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LCD for Biomarkers for Oncology (L35396)

See also:
A52986-Biomarkers for Oncology

Contractor Information

Contractor Name: Novitas Solutions, Inc.

Contractor Number: 12502

Contractor Type: MAC B

LCD Information

LCD ID Number: L35396 Status: A-Approved

LCD Title: Biomarkers for Oncology

Geographic Jurisdiction: Pennsylvania Other Jurisdictions

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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, 80.1.1, 80.1.2, 80.1.3, Laboratory services must meet applicable requirements of CLIA
- CMS IOM Publication 100-08, *Medicare Program Integrity Manual*, Chapter 3
  - Section 3.4.1.3 Diagnosis Code Requirements
  - Section 3.6.2.3 Limitation of Liability Determinations

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.
- Title XVIII of the Social Security Act, Section 1833(e) states that no payment shall be made to any provider for any claim that lacks the necessary information to process the claim.

Federal Register References:

- 42 CFR, Section 410.32(d)(3) Diagnostic x-ray tests, diagnostic laboratory tests, and other diagnostic tests: Conditions. Diagnostic laboratory tests

Indications and Limitations of Coverage and/or Medical Necessity:

Notice: It is not appropriate to bill Medicare for services that are not covered (as described by this entire LCD) as if they are covered. When billing for non-covered services, use the appropriate modifier.

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. Third, 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 (CPT code 81525)
    - Hereditary colon cancer disorders (CPT codes 81435 and 81436)
    - Sept9 – (CPT code 81327)

    ColonSeq®

    This testing provides information to the patient and provider regarding potential treatment options and implications for RAS and BRAF mutations.
    Please refer to A52986-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.

    The literature does appear to show clinical validity for all tests and utility for the companion testing. Clinical trials ongoing for the remainder of the panel and as such will not be addressed here. Decision on coverage is based on the companion testing only.

    LungSeq®

    Testing for genetic alteration in these genes can determine targeted therapy options that have the potential to decrease tumor burden, decrease syjptoms, increase survival, and dramatically improve the quality of life for patients with specific genetic alterations.
    Please refer to A52986-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
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 (CPT 81479) 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.

   CPT code 81545, 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 ThyGenX when ThyGenX results are inconclusive.

   - ThyraMIR, ThyGenX (CPT 81445) 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, ThyGenX 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, ThyGenX 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 Stromal Tumor
    - KIT - PRED for Sumatinib + DX
    - PDGFRA - PRED for Sumatinib + DX
12. Cancer of Unknown Primary (CUP)

    Molecular testing (via CPT code 81479), 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) represented by CPT code 81540 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)
        - BCR/ABL1 - DX
        - ABL1 (kinase domain) - PROG
        - IGH - DX
        - TCRB - DX
        - TCRG - DX
        - TP53 - PROG
        - MLL/AF4 - DX
        - E2A/PBX1 - DX
        - ETV6/RUNX1 - DX
    - Acute myeloid leukemia (AML, and including acute promyelocytic leukemia): All PROG, except where noted below.
        - 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 (CPT code 81316)
    - Hairy cell leukemia
        - 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])
        - 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) (CPT code 81219)
    - Chronic myeloid leukemia (CML) and chronic myelomonocytic leukemia (CMML)
        - 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 (CPT code 81262)
    - Follicular lymphoma
        - IGH/BCL2 - DX (CPT code 81401 or 81402)
    - 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
        - TCRB - DX
        - TCRG - DX
    - 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.

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 (i.e., please use ICD-10-CM code C90.00). 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 (i.e., please use ICD-10-CM code C90.02).

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

15. Hereditary neuroendocrine tumor disorders (CPT code 81437) – Must include at least 6 genes with genomic sequence analysis NEX GEN including:

    - MAX
    - SDHB
    - SDHC
    - SDHD

- TMEM127
- VHL

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

16. Hereditary neuroendocrine tumor disorders; duplication/deletion analysis panel (CPT code 81438) – 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) (CPT code 81520)

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 (FDA, 2013; FDA, 2015).

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).

Consistent with the FDA indications for use, this testing will be considered reasonable and necessary only for patients that meet the following criteria:

- Post-menopausal female with **either**
    - o ER+, lymph node-negative, stage I or II breast cancer; or
    - o ER+, lymph node-positive (1-3 positive nodes), stage II breast cancer.

19. Desmoid Fibromatosis
    - 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 (CPT code 81538) 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™ Bladder Cancer Kit (UroVysion™ Kit) will be considered medically reasonable and necessary only when performed according to the FDA label (Summary of Safety and Effectiveness Data, Food and Drug Administration, January 24, 2005) 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 using CPT code 81503:

   - OVA1™ identifies some women who will benefit from referral to a gynecological oncologist for their surgery, despite negative results from other clinical and radiographic tests for ovarian cancer. If other test results suggest cancer, referral to an oncologist is appropriate even with a negative OVA1™ result.
   - OVA1™ should be used by primary care physicians or gynecologists as an adjunctive test to complement, not replace, other diagnostic and clinical procedures.
   - OVA1™ uses a blood sample to test for levels of five proteins that change due to ovarian cancer. The test combines the five separate results into a single numerical score between 0 and 10 to indicate the likelihood that the pelvic mass is benign or malignant.

   OVA1 has been cleared by the FDA for women who meet all of the following criteria:

   - Are over 18 years of age
   - Have an ovarian mass
   - Have surgery planned

   It is not intended for ovarian cancer screening or for a definitive diagnosis of ovarian cancer. Interpreting the test result requires knowledge of whether the woman is pre- or post-menopausal.

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 following FDA labeling criteria:

   - Over age 18;
   - Ovarian adnexal mass present for which surgery is planned; and,
   - Not yet referred to an oncologist.

   ROMA™ must be interpreted in conjunction with an independent clinical and radiological assessment. The test is not intended as a screening or stand-alone diagnostic assay.

Limitations

Note: Please refer to the indications for any restrictions specific to the various assays.

1. Biomarkers not addressed in this LCD or any other Novitas LCD will be considered not reasonable and necessary unless specifically covered by national policy.

2. 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.

3. Non-conventional methods of next generation sequencing (NGS), which can generate much more extensive genomic information than conventional techniques, are currently non-covered. NGS methods which provide more "intermediate" range information (e.g., in the 5-50 mutation range) may be performed in the laboratory, pending adequate quality control, such as CLIA certification, but the actual coding and billing will continue to follow the "one-at-a-time" biomarker approach based on this LCD.

4. Services represented by 0003U, 0005U, 0016U and 0017U are very new tests without clinical utility having been established. These tests are considered investigational and experimental and therefore are non-covered at this time. Services represented by 0002U are considered screening services which are non-covered by Medicare.

For frequency limitations, please refer to the Utilization Guidelines section below.

Notice: This LCD imposes frequency limitations as well as diagnosis limitations that support diagnosis to procedure code automated denials. However, 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.

As published in CMS IOM 100-08, Chapter 13, Section 13.5.1, in order to be covered under Medicare, a service shall be reasonable and necessary. When appropriate, contractors shall describe the circumstances under which the proposed LCD for the service is considered reasonable and necessary under Section 1862 (a)(1)(A). Contractors shall consider a service to be reasonable and necessary if the contractor determines that the service is:

- Safe and effective.
- Not experimental or investigational (exception: routine costs of qualifying clinical trial services with dates of service on or after September 19, 2000, that meet the requirements of the Clinical Trials NCD are considered reasonable and necessary).
- Appropriate, including the duration and frequency that is considered appropriate for the service, in terms of whether it is:
    - Furnished in accordance with accepted standards of medical practice for the diagnosis or treatment of the patient's condition or to improve the function of a malformed body member.
    - Furnished in a setting appropriate to the patient's medical needs and condition.
    - Ordered and furnished by qualified personnel.
    - One that meets, but does not exceed, the patient's medical needs.
    - At least as beneficial as an existing and available medically appropriate alternative

The redetermination process may be utilized for consideration of services performed outside of the reasonable and necessary requirements in this LCD.

Coding Information

Bill Type Codes:

Contractors may specify Bill Types to help providers identify those Bill Types typically used to report this service. Absence of a Bill Type does not guarantee that the policy does not apply to that Bill Type. Complete absence of all Bill Types indicates that coverage is not influenced by Bill Type and the policy should be assumed to apply equally to all claims.

12	Hospital Inpatient (Medicare Part B only)
13	Hospital Outpatient
14	Hospital - Laboratory Services Provided to Non-patients
22	Skilled Nursing - Inpatient (Medicare Part B only)
23	Skilled Nursing - Outpatient
71	Clinic - Rural Health
72	Clinic - Hospital Based or Independent Renal Dialysis Center
73	Clinic - Freestanding
75	Clinic - Comprehensive Outpatient Rehabilitation Facility (CORF)
77	Clinic - Federally Qualified Health Center (FQHC)
83	Ambulatory Surgery Center
85	Critical Access Hospital

Revenue Codes:

Contractors may specify Revenue Codes to help providers identify those Revenue Codes typically used to report this service. In most instances Revenue Codes are purely advisory; unless specified in the policy services reported under other Revenue Codes are equally subject to this coverage determination. Complete absence of all Revenue Codes indicates that coverage is not influenced by Revenue Code and the policy should be assumed to apply equally to all Revenue Codes.

0319	Laboratory Pathology - Other Laboratory Pathology
0314	Laboratory Pathology - Biopsy
0309	Laboratory - Other Laboratory
0310	Laboratory Pathology - General Classification
0312	Laboratory Pathology - Histology
0311	Laboratory Pathology - Cytology
0300	Laboratory - General Classification

0307	Laboratory - Urology
0306	Laboratory - Bacteriology & Microbiology
0304	Laboratory - Non-Routine Dialysis
0305	Laboratory - Hematology
0303	Laboratory - Renal Patient (Home)
0302	Laboratory - Immunology
0301	Laboratory - Chemistry

CPT/HCPCS Codes:

Providers are reminded to refer to the long descriptors of the CPT codes in their CPT book.

Note: Please see the indications and limitations section of the LCD for details regarding CPT codes 81292, 81293, 81294, 81321, 81322, 81323, 81437, 81438, 81479, 81520, 81525, 81540, and 81545.

Please note that because the following CPT codes represent multiple biomarkers these codes will not have procedure to diagnosis code limitations at this time: 81246, 81350, 81400, 81401, 81402, 81403, 81404, 81405, 81406, 81407, 81408, 81435, 81436, and 81503.

Providers should refer to the covered indications section of the LCD to determine if biomarkers included in the above codes are considered reasonable and necessary.

Medicare is establishing limited coverage for the following CPT/HCPCS codes, as described in the preceding Coverage Guidance.

0022U	TARGETED GENOMIC SEQUENCE ANALYSIS PANEL, NON-SMALL CELL LUNG NEOPLASIA, DNA AND RNA ANALYSIS, 23 GENES, INTERROGATION FOR SEQUENCE VARIANTS AND REARRANGEMENTS, REPORTED AS PRESENCE/ABSENCE OF VARIANTS AND ASSOCIATED THERAPY(IES) TO CONSIDER
0026U	ONCOLOGY (THYROID), DNA AND MRNA OF 112 GENES, NEXT-GENERATION SEQUENCING, FINE NEEDLE ASPIRATE OF THYROID NODULE, ALGORITHMIC ANALYSIS REPORTED AS A CATEGORICAL RESULT ("POSITIVE, HIGH PROBABILITY OF MALIGNANCY" OR "NEGATIVE, LOW PROBABILITY OF MALIGNANCY")
81120	IDH1 (ISOCITRATE DEHYDROGENASE 1 [NADP+], SOLUBLE) (EG, GLIOMA), COMMON VARIANTS (EG, R132H, R132C)
81121	IDH2 (ISOCITRATE DEHYDROGENASE 2 [NADP+], MITOCHONDRIAL) (EG, GLIOMA), COMMON VARIANTS (EG, R140W, R172M)
81170	ABL1 (ABL PROTO-ONCOGENE 1, NON-RECEPTOR TYROSINE KINASE) (EG, ACQUIRED IMATINIB TYROSINE KINASE INHIBITOR RESISTANCE), GENE ANALYSIS, VARIANTS IN THE KINASE DOMAIN
81175	ASXL1 (ADDITIONAL SEX COMBS LIKE 1, TRANSCRIPTIONAL REGULATOR) (EG, MYELODYSPLASTIC SYNDROME, MYELOPROLIFERATIVE NEOPLASMS, CHRONIC MYELOMONOCYTIC LEUKEMIA), GENE ANALYSIS; FULL GENE SEQUENCE
81176	ASXL1 (ADDITIONAL SEX COMBS LIKE 1, TRANSCRIPTIONAL REGULATOR) (EG, MYELODYSPLASTIC SYNDROME, MYELOPROLIFERATIVE NEOPLASMS, CHRONIC MYELOMONOCYTIC LEUKEMIA), GENE ANALYSIS; TARGETED SEQUENCE ANALYSIS (EG, EXON 12)
81206	BCR/ABL1 (T(9;22)) (EG, CHRONIC MYELOGENOUS LEUKEMIA) TRANSLOCATION ANALYSIS; MAJOR BREAKPOINT, QUALITATIVE OR QUANTITATIVE
81207	BCR/ABL1 (T(9;22)) (EG, CHRONIC MYELOGENOUS LEUKEMIA) TRANSLOCATION ANALYSIS; MINOR BREAKPOINT, QUALITATIVE OR QUANTITATIVE
81208	BCR/ABL1 (T(9;22)) (EG, CHRONIC MYELOGENOUS LEUKEMIA) TRANSLOCATION ANALYSIS; OTHER BREAKPOINT, QUALITATIVE OR QUANTITATIVE
81210	BRAF (B-RAF PROTO-ONCOGENE, SERINE/THREONINE KINASE) (EG, COLON CANCER, MELANOMA), GENE ANALYSIS, V600 VARIANT(S)
81218	CEBPA (CCAAT/ENHANCER BINDING PROTEIN [C/EBP], ALPHA) (EG, ACUTE MYELOID LEUKEMIA), GENE ANALYSIS, FULL GENE SEQUENCE
81219	CALR (CALRETICULIN) (EG, MYELOPROLIFERATIVE DISORDERS), GENE ANALYSIS, COMMON VARIANTS IN EXON 9
81235	EGFR (EPIDERMAL GROWTH FACTOR RECEPTOR) (EG, NON-SMALL CELL LUNG CANCER) GENE ANALYSIS, COMMON VARIANTS (EG, EXON 19 LREA DELETION, L858R, T790M, G719A, G719S, L861Q)
81245	FLT3 (FMS-RELATED TYROSINE KINASE 3) (EG, ACUTE MYELOID LEUKEMIA), GENE ANALYSIS; INTERNAL TANDEM DUPLICATION (ITD) VARIANTS (IE, EXONS 14, 15)
81246	FLT3 (FMS-RELATED TYROSINE KINASE 3) (EG, ACUTE MYELOID LEUKEMIA), GENE ANALYSIS; TYROSINE KINASE DOMAIN (TKD) VARIANTS (EG, D835, I836)
81261	IGH@ (IMMUNOGLOBULIN HEAVY CHAIN LOCUS) (EG, LEUKEMIAS AND LYMPHOMAS, B-CELL), GENE REARRANGEMENT ANALYSIS TO DETECT ABNORMAL CLONAL POPULATION(S); AMPLIFIED METHODOLOGY (EG, POLYMERASE CHAIN REACTION)
81262	IGH@ (IMMUNOGLOBULIN HEAVY CHAIN LOCUS) (EG, LEUKEMIAS AND LYMPHOMAS, B-CELL), GENE REARRANGEMENT ANALYSIS TO DETECT ABNORMAL CLONAL POPULATION(S); DIRECT PROBE METHODOLOGY (EG, SOUTHERN BLOT)

