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CIRCULATING TUMOR CELL (CTC) TEST
FOR METASTATIC CANCERS (CELLSEARCH)

Policy # 401
Implementation Date: 5/19/08
Review Dates: 6/11/09, 6/17/10, 8/16/11, 8/16/12, 8/15/13, 8/28/14, 8/20/15, 8/25/16, 8/17/17, 9/18/18, 8/8/19, 12/28/20, 11/18/21
Revision Dates: 8/22/17

Related Medical Policies:
#570 Genetic Testing: Molecular Profiling for Determining Therapy of Malignant Tumors
#581 Genetic Testing: Liquid Biopsy

Description
Metastatic cancer is a cancer that has spread from its primary site (the part of the body in which it developed) to other parts of the body. If cells break away from a cancerous tumor, they can travel to other areas of the body. In patients with metastatic cancer, tumor cells may circulate in blood. These cells are called circulating tumor cells (CTCs).

The CellSearch test (Veridex LLC, Warren, NJ, a Johnson & Johnson company) is a blood test that captures and assesses CTCs to determine the prognosis of patients' various cancers. It has been FDA approved for assessment of patients with metastatic breast, colon, and/or prostate cancer. CellSearch is an automated method that identifies, counts, and characterizes epithelial-derived tumor cells circulating in peripheral blood by using CD45 markers (leukocyte marker); DAPI (nuclear marker); EpCam cytokeratin 8, 18, and/or 19 (epithelial cell markers). The CellSearch test works by using antibodies that are joined to microscopic iron particles, called ferrofluid. These antibody/ferrofluid combinations attach very specifically to CTCs. Powerful magnets then "pull" the CTCs out of the blood sample. They are then stained with additional bio-molecules and chemicals so that they can be positively identified as CTCs.

The CellSearch test differs from the current standard of care because it may detect tumors or changes in tumors much earlier than traditional imaging (e.g., CT scans), and is not subject to the variation observed with other blood tests, called serum tumor markers. However, the clinical role of CTC testing has not been established in patients with metastatic cancers; its use has not been established in clinical guidelines either.

Commercial Plan Policy/CHIP (Children’s Health Insurance Program)

SelectHealth does NOT cover circulating tumor cell (CTC) test for metastatic cancers (CellSearch).* The lack of evidence clarifying the role in the management of metastatic cancers meets the plan’s definition of investigational/experimental.

*Coverage will be allowed only for instances in which this testing was performed and qualified for coverage per criteria outlined in Medical Policy #570.
Genetic Disease Policies, Continued

Circulating Tumor Cell (CTC) Test for Metastatic Cancers (Cellsearch®), continued

**SelectHealth Advantage (Medicare/CMS)**

Coverage is determined by the Centers for Medicare and Medicaid Services (CMS); if a coverage determination has not been adopted by CMS, and InterQual criteria are not available, the SelectHealth Commercial policy applies. For the most up-to-date Medicare policies and coverage, please visit their search website [http://www.cms.gov/medicare-coverage-database/overview-and-quick-search.aspx?from2=search1.asp&](http://www.cms.gov/medicare-coverage-database/overview-and-quick-search.aspx?from2=search1.asp&) or the manual website.

**SelectHealth Community Care (Medicaid)**

Coverage is determined by the State of Utah Medicaid program; if Utah State Medicaid has no published coverage position and InterQual criteria are not available, the SelectHealth Commercial criteria will apply. For the most up-to-date Medicaid policies and coverage, please visit their website [http://health.utah.gov/medicaid/manuals/directory.php](http://health.utah.gov/medicaid/manuals/directory.php) or the Utah Medicaid code Look-Up tool.

**Summary of Medical Information**

The literature evaluating the CellSearch System is focused primarily on its use in breast cancer. Twelve studies were identified for this indication. Many of these studies were funded by Immunicon, manufacturer of the technology underlying CellSearch. These studies universally conclude that circulating tumor cells isolated through immunomagnetic separation are a reliable prognostic indicator in metastatic breast cancer. An early prospective trial by Cristofanilli et al., for example, involved 177 women tested at U.S. cancer centers prior to initiating treatment for metastatic breast cancer and 345 women with nonmalignant breast diseases who served as controls. The first 102 breast cancer patients served as a training set to determine the CTC count that best predicted survival, which was subsequently validated in the remaining 75 patients. Of 177 patients, 87 (49%) had ≥ 5 circulating tumor cells per 7.5 ml of blood at baseline. These 87 patients had a significantly shorter median progression-free survival (approximately 2.7 months) and median overall survival (approximately 10.1 months; 95% confidence interval, 6.3 to 14.6) than did patients with < 5 circulating tumor cells per 7.5 ml of blood (median progression-free survival, approximately 7.0 months; overall survival; > 18 months). CTCs were detected in only 1% of 345 control subjects, none of whom had > 3 cells per 7.5 ml of blood.

In 2007, a retrospective analysis of 151 patients with metastatic breast cancer compared the prognostic significance of CTCs with clinical and laboratory measures of tumor burden and phenotypic subtype of disease. Of these, 32 were participants in the Cristofanilli, et al. study from 2004. The remaining 119 were a new cohort of patients who had CTCs measured before initiating therapy. In addition to CTCs, Swenerton score, cancer antigen 27–29 level, age (< 50 years vs. ≥ 50 years), hormone-receptor status and HER2 status, metastatic site, and type and line of therapy were measured as prognostic indicators. A multivariable Cox model revealed CTCs to be the strongest predictor of survival with ≥ 5 CTCs having 2.2 times the risk of death (p = 0.003).

These studies suggest that CellSearch is a reliable prognostic indicator of survival in metastatic breast cancer patients. However, there are insufficient data to conclude how measurement of CTCs through this or any other method would improve survival or change clinical management of the disease. There are also insufficient data comparing it with alternative techniques to conclude that it is a more reliable means of estimating prognosis. Finally, data are insufficient to determine whether CellSearch can be used to monitor response to treatment.

The use of CellSearch in early stage breast cancer is promising and may predict the use of appropriate adjuvant therapy. Wong et al. states: “A study involving detection of CTCs by semi-automated fluorescence-based microscopy after immuno-magnetic enrichment in women who have completed adjuvant chemotherapy for early breast cancer is ongoing and survival data is not available yet.” Even in patients with metastatic disease the use of CellSearch in a predictive fashion is encouraging, but Budd et al. states: “Our results have implications for both standard care and clinical research. More accurate determination of treatment effectiveness early in the course of therapy might spare patient toxicity from futile therapy and allow treatment to be changed to a more effective regimen. Whether such an early assessment of response results in an improved overall outcome or quality of life will need to be prospectively assessed in clinical trials designed to investigate this question.” CellSearch was also more...
effective than standard radiological measures in evaluating progressive metastatic disease. The clinical utility of this finding has not been explored in prospective studies in treated patients.

