Gene Expression Profiling for Cancer Indications

INDEPENDENT CARE HEALTH PLAN

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Medicare Advantage Medical Coverage Policy

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Description

Gene expression profiling (GEP) is a laboratory test that measures the activity, or expression, of ribonucleic acid (RNA) of hundreds to thousands of genes at one time to give an overall picture of gene activity. GEP tests are typically performed on tumor tissue but may also be performed on other specimens such as blood. These tests often use microarray technology though other methodologies, such as next generation sequencing (NGS), whole transcriptome sequencing and reverse transcription polymerase chain reaction (RT-PCR), are also used.

GEP tests are currently offered primarily for the management of cancer, most notably breast. Other cancer indications include bladder, colon, cancer of unknown primary (CUP), cutaneous (skin) melanoma,

cutaneous squamous cell cancer (SCC), hematologic malignancies, lung cancer, oral cancer, pancreatic cancer, prostate cancer and uveal melanoma.

Breast cancer – Indicated to estimate risk of distant recurrence (metastasis) and predict likelihood of benefit from chemotherapy or extended use of endocrine (hormone) therapy for an individual diagnosed with early-stage invasive node negative (no cancer cells detected in lymph glands) or node positive (cancer cells detected in lymph glands) breast cancer. Several tests are commercially available, each analyzing the expression of different numbers of genes and are typically combined with a proprietary algorithm to produce test scores. A low-risk test result may indicate that an individual can safely forgo chemotherapy while a high-risk test score suggests that chemotherapy in addition to endocrine therapy may be necessary. Examples include, but may not be limited to:

- **Breast Cancer Index (BCI)**
- **EndoPredict Prognosis Breast Cancer**
- **MammaPrint**
- **Oncotype DX Breast Recurrence Score**
- **Prosigna Breast Cancer Prognostic Gene Signature Assay (PAM50)**

Molecular subtyping has been developed to predict response to chemotherapy as well as risk of distant recurrence. Tumors are grouped into distinct categories based on the gene expression pattern of the tumor. Subtypes appear to be associated with different prognoses and responses to treatment options. Examples include, but may not be limited to, **BluePrint** (offered in conjunction with MammaPrint) and **Insight TNBCtype**.

GEP has also been established to predict likelihood of breast cancer for an individual diagnosed with precancerous lesions such as ductal hyperplasia (ADH), atypical lobular hyperplasia (ALH), usual ductal hyperplasia (UDH), papilloma and sclerosing adenosis. **BBDRisk Dx** is an example of this type of test.

Ductal in situ carcinoma (DCIS) of the breast - To estimate risk of local recurrence and predict likelihood of benefit from radiation therapy. An example is **Oncotype DX Breast DCIS Score**.

Bladder cancer – Used for the diagnosis, monitoring and molecular subtyping for urothelial cancer. Examples include, but may not be limited to, **Bladder EpiCheck, Cxbladder Detect, Cxbladder Monitor, Cxbladder Triage, Decipher Bladder Genomic Classifier, Decipher Bladder TURBT, Xpert Bladder Cancer Detection and Xpert Bladder Cancer Monitor**.

Colon cancer – A method to determine risk of relapse for node positive or node negative stage II colon cancer and for metastatic colon cancer to assist in treatment decisions. **Oncotype DX Colon Cancer Recurrence Score Test** is an example of this type of test.

CUP (also referred to tumor of unknown origin or tissue of origin [TOO])- For the identification of the site of origin for an uncertain cancer diagnosis. **CancerTYPE ID** is an example of this type of test. NeoTYPE Cancer Profile, a molecular profiling test for cancer, is available for use in conjunction with CancerTYPE ID.

Cutaneous melanoma – Several tests are offered for the management of melanoma including, but may not be limited to:

- **DecisionDx-Melanoma** – To aid in determining risk of recurrence or metastasis and likelihood of sentinel lymph node (SLN) positivity in an individual diagnosed with melanoma.
- **DecisionDx DiffDx-Melanoma and myPath Melanoma** – To differentiate benign nevi (a birthmark or mole) from malignant melanoma in an individual with melanocytic lesions.
- **Merlin Test** – To predict risk of metastasis in an individual with diagnosed with melanoma.
- **Pigmented Lesion Assay** – To assist in ruling out melanoma and need for a surgical biopsy for an individual with atypical pigmented lesions.

Cutaneous SCC – Developed for squamous cell cancer, a type of skin cancer, to identify metastatic risk and assist in treatment decisions. **DecisionDx-SCC** is an example of this type of testing.

Hematologic malignancies – Used for the classification of hematologic cancers to assist in treatment decisions for leukemia, lymphoma, multiple myeloma, myelodysplastic syndromes (MDS) and myeloproliferative neoplasms (MPNs). **Lymph2Cx** (also referred to as Lymphoma Subtyping Test) and **Lymph3Cx** are examples of assays proposed to subclassify lymphoma.

