Local Coverage Determination (LCD): Biomarkers for Oncology (L35396)

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LCD Information

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CMS National Coverage Policy

This LCD supplements but does not replace, modify or supersede existing Medicare applicable National Coverage Determinations (NCDs) or payment policy rules and regulations for biomarkers for oncology services. Federal statute and subsequent Medicare regulations regarding provision and payment for medical services are lengthy. They are not repeated in this LCD. Neither Medicare payment policy rules nor this LCD replace, modify or supersede applicable state statutes regarding medical practice or other health practice professions acts, definitions and/or scopes of practice. All providers who report services for Medicare payment must fully understand and follow all existing laws, regulations and rules for Medicare payment for biomarkers for oncology services and must properly submit only valid claims for them. Please review and understand them and apply the medical necessity provisions in the policy within the context of the manual rules. Relevant CMS manual instructions and policies may be found in the following Internet-Only Manuals (IOMs) published on the CMS Web site.

IOM Citations:

- CMS IOM Publication 100-02, *Medicare Benefit Policy Manual*,
  - Chapter 15, Section 80.1 Clinical Laboratory Services
- CMS IOM Publication 100-03, *Medicare National Coverage Determinations (NCD) Manual,*
  - Chapter 1, Part 2, Section 90.2 Next-Generation Sequencing for Patients with Advanced Cancer
  - Chapter 1, Part 4, Section 210.3 Colorectal Cancer Screening Tests
- CMS IOM Publication 100-08, *Medicare Program Integrity Manual,*
  - Chapter 3, Section 3.4.1.3 Diagnosis Code Requirements, Section 3.6.2.3 Limitations of Liability Determinations
  - Chapter 13, Section 13.5.4 Reasonable and Necessary Provisions in an LCD

Social Security Act (Title XVIII) Standard References:

- Title XVIII of the Social Security Act, Section 1862(a)(1)(A) states that no Medicare payment shall be made for items or services which are not reasonable and necessary for the diagnosis or treatment of illness or injury.

- Title XVIII of the Social Security Act, Section 1862(a)(7). This section excludes routine physical examinations.

Code of Federal Regulations (CFR) References:

- CFR, Title 42, Volume 2, Chapter IV, Part 410.32(d)(3) Diagnostic x-ray tests, diagnostic laboratory tests, and other diagnostic tests: Conditions.

Coverage Guidance

Coverage Indications, Limitations, and/or Medical Necessity

Compliance with the provisions in this policy may be monitored and addressed through post payment data analysis and subsequent medical review audits.

History/Background and/or General Information

The emergence of personalized laboratory medicine has been characterized by a multitude of testing options which can more precisely pinpoint management needs of individual patients. As a result, the growing compendium of products described as biomarkers requires careful evaluation by both clinicians and laboratorians as to what testing configurations are reasonable and necessary under the Medicare Act. There are a plethora of burgeoning tools, including both gene-based (genomic) and protein-based (proteomic) assay formats, in tandem with more conventional (longstanding) flow cytometric, cytogenetic, etc. biomarkers. Classified somewhat differently, there are highly-diverse approaches ranging from single mutation biomarkers to multiple biomarker platforms, the latter of which often depend upon sophisticated biomathematical interpretative algorithms.

The term “biomarker” refers to a broad subcategory of medical signs (i.e., objective indications of medical state observed from outside the patient) which can be measured accurately and reproducibly. Medical signs stand in contrast to medical symptoms, which are limited to indications of health or illness perceived by the patient. In 1998, the National Institute of Health (NIH) defined a biomarker as: "a characteristic that is objectively measured and evaluated as an indicator of normal biologic processes pathogenic processes, or pharmacologic response to a therapeutic intervention."

This current LCD focuses upon selected testing in oncology, with some emphasis upon applying the revised 2016 CPT molecular coding format. The LCD primarily applies to molecular biomarker testing but does involve some other types of related biomarker testing, such as proteomics.

There are separate Local Coverage Determinations (LCDs) that address other biomarkers, which include a multitude of assays which are not specifically discussed below. (Please refer to the Novitas website at www.novitas-solutions.com for a complete listing of LCDs.)

Local Medicare coverage of such biomarkers must be predicated upon four fundamental principles:

1. First, the biomarkers must have proven clinical validity/utility (CVU).
2. Second, to support the medical necessity of the service, there must be acceptance/uptake of specific testing into patient management. **It is essential that physicians be familiar enough with all specific biomarkers, which they order, such that all test results may become clinically actionable.**
3. Providers managing oncological conditions must demonstrate that the use of biomarkers will be used to assist in the management/treatment of the beneficiary.
4. Peer-reviewed full manuscript evidence is required to support combination panels for multiple biomarkers, particularly regarding their alleged composite clinical validity/utility. For example; such potential billing for

multiple, diverse biomarkers (e.g., diagnostic/monitoring/prognostic/predictive) can only achieve medical necessity when it is clearly evident how each requested biomarker can be individually contributory.

It is useful to categorize oncology biomarkers into functional clusters which reflect both (1) The predominant intent of testing (with the caveat that individual assays may cross over into more than one category) and (2) the relative evidentiary expectations:

1. Oncology Biomarkers Used for Diagnosis/Classification/Monitoring/Surveillance: These types of assays are supportable by case-control sensitivity/specificity studies, with appropriate designs in place to minimize the extent of bias and confounding.
2. Oncology Biomarkers Used for Prognosis/Prediction: Oncology biomarkers used for prognosis/prediction (i.e., a predictive biomarker is associated with response [benefit] or lack of response to a particular therapy, relative to other available therapy, whereas a prognostic biomarker provides information on the likely outcome of the disease in an untreated individual).

There is a complex and diverse set of study methods which can drive the robust formulation of evidence for such esoteric testing, which are well-summarized by Deverka et al. at the Center for Medical Technology Policy, but there are currently NO standardized thresholds or benchmarks for evaluating the CVU/medical necessity of emerging biomarkers. However, the following sources (although not exhaustive and complete) may help support CVU when requesting reconsideration for coverage of biomarkers that are not included in this LCD:

1. FDA labeling documentation.
2. National Comprehensive Cancer Network (NCCN) Biomarkers Compendium recommendations, particularly where Category 1 evidence is noted.
3. Findings from well-established, independent technology assessments (e.g., Evaluation of Genomic Applications in Practice and Prevention [EGAPP], Agency for Healthcare Research and Quality [AHRQ], Blue Cross and Blue Shield Association Technology Evaluation Center [BCBSA TEC] and the Cochrane Collaboration).
4. Other independent, objective evaluations or systematic literature reviews, which can substantively contribute to the evidence base, including, but not restricted to, emerging National Institutes of Health (National Cancer Institute) guidelines for the accrual of genomics/proteomics clinical validity/utility evidence. Although there is not a prescriptive format for such systematic reviews, the documentation (submitted to Novitas) for reconsideration purposes should include the following three elements:
    - Some type of recurring/periodic Committee structure, which is comprised of at least qualified biomathematicians/methodologists, molecular pathology laboratory specialists and relevant clinicians (e.g., oncologists).
    - Evidence of active sharing of the critical evaluations in a manner that enables sufficiently broad input into this process, and a feasibly wide acceptance of this process by representative molecular pathology stakeholders. There is no preference between such a Committee being based at a single site, or even rotating among several sites.
    - Transparency of the biomarker evaluations via minutes (or a summary of minutes).

Covered Indications

MOLECULAR TESTS

Covered clinical types of application(s) are identified below as diagnostic (DX), prognostic (PROG) or predictive (PRED).

