



MASSACHUSETTS

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## Medical Policy

# Expanded Molecular Panel Testing of Cancers to Identify Targeted Therapies

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### Policy Number: 790

BCBSA Reference Number: N/A

NCD/LCD:

- Local Coverage Determination (LCD): Genomic Sequence Analysis Panels in the Treatment of Non-Small Cell Lung Cancer (L36376)
- Local Coverage Determination (LCD): Genomic Sequence Analysis Panels in the Treatment of Acute Myelogenous Leukemia (AML) (L36926)

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Assays of Genetic Expression in Tumor Tissue as a Technique to Determine Prognosis in Patients with Breast Cancer, [#055](#)  
BCR-ABL1 Testing in Chronic Myelogenous Leukemia and Acute Lymphoblastic Leukemia, [#612](#)  
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Proteomic Testing for Targeted Therapy in Non-Small-Cell Lung Cancer, [#709](#)  
Use of Common Genetic Variants to Predict Risk of Nonfamilial Breast Cancer, [#252](#)

## Policy<sup>1</sup>

### Commercial Members: Managed Care (HMO and POS), PPO, and Indemnity Medicare HMO Blue<sup>SM</sup> and Medicare PPO Blue<sup>SM</sup> Members

The use of a NGS cancer mutation panel including analyses of the genes for solid tumors listed in Table 1a or for hematologic malignancies listed in Table 1b is considered **MEDICALLY NECESSARY** for selecting targeted cancer treatment in specific cancer types as indicated in Tables 2a and 2b respectively.

The use of a NGS cancer mutation panel may also be considered **MEDICALLY NECESSARY** to exclude the use of ineffective targeted therapies, to select alternative treatment modalities, to determine suitability for directing patients toward promising investigational therapies, or to establish a definitive diagnosis when other diagnostic approaches yield ambiguous results.

*Repeat testing may be required in the setting of patients who have clinically progressed per standardized professional guidelines after therapy or, in the case of myeloid diseases, for periodic monitoring of disease response no more frequently than once per six months.*

The use of NGS panels containing fewer genes than those in Tables 1a or 1b may be considered **MEDICALLY NECESSARY** if all the genes in the smaller panel are listed in Tables 1a or 1b. **For panels that contain genes that are not listed in Tables 1a or 1b, the results of those gene analyses must be reported separately as INVESTIGATIONAL.**

Tumor tissue genomic panels are **MEDICALLY NECESSARY** only for the indications in Tables 2a and 2b. **All tumor tissue genomic panels must be registered in the Diagnostic Exchange (DEX) and approved by Blue Cross Blue Cross Blue Shield of Massachusetts.**

**Table 1a. Genes and analyses included in NGS Solid Tumor Panel**

Gene	Hotspots	All exons	Copy number	Fusions	Gene	Hotspots	All exons	Copy number	Fusions
AKT1	H				MAP3K1		E		
ALK	H			F	MDM2			C	
APC		E	C		MDM4			C	
ARID1A		E			MET	H		C	F
BRAF	H			F	MSH6		E		
BRCA1		E			MYC			C	
BRCA2		E			MYCN			C	
CCND1	H		C		NF1		E	C	
CCNE1			C		NOTCH1	H			
CDH1		E			NRAS	H			
CDK4	H		C		NTRK1		E		F
CDKN2A		E	C		NTRK2		E		F
CTNNB1	H				NTRK3		E		F
DDR2		E			PDGFRA	H			
EGFR	H		C	F	PIK3CA	H		C	

ERBB2	H		C	F	PIK3R1		E		
ERBB3		E			PTCH		E	C	
ERBB4		E			PTEN		E	C	
ESR1	H			F	RB1		E	C	
FGFR1	H		C	F	RELA				F
FGFR2	H		C	F	RET	H			F
FGFR3	H		C	F	ROS1		E		F
GATA3		E			SMAD2		E		
GLI2		E	C		SMAD4		E		
GNA11	H				SMARCA4		E		
GNAQ	H				SMARCB1			C	
GNAS	H				SMO	H			
HRAS	H				STAG2		E		
IDH1	H				STK11		E	C	
IDH2	H				SUFU		E	C	
KIT	H				TP53		E	C	
KRAS	H		C		TSC1		E	C	
MAP2K1	H				TSC2		E	C	

**Table 1b. Genes and analyses included in Hematologic Malignancy NGS Panel**

Gene	Hotspots	All exons	Copy number	Gene	Hotspots	All exons	Copy number
ABL1		E		JAK2	H		
ASXL1		E		KIT	H		
ATM		E	C	KRAS	H		
BCL6			C	MAP2K1	H		
BCOR		E		MPL	H		
BRAF	H			MYD88	H		
CALR	H			NOTCH1		E	
CBL	H			NOTCH2		E	
CBLB		E	C	NPM1	H		
CEBPA		E		NRAS	H		
CHEK2	H			PDGFRA	H		
CREBBP	H			PTEN		E	C
CSF3R	H			RB1		E	C
CXCR4		E		RUNX1		E	
DNMT3A	H			SETBP1	H		

EZH2	H			SF3B1	H		
FBXW7	H			SRSF2	H		
FLT3	H			STAT3	H		
GATA2	H			TET2		E	
GATA3	H			TP53		E	C
IDH1	H			U2AF1	H		
IDH2	H			WT1		E	
IKZF1			C	ZRSR2		E	

**Table 2a. Conditions for which Solid Tumor NGS Panel Testing is [MEDICALLY NECESSARY](#)**

Disease For Which Test is Covered	Additional Requirements
B-Cell NHL	Diagnostic, Prognostic, Monitoring
Bladder Urothelial Carcinoma	Stage IV or recurrent or unresectable
Breast	Stage IV or refractory or recurrent
Cholangiocarcinoma	Stage IV or recurrent or unresectable
Colorectal Cancer	Stage IV or recurrent or unresectable
Endometrial Carcinoma	Stage IV or recurrent or unresectable
GI Stromal Tumor	Any stage
Glioma	Diagnostic, Prognostic, Monitoring
Medulloblastoma	Diagnostic, Prognostic, Monitoring
Melanoma	Stage IIIB, IIIC, IV or recurrent or unresectable
Meningioma	Grade 2 to 4 (only recurrent or unresectable)
Neuroblastoma	Any stage
Non-Small Cell Lung Cancer	Stage IIIB, IV or recurrent
Rare Tumors	Less than 5,000/year in US; Metastatic or recurrent or unresectable
Stomach/Esophageal Cancer	Stage IV or recurrent or unresectable
T-Cell NHL	Diagnostic, Prognostic
Thyroid Cancer	Stage IV or recurrent or unresectable
Unknown Primary	May be used for Diagnosis or Therapeutic Decision Making

**Table 2b. Conditions for which Hematologic Malignancy NGS Panel Testing or is [MEDICALLY NECESSARY](#)**

Disease For Which Test is Covered	Purpose/Use of Test
Acute Myeloid Leukemia	Diagnostic, Prognostic, Therapeutic, Monitoring
B-ALL	Diagnostic, Prognostic, Monitoring
B-Cell NHL/ Plasma Cell Dyscrasia	Diagnostic, Prognostic, Monitoring

Myelodysplasia	Diagnostic, Prognostic, Monitoring
Myeloproliferative Diseases	Diagnostic, Prognostic, Therapeutic, Monitoring
T-ALL	Diagnostic, Prognostic, Monitoring
T-Cell NHL	Diagnostic, Prognostic

The use of NGS panels containing fewer genes or a greater number of genes than those listed in Tables 1a and 1b for the indications in Tables 2a and 2b are required to be approved by BCBSMA in our Diagnostic Exchange.

