

# Multianalyte Assays with Algorithmic Analyses for Cancer Indications



INDEPENDENT CARE HEALTH PLAN

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## Medicare Advantage Medical Coverage Policy

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#### Disclaimer

The Coverage Summaries are reviewed by the iCare Medicare Utilization Management Committee. Policies in this document may be modified by a member's coverage document. Clinical policy is not intended to preempt the judgment of the reviewing medical director or dictate to health care providers how to practice medicine. Health care providers are expected to exercise their medical judgment in rendering appropriate care. Identification of selected brand names of devices, tests and procedures in a medical coverage policy is for reference only and is not an endorsement of any one device, test, or procedure over another. Clinical technology is constantly evolving, and we reserve the right to review and update this policy periodically. References to CPT® codes or other sources are for definitional purposes only and do not imply any right to reimbursement or guarantee of claims payment. No part of this publication may be reproduced, stored in a retrieval system or transmitted, in any shape or form or by any means, electronic, mechanical, photocopying or otherwise, without permission from iCare.

## Related Medicare Advantage Medical/Pharmacy Coverage Policies

Gene Expression Profiling for Cancer Indications

Genetic Testing

## Related Documents

Please refer to [CMS website](#) for the most current applicable CMS Online Manual System (IOMs)/National Coverage Determination (NCD)/ Local Coverage Determination (LCD)/Local Coverage Article (LCA)/ Transmittals.

| Type | Title | ID Number | Jurisdiction<br>Medicare<br>Administrative | Applicable<br>States/Territories |
|------|-------|-----------|--|----------------------------------|
|------|-------|-----------|--|----------------------------------|

**Multianalyte Assays with Algorithmic Analyses for Cancer Indications**

|                |  |  | <b>Contractors<br/>(MACs)</b>                               |  |
|----------------|--|--|---|--|
| LCD<br><br>LCA | <p>MolDX: Molecular Testing for Detection of Upper Gastrointestinal Metaplasia, Dysplasia, and Neoplasia</p> <p>Response to Comments: MolDX: Molecular Testing for Detection of Upper Gastrointestinal Metaplasia, Dysplasia, and Neoplasia</p> <p>MolDX: Prognostic and Predictive Molecular Classifiers for Bladder Cancer</p> | <p><a href="#"><u>L39356</u></a></p> <p><a href="#"><u>A59360</u></a></p> <p><a href="#"><u>L38684</u></a></p> | J5, J8 - Wisconsin Physicians Service Insurance Corporation | IA, IN, KS, MI, MO, NE                                     |
| LCD<br><br>LCA | <p>Molecular Pathology Procedures</p> <p>Billing and Coding: Molecular Pathology Procedures</p> <p>Multimarker Serum Tests Related to Ovarian Cancer Testing</p>   | <p><a href="#"><u>L35000</u></a></p> <p><a href="#"><u>A56199</u></a></p> <p><a href="#"><u>L38371</u></a></p> | J6, JK - National Government Services, Inc.                 | CT, IL, ME, MA, MN, NH, NY, RI, VT, WI                     |
| LCD<br><br>LCA | <p>MolDX: Molecular Testing for Detection of Upper Gastrointestinal Metaplasia, Dysplasia, and Neoplasia</p> <p>Response to Comments: MolDX: Molecular Testing for Detection of Upper Gastrointestinal Metaplasia, Dysplasia, and Neoplasia</p> <p>MolDX: Prognostic and Predictive Molecular Classifiers for Bladder Cancer</p> | <p><a href="#"><u>L39276</u></a></p> <p><a href="#"><u>A59344</u></a></p> <p><a href="#"><u>L38586</u></a></p> | J15 - CGS Administrators, LLC                               | KY, OH   |
| LCD            | <p>MolDX: Molecular Testing for Detection of Upper Gastrointestinal Metaplasia, Dysplasia, and Neoplasia</p> <p>Response to Comments: MolDX: Molecular Testing for Detection</p>   | <p><a href="#"><u>L39262</u></a></p> <p><a href="#"><u>A59353</u></a></p>                                      | JE - Noridian Healthcare Solutions, LLC                     | CA, HI, NV, American Samoa, Guam, Northern Mariana Islands |