1. Colorectal Cancer

- KRAS (12/13) - PRED of resistance to an anti-EGFR agent
- KRAS codon 61 - PRED of resistance to an anti-EGFR agent
- KRAS codon 146 - PRED of resistance to an anti-EGFR agent
- NRAS - PRED of resistance to an anti-EGFR agent
- BRAF - PRED of resistance to an anti-EGFR agent + DX (sporadic vs. Lynch syndrome)
- PIK3CA - PRED of resistance to an anti-EGFR agent + PROG for local recurrence
- MSI by PCR - PRED of 5-FU resistance + DX
- MLH1 promoter hypermethylation - PRED of 5-FU resistance + DX
- mRNA (oncotype-Colon) – PRED for the recurrence risk for patients with Stage II colon cancer
- Hereditary colon cancer disorders
- Sept9

ColonSeq®

This testing provides information to the patient and provider regarding potential treatment options and implications for RAS and BRAF mutations.

Please refer to DA52986-Billing and Coding: Biomarkers for Oncology regarding coding and billing information.

2. Non-Small Cell Lung Cancer (NSCLC)

- EGFR- PRED of anti-EGFR response
- KRAS (12/13) - PRED of anti-EGFR resistance
- KRAS codon 61 - PRED of anti-EGFR resistance
- KRAS codon 146 - PRED of anti-EGFR resistance
- BRAF - PROG + PRED for anti-RAF inhibitor
  ThermoFisher Oncomine DX Target Test for Non-Small Cell Lung Cancer (NSCLC) is a 23 gene panel including a 3 gene target test (companion test) approved by the FDA in June 2017 for NSCLC from tissue specimens. It can simultaneously identify the three gene variants that are a key to targeted therapy selection: BRAF and ROS1, and EGFR. The targeted therapies are dabrafenib (Tafinlar) in combination with trametinib (Mekinist), crizotinib (Xalkori), and gefitinib (Iressa), respectively. These three drugs are approved therapies for NSCLC patients with the above gene variants. Oncomine DX Target Test is the only FDA approved companion test that detects ROS1 fusions and that detects BRAF V600E, but it does not detect ALK fusions. Coverage is limited as specified in NCD 90.2, Next Generation Sequencing (NGS) for Patients with Advanced Cancer. Please refer to the NCD at https://www.cms.gov/medicare-coverage-database/details/ncd-details.aspx?NCDId=372&ncdver=1&bc=AAAAQAAAAAAA for full coverage details.

LungSeq®

Testing for genetic alteration in these genes can determine targeted therapy options that have the potential to decrease tumor burden, decrease symptoms, increase survival, and dramatically improve the quality of life for patients with specific genetic alterations.

Please refer to A52986, Billing and Coding: Biomarkers for Oncology regarding coding and billing information.

3. Melanoma

- BRAF - PRED of response to Vemurafenib
- KIT - PRED of response to Imatinib (TKI)
- NRAS - PROG + PRED for anti-MEK inhibitor

4. Uveal Melanoma
   - GNAQ – PROG
   - GNA11 - PROG

5. Brain

   - BRAF - PRED
   - EGFR - PRED
   - MGMT - PRED
   - IDH1 - DX + PROG
   - IDH2 - DX + PROG
   - PIK3CA - PRED
   - PTEN - PRED
   - CIMP - PRED
   - TERT - DX

6. Thyroid

   - BRAF - DX + PRED
   - KRAS - PRED for Selumetinib
   - HRAS - PRED for Selumetinib
   - NRAS - PRED for Selumetinib
   - PIK3CA - PRED
   - RET - DX
   - PAX8/PPARG- DX

   ThyraMIR Thyroid miRNA classifier (aPCR based microRNA gene expression classifier) (PRED) evaluates the expression levels of 10miRNA genes within an FNA biopsy: miR-29b-1-5p, miR-31-5p, miR-138-1-3p, miR-139-5p, miR-146b-5p, miR-155, miR-204-5p, miR-222-3p, miR-375, and miR-551b-3p.

   Oncology Thyroid, provides gene expression analysis of 142 genes utilizing fine needle aspirate, algorithm reported as a categorical result (Afirma - PRED).

   ThyraMIR is used as a companion test to ThyGeNEXT when ThyGeNEXT results are inconclusive.

   - ThyraMIR, ThyGeNEXT and Afirma services will be considered reasonable and necessary for patients with any of the following conditions:
     - An indeterminate pathology on fine needle aspiration
     - Patients with one or more thyroid nodules with a history or characteristics suggesting malignancy such as:
       - Nodule growth over time
       - Family history of thyroid cancer
       - Hoarseness, difficulty swallowing or breathing
       - History of exposure to ionizing radiation
       - Hard nodule compared with rest of gland consistency

        - Presence of cervical adenopathy
    - RosettaGX Reveal thyroid MicroRNA test, an assay used for the classification of indeterminate thyroid nodules, will be considered reasonable and necessary when the conditions outlined above for ThyraMIR, ThyGeNEXT and Afirma are met.
    - ThyroSeq is a test utilized to better define the need for thyroid surgery and the type of such surgery. ThyroSeq will be considered reasonable and necessary when the conditions outlined above for ThyraMir, ThyGeNEXT and Afirma are met.

7. Ovary/Fallopian Tube/Peritoneum

    - AKT1 - PRED for PI3K/AKT/mTOR inhibitors
    - BRAF - DX + PROG
    - KRAS - DX + PROG
    - MLH1 promoter hypermethylation - DX
    - MSI by PCR - DX
    - PIK3CA - PRED for PI3K/AKT/mTOR inhibitors
    - PTEN - PRED for PI3K/AKT/mTOR inhibitors
    - TP53 - DX + PROG

8. Uterus

    - AKT1 - PRED for PI3K/AKT/mTOR inhibitors
    - BRAF - PRED
    - KRAS - PRED
    - MLH1 promoter hypermethylation - DX
    - MSI by PCR - DX
    - PIK3CA - PRED for PI3K/AKT/mTOR inhibitors
    - PTEN - PRED for PI3K/AKT/mTOR inhibitors + DX + PROG
    - TP53 - DX + PROG

9. Urinary Tract

    - FGFR3 - PROG
    - MSI by PCR - DX
    - MLH1 promoter hypermethylation - DX

10. Prostate

    - The PROGENSA® PCA3 Assay (PRED) is an FDA-approved, automated molecular test (assay) that helps physicians determine the need for repeat prostate biopsies in men who have had a previous negative biopsy.
    - PTEN – PROG and THER
    - RB1 – DX and PROG
    - TP53 - PROG

11. Gastrointestinal Stomal Tumor

    - KIT - PRED for Sumatinib + DX

- PDGFRA - PRED for Sumatinib + DX

12. Cancer of Unknown Primary (CUP)

    Molecular testing, using the Rosetta Cancer Origin Test™ (PROG), is considered reasonable and necessary in the pathologic diagnoses of CUP when a conventional surgical pathology/imaging work-up is unable to identify a primary neoplastic site. Other applications of this technology are considered not reasonable and necessary and are considered investigational in the use of diagnosis of specific tumor types such as NSCLC and renal cancers.

    TUO CTID (Cancer Type ID) (DX) is considered reasonable and necessary in the pathologic diagnoses of CUP when a conventional surgical pathology/imaging work-up is unable to identify a primary neoplastic site. Other applications of this technology are considered not reasonable and necessary and are considered investigational in the use of diagnosis of specific tumor types such as NSCLC and renal cancers.