The literature on use of CellSearch for prostate and colorectal cancers is insufficient to determine whether the technique is useful for these indications. The 2 studies evaluating CellSearch in colorectal surgery postoperatively did not show prognostic significance.

Billing/Coding Information

**Not covered:** Investigational/Experimental/Unproven for this indication

**CPT CODES**

- **81479** Unlisted molecular pathology procedure
- **86152** Cell enumeration using immunologic selection and identification in fluid specimen (eg, circulating tumor cells in blood);
- **86153** ; physician interpretation and report, when required
- **86849** Unlisted immunology procedure

**HCPCS CODES**

- **G0452** Molecular pathology procedure; physician interpretation and report

**Key References**

Circulating Tumor Cell (CTC) Test for Metastatic Cancers (Cellsearch®), continued


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GENE EXPRESSION TESTING FOR INDETERMINATE THYROID NODULE BIOPSY

Policy # 538
Implementation Date:  8/13/13
Review Dates:   10/15/15, 10/20/16, 12/19/18, 10/15/20, 11/18/21
Revision Dates:  10/13/14, 1/30/17, 1/25/18, 2/28/18, 8/7/18, 1/29/21

Description
A thyroid nodule is an abnormal structure that is anatomically distinct from the surrounding thyroid parenchyma. Thyroid nodules can be visible or palpable when they are big enough or superficially located; however, most nodules are found incidentally on an imaging study performed for a different purpose. Nodules may be single or multiple and may occur with or without symptoms of thyroid hormone excess or deficiency. Most thyroid nodules are benign, but they may be malignant in 5% to 15% of cases. The primary objective of the evaluation of a thyroid nodule is to determine whether the nodule is benign or malignant; the secondary objective is to determine whether the nodule is associated with thyroid dysfunction.

The prevalence of thyroid nodules varies depending on the population studied and is estimated at 2% to 6% with palpation, 19% to 35% with ultrasonography and 8% to 65% at autopsy. Nodules are found up to six times more often in women, based on clinical examination, with smaller differences when imaging is used. The rates of malignancy in nodules are higher in men.

Ruling out malignancy in thyroid nodules historically depended on thyroid resection and histopathological evaluation until fine needle aspiration (FNA) biopsy was introduced into the United States in the 1970s. Thyroid FNA biopsy identified a majority of thyroid nodules as benign, obviating the need for surgery in over half of the patients. However, 15%–30% of thyroid FNAs yields an indeterminate cytological interpretation that leads to surgical biopsy, even though most of these biopsied nodules prove to be benign. These indeterminate nodules harbor a 24% risk of malignancy; too high to ignore but driving surgery where most nodules are benign. FNA is the preferred technique for obtaining thyroid follicular cells from thyroid nodules in the office setting. Cytopathologic examination of these cells provides the best information available, short of surgical excision, to assess whether a nodule is benign or malignant.

Several genetic testing panels have been developed to improve diagnosis of thyroid FNA. These include the Afirma Gene Expression Classifier (GEC) test (Veracyte, Inc., South San Francisco, CA) and the ThyroSeq Gene Expression Classifier (GEC) test (Afirma, Veracyte, Inc., South San Francisco, CA), which tests have been developed and can be run on the FNA sample in order to predict which cytologically indeterminate thyroid nodules are benign and to potentially avoid surgery on these nodules. These tests assess PAX8-PPARγ translocation, PPARγ-CREB3L2 fusions, RAS mutation, LGALS3 expression, BRAF mutation, RET-PTC rearrangement, PCSK2 CCDN2 and PLAB expression and TFF3 expression among other abnormalities have all been associated with thyroid cancer with varying degrees of evidence.

The Afirma Thyroid FNA Analysis combines specialized cytopathology and the novel Afirma GEC. Physicians submit to Veracyte thyroid nodule FNA samples collected in a single patient visit. Then, a thyroid cytopathology specialist at Thyroid Cytopathology Partners (TCP), an independent partner of Veracyte, performs cytopathology assessment of a thyroid nodule FNA sample under the microscope. If the cytopathology diagnosis is benign or malignant, the analysis is complete. Only when TCP’s cytopathology diagnosis is indeterminate (a recent study showed TCP’s indeterminate rate to be 16%) is
the proprietary Gene Expression Classifier performed. The TCP team reads thousands of cases each month, making them the largest thyroid-only cytopathology group. Their volume and specialization expose them to rare neoplasms, including medullary thyroid cancer, on a routine basis.

ThyroSeq v3 is also based on next-generation sequencing of DNA and RNA. However, it is expanded to analyze 112 genes, providing information on > 12,000 mutation hotspots and > 120 gene fusion types. The test detects 4 classes of genetic alterations: mutations (SNVs, indels); gene fusions; gene expression alterations; and copy number variations (CNVs). The test utilizes a proprietary genomic classifier (GC) based on the algorithmic analysis of all detected genetic alterations to report the test result as positive or negative.

ThyraMIR and ThyGenX were developed in-house by Interpace Diagnostics, Inc. and are performed in a laboratory regulated by and certified under the Clinical Laboratory Improvement Amendments. ThyraMIR is a PCR-based micro-RNA (miRNA) expression classifier which evaluates the expression of 10 miRNA genes. ThyGenX performs targeted next-generation sequencing (NGS) analysis to identify over 100 genetic alterations within 5 thyroid cancer relevant genes. The test combination has been designed to both rule out malignancy as well as confirm it, if present.

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<thead>
<tr>
<th>Commercial Plan Policy/CHIP (Children’s Health Insurance Program)</th>
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<td>Application of coverage criteria is dependent upon an individual’s benefit coverage at the time of the request.</td>
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<tr>
<td>SelectHealth covers genetic testing for indeterminate thyroid biopsy using the Afirma GSC test, ThyroSeq, and ThyGeNEXT/ThyraMIR, when criteria are met:</td>
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<tr>
<td>• One fine needle aspiration (FNA) of the thyroid nodule interpreted as meeting one of the Bethesda guidelines (either III or IV) listed below*</td>
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*Bethesda Guidelines:
I. Nondiagnostic
II. Benign – This includes macrofollicular or adenomatoid/hyperplastic nodules, colloid adenomas, nodular goiter, and Hashimoto’s thyroiditis
III. Follicular lesion or atypia of undetermined significance (FLUS or AUS) – This includes lesions with atypical cells, or mixed macro- and microfollicular nodules
IV. Follicular neoplasm – This includes microfollicular nodules, including Hürthle cell lesions
V. Suspicious for malignancy
VI. Malignant

SelectHealth does NOT cover other genetic testing for indeterminate thyroid biopsies/fine needle aspirates as current evidence is inadequate to reach conclusions on the clinical and statistical validity of these tests. These tests meet the plan’s definition of investigational/experimental.

