MOLECULAR PROFILING TO GUIDE CANCER TREATMENT

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INSTRUCTIONS FOR USE

This protocol provides assistance in interpreting UnitedHealthcare benefit plans. When deciding coverage, the enrollee specific document must be referenced. The terms of an enrollee's document (e.g., Certificate of Coverage (COC) or Evidence of Coverage (EOC)) may differ greatly. In the event of a conflict, the enrollee's specific benefit document supersedes this protocol. All reviewers must first identify enrollee eligibility, any federal or state regulatory requirements and the plan benefit coverage prior to use of this Protocol. Other Protocols, Policies and Coverage Determination Guidelines may apply. UnitedHealthcare reserves the right, in its sole discretion, to modify its Protocols, Policies and Guidelines as necessary. This protocol is provided for informational purposes. It does not constitute medical advice. This policy does not govern Medicare Group Retiree members.

UnitedHealthcare may also use tools developed by third parties, such as the MCG™ Care Guidelines, to assist us in administering health benefits. The MCG™ Care Guidelines are intended to be used in connection with the independent professional medical judgment of a qualified health care provider and do not constitute the practice of medicine or medical advice.

COMMERCIAL & MEDICAID COVERAGE RATIONALE

Molecular profiling using multiplex or next generation sequencing (NGS) technology is medically necessary for guiding systemic chemotherapy in patients with metastatic stage IV non-small cell lung cancer (NSCLC) when the following criteria are met:

- Molecular profiling using multiplex or NGS technology to test for epidermal growth factor receptor (EGFR) mutations, human epidermal growth factor receptor 2 (HER2) mutations, RET rearrangements, and anaplastic lymphoma kinase (ALK) gene arrangements.
Molecular profiling using multiplex or NGS technology is not medically necessary for ALL other indications. There is insufficient evidence in the clinical literature demonstrating that molecular profiling has a role in clinical decision-making or has a beneficial effect on health outcomes for other indications. Further studies are needed to determine the analytic validity, clinical validity and/or clinical utility of molecular profiling using multiplex or NGS technology for other indications.

MEDICARE COVERAGE RATIONALE

Medicare does not have a National Coverage Determination (NCD) specifically for molecular profiling using multiplex or next generation sequencing (NGS) technology to guide cancer treatment(s).


MolDX: Breast Cancer Index℠ Genetic Assay (L36314)

Coverage Indications, Limitations, and/or Medical Necessity
This policy limits coverage of the Breast Cancer Index (aka BCI) (bioTheranostics) to patients that meet the following criteria:

- Post-menopausal female with non-relapsed, ER+ breast cancer, and
- Was lymph node negative, and
- Is completing five (5) years of tamoxifen therapy, and
- Patient must be eligible for consideration of extended endocrine therapy based on published clinical trial data or practice guidelines, and
- Physician or patient is concerned about continuing anti-hormonal therapy because of documented meaningful toxicity or possible significant patient-specific side effects, and

• The test results will be discussed with the patient (including the limitations of the testing method, the risks and benefits of either continuing or stopping the therapy based on the test, and current cancer management guidelines).

Claims for BCI testing will be denied when testing does not meet all of the above criteria.
Background
The body of evidence for the adjuvant endocrine treatment of ER+ breast cancer is continuing to evolve. Most recently, with the results of the ATLAS and aTTom trials, tamoxifen for an additional 5 years of adjuvant therapy has been added to the standard of care regimens as a NCCN recommendation to reduce late recurrences (defined as cancer recurring after 5 years of therapy).

The BCI assay (which was initially developed before ATLAS and aTTom data was available), uses PCR to interrogate selected proliferation-related and endocrine signaling-related genes, and may identify a subset of postmenopausal women who are at increased risk of late relapses for ER+ breast cancer and who may derive a greater benefit from extended hormone therapy. Current guidelines recommend adjuvant hormone therapy for postmenopausal patients with ER+ disease consisting of tamoxifen for 10 years (5 years initially and then strong consideration for an additional 5 years based on ATLAS and aTTom trials), aromatase Inhibitor (AI) for 5 years (ATAC), tamoxifen for 5 years followed by AI for 5 years (MA.17), or AI for 2-3 years followed by tamoxifen to complete 5 years. Extended (> 5 years) hormone therapy in each scenario is based on large randomized trials. Although there can be significant side effects of these therapies in some women, generally the side affect profile is manageable when compared to the significant benefit of these interventions. The optimal sequence and duration of AI therapy, the benefit of tamoxifen after prolonged AI therapy, and result of tamoxifen use beyond 10 years remain unknown.

