes with clinical or preclinical relevance in cancer (FoundationMedicine, 2019; Wagle et al., 2012). Although less comprehensive than whole genome sequencing (WGS) or whole exome sequencing (WES), targeted NGS does provide a comprehensive analysis of known genes with potential therapeutic and prognostic importance, a quick turnaround time, and a standardized analytics pipeline (Frampton et al., 2013; Johnson et al., 2014).

Currently, a variety of molecular diagnostic platforms are available (Meador et al., 2014). The most common clinically used sequencing platforms assess a limited number of the most extensively validated mutations (hotspots)(Dias-Santagata et al., 2010; Halait et al., 2012; Lovly et al., 2012; Shaw et al., 2013). These range from polymerase chain reaction (PCR)-based assays of a single point mutation to more extensive PCR- or mass spectrometry-based platforms assessing multiple point mutations across several genes (SNaPshot or Sequenom) (Halait et al., 2012; Lovly et al., 2012). However, activating mutations at non-hotspot locations that confer sensitivity to approved therapies (Bahadoran et al., 2013; Dahlman et al., 2012) and other clinically relevant gene fusions are not detected with hotspot testing methods (Drilon et al., 2013). A proportion of patients may therefore be excluded from potentially effective therapeutics based on incomplete genetic profiling(Johnson et al., 2014).

Clinical Validity and Utility

Findings such as pathogenic variants are traditionally confirmed by Sanger sequencing, which is considered the gold standard of gene sequencing (>99.99% accuracy). NGS compares favorably to Sanger sequencing. In a study performed by Strom et al. (2014), 110 single-nucleotide variants (SNVs) were found by NGS with 103 of those SNVs meeting the minimum quality score threshold of 500 set by the lab and seven falling below this threshold. Moreover, 109 of the 110 total SNVs were validated by Sanger sequencing (Strom et al., 2014). Another study focusing on the agreement between Sanger sequencing and NGS results found only two variants out of 5800 that

did not have cross-method agreement. Overall, the agreement rate was 99.965%. The authors concluded that a single round of Sanger sequencing was "more likely to incorrectly refute a true-positive variant from NGS than to correctly identify a false-positive variant from NGS" (Beck, Mullikin, & Biesecker, 2016).

Harada et al (2017) found that in 132 cases selected by a tumor board for comprehensive next generation sequencing, Forty-six cases (34.8%) had driver mutations that were associated with an active targeted therapeutic agent, including *BRAF, PIK3CA, IDH1, KRAS*, and *BRCA1*. An additional 56 cases (42.4%) had driver mutations previously reported in some type of cancer. Twenty-two cases (16.7%) did not have any clinically significant mutations. Eight cases did not yield adequate DNA. 15 cases were considered for targeted therapy, 13 of which received targeted therapy. One patient experienced a near complete response. Seven of 13 had stable disease or a partial response.

A comprehensive study by Singal et al. (2019) examined the electronic health records (EHR) of 4064 individuals with non-small cell lung cancer (NSCLC) from 275 different oncology practices to explore "associations between tumor genomics and patient characteristics with clinical outcomes…" The authors note that 21.4% of these individuals had a mutation in *EGFR*, *ALK*, or *ROS1*, and that patients with driver mutations who had targeted therapies had significantly improved overall survival times than individuals who did not have targeted therapies (median of 18.6 versus 11.4 months, respectively); moreover, a tumor mutational burden (TMB) of 20 or higher was associated with improved overall survival for patients on PD-L1-targeted therapy than those patients with a TMB less than 20. TMBs measure the quality of a mutation in a tumor, suggesting whether a patient will benefit from immunology-based cancer therapies or not. The authors concluded that similar associations from previous research were replicated "between clinical and genomic characteristics, between driver mutations and response to targeted therapy, and between TMB and response to immunotherapy (Singal et al., 2019)."