13. Leukemias and Lymphomas

    - Acute lymphoid leukemia (ALL)
        - JAK1
        - JAK2
        - BCR/ABL1 - DX
        - ABL1 (kinase domain) - PROG
        - IGH - DX
        - TCRB - DX
        - TCRG - DX
        - TP53 - PROG
        - MLL/AF4 - DX
        - E2A/PBX1 - DX
        - ETV6/RUNX1 - DX
        - KRAS
        - NRAS
        - NOTCH1
        - FBXW7
    - Acute myeloid leukemia (AML, and including acute promyelocytic leukemia): All PROG, except where noted below.
        - TP53
        - PML/RARA - DX
        - RUNX1/RUNX1T1 - DX
        - CBFB/MYH11 - DX
        - FLT3 ITD
        - FLT3 D835
        - NPM1
        - KRAS
        - NRAS
        - KIT
        - CEBPA
        - IDH1
        - IDH2
        - DNMT3A

    - JAK2 (p.V617F)
    - JAK2 (exon 12)
    - MPL
    - DEK/CAN - DX
    - ASXL1
    - EZH2
    - TET2
    - PML/RARalpha
    - U2AF1
    - SRSF2
    - ZRSR2
- Hairy cell leukemia
    - BRAF
    - IGH somatic hypermutation - PROG
    - IGH - DX
- Aplastic anemia
    - TCRB - DX
    - TCRG - DX
- Burkitt’s lymphoma
    - IGH - DX
    - TP53 - PROG
- Myeloproliferative diseases (MPD - essential thrombocytosis [ET], myelofibrosis & polycythemia vera [PV])
    - KIT
    - TP53
    - BCR/ABL1 - DX
    - JAK2 (p.V617F) - DX
    - JAK2 (exon 12) - DX
    - MPL - DX
    - CALR - DX
    - CSF3R - DX
    - ASXL1 - PROG
    - TET2 - PROG
    - EZH2 - PROG
    - Calr (exon 9)
- Chronic myeloid leukemia (CML) and chronic myelomonocytic leukemia (CMML)
    - ABL1 T3151 – CML only
    - KRAS - PROG
    - NRAS - PROG
    - BCR/ABL1 - DX
    - ABL1 (kinase domain) - PRED for Imatinib
    - FLT3 ITD - PROG
    - FLT3 D835 - PROG
    - KIT - PROG
    - JAK2 (p.V617F) - PROG
    - JAK2 (exon 12) - PROG
- Chronic lymphoid leukemia (CLL)
    - IGH - DX
    - IGH somatic hypermutation - PROG
    - TP53 - PROG
    - IGH direct probe method
    - BTK

        - PLCG2
        - BIRC3
        - BTK
        - NOTCH1
        - SF3B1
    - Follicular lymphoma
        - IGH/BCL2 - DX
    - Hypereosinophilia Syndrome (HES)
        - KIT (including p.D816V) - PROG + DX
        - FIP1L1/PDGFRA Fusion - DX
    - Mantle cell lymphoma
        - CCND1/IGH - DX
    - Mastocytosis
        - KIT (including p.D816V) - PROG + DX
        - FIP1L1/PDGFRA Fusion - DX
        - TCRG - DX
    - T-cell prolymphocytic leukemia
        - JAK1
        - JAK3
        - TCRB - DX
        - TCRG - DX
    - T-cell large granular lymphocytic leukemia(TLGLL)
        - STAT3
        - STAT5B
    - Myelodysplastic syndrome (MDS): All below biomarkers are PROG.
        - FLT3 ITD
        - FLT3 D835
        - NPM1
        - KRAS
        - NRAS
        - KIT
        - CEBPA
        - IDH1
        - IDH2
        - DNMT3A
        - JAK2 (p.V617F)
        - JAK2 (exon 12)
        - MPL
        - ASXL1
        - EZH2
        - TET2
    - Cytogenomic microarray analysis, or alternatively, a single nucleotide polymorphism (SNP) array for the same testing, is covered for the identification of various mutations. These tests are used in the diagnosis/prognosis of various hematological malignancies.
    - Waldenstrom's Lymphoplasmacytic Lymphoma
        - MYD88

14. Myeloma Gene Expression Profile (MyPRS) (PROG) isolates plasma cells from myeloma patients, extracts DNA, which is then subjected to MicroArray testing and application of validated software programs to identifying patterns of genetic abnormalities. Seventy highly predictive genes have been identified and correlated to myeloma early relapse. MyPRS gives a predictive risk signature as high-risk or low-risk at this

time. A high risk score predicts a less than 20% three-year complete remission where as a low-risk predicts a five-year complete remission of greater than 60%. The predictive value for the stratification of therapeutic interventions allows these patients to be treated in a more personalized manner based on their own genetic profile.

This test is considered reasonable and necessary only after the initial diagnosis of multiple myeloma has been made and will be available to be used in the stratification of therapeutic interventions. It would be inappropriate to use this test as a diagnostic tool or as a monitoring device of ongoing therapy. Other testing is available for this function.

The coverage is set to include only two clinical settings:

- Once after initial diagnosis is made. In the event MyPRS was not tested at diagnosis of myeloma and there is ongoing initial therapy with persistent disease, MyPRS can be done still as an initial test.
  OR
- If relapse has occurred and a change in the therapeutic modalities is contemplated.

Please refer to the limitations section of this policy for frequency limitations.

15. Hereditary neuroendocrine tumor disorders - Must include 6 genes with genomic sequence analysis NEX GEN including:

- MAX
- SDHB
- SDHC
- SDHD
- TMEM127
- VHL

Please refer to the limitations section of this policy for frequency limitations.

16. Hereditary neuroendocrine tumor disorders; duplication/deletion analysis panel - must include analysis for:

- SDHB
- SDHC
- SDHD
- VHL

17. Neuroendocrine Tumors

- MGMT - PROG
- PTEN – PROG and THER
- RB1 – DX and PROG
- TP53 – DX and PROG
- TSC2 - PROG

18. Prosigna breast cancer gene signature assay (PROG)

Background

Women with early breast cancer and up to 3 locally positive lymph nodes whose tumor is estrogen-receptor positive will usually receive anti-hormonal therapy such as tamoxifen or aromatase inhibitors. U.S. (NCCN) and international (St. Gallen) guidelines predicate the decision for adjuvant chemotherapy on the size and grade of the breast cancer and other factors including genomic assays that provide additional information on risk of recurrence (Hernandez-Ava et al., 2013). According to a 2014 review, "Prognostic factors provide an indication of whether a patient needs subsequent therapy." (Paoletti & Hayes, 2014). Similarly, another 2014 review article states, "Efforts should be focused on reducing chemotherapy in patients unlikely to benefit." (Rampurwala et al., 2014).

The PAM50 breast cancer gene signature test was developed in the late 1990s and initial studies showed a strong correlation with breast cancer recurrence and with complete pathologic response to neoadjuvant chemotherapy (Parker et al., 2009). While test results are reported on a scale of 1-100 as a Risk of Recurrence (ROR) score, the underlying algorithm is also able to classify cases into the luminal A and B, Her2neu, and triple-negative subtype classifications.

The Nanostring nCounter® nucleic acid analysis system replicates the PAM50 algorithm, as an FDA cleared kit, the Prosigna Breast Cancer Gene Signature Assay (FDA, 2013). The Prosigna package insert was most recently updated in January, 2015 (FDA, 2015) reflecting additional studies (Sestak et al., 2014). Notably, the Prosigna platform and the original PAM50 platform have a 0.997 correlation (Dowsett et al., 2013).

For the FDA, the Prosigna test was validated in a large population of post-menopausal, estrogen-receptor positive women based on 1,017 cases of the TransATAC study (Dowsett et al., 2013). The study showed a strong correlation with long-term breast cancer recurrence and added substantial additional prognostic information over a clinical treatment score based on standard clinical variables. This study was replicated in an independent population, also on the Prosigna test, using 1,620 samples from the ABCSG8 trial (Gnant, 2014). A separate analysis of these trials validated prediction of distant recurrence in years 5-10 after initial diagnosis (Sestak et al., 2014) and has been incorporated in the FDA labeling (FDA, 2015). The Prosigna test is issued as separate reports, consistent with FDA review and labeling, for node-negative and node-positive (1-3 node) populations. Analytic performance, precision, reproducibility, and analysis of the clinical validations are provided in the FDA labeling (https://www.accessdata.fda.gov/cdrh_docs/reviews/K130010.pdf).

Clinical utility of this breast cancer gene signature has also been assessed. The study of Martin et al. (2015) showed a 20% decision impact on decisions for or against adjuvant chemotherapy in an all-comers population of 200 new cases of incident breast cancer, when Prosigna test information became available after all other clinical information had been considered. The net rates of selecting adjuvant chemotherapy for low, intermediate, and high risk cases was similar to that observed in a meta-analysis of Oncotype DX decision data (Carlson & Roth, 2013). Additional support for the use of these test results in treatment decisions comes from Parker et al. (2009), in which there was a strong association with neoadjuvant chemotherapy response. Low-scoring cases have a very low chance of complete pathological response to neoadjuvant chemotherapy, while high-scoring cases approach a 50% chance of complete pathological response. The same findings have been observed for other breast cancer gene signatures based on prognostic algorithms (Chang et al., 2008).