Lung cancer – For use in an individual diagnosed or at risk for lung cancer. Examples include, but may not be limited to:

- **DetermaRx** has been proposed to determine risk of recurrence and chemotherapy treatment decisions in an individual diagnosed with stage I or stage IIA nonsquamous non-small cell lung cancer (NSCLC).
- **Percepta Bronchial Genomic Sequencing Classifier** to purportedly assess risk and stratify an individual who is a current or former smoker when results of bronchoscopy are indeterminate.

Oropharyngeal/oral cancer – For the diagnosis of oral and/or oropharyngeal cancer. **CancerDetect** is an example of this type of testing.

Pancreatic cancer – A method to evaluate pancreatic cyst fluid for the early detection of pancreatic cancer. An example is **PancreaSeq Genomic Classifier**.

Prostate cancer - While prostate-specific antigen (PSA) testing is considered the gold standard for prostate cancer screening and management, only biopsy of the prostate gland can establish a prostate cancer diagnosis. However, studies indicate that biopsies fail to identify prostate cancer in some individuals and in certain circumstances, biopsy may be avoidable. To assist with clinical decision making regarding initial or repeat prostate biopsies, laboratory tests such as GEP have been suggested for cancer management. Examples of GEP assays for prostate cancer include, but may not be limited to, **ConfirmMDx for Prostate Cancer, Decipher Prostate Biopsy Genomic Classifier, Decipher Prostate RP Genomic Classifier, ExoDx**

Prostate Test, Oncotype DX Genomic Prostate Score (GPS), Prolaris Biopsy Test and Prolaris Post-Prostatecomy Test.

Uveal melanoma – Utilized to predict risk of metastasis for uveal melanoma. Examples include, but may not be limited to, **DecisionDx-PRAME, DecisionDx-UM, DecisionDx-UMSeq**.

GEP tests differ from germline genetic tests. GEP tests analyze RNA which is dynamic, responds to cellular environmental signals, are not usually representative of an individual's germline DNA and are not inheritable. Germline genetic testing analyzes an individual's deoxyribonucleic acid (DNA) to detect genetic variants (mutations). Germline mutations are inherited, are constant throughout an individual's lifetime and are identical in every cell of the body.

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 GENE EXPRESSION PROFILING FOR CANCER INDICATIONS

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

Gene expression profiling for cancer will be considered medically reasonable and necessary when the following requirements are met:

- Individual to be tested is under active management or being evaluated for cancer; **AND**

- Individual is within the population and has the indication for the test's intended use; **AND**
- Results of testing must directly impact treatment or management of the Medicare beneficiary; **AND**

- Analytic validity, clinical validity and clinical utility of the genetic test is supported by the MolDX program; **AND**

- Test is ordered by a physician who is treating the individual

CRITERIA FOR SPECIFIC TESTS

Breast Cancer

Breast Cancer Index (BCI) (81518) will be considered medically reasonable and necessary when the following requirements are met:[50,51,52,53,54]

- Individual is a postmenopausal female diagnosed with early-stage invasive disease (tumor, node, metastasis [TNM] stage T1-3, pN0-N1, M0) that is estrogen receptor (ER) positive and/or progesterone receptor (PR) positive and human epidermal growth factor receptor (HER2) negative; **AND**

- Individual has no evidence of distant breast cancer metastasis (nonrelapsed); **AND**

- Test results will be used to determine treatment with chemotherapy and/or endocrine therapy

NOTE: BCI is tested once per patient lifetime on formalin-fixed, paraffin-embedded (FFPE) tissue from the primary tumor specimen obtained prior to adjuvant treatment.[49,50,51,52,53]

EndoPredict Prognosis Breast Cancer Test (81522) will be considered medically reasonable and necessary when the following requirements are met:[61,62,63,64,65]

- Individual is a postmenopausal female diagnosed with early-stage disease (TNM stage T103, N0-1) that is ER positive and HER2 negative; **AND**

- Lymph node negative or 1-3 positive nodes; **AND**

- No evidence of distant metastasis; **AND**

- Treatment with adjuvant endocrine therapy (eg, tamoxifen or aromatase inhibitors) is under consideration

MammaPrint (81521, 81523) will be considered medically reasonable and necessary when the following requirements are met:[25,26,27,28,29]

- Individual diagnosed with early stage (I or II) breast cancer; **AND**
- Tumor size less than 5.0 cm; **AND**
- Lymph node negative or 1-3 positive lymph nodes

NOTE: MammaPrint may be performed one time on a given date of service for a given individual. This test may be performed upon occasion twice per individual lifetime for bilateral disease.[25,26,27,28,29]

Oncotype DX Breast Recurrence Score (81519) will be considered medically reasonable and necessary when the following indications:[30,31,32,33,34,111]