Testing for other types of cancers is considered **INVESTIGATIONAL**.

Inclusion of any additional genes in the panel is considered **INVESTIGATIONAL**.

**Local Coverage Determination (LCD): Genomic Sequence Analysis Panels in the Treatment of Non-Small Cell Lung Cancer (L36376)**

[https://www.cms.gov/medicare-coverage-database/details/lcd-details.aspx?LCDId=36376&ContrlId=310&ver=3&ContrVer=1&CtrctrSelected=310\\*1&Ctrctr=310&s=24&DocType=All&bc=AggAAAQAAAAAAAA%3d%3d&](https://www.cms.gov/medicare-coverage-database/details/lcd-details.aspx?LCDId=36376&ContrlId=310&ver=3&ContrVer=1&CtrctrSelected=310*1&Ctrctr=310&s=24&DocType=All&bc=AggAAAQAAAAAAAA%3d%3d&)

**Local Coverage Determination (LCD): Genomic Sequence Analysis Panels in the Treatment of Acute Myelogenous Leukemia (AML) (L36926)**

[https://www.cms.gov/medicare-coverage-database/details/lcd-details.aspx?LCDId=36926&ContrlId=310&ver=5&ContrVer=1&CtrctrSelected=310\\*1&Ctrctr=310&s=24&DocType=All&bc=AggAAAQAAAAAAAA%3d%3d&](https://www.cms.gov/medicare-coverage-database/details/lcd-details.aspx?LCDId=36926&ContrlId=310&ver=5&ContrVer=1&CtrctrSelected=310*1&Ctrctr=310&s=24&DocType=All&bc=AggAAAQAAAAAAAA%3d%3d&)

**Prior Authorization Information**

Pre-service approval is required for all inpatient services for all products.

See below for situations where prior authorization may be required or may not be required.

Yes indicates that prior authorization is required.

No indicates that prior authorization is not required.

N/A indicates that this service is primarily performed in an inpatient setting.

	<b>Outpatient</b>
<b>Commercial Managed Care (HMO and POS)</b>	No
<b>Commercial PPO and Indemnity</b>	No
<b>Medicare HMO Blue<sup>SM</sup></b>	No
<b>Medicare PPO Blue<sup>SM</sup></b>	No

**CPT Codes / HCPCS Codes / ICD Codes**

*Inclusion or exclusion of a code does not constitute or imply member coverage or provider reimbursement. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage as it applies to an individual member.*

*Providers should report all services using the most up-to-date industry-standard procedure, revenue, and diagnosis codes, including modifiers where applicable.*

*The following codes are included below for informational purposes only; this is not an all-inclusive list.*

**The above medical necessity criteria MUST be met for the following codes to be covered for Commercial Members: Managed Care (HMO and POS), PPO, Indemnity, Medicare HMO Blue and Medicare PPO Blue:**

## CPT Codes

CPT codes:	Code Description
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 variants and copy number variants or rearrangements, if performed
81450	Targeted genomic sequence analysis panel, hematolymphoid neoplasm or disorder, DNA analysis, 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
81455	Targeted genomic sequence analysis panel, solid organ or hematolymphoid neoplasm, DNA analysis, 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

The following ICD Diagnosis Codes are considered medically necessary when submitted with the CPT codes above if medical necessity criteria are met:

## ICD-10 Diagnosis Codes

ICD-10-CM diagnosis codes:	Code Description
C15.3	Malignant Neoplasm Of Upper Third Of Esophagus
C15.4	Malignant Neoplasm Of Middle Third Of Esophagus
C15.5	Malignant Neoplasm Of Lower Third Of Esophagus
C15.8	Malignant Neoplasm Of Overlapping Sites Of Esophagus
C15.9	Malignant Neoplasm Of Esophagus, Unspecified
C16.0	Malignant Neoplasm Of Cardia
C16.1	Malignant Neoplasm Of Fundus Of Stomach
C16.2	Malignant Neoplasm Of Body Of Stomach
C16.3	Malignant Neoplasm Of Pyloric Antrum
C16.4	Malignant Neoplasm Of Pylorus
C16.9	Malignant Neoplasm Of Stomach, Unspecified
C18.0	Malignant Neoplasm Of Cecum
C18.2	Malignant Neoplasm Of Ascending Colon
C18.3	Malignant Neoplasm Of Hepatic Flexure
C18.4	Malignant Neoplasm Of Transverse Colon
C18.5	Malignant Neoplasm Of Splenic Flexure
C18.6	Malignant Neoplasm Of Descending Colon
C18.7	Malignant Neoplasm Of Sigmoid Colon
C18.8	Malignant Neoplasm Of Overlapping Sites Of Colon
C18.9	Malignant Neoplasm Of Colon, Unspecified
C22.1	Intrahepatic Bile Duct Carcinoma
C34.00	Malignant Neoplasm Of Unspecified Main Bronchus
C34.01	Malignant neoplasm of right main bronchus