X. Li et al. (2017) examined the effect of number of *EGFR* mutations on the efficacy of *EGFR* TKIs (tyrosine kinase inhibitor therapy). A total of 201 patients with *EGFR* mutations were evaluated, and these patients were quantitatively separated into "low" and "high" groups based on "amplification refractory mutation system (ARMS) method optimized with competitive blockers and specific mutation quantitation (ARMS+)." The cutoff value was determined by a receiving operating characteristic analysis in a training group and further validated in another group. The investigators found the median progression-free survival (PFS) to be 15 months in the high group compared to the 2 months in the low group, and similar results were found in the validation group. The authors concluded that the abundance of *EGFR* mutations was significantly associated with objective response to *EGFR* TKIs. However, it was also noted the abundance of *EGFR* T790M mutations may adversely affect PFS rather than objective response rate (X. Li et al., 2017).

Zehir et al. (2017) investigated the MSK-IMPACT gene panel. This panel of 410 cancer-related genes was used to sequence 10945 tumors from 10336 patients. Approximately 36.7% (3792/10336) of these patients were found to have a "clinically actionable" gene variant, such as *TP53* and *KRAS*. Of these, 527 patients were enrolled in clinical trials. MAPK and PI3K signaling pathways were found to be the most common targets of these trials, patients were matched to trials based on the results of over 50 genes (Zehir et al., 2017).

Unim et al. (2020) researched the cost-effectiveness of *RAS* mutation testing before anti-*EGFR* therapy for the treatment of metastatic colorectal cancer. A systematic review was completed in articles published between 2000 and 2018. A total of "Six economic evaluations (2 cost-effectiveness analyses, 2 cost-utility analyses, and 2 combined cost-effectiveness and cost-utility analyses) were included" for final analyses (Unim et al., 2020). The authors concluded that *RAS* status testing of patients with metastatic colorectal cancer and the administration of *EGFR* inhibitors to patients only with *RAS* wild-type tumors "is a more cost-effective strategy than treating all patients without testing"; further, "Future economic assessments should take into account other parameters that reflect the real world (eg, NRAS mutation analysis, toxicity of biological agents, genetic test sensitivity and specificity (Unim et al., 2020)."

Applicable Federal Regulations

The FDA has approved more than 50 companion diagnostic devices to detect mutations in 12 different genes for the targeted treatment of cancer. Methodologies include immunohistochemistry, real-time or multiplex PCR,

FISH, and next generation sequencing. The FDA has also approved additional nucleic acid-based tests for cancer, not specifically as companion diagnostics.

On October 23, 2019, the FDA approved the MyChoice HRD CDx (Myriad Genetic Laboratories) which is a cancer-related germline gene mutation detection system. This NGS in vitro diagnostic test assesses SNVs, insertions and deletions, and large rearrangement variants of the *BRCA1* and *BRCA2* genes. "The results of the test are used as an aid in identifying ovarian cancer patients with positive homologous recombination deficiency (HRD) status for treatment with the targeted therapy (FDA, 2019)."

On June 22, 2017 the FDA approved the Oncomine™ Dx Target Test (Thermo Fisher Scientific) as a next generation sequencing (NGS) test to detect multiple gene mutations for lung cancer in a single test from a single tissue specimen. This test detects the presence of BRAF, ROS1, and EGFR gene mutations or alterations in tumor tissue of patients with NSCLC. This test can be used to select patients with NSCLC with the BRAF V600E mutation for treatment with the combination of dabrafenib and trametinib.

On June 30, 2017 the FDA approved the Praxis Extended RAS Panel as a qualitative in vitro diagnostic test using targeted high throughput parallel sequencing for the detection of 56 specific mutations in RAS genes [KRAS (exons 2, 3, and 4) and NRAS (exons 2, 3, and 4)] in DNA extracted from formalin-fixed, paraffin-embedded (FFPE) colorectal cancer (CRC) tissue samples. The Praxis™ Extended RAS Panel is indicated to aid in the identification of patients with colorectal cancer for treatment with Vectibix® (panitumumab) based on a no mutation detected test result. The test is intended to be used on the Illumina MiSeqDx® instrument.