- ER positive, lymph node-negative carcinoma of the breast; **OR**
- ER positive micrometastases of carcinoma of the breast; **OR**
- ER positive, lymph node-positive (1-3 nodes)

Prosigna Breast Cancer Prognostic Gene Signature Assay (81520) will be considered medically reasonable and necessary for a postmenopausal female for the following indications:[45,46,47,48,49,111]

- ER positive, lymph node-negative, stage I or II breast cancer; **OR**
- ER positive, lymph node-positive (1-3), stage II breast cancer

Oncotype DX DCIS Breast Cancer Test (0045U) will be considered medically reasonable and necessary when the following requirements are met:[82,83,84,85]

- Individual diagnosed with ductal carcinoma in situ (DCIS) of the breast; **AND**
- Tissue specimen is at least 0.5 mm in length; **AND**
- Individual is a candidate for breast conserving surgery and is considering the addition of radiation therapy and testing will help inform the choice between surgery alone versus surgery with radiation therapy; **AND**
- Has not undergone or is not planning a mastectomy

Cancer of Unknown Primary

CancerTYPE ID (81540) will be considered medically reasonable and necessary in the pathologic diagnosis of cancer of unknown primary (CUP) when a conventional surgical pathology/imaging work-up has not identified a primary neoplastic site. Other applications of this technology are considered not medically reasonable and necessary. (CancerTYPE ID is covered once per lifetime).[43]

Colon Cancer

Oncotype DX Colon Recurrence Score Test (81525) will be considered medically reasonable and necessary for the management of stage II colon cancer.[35,36,37,38,41]

Cutaneous Melanoma

Melanoma risk stratification molecular testing (eg, DecisionDx-Melanoma [81529], DecisionDx DiffDx-Melanoma [0314U], Merlin Test, myPath Melanoma [0090U]) will be considered medically reasonable and necessary when the following requirements are met:[66,67,68,69,70]

- The individual to be tested has a personal history of melanoma; **AND**
    - Has stage T1b or above disease; **OR**
    - Has stage T1a disease with documented concern about adequacy of microstaging; **AND**
- Is undergoing workup or being evaluated for treatment; **AND**
- Does not have metastatic disease; **AND**
- Presumed risk of 5% or greater for a positive sentinel lymph node biopsy (SLNB) based on clinical, histological or other information; **AND**
- Has a disease stage, grade and Breslow thickness (or other qualifying conditions) within the intended use of the test; **AND**
- Analytic validity, clinical validity and clinical utility of the genetic test is supported by the MolDX program

Pigmented Lesion Assay (0089U) will be considered medically reasonable and necessary when the following requirements are met:[91,92,93,94,95]

- For the evaluation of pigmented skin lesions (suspicious areas of the skin) for which a diagnosis of melanoma (skin cancer) is being considered; **AND**
- Test ordered by clinicians who evaluate pigmented skin lesions and perform biopsies; **AND**
- The lesion must meet one or more ABCDE (asymmetry, border, color, diameter, evolving) criteria for skin cancer; **AND**
- Pigmented skin lesions between 5mm and 19mm in size; **AND**
- Lesions where the skin is intact (non-ulcerated, non-bleeding); **AND**

- Lesions that do not contain a scar or were previously biopsied; **AND**
- Lesions not located in areas of skin conditions (eg, eczema or psoriasis); **AND**
- Lesions not clinically diagnosed as melanoma or clinical suspicion is sufficiently high that the treating clinician believes melanoma is a more likely diagnosis than not; **AND**
- Lesions are not on the palms of the hands, soles of the feet, under the nails, in the mucous membranes (eg, inside of the mouth) or hair-covered areas that cannot be trimmed; **AND**
- For skin lesions already under consideration for biopsy; **AND**
- Only one test may be used per individual per clinical encounter. In the rare instance that a second test may be indicated for the same clinical encounter, submit an appeal with supporting documentation

Lung Cancer

DetermaRx (0288U) will be considered medically reasonable and necessary when the following requirements are met:[96,97,98,99,100]

- Individual to be tested diagnosed with non-squamous non-small cell lung cancer (NSCLC); **AND**
- Tumor size is less than 5cm; **AND**
- No positive lymph nodes (stages I and IIa); **AND**
- Individual is sufficiently healthy to tolerate chemotherapy; **AND**
- Adjuvant platinum-containing chemotherapy is being considered; **AND**
- Test will help inform the decision to pursue adjuvant chemotherapy

Percepta Genomic Sequencing Classifier will be considered medically reasonable and necessary for the evaluation of potentially cancerous lung nodules when the following requirements are met:[86,87,88,89,90]