C34.02	Malignant neoplasm of left main bronchus
C34.10	Malignant Neoplasm Of Upper Lobe, Unspecified Bronchus Or Lung
C34.11	Malignant neoplasm of upper lobe, right bronchus or lung
C34.12	Malignant neoplasm of upper lobe, left bronchus or lung
C34.2	Malignant Neoplasm Of Middle Lobe, Bronchus Or Lung
C34.30	Malignant Neoplasm Of Lower Lobe, Unspecified Bronchus Or Lung
C34.31	Malignant neoplasm of lower lobe, right bronchus or lung
C34.32	Malignant neoplasm of lower lobe, left bronchus or lung
C34.80	Malignant Neoplasm Of Overlapping Sites Of Unspecified Bronchus And Lung
C34.81	Malignant neoplasm of overlapping sites of right bronchus and lung
C34.82	Malignant neoplasm of overlapping sites of left bronchus and lung
C41.2	Malignant Neoplasm Of Vertebral Column
C43.0	Malignant Melanoma Of Lip
C43.10	Malignant Melanoma Of Unspecified Eyelid, Including Canthus
C43.11	Malignant melanoma of right eyelid, including canthus
C43.12	Malignant melanoma of left eyelid, including canthus
C43.20	Malignant Melanoma Of Unspecified Ear And External Auricular Canal
C43.21	Malignant melanoma of right ear and external auricular canal
C43.22	Malignant melanoma of left ear and external auricular canal
C43.30	Malignant Melanoma Of Unspecified Part Of Face
C43.31	Malignant Melanoma Of Nose
C43.39	Malignant Melanoma Of Other Parts Of Face
C43.4	Malignant Melanoma Of Scalp And Neck
C43.51	Malignant melanoma of anal skin
C43.52	Malignant melanoma of skin of breast
C43.59	Malignant Melanoma Of Other Part Of Trunk
C43.60	Malignant Melanoma Of Unspecified Upper Limb, Including Shoulder
C43.61	Malignant melanoma of right upper limb, including shoulder
C43.62	Malignant melanoma of left upper limb, including shoulder
C43.70	Malignant Melanoma Of Unspecified Lower Limb, Including Hip
C43.71	Malignant melanoma of right lower limb, including hip
C43.72	Malignant melanoma of left lower limb, including hip
C43.8	Malignant Melanoma Of Overlapping Sites Of Skin
C43.9	Malignant Melanoma Of Skin, Unspecified
C47.4	Malignant neoplasm of peripheral nerves of abdomen
C49.0	Malignant Neoplasm Of Connective And Soft Tissue Of Head, Face And Neck
C49.3	Malignant Neoplasm Of Connective And Soft Tissue Of Thorax
C49.4	Malignant Neoplasm Of Connective And Soft Tissue Of Abdomen
C50.011	Malignant neoplasm of nipple and areola, right female breast
C50.012	Malignant neoplasm of nipple and areola, left female breast
C50.019	Malignant Neoplasm Of Nipple And Areola, Unspecified Female Breast
C50.211	Malignant neoplasm of upper-inner quadrant of right female breast
C50.212	Malignant neoplasm of upper-inner quadrant of left female breast

C50.219	Malignant Neoplasm Of Upper-Inner Quadrant Of Unspecified Female Breast
C50.311	Malignant neoplasm of lower-inner quadrant of right female breast
C50.312	Malignant neoplasm of lower-inner quadrant of left female breast
C50.319	Malignant Neoplasm Of Lower-Inner Quadrant Of Unspecified Female Breast
C50.411	Malignant neoplasm of upper-outer quadrant of right female breast
C50.412	Malignant neoplasm of upper-outer quadrant of left female breast
C50.419	Malignant Neoplasm Of Upper-Outer Quadrant Of Unspecified Female Breast
C50.511	Malignant neoplasm of lower-outer quadrant of right female breast
C50.512	Malignant neoplasm of lower-outer quadrant of left female breast
C50.519	Malignant Neoplasm Of Lower-Outer Quadrant Of Unspecified Female Breast
C50.611	Malignant neoplasm of axillary tail of right female breast
C50.612	Malignant neoplasm of axillary tail of left female breast
C50.619	Malignant Neoplasm Of Axillary Tail Of Unspecified Female Breast
C50.811	Malignant neoplasm of overlapping sites of right female breast
C50.812	Malignant neoplasm of overlapping sites of left female breast
C50.819	Malignant Neoplasm Of Overlapping Sites Of Unspecified Female Breast
C50.911	Malignant neoplasm of unspecified site of right female breast
C50.912	Malignant neoplasm of unspecified site of left female breast
C50.919	Malignant Neoplasm Of Unspecified Site Of Unspecified Female Breast
C54.1	Malignant Neoplasm Of Endometrium
C54.2	Malignant Neoplasm Of Myometrium
C54.3	Malignant Neoplasm Of Fundus Uteri
C54.9	Malignant Neoplasm Of Corpus Uteri, Unspecified
C64.9	Malignant Neoplasm Of Unspecified Kidney, Except Renal Pelvis
C65.9	Malignant Neoplasm Of Unspecified Renal Pelvis
C66.1	Malignant neoplasm of right ureter
C66.2	Malignant neoplasm of left ureter
C66.9	Malignant Neoplasm Of Unspecified Ureter
C67.0	Malignant Neoplasm Of Trigone Of Bladder
C67.1	Malignant Neoplasm Of Dome Of Bladder
C67.2	Malignant Neoplasm Of Lateral Wall Of Bladder
C67.3	Malignant Neoplasm Of Anterior Wall Of Bladder
C67.4	Malignant Neoplasm Of Posterior Wall Of Bladder
C67.5	Malignant Neoplasm Of Bladder Neck
C67.6	Malignant Neoplasm Of Ureteric Orifice
C67.7	Malignant Neoplasm Of Urachus
C67.8	Malignant Neoplasm Of Overlapping Sites Of Bladder
C67.9	Malignant Neoplasm Of Bladder, Unspecified
C68.0	Malignant Neoplasm Of Urethra
C68.1	Malignant Neoplasm Of Paraurethral Glands
C68.8	Malignant Neoplasm Of Overlapping Sites Of Urinary Organs
C68.9	Malignant Neoplasm Of Urinary Organ, Unspecified
C70.0	Malignant Neoplasm Of Cerebral Meninges