In November 2017 the FDA approved the marketing of the MSK-IMPACT assay as a qualitative in vitro diagnostic test that uses targeted next generation sequencing of formalin-fixed paraffin-embedded tumor tissue matched with normal specimens from patients with solid malignant neoplasms to detect tumor gene alterations in a broad multi gene panel. The test is intended to provide information on somatic mutations (point mutations and small insertions and deletions) and microsatellite instability for use by qualified health care professionals in accordance with professional guidelines, and is not conclusive or prescriptive for labeled use of any specific therapeutic product. MSK-IMPACT is a single-site assay performed at Memorial Sloan Kettering Cancer Center.

On November 30, 2017 the FDA approved FoundationOne CDx™ (F1CDx) as a next generation sequencing based in vitro diagnostic device for detection of substitutions, insertion and deletion alterations (indels), and copy number alterations (CNAs) in 324 genes and select gene rearrangements, as well as genomic signatures including microsatellite instability (MSI) and tumor mutational burden (TMB) using DNA isolated from formalin-fixed paraffin embedded (FFPE) tumor tissue specimens. The test is intended as a companion diagnostic to identify patients who may benefit from treatment with the targeted therapies in accordance with the approved therapeutic product labeling. Additionally, F1CDx is intended to provide tumor mutation profiling to be used by qualified health care professionals in accordance with professional guidelines in oncology for patients with solid malignant neoplasms. The F1CDx assay is a single-site assay performed at Foundation Medicine, Inc.

Guidelines and Recommendations

Practice Guidelines and Position Statements
National Comprehensive Cancer Network (NCCN, 2020n)
NCCN guidelines for hereditary forms of cancers state that multi-gene testing should be offered to patients and families in the context of professional genetic expertise for pre- and post-test counseling. NCCN recommends that "patients who have a personal or family history suggestive of a single inherited cancer syndrome (NCCN, 2020n) are most appropriately managed by genetic testing for that specific syndrome. When more than one gene can explain an inherited cancer syndrome, then multi-gene testing may be more efficient and/or cost-effective."

The guidelines state that "there may be a role for multi-gene testing in individuals who have tested negative (indeterminate) for a single syndrome, but whom personal or family history remains suggestive of an inherited susceptibility." NCCN further recommends that "multi-gene testing can include intermediate penetrant (moderate-

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risk) genes", however, cautions that "not all genes included on available multi-gene tests are necessarily clinically actionable".

EuroGentest and the European Society of Human Genetics (ESHG) (Matthijs et al., 2016)

EuroGentest and the ESHG state that "For diagnostic purpose, only genes with a known (ie, published and confirmed) relationship between the aberrant genotype and the pathology should be included in the [NGS] analysis (Matthijs et al., 2016)."

Center for Medical Technology Policy (CMTP): Green Park Collaborative (CMTP, 2015)
In 2015, the Green Park Collaborative recommended that panels containing from 5 to 50 genes should be covered when the following criteria are met:

a. A subset of at least 5 constituent genes or variants is cited in the label of an FDA-approved companion diagnostic indicated for the treatment of the patient; OR
b. A subset of at least 5 constituent genes or variants is recommended for decision-making for the underlying diagnosis in nationally recognized clinical guidelines, such as those of the National Cancer Comprehensive Network (NCCN), or the American Society of Clinical Oncology (ASCO) or other guidelines that meet the IOM criteria for clinical guidelines; 10 OR
c. A subset of at least 5 constituent genes are designated as standard of care for the underlying condition by the molecular testing committees of at least 3 NCCN member institutions; OR
d. The provider has submitted two peer-reviewed journal articles of studies designed to demonstrate the safety and effectiveness of using the genomic information in question for clinical management of the patient's diagnosis and support the conclusion that use of the information is reasonably likely to provide a health benefit for the patient.

AND, in all cases:

e. The cost of analysis by NGS does not exceed the cost of individual sequencing of the target genes by other methods, AND
f. The laboratory conducting the analysis is CLIA-certified and accredited by CAP for NGS testing.