**Multianalyte Assays with Algorithmic Analyses for Cancer Indications**

|                |   |  |   |  |
|----------------|---|--|---|--|
| LCA            | of Upper Gastrointestinal Metaplasia, Dysplasia, and Neoplasia<br><br>MoIDX: Prognostic and Predictive Molecular Classifiers for Bladder Cancer   | <a href="#">L38647</a>   |   |  |
| LCD<br><br>LCA | MoIDX: Molecular Testing for Detection of Upper Gastrointestinal Metaplasia, Dysplasia, and Neoplasia<br><br>Response to Comments: MoIDX: Molecular Testing for Detection of Upper Gastrointestinal Metaplasia, Dysplasia, and Neoplasia<br><br>MoIDX: Prognostic and Predictive Molecular Classifiers for Bladder Cancer | <a href="#">L39264</a><br><br><a href="#">A59354</a><br><br><a href="#">L38649</a>                               | JF - Noridian Healthcare Solutions, LLC | AK, AZ, ID, MT, ND, OR, SD, UT, WA, WY           |
| LCD<br><br>LCA | Biomarkers for Oncology<br><br>Billing and Coding: Biomarkers for Oncology<br><br>Loss-of-Heterozygosity Based Topographic Genotyping with PathfinderTG®<br><br>Billing and Coding: Loss-of-Heterozygosity Based Topographic Genotyping with Pathfinder TG®   | <a href="#">L35396</a><br><br><a href="#">A52986</a><br><br><a href="#">L34864</a><br><br><a href="#">A56897</a> | JH, JL - Novitas Solutions, Inc.        | AR, CO, DE, LA, MD, MS, NJ, NM, OK, PA, TX, D.C. |
| LCD<br><br>LCA | MoIDX: Molecular Testing for Detection of Upper Gastrointestinal Metaplasia, Dysplasia, and Neoplasia<br><br>Response to Comments: MoIDX: Molecular Testing for Detection of Upper Gastrointestinal Metaplasia, Dysplasia, and Neoplasia  | <a href="#">L39256</a><br><br><a href="#">A59343</a>   | JJ, JM - Palmetto GBA                   | AL, GA, NC, SC, TN, VA, WV                       |

|     |   |                        |  |                 |
|-----|---|------------------------|--|-----------------|
|     | MolDX: Prognostic and Predictive Molecular Classifiers for Bladder Cancer | <a href="#">L38576</a> |  |                 |
| LCD | Molecular Pathology Procedures  | <a href="#">L34519</a> | JN - First Coast Service Options, Inc. | FL, PR, U.S. VI |

## Description

Multianalyte assays with algorithmic analyses (MAAAs) are laboratory measurements that use a mathematic formula to analyze multiple markers that may be associated with a particular disease state and are designed to evaluate disease activity or an individual’s risk for disease. The laboratory performs an algorithmic analysis using the results of the assays and sometimes other individual information, such as gender and age and converts the information into a numeric score, which is conveyed on a laboratory report. Generally, MAAAs are exclusive (and/or proprietary) to a single laboratory which owns the algorithm. MAAA testing is used to aid in the diagnosis and evaluation of many malignancies including, but may not be limited to:

- **Adrenal Cortical Carcinoma (ACC)**
  - **ACC Adrenal Mass Panel** utilizes a 24-hour urine specimen, a biochemical assay of 25 steroid markers and clinical parameters (age at diagnosis, gender, mode of discovery and hormonal status along with tumor diameter and an unenhanced CT density measurement of the tumor) to report a clinical risk score for the probability of a malignant ACC or other malignancy (eg, sarcoma, lymphoma) as well as the probability of a benign mass (eg, adenoma, myelolipoma, cyst).
- **Bladder Cancer**
  - **Oncuria Detect, Oncuria Monitor and Oncuria Predict** are multiplex assays that analyze 10 protein biomarkers (A1AT, ANG, APOE, CA9, IL8, MMP9, MMP10, PAI1, SDC1 and VEGFA) in urine for different indications as described below:
    - **Oncuria Detect** is purported to detect urothelial cancer in an individual presenting with hematuria.
    - **Oncuria Monitor** is indicated for monitoring an individual diagnosed with nonmuscle-invasive or muscle-invasive bladder cancer to supposedly determine risk of recurrence.
    - **Oncuria Predict** is proposed to predict if an individual with intermediate- to high-risk urothelial cancer will respond to bacillus Calmette-Guerin (BCG) therapy.
- **Breast Cancer**