The Prosigna test is reasonable and necessary when performed according to the FDA label (https://www.accessdata.fda.gov/cdrh_docs/reviews/K130010.pdf).

19. Desmoid Fibromatosi

- CTNNB1 – DX and PROG

20. Hepatic Adenoma

- CTNNB1 – DX and PROG

21. Bladder

- CDKN2A – PROG
- FGFR1 – PROG
- FGFR3 – PROG
- MTOR – PROG
- PIK3CA – DX and PROG
- PTEN – PROG
- RB1 – PROG
- TP53 - PROG

NON-MOLECULAR ASSAYS

1. The VeriStrat® assay is a mass spectrophotometric, serum-based predictive proteomics assay for NSCLC patients, where "first line" EGFR mutation testing is either wild-type or not able to be tested (e.g., if tissue might not be available). This test is a driver of therapy, most notably EGFR inhibitors such as erlotinib, and it has been validated by randomized controlled studies (Carbone et al. and Stinchecomb et al.) and physician uptake data (Akerley et al.) to support this particular coverage niche.
2. This LCD does not address ALK and ROS1 FISH assays, which are indicated as predictive biomarkers for Crizotinib therapy, since they are currently covered assays. However, it is expected that non-molecular testing for these two biomarkers should provide adequate predictive information.
3. FISH tests for bladder cancer are complex tests based on precision reagents, controls, and mathematical algorithms, all of which must be validated in clinical trials in order to support cutoff points for critical patient care decisions. Therefore, in each local physician's office or laboratory, this category of testing is not easily replicated by miscellaneous research use or ASR reagents. Novitas will consider the coverage of FISH test kits based on peer-reviewed literature and approved manufacturer claims.
4. Although multiple bladder cancer FISH tests may be covered according to the above general criteria, UroVysion TM Bladder Cancer Kit (UroVysion™ Kit) will be considered medically reasonable and necessary only when performed according to the FDA label (https://www.accessdata.fda.gov/cdrh_docs/pdf3/P030052b.pdf) as follows:
   The UroVysion Bladder Cancer Kit (UroVysion™ Kit) is designed to detect aneuploidy for chromosomes 3, 7, 17, and loss of the 9p2l locus via fluorescence in situ hybridization (FISH) in urine specimens from persons with hematuria suspected of having bladder cancer. Results from the UroVysion Kit are intended for use, in conjunction with and not in lieu of current standard diagnostic procedures, as an aid for initial diagnosis of bladder carcinoma in patients with hematuria and subsequent monitoring for tumor recurrence in patients previously diagnosed with bladder cancer.
5. The OVA1™ proteomic assay (PROG) will be considered reasonable and necessary when performed according to the FDA label (https://www.accessdata.fda.gov/cdrh_docs/pdf15/K150588.pdf).
6. The Risk of Ovarian Malignancy Algorithm (ROMA™) is a qualitative serum test (PROG) that combines the results of HE4 EIA, ARCHITECT CA 125 II ™ and menopausal status into a numerical score. ROMA™ is intended (per FDA clearance) to aid in assessing whether a premenopausal or postmenopausal woman who presents with an ovarian adnexal mass is at high or low likelihood of finding malignancy at surgery. ROMA™ will be considered reasonable and necessary for women who meet the FDA labeling criteria (https://www.accessdata.fda.gov/cdrh_docs/pdf10/K103358.pdf).

Limitations

Note: Please refer to the indications for any restrictions specific to the various assays. Please see NCD 90.2 for coverage details related to Next Generation Sequencing (NGS) for Patients with Advanced Cancer.

1. Most genomic testing should be a once in a lifetime test. Documentation in the medical record should clearly support the need for repeat testing to include the following: recurrence of disease, change in behavior of disease, etc.
2. The following tests will all be covered once per lifetime per beneficiary:
    - Brain Molecular Biomarkers
    - Hereditary neuroendocrine tumor disorders
    - Hereditary neuroendocrine tumor disorders; duplication/deletion analysis
    - ThyraMIR, Afirma, ThyGeNEXT, RosettaGX Reveal and ThyroSeq tests
        - Should the unlikely situation of a second, unrelated thyroid nodule with indetermindate pathology occur, coverage may be considered upon appeal with supporting documentation
    - TUO CTID (Caner TYPE ID)
3. While some biomarkers have utility for testing once per lifetime, there are some tumor specific scenarios where repeat testing would be needed for assessment of response to therapy or to identify basis of disease progression. In cases with metastatic or recurrent tumors, repeat testing may be useful in determining further clinical management. Also, biomarkers such as BCR-ABL1 fusion, PML-RARA fusion are useful in monitoring response to therapy and predict a response up to four times per annum.

Notice: Services performed for any given diagnosis must meet all of the indications and limitations stated in this policy, the general requirements for medical necessity as stated in CMS payment policy manuals, any and all existing CMS national coverage determinations, and all Medicare payment rules.

Summary of Evidence

Please refer to the "History/Background and/or General Information" section for general information on biomarkers.

Multiple sources of literature were submitted for consideration. The literature consisted of various investigational, observational, and experimental studies, as well as some letters to the editor in support of the leukemia biomarkers expansion, and ThyGeNEXT panel. The literature was reviewed; the following is a summary of the evidence submitted:

Numerous articles were submitted in support of the Leukemia biomarker expansion request. Taking into consideration the independent, objective evaluation and systematic literature review, which substantively contributed to the evidence base of the requested leukemia biomarkers and subsequently approved by the Molecular Testing Evaluation Committee (MTEC), all the requested biomarkers are considered reasonable and necessary for the listed disease states below:

- Acute Lymphoblastic Leukemia
    - JAK1
    - JAK2
    - KRAS
    - NRAS
    - NOTCH1
    - FBXW7

- Acute Myeloid Leukemia
  - TP53
  - U2AF1
  - SRSF2
  - ZRSR2
- Chronic Lymphocytic Leukemia
  - BIRC3
  - BTK
  - PLCG2
  - NOTCH1
  - SF3B1
- Chronic Myeloid Leukemia
  - ABL1 T315I
- Hairy Cell Leukemia
  - BRAF
- Myeloproliferative Diseases
  - KIT
  - TP53
- Prolymphocytic Leukemia
  - JAK1
  - JAK3
- T-cell Large Granular Lymphocytic Leukemia
  - STAT3
  - STAT5B

Consistent with the literature review, NCCN rating and quality of the evidence submitted, the following Biomarker Panel will be considered medically reasonable and necessary:

- ThyGeNEXT
  - Xing, et al (2014),[1] is a retrospective multicenter study that reviewed all known fusion and their prevalence in Papillary, poorly differentiated anaplastic, follicular, and medullary carcinomas. The study was a review and no new data was presented. The study conclusion demonstrates the prognostic value and perspectives of the utilization of gene fusions as therapeutic targets. The study conclusion is limited due to clinical utility not being achieved in reporting statistical findings, no available conflict of interest and no patient inhomogeneity. The quality of evidence for this study is moderate due to lack of peer review and the strength was conditional for the same reason.
  - Xing, et al (2015),[2] is a retrospective study to investigate the prognostic value of BRAF V600E mutation for the recurrence of papillary thyroid cancer in 2099 patients. The study conclusion demonstrates the overall BRAF V600E mutation prevalence was 48.5%. BRAF mutation was associated with poorer recurrence-free probability in Kaplan-Meier survival analyses in various clinicopathologic categories. The quality of evidence is high and the strength of recommendation is conditional for the population tested.
  - Labourier, et al (2015),[3] is a cross-sectional cohort study conducted at 12 endocrinology centers across the United States. The study results found that mutations were detected with malignant outcome. Among mutation negative specimens, miRNA testing correctly identified 64% of malignant cases and 98% of benign cases. The diagnostic sensitivity and specificity of the combined algorithm was 89% (95% confidence intervals (CI): 73 – 97%) and 85% (95% CI: 75 – 92%), respectively. At 32% cancer prevalence, 61% of the molecular results were benign with a negative predictive value of 94% (95% CI: 85 – 98%). Independently of variations in cancer prevalence, the test increased the yield of true benign results by 65% relative to mRNA-based gene expression classification and decreased the rate of avoidable diagnostic surgeries by 69%. This was purely supposition. The authors concluded: multi-

platform testing for DNA, mRNA and miRNA can accurately classify benign and malignant thyroid nodules, increase diagnostic yield of molecular cytology, and further improve the preoperative risk-based management of benign nodules with AUS/FLUS or FN/SFN cytology. The quality of evidence is moderate as this was not peer reviewed, a conflict of interest was present in that one of the authors was employed by the company, and the clinical utility is implied but not proven.

