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)

## Related Policies

- Analysis of Human DNA in Stool Samples as a Technique for Colorectal Cancer Screening, #557
- 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
- Molecular Analysis for Targeted Therapy of Non-Small-Cell Lung Cancer, #563
- Gene-Based Tests for Screening, Detection, and Management of Prostate Cancer, #333
- General Approach to Evaluating the Utility of Genetic Panels, #734
- General Approach to Genetic Testing, #735
- Genetic Cancer Susceptibility Panels Using Next Generation Sequencing, #574
- Genetic Testing for CHEK2 Mutations for Breast Cancer, #741
- Genetic Testing for Familial Cutaneous Malignant Melanoma, #300
- Genetic Testing for FLT3 and NPM1 Variants in Cytogenetically Normal Acute Myeloid Leukemia, #693
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- Use of Common Genetic Variants (Single Nucleotide Variants) to Predict Risk of Nonfamilial Breast Cancer, #252

## Policy[1]

### Commercial Members: Managed Care (HMO and POS), PPO, and Indemnity Medicare HMO Blue℠ and Medicare PPO Blue℠ 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.

**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 |

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

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

Medical necessity criteria and coding guidance for **Medicare Advantage members living in Massachusetts** can be found through the link below.

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)

For medical necessity criteria and coding guidance for **Medicare Advantage members living outside of Massachusetts**, please see the Centers for Medicare and Medicaid Services website for information regarding your specific jurisdiction at https://www.cms.gov.

## 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.

| | **Outpatient** |
|---|---|
| **Commercial Managed Care (HMO and POS)** | No |
| **Commercial PPO and Indemnity** | No |
| **Medicare HMO Blue℠** | No |
| **Medicare PPO Blue℠** | 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 <u>medical necessity criteria</u> 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 |
| C20 | Malignant neoplasm of rectum |
| 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 |
| C34.90 | Malignant neoplasm of unspecified part of unspecified bronchus or lung |
| C34.91 | Malignant neoplasm of unspecified part of right bronchus or lung |
| C34.92 | Malignant neoplasm of unspecified part of left bronchus or 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 |

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|---|---|
| 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 |

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|---|---|
| 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 |

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| 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 |

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| 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 |

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| 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 |

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| 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 |

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| 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 |
| C88.0 | Waldenstrom macroglobulinemia |
| 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 |
| C91.40 | Hairy cell leukemia not having achieved remission |
| C91.42 | Hairy cell leukemia, 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 |
| C92.10 | Chronic myeloid leukemia, BCR/ABL-positive, not having achieved remission |
| C92.11 | Chronic myeloid leukemia, BCR/ABL-positive, in remission |
| C92.40 | Acute Promyelocytic Leukemia, Not Having Achieved Remission |
| C92.41 | Acute Promyelocytic Leukemia, In Remission |
| C92.42 | Acute Promyelocytic Leukemia, In Relapse |

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| 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 |
| C96.20 | Malignant mast cell neoplasm, unspecified |
| C96.21 | Aggressive systemic mastocytosis |
| C96.22 | Mast cell sarcoma |
| C96.29 | Other malignant mast cell neoplasm |
| 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 |
| D47.01 | Cutaneous mastocytosis |
| D47.02 | Systemic mastocytosis |
| D47.09 | Other mast cell neoplasms of uncertain behavior |
| D47.1 | Chronic Myeloproliferative Disease |
| D47.2 | Monoclonal gammopathy |
| D47.3 | Essential (hemorrhagic) thrombocythemia |
| 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 |

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| 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 |
| D75.81 | Myelofibrosis |
| J82 | Pulmonary eosinophilia, not elsewhere classified |
| Q82.2 | Congenital cutaneous mastocytosis |
| Q87.2 | Congenital malformation syndromes predominantly involving limbs |

**The following CPT code is considered investigational for <u>Commercial Members: Managed Care (HMO and POS), PPO, and Indemnity:</u>**

## CPT Codes

| CPT codes: | Code Description |
|---|---|
| 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 |

## Description

Advances in cancer care over the past two decades have shown improved outcomes, as compared to conventional cytototoxic 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 collective 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.[1-6] 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).[7]

**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.[8] 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.[9] 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.[10-13] 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 |
|---|---|
| 4/2018 | Clarified coding information. |
| 3/2018 | Diagnostic Exchange (DEX) registration requirement removed. 3/21/2018 |
| 10/2017 | Clarified coding information. |
| 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. |

## Information Pertaining to All Blue Cross Blue Shield Medical Policies

Click on any of the following terms to access the relevant information:
Medical Policy Terms of Use
Managed Care Guidelines
Indemnity/PPO Guidelines
Clinical Exception Process
Medical Technology Assessment Guidelines

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## Endnotes

[1] Based on expert opinion