- **DCISionRT** uses breast tissue from a biopsy or surgery to estimate the risk of recurrence of ductal carcinoma in situ (DCIS) or invasive carcinoma in an individual with DCIS as well as the benefit of adjuvant radiation therapy. The test analyzes individual tumor biology along with other clinical factor algorithms to identify a personalized recurrence risk score of low or elevated.
- **PreciseDx Breast Biopsy Test** provides algorithmic analysis of digitized whole slide imaging of histologic and immunohistochemical features to determine the risk of recurrence for an individual diagnosed with breast cancer.
- **PreciseDx Breast Cancer Test** uses an algorithm of 12 histologic and immunohistochemical features, AI analysis software and hematoxylin and eosin (H&E) digital images to provide a recurrence score for breast cancer.
- **Colorectal Cancer**
  - **Immunoscore** is a test that uses image analysis with AI assessment of four histologic and immunohistochemical features (CD3 and CD8 within tumor-stroma border and tumor core), tissue, reported as immune response and recurrence-risk score to purportedly predict the risk of relapse in an individual with localized colon cancer to assist with treatment (eg, chemotherapy).
- **Esophageal Cancer and Barrett's Esophagus**
  - **Envisage** and **Esopredict** are tests that analyze P16, RUNX3, HPP1 and FBN1 methylation to purportedly determine the risk of progression to high-grade dysplasia or esophageal cancer in an individual diagnosed with precancerous Barrett's esophagus.
  - **EsoGuard** is a biomarker-based, non-endoscopic method for detecting Barrett's esophagus using methylated DNA retrieved via a swallowed balloon-based, esophageal sampling device. This test uses next-generation sequencing (NGS) of bisulfate converted DNA to detect the presence of Vimentin (mVIM) and CyclinA1 (mCCNA1) methylation signatures at 31 sites within those genes, to purportedly identify individuals with Barrett's esophagus.
  - **Esophageal String Test** is designed to allow frequent, quantitative monitoring of an individual with eosinophilic esophagitis. A capsule containing a yard-long string is swallowed after one end of the string is taped to the individual's cheek. The string passes through the gastrointestinal tract (stretching through the esophagus, stomach and the upper region of the small intestine) and becomes coated with digestive secretions. It is then removed and analyzed for eosinophil-derived protein biomarkers that may indicate inflammation (eg, active eosinophilic esophagitis).
  - **TissueCypher Barrett's Esophagus Assay** analyzes multiple protein-based biomarkers and tissue structure information along with whole slide digital imaging technology to identify if an individual with Barrett's esophagus is at high risk for developing of esophageal cancer within 5 years of undergoing endoscopy.
- **Liver Cancer**

- **HeproDx-TM** for hepatocellular carcinoma (HCC) incorporates levels of 161 genes, fresh hepatocellular carcinoma tumor tissue,  $\alpha$ -fetoprotein (AFP) level and an algorithm to purportedly report a risk classifier related to HCC recurrence and metastasis.
  
- **Lung Cancer**
  - **CyPath Lung** is a noninvasive test for the early detection of lung cancer. The test evaluates sputum using flow cytometry and machine learning when an individual has a suspicious finding on computed tomography (CT).
  
  - **Nodify Lung** testing consists of two blood-based proteomic tests (Nodify CDT and Nodify XL2) to purportedly aid in determining the risk of malignancy of a lung nodule.
    - **Nodify CDT test** is intended to detect early-stage lung cancer in an individual who is at moderate to high risk. The test measures the presence of 7 autoantibodies (CAGE, GBU4-5, HuD, MAGE A4, NY-ESO-1, p53 and SOX-2) that are asserted to be involved in early stages of lung cancer development. Results are to be used in conjunction with other clinical data to determine the appropriate diagnostic follow up.
  