Although the BCI assay may identify a group of patients at highest risk of recurrence after 5 years post surgery it cannot be used independently without consideration of other clinical factors (such as age, tumor size and number of lymph nodes involved). A significant concern exists as to whether the assay can identify any group at such a low risk that it is safe to depart from a strong expert recommendation and safely stop therapy. Data from the prospective-retrospective review of the ATAC trial (trans-ATAC) shows a late recurrence risk in all patients, independent of risk category (BCI-H, BCI-I or BCI-L). Although the BCI-L group is lower than the others, it is still roughly 5% and the annual risk of relapse steadily climbs in the years after stopping adjuvant endocrine therapy at 5 years. Given the substantial number of patients at risk in the BCI-Low group (over 60%), the total number of women at risk that may benefit from extended hormone therapy at the end of 5 years of tamoxifen therapy is not negligible.

Analysis of the prospective-retrospective review of MA.17 data, extended adjuvant therapy may be helpful in all groups studied. Although the H/I-low group did not meet statistical significance, the recurrence rate was decreased from 13% to 9% with the use of extended letrozole therapy with a relative risk reduction of 30%. In the H/I-High group the relative risk reduction was similar at 38%, which did meet statistical significance.

The risk BCI-C model developed from the trans-ATAC data provides a continuous risk predicted by the test. The risk curve is flat in only the very lowest BCI values. Starting around BCI of 2 (in the middle of the BCI-Low category), there is a linear increase in recurrence risk. At the 95% confidence interval (CI), the risk in some individuals categorized in the BCI-low group could be as high as 20%. Due to the data complexity, there is a significant possibility that a physician might consider all BCI-L patients at negligible risk, and thus not consider extended hormone therapy and consequently lead women from the NCCN recommended interventions. Given the low toxicity and low cost of extended therapy, the false sense of security could deny many women from lifesaving therapy.
In women who have received an AI for 5 years, data is lacking on the utility of extended adjuvant hormonal therapy.

The data defined benefit of the BCI test appears to be when a woman is having significant side effects or has other concerns regarding adjuvant tamoxifen therapy and is opposed to taking more than 5 years of tamoxifen or starting on an AI (letrazole) after tamoxifen. If the toxicity or concern of extending hormone therapy is significant then it may be reasonable to use the BCI test to help make a risk/benefit decision with the patient on continued adjuvant endocrine therapy. In the majority of patients, the toxicity of extended hormone therapy is tolerable especially in those who already have been on adjuvant hormonal therapy for 5 years. Even with the small benefit in all patients the MA.17, ATLAS and aTTom trials all demonstrated benefit from longer endocrine therapy. These trials established that the low toxicity of hormone therapy allows its long-term usage.

BCI Use for Newly Diagnosed Breast Cancer Patients:
It is possible that the BCI assay could identify patients who would most benefit from chemotherapy in the upfront setting, but this benefit has not been adequately studied. In one observational study the BCI risk recurrence level correlated with complete response to chemotherapy, but this trial does not provide sufficient evidence to warrant consideration for decision making in the newly diagnosed breast cancer patient. Further data will need to be published before the benefit of BCI can be confirmed or refuted in this setting.

Molecular Diagnostic Tests (MDT) (L35160) effective 10/01/2015
Coverage Indications, Limitations, and/or Medical Necessity
As of September 16, 2013 Noridian, working together with the CMS MolDx contractor accepts coverage determinations made by CMS MolDx contractor through the MolDX Program, which are discussed in the details of this policy.

This coverage policy provides the following information:

- defines tests required to register for a unique identifier
- defines tests required to submit a complete technical assessment (TA) for coverage determination
- defines the payment rules applied to covered tests that are not reported with specific CPT codes
- lists some examples of specific covered tests that have completed the registration and TA process and meet Medicare’s reasonable and necessary criteria for coverage. This listing is not inclusive.

Tests evaluated through the application process and/or technical assessment will be reviewed to answer the following questions:

- Is the test performed in the absence of clinical signs and symptoms of disease?
- Will the test results provide the clinician with information that will improve patient outcomes and/or change physician care and treatment of the patient?
- Will the test results confirm a diagnosis or known information?
- Is the test performed to determine risk for developing a disease or condition?
- Will risk assessment change management of the patient?
- Is there a diagnosis specific indication to perform the test?
- Is the test performed to measure the quality of a process or for Quality Control/Quality Assurance (QC/QA), i.e., a test to ensure a tissue specimen matches the patient?

**MDT Policy Specific Definitions**

**MDT**: Any test that involves the detection or identification of nucleic acid(s) (DNA/RNA), proteins, chromosomes, enzymes, cancer chemotherapy sensitivity and/or other metabolite(s). The test may or may not include multiple components. A MDT may consist of a single mutation analysis/identification, and/or may or may not rely upon an algorithm or other form of data evaluation/derivation.