81263 IGH@ (IMMUNOGLOBULIN HEAVY CHAIN LOCUS) (EG, LEUKEMIA AND LYMPHOMA, B-CELL), VARIABLE REGION SOMATIC MUTATION ANALYSIS
81270 JAK2 (JANUS KINASE 2) (EG, MYELOPROLIFERATIVE DISORDER) GENE ANALYSIS, P.VAL617PHE (V617F) VARIANT
81272 KIT (V-KIT HARDY-ZUCKERMAN 4 FELINE SARCOMA VIRAL ONCOGENE HOMOLOG) (EG, GASTROINTESTINAL STROMAL TUMOR [GIST], ACUTE MYELOID LEUKEMIA, MELANOMA), GENE ANALYSIS, TARGETED SEQUENCE ANALYSIS (EG, EXONS 8, 11, 13, 17, 18)
81273 KIT (V-KIT HARDY-ZUCKERMAN 4 FELINE SARCOMA VIRAL ONCOGENE HOMOLOG) (EG, MASTOCYTOSIS), GENE ANALYSIS, D816 VARIANT(S)
81275 KRAS (KIRSTEN RAT SARCOMA VIRAL ONCOGENE HOMOLOG) (EG, CARCINOMA) GENE ANALYSIS; VARIANTS IN EXON 2 (EG, CODONS 12 AND 13)
81276 KRAS (KIRSTEN RAT SARCOMA VIRAL ONCOGENE HOMOLOG) (EG, CARCINOMA) GENE ANALYSIS; ADDITIONAL VARIANT(S) (EG, CODON 61, CODON 146)
81287 MGMT (O-6-METHYLGUANINE-DNA METHYLTRANSFERASE) (EG, GLIOBLASTOMA MULTIFORME), METHYLATION ANALYSIS
81292 MLH1 (MUTL HOMOLOG 1, COLON CANCER, NONPOLYPOSIS TYPE 2) (EG, HEREDITARY NON-POLYPOSIS COLORECTAL CANCER, LYNCH SYNDROME) GENE ANALYSIS; FULL SEQUENCE ANALYSIS
81293 MLH1 (MUTL HOMOLOG 1, COLON CANCER, NONPOLYPOSIS TYPE 2) (EG, HEREDITARY NON-POLYPOSIS COLORECTAL CANCER, LYNCH SYNDROME) GENE ANALYSIS; KNOWN FAMILIAL VARIANTS
81294 MLH1 (MUTL HOMOLOG 1, COLON CANCER, NONPOLYPOSIS TYPE 2) (EG, HEREDITARY NON-POLYPOSIS COLORECTAL CANCER, LYNCH SYNDROME) GENE ANALYSIS; DUPLICATION/DELETION VARIANTS
81301 MICROSATELLITE INSTABILITY ANALYSIS (EG, HEREDITARY NON-POLYPOSIS COLORECTAL CANCER, LYNCH SYNDROME) OF MARKERS FOR MISMATCH REPAIR DEFICIENCY (EG, BAT25, BAT26), INCLUDES COMPARISON OF NEOPLASTIC AND NORMAL TISSUE, IF PERFORMED
81310 NPM1 (NUCLEOPHOSMIN) (EG, ACUTE MYELOID LEUKEMIA) GENE ANALYSIS, EXON 12 VARIANTS
81311 NRAS (NEUROBLASTOMA RAS VIRAL [V-RAS] ONCOGENE HOMOLOG) (EG, COLORECTAL CARCINOMA), GENE ANALYSIS, VARIANTS IN EXON 2 (EG, CODONS 12 AND 13) AND EXON 3 (EG, CODON 61)
81313 PCA3/KLK3 (PROSTATE CANCER ANTIGEN 3 [NON-PROTEIN CODING]/KALLIKREIN-RELATED PEPTIDASE 3 [PROSTATE SPECIFIC ANTIGEN]) RATIO (EG, PROSTATE CANCER)
81314 PDGFRA (PLATELET-DERIVED GROWTH FACTOR RECEPTOR, ALPHA POLYPEPTIDE) (EG, GASTROINTESTINAL STROMAL TUMOR [GIST]), GENE ANALYSIS, TARGETED SEQUENCE ANALYSIS (EG, EXONS 12, 18)
81315 PML/RARALPHA, (T(15;17)), (PROMYELOCYTIC LEUKEMIA/RETINOIC ACID RECEPTOR ALPHA) (EG, PROMYELOCYTIC LEUKEMIA) TRANSLOCATION ANALYSIS; COMMON BREAKPOINTS (EG, INTRON 3 AND INTRON 6), QUALITATIVE OR QUANTITATIVE
81316 PML/RARALPHA, (T(15;17)), (PROMYELOCYTIC LEUKEMIA/RETINOIC ACID RECEPTOR ALPHA) (EG, PROMYELOCYTIC LEUKEMIA) TRANSLOCATION ANALYSIS; SINGLE BREAKPOINT (EG, INTRON 3, INTRON 6 OR EXON 6), QUALITATIVE OR QUANTITATIVE
81321 PTEN (PHOSPHATASE AND TENSIN HOMOLOG) (EG, COWDEN SYNDROME, PTEN HAMARTOMA TUMOR SYNDROME) GENE ANALYSIS; FULL SEQUENCE ANALYSIS
81322 PTEN (PHOSPHATASE AND TENSIN HOMOLOG) (EG, COWDEN SYNDROME, PTEN HAMARTOMA TUMOR SYNDROME) GENE ANALYSIS; KNOWN FAMILIAL VARIANT
81323 PTEN (PHOSPHATASE AND TENSIN HOMOLOG) (EG, COWDEN SYNDROME, PTEN HAMARTOMA TUMOR SYNDROME) GENE ANALYSIS; DUPLICATION/DELETION VARIANT
81327 SEPT9 (SEPTIN9) (EG, COLORECTAL CANCER) METHYLATION ANALYSIS
81334 RUNX1 (RUNT RELATED TRANSCRIPTION FACTOR 1) (EG, ACUTE MYELOID LEUKEMIA, FAMILIAL PLATELET DISORDER WITH ASSOCIATED MYELOID MALIGNANCY), GENE ANALYSIS, TARGETED SEQUENCE ANALYSIS (EG, EXONS 3-8)
81340 TRB@ (T CELL ANTIGEN RECEPTOR, BETA) (EG, LEUKEMIA AND LYMPHOMA), GENE REARRANGEMENT ANALYSIS TO DETECT ABNORMAL CLONAL POPULATION(S); USING AMPLIFICATION METHODOLOGY (EG, POLYMERASE CHAIN REACTION)
81342 TRG@ (T CELL ANTIGEN RECEPTOR, GAMMA) (EG, LEUKEMIA AND LYMPHOMA), GENE REARRANGEMENT ANALYSIS, EVALUATION TO DETECT ABNORMAL CLONAL POPULATION(S)
81350 UGT1A1 (UDP GLUCURONOSYLTRANSFERASE 1 FAMILY, POLYPEPTIDE A1) (EG, IRINOTECAN METABOLISM), GENE ANALYSIS, COMMON VARIANTS (EG, *28, *36, *37)
81400 MOLECULAR PATHOLOGY PROCEDURE, LEVEL 1 (EG, IDENTIFICATION OF SINGLE GERMLINE VARIANT [EG, SNP] BY TECHNIQUES SUCH AS RESTRICTION ENZYME DIGESTION OR MELT CURVE ANALYSIS)
81401 MOLECULAR PATHOLOGY PROCEDURE, LEVEL 2 (EG, 2-10 SNPS, 1 METHYLATED VARIANT, OR 1 SOMATIC VARIANT [TYPICALLY USING NONSEQUENCING TARGET VARIANT ANALYSIS], OR DETECTION OF A DYNAMIC MUTATION DISORDER/TRIPLET REPEAT)
81402 MOLECULAR PATHOLOGY PROCEDURE, LEVEL 3 (EG, >10 SNPS, 2-10 METHYLATED VARIANTS, OR 2-10 SOMATIC VARIANTS [TYPICALLY USING NON-SEQUENCING TARGET VARIANT ANALYSIS], IMMUNOGLOBULIN AND T-CELL RECEPTOR GENE REARRANGEMENTS, DUPLICATION/DELETION VARIANTS OF 1 EXON, LOSS OF HETEROZYGOSITY [LOH], UNIPARENTAL DISOMY [UPD])
81403 MOLECULAR PATHOLOGY PROCEDURE, LEVEL 4 (EG, ANALYSIS OF SINGLE EXON BY DNA SEQUENCE ANALYSIS, ANALYSIS OF >10 AMPLICONS USING MULTIPLEX PCR IN 2 OR MORE INDEPENDENT REACTIONS, MUTATION SCANNING OR DUPLICATION/DELETION VARIANTS OF 2-5 EXONS)
81404 MOLECULAR PATHOLOGY PROCEDURE, LEVEL 5 (EG, ANALYSIS OF 2-5 EXONS BY DNA SEQUENCE ANALYSIS, MUTATION SCANNING OR DUPLICATION/DELETION VARIANTS OF 6-10 EXONS, OR CHARACTERIZATION OF A DYNAMIC MUTATION DISORDER/TRIPLET REPEAT BY SOUTHERN BLOT ANALYSIS)
81405 MOLECULAR PATHOLOGY PROCEDURE, LEVEL 6 (EG, ANALYSIS OF 6-10 EXONS BY DNA SEQUENCE ANALYSIS, MUTATION SCANNING OR DUPLICATION/DELETION VARIANTS OF 11-25 EXONS, REGIONALLY TARGETED CYTOGENOMIC ARRAY ANALYSIS)

81406 MOLECULAR PATHOLOGY PROCEDURE, LEVEL 7 (EG, ANALYSIS OF 11-25 EXONS BY DNA SEQUENCE ANALYSIS, MUTATION SCANNING OR DUPLICATION/DELETION VARIANTS OF 26-50 EXONS, CYTOGENOMIC ARRAY ANALYSIS FOR NEOPLASIA)

81407 MOLECULAR PATHOLOGY PROCEDURE, LEVEL 8 (EG, ANALYSIS OF 26-50 EXONS BY DNA SEQUENCE ANALYSIS, MUTATION SCANNING OR DUPLICATION/DELETION VARIANTS OF >50 EXONS, SEQUENCE ANALYSIS OF MULTIPLE GENES ON ONE PLATFORM)

81408 MOLECULAR PATHOLOGY PROCEDURE, LEVEL 9 (EG, ANALYSIS OF >50 EXONS IN A SINGLE GENE BY DNA SEQUENCE ANALYSIS)

81435 HEREDITARY COLON CANCER DISORDERS (EG, LYNCH SYNDROME, PTEN HAMARTOMA SYNDROME, COWDEN SYNDROME, FAMILIAL ADENOMATOSIS POLYPOSIS); GENOMIC SEQUENCE ANALYSIS PANEL, MUST INCLUDE SEQUENCING OF AT LEAST 10 GENES, INCLUDING APC, BMPR1A, CDH1, MLH1, MSH2, MSH6, MUTYH, PTEN, SMAD4, AND STK11

81436 HEREDITARY COLON CANCER DISORDERS (EG, LYNCH SYNDROME, PTEN HAMARTOMA SYNDROME, COWDEN SYNDROME, FAMILIAL ADENOMATOSIS POLYPOSIS); DUPLICATION/DELETION ANALYSIS PANEL, MUST INCLUDE ANALYSIS OF AT LEAST 5 GENES, INCLUDING MLH1, MSH2, EPCAM, SMAD4, AND STK11

81437 HEREDITARY NEUROENDOCRINE TUMOR DISORDERS (EG, MEDULLARY THYROID CARCINOMA, PARATHYROID CARCINOMA, MALIGNANT PHEOCHROMOCYTOMA OR PARAGANGLIOMA); GENOMIC SEQUENCE ANALYSIS PANEL, MUST INCLUDE SEQUENCING OF AT LEAST 6 GENES, INCLUDING MAX, SDHB, SDHC, SDHD, TMEM127, AND VHL

81438 HEREDITARY NEUROENDOCRINE TUMOR DISORDERS (EG, MEDULLARY THYROID CARCINOMA, PARATHYROID CARCINOMA, MALIGNANT PHEOCHROMOCYTOMA OR PARAGANGLIOMA); DUPLICATION/DELETION ANALYSIS PANEL, MUST INCLUDE ANALYSES FOR SDHB, SDHC, SDHD, AND VHL

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

81479 UNLISTED MOLECULAR PATHOLOGY PROCEDURE

81503 ONCOLOGY (OVARIAN), BIOCHEMICAL ASSAYS OF FIVE PROTEINS (CA-125, APOLIPOPROTEIN A1, BETA-2 MICROGLOBULIN, TRANSFERRIN, AND PRE-ALBUMIN), UTILIZING SERUM, ALGORITHM REPORTED AS A RISK SCORE

81520 ONCOLOGY (BREAST), MRNA GENE EXPRESSION PROFILING BY HYBRID CAPTURE OF 58 GENES (50 CONTENT AND 8 HOUSEKEEPING), UTILIZING FORMALIN-FIXED PARAFFIN-EMBEDDED TISSUE, ALGORITHM REPORTED AS A RECURRENCE RISK SCORE

81525 ONCOLOGY (COLON), MRNA, GENE EXPRESSION PROFILING BY REAL-TIME RT-PCR OF 12 GENES (7 CONTENT AND 5 HOUSEKEEPING), UTILIZING FORMALIN-FIXED PARAFFIN-EMBEDDED TISSUE, ALGORITHM REPORTED AS A RECURRENCE SCORE

81538 ONCOLOGY (LUNG), MASS SPECTROMETRIC 8-PROTEIN SIGNATURE, INCLUDING AMYLOID A, UTILIZING SERUM, PROGNOSTIC AND PREDICTIVE ALGORITHM REPORTED AS GOOD VERSUS POOR OVERALL SURVIVAL

81540 ONCOLOGY (TUMOR OF UNKNOWN ORIGIN), MRNA, GENE EXPRESSION PROFILING BY REAL-TIME RT-PCR OF 92 GENES (87 CONTENT AND 5 HOUSEKEEPING) TO CLASSIFY TUMOR INTO MAIN CANCER TYPE AND SUBTYPE, UTILIZING FORMALIN-FIXED PARAFFIN-EMBEDDED TISSUE, ALGORITHM REPORTED AS A PROBABILITY OF A PREDICTED MAIN CANCER TYPE AND SUBTYPE

81545 ONCOLOGY (THYROID), GENE EXPRESSION ANALYSIS OF 142 GENES, UTILIZING FINE NEEDLE ASPIRATE, ALGORITHM REPORTED AS A CATEGORICAL RESULT (EG, BENIGN OR SUSPICIOUS)

The following CPT codes are **non-covered.**

0002U ONCOLOGY (COLORECTAL), QUANTITATIVE ASSESSMENT OF THREE URINE METABOLITES (ASCORBIC ACID, SUCCINIC ACID AND CARNITINE) BY LIQUID CHROMATOGRAPHY WITH TANDEM MASS SPECTROMETRY (LC-MS/MS) USING MULTIPLE REACTION MONITORING ACQUISITION, ALGORITHM REPORTED AS LIKELIHOOD OF ADENOMATOUS POLYPS

0003U ONCOLOGY (OVARIAN) BIOCHEMICAL ASSAYS OF FIVE PROTEINS (APOLIPOPROTEIN A-1, CA 125 II, FOLLICLE STIMULATING HORMONE, HUMAN EPIDIDYMIS PROTEIN 4, TRANSFERRIN), UTILIZING SERUM, ALGORITHM REPORTED AS A LIKELIHOOD SCORE

0005U ONCOLOGY (PROSTATE) GENE EXPRESSION PROFILE BY REAL-TIME RT-PCR OF 3 GENES (ERG, PCA3, AND SPDEF), URINE, ALGORITHM REPORTED AS RISK SCORE

0009U ONCOLOGY (BREAST CANCER), ERBB2 (HER2) COPY NUMBER BY FISH, TUMOR CELLS FROM FORMALIN FIXED PARAFFIN EMBEDDED TISSUE ISOLATED USING IMAGE-BASED DIELECTROPHORESIS (DEP) SORTING, REPORTED AS ERBB2 GENE AMPLIFIED OR NON-AMPLIFIED

0013U ONCOLOGY (SOLID ORGAN NEOPLASIA), GENE REARRANGEMENT DETECTION BY WHOLE GENOME NEXT-GENERATION SEQUENCING, DNA, FRESH OR FROZEN TISSUE OR CELLS, REPORT OF SPECIFIC GENE REARRANGEMENT(S)

0014U HEMATOLOGY (HEMATOLYMPHOID NEOPLASIA), GENE REARRANGEMENT DETECTION BY WHOLE GENOME NEXT-GENERATION SEQUENCING, DNA, WHOLE BLOOD OR BONE MARROW, REPORT OF SPECIFIC GENE REARRANGEMENT(S)

0016U ONCOLOGY (HEMATOLYMPHOID NEOPLASIA), RNA, BCR/ABL1 MAJOR AND MINOR BREAKPOINT FUSION TRANSCRIPTS, QUANTITATIVE PCR AMPLIFICATION, BLOOD OR BONE MARROW, REPORT OF FUSION NOT DETECTED OR DETECTED WITH QUANTITATION

0017U	ONCOLOGY (HEMATOLYMPHOID NEOPLASIA), JAK2 MUTATION, DNA, PCR AMPLIFICATION OF EXONS 12-14 AND SEQUENCE ANALYSIS, BLOOD OR BONE MARROW, REPORT OF JAK2 MUTATION NOT DETECTED OR DETECTED
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

ICD-10 Codes that Support Medical Necessity:

It is the provider's responsibility to select codes carried out to the highest level of specificity and selected from the ICD-10-CM code book appropriate to the year in which the service is rendered for the claim(s) submitted.