C70.1	Malignant Neoplasm Of Spinal Meninges
C70.9	Malignant Neoplasm Of Meninges, Unspecified
C71.0	Malignant Neoplasm Of Cerebrum, Except Lobes And Ventricles
C71.1	Malignant Neoplasm Of Frontal Lobe
C71.2	Malignant Neoplasm Of Temporal Lobe
C71.3	Malignant Neoplasm Of Parietal Lobe
C71.4	Malignant Neoplasm Of Occipital Lobe
C71.5	Malignant Neoplasm Of Cerebral Ventricle
C71.6	Malignant Neoplasm Of Cerebellum
C71.7	Malignant Neoplasm Of Brain Stem
C71.8	Malignant Neoplasm Of Overlapping Sites Of Brain
C71.9	Malignant Neoplasm Of Brain, Unspecified
C73	Malignant Neoplasm Of Thyroid Gland
C74.00	Malignant neoplasm of cortex of unspecified adrenal gland
C74.01	Malignant neoplasm of cortex of right adrenal gland
C74.02	Malignant neoplasm of cortex of left adrenal gland
C74.10	Malignant neoplasm of medulla of unspecified adrenal gland
C74.11	Malignant neoplasm of medulla of right adrenal gland
C74.12	Malignant neoplasm of medulla of left adrenal gland
C74.90	Malignant Neoplasm Of Unspecified Part Of Unspecified Adrenal Gland
C74.91	Malignant neoplasm of unspecified part of right adrenal gland
C74.92	Malignant neoplasm of unspecified part of left adrenal gland
C78.00	Secondary Malignant Neoplasm Of Unspecified Lung
C78.01	Secondary malignant neoplasm of right lung
C78.02	Secondary malignant neoplasm of left lung
C78.5	Secondary Malignant Neoplasm Of Large Intestine And Rectum
C78.7	Secondary Malignant Neoplasm Of Liver And Intrahepatic Bile Duct
C78.89	Secondary Malignant Neoplasm Of Other Digestive Organs
C79.00	Secondary Malignant Neoplasm Of Unspecified Kidney And Renal Pelvis
C79.01	Secondary malignant neoplasm of right kidney and renal pelvis
C79.02	Secondary malignant neoplasm of left kidney and renal pelvis
C79.10	Secondary malignant neoplasm of unspecified urinary organs
C79.11	Secondary Malignant Neoplasm Of Bladder
C79.19	Secondary Malignant Neoplasm Of Other Urinary Organs
C79.31	Secondary Malignant Neoplasm Of Brain
C79.81	Secondary Malignant Neoplasm Of Breast
C79.82	Secondary Malignant Neoplasm Of Genital Organs
C79.89	Secondary Malignant Neoplasm Of Other Specified Sites
C82.50	Diffuse follicle center lymphoma, unspecified site
C82.51	Diffuse follicle center lymphoma, lymph nodes of head, face, and neck
C82.52	Diffuse follicle center lymphoma, intrathoracic lymph nodes
C82.53	Diffuse follicle center lymphoma, intra-abdominal lymph nodes
C82.54	Diffuse follicle center lymphoma, lymph nodes of axilla and upper limb

C82.55	Diffuse follicle center lymphoma, lymph nodes of inguinal region and lower limb
C82.56	Diffuse follicle center lymphoma, intrapelvic lymph nodes
C82.57	Diffuse follicle center lymphoma, spleen
C82.58	Diffuse follicle center lymphoma, lymph nodes of multiple sites
C82.59	Diffuse follicle center lymphoma, extranodal and solid organ sites
C83.00	Small cell B-cell lymphoma, unspecified site
C83.01	Small cell B-cell lymphoma, lymph nodes of head, face, and neck
C83.02	Small cell B-cell lymphoma, intrathoracic lymph nodes
C83.03	Small cell B-cell lymphoma, intra-abdominal lymph nodes
C83.04	Small cell B-cell lymphoma, lymph nodes of axilla and upper limb
C83.05	Small cell B-cell lymphoma, lymph nodes of inguinal region and lower limb
C83.06	Small cell B-cell lymphoma, intrapelvic lymph nodes
C83.07	Small cell B-cell lymphoma, spleen
C83.08	Small cell B-cell lymphoma, lymph nodes of multiple sites
C83.09	Small cell B-cell lymphoma, extranodal and solid organ sites
C83.10	Mantle Cell Lymphoma, Unspecified Site
C83.11	Mantle Cell Lymphoma, Lymph Nodes Of Head, Face, And Neck
C83.12	Mantle Cell Lymphoma, Intrathoracic Lymph Nodes
C83.13	Mantle Cell Lymphoma, Intra-Abdominal Lymph Nodes
C83.14	Mantle Cell Lymphoma, Lymph Nodes Of Axilla And Upper Limb
C83.15	Mantle Cell Lymphoma, Lymph Nodes Of Inguinal Region And Lower Limb
C83.16	Mantle Cell Lymphoma, Intrapelvic Lymph Nodes
C83.17	Mantle Cell Lymphoma, Spleen
C83.18	Mantle Cell Lymphoma, Lymph Nodes Of Multiple Sites
C83.19	Mantle Cell Lymphoma, Extranodal And Solid Organ Sites
C83.30	Diffuse Large B-Cell Lymphoma, Unspecified Site
C83.31	Diffuse Large B-Cell Lymphoma, Lymph Nodes Of Head, Face, And Neck
C83.31	Diffuse Large B-Cell Lymphoma, Lymph Nodes Of Head, Face, And Neck
C83.32	Diffuse Large B-Cell Lymphoma, Intrathoracic Lymph Nodes
C83.32	Diffuse Large B-Cell Lymphoma, Intrathoracic Lymph Nodes
C83.33	Diffuse Large B-Cell Lymphoma, Intra-Abdominal Lymph Nodes
C83.34	Diffuse Large B-Cell Lymphoma, Lymph Nodes Of Axilla And Upper Limb
C83.35	Diffuse Large B-Cell Lymphoma, Lymph Nodes Of Inguinal Region And Lower Limb
C83.36	Diffuse Large B-Cell Lymphoma, Intrapelvic Lymph Nodes
C83.37	Diffuse Large B-Cell Lymphoma, Spleen
C83.38	Diffuse Large B-Cell Lymphoma, Lymph Nodes Of Multiple Sites
C83.39	Diffuse Large B-Cell Lymphoma, Extranodal And Solid Organ Sites
C83.50	Lymphoblastic (Diffuse) Lymphoma, Unspecified Site
C83.51	Lymphoblastic (Diffuse) Lymphoma, Lymph Nodes Of Head, Face, And Neck
C83.52	Lymphoblastic (Diffuse) Lymphoma, Intrathoracic Lymph Nodes
C83.53	Lymphoblastic (Diffuse) Lymphoma, Intra-Abdominal Lymph Nodes
C83.54	Lymphoblastic (Diffuse) Lymphoma, Lymph Nodes Of Axilla And Upper Limb
C83.55	Lymphoblastic (Diffuse) Lymphoma, Lymph Nodes Of Inguinal Region And Lower Limb