- Individual to be tested is a current or former smoker; **AND**
- Physician-assessed low or intermediate pretest risk of malignancy based upon the following clinical characteristic stratification:
    - Low pretest risk of malignancy (lung nodules are smaller than 10 mm and individual has less than a 10 pack per year smoking history); **OR**
    - Intermediate pretest risk of malignancy (lung nodules measure between 10 and 30 mm and/or the individual has a 10 to 60 pack per year smoking history; **AND**

- Bronchoscopy is nondiagnostic; **AND**

- Test results will be utilized to determine whether computed tomography (CT) surveillance is appropriate in lieu of further invasive biopsies or surgical procedures; **AND**

- Ordering physician is certified in Percepta Certification and Training Registry (CTR); **AND**

- Individual monitored for malignancy (suggested monitoring includes serial CT scans at 3 to 6, 9 to 12 and 18 to 24 months, using thin sections and noncontrast, low-dose techniques)

Prostate Cancer

NOTE: For prostate cancer, only one molecular biomarker may be performed unless a second test, meeting criteria for a specific test, is medically reasonable and necessary as an adjunct to the first test.[72,73,74,75,76]

ConfirmMDx for Prostate Cancer (81551) will be considered medically reasonable and necessary for an individual without an established diagnosis of prostate cancer when the following requirements are met:[72,73,74,75,76]

- 75 years of age or younger with a prostate specific antigen (PSA) (or adjusted PSA for an individual receiving 5-alpha-reductase inhibitors) of greater than 3 but less than 10 ng/mL and/or digital rectal exam (DRE) findings are suspicious for cancer; **OR**

- Less than 75 years of age with a PSA (or adjusted PSA for an individual receiving 5-alpha-reductase inhibitors) of greater than or equal to 4 but less than 10 ng/mL and/or DRE findings are suspicious for cancer; **AND**

    - Is a candidate for an initial prostate biopsy; **OR**

    - Is a candidate for repeat prostate biopsy (following repeat PSA and/or DRE) and previous prostate biopsy was negative or benign but with abnormal histopathology (ie, atypical small acinar proliferation [ASAP] or high-grade prostatic intraepithelial neoplasia [HGPIN]); **OR**

    - Is a candidate for repeat biopsy (following repeat PSA and/or DRE) and PSA is greater than 10 ng/mL and multiparametric magnetic resonance imaging (mpMRI) is negative, if performed

Decipher Prostate Biopsy Genomic Classifier (81542) will be considered medically reasonable and necessary when the following requirements are met:[106,107,108,109,110]

- Diagnosed with localized prostate cancer or biochemically recurrent adenocarcinoma of the prostate; **AND**

- No clinical evidence of metastasis; **AND**
- Life expectancy of at least 10 years; **AND**
- Candidate for active surveillance based on National Comprehensive Cancer Network (NCCN) guidelines (category 1 or 2A recommendation); **AND**
- Assay is performed on formalin-fixed paraffin embedded (FFPE) prostate biopsy tissue with at least 0.5 mm of linear tumor diameter or FFPE tissue from a prostate resection specimen; **AND**
- Has not received pelvic radiation or androgen deprivation therapy (ADT) prior to the biopsy or prostate resection specimen; **AND**
- Is being monitored for disease progression; **AND**
- Is considering the following:
    - Conservative management and is eligible for definitive therapy such as radical prostatectomy (RP), radiation or brachytherapy; **OR**
    - Radiation therapy and is eligible for the addition of a brachytherapy boost; **OR**
    - Radiation therapy and is eligible for the addition of short-term ADT; **OR**
    - Radiation therapy with short-term ADT and is eligible for the use of long-term ADT; **OR**
    - Radiation with standard ADT and is eligible for systemic therapy intensification using next generation androgen signaling inhibitors or chemotherapy; **OR**
    - Observation post-prostatectomy and is eligible for the addition of postoperative adjuvant radiotherapy; **OR**
    - Salvage radiotherapy post-prostatectomy and is eligible for the addition of ADT

ExoDx Prostate Test (also known as ExoDx Prostate IntelliScore [EPI]) (0005U) will be considered medically reasonable and necessary when the following requirements are met:[42]

- Testing is performed prior to initial prostate biopsy and individual to be tested is at least 50 years of age with PSA***** greater than 4 ng/mL; **AND**
    - No other relative indication for prostate biopsy including any of the following:
        - DRE suspicious for cancer (eg, nodules, induration or asymmetry); **OR**

- Positive multiparametric MRI (Prostate Imaging Reporting and Data System [PI-RADS] greater than or equal to 3), if available; **OR**
- Positive prior biopsy (cancer Histologic Grade Group greater than or equal to 1, intraductal carcinoma [IDC], atypical intraductal proliferation [AIP]); **AND**

o No other relative contraindication for prostate biopsy including any of the following:

- Less than 10 year life expectancy or is otherwise not a candidate for prostate cancer treatment; **OR**
- Invasive treatment for benign prostatic disease or taking medications that influence serum PSA levels within 6 months; **OR**
- Active prostatitis on antibiotics; **OR**

- Testing is performed prior to repeat biopsy in an individual who is at higher risk despite a negative prior prostate biopsy and has a confirmed moderately elevated PSA* (greater than 3ng/mL and less than 10 ng/mL for an individual 75 years of age or younger or PSA greater than 4 ng/mL and less than 10 ng/mL for an individual greater than 75 years of age); **AND**

o No other relative indication for prostate biopsy including any of the following:

- DRE suspicious for cancer (eg, nodules, induration or asymmetry); **OR**
- Positive multiparametric MRI (Prostate Imaging Reporting and Data System [PI-RADS] greater than or equal to 3), if available; **OR**
- Positive prior biopsy (cancer Histologic Grade Group greater than or equal to 1, intraductal carcinoma [IDC], atypical intraductal proliferation [AIP]); **OR**
- Other major risk factor for prostate cancer including any of the following:
  - ❖ Ethnicity at higher risk for prostate cancer (eg, Ashkenazi Jewish ancestry); **OR**
  - ❖ First-degree relative with prostate cancer; **OR**
  - ❖ High-penetrance prostate cancer risk gene(s) (those most linked to prostate cancer such as *BRCA1, BRCA2, ATM, CHEK2* and *HOXB13*) per NCCN (category 1 or 2A recommendation), if known; **AND**

o No other relative contraindication for prostate biopsy including any of the following:

- Less than 10 year life expectancy or is otherwise not a candidate for prostate cancer treatment; **OR**

- Invasive treatment for benign prostatic disease or taking medications that influence serum PSA levels within 6 months; **OR**

- Active prostatitis on antibiotics

Oncotype DX Genomic Prostate Score (GPS) (0047U) will be considered medically reasonable and necessary for Prostate Cancer Risk Group very-low-risk, low-risk, and favorable-intermediate risk prostate cancer.[39]

Prolaris Biopsy Test (81541) will be considered medically reasonable and necessary for Prostate Cancer Risk Group low, favorable-intermediate, unfavorable-intermediate or high-risk prostate cancer with a life expectancy of at least 10 years.[206]

SelectMDx (0339U) will be considered medically reasonable and necessary when the following requirements are met:[42]

- Testing is performed prior to initial prostate biopsy and individual to be tested is at least 50 years of age with PSA***** greater than 4 ng/mL; **AND**

- No other relative indication for prostate biopsy including any of the following:

  - DRE suspicious for cancer (eg, nodules, induration or asymmetry)

  - Positive multiparametric MRI (Prostate Imaging Reporting and Data System [PI-RADS] greater than or equal to 3), if available

  - Positive prior biopsy (cancer Grade Group greater than or equal to 1, intraductal carcinoma [IDC], atypical intraductal proliferation [AIP]); **AND**

  - Other major risk factor for prostate cancer including any of the following:

    - Ethnicity at higher risk for prostate cancer (eg, Ashkenazi Jewish ancestry); **OR**

    - First-degree relative with prostate cancer; **OR**

    - High-penetrance prostate cancer risk gene(s) (those most linked to prostate cancer such as *BRCA1, BRCA2, ATM, CHEK2* and *HOXB13*) per NCCN (category 1 or 2A recommendation), if known

- No other relative contraindication for prostate biopsy including any of the following:

- Less than 10 year life expectancy or is otherwise not a candidate for prostate cancer treatment
- Invasive treatment for benign prostatic disease or taking medications that influence serum PSA levels within 6 months

- Active prostatitis on antibiotics

*****PSA elevation should be confirmed after a few weeks under standardized conditions (ie, no ejaculation, manipulations and urinary tract infections) in the same laboratory before considering a biopsy.[41]

Uveal Melanoma

DecisionDx-UM (81552) will be considered medically reasonable and necessary when the following requirements are met:[56,57,58,59,60]

- Individual to be tested is newly diagnosed with uveal melanoma; **AND**
- No evidence of metastatic disease

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):

- BluePrint Test;[24] **OR**

- Tests considered screening in the absence of clinical signs and symptoms of disease that are not specifically identified by the law;[218] **OR**

- Tests that confirm a diagnosis or known information;[218] **OR**

- Tests to determine risk for developing a disease or condition;[218] **OR**

- Tests performed to measure the quality of a process;[218] **OR**

- Tests without diagnosis specific indications;[218] **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[218]

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 MolDX Program

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.

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

- Pigmented Lesion Assay when used for screening for an individual without melanocytic skin lesions[91,92,93,94,95]

A review of the current medical literature shows that there is no evidence to determine that this service is standard medical treatment for these indications. There is an absence of randomized, blinded clinical studies examining benefit and long-term clinical outcomes establishing the value of this service in clinical management for these indications.