Medicare is establishing the following limited coverage for the colorectal cancer molecular biomarkers (also including the small intestine) listed below and for MAAA CPT code 81525, mRNA gene expression profiling by real time RT-PCR of 12 genes utilizing ffpe tissue, algorithm and report:

KRAS (12/13) **81275**
KRAS codon 61 **81276**
KRAS codon 146 **81276**
NRAS **81311**
BRAF **81210**
MSI by PCR **81301**
MLH1 promoter hypermethylation **81292, 81293, 81294**
mRNA **81525**
Sept9 **81327**
ColonSeq® **81445**

C17.0	Malignant neoplasm of duodenum
C17.1	Malignant neoplasm of jejunum
C17.2	Malignant neoplasm of ileum
C17.3	Meckel's diverticulum, malignant
C17.8	Malignant neoplasm of overlapping sites of small intestine
C17.9	Malignant neoplasm of small intestine, unspecified
C18.0	Malignant neoplasm of cecum
C18.1	Malignant neoplasm of appendix
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
C19	Malignant neoplasm of rectosigmoid junction
C20	Malignant neoplasm of rectum
C21.0	Malignant neoplasm of anus, unspecified
C21.1	Malignant neoplasm of anal canal
C21.2	Malignant neoplasm of cloacogenic zone
C21.8	Malignant neoplasm of overlapping sites of rectum, anus and anal canal

Medicare is establishing the following limited coverage for non-small cell lung carcinoma (NSCLC) molecular biomarkers:

EGFR **81235**
KRAS (12/13) **81275**
KRAS codon 61 **81276**
KRAS codon 146 **81276**
BRAF **81210**
Oncology Lung (Veristrat) **81538**
Oncomine DX **0022U**
LungSeq® **81445**

C33	Malignant neoplasm of trachea
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
C38.4	Malignant neoplasm of pleura
C45.0	Mesothelioma of pleura

Medicare is establishing the following limited coverage for melanoma molecular biomarkers:

BRAF **81210**
KIT **81272**
NRAS **81311**

C43.0	Malignant melanoma of lip
C43.10	Malignant melanoma of unspecified eyelid, including canthus
C43.111	Malignant melanoma of right upper eyelid, including canthus
C43.112	Malignant melanoma of right lower eyelid, including canthus
C43.121	Malignant melanoma of left upper eyelid, including canthus
C43.122	Malignant melanoma of left lower 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
D03.0	Melanoma in situ of lip
D03.10	Melanoma in situ of unspecified eyelid, including canthus
D03.111	Melanoma in situ of right upper eyelid, including canthus
D03.112	Melanoma in situ of right lower eyelid, including canthus
D03.121	Melanoma in situ of left upper eyelid, including canthus
D03.122	Melanoma in situ of left lower eyelid, including canthus
D03.20	Melanoma in situ of unspecified ear and external auricular canal
D03.21	Melanoma in situ of right ear and external auricular canal
D03.22	Melanoma in situ of left ear and external auricular canal
D03.30	Melanoma in situ of unspecified part of face
D03.39	Melanoma in situ of other parts of face
D03.4	Melanoma in situ of scalp and neck
D03.51	Melanoma in situ of anal skin
D03.52	Melanoma in situ of breast (skin) (soft tissue)
D03.59	Melanoma in situ of other part of trunk
D03.60	Melanoma in situ of unspecified upper limb, including shoulder
D03.61	Melanoma in situ of right upper limb, including shoulder
D03.62	Melanoma in situ of left upper limb, including shoulder
D03.70	Melanoma in situ of unspecified lower limb, including hip
D03.71	Melanoma in situ of right lower limb, including hip
D03.72	Melanoma in situ of left lower limb, including hip
D03.8	Melanoma in situ of other sites
D03.9	Melanoma in situ, unspecified

Medicare is establishing the following limited coverage for Uveal Melanoma

GNA11 - **81479**

C69.01	Malignant neoplasm of right conjunctiva
C69.02	Malignant neoplasm of left conjunctiva
C69.11	Malignant neoplasm of right cornea
C69.12	Malignant neoplasm of left cornea
C69.21	Malignant neoplasm of right retina
C69.22	Malignant neoplasm of left retina
C69.31	Malignant neoplasm of right choroid
C69.32	Malignant neoplasm of left choroid
C69.41	Malignant neoplasm of right ciliary body
C69.42	Malignant neoplasm of left ciliary body
C69.51	Malignant neoplasm of right lacrimal gland and duct
C69.52	Malignant neoplasm of left lacrimal gland and duct
C69.61	Malignant neoplasm of right orbit
C69.62	Malignant neoplasm of left orbit
C69.81	Malignant neoplasm of overlapping sites of right eye and adnexa

C69.82	Malignant neoplasm of overlapping sites of left eye and adnexa

Medicare is establishing the following limited coverage for brain molecular biomarkers:

BRAF **81210**
EGFR **81235**
MGMT **81287**
PTEN **81321, 81322, 81323, 81479**
CIMP **81479**
IDH1 **81120**
IDH2 **81121**

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

Medicare is establishing the following limited coverage for thyroid molecular biomarkers:

BRAF - **81210**
KRAS - **81275, 81276**
NRAS - **81311**
ThyraMIR - **81479**
Afirma - **81545**
ThyGenX - **81445**
RosettaGX Reveal Thyroid miRNA - **81479**
ThyroSeq – **0026U**

C73 *	Malignant neoplasm of thyroid gland
D34	Benign neoplasm of thyroid gland
D44.0	Neoplasm of uncertain behavior of thyroid gland
D44.2 *	Neoplasm of uncertain behavior of parathyroid gland
D44.9	Neoplasm of uncertain behavior of unspecified endocrine gland
E01.0	Iodine-deficiency related diffuse (endemic) goiter
E01.1	Iodine-deficiency related multinodular (endemic) goiter
E01.2	Iodine-deficiency related (endemic) goiter, unspecified
E04.0	Nontoxic diffuse goiter
E04.1	Nontoxic single thyroid nodule
E04.2	Nontoxic multinodular goiter
E04.8	Other specified nontoxic goiter
E04.9	Nontoxic goiter, unspecified

***Note**: C73 and D44.2 should not be reported for ThyraMIR, Afirma, ThyGenX, Rosetta GX Reveal or ThyroSeq.

Medicare is establishing the following limited coverage for uterus/ovary/fallopian tube/peritoneum molecular biomarkers:

AKT1 **81479**
BRAF **81210**
KRAS **81275, 81276**

MLH1 promoter hypermethylation **81292, 81293, 81294**
MSI by PCR **81301**
PTEN **81321, 81322, 81323, 81479**

C45.1	Mesothelioma of peritoneum
C48.1	Malignant neoplasm of specified parts of peritoneum
C48.2	Malignant neoplasm of peritoneum, unspecified
C48.8	Malignant neoplasm of overlapping sites of retroperitoneum and peritoneum
C54.0	Malignant neoplasm of isthmus uteri
C54.1	Malignant neoplasm of endometrium
C54.2	Malignant neoplasm of myometrium
C54.3	Malignant neoplasm of fundus uteri
C54.8	Malignant neoplasm of overlapping sites of corpus uteri
C54.9	Malignant neoplasm of corpus uteri, unspecified
C55	Malignant neoplasm of uterus, part unspecified
C56.1	Malignant neoplasm of right ovary
C56.2	Malignant neoplasm of left ovary
C56.9	Malignant neoplasm of unspecified ovary
C57.00	Malignant neoplasm of unspecified fallopian tube
C57.01	Malignant neoplasm of right fallopian tube
C57.02	Malignant neoplasm of left fallopian tube
C57.10	Malignant neoplasm of unspecified broad ligament
C57.11	Malignant neoplasm of right broad ligament
C57.12	Malignant neoplasm of left broad ligament
C57.20	Malignant neoplasm of unspecified round ligament
C57.21	Malignant neoplasm of right round ligament
C57.22	Malignant neoplasm of left round ligament
C57.3	Malignant neoplasm of parametrium
C57.4	Malignant neoplasm of uterine adnexa, unspecified

Medicare is establishing the following limited coverage for urinary tract molecular biomarkers:

MSI by PCR **81301**
MLH1 promoter hypermethylation **81292, 81293, 81294**

C65.1	Malignant neoplasm of right renal pelvis
C65.2	Malignant neoplasm of left 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
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

Medicare is establishing the following limited coverage for prostate cancer molecular biomarkers:

PROGENSA® PCA3 Assay - **81313**
PTEN – **81321, 81322, 81323**
RB1 - **81479**

C61	Malignant neoplasm of prostate
D29.1	Benign neoplasm of prostate

D40.0	Neoplasm of uncertain behavior of prostate
N40.0	Benign prostatic hyperplasia without lower urinary tract symptoms
N40.1	Benign prostatic hyperplasia with lower urinary tract symptoms
N40.2	Nodular prostate without lower urinary tract symptoms
N40.3	Nodular prostate with lower urinary tract symptoms
N42.31	Prostatic intraepithelial neoplasia
N42.32	Atypical small acinar proliferation of prostate
N42.39	Other dysplasia of prostate
N42.83	Cyst of prostate
R31.1	Benign essential microscopic hematuria
R31.29	Other microscopic hematuria

Medicare is establishing the following limited coverage for gastrointestinal stromal tumor molecular biomarkers:

KIT **81272**
PDGFRA **81314**

C49.A0	Gastrointestinal stromal tumor, unspecified site
C49.A1	Gastrointestinal stromal tumor of esophagus
C49.A2	Gastrointestinal stromal tumor of stomach
C49.A3	Gastrointestinal stromal tumor of small intestine
C49.A4	Gastrointestinal stromal tumor of large intestine
C49.A5	Gastrointestinal stromal tumor of rectum
C49.A9	Gastrointestinal stromal tumor of other sites
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

Medicare is establishing the following limited coverage for acute lymphoid leukemia (ALL) molecular biomarkers:

BCR/ABL1 **81206, 81207, 81208**
ABL1 (kinase domain) **81170**
IGH **81261**
TCRB **81340**
TCRG **81342**
MLL/AF4 **81479**
RUNX1 **81334**

C91.00	Acute lymphoblastic leukemia not having achieved remission
C91.01	Acute lymphoblastic leukemia, in remission
C91.02	Acute lymphoblastic leukemia, in relapse

Medicare is establishing the following limited coverage for acute myeloid leukemia (AML, and including acute promyelocytic leukemia) molecular biomarkers:

PML/RARA **81315**
PML/RARalpha **81316**
FLT3 ITD **81245**
NPM1 **81310**
KRAS **81275, 81276**
NRAS **81311**
KIT **81273**
CEBPA **81218**
JAK2 (p.V617F) **81270**
DEK/CAN **81479**
ASXL1 **81175, 81176**
EZH2 **81479**

TET2 **81479**
IDH1 **81120**
IDH2 **81121**
RUNX1 **81334**

C92.00	Acute myeloblastic leukemia, not having achieved remission
C92.01	Acute myeloblastic leukemia, in remission
C92.02	Acute myeloblastic leukemia, in relapse
C92.40	Acute promyelocytic leukemia, not having achieved remission
C92.41	Acute promyelocytic leukemia, in remission
C92.42	Acute promyelocytic leukemia, in relapse
C92.50	Acute myelomonocytic leukemia, not having achieved remission
C92.51	Acute myelomonocytic leukemia, in remission
C92.52	Acute myelomonocytic leukemia, in relapse
C92.60	Acute myeloid leukemia with 11q23-abnormality not having achieved remission
C92.61	Acute myeloid leukemia with 11q23-abnormality in remission
C92.62	Acute myeloid leukemia with 11q23-abnormality in relapse
C92.A0	Acute myeloid leukemia with multilineage dysplasia, not having achieved remission
C92.A1	Acute myeloid leukemia with multilineage dysplasia, in remission
C92.A2	Acute myeloid leukemia with multilineage dysplasia, in relapse

Medicare is establishing the following limited coverage for hairy cell leukemia molecular biomarkers:

IGH somatic hypermutation **81263**
IGH **81261**

C91.40	Hairy cell leukemia not having achieved remission
C91.41	Hairy cell leukemia, in remission
C91.42	Hairy cell leukemia, in relapse

Medicare is establishing the following limited coverage for aplastic anemia molecular biomarkers:

TCRB **81340**
TCRG **81342**

D60.0	Chronic acquired pure red cell aplasia
D60.1	Transient acquired pure red cell aplasia
D60.8	Other acquired pure red cell aplasias
D60.9	Acquired pure red cell aplasia, unspecified
D61.01	Constitutional (pure) red blood cell aplasia
D61.09	Other constitutional aplastic anemia
D61.1	Drug-induced aplastic anemia
D61.2	Aplastic anemia due to other external agents
D61.3	Idiopathic aplastic anemia
D61.89	Other specified aplastic anemias and other bone marrow failure syndromes
D61.9	Aplastic anemia, unspecified

Medicare is establishing the following limited coverage for Burkitt's lymphoma molecular biomarkers:

IGH **81261**

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

Medicare is establishing the following limited coverage for myeloproliferative diseases (MPD - essential thrombocytosis [ET], myelofibrosis & polycythemia vera [PV]) molecular biomarkers:

BCR/ABL1 **81206, 81207, 81208**
JAK2 (p.V617F) **81270**
CALR **81479**
CALR (exon 9) **81219**
CSF3R **81479**
ASXL1 **81175, 81176**
TET2 **81479**
EZH2 **81479**

D45	Polycythemia vera
D47.1	Chronic myeloproliferative disease
D47.3	Essential (hemorrhagic) thrombocythemia
D75.81	Myelofibrosis

Medicare is establishing the following limited coverage for chronic myeloid leukemia (CML) and chronic myelomonocytic leukemia (CMML) molecular biomarkers:

KRAS **81275, 81276**
NRAS **81311**
BCR/ABL1 **81206, 81207, 81208**
ABL1 (kinase domain) **81170**
FLT3 ITD **81245**
KIT **81273**
JAK2 (p.V617F) **81270**

C92.10	Chronic myeloid leukemia, BCR/ABL-positive, not having achieved remission
C92.11	Chronic myeloid leukemia, BCR/ABL-positive, in remission
C92.12	Chronic myeloid leukemia, BCR/ABL-positive, in relapse
C93.10	Chronic myelomonocytic leukemia not having achieved remission
C93.11	Chronic myelomonocytic leukemia, in remission
C93.12	Chronic myelomonocytic leukemia, in relapse

Medicare is establishing the following limited coverage for chronic lymphoid leukemia (CLL) molecular biomarkers:

IGH **81261**
IGH direct probe method **81262**
IGH somatic hypermutation **81263**

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

Medicare is establishing the following limited coverage for Hypereosinophilia Syndrome (HES) molecular biomarkers:

KIT (including p.D816V) **81273**

D72.1	Eosinophilia

Medicare is establishing the following limited coverage for mastocytosis molecular biomarkers:

KIT (including p.D816V) **81273**
TCRG **81342**

C96.20	Malignant mast cell neoplasm, unspecified
C96.22	Mast cell sarcoma
C96.29	Other malignant mast cell neoplasm

Medicare is establishing the following limited coverage for T-cell prolymphocytic leukemia molecular biomarkers:

TCRB **81340**
TCRG **81342**

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
C95.90	Leukemia, unspecified not having achieved remission
C95.91	Leukemia, unspecified, in remission
C95.92	Leukemia, unspecified, in relapse

Medicare is establishing the following limited coverage for myelodysplastic syndrome (MDS) molecular biomarkers:

FLT3 ITD **81245**
NPM1 **81310**
KRAS **81275, 81276**
NRAS **81311**
KIT **81273**
CEBPA **81218**
JAK2 (p.V617F) **81270**
ASXL1 **81175, 81176**
EZH2 **81479**
TET2 **81479**
IDH1 **81120**
IDH2 **81121**

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.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
D46.4	Refractory anemia, unspecified
D46.Z	Other myelodysplastic syndromes
D46.9	Myelodysplastic syndrome, unspecified

Medicare is establishing the following limited coverage for Myeloma gene expression profile (MyPRS) (CPT code 81479):

C90.00 *	Multiple myeloma not having achieved remission
C90.02 *	Multiple myeloma in relapse

***Note: C90.00** should be reported after initial diagnosis has been made and **C90.02** should be reported if there has been a relapse with a change in treatment planned.