- Giordano, et al (2014),[4] is a case-control study conducted in 413 surgical cases comprising 17 distinct histopathologic categories. The study results found that, in the authors opinion, "standardized and validated multianalyte molecular panels can complement the preoperative and postoperative assessment of thyroid nodules and support a growing number of clinical and translational applications with potential diagnostic, prognostic, or theranostic utility." The quality of evidence is moderate as this was a validation study only and the clinical utility is not addressed. There is an obvious conflict of interest in that the laboratory represented in authors of this study and the correspondence is through the laboratory.
- Landa, et al (2013),[5] is a retrospective study. The objectives of the study were: 1) to determine the prevalence of TERT promoter mutations C228T and C250T in different thyroid cancer histological types and cell lines; and 2) to establish the possible association of TERT mutations with mutations of BRAF, RAS, or RET/PTC. The study results found that TERT promoter mutations were found in 98 of 225 (44%) of specimens. TERT promoters C228T and C250T were mutually exclusive. The study conclusion demonstrates potential diagnostic, prognostic and therapeutic are suggested. TERT promoter mutations are highly prevalent in advanced thyroid cancers, particularly those harboring BRAF or RAS mutations which are most often TERT promoter wild type. Acquisition of a TERT promoter mutation could extend survival of BRAF- or RAS- driven clones and enable accumulation of additional genetic defects leading to disease progression. The quality of evidence is moderate as this is retrospective of variable tumor types and the clinical utility is only inferred.

Analysis of Evidence
(Rationale for Determination)

Leukemia

The literature submitted for the addition of several biomarkers for various leukemia disease states was carefully reviewed. The literature submitted was also reviewed and approved by the Molecular Testing Evaluation Committee (MTEC). The MTEC reviews and votes on clinical requests for molecular testing based upon levels of evidence, including publications in the medical literature, and need for biomarkers in integral marker clinical trials. The MTEC is charged with establishing evidence-based standard-of-care testing, monitoring physician ordering of molecular tests, assuring documentation of medical necessity, analyzing utilization data, and reviewing outcomes data related to the use of molecular biomarkers. Taking into consideration the MTEC approval and taking into account item 4 of the General Information section of this policy, which allows for consideration of other independent, objective evaluations or systematic literature reviews, the requested leukemia biomarkers are considered reasonable and necessary.

ThyGeNEXT

The literature submitted for the requested addition of the ThyGeNEXT panel was carefully reviewed. After consideration of the literature, NCCN rating, and relevance to the Medicare population, the coverage of the ThyGeNEXT panel will be added in replace of the ThyGenX panel. The coverage of this panel is being added as there were enough genes requested in the panel achieving an NCCN 2A rating that when combined with the genes covered in the ThyGenX panel with a 2A rating, a minimum total of 51 genes achieved the NCCN rating of 2A. Further, the literature supported the clinical utility and clinical validity, and was relevant to the Medicare population.

General Information

Associated Information

Refer to the Local Coverage Article: Billing and Coding: Biomarkers for Oncology, (DA52986) for documentation requirements, utilization parameters and all coding information.

Sources of Information

Contractor is not responsible for the continued availability of websites listed.

Other Contractor Policies

Noridian Local Coverage Determination (LCD), DL36380 - MolDX: Breast Cancer Assay: Prosigna

Contractor Medical Directors

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771. http://www.cms.gov/medicare-coverage-database/ details/medcac-meeting-details.aspx? MEDCACId=67&bc=AAAIAAAAAAAAAA%3d%3d& (Minutes from this May 1, 2013 MEDCAC to be posted

between July 1-September 1, 2013)
772. http://www.egappreviews.org/recommendations/colorectal.htm
773. http://www.fda.gov/MedicalDevices/Productsand MedicalProcedures/DeviceApprovalsand Clearances/Recently-ApprovedDevices/ ucm294907.htm
774. http://www.fda.gov/NewsEvents/Newsroom /PressAnnouncements/ucm268241.htm
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There were extensive in-person consultations with both CAC representatives and nationally-recognized experts in order to assist with the above medical necessity language and procedure-to-diagnosis code pairings.

Revision History Information

REVISION HISTORY DATE	REVISION HISTORY NUMBER	REVISION HISTORY EXPLANATION	REASON(S) FOR CHANGE
12/13/2020	R32	LCD revised and published on 11/5/2020 effective for dates of service on and after 12/13/2020 to update wording of utilization guidelines to appear as limitations.	• Typographical Error
12/13/2020	R31	LCD posted for notice on 10/29/2020. LCD becomes effective for dates of service on and after 12/13/2020. 10/31/2019 DL35396 Draft LCD posted for comment.	• Creation of Uniform LCDs With Other MAC Jurisdiction
07/01/2020	R30	LCD revised and published on 06/25/2020 effective for dates of service on and after 07/01/2020, as a non-discretionary update to remove limitations 1 and 3, these services will now be covered when medically reasonable and necessary and performed within the indications of the LCD consistent with CMS direction. Minor formatting changes have been made.	• Other (revised in response to CMS direction)
11/14/2019	R29	LCD revised and published on 11/14/2019. Consistent with CMS Change Request 10901, the entire coding section has been removed from the LCD and placed into the related Billing and	• Other (CMS Change Request 10901)

REVISION HISTORY DATE	REVISION HISTORY NUMBER	REVISION HISTORY EXPLANATION	REASON(S) FOR CHANGE
		Coding Article, A52986. All CPT codes and coding information within the text of the LCD has been placed in the Billing and Coding Article.	
06/13/2019	R28	LCD revised and published on 06/27/2019. Per current LCD format, the 'Coding Information' statement has been placed after the Analysis of Evidence section. There has been no change in coverage with this LCD revision.	• Typographical Error
06/13/2019	R27	LCD revised and published on 06/13/2019. Effective for dates of service on and after 03/27/2019 the following coding changes have been made in the related Billing and Coding Article (A52986); CPT code 81450 has been removed from CPT/HCPCS Code Group 2 and added to CPT/HCPCS Code Group 1 with no diagnosis to procedure code restrictions at this time. This coding change is a clarification, in response to an inquiry, since the LCD provides coverage for at least 5 of the biomarkers included in the service represented by 81450. Consistent with Change Request (CR) 10901 all CPT and ICD-10 codes have been removed from the LCD and placed in the related Billing and Coding Article, A52986. Language has been added in place of removed codes in Limitation #3. IOM citations for related NCDs have been added and the references have been moved to the Bibliography section. There has been no change in coverage with this LCD revision.	• Other (Change in LCD process per CMS CR 10901; Inquiry)
04/04/2019	R26	LCD revised and published on 04/04/2019 effective for dates of service on and after 03/16/2018 to remove references to next generation sequencing due to implementation of NCD 90.2. Revised Molecular Test Indication related to Oncomine DX to refer to NCD 90.2. Removed CPT code 0022U from CPT/HCPCS Code Group 1, ICD-10 Group 2 Paragraph and Utilization Guidelines. NCD 90.2 listed as a Related National Coverage Document.	• Other (New NCD)
01/01/2019	R25	LCD revised and published on 02/14/2019 effective for dates of service on and after 01/01/2019 to reflect the annual CPT/HCPCS code updates. The following CPT/HCPCS code(s) have been added to Group 1 Codes: 81233, 81236, 81237, 81305, 81320, and 81345. For the following CPT/HCPCS codes either the short description and/or the long description was changed. Depending on which description is used in this LCD, there may not be any change in how the code displays in the document: 81287, 81327, 81400, 81401, 81403, 81404, 81405, and 81407. Covered Indications for Molecular Tests (#5) updated to include	• Revisions Due To CPT/HCPCS Code Changes • Other (CMS Requirement)