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
81401	MOLECULAR PATHOLOGY PROCEDURE LEVEL 2	
81479	Unlisted molecular pathology procedure	
81504	Oncology (tissue of origin), microarray gene expression profiling of > 2000 genes, utilizing formalin-fixed paraffin-embedded tissue, algorithm reported as tissue similarity scores	

81518	Oncology (breast), mRNA, gene expression profiling by real-time RT-PCR of 11 genes (7 content and 4 housekeeping), utilizing formalin-fixed paraffin-embedded tissue, algorithms reported as percentage risk for metastatic recurrence and likelihood of benefit from extended endocrine therapy	
81519	Oncology (breast), mRNA, gene expression profiling by real-time RT-PCR of 21 genes, utilizing formalin-fixed paraffin embedded tissue, algorithm reported as recurrence 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	
81521	Oncology (breast), mRNA, microarray gene expression profiling of 70 content genes and 465 housekeeping genes, utilizing fresh frozen or formalin-fixed paraffin-embedded tissue, algorithm reported as index related to risk of distant metastasis	
81522	Oncology (breast), mRNA, gene expression profiling by RT-PCR of 12 genes (8 content and 4 housekeeping), utilizing formalin-fixed paraffin-embedded tissue, algorithm reported as recurrence risk score	
81523	Oncology (breast), mRNA, next-generation sequencing gene expression profiling of 70 content genes and 31 housekeeping genes, utilizing formalin-fixed paraffin-embedded tissue, algorithm reported as index related to risk to distant metastasis	
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	
81529	Oncology (cutaneous melanoma), mRNA, gene expression profiling by real-time RT-PCR of 31 genes (28 content and 3 housekeeping), utilizing formalin-fixed paraffin-embedded tissue, algorithm reported as recurrence risk, including likelihood of sentinel lymph node metastasis	
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	

81541	Oncology (prostate), mRNA gene expression profiling by real-time RT-PCR of 46 genes (31 content and 15 housekeeping), utilizing formalin-fixed paraffin-embedded tissue, algorithm reported as a disease-specific mortality risk score	
81542	Oncology (prostate), mRNA, microarray gene expression profiling of 22 content genes, utilizing formalin-fixed paraffin-embedded tissue, algorithm reported as metastasis risk score	
81551	Oncology (prostate), promoter methylation profiling by real-time PCR of 3 genes (GSTP1, APC, RASSF1), utilizing formalin-fixed paraffin-embedded tissue, algorithm reported as a likelihood of prostate cancer detection on repeat biopsy	
81552	Oncology (uveal melanoma), mRNA, gene expression profiling by real-time RT-PCR of 15 genes (12 content and 3 housekeeping), utilizing fine needle aspirate or formalin-fixed paraffin-embedded tissue, algorithm reported as risk of metastasis	
81599	Unlisted multianalyte assay with algorithmic analysis	
84999	Unlisted chemistry procedure	
0005U	Oncology (prostate) gene expression profile by real-time RT-PCR of 3 genes (ERG, PCA3, and SPDEF), urine, algorithm reported as risk score	
0012M	Oncology (urothelial), mRNA, gene expression profiling by real-time quantitative PCR of five genes (MDK, HOXA13, CDC2 [CDK1], IGFBP5, and CXCR2), utilizing urine, algorithm reported as a risk score for having urothelial carcinoma	
0013M	Oncology (urothelial), mRNA, gene expression profiling by real-time quantitative PCR of five genes (MDK, HOXA13, CDC2 [CDK1], IGFBP5, and CXCR2), utilizing urine, algorithm reported as a risk score for having recurrent urothelial carcinoma	
0016M	Oncology (bladder), mRNA, microarray gene expression profiling of 209 genes, utilizing formalin-fixed paraffin-embedded tissue, algorithm reported as molecular subtype (luminal, luminal infiltrated, basal, basal claudin-low, neuroendocrine-like)	
0017M	Oncology (diffuse large B-cell lymphoma [DLBCL]), mRNA, gene expression profiling by fluorescent probe hybridization of 20 genes, formalin-fixed paraffin-embedded tissue, algorithm reported as cell of origin	