Medicare is establishing the following limited coverage for CPT code 81520:

C50.011	Malignant neoplasm of nipple and areola, right female breast
C50.012	Malignant neoplasm of nipple and areola, left female breast
C50.111	Malignant neoplasm of central portion of right female breast
C50.112	Malignant neoplasm of central portion of left 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
C50.311	Malignant neoplasm of lower-inner quadrant of right female breast
C50.312	Malignant neoplasm of lower-inner quadrant of left 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
C50.511	Malignant neoplasm of lower-outer quadrant of right female breast
C50.512	Malignant neoplasm of lower-outer quadrant of left female breast
C50.611	Malignant neoplasm of axillary tail of right female breast
C50.612	Malignant neoplasm of axillary tail of left female breast
C50.811	Malignant neoplasm of overlapping sites of right female breast
C50.812	Malignant neoplasm of overlapping sites of left female breast
C50.911	Malignant neoplasm of unspecified site of right female breast
C50.912	Malignant neoplasm of unspecified site of left female breast

Medicare is establishing the following limited coverage for Neuroendocrine Tumors:

MAX – **81437**
MGMT – **81287**
PTEN – **81321, 81322, 81323**
RB1 - **81479**
SDHB – **81437, 81438**
SDHC – **81437, 81438**
SDHD – **81437, 81438**
TMEM127 – **81437**
TSC2 - **81479**
VHL – **81437, 81438**

C7A.010	Malignant carcinoid tumor of the duodenum
C7A.011	Malignant carcinoid tumor of the jejunum
C7A.012	Malignant carcinoid tumor of the ileum
C7A.019	Malignant carcinoid tumor of the small intestine, unspecified portion
C7A.020	Malignant carcinoid tumor of the appendix
C7A.021	Malignant carcinoid tumor of the cecum
C7A.022	Malignant carcinoid tumor of the ascending colon
C7A.023	Malignant carcinoid tumor of the transverse colon
C7A.024	Malignant carcinoid tumor of the descending colon
C7A.025	Malignant carcinoid tumor of the sigmoid colon
C7A.026	Malignant carcinoid tumor of the rectum
C7A.029	Malignant carcinoid tumor of the large intestine, unspecified portion
C7A.090	Malignant carcinoid tumor of the bronchus and lung
C7A.091	Malignant carcinoid tumor of the thymus
C7A.092	Malignant carcinoid tumor of the stomach
C7A.093	Malignant carcinoid tumor of the kidney
C7A.094	Malignant carcinoid tumor of the foregut, unspecified

C7A.095	Malignant carcinoid tumor of the midgut, unspecified
C7A.096	Malignant carcinoid tumor of the hindgut, unspecified
C7A.098	Malignant carcinoid tumors of other sites
C7A.1	Malignant poorly differentiated neuroendocrine tumors
C7A.8	Other malignant neuroendocrine tumors
C7B.01	Secondary carcinoid tumors of distant lymph nodes
C7B.02	Secondary carcinoid tumors of liver
C7B.03	Secondary carcinoid tumors of bone
C7B.04	Secondary carcinoid tumors of peritoneum
C7B.09	Secondary carcinoid tumors of other sites
C7B.1	Secondary Merkel cell carcinoma
C7B.8	Other secondary neuroendocrine tumors
D3A.010	Benign carcinoid tumor of the duodenum
D3A.011	Benign carcinoid tumor of the jejunum
D3A.012	Benign carcinoid tumor of the ileum
D3A.019	Benign carcinoid tumor of the small intestine, unspecified portion
D3A.020	Benign carcinoid tumor of the appendix
D3A.021	Benign carcinoid tumor of the cecum
D3A.022	Benign carcinoid tumor of the ascending colon
D3A.023	Benign carcinoid tumor of the transverse colon
D3A.024	Benign carcinoid tumor of the descending colon
D3A.025	Benign carcinoid tumor of the sigmoid colon
D3A.026	Benign carcinoid tumor of the rectum
D3A.029	Benign carcinoid tumor of the large intestine, unspecified portion
D3A.090	Benign carcinoid tumor of the bronchus and lung
D3A.091	Benign carcinoid tumor of the thymus
D3A.092	Benign carcinoid tumor of the stomach
D3A.093	Benign carcinoid tumor of the kidney
D3A.094	Benign carcinoid tumor of the foregut, unspecified
D3A.095	Benign carcinoid tumor of the midgut, unspecified
D3A.096	Benign carcinoid tumor of the hindgut, unspecified
D3A.098	Benign carcinoid tumors of other sites
D3A.8	Other benign neuroendocrine tumors

Medicare is establishing the following limited coverage for CPT code 81540 – TUO CTID (Cancer Type ID):

C18.1	Malignant neoplasm of appendix
C18.9	Malignant neoplasm of colon, unspecified
C22.0	Liver cell carcinoma
C22.2	Hepatoblastoma
C22.3	Angiosarcoma of liver
C22.4	Other sarcomas of liver
C22.7	Other specified carcinomas of liver
C22.8	Malignant neoplasm of liver, primary, unspecified as to type
C22.9	Malignant neoplasm of liver, not specified as primary or secondary
C25.2	Malignant neoplasm of tail of pancreas
C25.7	Malignant neoplasm of other parts of pancreas
C25.8	Malignant neoplasm of overlapping sites of pancreas
C25.9	Malignant neoplasm of pancreas, unspecified
C33	Malignant neoplasm of trachea
C34.01	Malignant neoplasm of right main bronchus
C34.02	Malignant neoplasm of left main bronchus

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
C34.32	Malignant neoplasm of lower lobe, left bronchus or 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
C34.91	Malignant neoplasm of unspecified part of right bronchus or lung
C34.92	Malignant neoplasm of unspecified part of left bronchus or lung
C43.51	Malignant melanoma of anal skin
C43.52	Malignant melanoma of skin of breast
C43.59	Malignant melanoma of other part of trunk
C45.9	Mesothelioma, unspecified
C47.0	Malignant neoplasm of peripheral nerves of head, face and neck
C47.9	Malignant neoplasm of peripheral nerves and autonomic nervous system, unspecified
C48.0	Malignant neoplasm of retroperitoneum
C49.0	Malignant neoplasm of connective and soft tissue of head, face and neck
C49.9	Malignant neoplasm of connective and soft tissue, unspecified
C50.411	Malignant neoplasm of upper-outer quadrant of right female breast
C50.412	Malignant neoplasm of upper-outer quadrant of left female breast
C50.511	Malignant neoplasm of lower-outer quadrant of right female breast
C50.512	Malignant neoplasm of lower-outer quadrant of left female breast
C50.811	Malignant neoplasm of overlapping sites of right female breast
C50.812	Malignant neoplasm of overlapping sites of left female breast
C50.911	Malignant neoplasm of unspecified site of right female breast
C50.912	Malignant neoplasm of unspecified site of left female breast
C56.1	Malignant neoplasm of right ovary
C56.2	Malignant neoplasm of left ovary
C61	Malignant neoplasm of prostate
C64.1	Malignant neoplasm of right kidney, except renal pelvis
C64.2	Malignant neoplasm of left kidney, except renal pelvis
C67.5	Malignant neoplasm of bladder neck
C67.9	Malignant neoplasm of bladder, unspecified
C76.0	Malignant neoplasm of head, face and neck
C77.0	Secondary and unspecified malignant neoplasm of lymph nodes of head, face and neck
C77.1	Secondary and unspecified malignant neoplasm of intrathoracic lymph nodes
C77.2	Secondary and unspecified malignant neoplasm of intra-abdominal lymph nodes
C77.3	Secondary and unspecified malignant neoplasm of axilla and upper limb lymph nodes
C77.4	Secondary and unspecified malignant neoplasm of inguinal and lower limb lymph nodes
C77.5	Secondary and unspecified malignant neoplasm of intrapelvic lymph nodes
C77.8	Secondary and unspecified malignant neoplasm of lymph nodes of multiple regions
C77.9	Secondary and unspecified malignant neoplasm of lymph node, unspecified
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
C78.6	Secondary malignant neoplasm of retroperitoneum and peritoneum
C78.7	Secondary malignant neoplasm of liver and intrahepatic bile duct
C79.01	Secondary malignant neoplasm of right kidney and renal pelvis
C79.02	Secondary malignant neoplasm of left kidney and renal pelvis
C79.2	Secondary malignant neoplasm of skin
C79.31	Secondary malignant neoplasm of brain
C79.49	Secondary malignant neoplasm of other parts of nervous system

C79.51	Secondary malignant neoplasm of bone
C79.52	Secondary malignant neoplasm of bone marrow
C79.61	Secondary malignant neoplasm of right ovary
C79.62	Secondary malignant neoplasm of left ovary
C79.89	Secondary malignant neoplasm of other specified sites
C80.0	Disseminated malignant neoplasm, unspecified
C80.1	Malignant (primary) neoplasm, unspecified
C82.57	Diffuse follicle center lymphoma, spleen
C84.A7	Cutaneous T-cell lymphoma, unspecified, spleen
C84.Z7	Other mature T/NK-cell lymphomas, spleen
C84.97	Mature T/NK-cell lymphomas, unspecified, spleen
C85.17	Unspecified B-cell lymphoma, spleen
C85.27	Mediastinal (thymic) large B-cell lymphoma, spleen
C85.87	Other specified types of non-Hodgkin lymphoma, spleen
C85.97	Non-Hodgkin lymphoma, unspecified, spleen
C86.1	Hepatosplenic T-cell lymphoma
D01.5	Carcinoma in situ of liver, gallbladder and bile ducts
D01.7	Carcinoma in situ of other specified digestive organs
D01.9	Carcinoma in situ of digestive organ, unspecified
D02.21	Carcinoma in situ of right bronchus and lung
D02.22	Carcinoma in situ of left bronchus and lung
D03.51	Melanoma in situ of anal skin
D03.52	Melanoma in situ of breast (skin) (soft tissue)
D03.59	Melanoma in situ of other part of trunk
D49.0	Neoplasm of unspecified behavior of digestive system
D49.1	Neoplasm of unspecified behavior of respiratory system
D49.2	Neoplasm of unspecified behavior of bone, soft tissue, and skin
D49.3	Neoplasm of unspecified behavior of breast
D49.4	Neoplasm of unspecified behavior of bladder
D49.511	Neoplasm of unspecified behavior of right kidney
D49.512	Neoplasm of unspecified behavior of left kidney
D49.59	Neoplasm of unspecified behavior of other genitourinary organ
D49.6	Neoplasm of unspecified behavior of brain
D49.7	Neoplasm of unspecified behavior of endocrine glands and other parts of nervous system
D49.89	Neoplasm of unspecified behavior of other specified sites
D49.9	Neoplasm of unspecified behavior of unspecified site
J91.0	Malignant pleural effusion

Medicare is establishing the following limited coverage for Bladder:
FGFR1 – **81479**
MTOR – **81479**
PTEN – **81321, 81322, 81323**
RB1 – **81479**

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

General Information

Associated Information

Please refer to Local Coverage Article: Biomarkers for Oncology (A52986) for billing information.

Documentation Requirements

1. All documentation must be maintained in the patient's medical record and made available to the contractor upon request.
2. Every page of the record must be legible and include appropriate patient identification information (e.g., complete name, dates of service[s]). The documentation must include the legible signature of the physician or non-physician practitioner responsible for and providing the care to the patient.
3. The submitted medical record must support the use of the selected ICD-10-CM code(s). The submitted CPT/HCPCS code must describe the service performed.
4. The medical record documentation must support the medical necessity of the services as stated in this policy. Specifically, the medical record should reflect whether any biomarker ordered is diagnostic, prognostic or predictive, as well as be able to clearly correlate any test results with given interventions **(e.g., particular selection of chemotherapy)**.

Utilization Guidelines

In accordance with CMS Ruling 95-1 (V), utilization of these services should be consistent with locally acceptable standards of practice.

The following tests will all be covered once per lifetime per beneficiary:

- CPT code 81437 – Hereditary neuroendocrine tumor disorders
- CPT code 81438 – Hereditary neuroendocrine tumor disorders; duplication/deletion analysis
- ThyraMIR ,Afirma,ThyGenX, RosettaGX Reveal and ThyroSeq tests
    - Should the unlikely situation of a second, unrelated thyroid nodule with indeterminate pathology occur, coverage may be considered upon appeal with supporting documentation
- CPT code 81540 TUO CTID (Cancer TYPE ID)
- CPT code 0022U when reported for the Oncomine DX Test

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.

Sources of Information and Basis for Decision

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

Abdul-Maksoud RS, Shalaby SM, Elsayed WS, et al. Fibroblast growth factor receptor 1 and cytokeratin 20 expressions and their relation to prognostic variables in bladder cancer. *Gene*. 2016; 591: 320-326.

Abraham D, Jackson N, Gundara JS, et al. MicroRNA profiling of sporadic and hereditary medullary thyroid cancer identifies predictors of nodal metastasis, prognosis, and potential therapeutic targets. *Clinical Cancer Research*. 2011; 1: 4772–4781.

Abubaker J, Jehan Z, Bavi P, et al. Clinicopathological Analysis of Papillary Thyroid Cancer with PIK3CA Alterations in a Middle Eastern Population.*J Clin Endocrinol Metab*. 2008; 93(2): 611-618.

Akerley WL, Nelson RE, Cowie RH, et al. The Impact of Serum based Proteomic Mass Spectrometry Test on Treatment Recommendations in Advanced Non Small Cell Lung Cancer. *Current Medical Research & Opinion.* 2013; 29(5): 517-25.

Al-Ahmadie HA, Iyer G, Janakiraman M, et al. Somatic mutation of fibroblast growth factor receptor-3 (FGFR3) defines a distinct morphological subtype of high-grade urothelial carcinoma. *J Pathol*. 2011; 224: 270-279.

Albain K, Barlow W, Shak S, et al. Prognostic and predictive value of the 21-gene recurrence score assay in postmenopausal women with node-positive, estrogen-receptor-positive breast cancer on chemotherapy: a retrospective analysis of a randomized trial. *Lancet Oncol.* 2010; 11: 55-65.

Albitar M, Manshouri, Kantarjian H, et al. Correlation between Lower C-MPL Protein Expression and Favorable Cytogenetic Groups in Acute Myeloid Leukemia. *Leukemia Research.* 1999; (23): 63-69.

Alexander EK, Kennedy GC, Zubair WB, et al. Preoperative Diagnosis of Benign Thyroid Nodules with Indeterminate Cytology. *New England Journal of Medicine*. 2012; 367: 705-15.

Alexander EK, Schorr M, Klopper J, et al. Multi-center experience with the Afirma Gene Expression Classifier. *Journal of Clinical Endocrinology Metabolism*. 2014; 99(1): 119-25.

Ali SZ, Cibas ES. *The Bethesda System for Reporting Thyroid Cytopathology. Definitions, criteria and explanatory notes*. New York, Springer. 2010.

Allegra C, Jessup J, Somerfield R, et al. American Society of Clinical Oncology Provisional clinical Opinion: Testing for KRAS Gene Mutations in Patients with Metastatic Colorectal Carcinoma to Predict Response to Anti-Epidermal Growth Factor Receptor Monoclonal Antibody Therapy. *Journal of Clinical Oncology.* 2009; 27 (12): 2091-2096.

An HJ, Kim KI, Kim JY, et al. Microsatellite Instability in Endometrioid Type Endometrial Adenocarcinoma is Associated With Poor Prognostic Indicators. *Am J Surg Pathol.* 2007; 31: 846-853.

Andre T, Boni C, Mounedji-Boudiaf L, et al. Oxaliplatin, fluorouracil, and leucovorin as adjuvant treatment for colon cancer. *N Engl J Med.* 2004; 350(23): 2343-2351.

Andre T, Boni C, Navarro M, et al. Improved overall survival with oxaliplatin, fluorouracil, and leucovorin as adjuvant treatment in stage II or III colon cancer in the MOSAIC trial. *J Clin Oncol.* 2009; 27: 3109-3116.