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Coverage is determined by the State of Utah Medicaid program; if Utah State Medicaid has no published coverage position and InterQual criteria are not available, the SelectHealth Commercial criteria will apply. For the most up-to-date Medicaid policies and coverage, please visit their website http://health.utah.gov/medicaid/manuals/directory.php or the Utah Medicaid code Look-Up tool.

Summary of Medical Information
Thyroid cancer is most found on routine physical examination as a palpable thyroid nodule. A fine-needle aspiration (FNA) biopsy is usually performed to rule out malignancy. In some cases, the nodules are not clearly benign or malignant based on FNA results alone. Those patients with cytologically indeterminate nodules are often referred for diagnostic surgery, though, most of these nodules turn out to be benign.

The 2013 guidelines from the National Comprehensive Cancer Network (NCCN) state that: “Molecular diagnostics ... using molecular classifiers may be useful in the evaluation of FNA samples that are indeterminate.” Several tests have been developed to reduce the incidence of nondiagnostic biopsy results to better guide surgical decision making. The bulk of the literature focuses on the Veracyte, Afirma test. The literature on the other genetic tests used in the evaluation of indeterminate thyroid biopsies is inadequate to draw conclusions regarding the clinical validity and clinical utility of these tests.

Afirma: No approval by the FDA is required for the Afirma analysis, as it was developed in-house by Veracyte, Inc. All tests are performed by Veracyte in their laboratory which is certified under the Clinical Laboratory Improvement Amendments.

A single study has examined the analytical validity of the Afirma analysis. Chudova and colleagues (2010) reported on the development process and performance validation of the GEC. Microarray data was generated from 178 thyroid tissue specimens representing the 8 most common types of benign and malignant lesions. Messenger RNA transcripts were used to develop a molecular classifier. After testing of the final test set, the sensitivity was determined to be 100%, and the specificity at 73.3%, to yield a negative predictive value (NPV) of 96%.

Clinical validity of the GEC was evaluated by Alexander et al. (2012) in a multicenter study of independently and prospectively collected thyroid FNA specimens. Of 3,789 samples, 265 were classified as indeterminate, had an adequate specimen for analysis, and had results of a histopathological examination, and were included in the analysis. 142 genes were used in the main GEC, which would classify the FNA samples as benign or suspicious. Of the 265 indeterminate specimens, 85 were classified as malignant after evaluation of thyroid tissue. Of these 85 specimens, 78 were correctly classified as suspicious by the Afirma® analysis for a sensitivity of 92%. There were therefore 7 incorrectly classified malignancies. Of the 180 nonmalignant samples, 93 were correctly classified as benign by the GEC for a specificity of 52%. For the entire set of test samples, the positive predictive value (PPV) and NPV was reported at 47% and 93%, respectively.

A single study by Duick et al., in 2012 has documented the impact of the Afirma FNA analysis on the management of patients with indeterminate thyroid nodules. In a retrospective, multicenter study, the researchers evaluated data from endocrinology practices that ordered the Afirma analysis for which the result was benign for at least three patients. A total of 51 endocrinologists from 21 centers reported data on a total of 368 patients. Physicians reported on their management decisions for each patient. According to the survey, surgery was performed in 28 patients with a benign GEC result; the reasons most often given for surgery was nodule size, a nodule causing symptoms of pressure, and a rapidly growing nodule. Hemithyroidectomy was performed in 19 and total thyroidectomy was recommended in 8. The percentage of patients who were operated on (7.4%) represented a significant decrease from the previously reported rate of diagnostic surgery (74%).

ThyraMIR and ThyGenX: The tests were developed in-house by Interpace Diagnostics, Inc. and are performed in a laboratory regulated by and certified under the Clinical Laboratory Improvement Amendments. No approval by the FDA is required.

In terms of analytic validity, the methodologies used in these tests are reliable, well-known, and reproducible. ThyraMIR is a PCR-based micro-RNA (miRNA) expression classifier which evaluates the expression of 10 miRNA genes. ThyGenX performs targeted next-generation sequencing (NGS) analysis to identify over 100 genetic alterations within 5 thyroid cancer-relevant genes. The test combination has been designed to both rule out malignancy as well as confirm it, if present.
Clinical validity has been studied prospectively using a high number of samples in multiple settings. In a recent study by Labourier et al. in 2015, 638 FNA and surgical specimens were tested for 17 validated gene alterations. The molecular results were compared to surgical histopathology to determine the diagnostic accuracy. miRNA testing correctly identified 64% of malignant cases and 98% of benign cases. Negative predictive value was reported at 94%. The authors reported that the rate of avoidable diagnostic surgeries was reduced by 69%. In another study by Beaudenon et al., 2014, in a prospective, multicenter, double-blind study, 769 FNAs were evaluated. Based on the high rate of cancer detection when present, the authors concluded that the use of molecular testing decreases the rate of two-stage thyroidectomy surgeries.

Clinical utility specific to this testing has not been established and relies on the general acceptance of molecular genomic testing in avoiding unnecessary surgeries and reducing the need for two-stage surgeries.

**ThyroSeq:** The ThyroSeq test was developed by researchers at the University of Pittsburgh Medical Center. The available evidence for this test is not as decisive as that for the other commercially available tests, but the methodology used is established, and known to be reproducible. There is adequate validation that ThyroSeq can accurately identify point mutations in the genes and fusions in an FNA sample, facilitating treatment decisions in patients with indeterminate thyroid FNA biopsies. The latest version (ThyroSeq v3) offers detection of more than 1,000 cancer "hotspots" (single nucleotide polymorphisms, or SNPs) on 14 thyroid cancer-related genes and 42 fusion genes known to occur in thyroid cancer. In a validation study of 143 consecutive FNA samples with indeterminate diagnosis of follicular neoplasm or suspicious for follicular neoplasm, the test resulted in 104 benign nodules and 39 malignant nodules, which correlated with surgical pathology results for a 90% sensitivity, 83% positive predictive value, and negative predictive value of 96%.

### Billing/Coding Information

**CPT CODES**

- **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")
- **81545** Oncology (thyroid), gene expression analysis of 142 genes, utilizing fine needle aspirate, algorithm reported as a categorical result (eg, benign or suspicious)

**HCPCS CODES**

No specific codes identified

**Key References**

7. Chen et al. The Role of the ThyroSeq v3 Molecular Test in the Surgical Management of Thyroid Nodules in the Canadian Public Health Care Setting Thyroid. Sep 2020. 1280-1287.
Gene Expression Testing for Indeterminate Thyroid Nodule Biopsy, continued


17. Hila Benjamin, MSc; Temima Schnitzer-Perlman, MSc; Alexander Shtabayek, MD, PhD; Christopher J. VandenBussche, MD; Syed Z. Ali, MD; Zdenek Kolar, MD, PhD; Fabio Pagini, MD; Rosetta Genomics Group; Dgantir Bar, PhD; and Ei Mei, PhD. Analytical Validity of a MicroRNA-Based Assay for Diagnosing Indeterminate Thyroid FNA Smears From Routinely Prepared Cytology Slides. Cancer Cytopathol. 2018;126:71-21.