    - **Nodify XL2** has been suggested to identify benign versus malignant pulmonary nodules using a mass spectrometric analysis of 2 proteins (galectin-3-binding protein [LGALS3BP] and scavenger receptor cysteine-rich type 1 protein M130) and 5 clinical risk factors (age, smoking status, nodule diameter, nodule-spiculation status and nodule location) utilizing plasma and an algorithm reported as a categorical probability of malignancy.
  
  - **REVEAL Lung Nodule Characterization** is an algorithm-based measurement of three clinical factors and three blood proteins associated with the presence of lung cancer to purportedly aid the evaluation of indeterminate pulmonary nodules (4mm – 30mm) in current smokers 25 years of age and older. The results, combined with other clinical risk factors may aid in the decision to perform a biopsy or consider routine monitoring. It is not intended as a screening or stand-alone diagnostic assay.
  
  - **VeriStrat** is a serum based mass spectrometric, eight proteins, including amyloid A, signature proteomic test. It is intended to aid in evaluating prognosis and predicting response to systemic or targeted therapies in an individual with advanced NSCLC.
  
- **Melanoma**
  - **DAWN IO Melanoma** is a quantitative mass spectrometry test that uses artificial intelligence (AI) to analyze glycopeptides to purportedly determine benefit from immunotherapy for the treatment of melanoma.
  
- **Neuroendocrine Tumors**

- **NETest** is a multianalyte algorithm, polymerase chain reaction (PCR)-based gene blood test that measures 51 neuroendocrine tumor specific gene transcripts in combination with molecular biomarkers which purportedly allows monitoring of neuroendocrine tumor gene activity levels.
- **Oral Cancer**
  - **SaliMark OSCC – Oral Cancer Salivary Diagnostic Test** is a molecular DNA biomarker test performed on saliva when suspicious lesions are observed to purportedly aid in the early detection of oral squamous cell carcinoma.
- **Ovarian Cancer**
  - **OvaSuite** is a collection of blood tests (Ova1 Plus [Ova1 and Overa] and OvaWatch) proposed to assess risk of ovarian cancer in an individual diagnosed with an adnexal mass. Proprietary algorithms are applied, along with an individual's features as well as the levels of certain biomarkers. These biomarkers include apolipoprotein A1 (Apo A-1), beta-2 microglobulin (B2M), CA-125, follicle stimulating hormone (FSH), human epididymis protein (HE4), prealbumin and transferrin (TRF). Each test has a specific indication:
    - **Ova1 Plus is comprised of Ova1 and Overa.** Ova1, an FDA-approved test, is performed for an individual with adnexal mass when surgery has been scheduled. If an individual has an intermediate risk result, Overa is automatically reflexed (performed in succession of original test).
    - **OvaWatch** is indicated for an individual diagnosed with adnexal mass when the initial clinical assessment is classified as benign or indeterminate.
  - **Risk of Ovarian Malignancy Algorithm (ROMA)** is an FDA-approved blood test that measures HE4 and CA-125 to evaluate an individual with an adnexal mass to purportedly determine the likelihood of ovarian cancer.
- **Pancreatic Cancer**
  - **IMMray PanCan-d** measures 9 serum biomarkers (C5, C4, cystatin C, factor B, osteoprotegerin, gelsolin, IGFBP3, CA125 and multiplex electrochemiluminescent immunoassay (ECLIA) for CA19-9) combined with an algorithm to purportedly detect pancreatic ductal adenocarcinoma with a result of high-risk signature present, negative high-risk signature or borderline.
  - **PancraGEN (formerly PathFinderTG)** is a topographic genotyping test that purportedly assesses the risk of malignancy in an individual with a pancreatic cyst.
- **Solid Organ Tumors**
  - **LC-MS/MS Targeted Proteomic Assay** is a liquid chromatography (LC) mass spectrometric analysis of 30 protein targets that uses formalin-fixed, paraffin-embedded (FFPE) tissue of solid organ tumors. The results are intended to be used as a prognostic and predictive algorithm reported as likely,

unlikely or uncertain benefit for treatment of 39 chemotherapy and targeted therapeutic oncology agents.