0019U	Oncology, RNA, gene expression by whole transcriptome sequencing, formalin-fixed paraffin embedded tissue or fresh frozen tissue, predictive algorithm reported as potential targets for therapeutic agents	
0045U	Oncology (breast ductal carcinoma in situ), 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 recurrence score	
0047U	Oncology (prostate), mRNA, gene expression profiling by real-time RT-PCR of 17 genes (12 content and 5 housekeeping), utilizing formalin-fixed paraffin-embedded tissue, algorithm reported as a risk score	
0067U	Oncology (breast), immunohistochemistry, protein expression profiling of 4 biomarkers (matrix metalloproteinase-1 [MMP-1], carcinoembryonic antigen-related cell adhesion molecule 6 [CEACAM6], hyaluronoglucosaminidase [HYAL1], highly expressed in cancer protein [HEC1]), formalin-fixed paraffin-embedded precancerous breast tissue, algorithm reported as carcinoma risk score	
0069U	Oncology (colorectal), microRNA, RT-PCR expression profiling of miR-31-3p, formalin-fixed paraffin-embedded tissue, algorithm reported as an expression score	
0089U	Oncology (melanoma), gene expression profiling by RTqPCR, PRAME and LINC00518, superficial collection using adhesive patch(es)	
0090U	Oncology (cutaneous melanoma), mRNA gene expression profiling by RT-PCR of 23 genes (14 content and 9 housekeeping), utilizing formalin-fixed paraffin-embedded tissue, algorithm reported as a categorical result (ie, benign, indeterminate, malignant)	
0120U	Oncology (B-cell lymphoma classification), mRNA, gene expression profiling by fluorescent probe hybridization of 58 genes (45 content and 13 housekeeping genes), formalin-fixed paraffin-embedded tissue, algorithm reported as likelihood for primary mediastinal B-cell lymphoma (PMBCL) and diffuse large B-cell lymphoma (DLBCL) with cell of origin subtyping in the latter	

0153U	Oncology (breast), mRNA, gene expression profiling by next-generation sequencing of 101 genes, utilizing formalin-fixed paraffin-embedded tissue, algorithm reported as a triple negative breast cancer clinical subtype(s) with information on immune cell involvement	
0262U	Oncology (solid tumor), gene expression profiling by real-time RT-PCR of 7 gene pathways (ER, AR, PI3K, MAPK, HH, TGFB, Notch), formalin-fixed paraffin-embedded (FFPE), algorithm reported as gene pathway activity score	
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	
0296U	Oncology (oral and/or oropharyngeal cancer), gene expression profiling by RNA sequencing at least 20 molecular features (eg, human and/or microbial mRNA), saliva, algorithm reported as positive or negative for signature associated with malignancy	
0313U	Oncology (pancreas), DNA and mRNA next-generation sequencing analysis of 74 genes and analysis of CEA (CEACAM5) gene expression, pancreatic cyst fluid, algorithm reported as a categorical result (ie, negative, low probability of neoplasia or positive, high probability of neoplasia)	
0314U	Oncology (cutaneous melanoma), mRNA gene expression profiling by RT-PCR of 35 genes (32 content and 3 housekeeping), utilizing formalin-fixed paraffin-embedded (FFPE) tissue, algorithm reported as a categorical result (ie, benign, intermediate, malignant)	
0315U	Oncology (cutaneous squamous cell carcinoma), mRNA gene expression profiling by RT-PCR of 40 genes (34 content and 6 housekeeping), utilizing formalin-fixed paraffin-embedded (FFPE) tissue, algorithm reported as a categorical risk result (ie, Class 1, Class 2A, Class 2B)	
0339U	Oncology (prostate), mRNA expression profiling of HOXC6 and DLX1, reverse transcription polymerase chain reaction (RT-PCR), first-void urine following digital rectal examination, algorithm reported as probability of high-grade cancer	

0363U	Oncology (urothelial), mRNA, gene- expression profiling by real-time quantitative PCR of 5 genes (MDK, HOXA13, CDC2 [CDK1], IGFBP5, and CXCR2), utilizing urine, algorithm incorporates age, sex, smoking history, and macrohematuria frequency, reported as a risk score for having urothelial carcinoma	
0420U	Oncology (urothelial), mRNA expression profiling by real-time quantitative PCR of MDK, HOXA13, CDC2, IGFBP5, and CXCR2 in combination with droplet digital PCR (ddPCR) analysis of 6 single-nucleotide polymorphisms (SNPs) genes TERT and FGFR3, urine, algorithm reported as a risk score for urothelial carcinoma	
CPT® Category III Code(s)	**Description**	**Comments**
No code(s) identified		
HCPCS 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

Appendix B
Prostate Cancer Risk Groups[201]

Risk Group	Clinical/Pathologic Features
Very low	All of the following: • cT1c; **AND** • Grade group 1; **AND** • PSA less than 10 ng/mL; **AND** • Fewer than 3 prostate biopsy fragments/cores positive, less than or equal to 50% cancer in each fragment/core; **AND** • PSA density less than 0.15 ng/mL/g
Low	All of the following but does not qualify for very low risk: • cT1 – cT2a; **AND** • Grade group 1; **AND** • PSA less than 10 ng/mL

Intermediate	All of the following:
	• No high-risk group features; **AND**
	• No very-high-risk group features; **AND**
	• At least 1 of the following intermediate risk factors:
	  ○ cT2b – cT2c
	  ○ Grade group 2 or 3
	  ○ PSA 10 – 20 ng/mL