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GENE THERAPY, TESTING, AND COUNSELING

Policy # 123
Implementation Date: 7/98
Review Dates: 1/4/00, 2/27/01, 8/27/02, 1/03, 10/23/03, 11/18/04, 12/15/05, 12/20/07, 12/18/08, 11/29/12, 10/24/13, 10/23/14, 10/15/15, 10/20/16, 4/23/18, 6/20/19, 6/2/20, 5/31/21
Revision Dates: 3/8/04, 9/14/06, 6/25/07, 12/17/09, 10/21/10, 10/12/11, 6/7/17, 6/5/18, 12/5/18
Related Medical Policies:
#636 Molecular Genetic Testing Guidelines

Disclaimer:
1. Policies are subject to change without notice.
2. Policies outline coverage determinations for SelectHealth Commercial, SelectHealth Advantage (Medicare/CMS) and SelectHealth Community Care (Medicaid/CHIP) plans. Refer to the “Policy” section for more information.

Description
Gene Therapy
Gene therapy or gene-based therapies are any treatments which try to replace a portion of a person's DNA code with material from an external source with the purpose of correcting a genetic defect related to a specific disease or to treat a specific condition. The external DNA can be in the form of intact genes, portions of genes, or the building blocks of genes—nucleic acids.

Genetic Testing
Genetic testing is the analysis, for clinical purposes, of human genetic material (i.e., DNA, RNA, and chromosomes), proteins, and metabolites to detect abnormalities related to an inheritable disorder or trait. There are 6 categories of genetic testing: diagnostic, predictive (for disease assessment), predictive/presymptomatic, prenatal, newborn, preimplantation, and carrier testing (gender analysis).

Genetic Counseling
Genetic Counseling is a communication process, which deals with the human problems associated with the occurrence, or the risk of occurrence, of a genetic disorder in a family. This process involves an interaction with appropriately trained health professionals (geneticists and genetic counselors) to help the individual or family:

- Comprehend the medical facts, including the diagnosis, the probable course of the disorder, and the available management
- Appreciate the way heredity contributes to the disorder, and the risk of recurrence in specified relatives
- Understand the options for dealing with risk of recurrence
- Choose the course of action which seems appropriate to them in view of their risk and their family goals and act in accordance with that decision, and
- Make the best possible adjustment to the disorder in an affected family member and/or to the risk of recurrence of that disorder
Commercial Plan Policy/CHIP (Children’s Health Insurance Program)

Application of coverage criteria is dependent upon an individual's benefit coverage at the time of the request.

SelectHealth covers gene therapy (gene-based therapy) when the P&T committee AND the Chief Medical Officer (CMO) determine that the proposed gene therapy will affect clinical outcome.

SelectHealth covers genetic testing when ordered or recommended by a medical geneticist, a genetic counselor, or a provider with recognized expertise in the area being assessed.

SelectHealth covers genetic testing as follows:

I. Genetic Testing for Inherited Disease:
   a. Genetic testing to establish a diagnosis or susceptibility for an inherited disease may be medically necessary when all the following criteria are met:
      i. Diagnostic results from physical examination, pedigree analysis, and conventional testing are inconclusive and a definitive diagnosis is uncertain.
      ii. The clinical utility of all requested genes and gene mutations must be established (including the genes and gene mutations in a panel test, as applicable). The clinical record must document:
         • How test results will guide decisions regarding: disease treatment, prevention, or management, such as averting treatment for other possible diagnosis.

OR

II. Genetic Testing Not Related to Inherited Condition:
   a. Genetic testing for indications other than determining risk or establishing a diagnosis for a genetically inherited disease (e.g., genetic expression analysis in breast cancer) may be considered medically necessary when all the following criteria are met:
      i. Diagnostic results from physical examination, pedigree analysis, and conventional testing are inconclusive and a definitive diagnosis is uncertain.
      ii. The clinical utility of all requested genes and gene mutations must be established (including all genes and gene mutations in a panel test, as applicable). The clinical records must document:
         • How test results will guide decisions regarding: disease treatment, prevention, or management, such as averting treatment for other possible diagnoses.
SelectHealth does NOT cover genetic testing under the following circumstances:

- Home genetic test
- Other genetic test for population screening

**SelectHealth Advantage (Medicare/CMS)**

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**Summary of Medical Information**

"A genetic test is the analysis of human DNA, RNA, chromosomes, proteins, or certain metabolites in order to detect alterations related to heritable disorder. This can be accomplished by directly examining the DNA or RNA that makes up the gene (direct testing), looking at markers co-inherited with a disease-causing gene (linkage testing), assaying certain metabolites (biochemical testing), or examining the chromosomes (cytogenetic testing)." Genetic tests are conducted for various purposes, including predicting disease risk, newborn screening, determining clinical management, identifying carriers, and establishing prenatal or clinical diagnoses or prognoses in an individual, families, or populations.

**General Categories of Genetic Tests**

**Diagnostic Genetic Testing:** Occurs in a symptomatic patient with a clinical presentation in association with or without a family history that leads the clinician to suspect a genetic disorder. Test results may confirm the suspected diagnosis, provide prognostic information, and assist in care management decisions, including treatment, preventative care recommendations, and condition specific surveillance.

**Predictive Genetic Testing for Disease Assessment:** Occurs in a patient with or without symptoms which would indicate a high probability of a genetic mutation; this test should be prognostic and assist in care management decisions including treatment, preventive care recommendations and condition-specific surveillance.

**Prenatal Genetic Testing:** A diagnostic test of the fetus to predict disease.

**Population Genetic Screening** applies to testing individuals without regard to the family history or phenotypic expression of a genetic disease, which may include newborn screening, maternal serum screening, or screening as specific ethnic population.

**Newborn Screening:** May include genetic and metabolic testing for early, presymptomatic detection, when diagnosed and treated, and prevents possibly irreversible health consequences.

**Preimplantation Testing:** Preimplantation genetic testing is a technique used to identify genetic defects in embryos created through in vitro fertilization (IVF) before pregnancy. Preimplantation genetic diagnosis (PGD) refers specifically to when one or both genetic parents have a known genetic abnormality and testing is performed on an embryo to determine if it also carries a genetic abnormality. In contrast, preimplantation genetic screening (PGS) refers to techniques where embryos from presumed chromosomally normal genetic parents are screened for aneuploidy.
Carrier Genetic Testing: Used to evaluate the potential of transmission of genetic mutations in asymptomatic, disease-free individuals; this includes testing parents in the preconception or prenatal periods to assess risk of having a child with a genetic disorder in a planned or ongoing pregnancy.