REVISION HISTORY DATE	REVISION HISTORY NUMBER	REVISION HISTORY EXPLANATION	REASON(S) FOR CHANGE
		biomarker TERT for brain molecular biomarkers. ICD-10 Code Group #5 has been updated to include TERT reported with CPT code 81345. Utilization Guidelines have been updated to include the test for Brain Molecular Biomarkers (CPT code 81345) once per lifetime per beneficiary. Covered Indications for Molecular Tests (#13) includes biomarker EZH2 for Myeloproliferative diseases. ICD-10 Code Groups #12, #16, and #22 have been updated to report EZH2 with CPT code 81236 or CPT code 81327. Covered Indications for Molecular Tests (#13) updated to include biomarkers BTK and PLCG2 for Chronic lymphoid leukemia (CLL). ICD-10 Code Group #18 for CLL has been updated to include BTK reported with CPT code 81233 and PLCG2 reported with CPT code 81320. Covered Indications for Molecular Tests (#13) updated to include biomarker MYD88 for Waldenstrom's/Lymphoplasmacytic Lymphoma. New ICD-10 Code Group #28 for Waldenstrom's/Lymphoplasmacytic Lymphoma has been added to include MYD88 reported with CPT code 81305. The following ICD-10 Code has been added for MYD88 reported with CPT code 81305 to ICD-10 Code Group 28: C88.0 CMS IOM language has been removed from the LCD per Change Request 10901.	
10/04/2018	R24	LCD revised and published on 10/04/2018 to update the policy in response to inquiry and reconsideration requests; all literature reviewed and added to policy. Non-coverage reaffirmed for CPT codes 0012M and 0013M for CxBladder. Non-coverage reaffirmed for CPT code 0002U for PolypDx™ Assay and Algorithm. Effective for dates of service on and after 05/15/2018 the following changes have been made to the policy: Covered Indications for Molecular Tests updated to include a new group (#4) for Uveal Melanoma with biomarkers GNAQ and GNA11. GNAQ is reported with CPT code 81403 and currently does not have ICD-10 diagnosis code pairing. The following ICD-10 diagnosis codes have been added for GNA11 reported with CPT code 81479 to ICD-10 Code Group 4: C69.01, C69.02, C69.11, C69.12, C69.21, C69.22, C69.31, C69.32, C69.41, C69.42, C69.51, C69.52, C69.61, C69.62, C69.81, C69.82.	• Revisions Due To ICD-10-CM Code Changes • Reconsideration Request

REVISION HISTORY DATE	REVISION HISTORY NUMBER	REVISION HISTORY EXPLANATION	REASON(S) FOR CHANGE
		ThyroSeq has been added to the thyroid test group (new group #6). CPT Code 0026U has been added to CPT Group 1 Codes. ThyroSeq for CPT code 0026U has been added to ICD-10 Code Group 6 (new) and added to the asterisk note indicating ICD-10 diagnosis codes C73 and D44.2 should not be reported for this test. Utilization Guidelines have been updated to include the ThyroSeq test once per lifetime per beneficiary. Covered Indications for Molecular Tests updated to include biomarker FGFR3 as covered under Urinary Tract (new #9). FGFR3 is reported with CPT code 81404 and currently does not have ICD-10 code pairing. Covered Indications for Molecular Tests updated to include biomarkers PTEN, RB1 and TP53 to Prostate (new group #10). TP53 is reported with CPT code 81405 and currently does not have ICD-10 code pairing. ICD-10 Code Group 9 (new) has been updated to include PTEN for CPT codes 81321, 81322, 81323 and RB1 for CPT code 81479. Covered Indications for Molecular Tests updated to include biomarkers MGMT, PTEN, RB1, TP53 and TSC2 for Neuroendocrine tumors (new group #17). TP53 is reported with CPT code 81405 and currently does not have ICD-10 diagnosis code pairing. ICD-10 Code Group for neuroendocrine tumors (new #25) has been updated to include MGMT reported with CPT code 81287, PTEN reported with CPT codes 81321, 81322, or 81323; and RB1 or TSC2 reported with CPT code 81479. Covered Indications for Molecular Tests updated to include biomarker CTNNB1 to Desmoid Fibromatosis (new group #19). CTNNB1 is reported with CPT code 81403 and currently does not have ICD-10 diagnosis code pairing. Covered Indications for Molecular Tests updated to include biomarker CTNNB1 to Hepatic Adenoma (new group #20). CTNNB1 is reported with CPT code 81403 and currently does not have ICD-10 diagnosis code pairing. Covered Indications for Molecular Tests updated to include biomarkers CDKN2A, FGFR3, PIK3CA and TP53 for Bladder (new group #21). CDKN2A, FGFR3, PIK3CA and TP53 reported with CPT code 81404 or 81405 and currently does not have ICD-10 diagnosis code pairing. CPT codes 81321, 81322 and 81323 for biomarker PTEN and CPT code 81479 for biomarkers FGFR1, MTOR and RB1 added to new ICD-10 Diagnosis Code Group 27 for Bladder. The following ICD-10 diagnosis codes have been added to	

REVISION HISTORY DATE	REVISION HISTORY NUMBER	REVISION HISTORY EXPLANATION	REASON(S) FOR CHANGE
		new ICD-10 Code Group 27: C67.0, C67.1, C67.2, C67.3, C67.4, C67.5, C67.6, C67.7, C67.8 and C67.9. Effective for dates of service on and after 05/18/2018, CPT code 0022U added to CPT Group 1 Codes. Utilization Guidelines and ICD-10 Code Group 2 updated to reflect Oncomine DX CPT code changed from 81445 to 0022U. Covered Indications for Molecular Tests (#1) updated to include ColonSeq® for Colorectal Cancer and (#2) LungSeq® for Non-Small Cell Lung Cancer. ICD-10 Code Group 1 updated to add ColonSeq® for CPT code 81445. ICD-10 Code Group 2 updated to add LungSeq® for CPT code 81445. In response to the annual ICD-10 code update, effective for dates of service 10/1/2018 and after the following ICD-10 codes have been deleted from ICD-10 code group 3: C43.11, C43.12, D03.11 and D03.12 and the following ICD-10 codes have been added to ICD-10 code group 3: C43.111, C43.112, C43.121, C43.122, D03.111, D03.112, D03.121, D03.122. At this time 21st Century Cures Act will apply to new and revised LCDs that restrict coverage which requires comment and notice. This revision is not a restriction to the coverage determination; therefore, not all the fields included on the LCD are applicable as noted in this policy.	
07/26/2018	R23	LCD revised and published on 07/26/2018. The following revisions have been made in the covered indications section of the policy: ThyGenX represented by CPT code 81445 has been added under Molecular Tests for Thyroid, ICD-10 Code Group Paragraph 5 and Utilization Guidelines effective for dates of service on and after 04/09/2018. RosettaGX Reveal Thyroid miRNA has been added as a covered service under Molecular Tests for Thyroid, ICD-10 Code Group Paragraph 5 and Utilization Guidelines effective for dates of service on and after 04/09/2018. Literature submitted has been reviewed and added to the policy. FLT3 D836 has been revised to FLT3 D835 under Molecular Tests for AML, CML/CMML and MDS covered indication sections. FLT3 D835 has also been removed from the following ICD-10 Code Group Paragraphs; Group 11, Group 16 and the newly numbered Group 21 (formerly group 22 before renumbering with this revision) since CPT 81246 does not have any diagnosis restrictions	• Typographical Error • Other (Recon, Inquiry)