**In vitro chemoresistance and chemosensitivity assays** are laboratory tests that compare a variety of chemotherapeutic agents performed on a tumor sample to allegedly determine which drugs may effectively or ineffectively inhibit tumor growth. While both are similar, they each offer different results. Chemoresistance assays supposedly determine which drugs are ineffective and chemosensitivity assays purportedly provide results for those that are effective. Laboratories often use different methodologies and processes (eg, staining techniques, tumor cloning or motility contrast tomography) to measure sensitivity and resistance. **ChemoFx** is an example of this type of testing.

### Coverage Determination

*iCare follows the CMS requirements that only allows coverage and payment for services that are reasonable and necessary for the diagnosis and treatment of illness or injury or to improve the functioning of a malformed body member except as specifically allowed by Medicare.*

*Genetic tests must demonstrate clinical utility, analytical and clinical validity and fulfill the CMS “reasonable and necessary” criteria. Analytic validity (test accurately identifies the gene variant), clinical validity (test identifies or predicts the clinically defined disorder) and clinical utility (test measurably improves clinical outcomes) of the genetic test is supported by generally accepted standards that are based on credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community, specialty society recommendations, and views of physicians practicing in relevant clinical areas. The test must be ordered by a physician who is treating the beneficiary and the results will be used in the management of a beneficiary’s specific medical problem.*

*For jurisdictions with no Medicare guidance for a particular test, iCare will utilize the [MolDX program](#) and Technical Assessments for molecular assays as the standard to evaluate clinical utility, analytical and clinical validity in conjunction with adhering to Medicare’s reasonable and necessary requirement.*

*In interpreting or supplementing the criteria above and in order to determine medical necessity consistently, iCare may consider the following criteria:*

#### **General Criteria for MAAAs for Cancer Indications**

Apply General Criteria for MAAAs for Cancer Indications when test specific criteria are not available on this medical coverage policy.

**MAAAs for cancer** will be considered medically reasonable and necessary when the following requirements are met:

- Analytic validity, clinical validity and clinical utility of the genetic test is supported by the [MolDX program](#); **AND**
- Individual to be tested is within the population and has the indication for which the test was developed; **AND**



- Results of testing must directly impact treatment or management of the Medicare beneficiary

### **Criteria for Specific Tests**

#### **Lung Cancer**

**Veristrat** (81538) will be considered medically reasonable and necessary for an individual diagnosed with non-small cell lung cancer (NSCLC) when the following requirements are met:<sup>24</sup>

- *EGFR* mutation testing is either wild-type (normal/negative); **OR**
- Individual cannot be tested (eg, unavailable tissue)

#### **Ovarian Cancer**

**OVA1 proteomic assay** (81503) or **Risk of Ovarian Malignancy Algorithm (ROMA)** (81500) will be considered medically reasonable and necessary when the following requirements are met:<sup>24</sup>

- At least 18 years of age; **AND**
- Presence of an ovarian adnexal mass for which surgery is planned; **AND**
- Has not yet been referred to an oncologist

#### **Pancreatic Cancer**

**PancraGEN (formerly PathFinder TG)** (84999, 81599) will be considered medically reasonable and necessary when the following requirements are met:<sup>16,25</sup>

- There remains uncertainty after an extensive medical evaluation that the pancreatic cyst might have cancer or be at risk of developing into cancer; **AND**
- A decision regarding treatment (eg, surgery) has not already been made and this test is needed to decide if more aggressive treatment than what is being currently considered is necessary; **AND**
- Previous first-line diagnostic studies are suspicious for cancer (malignancy), but more information is needed to form a plan of care. Examples of these types of diagnostic studies include a tumor marker of the pancreatic cyst fluid (eg, carcinoembryonic antigen [CEA]) that is greater than or equal to 200 ng/mL, examination of cells (cyst cytopathology) that are suspicious for cancer or concerning x-ray (radiographic) findings; **AND**
- Testing of the cyst does not show cancer and the cyst meets American Gastroenterological Association (AGA) Guidelines on the *Diagnosis and Management of Asymptomatic Neoplastic Pancreatic Cysts* that classify it as most likely benign