Billing/Coding Information
Covered: ONLY for the conditions outlined above

CPT CODES
81170-81383  Gene Analysis: Tier 1 Procedures
81400  Molecular pathology procedure level 1
81401  Molecular pathology procedure level 2
81402  Molecular pathology procedure level 3
81403  Molecular pathology procedure level 4
81404  Molecular pathology procedure level 5
81405  Molecular pathology procedure level 6
81406  Molecular pathology procedure level 7
81407  Molecular pathology procedure level 8
81408  Molecular pathology procedure level 9
81410-81471  Genomic Sequencing
81479  Unlisted molecular pathology procedure
81490-81599  Multianalyte Assays with Algorithmic Analyses
88235  Tissue culture for non-neoplastic disorders; amniotic fluid or chorionic villus cells
88245  Chromosome analysis for breakage syndromes; baseline Sister Chromatid Exchange (SCE), 20-25 cells
88248  Chromosome analysis for breakage syndromes; baseline breakage, score 50-100 cells, count 20 cells, 2 karyotypes (eg, for ataxia telangiectasia, Fanconi anemia, fragile X)
88249  Chromosome analysis for breakage syndromes; score 100 cells, clastogen stress (eg, diepoxybutane, mitomycin C, ionizing radiation, UV radiation)
88261  Chromosome analysis; count 5 cells, 1 karyotype, with banding
88262  Chromosome analysis; count 15-20 cells, 2 karyotypes, with banding
88263  Chromosome analysis; count 45 cells for mosaicism, 2 karyotypes, with banding
88264  Chromosome analysis; analyze 20-25 cells
88267  Chromosome analysis, amniotic fluid or chorionic villus, count 15 cells, 1 karyotype, with banding
88269  Chromosome analysis, in situ for amniotic fluid cells, count cells from 6-12 colonies, 1 karyotype, with banding
88280  Chromosome analysis; additional karyotypes, each study
88283  Chromosome analysis; additional specialized banding technique (eg, NOR, C-banding)
88285  Chromosome analysis; additional cells counted, each study
96040  Medical genetics and genetic counseling services, each 30 minutes face-to-face with patient/family

HCPCS CODES
G0452  Molecular pathology procedure; physician interpretation and report
S0265 Genetic counseling, under physician supervision, each 15 minutes

Key References

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GENETIC TESTING FOR PROSTATE CANCER PROGNOSIS

Policy # 544
Implementation Date: 11/11/13
Review Dates: 6/11/15, 6/16/16, 10/20/16, 10/19/17, 5/17/21
Revision Dates: 9/9/21

Related Medical Policies:
#510 Genetic Testing: PCA3 Testing for Prostate Cancer
#272 Genetic Testing: Screening, Diagnosis or Management of Prostate Cancer

Description
Prostate cancer (PCa) is the second leading cause of cancer death in men, exceeded only by lung cancer. A man’s lifetime risk of PCa is 1 in 6. Not everyone experiences symptoms of prostate cancer. Many times, signs of PCa are first detected by a doctor during a routine check-up. Part of the annual exam that men over the age of 50 undergo includes a digital rectal exam (DRE) to feel the prostate and a PSA to screen for asymptomatic prostate cancer. Use of the PSA has become controversial in the last couple of years due to the low sensitivity in screening for prostate cancer. Consequently, new tests which may be more sensitive and specific for identifying early or aggressive prostate cancer are being developed.

One such test is the Oncotype DX® Prostate test. This gene expression test measures specific RNA markers and generates the Genomic Prostate Score (GPS). The GPS is purported to assist in determining the aggressiveness of an individual’s prostate cancer and assist in determining the appropriate approach to management.

Commercial Plan Policy/CHIP (Children’s Health Insurance Program)

Application of coverage criteria is dependent upon an individual’s benefit coverage at the time of the request.

SelectHealth covers the following prostate cancer screening tests, when criteria are met.

1. Oncotype DX for the following indications post-biopsy (either a or b):
   a) Men with NCCN very-low-risk, low-risk, and favorable intermediate-risk prostate cancer who have greater than 10-year life expectancy and who have not received treatment for prostate cancer and are candidates for active surveillance or definitive therapy; or
   b) Men with intermediate-risk prostate cancer when deciding whether to add androgen-deprivation therapy to radiation.
2. **Prolaris for the following indications post-biopsy (either a or b):**
   a) Men with NCCN very-low-risk, low-risk, and favorable intermediate-risk prostate cancer who have greater than 10-year life expectancy and who have not received treatment for prostate cancer and are candidates for active surveillance or definitive therapy; or
   b) Men with intermediate-risk prostate cancer when deciding whether to add androgen-deprivation therapy to radiation

3. **ProMark for the following indications post-biopsy (either a or b):**
   a) Men with NCCN very-low-risk, low-risk men, and favorable intermediate risk prostate cancer who have greater than 10-year life expectancy and who have not received treatment for prostate cancer and are candidates for active surveillance or definitive therapy; or
   b) Men with intermediate-risk prostate cancer when deciding whether to add androgen-deprivation therapy to radiation

4. **Decipher for the following indications: (either a or b):**
   a) Post biopsy in men with NCCN very-low-risk, low-risk, and favorable intermediate-risk prostate cancer who have a greater than 10-year life expectancy who have not received treatment for prostate cancer and are candidates for active surveillance or definitive therapy; or
   b) Post biopsy in men with intermediate-risk prostate cancer when deciding whether to add androgen-deprivation therapy to radiation

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**SelectHealth Advantage (Medicare/CMS)**

Coverage is determined by the Centers for Medicare and Medicaid Services (CMS); if a coverage determination has not been adopted by CMS, and InterQual criteria are not available, the SelectHealth Commercial policy applies. For the most up-to-date Medicare policies and coverage, please visit their search website [http://www.cms.gov/medicare-coverage-database/overview-and-quick-search.aspx?from2=search1.asp&](http://www.cms.gov/medicare-coverage-database/overview-and-quick-search.aspx?from2=search1.asp&) or the manual website.

**SelectHealth Community Care (Medicaid)**

Coverage is determined by the State of Utah Medicaid program; if Utah State Medicaid has no published coverage position and InterQual criteria are not available, the SelectHealth Commercial criteria will apply. For the most up-to-date Medicaid policies and coverage, please visit their website [http://health.utah.gov/medicaid/manuals/directory.php](http://health.utah.gov/medicaid/manuals/directory.php) or the Utah Medicaid code Look-Up tool.

**Summary of Medical Information**

Currently, no systematic reviews or primary literature are available regarding the Oncotype DX Prostate Test. A validation study was presented at the 2013 American Urology Association annual meeting, which is purported to: “... strongly predicted disease aggressiveness (p = 0.002) offering information beyond currently available clinical factors, such as PSA and biopsy Gleason Score.” However, that presentation is not available nor have these findings been published.
As no literature on this technology has been published to date, an assessment regarding safety or efficacy of the test is not possible at this time (GRADE 2C).