Aparicio AM, Shen L, Tapia EL, et al. Combined tumor suppressor defects characterize clinically defined aggressive variant prostate cancers. *Clin Cancer Res*. 2016; 22(6): 1520-1530.

Arcila ME, Chaft JE, Nafa K, et al. Prevalence, clinicopathologic associations, and molecular spectrum of ERBB2 (HER2) tyrosine kinase mutations in lung adenocarcinomas. *Clin Cancer Res.* 2012; 18(18): 4910-4918.

Arcila M, Drilon A, Sylvester B, et al. MAP2K1 (MEK1) mutations define a distinct subset of lung adenocarcinoma associated with smoking. Author manuscript. *Clin Cancer Res*. 2015: 21(8): 1935-1943.

Asari R, Passler C, Kaczirek K, et al. Hypoparathyroidism After Total Thyroidectomy: A Prospective Study. *Archives of Surgery*. 2008; 143(2): 132-137.

Asnis-Alibozek A, Fine M, Russo P, et al. Cost of Care for Malignant and Benign Renal Masses. *The American Journal of Management Care.* 2013; 19(8): 617-624.

Avet-Loiseau H, Li C, Magrangeas F, et.al. Prognostic significance of copy-number alterations in multiple myeloma. *J. Clin. Oncol*. 2009; 27: 4585-4590.

Bacher U, Kern W, Haferlach C, et al. *Cyclin D1 (CCND1)* Messenger RNA Expression as Assessed by Real-Time PCR contributes to Diagnosis and Follow-up Control in Patients with Mantle Cell Lymphoma. *Experimental Hematology.* 2013; 41(12): 1028-1037.

Bae JS, Kim Y, Jeon S, et al. Clinical utility of TERT promoter mutations and ALK rearrangement in thyroid cancer patients with a high prevalence of the BRAF V600E mutation.

Diagnostic Pathology. 2016;11(21): 1-10.

Bagrodia A, Cha EK, Sfakianos JP, et al. Genomic biomarkers for the prediction of stage and prognosis of upper tract urothelial carcinoma. Author manuscript. *J Urol*. 2016; 195(6): 1684-1689.

Baik CS, Myall NJ,and Wakelee HA. Targeting BRAF-Mutant Non-Small Cell Lung Cancer: From Molecular Profiling to Rationally Designed Therapy. *The Oncologist*. 2017;22: 786-796.

Bain B. Myeloid and Lymphoid Neoplasms with Eosinophilia and Abnormalities of PDGFRA, PDGFRB or FGFR1. *Haematologica.* 2010; 95: 696-698.

Bains A, Luthra R, Medeiros L, Zuo Z. FLT3 and NPM1 Mutations in Myelodysplastic Syndromes: Frequency and Potential Value for Predicting Progression to Acute Myeloid Leukemia. *Am J Clin Pathol.* 2011; 135: 62-69.

Ball DW. Medullary Thyroid Cancer: Monitoring and Therapy. *Endocrinology Metabolism Clin North Am*. 2007; 36(3): 823–837.

Balschun K, Haag J, Wenke A K, et al. KRAS, NRAS, PIK3CA Exon 20, and BRAF Genotypes in Synchronous and Metachronous Primary Colorectal Cancers, Diagnostic and Therapeutic Implications. *The Journal of Molecular Diagnostics.* 2011; 13 (4): 436-445.

Baro C, Espinet B, Salido M, et al. Cryptic IGH/BCL2 Rearrangements with Variant FISH Patterns in Follicular. *Leukemia Research.* 2011; 35(2): 256-259.

Bartel DP. MicroRNAs: genomics, biogenesis, mechanism, and function. *Cell*. 2004; 116: 281–297.

Bartoletti R, Cai T, Nesi G, et al. Loss of P16 expression and chromosome 9p21 LOH in predicting outcome of patients affected by superficial bladder cancer. *J Surg Res*. 2007; 143: 422-427.

Base RC, Hans L, Urban N, et al. Translational Crossroads for Biomarkers. *Clin Cancer Res.* 2005; 11: 6103. doi: 10.1158/1078-0432.CCR-04-2213.

Baysan M, Bozdag S, Cam M, et al. G-Cimp Status Prediction of Glioblastoma Samples Using mRNA Expression Data. *PLOS ONE.* 2012; 7 (11): 1-10.

Beaudenon-Huibregtse S, Alexander EK, Guttler RB, et al. Centralized Molecular Testing for Oncogenic Gene Mutations Complements the Local Cytopathologic Diagnosis of Thyroid Nodule. *Thyroid*. 2014; 24(10): 1479-1487.

Beltran H, Prandi D, Mosquera JM, et al. Divergent clonal evolution of castration-resistant neuroendocrine prostate cancer. *Nature Medicine.* 2016; 22(3):298-305.

Berggren P Steineck G, Adolfsson J, et al. p53 mutations in urinary bladder cancer. *British Journal of Cancer*. 2001; 84 (11): 1505-1511.

Bergethon K, Shaw AT, Ou SHI, et al. ROS1 rearrangements define a unique molecular class of lung cancers. *J Clin Oncol*. 2012;30(8): 863-870.

Berruti A, Amoroso V, Gallo F, et al. Pathologic complete response as a potential surrogate for the clinical outcome in patients with breast cancer after neoadjuvant therapy: A meta-regression of 29 randomized prospective studies. *Journal of Clinical Oncology.* 2014; 32(34): 3883-3891.

Besaratinia A and Pfeifer GP. Uveal melanoma and GNA11 mutations: a new piece added to the puzzle. *News and Views*. 2010: 18-20.

Bettendorf O, Schmidt H, Staebler A, et al. Chromosomal imbalances, loss of heterozygosity,

and immunohistochemical expression of TP53, RB1 and PTEN in intraductal cancer, intraepithelial neoplasia, and invasive adenocarcinoma of the prostate. *Genes Chromosomes Cancer*. 2008; 47: 565-572.

Biekowski M, Piaskowski S, Stoczyska-Fidelus E, et al. Screening for EGFR Amplifications with a Novel Method and their Significance for the Outcome of Glioblastoma Patients. *PLOS ONE.* 2013; 8 (6): 1-10.

Billerey C, Chopin D, Aubriot-Lorton MH, et al. Frequent FGFR3 mutations in papillary non-invasive bladder (pTa) tumors. *Am J Pathol.* 2001; 158(6): 1955-1959.

Bioulac-Sage P, Sempoux C, and Balabaud C. Hepatocellular adenoma: classification, variants and clinical relevance. *Seminars in Diagnostic Pathology.* 2017; 34: 112-125.

Birkeland E, Wik E, Mjos S, et al. KRAS gene amplification and overexpression but not mutation associates with aggressive and metastatic endometrial cancer. *British Journal of Cancer*. 2012; 107: 1997-2004.

Bischoff J, Ignatov A, Semczuk A, et al. hMLH1 promoter hypermethylation and MSI status in human endometrial carcinomas with and without metastases. *Clin Exp Metastasis.* 2012; 29: 889-900.

Bishop JA, Benjamin H, Cholakh H, et al. Accurate Classification of Non-Small Cell Lung Carcinoma Using a Novel MicroRNA-Based Approach. *Clin Cancer Res.* 2010; 16(2): 610-19.

Blaszyk H, Wang L, Dietmaier W, et al. Upper Tract Urothelial Carcinoma: A Clinicopathologic Study Including Microsatellite Instability Analysis. *Modern Pathology*. 2002; 15(8): 790-797.

Bo Wu, Schoedel K, Carty S, et al. Incidental diagnosis of parathyroid lesions by preoperative use of next-generation molecular testing. *World J Surg*. 2018. https://doi.org/10.1007/s00268-018-4548-3

Bohm MR, Tsianakas A, Merte RL, et al. Mutational analysis of GNAQ and GNA11 to aid therapy management of a choroidal melanoma metastatic to the contralateral orbit. *JAMA Ophthalmol*. 2013; 131(6): 812-814.

Bongiovanni M, Spitale A, Faquin WC, et al. The Bethesda System for Reporting Thyroid Cythopathology: A Meta-Analysis. *Acta Cytologica*. 2012; 56: 333–339.

Bossuyt P, Reitsma J, Linnet, K, et al. Beyond Diagnostic Accuracy: The Clinical Utility of Diagnostic Tests. *Clinical Chemistry.* 2012; 58(12): 1636-1643.

Bouscary D, Preudhomme C, Ribrag V, et al. Prognostic value of c-mpl expression in myelodysplastic syndromes. *Leukemia.* 1995; 9: 783-788.

Bowen D, Frew M, Hills R, et al. RAS Mutation in Acute Myeloid Leukemia is Associated with Distinct Cytogenetic Subgroups but does not Influence Outcome in Patients Younger than 60 Years. *Blood.* 2005; 106 (6): 2113-2119.

Boyd E, Bench A, Goday-Fernandez A, et al. Clinical utility of routine MPL exon 10 analysis in the diagnosis of essential thrombocythaemia and primary myelofibrosis. *British Journal of Haematology.* 2010; 149: 250-257.

Breen V, Kasabov N, Kamat A, et al. A holistic comparative analysis of diagnostic tests for urothelial carcinoma: a study of Cxbladder Detect, Urovysion® FISH, NMP22® and cytology based on imputation of multiple datasets. *BMC Medical Research Methodology.* 2015; 15:45 doi:10.1186/s12874-015-0036-8.

Breyer J, Wirtz RM, Erben P, et al. High CDKN2A/p16 and low FGFR3 expression predict

progressive potential of stage pT1 urothelial bladder carcinoma. *Clin Genitourin Cancer*. 2018: 1-9.

Broderick D, Di C, Parrett T, et al. Mutations of PIK3CA in Anaplastic Oligodendrogliomas, High-Grade Astrocytomas, and Medulloblastomas. *Cancer Research.* 2004; 64(15): 5048-5050.

Broyl A, Hose D, Lokhorst H, et al. Gene expression profiling for molecular classification of multiple myeloma in newly diagnosed patients. *Blood.* 2010; 116(14): 2543-2553.

Brüggemann M, Gökbuget N, Kneba M. Acute Lymphoblastic Leukemia: Monitoring Minimal Residual Disease as a Therapeutic Principle. *Seminars in Oncology*. 2012; 39 (1): 47-57.

Brüggemann M, van der Velden VHJ, Raff T, et al. Rearranged T-Cell Receptor Beta Genes Represent Powerful Targets for Quantification of Minimal Residual Disease in Childhood and Adult T-Cell Acute Lymphoblastic Leukemia. *Leukemia* 2004; 18: 710-719.

Brustugun OT, Khattak AM, Tromborg AK, et al. BRAF-mutations in non-small cell lung cancer. *Lung Cancer.* 2014; 84: 36-38.

Bucheit AD, Syklawer E, Jakob JA, et al. Clinical characteristics and outcomes with specific BRAF and NRAS mutations in patients with metastatic melanoma. *Cancer*. 2013; 119(21): 3821-9.

Bullinger L, Kronke J, Schon C, et al. Identification of acquired copy number alterations and uniparental disomies in cytogenetically normal acute myeloid leukemia using high-resolution single-nucleotide polymorphism analysis. *Leukemia*. 2010; 24: 438-449.

Burger M, van der Aa MN, van Oers JM, et al. Prediction of progression of non-muscle-invasive bladder cancer by WHO 1973 and 2004 grading and by FGFR3 mutation status: A prospective study. *Eur Urol*. 2008; 54: 835-844.

Burken MI, Wilson KS, Heller K, et al. The Interface of Medicare Coverage Decision-Making and Emerging Molecular-Based Laboratory Testing. *Genet Med.* 2009; 11(4): 225-31.

Busch K, Keller T, Fuchs U, et al. Identification of Two Distinct MYC Breakpoint Clusters and their Association with Various IGH Breakpoint Regions in the t(8;14) Translocations in Sporadic Burkitt-Lymphoma. *Leukemia.* 2007: 1739-1751.

Cabanero M, Sangha R, Sheffield BS, et al. Management of EGFR-mutated non-small-cell lung cancer: practical implications from a clinical and pathology perspective. *Curr Oncol.* 2017;24(2): 111-119.

Cahill S, Smyth P, Denning K, et al. Effect of BRAFV600E mutation on transcription and post-transcriptional regulation in a papillary thyroid carcinoma model. *Molecular Cancer*. 2007; 6:21.

Cahill S, Smyth P, Finn SP, et al. Effect of ret/PTC 1 rearrangement on transcription and post-transcriptional regulation in a papillary thyroid carcinoma model. *Molecular Cancer*. 2006; 5: 70.

Calin GA, Ferracin M, Cimmino A, et al. A microRNA signature associated with prognosis and progression of chronic lymphocytic leukemia. *New England Journal of Medicine*. 2005; 353: 1793-1801.

Campana D, Walter T, Pusceddu S, et al. Correlation between MGMT promoter methylation and response to temozolmide-based therapy in neuroendocrine neoplasms: an observational retrospective multicenter study. *Endocrine.* 2017. Doi 10.1007/s12020-017-1474-3

Campanella N, De Oliveira A, Scapulatempo-Neto C, et al. Biomarkers and Novel Therapeutic Targets in Gastrointestinal Stromal Tumors (GISTs). *Recent Patents on Anti-Cancer Drug*

Discovery. 2013; 8 (3): 288-297.

Cantara S, Capezzone M, Marchisotta S, et al. Impact of proto-oncogene mutation detection in cytological specimens from thyroid nodules improves the diagnostic accuracy of cytology. *J Clin Endocrinol Metab.* 2010; 95(3): 1365-9.

Cappetta M, Perez V, Zubillaga MN, et al. Concomitant detection of BCR-ABL translocation and JAK2 V617F mutation in five patients with myeloproliferative neoplasm at diagnosis. *International Journal of Laboratory Hematology.* 2013; 35: e4-e5.

Carbone DP, Ding K, Roder H, et al. Prognostic and Predictive Role of the Veristrat Plasma Test in Patients With Advanced Non-Small-Cell Lung Cancer Treated With Erlotinib or Placebo in the NCIC Clinical Trials Group BR.21 Trial. *J Thorac Oncol.* 2012; 7(11): 1653-60.

Carlson J, Roth J. The impact of the Oncotype Dx breast cancer assay in clinical practice: a systematic review and meta-analysis. Breast Cancer Res and Treat. 2013; 14(1): 12-22.

Care R, Valk P, Goodeve A, et al. Incidence and Prognosis of c-KIT and FLT3 Mutations in Core Binding Factor (CBF) Acute Myeloid Leukaemias. *British Journal of Haematology.* 2003; 121(5): 775-777.

Carlson J, Roth J. The impact of the Oncotype Dx breast cancer assay in clinical practice: a systematic review and meta-analysis. *Breast Cancer Res and Treat.* 2013; 14(1): 12-22.

Cartwright T, Chao C, Lee M, et al. Effect of the 12-gene colon cancer assay results on adjuvant treatment recommendations in patients with stage II colon cancer. *Curr Med Res Opin*. 2014; 30(2): 321-328.

Carvajal RD, Antonescu CR, Wolchok JD, et al. KIT as a therapeutic target in metastatic melanoma. *JAMA*. 2011; 305(22): 2327-34.

Catto JWF, Xinarianos G, Burton JL, Meuth M, Hamdy FC. Differential Expression of hMLH1 and hMSH2 is Related to Bladder Cancer Grade, Stage and Prognosis but Not Microsatellite Instability. *Int J Cancer.* 2003; 105: 484-490.

Chang SS, Boorjian SA, Chou R, et al. Diagnosis and treatment of non-muscle invasive bladder cancer: AUA/SUO Guideline. *American Urological Association Education and Research*. 2016: 1-45.

Chaux A, Comperat E, Varinot J, et al. High levels of phosphatase and tensin homolog expression are associated with tumor progression, tumor recurrence, and systemic metastases in pT1 urothelial carcinoma of the bladder: A tissue microarray study of 156 patients treated by transurethral resection. *Urology*. 2013; 81(1): 116-122.

Chee CE, Meropol NJ. Current status of gene expression profiling to assist decision making in stage II colon cancer. *Oncologist*. 2014; 19(7): 704-711.

Chen D, Zhang LQ, Huang JF, et al. BRAF Mutations in Patients with Non-Small Cell Lung Cancer: A Systematic Review and Meta-Analysis. *PLoS One*. 2014;9(6): e101354.

Chen H, Sippel RS, Pacak K. The NANETS Consensus Guideline for the Diagnosis and Management of Neuroendocrine Tumors: Pheochromocytoma, Paraganglioma & Medullary Thyroid Cancer. *Pancreas.* 2010; 39(6): 775-783.