Favorable intermediate	All of the following:
	• Grade group 1 or 2; **AND**
	• Less than 50% biopsy cores positive; **AND**
	• At least 1 of the following intermediate risk factors:
	  ○ cT2b – cT2c
	  ○ Grade group 2 or 3
	  ○ PSA 10 – 20 ng/mL

Unfavorable intermediate	At least 1 of the following:

	• Grade group 3; **AND** • Greater than or equal to 50% biopsy cores positive; **AND** • At least 2 of the following intermediate risk factors: ○ cT2b – cT2c ○ Grade group 2 or 3 ○ PSA 10 – 20 ng/mL
High	No very-high-risk features and has exactly 1 of the following high-risk features: • cT3a; **OR** • Grade group 4 or 5; **OR** • PSA greater than 20 ng/mL
Very high	At least 1 of the following: • cT3b – cT4 • Primary Gleason pattern • Greater than 4 cores with grade group 4 or 5 • At least 2 of the following high-risk features: ○ cT3a; **OR** ○ Grade group 4 or 5; **OR** ○ PSA greater than 20 ng/mL

Appendix C
American Joint Committee on Cancer (AJCC) TNM Staging System for Prostate Cancer[201]

Primary tumor (T)	
Clinical T (cT)	
T category	**T criteria**
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
T1	Clinically inapparent tumor that is not palpable
T1a	Tumor incidental histologic finding in 5% or less of tissue resected
T1b	Tumor incidental histologic finding in more than 5% of tissue resected
T1c	Tumor identified by needle biopsy found in one or both sides, but not palpable
T2	Tumor is palpable and confined within prostate
T2a	Tumor involves one-half of one side or less
T2b	Tumor involves more than one-half of one side but not both sides
T2c	Tumor involves both sides
T3	Extraprostatic tumor that is not fixed or does not invade adjacent structures

T3a	Extraprostatic extension (unilateral or bilateral)
T3b	Tumor invades seminal vesicle(s)
T4	Tumor is fixed or invades adjacent structures other than seminal vesicles such as external sphincter, rectum, bladder, levator muscles, and/or pelvic wall.
Pathological T (pT)	
T category	**T criteria**
T2	Organ confined
T3	Extraprostatic extension
T3a	Extraprostatic extension (unilateral or bilateral) or microscopic invasion of bladder neck
T3b	Tumor invades seminal vesicle(s)
T4	Tumor is fixed or invades adjacent structures other than seminal vesicles such as external sphincter, rectum, bladder, levator muscles, and/or pelvic wall
Note: There is no pathological T1 classification. Note: Positive surgical margin should be indicated by an R1 descriptor, indicating residual microscopic disease.	
Regional lymph nodes (N)	
N category	**N criteria**
NX	Regional nodes were not assessed
N0	No positive regional nodes
N1	Metastases in regional node(s)
Distant metastasis (M)	
M category	**M criteria**
M0	No distant metastasis
M1	Distant metastasis
M1a	Nonregional lymph node(s)
M1b	Bone(s)
M1c	Other site(s) with or without bone disease
Note: When more than one site of metastasis is present, the most advanced category is used. M1c is most advanced.	

Appendix D

AJCC Prognostic Groups[201] (When either PSA or Grade Group is not available, grouping should be determined by T category and/or either PSA or Grade Group as available)

Group	T	N	M	PSA (ng/mL)	Grade Group
Stage I	cT1a-c	N0	M0	Less than 10	1
	cT2a	N0	M0	Less than 10	1
	pT2	N0	M0	Less than 10	1
Stage IIA	cT1-c	N0	M0	At least 10 but less than 20	1

	cT2a	N0	M0	At least 10 but less than 20	1
	pT2	N0	M0	At least 10 but less than 20	1
	cT2b	N0	M0	Less than 20	1
	cT2c	N0	M0	Less than 20	1
Stage IIB	T1-2	N0	M0	Less than 20	1
Stage IIC	T1-2	N0	M0	Less than 20	3
	T1-2	N0	M0	Less than 20	4
Stage IIIA	T1-2	N0	M0	At least 20	1-4
Stage IIIB	T3-4	N0	M0	Any	1-4
Stage IIIC	Any	N0	M0	Any	Any
Stage IVA	Any	N1	M0	Any	Any
Stage IVB	Any	Any	M1	Any	Any

Appendix E
Definition of Histologic Grade Group[201] (The Gleason system has recently been compressed into Grade Groups)

Grade Group	Gleason Score	Gleason Pattern
1	Less than or equal to 6	Less than or equal to 3+3
2	7	3+4
3	7	4+3
4	8	4+4, 3+5, 5+3
5	9 or 10	4+5, 5+4, 5+5

Change Summary

- 01/01/2024 New Policy.