The Collaborative proposed panels over 50 genes that "should be considered" for coverage if providers have sought prior authorization demonstrating the following diagnoses:

- Stage IV adenocarcinoma of the lung
- Carcinoma of unknown primary site
- Stage IV rare or uncommon solid tumors for whom no systemic treatment exists in clinical care guidelines and/or pathways;
- Stage IV solid tumors where the median overall survival is less than two years (such as pancreatic cancer)
- Stage IV solid tumors and has exhausted established guideline-driven systemic therapy options and requisite molecular testing and maintains functional status (ECOG score 0-2) **OR**
  newly diagnosed hematologic malignancies with limited treatment options in defined clinical care guidelines (CMTP, 2015).

Billing/Coding/Physician Documentation Information

This policy may apply to the following codes. Inclusion of a code in this section does not guarantee that it will be reimbursed. For further information on reimbursement guidelines, please see Administrative Policies on the Blue Cross Blue Shield of North Carolina web site at www.bcbsnc.com. They are listed in the Category Search on the Medical Policy search page.

Applicable service codes: 81347, 81348, 81357, 81360, 81445, 81450, 81455, 81479, 81599, 0016M, 0017M, 0022U, 0037U, 0048U, 0050U, 0171U

BCBSNC may request medical records for determination of medical necessity. When medical records are requested, letters of support and/or explanation are often useful, but are not sufficient documentation unless all specific information needed to make a medical necessity determination is included.

Scientific Background and Reference Sources

For Policy Titled: Molecular Panel Testing of Cancers to Identify Targeted Therapy

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Specialty Matched Consultant Advisory Panel 8/2019

Medical Director review 8/2019

For Policy Titled: Molecular Panel Testing of Cancers for Diagnosis, Prognosis, and Identification of Targeted Therapy

Specialty Matched Consultant Advisory Panel 8/2020

Medical Director review 8/2020

Medical Director review 10/2020

Medical Director review 1/2021

Policy Implementation/Update Information

For Policy Titled: Molecular Panel Testing of Cancers to Identify Targeted Therapy

1/1/2019 New policy developed. BCBSNC will provide coverage for molecular panel testing of cancers to identify targeted therapy when it is determined to be medically necessary and criteria are met. Medical Director review 1/1/2019. Policy noticed 1/1/2019 for effective date 4/1/2019. (lpr)

10/1/19 Specialty Matched Consultant Advisory Panel 8/21/19. Reviewed by Avalon 2nd Quarter 2019 CAB. Added genes HER2, PALB2 for Breast Ca Solid Tumors and added gene MEN2A for Thyroid Ca. Deleted the coding table and deleted the following CPT codes from Billing/Coding section: 81170, 81206, 84999. Added the following PLA codes to the Billing/Coding section: 0022U, 0037U, 0048U, 0050U, 0056U, 0057U. Medical Director review 8/2019. (lpr)

11/12/19 Wording in the Policy, When Covered, and/or Not Covered section(s) changed from Medical Necessity to Reimbursement language, where needed.

For Policy Titled: Molecular Panel Testing of Cancers for Diagnosis, Prognosis, and Identification of Targeted Therapy

5/12/20 Per request from Avalon, policy title changed from "Molecular Panel Testing of Cancers to Identify Targeted Therapy" to Molecular Panel Testing of Cancers for Diagnosis, Prognosis, and Identification of Targeted Therapy." (lpr)

9/8/20 Specialty Matched Consultant Advisory Panel review 8/19/2020. No changes to policy statement. (lpr)

10/1/20 Reviewed by Avalon 2nd Quarter 2020 CAB. Added statement: all other multiplex RNA panels not listed are investigational. Added CPT code 0171U and deleted CPT codes 0056U, 0057U in the Billing/Coding section effective 10/1/2020. Updated policy guidelines, references, table of genes. Medical Director review 8/2020. (lpr)

11/10/20 Reviewed by Avalon 3rd Quarter 2020 CAB. Added CPT code 0016M to Billing/Coding section. Medical Director review 10/2020. (lpr)

2/9/21 Added the following CPT codes to the Billing/Coding section after code review by Avalon: 0017M, 81347, 81348, 81357, 81360. No change to policy statement. (lpr)

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