Chen W, Huang Q. Detection of FLT3/ITD, JAK2(V617F) and NPM1 Gene Mutations in Chronic Myelomonocytic Leukemia. *Leukemia Research.* 2009; 33(11): E207-E209.

Chen YT, Kitabayashi N, Zhou XK, et al. MicroRNA analysis as a potential diagnostic tool for papillary thyroid carcinoma. *Modern Patholology*. 2008; 21: 1139-1146.

Chiaretti S, Tavolaro S, Chia E M, et al. Characterization of ABL1 Expression in Adult T-Cell Acute Lymphoblastic Leukemia by Oligonucleotide Array Analysis. *Haematologica/The Hematology Journal* .2007; 92(5): 619-626.

Chiaretti S, Vitale A, Cazzaniga G, et al. Clinico-Biological Features of 5202 Patients with Acute Lymphoblastic Leukemia Enrolled in the Italian AIEOP and GIMEMA Protocols and Stratified in Age Cohorts. *Haematologica.* 2013; 98(11): 1702-1710.

Chillón M, Santamaría C, García-Sanz R, et al. Long FLT3 Internal Tandem Duplications and Reduced PML-RARa Expression at Diagnosis Characterize a High-Risk Subgroup of Acute Promyelocytic Leukemia Patients. *Haematologica.* 2010; 95: 745-751.

Chou A, Fraser S, Toon CW, et al. A detailed clinicopathologic study of ALK-translocated papillary thyroid carcinoma. *Am J Surg Pathol*. 2015;39:652-659.

Chng WJ, Kuehl WM, Bergsage PL, et al. Translocation t(4:14) retains prognostic significance even in the setting of high-risk molecular signature. Letter to the Editor. *Leukemia.* 2007; 22: 459-461.

Cho M, Oweity T, Brandler T, et al. Distinguishing parathyroid and thyroid lesions on ultrasound-guided fine-needle aspiration: A correlation of clinical data, ancillary studies, and molecular analysis. *Cancer Cytopathol.* 2017;125: 674-82.

Chou A, Fraser S, Toon CW, et al. A detailed clinicopathologic study of ALK-translocated papillary thyroid carcinoma. Am J Surg Pathol. 2015;39:652-659.

Chua V, Lapadula D, Randolph C, et al. Dysregulated GPCR signaling and therapeutic options in uveal melanoma. *Mol Cancer Res*. 2017; 15(5): 501-506.

Cibas ED, Ali SZ. The Bethesda System for Reporting Thyroid Cytopathology. *American Journal of Clinical Pathology*. 2009; 132: 658-665.

Cibas ES, Baloch ZW, Fellegara G, et al. A prospective assessment defining the limitations of thyroid nodule pathologic evaluation. *Annals of Internal Medicine.* 2013; 159(5): 325-32.

Ciccarese C, Massari F, Blanca A, et al. Tp53 and its potential therapeutic role as a target in bladder cancer. *Expert Opinion on Therapeutic Targets*. 2017; 21(4): 401-414.

Cingarlini S, Bonomi M, Corbo V, et al. Profiling mTOR pathway in neuroendocrine tumors. *Target Oncol.* 2012; 7: 183-188.

Coates A, Winer E, Goldhirsch A, et al. Tailoring therapies – improving the management of early breast cancer: St Gallen International Expert Consensus on the Primary Therapy of Early Breast Cancer 2015. *Annals of Oncology Advance Access.* 2015; 26(8): 1-38.

Cobain E, Hayes, D. Indications of Prognostic Gene Expression Profiling in Early Breast Cancer. *Curr. Treat. Options in Oncol.* 2015; 16(23): 1-14.

Colamaio M, Calì G, Sarnataro D, et al. Let-7a down-regulation plays a role in thyroid neoplasias of follicular histotype affecting cell adhesion and migration through its ability to target the FXYD5 (Dysadherin) gene. *Journal of Clinical Endocrinolology Metabolism*. 2012; 97: E2168–E2178.

Colamaio M, Borbone E, Russo L, et al. miR 191 down-regulation plays a role in thyroid follicular tumors through CDK6 targeting. *Journal of Clinical Endocrinology Metabolism*. 2011; 96: E1915–E1924.

Collaud S, Tischler V, Atanassoff A, et al. Lung neuroendocrine tumors: correlation of ubiquitinylation and sumoylation with nucleo-cytosolic partitioning of PTEN. *BMC Cancer*. 2015 15(74): 1-10.

College of American Pathologists (CAP), International Association for the Study of Lung Cancer (IASLC), and Association for Molecular Pathology (AMP). Molecular Testing Guideline for Selection of Lung Cancer Patients – Revision 2016 Draft Recommendations. Accessed July 17, 2017:https://www.iaslc.org/sites/ default/files/wysiwyg-assets/5-20160616 capiaslcamplungguideline-2016 draftrecommendations_ocpfinal.pdf

Colombo C, Bolshakov S, Hajibashi S, et al. 'Difficult to diagnose' desmoid tumours: a potential role for CTNNB1 mutational analysis. *Histopathology*. 2011; 59: 336-340.

Colombo C, Miceli R, Lazar AJ, et al. CTNNB1 45F Mutation is a molecular prognosticator of increased postoperative primary desmoid tumor recurrence: An independent, multicenter validation study. *Cancer*. 2013; 3696-3702.

Cooper DS, Doherty GM, Haugen BR, et al. Revised American Thyroid Association Management Guidelines for Patients with Thyroid Nodules and Differentiated Thyroid Cancer. *Thyroid.* 2009; 19(11): 1167-1214.

Corbacioglu A, Scholl C, Schlenk R, et al. Prognostic Impact of Minimal Residual Disease in *CBFB-MYH11*-Positive Acute Myeloid Leukemia. *Journal of Clinical Oncology.* 2010; 28 (23): 3724-3729.

Cordes I, Kluth M, Zygis D, et al. PTEN deletions are related to disease progression and unfavourable prognosis in early bladder cancer. *Histopathology*. 2013; 63: 670-677.

Cordon-Cardo C, Wartinger D, Petrylak D, et al. Altered expression of the retinoblastoma gene product: Prognostic indicator in bladder cancer. *J Natl Cancer Inst*. 1992; 84(16): 1251-56.

Cortazar P, Zhang L, Untch M, et al. Pathological complete response and long-term clinical benefit in breast cancer: the CTNeoBC pooled analysis. *The Lancet.* 2014; 384: 164-172.

Costa C, Pereira S, Lima L, et al. Abnormal protein glycosylation and activated PI3K/Akt/mTOR pathway: Role in bladder cancer prognosis and targeted Therapeutics. *PLoS One*. 2015; 10(11): 1-19.

Cros J, Hentic O, Rebours V, et al. MGMT expression predicts response to temozolomide in pancreatic neuroendocrine tumors. *Endocrine Related Cancer*. 2016; 23(8): 625-633.

Curtin J, Busam K, Pinkel D, Bastian B. Somatic Activation of KIT in Distinct Subtypes of Melanoma. *Journal of Clinical Oncology.* 2006; 24(26): 4340-4346.

Damie R, Wasil T, Fais F, et al. Ig V Gene Mutation Status and CD38 Expression as Novel Prognostic Indicators in Chronic Lymphocytic Leukemia. *Blood.* 1999; 94 (6): 1840-1847.

Daneshmand S, Bazargani S, Bivalacqua T, et. al. Blue light cystoscopy for the diagnosis of bladder cancer: Results from the US prospective multicenter registry. *Urologic Oncology.* https://doi.org/10.1016/j.urolonc.2018.04.013

Daniilidou K, Frangou-Plemenou M, Grammatikakis J, et al. Prognostic significance and diagnostic value of PTEN and p53 expression in endometrial carcinoma. A retrospective clinicopathological and immunohistochemical study. *J BUON*. 2013; 18(1): 195-201.

Daver N, Strati P, Jabbour E, et al. *FLT3* Mutations in Myelodysplastic Syndrome and Chronic Myelomonocytic Leukemia. *American Journal of Hematology*. 2013; 88(1): 56-59.

David, S, Patil, D, Alemozaffar M, et al. Urologist use of cystoscopy for patients presenting with hematuria in the United States. *Urology*. 2017; 100: 20-26.

Davies L , Welch GH. Increasing Incidence of Thyroid Cancer in the United States, 1973-2002. *JAMA*. 2006; 295: 2164-2167.

Davis R, Jones JS, Barocas DA, et al. Diagnosis, evaluation and follow-up of asymptomatic microhematuria (AMH) in adults: AUA guideline, American Urological Association (AUA) guideline. 2012: 1-30.

Dawson A, Bal S, McTavish B, et al. Inversion and Deletion of 16q22 Defined by Array CGH, FISH and RT-PCR in a Patient with AML. *Cancer Genetics.* 2011; 204(6): 344-347.

Day F, Jorissen R, Lipton L, et al. PIK3CA and PTEN Gene and Exon Mutation-Specific Clinicopathologic and Molecular Associations in Colorectal Cancer. *Clinical Cancer Research.* 2013; 19(12): 3285-3296.

Decaux O, Lode L, Magrangeas F, et al. Prediction of Survival in Multiple Myeloma Based on Gene Expression Profiles Reveals Cell Cycle and Chromosomal Instability Signatures in High-Risk Patients and Hyperdiploid Signatures in Low-Risk Patients: A Study of the Intergroupe Francophone du Myelome. *Journal of Clinical Oncology.* 2008; 26(24): 4798-4805.

De Divitiis C, von Arx C, Grimaldi AM, et al. Metronomic temozolomide as second line treatment for metastatic poorly differentiated pancreatic neuroendocrine carcinoma. *J Transl Med.* 2016; 14(113): 1-12.

Dekking E, van der Velden V, Varro R, et al. Flow Cytometric Immunobead Assay for Fast and Easy Detection of PML-RARA Fusion Proteins for the Diagnosis of Acute Promyelocytic Leukemia. *Leukemia.* 2012; 26: 1976-1985.

Deng L, Chang D, Foshaug R, et al. Development and validation of a high-throughput mass spectrometry based urine metabolomic test for the detection of colonic adenomatous polyps. *Metabolites*. 2017; 7(32): 1-12. doi:10.3390/metabo7030032.

Deng L, Fang H, Tso V, et al. Clinical validation of a novel urine-based metabolomic test for the detection of colonic polyps on Chinese population. *Int J Colorectal Dis*. 2017; 32:741-743.

Derks J, Leblay N, Lantuejoul S, et al. New insights into the molecular characteristics of pulmonary carcinoids and large cell neuroendocrine carcinomas, and the impact on their clinical management. *J Thorac Oncol*. 2018: 1-15.

Derks JL, Leblay N, Thunnissen E, et al. Molecular subtypes of pulmonary large-cell neuroendocrine carcinoma predict chemotherapy treatment outcome. Clin Cancer Res. 2018: 24(1): 33-42.

De Roock W, Claes B, Bernasconi D, et al. Effects of KRAS, BRAF, NRAS, and PIK3CA mutations on the efficacy of cetuximab plus chemotherapy in chemotherapy-refractory metastatic colorectal cancer: a retrospective consortium analysis. *Lancet Oncol.* 2010;11(8): 753-62.

Dettmer MS, Perren A, Moch H, et al. MicroRNA profile of poorly differentiated thyroid carcinomas – new diagnostic and prognostic insights. *Thyroid*. 2013; 23(11): 1383-1389.

Devaraj P, Foroni L, Kitra-Roussos V, et al. Detection of BCR-ABL and E2A-PBX1 Fusion Genes by RT-PCR in Acute Lymphoblastic Leukemia with Failed or Normal Cytogenetics. *British Journal of Haematology.* 1995: 349-355.

Deverka P, Messner D, Dutta T. Center for Medical Technology Policy Effectiveness Guidance Document. Evaluation of Clinical Validity and Clinical Utility of Actionable Molecular Diagnostic Tests in Adult Oncology. Release Date: May 1, 2013.

Di Narzo AF, Tejpar S, Rossi S, et al. Test of four colon cancer risk-scores in formalin fixed paraffin embedded microarray gene expression data. *J Natl Cancer Inst*. 2014; 106(10): 1-8.

Di Nicolantonio F, Martini M, Molinari F, et al. Wild-Type BRAF is Required for Response to Panitumumab or Cetuximab in Metastatic Colorectal Cancer. *Journal of Clinical Oncology* . 2008; 26 (35): 5705-5712.

Di Noto R, Pardo C, Schiavone EM, et al. Stem Cell Factor Receptor (c-Kit, CD117) is Expressed on Blast Cells from most Immature Types of Acute Myeloid Malignancies but is also a Characteristic of a Subset of Acute Promyelocytic Leukaemia. *British Journal of Haematology.* 1996; 92(3): 562-564.

Dos Santos LC, da Costa Ribeiro JC, Silva NP, et al. Cytogenetics, JAK2 and MPL mutations in polycythemia vera, primary myelofibrosis and essential thrombocythemia. *Rev Bras Hematol Hemoter.* 2011; 33(6): 417-24.

Dos Santos MT, Mitne-Neto M, Miyashiro K, et al. Molecular genetic tests for JAK2V617F, Exon12_JAK2 and MPLW515K/L are highly informative in the evaluation of patients suspected to have BCR-ABL1-negative myeloproliferative neoplasms. *J Clin Pathol.* 2014; 67: 176-178.

Dougherty M, Santi M, Brose M, et al. Activating Mutations in *BRAF* Characterize a Spectrum of Pediatric Low-Grade Gliomas. *Neuro-Oncology.* 2010; 12(7): 621-630.

Downes, MR, Weening B, and van Rhijn VW, et al. Analysis of papillary urothelial carcinomas of the bladder with grade heterogeneity: supportive evidence for an early role of CDKN2A deletions in the FGFR3 pathway. *Histopathology*. 2017; 70: 281-289.

Dowsett M, Cuzick J, Wale C, et al. Prediction of risk of distant recurrence using the 21-gene recurrence score in node-negative and node-positive postmenopausal patients with breast cancer treated with anastrozole or tamoxifen: A TransATAC study. *Journal of Clinical Oncology.* 2010; 28(11): 1829-1834.

Dowsett M, Sestak I, Lopez-Knowles E, et al. Comparison of PAM50 Risk of Recurrence Score With Oncotype DX and IHC4 for Predicting Risk of Distant Recurrence After Endocrine Therapy. *J Clin Oncol.* 2013; 31: 2783-2790. doi: 10.1200/JCO.2012.46.1558. Epub 2013 Jul 1.

Duenas M, Martinez-Fernandez M, Garcia-Escudero R, et al. PIK3CA gene alterations in bladder cancer are frequent and associate with reduced recurrence in non-muscle invasive tumors. *Molecular Carcinogenesis*. 2015; 54: 566-576.

Duick DS, Klopper JP, Diggans JC, et al. Test Results on the Endocrinologist–Patient Decision to Operate on Patients with Thyroid Nodules with Indeterminate Fine-Needle Aspiration Cytopathology. *Thyroid*. 2012; 22(10): 996-1001.

Duployez N, Nibourel O, Marceau-Renaut A, et al. Minimal Residual Disease Monitoring in t(8;21) Acute Myeloid Leukemia Based on *RUNX1-RUNX1T1* Fusion Quantification on Genomic DNA. *American Journal of Hematology. 2*014; 89(6): 1-6.

Early Breast Cancer Trialists' Collaborative Group (EBCTCG) Report. *Lancet.* 2012; 379: 432-434.

Ecke TH, Sach MD, Lenk SV, et al. TP53 gene mutations as an independent marker for urinary bladder cancer progression. *International Journal of Molecular Medicine*. 2008; 21: 655-661.

Ecke TH, Schlechte HH, Hubsch A, et al. TP53 mutation in prostate needle biopsies-comparison with patients follow-up. *Anticancer Res*. 2007; 27: 4143-4148.

Ecke TH, Schlechte HH, Schiemenz K, et al. TP53 gene mutations in prostate cancer progression. *Anticancer Research*. 2010; 30:1579-1586.

Eisner R, Greiner R, Tso V, et al. A machine-learned predictor of colonic polyps based on urinary metabolomics. *BioMed Research International*. 2013; 303982: 1-11.

http://dx.doi.org/10.1155/2013/303982

Erickson LA. Papillary Thyroid Carcinoma. *Atlas of Anatomic Pathology*. 2014; 31-50.