#### **Upper Gastrointestinal Metaplasia, Dysplasia and Neoplasia**

MAAAs for upper gastrointestinal metaplasia, dysplasia and neoplasia will be considered medically reasonable and necessary when the following requirements are met:

- Individual to be tested is being actively managed for chronic gastroesophageal reflux disease (GERD) and/or nondysplastic Barrett’s esophagus;<sup>26,27,28,29,30</sup> **AND**
- The presence of at least three of the following additional risk factors for Barrett’s esophagus:<sup>1,26,27,28,29,30</sup>
  - Male
  - 50 years of age or older
  - White race
  - Tobacco smoking
  - Obesity
  - Family history of Barrett’s esophagus or esophageal adenocarcinoma in a [first-degree relative](#); **AND**
- Has not been previously diagnosed with dysplasia or esophageal carcinoma;<sup>26,27,28,29,30</sup> **AND**
- Is tested no more than once every 3 years;<sup>18,19,20,21,22,26,27,28,29,30</sup> **AND**
- Test identifies an individual with dysplastic disease that may benefit from endoscopic treatment or surveillance or for an individual with nondysplastic disease who may benefit from surveillance;<sup>18,19,20,21,22</sup> **AND**
- Test results will be used to determine treatment or management of the beneficiary;<sup>26,27,28,29,30</sup> **AND**
- Individual is within the population for which the test was developed and validated;<sup>26,27,28,29,30</sup> **AND**
- Analytic validity, clinical validity and clinical utility of the test is supported by the [MolDX program](#)<sup>26,27,28,29,30</sup>

*The use of the criteria in this Medicare Advantage Medical Coverage Policy provides clinical benefits highly likely to outweigh any clinical harms. Services that do not meet the criteria above are not medically necessary and thus do not provide a clinical benefit. Medically unnecessary services carry risks of adverse outcomes and may interfere with the pursuit of other treatments which have demonstrated efficacy.*

## Coverage Limitations

[US Government Publishing Office. Electronic code of federal regulations: part 411 – 42 CFR § 411.15 - Particular services excluded from coverage](#)

The following tests may not be considered a benefit (statutory exclusion):<sup>78</sup>

- Tests considered screening in the absence of clinical signs and symptoms of disease that are not specifically identified by the law; **OR**

- Tests that confirm a diagnosis or known information; **OR**
- Tests to determine risk for developing a disease or condition; **OR**
- Tests performed to measure the quality of a process; **OR**
- Tests without diagnosis specific indications; **OR**
- Tests identified as investigational by available literature and/or the literature supplied by the developer and are not a part of a clinical trial

These treatments and services fall within the Medicare program's statutory exclusion that prohibits payment for items and services that have not been demonstrated to be reasonable and necessary for the diagnosis and treatment of illness or injury (§1862(a)(1) of the Act). Other services/items fall within the Medicare program's statutory exclusion at 1862(a)(12), which prohibits payment.

The following items will not be considered medically reasonable and necessary:

- Genetic tests that have not demonstrated clinical utility, analytical and clinical validity via the [MoIDX Program](#)
- ChemoFx assay, tumor drug response testing (81535 and 81536)<sup>17</sup>
- DCISionRT (0295U)
- Neuroendocrine tumors/neoplasms biomarker tests (eg, NETest [0007M])<sup>23</sup>

A review of the current medical literature shows that the evidence is insufficient to determine that these services are standard medical treatments. There remains an absence of randomized, blinded clinical studies examining benefit and long-term clinical outcomes establishing the value of these services in clinical management.