C83.56	Lymphoblastic (Diffuse) Lymphoma, Intrapelvic Lymph Nodes
C83.57	Lymphoblastic (Diffuse) Lymphoma, Spleen
C83.58	Lymphoblastic (Diffuse) Lymphoma, Lymph Nodes Of Multiple Sites
C83.59	Lymphoblastic (Diffuse) Lymphoma, Extranodal And Solid Organ Sites
C83.70	Burkitt Lymphoma, Unspecified Site
C83.71	Burkitt Lymphoma, Lymph Nodes Of Head, Face, And Neck
C83.72	Burkitt lymphoma, intrathoracic lymph nodes
C83.73	Burkitt Lymphoma, Intra-Abdominal Lymph Nodes
C83.74	Burkitt Lymphoma, Lymph Nodes Of Axilla And Upper Limb
C83.75	Burkitt Lymphoma, Lymph Nodes Of Inguinal Region And Lower Limb
C83.76	Burkitt Lymphoma, Intrapelvic Lymph Nodes
C83.77	Burkitt Lymphoma, Spleen
C83.78	Burkitt Lymphoma, Lymph Nodes Of Multiple Sites
C83.79	Burkitt Lymphoma, Extranodal And Solid Organ Sites
C83.80	Other non-follicular lymphoma, unspecified site
C83.81	Other non-follicular lymphoma, lymph nodes of head, face, and neck
C83.82	Other non-follicular lymphoma, intrathoracic lymph nodes
C83.83	Other non-follicular lymphoma, intra-abdominal lymph nodes
C83.84	Other non-follicular lymphoma, lymph nodes of axilla and upper limbs
C83.85	Other non-follicular lymphoma, lymph nodes of inguinal region and lower limbs
C83.86	Other non-follicular lymphoma, intrapelvic lymph nodes
C83.87	Other non-follicular lymphoma, spleen
C83.88	Other non-follicular lymphoma, lymph nodes of multiple sites
C83.89	Other non-follicular lymphoma, extranodal and solid organ sites
C84.00	Mycosis Fungoides, Unspecified Site
C84.01	Mycosis Fungoides, Lymph Nodes Of Head, Face, And Neck
C84.02	Mycosis Fungoides, Intrathoracic Lymph Nodes
C84.03	Mycosis Fungoides, Intra-Abdominal Lymph Nodes
C84.04	Mycosis Fungoides, Lymph Nodes Of Axilla And Upper Limb
C84.05	Mycosis Fungoides, Lymph Nodes Of Inguinal Region And Lower Limb
C84.06	Mycosis Fungoides, Intrapelvic Lymph Nodes
C84.07	Mycosis Fungoides, Spleen
C84.08	Mycosis Fungoides, Lymph Nodes Of Multiple Sites
C84.09	Mycosis Fungoides, Extranodal And Solid Organ Sites
C84.40	Peripheral T-Cell Lymphoma, Not Classified, Unspecified Site
C84.41	Peripheral T-Cell Lymphoma, Not Classified, Lymph Nodes Of Head, Face, And Neck
C84.42	Peripheral T-Cell Lymphoma, Not Classified, Intrathoracic Lymph Nodes
C84.43	Peripheral T-Cell Lymphoma, Not Classified, Intra-Abdominal Lymph Nodes
C84.44	Peripheral T-Cell Lymphoma, Not Classified, Lymph Nodes Of Axilla And Upper Limb
C84.45	Peripheral T-Cell Lymphoma, Not Classified, Lymph Nodes Of Inguinal Region And Lower Limb
C84.46	Peripheral T-Cell Lymphoma, Not Classified, Intrapelvic Lymph Nodes
C84.47	Peripheral T-Cell Lymphoma, Not Classified, Spleen

C84.48	Peripheral T-Cell Lymphoma, Not Classified, Lymph Nodes Of Multiple Sites
C84.49	Peripheral T-Cell Lymphoma, Not Classified, Extranodal And Solid Organ Sites
C84.60	Anaplastic Large Cell Lymphoma, Alk-Positive, Unspecified Site
C84.61	Anaplastic Large Cell Lymphoma, Alk-Positive, Lymph Nodes Of Head, Face, And Neck
C84.62	Anaplastic Large Cell Lymphoma, Alk-Positive, Intrathoracic Lymph Nodes
C84.63	Anaplastic Large Cell Lymphoma, Alk-Positive, Intra-Abdominal Lymph Nodes
C84.64	Anaplastic Large Cell Lymphoma, Alk-Positive, Lymph Nodes Of Axilla And Upper Limb
C84.65	Anaplastic Large Cell Lymphoma, Alk-Positive, Lymph Nodes Of Inguinal Region And Lower Limb
C84.66	Anaplastic Large Cell Lymphoma, Alk-Positive, Intrapelvic Lymph Nodes
C84.67	Anaplastic Large Cell Lymphoma, Alk-Positive, Spleen
C84.68	Anaplastic Large Cell Lymphoma, Alk-Positive, Lymph Nodes Of Multiple Sites
C84.69	Anaplastic Large Cell Lymphoma, Alk-Positive, Extranodal And Solid Organ Sites
C84.70	Anaplastic Large Cell Lymphoma, Alk-Negative, Unspecified Site
C84.71	Anaplastic Large Cell Lymphoma, Alk-Negative, Lymph Nodes Of Head, Face, And Neck
C84.72	Anaplastic Large Cell Lymphoma, Alk-Negative, Intrathoracic Lymph Nodes
C84.73	Anaplastic Large Cell Lymphoma, Alk-Negative, Intra-Abdominal Lymph Nodes
C84.74	Anaplastic Large Cell Lymphoma, Alk-Negative, Lymph Nodes Of Axilla And Upper Limb
C84.75	Anaplastic Large Cell Lymphoma, Alk-Negative, Lymph Nodes Of Inguinal Region And Lower Limb
C84.76	Anaplastic Large Cell Lymphoma, Alk-Negative, Intrapelvic Lymph Nodes
C84.77	Anaplastic Large Cell Lymphoma, Alk-Negative, Spleen
C84.78	Anaplastic Large Cell Lymphoma, Alk-Negative, Lymph Nodes Of Multiple Sites
C84.79	Anaplastic Large Cell Lymphoma, Alk-Negative, Extranodal And Solid Organ Sites
C84.90	Mature T/NK-cell lymphomas, unspecified, unspecified site
C84.91	Mature T/NK-cell lymphomas, unspecified, lymph nodes of head, face, and neck
C84.92	Mature T/NK-cell lymphomas, unspecified, intrathoracic lymph nodes
C84.93	Mature T/Nk-Cell Lymphomas, Unspecified, Intra-Abdominal Lymph Nodes
C84.95	Mature T/NK-cell lymphomas, unspecified, lymph nodes of inguinal region and lower limb
C84.96	Mature T/NK-cell lymphomas, unspecified, intrapelvic lymph nodes
C84.97	Mature T/NK-cell lymphomas, unspecified, spleen
C84.98	Mature T/NK-cell lymphomas, unspecified, lymph nodes of multiple sites
C84.99	Mature T/NK-cell lymphomas, unspecified, extranodal and solid organ sites
C84.A0	Cutaneous T-cell lymphoma, unspecified, unspecified site
C84.A1	Cutaneous T-cell lymphoma, unspecified lymph nodes of head, face, and neck
C84.A2	Cutaneous T-cell lymphoma, unspecified, intrathoracic lymph nodes
C84.A3	Cutaneous T-cell lymphoma, unspecified, intra-abdominal lymph nodes
C84.A4	Cutaneous T-cell lymphoma, unspecified, lymph nodes of axilla and upper limb
C84.A5	Cutaneous T-cell lymphoma, unspecified, lymph nodes of inguinal region and lower limb
C84.A6	Cutaneous T-cell lymphoma, unspecified, intrapelvic lymph nodes
C84.A7	Cutaneous T-cell lymphoma, unspecified, spleen
C84.A8	Cutaneous T-cell lymphoma, unspecified, lymph nodes of multiple sites
C84.A9	Cutaneous T-cell lymphoma, unspecified, extranodal and solid organ sites
C84.Z0	Other mature T/NK-cell lymphomas, unspecified site