REVISION HISTORY DATE	REVISION HISTORY NUMBER	REVISION HISTORY EXPLANATION	REASON(S) FOR CHANGE
		effective for dates of service 01/01/2015 and after. Biomarker ATM listed under Molecular Tests for CLL covered indications has been removed from the LCD. This biomarker has also been removed from ICD-10 Code Group Paragraph 17 as there are no coverage restrictions for ATM at this time. The CPT codes listed with IGH/BCL2 under Molecular Tests in the Follicular lymphoma section have been changed to 81401 and 81402. ICD-10 diagnosis code Group 18 has been deleted as 81401 and 81402 do not have any diagnosis limitations effective for dates of service on and after 01/01/2016. In response to removing Group 18 the ICD-10 code groups have been renumbered. A clarifying statement has been added under the CPT Code Group 1 Paragraph to explain that these CPT codes do not have diagnosis limitations and providers should refer to the covered indications of the LCD for reasonable and necessary guidelines for biomarkers included in these CPT codes. PIK3CA has been removed from the following ICD-10 Code Group Paragraphs list of biomarkers; Group 1, Group 4, Group 5 and Group 6 effective for dates of service on and after 01/01/2015. Diagnosis codes C21.0, C21.2 and C21.8 have been added to ICD-10 Code Group 1 as covered diagnoses effective for dates of service on or after 12/01/2016. Diagnosis code C55 has been added to ICD-10 Code Group 6 as a covered diagnosis effective for dates of service on or after 12/01/2016. A typographical error was made during the ICD-9 to ICD-10 translation resulting in ICD-10 code C92.02 being placed in ICD-10 Code Group 10 instead of the correct ICD-10 code, C91.02. C92.02 is being deleted from ICD-10 Code Group 10 and C91.02 is being added effective for dates of service 12/01/2016 and after. Diagnosis codes C93.10, C93.11 and C93.12 have been added to ICD-10 Code Group 16 as covered diagnoses effective for dates of service 12/01/2016 and after. Diagnosis codes C91.60, C91.61 and C91.62 have been added to newly numbered ICD-10 Code Group 20 (formerly group 21 before renumbering with this revision) as covered diagnoses for T-cell leukemia effective for dates of service on or after 12/01/2016.	

REVISION HISTORY DATE	REVISION HISTORY NUMBER	REVISION HISTORY EXPLANATION	REASON(S) FOR CHANGE
03/08/2018	R22	LCD revised and published on 03/08/2018 effective for dates of service on and after 12/22/2017 to add limited coverage for Oncomine DX test reported with CPT code 81445 for Non-Small Cell Lung Cancer (NSCLC). Language has been added to #2 under Molecular Tests in the Covered Indications area and CPT code 81445 has been added to ICD-10 Group 2 Paragraph for NSCLC. Utilization guidelines have been added for the Oncomine DX test when reported with CPT code 81445. References received with a reconsideration request for the Oncomine DX test have been reviewed and added to the policy. Link to L36715-BRCA1 and BRCA2 Genetic Testing and L35062-Biomarkers Overview added to the Related Local Coverage Documents section. For provider education/guidance, per Annual Review, removed Bill Types 18x and 21x as those Bill Types are not for inpatient services claims; update to CFR listing per template. At this time 21st Century Cures Act will apply to new and revised LCDs that restrict coverage which requires comment and notice. This revision is not a restriction to the coverage determination; therefore, not all the fields included on the LCD are applicable as noted in this policy.	• Reconsideration Request • Other (Annual Review)
01/01/2018	R21	LCD revised and published on 01/25/2018 effective for dates of service on and after 01/01/2018 to reflect the annual CPT/HCPCS code updates. For the following CPT/HCPCS codes either the short description and/or the long description was changed: 81400, 81401, 81403, 81404, 81405, 81406. Depending on which description is used in this LCD there may not be any change in how the code displays in the document. The following CPT/HCPCS codes have been added to CPT/HCPCS Code Group 1: 81120, 81121, 81175, 81176, 81334, 81520. The following CPT/HCPCS code has been deleted from CPT code group 1: 0008M. To clarify coverage for the new CPT/HCPCS code additions, ICD-10 Group Code Paragraphs have been updated as follows: Group 4: IDH1 (81120) and IDH2 (81121); Group 10: RUNX1 (81334); Group 11: ASXL1 (81175, 81176), IDH1 (81120), IDH2 (81121) and RUNX1 (81334); Group 15: ASXL1 (81175, 81176); Group 22: ASXL1 (81175, 81176), IDH1 (81120) and IDH2 (81121); and Group 24: 81520 has been added and 0008M has been deleted. At this time 21st Century Cures Act will apply to new and revised LCDs that restrict coverage which requires comment and notice. This revision is not a restriction to the coverage determination; therefore, not all the fields included on the LCD are applicable as noted in this policy.	• Revisions Due To CPT/HCPCS Code Changes

REVISION HISTORY DATE	REVISION HISTORY NUMBER	REVISION HISTORY EXPLANATION	REASON(S) FOR CHANGE
11/09/2017	R20	LCD revised and published on 11/09/2017 effective for dates of service on and after 08/01/2017 to add the following new CPT/HCPCS codes for Proprietary Laboratory Analyses (PLA) to Group 2 CPT/HCPCS Codes as non-covered: 0009U, 0013U, 0014U, 0016U, and 0017U. LCD revised with effective dates of service on and after 10/02/2017 to reflect the 4Q17 CPT/HCPCS code updates. For the following CPT/HCPCS code(s) either the short description and/or the long description was changed: 81405 and 0002U. Depending on which description is used in this LCD, there may not be any change in how the code displays in the document. At this time 21st Century Cures Act will apply to new and revised LCDs that restrict coverage which requires comment and notice. This revision is not a restriction to the coverage determination; therefore, not all the fields included on the LCD are applicable as noted in this policy.	• Revisions Due To CPT/HCPCS Code Changes
10/01/2017	R19	LCD revised and published on 10/05/2017 effective for dates of service on and after 10/01/2017 to reflect the ICD-10 Annual Code Updates. The following ICD-10 code has been deleted from Group 20 codes: C96.2. The following ICD-10 codes have been added to Group 20 codes: C96.20, C96.22, C96.29. At this time 21st Century Cures Act will apply to new and revised LCDs that restrict coverage which requires comment and notice. This revision is not a restriction to the coverage determination; therefore, not all the fields included on the LCD are applicable as noted in this policy.	• Revisions Due To ICD-10-CM Code Changes
08/10/2017	R18	LCD revised and published on 08/10/2017 effective for dates of service on and after 05/01/2017 to add the following CPT code as non-covered to Group 2 Codes: 0005U. At this time 21st Century Cures Act will apply to new and revised LCDs that restrict coverage which requires comment and notice. This revision is not a restriction to the coverage determination; and, therefore not all the fields included on the LCD are applicable as noted in this policy.	• Revisions Due To CPT/HCPCS Code Changes
02/01/2017	R17	LCD revised and published on 07/13/2017 to add references received with a reconsideration request for CxBladder coverage. After review of the submitted literature it has been determined that non-coverage of CxBladder will remain. No substantial	• Reconsideration Request