### **Summary of Evidence**

#### ***DCISionRT***

Insufficient evidence exists to make a conclusive decision regarding DCISionRT due to a lack of comprehensive studies. A meta-analysis of three retrospective studies (n=1485) focusing on the test revealed that a majority of individuals with high-risk test scores benefited from radiation therapy in preventing ipsilateral invasive breast cancer over a 10-year period. The risk of invasive cancer ranged from 3.1% to 9.0% in high-risk individuals who received radiation therapy in addition to surgery compared to 12.4% to 21.0% in those who had surgery alone. In contrast, radiation did not show a significant reduction

in invasive cancer among individuals with low-risk test scores. In this group, the risk of invasive cancer ranged from 3.0% to 6.5% with radiation and 5.0% to 7.7% without it.<sup>52,72</sup>

**Coding Information**

Any codes listed on this policy are for informational purposes only. Do not rely on the accuracy and inclusion of specific codes. Inclusion of a code does not guarantee coverage and/or reimbursement for a service or procedure.

| CPT® Code(s) | Description   | Comments |
|--------------|---|----------|
| 81479        | Unlisted molecular pathology procedure  |          |
| 81500        | Oncology (ovarian), biochemical assays of two proteins (CA-125 and HE4), utilizing serum, with menopausal status, algorithm reported as a risk score  |          |
| 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  |          |
| 81535        | Oncology (gynecologic), live tumor cell culture and chemotherapeutic response by DAPI stain and morphology, predictive algorithm reported as a drug response score; first single drug or drug combination   |          |
| 81536        | Oncology (gynecologic), live tumor cell culture and chemotherapeutic response by DAPI stain and morphology, predictive algorithm reported as a drug response score; each additional single drug or drug combination (List separately in addition to code for primary procedure) |          |
| 81538        | Oncology (lung), mass spectrometric 8-protein signature, including amyloid A, utilizing serum, prognostic and predictive algorithm reported as good versus poor overall survival  |          |
| 81599        | Unlisted multianalyte assay with algorithmic analysis   |          |
| 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  |          |
| 0006M        | Oncology (hepatic), mRNA expression levels of 161 genes, utilizing fresh hepatocellular carcinoma tumor tissue, with alpha-fetoprotein level, algorithm reported as a risk classifier   |          |
| 0007M        | Oncology (gastrointestinal neuroendocrine tumors), real-time PCR expression analysis of 51 genes, utilizing whole peripheral blood, algorithm reported as a nomogram of tumor disease index   |          |

|       |  |  |
|-------|--|--|
| 0015M | Adrenal cortical tumor, biochemical assay of 25 steroid markers, utilizing 24-hour urine specimen and clinical parameters, prognostic algorithm reported as a clinical risk and integrated clinical steroid risk for adrenal cortical carcinoma, adenoma, or other adrenal malignancy  |  |
| 0080U | Oncology (lung), mass spectrometric analysis of galectin-3-binding protein and scavenger receptor cysteine-rich type 1 protein M130, with five clinical risk factors (age, smoking status, nodule diameter, nodule-spiculation status and nodule location), utilizing plasma, algorithm reported as a categorical probability of malignancy                                |  |
| 0092U | Oncology (lung), three protein biomarkers, immunoassay using magnetic nanosensor technology, plasma, algorithm reported as risk score for likelihood of malignancy   |  |
| 0095U | Inflammation (eosinophilic esophagitis), ELISA analysis of eotaxin-3 (CCL26 [C-C motif chemokine ligand 26]) and major basic protein (PRG2 [proteoglycan 2, pro eosinophil major basic protein]), specimen obtained by swallowed nylon string, algorithm reported as predictive probability index for active eosinophilic esophagitis                                      |  |
| 0108U | Gastroenterology (Barrett's esophagus), whole slide-digital imaging, including morphometric analysis, computer-assisted quantitative immunolabeling of 9 protein biomarkers (p16, AMACR, p53, CD68, COX-2, CD45RO, HIF1a, HER-2, K20) and morphology, formalin-fixed paraffin-embedded tissue, algorithm reported as risk of progression to high-grade dysplasia or cancer |  |
| 0114U | Gastroenterology (Barrett's esophagus), VIM and CCNA1 methylation analysis, esophageal cells, algorithm reported as likelihood for Barrett's esophagus   |  |
| 0174U | Oncology (solid tumor), mass spectrometric 30 protein targets, formalin-fixed paraffin-embedded tissue, prognostic and predictive algorithm reported as likely, unlikely, or uncertain benefit of 39 chemotherapy and targeted therapeutic oncology agents   |  |
| 0261U | Oncology (colorectal cancer), image analysis with artificial intelligence assessment of 4 histologic and immunohistochemical features (CD3 and CD8 within tumor-stroma border and tumor core), tissue, reported as immune response and recurrence-risk score   |  |