C84.Z1	Other mature T/NK-cell lymphomas, lymph nodes of head, face, and neck
C84.Z2	Other mature T/NK-cell lymphomas, intrathoracic lymph nodes
C84.Z3	Other mature T/NK-cell lymphomas, intra-abdominal lymph nodes
C84.Z4	Other mature T/NK-cell lymphomas, lymph nodes of axilla and upper limb
C84.Z5	Other mature T/NK-cell lymphomas, lymph nodes of inguinal region and lower limb
C84.Z6	Other mature T/NK-cell lymphomas, intrapelvic lymph nodes
C84.Z7	Other mature T/NK-cell lymphomas, spleen
C84.Z8	Other mature T/NK-cell lymphomas, lymph nodes of multiple sites
C84.Z9	Other mature T/NK-cell lymphomas, extranodal and solid organ sites
C85.10	Unspecified B-cell lymphoma, unspecified site
C85.11	Unspecified B-cell lymphoma, lymph nodes of head, face, and neck
C85.12	Unspecified B-cell lymphoma, intrathoracic lymph nodes
C85.13	Unspecified B-cell lymphoma, intra-abdominal lymph nodes
C85.14	Unspecified B-cell lymphoma, lymph nodes of axilla and upper limb
C85.15	Unspecified B-cell lymphoma, lymph nodes of inguinal region and lower limb
C85.16	Unspecified B-cell lymphoma, intrapelvic lymph nodes
C85.17	Unspecified B-cell lymphoma, spleen
C85.18	Unspecified B-cell lymphoma, lymph nodes of multiple sites
C85.19	Unspecified B-cell lymphoma, extranodal and solid organ sites
C85.20	Mediastinal (thymic) large B-cell lymphoma, unspecified site
C85.21	Mediastinal (thymic) large B-cell lymphoma, lymph nodes of head, face, and neck
C85.22	Mediastinal (thymic) large B-cell lymphoma, intrathoracic lymph nodes
C85.23	Mediastinal (thymic) large B-cell lymphoma, intra-abdominal lymph nodes
C85.24	Mediastinal (thymic) large B-cell lymphoma, lymph nodes of axilla and upper limb
C85.25	Mediastinal (thymic) large B-cell lymphoma, lymph nodes of inguinal region and lower limb
C85.26	Mediastinal (thymic) large B-cell lymphoma, intrapelvic lymph nodes
C85.27	Mediastinal (thymic) large B-cell lymphoma, spleen
C85.28	Mediastinal (thymic) large B-cell lymphoma, spleen
C85.29	Mediastinal (thymic) large B-cell lymphoma, extranodal and solid organ sites
C85.80	Other Specified Types Of Non-Hodgkin Lymphoma, Unspecified Site
C85.81	Other Specified Types Of Non-Hodgkin Lymphoma, Lymph Nodes Of Head, Face, And Neck
C85.82	Other Specified Types Of Non-Hodgkin Lymphoma, Intrathoracic Lymph Nodes
C85.83	Other Specified Types Of Non-Hodgkin Lymphoma, Intra-Abdominal Lymph Nodes
C85.84	Other Specified Types Of Non-Hodgkin Lymphoma, Lymph Nodes Of Axilla And Upper Limb
C85.85	Other Specified Types Of Non-Hodgkin Lymphoma, Lymph Nodes Of Inguinal Region And Lower Limb
C85.86	Other Specified Types Of Non-Hodgkin Lymphoma, Intrapelvic Lymph Nodes
C85.87	Other Specified Types Of Non-Hodgkin Lymphoma, Spleen
C85.88	Other Specified Types Of Non-Hodgkin Lymphoma, Lymph Nodes Of Multiple Sites
C85.89	Other Specified Types Of Non-Hodgkin Lymphoma, Extranodal And Solid Organ Sites
C85.90	Non-Hodgkin lymphoma, unspecified, unspecified site
C85.91	Non-Hodgkin lymphoma, unspecified, lymph nodes of head, face, and neck
C85.92	Non-Hodgkin lymphoma, unspecified, intrathoracic lymph nodes

C85.94	Non-Hodgkin lymphoma, unspecified, lymph nodes of axilla and upper limb
C85.95	Non-Hodgkin lymphoma, unspecified, lymph nodes of inguinal region and lower limb
C85.96	Non-Hodgkin lymphoma, unspecified, intrapelvic lymph nodes
C85.97	Non-Hodgkin lymphoma, unspecified, spleen
C85.98	Non-Hodgkin lymphoma, unspecified, lymph nodes of multiple sites
C85.99	Non-Hodgkin lymphoma, unspecified, extranodal and solid organ sites
C86.0	Extranodal NK/T-cell lymphoma, nasal type
C86.1	Hepatosplenic T-cell lymphoma
C86.2	Enteropathy-type (intestinal) T-cell lymphoma
C86.3	Subcutaneous panniculitis-like T-cell lymphoma
C86.4	Blastic NK-cell lymphoma
C88.8	Other malignant immunoproliferative diseases
C91.00	Acute Lymphoblastic Leukemia Not Having Achieved Remission
C91.01	Acute Lymphoblastic Leukemia, In Remission
C91.02	Acute Lymphoblastic Leukemia, In Relapse
C91.10	Chronic lymphocytic leukemia of B-cell type not having achieved remission
C91.11	Chronic lymphocytic leukemia of B-cell type in remission
C91.12	Chronic lymphocytic leukemia of B-cell type in relapse
C91.30	Prolymphocytic leukemia of B-cell type not having achieved remission
C91.31	Prolymphocytic leukemia of B-cell type, in remission
C91.32	Prolymphocytic leukemia of B-cell type, in relapse
C91.50	Adult T-cell lymphoma/leukemia (HTLV-1-associated) not having achieved remission
C91.51	Adult T-cell lymphoma/leukemia (HTLV-1-associated), in remission
C91.52	Adult T-cell lymphoma/leukemia (HTLV-1-associated), in relapse
C91.60	Prolymphocytic leukemia of T-cell type not having achieved remission
C91.61	Prolymphocytic leukemia of T-cell type, in remission
C91.62	Prolymphocytic leukemia of T-cell type, in relapse
C91.A0	Mature B-cell leukemia Burkitt-type not having achieved remission
C91.A1	Mature B-cell leukemia Burkitt-type, in remission
C91.A2	Mature B-cell leukemia Burkitt-type, in relapse
C91.Z0	Other lymphoid leukemia not having achieved remission
C91.Z1	Other lymphoid leukemia, in remission
C91.Z2	Other lymphoid leukemia, in relapse
C92.00	Acute Myeloblastic Leukemia, Not Having Achieved Remission
C92.01	Acute Myeloblastic Leukemia, In Remission
C92.02	Acute Myeloblastic Leukemia, In Relapse
C92.40	Acute Promyelocytic Leukemia, Not Having Achieved Remission
C92.41	Acute Promyelocytic Leukemia, In Remission
C92.42	Acute Promyelocytic Leukemia, In Relapse
C92.50	Acute Myelomonocytic Leukemia, Not Having Achieved Remission
C92.51	Acute Myelomonocytic Leukemia, In Remission
C92.52	Acute Myelomonocytic Leukemia, In Relapse
C92.60	Acute myeloid leukemia with 11q23-abnormality not having achieved remission