Espiritu SMG, Liu LY, Rubanova Y, et al. The evolutionary landscape of localized prostate cancers drives clinical aggression. *Cell.* 2018; 173: 1-11.

Estep AL, Palmer C, McCormick F, Rauen KA. Mutation Analysis of BRAF, MEK1 and MEK2 in 15 Ovarian Cancer Cell Lines: Implications for Therapy. *PLoS ONE.* 2007; 2(12): e1279.

Estrella JS, Broaddus RR, Mathews A, et al. Progesterone receptor and PTEN expression predict survival in patients with low- and intermediate-grade pancreatic neuroendocrine tumors. *Arch Pathol Lab Med*. 2014; 138: 1027-1036.

Fahy K, Augustine L, Sanden M, et al. Clinicans' Real World Perceptions of Pre-Nephrectomy Diagnostic Biopsy Performance as a Driver of Reduction in Unnecessary Surgeries in Renal Tumors. *JKCVHL.* 2015; 2(1): 1-14.

Fang SH, Efron JE, Berho ME, et al. Dilemma of stage II colon cancer and decision making for adjuvant chemotherapy. *J Am Coll Surg.* 2014; 219(5): 1056-1069.

Faquin W, Baloch ZW. Fine-Needle Aspiration of Follicular Patterned Lesions of the Thyroid: Diagnosis, Management, and Follow-Up According to National Cancer Institute (NCI) Recommendations. *Diagnostic Cytopathology*. 2010; 38: 731–739.

Fekete M, Santiskulvong C, Eng C, Dorigo O. Effect of PI3K/Akt Pathway Inhibition-Mediated G1 Arrest on Chemosensitization in Ovarian Cancer Cells. *Anticancer Research.* 2012; 32: 445-452.

FDA Labeling for ROMA Assay (Fujirebio R Diagnostics, Inc.)

FDA 510(K) approval document. September 6, 2013

Feng YZ, Shiozawa T, Miyamoto T, et al. BRAF Mutation in Endometrial Carcinoma and Hyperplasia: Correlation with KRAS and p53 Mutations and Mismatch Repair Protein Expression. *Clin Cancer Res.* 2005; 11: 6133-6138.

Filipits M, Nielsen T, Rudas M, et al. The PAM50 Risk of Recurrence score predicts risk for late distant recurrence after endocrine therapy in postmenopausal women with endocrine-responsive early breast cancer. *Clin Cancer Res.* 2014; 20(5): 1-8.

Fonseca R, Bergasagel PL, Drach J, et al. International Myeloma Working Group molecular classification of multiple myeloma. *Leukemia.* 2009; 23: 2210-2221.

Forconi F, Sozzi E, Cencini E, et al. Hairy Cell Leukemias with Unmutated IGHV Genes Define the Minor Subset Refractory to Single-Agent Cladribine and with more Aggressive Behavior. *Blood.* 2009; 114 (21): 4696-4702.

Franc B, de la Salmoniere P, Lange F, et al. Interobserver and intraobserver reproducibility in the histopathology of follicular thyroid carcinoma. *Human Pathology*. 2003; 34(11): 1092-100.

Frates MC, Benson CB, Doubilet PM, et al. Prevalence and distribution of carcinoma in patients with solitary and multiple thyroid nodules on sonography. *Journal of Clinical Endocrinology Metabolism*. 2006; 91: 3411–3417.

Fridman E, Dotan Z, Barshack I, et al. Accurate Molecular Classification Of Renal Tumors Using MicroRNA Expression. *J Mol Diagn.* 2010; 12(5): 687-96.

Gale R, Green C, Allen C, et al. The Impact of *FLT3* Internal Tandem Duplication Mutant

Level, Number, Size, and Interaction with *NPM1* Mutations in a Large Cohort of Young Adult Patients with Acute Myeloid Leukemia. *Blood.* 2008; 111 (5): 2776-2784.

Gale R, Hills R, Pizzey A, et al. Relationship between FLT3 Mutation Status, Biologic Characteristics, and Response to Targeted Therapy in Acute Promyelocytic Leukemia. *Blood.* 2005; 106 (12): 3768-3776.

Gallia G, Rand V, Siu I, et al. PIK3CA Gene Mutations in Pediatric and Adult Glioblastoma Multiforme. *Mol Cancer Res.* 2006; 4(10): 709-714.

Gallucci MI, Guadagni F, Marzano R, et al. Status of the p53, p16, RB1, and HER-2 genes and chromosomes 3, 7, 9 and 17 in advanced bladder cancer: correlation with adjacent mucosa and pathological parameters. *J Clin Pathol*. 2005; 58: 367-71.

Gao Q, Ye F, Xia X, et al. Correlation between PTEN Expression and PI3K/Akt Signal Pathway in Endometrial Carcinoma. *Med Sci.* 2009; 29(1): 59-63.

Gao T, Mei Y, Sun H, et al. The association of phosphatase and tensin homolog (PTEN) deletion and prostate cancer risk: A meta-analysis. *Biomedicine & Pharmacotherapy*. 2016; 83:114-121.

Gan X, Lin X, He R, et al. Prognostic and clinicopathological significance of downregulated p16 expression in patients with bladder cancer: A systematic review and meta-analysis. *Dis Markers*. 2016: 1-13.

Garand R, Beldjord K, Cave H, et al. Flow Cytometry and IG/TCR Quantitative PCR for Minimal Residual Disease Quantitation in Acute Lymphoblastic Leukemia: a French Multicenter Prospective Study on Behalf of the FRALLE, EORTC and GRAALL. *Leukemia.* 2013; 27: 370-376.

Garcia-Rostan G, Costa AM, Pereira-Castro I, et al. Mutation of the PIK3CA Gene in Anaplastic Thyroid Cancer. *Cancer Res.* 2005; 65: 10199-10207.

Garcia-Saenz JA, Bermejo B, Estevez, G, et al. SEOM clinical guidelines in early-stage breast cancer 2015. *Clinical Transl Oncol.* 2015: 17(12); 939-945. DOI 10.1007/s12094-015-1427-3.

Garcon I, Libura M, Delabesse E, et al. *DEK-CAN* Molecular Monitoring of Myeloid Malignancies Could Aid Therapeutic Stratification. *Leukemia.* 2005; 19: 1338-1344.

Gazdar AF. Activating and resistance mutations of EGFR in non-small-cell lung cancer: role in clinical response to EGFR tyrosine kinase inhibitors. *Oncogene*. 2009;28(Suppl 1): s24–s31.

Geisler JP, Goodheart MJ, Sood AK, et al. Mismatch Repair Gene Expression Defects Contribute to Microsatellite Instability in Ovarian Carcinoma. *Cancer.* 2003; 98: 2199-2206.

George J, Walter V, Peifer M, et al. Integrative genomic profiling of large-cell neuroendocrine carcinomas reveals distinct subtypes of high-grade neuroendocrine lung tumors. *Nat Commun*. 2018; 9(1048): 1-13.

Geybels MS, Fang M, Wright JL, et al. PTEN loss is associated with prostate cancer recurrence and alterations in tumor DNA methylation profiles. *Oncotarget*. 2017; 8(48): 84338-84348.

Gharib H, Papini E, Paschke R, et al. American Association of Clinical Endocrinologists, Associazione Medici Endocrinologi, and European Thyroid Association Medical Guide lines for Clinical Practice. *Endocrinology Practice*. 2010; 16(Suppl 1): 1-43.

Gifford G, Paul J, Vasey PA, et al. The Acquisition of hMLH1 Methylation in Plasma DNA after Chemotherapy Predicts Poor Survival for Ovarian Cancer Patients. *Clin Cancer Res.* 2004; 10: 4420-4426.

Gillard M, Lack J, Pontier A, et al. Integrative genomic analysis of coincident cancer foci implicates CTNNB1 and PTEN alterations in ductal prostate cancer. *European Urology Focus.* 2017: 1-10.

Giordano TJ, Beaudenon-Huibregtse S, Shinde R, et al. Molecular testing for oncogenic gene mutations in thyroid lesions: a case-control validation study in 413 postsurgical specimens. *Human Patholology*. 2014; 45(7): 1339-47.

Giordano TJ, Kuick R, Thomas DG, et al. Molecular classification of papillary thyroid carcinoma: distinct BRAF, RAS, and RET/PTC mutation-specific gene expression profiles discovered by DNA microarray analysis. *Oncogene.* 2005; 24: 6646-6656.

Glaser AP, Fantini D, Shilatifard A, et al. The evolving genomic landscape of urothelial carcinoma. *Nature Reviews Urology*. 2017; 14: 215-229.

Gleeson FC, Voss JS, Kipp BR, et al. Assessment of pancreatic neuroendocrine tumor cytologic genotype diversity to guide personalized medicine using a custom gastroenteropancreatic next-generation sequencing panel. *Oncotarget*. 2017; 8(55): 93464-93475.

Gnant M, Filipits M, Greil R, et al. Predicting distant recurrence in receptor-positive breast cancer patients with limited clinicopathological risk: using the PAM50 Risk of Recurrence score in 1478 postmenopausal patients of the ABCSG-8 trial treated with adjuvant endocrine therapy alone. *Annals of Oncology.* 2013; 00:1-7.

Gnant M, Filipits M, Greil R, et al. Predicting distant recurrence in receptor-positive breast cancer patients with limited clinicopathological risk: using the PAM50 Risk of Recurrence score in 1478 postmenopausal patients of the ABCSG-8 trial treated with adjuvant endocrine therapy alone. *Annals of Oncology.* 2013 (Advance Access published December 16, 2013).

Gnant M., Sestak I, Filipits M, et al. Identifying clinically relevant prognostic subgroups of postmenopausal women with node-positive early stage breast cancer treated with endocrine therapy: A combined analysis of ABCSG-8 and ATAC using the PAM50 risk of recurrence score and Intrinsic Subtype. *Annals of Oncology.* Advance Access May 1, 2015.

Goebell PJ and Knowles MA. Bladder cancer or bladder cancers? Genetically distinct malignant conditions of the urothelium. *Urol Oncol*. 2010; 28: 409-428.

Goldhirsch A, Winer E, Coates A, et al. Personalizing the treatment of women with early breast cancer: highlights of the St. Gallen International Expert Consensus of the Primary Therapy of Early Breast Cancer. *Annals of Oncology.* 2013; 24: 2206-2223.

Goldman JW, Shi P, Reck M, et al. Treatment Rationale and Study Design for the JUNIPER Study: A Randomized Phase III Study of Abemaciclib With Best Supportive Care Versus Erlotinib With Best Supportive Care in Patients With Stage IV Non-Small-Cell Lung Cancer With a Detectable KRAS Mutation Whose Disease Has Progressed After Platinum-Based Chemotherapy. *Clinical Lung Cancer*. 2016; 17(1): 80-84.

Gomez Saez JM. Diagnostic and Prognostic Markers in Differentiated Thyroid Cancer. *Current Genomics.* 2011; 12: 597-608.

Goyal B, Duncavage EJ, Martinez D, et al. Next-generation sequencing of salivary high-grad neuroendocrine carcinomas identifies alterations in RB1 and the mTOR pathway. *Experimental & Molecular Pathology*. 2014; 97: 572-578.

Goyle S, Maraveyas A. Chemotherapy for colorectal cancer. *Dig Surg.* 2005; 22: 401-414.

Green C, Koo K, Hills R, et al. Prognostic Significance of *CEBPA* Mutations in a Large Cohort of Younger Adult Patients with Acute Myeloid Leukemia: Impact of Double CEBPA Mutations and the Interaction with *FLT3* and *NPM1* Mutations. *Journal of Clinical Oncology.* 2010; 28

(16): 2739-2747.

Griewank KG, van de Nes J, Schilling B, et al. Genetic and clinic-pathologic analysis of metastatic uveal melanoma. *Modern Pathology*. 2014; 27: 175-183.

Gruber JJ, Colevas AD. Differentiated Thyroid Cancer: Focus on Emerging Treatments for Radioactive Iodine-Refractory Patients. *Oncologist*. 2015; 20(2): 113-126. Epub 2015 Jan 23.

Guikema J, deBoer C, Haralambieva E, et al. IGH Switch Breakpoints in Burkitt Lymphoma: Exclusive Involvement of Noncanonical Class Switch Recombination. *Genes, Chromosomes & Cancer*. 2006; 45(9): 808-819.

Gunn S. Mohammed MS, Gorre ME, et.al. Whole-genome scanning by array comparative genomic hybridization as a clinical tool for risk assessment in chronic lymphocytic leukemia. *J. Mol. Diagn.* 2008; 10:442-451.

Haessler J, Shaughnessy JD, Zhan F, et al. Benefit of Complete Response in Multiple Myeloma Limited to High-Risk Subgroup Identified by Gene Expression Profiling. *Clin Cancer Res.* 2007; 13(23): 7073-7079.

Haferlach C, Bacher U, Haferlach T, et al. The inv(3)(q21q26)/t(3;3)(q21;q26) is frequently accompanied by alterations of the RUNX1, KRAS and NRAS and NF1 genes and mediates adverse prognosis both in MDS and in AML: a study in 39 cases of MDS or AML. *Leukemia.* 2011; 25: 874-877.

Hamada S, Futamura N, Ikuta K, et al. CTNNB1 S45F mutation predicts poor efficacy of meloxicam treatment for desmoid tumors: A pilot study. *PLoS One*. 2014 9(5): e96391, 1-6.

Hamada S, Urakawa H, Kozawa E, et al: Nuclear expression of β-catenin predicts the efficacy of meloxicam treatment for patients with sporadic desmoid tumors. *Tumour Biol*. 2014; 35: 4561-4566.

Hamaguchi H, Nagata K, Yamamoto K, et al. Establishment of a Novel Human Myeloid Leukaemia Cell Line (FKH-1) with T(6;9) (p23;q34) and the Expression of *dek-can* Chimaeric Transcript. *British Journal of Haematology.* 1998; 102(5): 1249-1256.

Han C, Ma J, Zhao J, et al. EGFR Mutations, Gene Amplification, and Protein Expression and KRAS Mutations in Primary and Metastatic Tumors of Nonsmall Cell Lung Cancers and Their Clinical Implications: A Meta-Analysis. *Cancer Investigation.* 2011; 29: 626-634.

Han X, Ji Y, Zhao J, et al. Expression of PTEN and mTOR in pancreatic neuroendocrine tumors. *Tumour Biol*. 2013; 34: 2871-2879.

Handolias D, Hamilton AL, Salemi R, et al. Clinical responses observed with imatinib or sorafenib in melanoma patients expressing mutations in KIT. *British Journal of Cancer.* 2010; 102: 1219-1223.

Hanna N, Johnson D, Temin S, et al. Systemic therapy for stage IV non–small-cell lung cancer: American Society of Clinical Oncology clinical practice guideline update. *Journal of Clinical Oncology.* 2017;35:3484-3515.

Hari PN, Zhang MJ, Roy V, et al. Is the international Staging System superior to the Durie-Salmon staging system? A comparison in multiple myeloma patients undergoing autologous transplant. *Leukemia.* 2009: 23(8); 1528-34. Doi: 10.1038/leu.2009.61

Hayette S, Tigaud I, Thomas X, et al. Identification of a Rare e6a2 BCR-ABL Fusion Gene During the Disease progression of Chronic Myelomonocytic Leukemia: A Case Report. *Leukemia*. 2004; 18: 1735-1736.

He H, Jazdzewski K, Li W, et al. The role of microRNA genes in papillary thyroid carcinoma.

Proceedings of the National Academy of Science. 2005; 102: 19075–19080.

He M, Breese V, Hang S, Zhang C, Xiong J, Jackson C. BRAF V600E Mutations in Endometrial Adenocarcinoma. *Diagn Mol Pathol.* 2013; 22(1): 35-40.

He Y, Van't Veer LJ, Mikolajewska-Hanclich I, et al. PIK3CA mutations predict local recurrences in rectal cancer patients. *Clin Cancer Res.* 2009; 15(22): 6956-62.

Hegedus L. Clinical practice. The thyroid nodule. *New England Journal of Medicine*. 2004; 351: 1764–1771.

Helmle KE, Otto CJ, Constantinescu G, Honore LH, Andrew SE. Variable MLH1 promoter methylation patterns in endometrial carcinomas of endometrioid subtype lacking DNA mismatch repair. *Int J Gynecol Cancer.* 2005; 15: 1089-1096.

Herandez-Aya L, Gonzalez-Angulo A. Adjuvant Systemic Therapies in Breast Cancer. *Surg Clin North Am.* 2013; 93(2): 473-491.