Billing/Coding Information

CPT CODES

Covered for the Indications Listed Above

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

81479 Unlisted molecular pathology procedure

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

Not Covered for the Indications Listed Above

0343U Oncology (prostate), exosome-based analysis of 442 small noncoding RNAs (sncRNAs) by quantitative reverse transcription polymerase chain reaction (RT-qPCR), urine, reported as molecular evidence of no-, low-, intermediate- or high-risk of prostate cancer

HCPCS CODES

No specific codes identified

Key References

Active Surveillance


Definitive Therapy

Genetic Testing for Prostate Cancer Prognosis, continued


After Radical Prostatectomy

Early vs. Salvage Radiation


Genetic Testing for Prostate Cancer Prognosis, continued


Salvage Therapy after Surgery


GRID


Genetic Testing for Prostate Cancer Prognosis, continued


136. Torres A, et al. ETS2 is a prostate basal cell marker and is highly expressed in prostate cancers aberrantly expressing p63. *Prostate* 2018;78(12):896-904. https://doi.org/10.1002/pros.23646


Genetic Testing for Prostate Cancer Prognosis, continued


Reviews


8
Genetic Disease Policies, Continued

Genetic Testing for Prostate Cancer Prognosis, continued


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MEDICAL POLICY

GENETIC TESTING: CELL-FREE TUMOR DNA/LIQUID BIOPSY

Policy # 581
Implementation Date: 7/8/16
Review Dates: 6/15/17, 9/18/18, 8/8/19, 10/21/20, 5/19/22
Revision Dates: 8/21/17, 8/16/19, 9/23/20, 1/29/21, 5/9/22

Related Medical Policies:
#570 Genetic Testing: Molecular Profiling for Determining Therapy of Malignant Tumors

Description
Detecting and monitoring cancer recurrence can sometimes be problematic. Additionally, for individuals who have a relapse while on therapy determining optimal approaches to therapy modification can also be problematic as tumor samples may not be accessible via biopsy, or the patient may not be able to well-tolerate an invasive procedure. New methods to identify and characterize the molecular characteristics of persistent or recurrent tumors are being developed which are intended to eliminate invasive biopsies but retain similar sensitivities and specificities. One such technology is the “liquid biopsy.” This technology uses next-generation sequencing to characterize tumors based on the capture and analysis of cell-free tumor DNA (ctDNA). This technology involves a blood test that provides detailed information on the genomic make up of any tumor present with the ability to identify the percentage of each mutation found in an individual’s blood. Though it has long been known that tumor cells release DNA into the blood, what is unknown is whether the DNA that is released will accurately represent the same genetic mutations as the primary cancer tumor, as well as other sites of metastasis. The concentration of tumor DNA in the blood stream has been speculated to also indicate how advanced the cancer may be and if current therapies are impacting.

Laboratories pursuing this technology include Pathway Genomics, the CancerIntercept test (designed for early cancer detection and monitoring), and also Circulogene’s (Theranostics) liquid biopsy uses a finger stick volume of blood and NGS to monitor known tumor mutations (=3000) in 50 cancer-associated genes for targeted therapy and others. This test uses a proprietary method to recover necrotic and apoptotic cell-death-associated cell-free DNA. Pathway Genomics Cancer Intercept is a 96-gene mutation panel designed to detect mutations in 9 driver genes involved primarily in breast, ovarian, lung, and colorectal cancers, as well as melanoma. Guardant Health and their Guardant360 test assess 70 actionable mutations on various solid tumors. Many other tests are in various stages of development.

Commercial Plan Policy/CHIP (Children’s Health Insurance Program)
Application of coverage criteria is dependent upon an individual’s benefit coverage at the time of the request.

A. SelectHealth covers either the Guardant360Cdx liquid biopsy assay or FoundationOne LiquidCdx if one of the following is present:
   1. Tissue-based CGP (comprehensive genomic profiling) is infeasible (i.e., quantity not sufficient for tissue-based CGP or invasive biopsy is medically contraindicated) specifically in non-small cell lung cancer (NSLC)
Genetic Testing: Cell-free Tumor DNA/Liquid Biopsy, continued

OR

2. Tissue-based CGP (comprehensive genomic profiling) is infeasible (i.e., quantity not sufficient for tissue-based CGP or invasive biopsy is medically contraindicated), and an FDA-approved indication or NCCN recommendation requires information about the presence or absence of a genetic biomarker

OR

3. Member is considering participating in a clinical trial* intended to assess the effectiveness of targeted therapies based on tumor marker, and tissue-based CGP is infeasible (i.e., quantity not sufficient for tissue-based CGP or invasive biopsy is medically contraindicated).

*Clinical trial must meet one (i−iii) of the following clinical conditions:

i. Any advanced stage III or IV solid tumors, or
ii. All lymphomas, or
iii. Multiple myeloma

SelectHealth Advantage (Medicare/CMS)

Coverage is determined by the Centers for Medicare and Medicaid Services (CMS); if a coverage determination has not been adopted by CMS, and InterQual criteria are no available, the SelectHealth Commercial policy applies. For the most up-to-date Medicare policies and coverage, please visit their search website [http://www.cms.gov/medicare-coverage-database/overview-and-quick-search.aspx?from2=search1.asp&](http://www.cms.gov/medicare-coverage-database/overview-and-quick-search.aspx?from2=search1.asp&) or the manual website

SelectHealth Community Care (Medicaid)

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Summary of Medical Information

For individuals who have cancer who receive molecular characterization of tumor using cell-free tumor DNA (ctDNA), the evidence includes case series and systematic reviews of these case series. Relevant outcomes are overall survival, disease-specific survival, test accuracy and validity, morbid events, and medication use. Ultrasensitive methods to detect mutations from ctDNA have been developed, but there is limited evidence on the analytic validity of these methods. There is a need for further optimization and standardization of testing methods. Clinical validity consists of case series that report correlations between mutations detected in ctDNA with mutations detected in tumor tissue. Results have shown variable results for clinical sensitivity. Although some reports have suggested that clinical sensitivity may be high, this finding has not been consistent. Published studies have consistently reported high clinical specificity; however, most study population have consisted of small and heterogeneous, and it is not known to what degree mutations detected by ctDNA are representative of the primary tumor. Published studies reporting clinical outcomes and/or clinical utility are lacking. The uncertainties concerning clinical
validity and clinical utility preclude conclusions about whether mutation analysis by ctDNA can replace mutation analysis in tissue. The evidence is insufficient to determine the effects of the technology on health outcomes.