REVISION HISTORY DATE	REVISION HISTORY NUMBER	REVISION HISTORY EXPLANATION	REASON(S) FOR CHANGE
		changes are being made to the LCD at this time. At this time 21st Century Cures Act will apply to new and revised LCDs that restrict coverage which requires comment and notice. This revision is not a restriction to the coverage determination; and, therefore not all the fields included on the LCD are applicable as noted in this policy.	
02/01/2017	R16	LCD revised and published on 05/11/2017 effective for dates of service on and after 02/01/2017 to add the following CPT codes as non-covered to Group 2 Codes: 0002U and 0003U. An explanation of non-coverage for these codes has been added to the Limitation section of the policy.	• Revisions Due To CPT/HCPCS Code Changes
01/01/2017	R15	LCD revised and published on 01/12/2017 effective for dates of service on and after 01/01/2017 to reflect the annual CPT/HCPCS code updates. For the following CPT/HCPCS codes either the short description and/or the long description was changed. Depending on which description is used in this LCD, there may not be any change in how the code displays in the document: 81402 and 81407. The following CPT/HCPCS code 81327 has been added to group 1 CPT codes and Group 1 Paragraph for ICD-10 codes of the LCD.	• Revisions Due To CPT/HCPCS Code Changes
12/01/2016	R14	LCD posted for notice on 10/13/2016. LCD becomes effective for dates of service and after 12/01/2016. 05/19/2016 DL35396 Draft LCD posted for comment.	• Automated Edits to Enforce Reasonable & Necessary Requirements
10/01/2016	R13	LCD revised and published on 09/29/2016 effective for dates of service on and after 10/01/2016 to reflect the ICD-10 Annual Code Updates. The following ICD-10 codes have been added to the list of Group 8 diagnosis codes: N42.31, N42.32 and N42.39. The following ICD-10 codes have been added to Group 9 diagnosis codes: C49.A0, C49.A1, C49.A2, C49.A3, C49.A4, C49.A5 and C49.A9. The following Group 8 ICD-10 codes have undergone a descriptor change: N40.0 and N40.1.	• Revisions Due To ICD-10-CM Code Changes
01/22/2016	R12	LCD revised and published on 05/12/2016 to correct source for Starczynowski.	• Typographical Error

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01/22/2016	R11	LCD revised and published on 04/14/2016, effective for dates of service 01/22/2016, to add limited coverage for Prosigna upon additional reconsideration request. A new Group for CPT/HCPCS code 0008M was created for the following ICD-10 codes for 0008M: C50.011, C50.012, C50.019, C50.111, C50.112, C50.119, C50.211, C50.212, C50.219, C50.311, C50.312, C50.319, C50.411, C50.412, C50.419, C50.511, C50.512, C50.519, C50.611, C50.612, C50.619, C50.811, C50.812, C50.819, C50.911, C50.912, C50.919. Submitted sources have been added to the LCD. **Please note:** The content of this LCD version remains the same as the prior version (R10) except that additional codes have been added to the Revision History for this version to accurately reflect all the code additions.	• Reconsideration Request
01/22/2016	R10	LCD revised and published on 04/14/2016, effective for dates of service on and after 01/22/2016, to add limited coverage for Prosigna upon additional reconsideration request. A new Group for CPT/HCPCS code 0008M was created for the following ICD-10 codes for 0008M: C50.011, C50.012, C50.111, C50.112, C50.211, C50.212, C50.311, C50.312, C50.411, C50.412, C50.511, C50.512, C50.611, C50.612, C50.811, C50.812, C50.911, C50.912. Submitted sources have been added to the LCD.	• Reconsideration Request
01/01/2016	R9	LCD revised and published on 02/11/2016, effective for dates of service 12/14/2015 and after, to add coverage for ThyraMIR services reported with CPT code 81479. The following ICD-10 codes have been added to Group 5 for ThyraMIR: E01.0, E01.2, E04.0, E04.8, E04.9.	• Reconsideration Request
01/01/2016	R8	LCD revised and published on 01/28/2016 to reflect the annual CPT/HCPCS code updates. For the following CPT/HCPCS codes, either the short description or the long description was changed. Depending on which description is used in this LCD, there may not be any change in how the code displays in the document: 81210, 81275, 81402, 81435, 81436, 81445, 81450. The following code has been added to CPT group 2 as NON-COVERED; 81595 as the service represented by this code is currently non-covered per the LCD under the non-conventional methods of NGS limitation. CPT code 81170 has been added to groups 10 and 16 to replace 81403 for reporting ABL1. CPT code 81218 has been added to groups 11 and 23 to replace 81403 for CEBPA. CPT code 81272 has been added to groups 3 and 9 to replace 81404 for KIT. CPT 81273 has been added to groups 11, 16, 19, 21, and 23 to replace 81402 for KIT. CPT 81276 has been added to groups 1, 2, 5, 6, 11, 16, and 23. CPT code 81311 has been added to groups 1, 3, 5, 11, 16,	• Revisions Due To CPT/HCPCS Code Changes

REVISION HISTORY DATE	REVISION HISTORY NUMBER	REVISION HISTORY EXPLANATION	REASON(S) FOR CHANGE
		and 23 to replace 81404 associated with NRAS. CPT code 81314 has been added to group 9 to replace 81404 associated with PDGFRA. CPT code 81538 has been added for VeriStrat® testing to group 2 diagnosis.	
10/01/2015	R7	LCD revised and published on 11/13/2015 to add ICD-10 diagnosis codes with higher specificity to Group 5 effective for dates of service on and after 10/01/2015. Diagnosis codes added to Group 5: D44.2, D44.9, E01.1. Sources from reconsideration requests have been reviewed and added to the LCD sources. No substantial changes have been made based on the reconsiderations.	• Reconsideration Request • Other (Clarification)
10/01/2015	R6	LCD revised and published on 10/08/2015 to reflect that OVA1 should be reported with CPT 81503 rather than 84999 effective for dates of service on and after 10/01/2015.	• Revisions Due To CPT/HCPCS Code Changes
10/01/2015	R5	LCD revised and published on 08/13/2015 to add multiple sources submitted with several reconsideration requests regarding Prosigna, molecular kidney cancer testing and bladder cancer testing. All literature was reviewed. No changes to the policy were made based on these reconsideration requests.	• Reconsideration Request
10/01/2015	R4	LCD revised and published on 01/23/2015 to reflect the annual CPT/HCPCS code updates For the following CPT/HCPCS code(s) either the short description and/or the long description was changed. Depending on which description is used in this LCD, there may not be any change in how the code displays in the document: *81245; 81402; 81403; 81404; 81405*. The following codes have been added to CPT group 2 as NON-COVERED; *81445, 81450* and *81455.*The following codes have been added to the LCD but will not have any diagnosis to procedure code editing at this time; *81246; 81435;* and *81436*.CPT code *81313* has been added to group 8 to replace *81479* for reporting PROGENSA® PCA3 Assay. Original and subsequent decisions to non-cover Prosigna are reaffirmed upon additional reconsideration request. Submitted sources have been added to the LCD.	• Revisions Due To CPT/HCPCS Code Changes • Reconsideration Request
10/01/2015	R3	LCD revised and published on 10/09/2014, effective for dates of service on or after 10/01/2015. Non-coverage for Prosigna reaffirmed upon reconsideration request. LCD revised to add ICD-10-CM codes under group 5 for indeterminate malignancy, as well as presumed or documented malignancy of the thyroid gland per a reconsideration request. LCD also revised to add limited coverage for MyPRS multiple myeloma testing.	• Reconsideration Request

REVISION HISTORY DATE	REVISION HISTORY NUMBER	REVISION HISTORY EXPLANATION	REASON(S) FOR CHANGE
10/01/2015	R2	10/01/2014 LCD revised and published on 08/14/2014 to provide clarifications to the statement regarding next generation sequencing methods in the limitations section and to the cancer of unknown primary testing area. Reference to Local Coverage Article A52986 was inserted into LCD.	• Typographical Error
10/01/2015	R1	10/01/2014 LCD revised and published on 08/14/2014 to provide clarifications to the statement regarding next generation sequencing methods in the limitations section and to the cancer of unknown primary testing area. Reference to Local Coverag Article A52986 was inserted into LCD.	• Other (Clarification)

Associated Documents

Attachments

N/A

Related Local Coverage Documents

Article(s)
A52986 - Billing and Coding: Biomarkers for Oncology
A58529 - Response to Comments: Biomarkers for Oncology
LCD(s)
DL35396 - Biomarkers for Oncology

Related National Coverage Documents

N/A

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Keywords

N/A