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|       |   |  |
|-------|---|--|
| 0288U | Oncology (lung), mRNA, quantitative PCR analysis of 11 genes (BAG1, BRCA1, CDC6, CDK2AP1, ERBB3, FUT3, IL11, LCK, RND3, SH3BGR, WNT3A) and 3 reference genes (ESD, TBP, YAP1), formalin-fixed paraffin-embedded (FFPE) tumor tissue, algorithmic interpretation reported as a recurrence risk score |  |
| 0342U | Oncology (pancreatic cancer), multiplex immunoassay of C5, C4, cystatin C, factor B, osteoprotegerin (OPG), gelsolin, IGFBP3, CA125 and multiplex electrochemiluminescent immunoassay (ECLIA) for CA19-9, serum, diagnostic algorithm reported qualitatively as positive, negative, or borderline   |  |
| 0356U | Oncology (oropharyngeal), evaluation of 17 DNA biomarkers using droplet digital PCR (ddPCR), cell-free DNA, algorithm reported as a prognostic risk score for cancer recurrence   |  |
| 0360U | Oncology (lung), enzyme-linked immunosorbent assay (ELISA) of 7 autoantibodies (p53, NY-ESO-1, CAGE, GBU4-5, SOX2, MAGE A4, and HuD), plasma, algorithm reported as a categorical result for risk of malignancy   |  |
| 0366U | Oncology (bladder), analysis of 10 protein biomarkers (A1AT, ANG, APOE, CA9, IL8, MMP9, MMP10, PAI1, SDC1 and VEGFA) by immunoassays, urine, algorithm reported as a probability of recurrent bladder cancer  |  |
| 0367U | Oncology (bladder), analysis of 10 protein biomarkers (A1AT, ANG, APOE, CA9, IL8, MMP9, MMP10, PAI1, SDC1 and VEGFA) by immunoassays, urine, diagnostic algorithm reported as a risk score for probability of rapid recurrence of recurrent or persistent cancer following transurethral resection  |  |
| 0387U | Oncology (melanoma), autophagy and beclin 1 regulator 1 (AMBRA1) and loricrin (AMLo) by immunohistochemistry, formalin-fixed paraffin-embedded (FFPE) tissue, report for risk of progression  |  |
| 0398U | Gastroenterology (Barrett esophagus), P16, RUNX3, HPP1, and FBN1 DNA methylation analysis using PCR, formalin-fixed paraffin-embedded (FFPE) tissue, algorithm reported as risk score for progression to high-grade dysplasia or cancer   |  |
| 0406U | Oncology (lung), flow cytometry, sputum, 5 markers (meso-tetra [4-carboxyphenyl] porphyrin [TCPP], CD206, CD66b, CD3, CD19), algorithm reported as likelihood of lung cancer  |  |
| 0414U | Oncology (lung), augmentative algorithmic analysis of digitized whole slide imaging for 8 genes (ALK, BRAF, EGFR, ERBB2, MET, NTRK1-3, RET, ROS1), and KRAS G12C and PD-L1, if performed, formalin-fixed paraffin-embedded (FFPE) tissue, reported as positive or negative for each biomarker       |  |

| 0418U                              | Oncology (breast), augmentative algorithmic analysis of digitized whole slide imaging of 8 histologic and immunohistochemical features, reported as a recurrence score |          |
|------------------------------------|--|----------|
| CPT®<br>Category<br>III<br>Code(s) | Description  | Comments |
| No code(s) identified              |  |          |
| HCPCS<br>Code(s)                   | Description  | Comments |
| No code(s) identified              |  |          |

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## Appendix

### Appendix A Family Relationships

| Degree of Relationship | Relative of the Individual to be Tested   |
|------------------------|---|
| First-degree           | Child, full-sibling, parent   |
| Second-degree          | Aunt, uncle, grandchild, grandparent, nephew, niece, half-sibling                                 |
| Third-degree           | First cousin, great aunt, great-uncle, great-grandchild, great-grandparent, half-aunt, half-uncle |

## Change Summary

- 01/01/2024 New Policy.