C92.61	Acute myeloid leukemia with 11q23-abnormality in remission
C92.62	Acute myeloid leukemia with 11q23-abnormality in relapse
C92.A0	Acute myeloid leukemia with multilineage dysplasia, not having achieved remission
C92.A1	Acute myeloid leukemia with multilineage dysplasia, in remission
C92.A2	Acute myeloid leukemia with multilineage dysplasia, in relapse
C94.40	Acute Panmyelosis With Myelofibrosis Not Having Achieved Remission
C94.41	Acute Panmyelosis With Myelofibrosis, In Remission
C94.42	Acute Panmyelosis With Myelofibrosis, In Relapse
C94.6	Myelodysplastic disease, not classified
C96.2	Malignant mast cell tumor
D45	Polycythemia vera
D46.0	Refractory Anemia Without Ring Sideroblasts, So Stated
D46.1	Refractory Anemia With Ring Sideroblasts
D46.20	Refractory Anemia With Excess Of Blasts, Unspecified
D46.21	Refractory Anemia With Excess Of Blasts 1
D46.22	Refractory Anemia With Excess Of Blasts 2
D46.4	Refractory anemia, unspecified
D46.9	Myelodysplastic Syndrome, Unspecified
D46.A	Refractory Cytopenia With Multilineage Dysplasia
D46.B	Refractory Cytopenia With Multilineage Dysplasia And Ring Sideroblasts
D46.C	Myelodysplastic Syndrome With Isolated Del(5q) Chromosomal Abnormality
D46.Z	Other myelodysplastic syndromes
D47.0	Histiocytic and mast cell tumors of uncertain behavior
D47.1	Chronic Myeloproliferative Disease
D47.2	Monoclonal gammopathy
D47.9	Neoplasm Of Uncertain Behavior Of Lymphoid, Hematopoietic And Related Tissue, Unspecified
D47.Z9	Other Specified Neoplasms Of Uncertain Behavior Of Lymphoid, Hematopoietic And Related Tissue
D48.1	Neoplasm Of Uncertain Behavior Of Connective And Other Soft Tissue
D48.2	Neoplasm of uncertain behavior of peripheral nerves and autonomic nervous system
D59.1	Other autoimmune hemolytic anemias
D59.4	Other nonautoimmune hemolytic anemias
D59.8	Other acquired hemolytic anemias
D59.9	Acquired hemolytic anemia, unspecified
D61.09	Other constitutional aplastic anemia
D61.3	Idiopathic aplastic anemia
D61.818	Other pancytopenia
D61.9	Aplastic anemia, unspecified
D64.9	Anemia, unspecified
D69.3	Immune thrombocytopenic purpura
D69.49	Other primary thrombocytopenia
D69.59	Other secondary thrombocytopenia
D69.6	Thrombocytopenia, unspecified

D70.4	Cyclic neutropenia
D70.8	Other neutropenia
D70.9	Neutropenia, unspecified
D72.1	Eosinophilia
D72.818	Other decreased white blood cell count
D72.819	Decreased white blood cell count, unspecified
D72.820	Lymphocytosis (symptomatic)
D72.829	Elevated white blood cell count, unspecified
D75.1	Secondary polycythemia
J82	Pulmonary eosinophilia, not elsewhere classified
Q82.2	Mastocytosis
Q87.2	Congenital malformation syndromes predominantly involving limbs

## Description

Advances in cancer care over the past two decades have shown improved outcomes, as compared to conventional cytotoxic chemotherapies, when treatment targets biological “pathways” that are characterized by specific genetic markers. Genetic testing offers the potential to evaluate molecular markers that identify the specific pathways that should be targeted in each patient's cancer. For some cancers, specific genetic tests are standard-of-care determinants for FDA-approved targeted therapies, and are incorporated into professional practice guidelines from the National Comprehensive Cancer Network (NCCN). For other cancers, genetic tests are used to exclude the use of a targeted therapy, and shift the focus of treatment instead towards other modalities. In still other cancers, genetic tests are used to indicate suitability for treatment with an investigational agent, as an alternative to an ineffective traditional therapy that is expected to have marginal, if any, benefit. Finally, genetic testing of cancer samples can be used to establish a definitive diagnosis or for stratification into risk-based treatment groups.

While individual gene tests have proven utility in these contexts, recent technical advances, in particular “next generation” or “massively parallel” sequencing (NGS), have enabled the simultaneous assessment of these markers in a single assay run. For patients, physicians, and laboratories, the advantages of the NGS panel tests are (1) more efficient use of limited samples, (2) more rapid time to a completed set of results, (3) more efficient resource utilization compared to performing multiple individual tests, (4) better ability to rapidly incorporate new genes into a panel in order to support clinical decision making since evidence in the field is rapidly evolving, and (5) identification of unexpected clinically actionable mutations that are not customarily associated with the tissue type of the tumor.

NGS-based genetic panels that test for a large number of cancer-associated mutations are commercially available and implemented currently as laboratory-developed tests (LDTs) offered primarily by academic centers and commercial laboratories. Clinical validity and clinical utility have been established for a number of individual genes and sets of genes in specific cancer types, based primarily upon single gene companion diagnostic assays. In this regard, NGS panels are a valid and useful technical means to efficiently combine multiple individually valid single gene tests, in defined clinical contexts where those single gene tests are also valid and useful. A growing body of evidence supports the use of expanded panel testing in selected tumor types. The evidence shows that for selected tumors, expanded panel testing reveals “driver mutations”, (mutations that activate signaling pathways which cause uncontrolled tumor cell growth) for which there are known and/or investigational drugs that will improve outcomes in patients with these tumors in comparison to conventional cytotoxic therapy.

## RATIONALE

The evaluation of a genetic test focuses on 3 main principles: (1) analytic validity (technical accuracy of the test in detecting a mutation that is present or in excluding a mutation that is absent); (2) clinical validity (diagnostic performance of the test [sensitivity, specificity, positive and negative predictive values]



in detecting clinical disease); and (3) clinical utility (how the results of the diagnostic test will be used to change management of the patient and whether these changes in management lead to clinically important improvements in health outcomes).