Herling M, Patel K, Teitell M, et al. High TCL1 expression and intact T-cell receptor signaling define a hyperproliferative subset of T-cell prolymphocytic leukemia. *Blood.* 2008; 111: 328-337.

Hershman J, Lyko A. Follicular Thyroid Carcinoma. *Endocrine Updates.* 2012; 32: 155-169.

Holmfeldt L, Wei L, Diaz-Flores E, et al. The Genomic Landscape of Hypodiploid Acute Lymphoblastic Leukemia. *Nature Genetics*. 2013; 45(3): 242-252.

Horny H, Lange K, Sotlar K, et. al. Increase of Bone Marrow Lymphocytes in Systemic Mastocytosis: Reactive Lymphocytosis or Malignant Lymphoma? Immunohistochemical and Molecular Findings on Routinely Processed bone Marrow Biopsy Specimens. *J Clin Pathol.* 2003; 56: 575-578.

Hose D, Reme T, Hielscher T, et al. Proliferation is a central independent prognostic factor and target for personalized and risk adapted treatment in multiple myeloma. *Haematologica.* Sept 2010.

Hou H, Kuo Y, Liu C, et al. *DNMT3A* Mutations in Acute Myeloid Leukemia: Stability during Disease Evolution and Clinical Implications. *Blood.* 2012; 119(2): 559-568.

Hughes T, Branford S. Molecular Monitoring of BCR-ABL as a Guide to Clinical Management in Chronic Myeloid Leukaemia. *Blood Rev.* 2006; 20 (1): 29-41.

Hummel J, Carmen Frias Kletecka M, Sanks J, et al. Concomitant *BCR-ABL1* Translocation and *JAK2V617F* Mutation in Three Patients with Myeloproliferative Neoplasms. *Diagn Mol Pathol.* 2012; 21: 176-183.

Hundahl SA, Cady B, Cunningham MP, et al. Initial results from a prospective cohort study of 5583 cases of thyroid carcinoma treated in the United States during 1996. U.S. and German Thyroid Cancer Study Group. An American College of Surgeons Commission on Cancer Patient Care Evaluation study. *Cancer.* 2000; 89(1): 202-17.

Huss S, Nehles J, Binot E, Et al. β catenin (CTNNB1) mutations and clinciopathological features of mesenteric desmoid-type fibromatosis. *Histopathology*. 2013; 62: 294-304.

Hussain M, Daignault-Newtown S, Twardowski PW, et al. Targeting androgen receptor and DNA repair in metastatic castration-resistant prostate cancer: Results from NCI 9012. *J Clin Oncol.* 2018; 36(10): 991-999.

Hyman DM, Puzanov I, Bubbiah V, et al. Vemurafenib in Multiple Nonmelanoma Cancers with BRAF V600 Mutations. *N.Eng J Med.* 2015; 373(8): 726-736.

Hyman D, Smyth L, Donoghue M, et al. AKT Inhibition in Solid Tumors with AKT1 Mutations. *Journal of Clinical Oncology*. 2017; 35(20); 2251-2259.

Ida C, Lambert S, Fausto J, et al. BRAF Alterations are Frequent in Cerebellar Low-Grade Astrocytomas with Diffuse Growth Pattern. *J Neuropathol Exp Neurol.* 2012; 71(7): 631-639.

Ikezoe T, Kojima S, Furihata M, et al. Expression of p-JAK2 Predicts Clinical Outcome and is a Potential Molecular Target of Acute Myelogenous Leukemia. *International Journal of Cancer.* 2011; 129(10): 2512-2521.

Iorio MV, Ferracin M, Liu CG, et al. MicroRNA gene expression deregulation in human breast cancer. *Cancer Research*. 2005; 65: 7065–7070.

Ishida H, Kasajima A, Kamei T, et al. SOX2 and Rb1 in esophageal small-cell carcinoma: their possible involvement in pathogenesis. *Modern Pathology*. 2017; 30: 660-671.

Itonaga H, Tsushima H, Imanishi D, et al. Molecular Analysis of the BCR-ABL1 Kinase Domain in Chronic-Phase Chronic Myelogenous Leukemia Treated with Tyrosine Kinase Inhibitors in Practice: Study by the Nagasaki CML Study Group. *Leukemia Research.* 2014;38 (1): 76-83.

Iyer G, Al-Ahmadie H, Schultz N, et al. Prevalence and co-occurrence of actionable genomic alterations in high-grade bladder cancer. *J Clin Oncol*. 2013; 31(25): 3133-3140.

Jain P, Kantarjian H, Patel K, et al. Mutated *NPM1* in Patients with Acute Myeloid Leukemia in Remission and Relapse. *Leukemia & Lymphoma* 2013: 1-8.

Jakob JA, Bassett RL Jr, Ng CS, et al. NRAS mutation status is an independent prognostic factor in metastatic melanoma. *Cancer*. 2012; 118(16): 4014-23.

Jamasphishvili T, Berman DM, Ross AE, et al. Clinical implications of PTEN loss in prostate cancer. *Nature Reviews Urology*. 2018; 15: 222-234.

Jeuken J, Sijben A, Alenda C, et al. Robust Detection of EGFR Copy Number Changes and EGFR Variant III: Technical Aspects and Relevance for Glioma Diagnostics. *Brain Pathology*. 2009; 19: 661-671.

Ji JH, Oh YL, Hong M, et al. Identification of driving ALK fusion genes and genomic landscape of medullary thyroid cancer. *PLoS Genet*. 2015;11(8):e1005467. https://doi.org/10.1371/journal.pgen.1005467

Jiang Y, Gao B, Zhang X, et al. Prevention and treatment of recurrent laryngeal nerve injury in thyroid surgery. *International Journal of Clinical Experience in Medicine*. 2014; 7(1): 101-7.

Jiao Y, Shi C, Edil BH, et al. DAXX/ATRX, MEN1, and mTOR pathway genes are frequently altered in pancreatic neuroendocrine tumors. *Science.* 2011; 331(6021): 1199-1203.

Jin S, Chang IH, Kim JW, et al. Identification of downstream genes of the mTOR pathway that predict recurrence and progression in non-muscle invasive high-grade urothelial carcinoma of the bladder. *J Korean Med Sci*. 2017; 32:1327-1336.

Jo VY, Stelow EB, Dustin SM, et al. Malignancy risk for fine-needle aspiration of thyroid lesions according to the Bethesda system for reporting thyroid cytopathology. *American Journal of Clinical Pathology*. 2010; 134: 450–6.

Jocham D, Stepp H, Waidelich R. Photodynamic diagnosis in urology: State-of-the-art. *European Urology*. 2008; 53: 1138-1150.

Joseph RW, Sullivan RJ, Harrell R, et al. Correlation of NRAS Mutations With Clinical

Response to High-dose IL-2 in Patients With Advanced Melanoma. *Journal of Immunotherapy.* 2012; 35: 66-72.

Jug R, Datto M, Jiang X. Molecular testing for indeterminate thyroid nodules: Performance of the afirma gene expression classifier and ThyroSeq panel. *Cancer Cytopathol.* 2018. DOI: 10.1002/cncy.21993, wileyonlinelibrary.com.

Kadia T, Kantarjian H, Kornblau S, et al. Clinical and Proteomic Characterization of Acute Myeloid Leukemia with Mutated RAS. *Cancer.* 2012; 118(22): 5550-5559.

Kaeferstein A, Krug U, Tiesmeier J, et al. The emergence of a C/EBPα mutation in the clonal evolution of MDS towards secondary AML. *Leukemia.* 2003; 17: 343-349.

Kaneki E, Oda Y, Ohishi Y, et al. Frequent Microsatellite Instability in Synchronous Ovarian and Endometrial Adenocarcinoma and Its Usefulness for Differential Diagnosis. *Human Pathology.* 2004; 35: 1484-1493.

Kavalieris L, O'Sullivan P, Frampton C, et al. Performance Characteristics of a Multigene Urine Biomarker Test for Monitoring for Recurrent Urothelial Carcinoma in a Multicenter Study. *The Journal of Urology*. (2017), DOI 10.1016/j.juro.2016.12.010

Kavalieris L, O'Sullivan PJ, Suttie JM, et al. A segregation index combining phenotypic (clinical Characteristics) and genotypic (gene expression) biomarkers from a urine sample to triage out patients presenting with hematuria who have a low probability of urothelial carcinoma. BMC Urology. 2015; 15: 23. DOI 10.1186/s12894-015-0018-5

Keedy VL, Temin S, Somerfield MR, et al. American Society of Clinical Oncology Provisional Clinical Opinion: Epidermal Growth Factor Receptor (EGFR) Mutation Testing for Patients With Advanced Non-Small-Cell Lung Cancer Considering First-Line EGFR Tyrosine Kinase Inhibitor Therapy. *J Clin Oncol.* 2011; 29: 2121-2127.

Kelemen K, Kovacsovics T, Braziel R, et al. RAS Mutations in Therapy-Related Acute Myeloid Leukemia after Successful Treatment of Acute Promyelocytic Leukemia. *Leukemia & Lymphoma.* 2012; 53(5): 999-1002.

Kennedy RD, Bylesjo M, Kerr P, et al. Development and independent validation of a prognostic assay for stage II colon cancer using formalin-fixed paraffin-embedded tissue. *J Clin Oncol*. 2011; 29(35): 4620-4626.

Keutgen XM, Filicori F, Crowley MJ, et al. A panel of four miRNAs accurately differentiates malignant from benign indeterminate thyroid lesions on fine needle aspiration. *Clinical Cancer Research*. 2012; 18:2032-2038.

Kilon A, Noel P, Akin C, et al. Elevated Serum Tryptase Levels Identify a Subset of Patients with a Myeloproliferative Variant of Idiopathic Hypereosinophilic Syndrome Associated with Tissue Fibrosis, Poor Prognosis, and Imatinib Responsiveness. *Blood.* 2003; 101(12): 4660-4666.

Kim I, Kim H, Choung H, et al. PML/RARA Rearrangement Associated with a t(15;19;17) in a Case of Acute Myeloid Leukemia with Abundant Myelocytes with Salmon-pink Cytoplasm. *Cancer Genetics and Cytogenetics.* 2006; 169(1): 81-82.

Kim PH, Cha EK, Sfakianos JP, et al. Genomic predictors of survival in patients with high-grade urothelial carcinoma of the bladder. *European Urology*. 2015; 67: 198-201.

Kim TH, Park YJ, Lim JA, et al. The Association of the BRAFV600E Mutation With Prognostic Factors and Poor Clinical Outcome in Papillary Thyroid Cancer: A Meta-Analysis. *Cancer*. 2012; 118: 1764-73.

Kitano M, Rahbari R, Patterson EE, et al. Evaluation of candidate diagnostic microRNAs in

thyroid fine-needle aspiration biopsy samples. *Thyroid*. 2012; 22: 285-291.

Kiyoi H, Naoe T, Nakano Y, et al. Prognostic Implication of FLT3 and N-RAS Gene Mutations in Acute Myeloid Leukemia. *Blood.* 1999; 93(9): 3074-3080.

Kluth M, Harasimowicz S, Burkhardt L, et al. Clinical significance of different types of p53 gene alteration in surgically treated prostate cancer. *Int J Cancer*. 2014; 135:1369-1380.

Kohlmann A, Grossmann V, Klein H, et al. Next-Generation Sequencing Technology Reveals a Characteristic pattern of Molecular Mutations in 72.8% of Chronic Myelomonocytic Leukemia by Detecting Frequent Alterations in *TET2, CBL, RAS,* and *RUNX1*. *Journal of Clinical Oncology.* 2010; 28 (24): 3858-3865.

Kolasa IK, Rembiszewska A, Janiec-Jankowska A, et al. PTEN mutation, expression and LOH at its locus in ovarian carcinomas. Relation to *TP53, K-RAS and BRCA1* mutations. *Gynecologic Oncology.* 2006; 103: 692-697.

Kolquist K, Schultz RA, Furrow A, et.al. Microarray-based comparative genomic hybridization of cancer targets reveals novel recurrent genetic aberrations in the myelodysplastic syndromes. *Cancer Genet.* 2011; 204: 603-628.

Kompier LC, Lurkin I, van der Aa MN, et al. FGFR3 HRAS, KRAS, NRAS and PIK3CA mutations in bladder cancer and their potential as biomarkers for surveillance and therapy. *PLoS One*. 2010; 5(11) e13821: 1-13.

Kondo T, Ezzat S, Asa SL. Pathogenetic mechanisms in thyroid follicular-cell neoplasia. *Nature Reviews Cancer*. 2006; 6(4): 292-306.

Konukiewitz B, Schlitter AM, Jesinghaus M, et al. Somatostatin receptor expression related to TP53 and RB1 alterations in pancreatic and extrapancreatic neuroendocrine neoplasms with a Ki67-index above 20%. *Modern Pathology*. 2017; 30: 587-598.

Kook H, Risitano An, Zeng W, et al. Changes in T-cell Receptor VB Repertoire in Aplastic Anemia: Effects of Different Immunosuppressive Regimens. *Blood.* 2002; 99 (10): 3668-3675.

Korkolopoulu P, Levidou G, Trigka EA, et al. A comprehensive immunohistochemical and molecular approach to the PI3K/AKT/mTOR (phosphoinositide 3-kinase/v-akt murine thymoma viral oncogene/mammalian target of rapamycin) pathway in bladder urothelial carcinoma. *BJU Int*. 2012; 110: E1237-1248.

Kosmider O, Gelsi-Boyer V, Slama L, et al. Mutations of IDH1 and IDH2 genes in early and accelerated phases of myelodysplastic syndromes and MDS/myeloproliferative neoplasms. *Leukemia.* 2010; 24: 1094-1096.

Krakstad C, Birkeland E, Seidel D, et al. High-Throughput Mutation Profiling of Primary and Metastatic Endometrial Cancers Identifies KRAS, FGFR2 and PIK3CA to Be Frequently Mutated. *PLoS ONE.* 2012; 7(12): e52795.

Krausch M, Raffel A, Anlauf M, Loss of PTEN Expression in neuroendocrine pancreatic tumors. *Horm Metab Res*. 2011; 43: 865-871

Kristensen T, Vestergaard H, Bindslev-Jensen C, et al. Sensitive KIT D816V Mutation Analysis of Blood as a Diagnostic Test in Mastocytosis. American Journal of Hematology. 2014: 1-6.

Kulac I, Arslankoz S, Netto GJ, et al. Reduced immunohistochemical PTEN staining is associated with higher progression rate and recurrence episodes in non-invasive low-grad papillary urothelial carcinoma of the bladder. *Virchows Arch*. 2018. https://doi.org/10.1007/s00428-018-2302-8

Kulke MH, Hornick JL, Frauenhoffer C, et al. 06-methylguanine DNA methyltransferase deficiency and response to Temozolomid-based therapy in patients with neuroendocrine tumors. *Clin Cancer Res*. 2009; 15(1): 338-345.

Labourier E, Shifrin A, Busseniers AE, et al. Molecular testing for miRNA, mRNA and DNA on fine needle aspiration improves the preoperative diagnosis of thyroid nodules with indeterminate cytology. *Journal of Clinical Endocrinology and Metabolism.* 2015; 100(7): 2743-2750. Doi:10.1210/jc.2015-1158

Lai A, Kharbanda S, Pope W, et al. Evidence for Sequenced Molecular Evolution of IDH1 Mutant Glioblastoma from a Distinct Cell of Origin. *Journal of Clinical Oncology.* 2011; 29 (34): 4482-4490.

Land SR, Kopec JA, Cecchini RS, et al. Neurotoxicity from oxaliplatin combined with weekly bolus fluorouracil and leucovorin as surgical adjuvant chemotherapy for stage II and III colon cancer: NSABP C-07. *J Clin Oncol.* 2007; 25(16): 2205-2211.

Laurent-Puig P, Gilles A, Buc M, et al. Analysis of PTEN, BRAF, and EGFR status in determining benefit from cetuximab therapy in wild-type KRAS metastatic colon cancer. *J Clin Oncol*. 2009; 27(35): 5924-5930.

Start Date of Notice Period 10/13/2016

Revision History Information

Revision History Date	Revision History Number	Revision History Explanation
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. 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 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 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.
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.
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.

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.
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.
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.
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 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.

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.
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.
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.
01/22/2016	R12	LCD revised and published on 05/12/2016 to correct source for Starczynowski.
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.
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.
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.
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, 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.
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.
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.
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.
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.
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.
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.

Related Documents

A52986-Biomarkers for Oncology