Billing/Coding Information

CPT CODES

Covered for the Indications Listed Above

0239U  Targeted genomic sequence analysis panel, solid organ neoplasm, cell-free DNA, analysis of 311 or more genes, interrogation for sequence variants, including substitutions, insertions, deletions, select rearrangements, and copy number variations

0242U  Targeted genomic sequence analysis panel, solid organ neoplasm, cell-free circulating DNA analysis of 55-74 genes, interrogation for sequence variants, gene copy number amplifications, and gene rearrangements

81479  Unlisted molecular pathology procedure

86152  Cell enumeration using immunologic selection and identification in fluid specimen (eg, circulating tumor cells in blood);

86153  ; physician interpretation and report, when required

86849  Unlisted immunology procedure

Not Covered for the Indications Listed Above

0326U  Targeted genomic sequence analysis panel, solid organ neoplasm, cell-free circulating DNA analysis of 83 or more genes, interrogation for sequence variants, gene copy number amplifications, gene rearrangements, microsatellite instability and tumor mutational burden

0334U  Oncology (solid organ), targeted genomic sequence analysis, formalin-fixed paraffin embedded (FFPE) tumor tissue, DNA analysis, 84 or more genes, interrogation for sequence variants, gene copy number amplifications, gene rearrangements, microsatellite instability and tumor mutational burden

HCPCS CODES

No specific codes identified

Key References


Disclaimer
Genetic Disease Policies, Continued

Genetic Testing: Cell-free Tumor DNA/Liquid Biopsy, continued

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GENETIC TESTING: GENETIC MUTATION ANALYSIS UTILIZING SOLID TUMOR TISSUE

Policy # 570
Implementation Date: 7/28/15
Review Dates: 10/20/16, 7/21/17, 9/18/18, 8/8/19, 10/21/20
Revision Dates: 7/21/17, 10/26/18, 11/29/18, 8/23/19, 10/18/19, 9/23/20, 1/29/21

Related Medical Policies:
#581 Genetic Testing: Cell-Free Tumor DNA/Liquid Biopsy

Description
Cancer is a complex genetic disease influenced by both inherited variants in germline DNA and somatic alterations acquired during formation of the tumor. Prior to tumor genome sequencing, many genes that play a role in cancer were discovered through studies of the germline. Linkage studies in families with inherited, typically childhood cancers, identified rare germline mutations in genes related to DNA damage repair, RAS signaling, or PIK3 signaling. In contrast to childhood cancers, adult tumors have largely been considered ‘sporadic’; however, mounting evidence points to a potentially substantial influence from the germline.

Somatic genetic testing for the purpose of cancer management guidance is a rapidly evolving field of molecular medicine. Genetic testing of a solid or hematologic tumor can provide important information regarding the prognosis, risk for recurrence, or help predict tumor response to chemotherapeutic agents. In addition, genetic testing of tissue (e.g., blood) or stool, for evidence of a tumor is becoming an important tool in the early detection of cancer. While this is an area of rapid and ongoing research, clinical validity and utility is proven for only a subset of companion diagnostic genetic tests at this time.

Commercial Plan Policy/CHIP (Children’s Health Insurance Program)

Application of coverage criteria is dependent upon an individual's benefit coverage at the time of the request.

SelectHealth covers multi-marker tumor panels using next-generation sequencing in the diagnosis and treatment of cancer as a method to guide the selection of therapeutic agents for malignant tumors in limited circumstances.

Members must meet one (A, B, C, or D) of the following to be eligible for next-generation sequencing:

A. Member is considering participating in a clinical trial* intended to assess the effectiveness of targeted therapies based on tumor marker, OR
B. Next-generation sequencing ≤ 50 genes can be performed in non-small cell lung cancer (NSCLC) when tissue is limited.

Disclaimer:
1. Policies are subject to change without notice.
2. Policies outline coverage determinations for SelectHealth Commercial, SelectHealth Advantage (Medicare/CMS) and SelectHealth Community Care (Medicaid/CHIP) plans. Refer to the “Policy” section for more information.
Genetic Disease Policies, Continued

Genetic Testing: Genetic Mutation Analysis Utilizing Solid Tumor Tissue, continued

OR

C. Next-generation sequencing ≥ 50 genes can be performed in non-small cell lung cancer (NSCLC) regardless of stage of cancer;

OR

D. For the evaluation of tumor mutation burden (TMB) and pembrolizumab (Keytruda) is being considered. If pembrolizumab is inclusive for this cancer per FDA-approved indication or NCCN recommendation, then this test is not medically necessary.

*Clinical trial must meet one (i−iii) of the following clinical conditions:

i. Any advanced stage III or IV solid tumors*, or
ii. All lymphomas, or
iii. Multiple myeloma

SelectHealth Advantage (Medicare/CMS)

Coverage is determined by the Centers for Medicare and Medicaid Services (CMS); if a coverage determination has not been adopted by CMS, and InterQual criteria are not available, the SelectHealth Commercial policy applies. For the most up-to-date Medicare policies and coverage, please visit their search website http://www.cms.gov/medicare-coverage-database/overview-and-quick-search.aspx?from2=search1.asp& or the manual website

SelectHealth Community Care (Medicaid)

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Summary of Medical Information

Molecular profiling for malignant tumors catalogues specific biomarker information and generates potential treatment options. The personalized tumor molecular profiling services or tests addressed in this document are similar in that they all take an individual's tumor tissue and, from it, produce a molecular profile of the tumor and a list of potential therapies. However, their individual testing methods vary from matching over-expressed genes with drugs to more complex systems biology approaches.

Foundation CDx uses next generation sequencing: “…to interrogate the entire coding sequence of 236 cancer-related genes (3,769 exons) plus 47 introns from 19 genes frequently altered or rearranged in cancer.” Foundation CDx helps match the genomic alterations present in a tumor with specific targeted therapies or clinical trials. Recent small studies (Drilon, 2013; Lipson, 2012; Vignot, 2013) have investigated next-generation sequencing in individuals with lung cancer. Others have used next-generation sequencing in those with breast cancer (Ross, 2013a); colorectal cancer (Lipson, 2012), ovarian cancer (Ross, 2013b), and prostate cancer (Beltran, 2013). Limitations of these studies include small sample sizes.

The most widely used of the tumor molecular profiles has been the Target Now Molecular Profiling Service (Caris Life Sciences). According to the Caris Life Sciences website, their tumor profiling service is
now being promoted as the Molecular Intelligence™ Service. The published literature addressing these services is limited. Von Hoff and colleagues (2010) evaluated 86 individuals with refractory metastatic cancer. Progression-free survival (PFS) using a treatment regimen selected by Target Now molecular profiling of a malignant tumor was compared with the PFS of the most recent treatment regimen on which the individual experienced progression. A molecular target was detected in 84 of 86 (98%) participants. A total of 86 (78.6%) individuals were treated according to the molecular profile results with 18 of the 86 (27%) having a PFS ratio (defined as PFS on molecular profile–selected therapy or PFS on prior therapy) of greater than or equal to 1.3 (95% confidence interval [CI], 17% to 38%; P=0.007).

An editorial (Doroshow, 2010) accompanying the study reported that the trial had a number of significant limitations, including uncertainty surrounding the achievement of time to progression (the study's primary endpoint), and a lack of a randomized design. Additional limitations include a small number of participants and lack of duplication of study results by an independent dataset. GeneKey and OncInsights have even less validation. To date, there are no studies in the published literature specifically addressing these tests.