### **Analytic Validity**

Multiple studies have demonstrated the analytic accuracy of next generation sequencing to be greater than 99%. Initial demonstration and ongoing maintenance of analytic validity is a legal requirement for clinical laboratories operating under the Clinical Laboratories Information Act (CLIA). Laboratories that perform NGS panels must possess valid CLIA certification, and must be prepared to provide documentation of their certification status, CLIA inspection reports, and performance in proficiency testing (PT) programs, if requested. Testing in non-CLIA laboratories is not appropriate.

### **Clinical Validity of Expanded Tumor Genomic Profiling**

The goal of genomic test panels in cancer is to identify molecular genetic alterations that, in the appropriate context, provide clinical benefit, either in terms of establishing a diagnosis, selecting a molecularly-targeted therapy, or determining prognosis in a way that has a tangible patient impact, such as influencing therapeutic decisions such as whether or not to undergo a bone marrow transplant, a high intensity chemotherapeutic or radiotherapy regimen, surgical procedures, or palliative care. These classes of alterations are collectively considered "actionable" in terms of their clinical potential. While different studies have used different definitions and "tier"-based classification schemes for actionability, several studies have shown that genomic sequencing panels afford the ability to detect actionable mutations in a high percentage of patients within diverse cancer populations. Diagnostic sensitivity for actionable alterations has ranged from 30% to 90%, depending on the population studied.<sup>1-6</sup> Clinical experience with the panels addressed in this medical policy indicates that actionable mutations are found in 58.5% of tested tumors (personal communication from Brigham and Women's Laboratory for Molecular Diagnostics).<sup>7</sup>

### **Clinical Utility of Expanded Tumor Genomic Profiling**

Research over the past 20 years has clearly demonstrated that cancer is caused by mutations in one or more genes in a cell that result in overriding the normal mechanisms that inhibit growth and reproduction of the cell and cause the cell to divide and multiply despite the signals in the cell's environment that should inhibit its growth and division. The association between specific mutations (often know as driver mutations) in particular genes and cancer has been well established through conventional technologies including Sanger sequencing, genotyping, PCR, and others. The mechanism of action of these "driver mutations" has been confirmed by the in vitro, in vivo, and clinical efficacy of compounds that serve as inhibitors in the altered signaling pathways of cancer cells. Many "targeted therapies" (therapeutic compounds that have inhibitory properties in the signaling pathways known to be driving uncontrolled growth and division due to a particular mutation) have been approved by the FDA for treatment of different cancers that contain the driver mutation associated with the effective therapeutic compound. The outcomes of targeted therapies have been impressive in comparison to conventional cytotoxic chemotherapy particularly when effective cytotoxic regimens have failed.

Typically a limited number of driver mutations are associated with a cancer of a particular tissue-type. In practice, when a cancer of a particular tissue type is identified, analyses of the commonly associated genes are run to determine if the particular tumor has an "actionable mutation", that is, a driver mutation against which a drug is known to be effective in controlling the progression of the disease. With the ability to identify new compounds that are active in inhibiting different pathways, there has been a rapid expansion of drugs (targeted therapies) that are effective against tumors with different driver mutations.

As next generation sequencing technology has been introduced into clinical practice, it has become more effective and efficient to analyze tumor tissue-associated genes concurrently as a panel rather than sequencing each individual gene separately. Evidence supporting the use of somatic cancer panels for the management of patients is rapidly progressing. Retrospective analysis of phase I molecularly targeted trials at a single cancer center has indicated improved response rates, progression-free survival and overall survival in patients whose tumors were genotyped and matched to a targeted agent.<sup>8</sup> Looking

across cancer centers, the multi-institutional Lung Cancer Mutation Consortium demonstrated improved patient outcomes for patients with advanced lung cancers when a panel of molecular biomarkers were assessed and used to guide treatment decisions.<sup>9</sup> An unexpected benefit of concurrently analyzing many genes for mutations is the discoveries that mutations are found that are not typically associated with the cancer's tissue-type, yet are known to be driver mutations in a different tissue-type.<sup>10-13</sup> Treating these cancers with a drug (targeted therapy) known to be active in the unexpected driver pathway has led to significantly improved outcomes.

There is documentation in the clinical literature that each of the genes included in this panel has clinical utility in one of the following ways:

- The mutation is a driver mutation that causes the uncontrolled growth and proliferation of the tumor cells and that by finding the mutation, a targeted therapy that is effective in slowing the growth of the cancer is available.
- The mutation indicates that a targeted therapy selected on the basis of a different (driver) mutation will be ineffective.
- The mutation is characteristic of a cancer whose origin cannot be determined by histologic and immunochemical means and helps make the diagnosis.
- The mutation may indicate prognosis that influences treatment unrelated to targeted therapies, such as decisions around bone marrow transplantation, high-intensity or low-intensity chemotherapy or radiation therapy, surgery, or palliation.

In addition to identifying mutations that are known to be associated with particular tumor tissue types, the panel provides additional clinical utility by identifying mutations in a particular tumor specimen that are not typically associated with that tissue type, but may be the actual driver mutation of that specimen. This gives the oncologist the option of treating the patient with a targeted therapy that would otherwise not have been available to this patient.

The quantity of DNA obtained from a sample of tumor tissue can frequently be a limiting factor in obtaining an accurate and complete analysis. It can also limit the ability to repeat the genomic analysis on the same piece of tumor tissue. As evidence emerges that mutations in genes on the panel in cancers in which the mutations are not typically found are susceptible to new compounds, the presence of these mutations in a particular patient's tumor has already been established, avoiding the need to re-run the specimen.

The turn-around time of one large genomic analysis is shorter than multiple analyses, and can result in earlier treatment.

## Summary

Tumor marker genomic analysis has been shown to reliably identify driver mutations that initiate proliferation of tumor cells. Expanded molecular panel testing provides the information needed for targeted cancer therapies and also increases efficiencies by providing a large amount of data in a short amount of time. Clinical outcomes can be directly impacted in certain cancers when particular driver mutations are known and treatment can be tailored appropriately. Therefore expanded molecular panel testing is considered medically necessary for specific genetic panels where the identified tumor markers have known treatment options.

## Policy History

Date	Action
1/2017	Glioblastoma and Medulloblastoma indications clarified. Effective 1/1/2017.
8/2016	Table 2a. Solid Tumor NGS Panel Testing clarified to include B- Cell NHL and T-Cell NHL. Clarified coding information. 8/1/2016.
7/2016	New medical policy describing medically necessary and investigational indications. Effective 7/1/2016.

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## Endnotes

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<sup>1</sup> Based on expert opinion