In a related study examining intratumor heterogeneity, Gerlinger and colleagues (2012) obtained multiple spatially separated biopsy samples from primary renal carcinomas and associated metastatic sites of 4 individuals. Intratumor heterogeneity was characterized using immunohistochemical analysis, profiling of messenger ribonucleic acid (mRNA) expression, and mutation functional analysis. An unexpected finding of this study revealed intratumor heterogeneity at the RNA-expression level, with gene expression signatures of good and poor prognosis detected in different regions of the same tumor. The authors concluded that genomics analyses from single tumor biopsy specimens may underestimate the mutational burden of heterogeneous tumors. It was also noted that this may explain difficulties encountered in the validation of oncology biomarkers owing to sampling bias, contribute to Darwinian selection of preexisting drug-resistant clones, and predict therapeutic resistance.

Molecular profiling has also been investigated for gastric cancer. Lei and colleagues (2013) sought to identify subtypes of gastric adenocarcinomas with particular biological properties and responses to chemotherapy and targeted agents. Gene expression patterns among 248 gastric tumors were compared. Three major subtypes of gastric adenocarcinoma were identified: proliferative, metabolic, and mesenchymal. Tumors of the proliferative subtype had high levels of genomic instability, TP53 mutations, and DNA hypomethylation. Cancer cells of the metabolic subtype were more sensitive to 5-fluorouracil than the other subtypes. Also, in two independent groups of subjects, those with tumors of the metabolic subtype appeared to have greater benefits with 5-fluorouracil treatment. Tumors of the mesenchymal subtype contain cells with features of cancer stem cells, and cell lines of this subtype were particularly sensitive to phosphatidylinositol 3-kinase-AKT-mTOR inhibitors in vitro. The authors concluded that if study results are confirmed and extended in future studies, the classification of gastric adenocarcinomas reported here could guide development of therapies tailored to the molecular subtypes.

In 2012, Tsimberidou and colleagues developed a personalized medicine program at a single facility in the context of early clinical trials. Their goal was to observe whether molecular analysis of advanced cancer and use of targeted therapy to counteract the effects of specific aberrations would be associated with improved clinical outcomes. Participants with advanced or metastatic cancer refractory to standard therapy underwent molecular profiling. A total of 175 subjects were treated with matched therapy, and the overall response rate was 27%. Of the 116 subjects treated with non-matched therapy, the response rate was 5%. The median time-to-failure was 5.2 months for those on matched therapy versus 2.2 months on non-matched therapy. At a median of 15 months follow-up, median survival was 13.4 months versus 9.0 months in favor of matched therapy.

Jameson and colleagues in 2012 performed a small pilot study investigating multi-omic molecular profiling (MMP) for the selection of breast cancer treatment. MMP treatment recommendations were selected in 25 cases and original treatment plans were revised accordingly. Partial responses were reported in 5/25 (25%), stable disease in 8/25 (32%) and 9/25 had no disease progression at 4 months. This study was limited by its small size and non-randomization. A large randomized prospective trial is needed for further evaluation. Primarily marketed to researchers, Life Technologies Inc. offers several variations of their Ion Torrent™ Next Generation Sequencing Ion AmpliSeq™ panels, according to the company website. The Ion AmpliSeq Comprehensive Cancer Panel analyzes more than 400 cancer-related genes and tumor suppressor genes. The Ion AmpliSeq Cancer Hotspot Panel v2 analyzes the “hotspot” regions of 50 cancer-related and tumor suppressor genes.

The nonrandomized study by Haslem et al. in 2016 adds some support to NGS from both the clinical utility and cost-effectiveness standpoint. In their retrospective matched cohort study of 72 patients (36 tested and 36 matched controls), the precision medicine treated cohort had longer progression-free
survival than did the control group (22.0 vs 12-week, p = .002) and had similar weekly costs ($4,665 vs $5000). The study is small, but the findings warrant validation in a larger prospective study. Some studies are finding a high rate of clinical actionability, at least in terms of tumors found to have mutations for which there is a therapy. Hirshfield and coworkers in 2016 found that 96% (88/92) patients with rare refractory tumors had at least one mutation that triggered a guided therapy in 35% of cases, but this study did not report on the effect of this therapy.

Other studies (also small) have been less supportive. Blumenthal et al. in 2016 reported use in 43 patients with glioblastoma. In 13 of these an actionable target was found but none responded to the therapy. Grenader et al. in 2016 studied 30 patients with advanced tumors using tumor sequencing. Ten of the patients received treatments based on genomic profiling. Of these only 3 benefited. Median progression-free survival in this small cohort was actually worse in the profile-guided group (12 weeks) compared to the control group (48 weeks).

In summary, there is a growing body of evidence which though insufficient to support the general use of molecular profiling to guide treatment decisions for all malignant tumors, provides a basis for allowing limited coverage of this testing in support of advancing current clinical knowledge and potentially improving patient outcomes.

**Billing/Coding Information**

**CPT CODES**

**Covered if above criteria met**

- **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

- **0037U** Targeted genomic sequence analysis, solid organ neoplasm, DNA analysis of 324 genes, interrogation for sequence variants, gene copy number amplifications, gene rearrangements, microsatellite instability and tumor mutational burden

- **0048U** Oncology (solid organ neoplasia), DNA, targeted sequencing of protein-coding exons of 468 cancer-associated genes, including interrogation for somatic mutations and microsatellite instability, matched with normal specimens, utilizing formalin-fixed paraffin-embedded tumor tissue, report of clinically significant mutation(s)

- **81445** Targeted genomic sequence analysis panel, solid organ neoplasm, DNA analysis, 5-50 genes (e.g., 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

- **81455** Targeted genomic sequence analysis panel, solid organ or hematolymphoid neoplasm, DNA and RNA analysis when performed, 51 or greater genes (e.g., ALK, BRAF, CDKN2A, CEBPA, DNMT3A, EGFR, ERBB2, EZH2, FLT3, IDH1, IDH2, JAK2, KIT, KRAS, MLL, NPM1, NRAS, MET, NOTCH1, PDGFRA, PDGFRB, PGR, PIK3CA, PTEN, RET), interrogation for sequence variants and copy number variants or rearrangements, if performed

- **81479** Unlisted molecular pathology procedure

**Not Covered**

- **0250U** Oncology (solid organ neoplasia), targeted genomic sequence DNA analysis of 505 genes, interrogation for somatic alterations (SNVs [single nucleotide variant], small insertions and deletions, one amplification, and four translocations), microsatellite instability and tumor-mutation burden

- **81450** Targeted genomic sequence analysis panel, hematolymphoid neoplasm or disorder, DNA and RNA analysis when performed, 5–50 genes (e.g., 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
**Key References**