**LDT**: Any test developed by a laboratory developed without FDA approval or clearance.

**Applicable Tests/Assays**

In addition to the MDT definition, this coverage policy applies to all tests that meet at least one of the following descriptions:

- All non-FDA approved/cleared laboratory developed tests (LDT)
- All modified FDA-approved/cleared kits/tests/assays
- All tests/assays billed with more than one CPT code to identify the service, including combinations of method-based, serology-based, and anatomic pathology codes
- All tests that meet the first three bullets and are billed with an NOC code

**Unique Test Identifier Requirement**

Because the available language in the HCPCS and CPT manuals to describe the pathology and laboratory categories and the tests included in those categories are not specific to the actual test results provided, all MDT services must include an identifier as additional claim documentation. Test providers must apply for an identifier specific to the applicable test and submit the test assigned identifier with the claim for reimbursement. The assigned identifier will provide a crosswalk between the test’s associated detail information on file and the submitted claim detail line(s) required to adjudicate each test’s claim. The unique identifier limits the need to submit the required additional information about the test on each claim.

Laboratory providers who bill MDT services must register services with the following methods:

- Z-Code Identifier Application
- Palmetto GBA Test Identifier (PTI) Application.

**Technology Assessments (TA)**

Noridian agrees that all test/assay clinical information will be reviewed through the MolDX Program to determine if a test meets Medicare’s reasonable and necessary requirement. Labs must submit a comprehensive dossier on each new test/assay prior to claim submission. Noridian and the MolDX Program will only cover and reimburse tests that demonstrate analytical and clinical validity, and clinical utility at a level that meets the requirement of Reasonable and Necessary. Prior to completion of this TA and published coverage determination, Noridian will consider all claims submitted for tests that have been submitted to the MolDX contractor for review on an individual consideration basis while the test or assay is being reviewed.

**Covered Tests**

Please refer to the MolDX website [http://www.palmettogba.com/MolDX](http://www.palmettogba.com/MolDX) for specific coding and billing information.
The following tests have completed the MolDX Program application review and/or technical assessment and meet Medicare reasonable and necessary criteria:

- Afirma™
- Allomap
- Avise PG
- Cancer TYPE ID
- cobas® 4800 BRAF V600
- cobas® EGFR
- ConfirmMDx Epigenetic Molecular Assay
- Corus® CAD
- HERmark®
- MammaPrint™
- Oncotype DX® Breast
- Oncotype DX® Colon
- Progensa® PCA3
- therascreen EGFR
- therascreen KRAS
- Tissue of Origin
- THXID™BRAF V600E/K Test
- Vectra™ DA
- Vysis

Other tests/assays may be covered by separate Noridian policy. In addition the CPT codes listed under Group 1 are covered. If a test is not listed, it may be covered under separate Noridian policy or it has not been approved for coverage as it has either not been vetted by the MolDx contractor or has been found to be considered statutorily excluded. A list of approved and excluded tests may be found on the MolDX website. Noridian will be adding a copy of such articles to our website in the near future.

To obtain a unique identifier for a test, to request a technical assessment, or for additional MolDX Program information, go to the MolDX home page, PalmettoGBA.com/MolDX.

Both Noridian and the CMS MolDX contractor expect laboratory providers to follow test indications published by the developer.

**MolIDX-CCD: Prolaris™ Prostate Cancer Genomic Assay (L36348)**

**Coverage Indications, Limitations, and/or Medical Necessity**

Noridian will provide limited coverage for the Prolaris™ prostate cancer assay (Myriad, Salt Lake City, UT) to help determine which patients with early stage, needle biopsy proven prostate cancer, can be conservatively managed rather than treated with definitive surgery or radiation therapy.

**Background**

In 2014, nearly 233,000 men in the US will be diagnosed with prostate cancer, which accounts for 14% of all new cancer diagnosis. More than 29,000 men will die from this disease representing 5% of all cancer deaths. Gratefully 98.9% of men are surviving at 5 years.
Many individuals do not need treatment for their prostate cancer in as much as their prognosis is excellent even without treatment. However, physicians and patients struggle to know who can safely be observed versus the subgroup that needs more aggressive treatment to achieve cure, and recognize that definitive treatment for localized prostate cancer can have lifelong morbidities.

Traditionally, clinicopathologic characteristics are utilized to determine risk and subsequent treatment. Several nomograms have been introduced to try to determine who is at risk of developing metastatic disease and who, if treated early, could avoid this outcome. A representative one taken from the NCCN (and AUA), divides early prostate cancer into several groups based initially on life expectancy, with a second stratification using clinical exam, reassessment of life expectancy, biopsy (Gleason score), PSA and imaging. These groups are detailed below:

<table>
<thead>
<tr>
<th>Risk Category</th>
<th>Very Low</th>
<th>Low</th>
<th>Intermediate</th>
<th>High</th>
</tr>
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<tbody>
<tr>
<td><strong>Clinicopathologic Findings</strong></td>
<td>T1c AND Gleason score ≤ 6 AND PSA ≤ 10 ng/mL AND &lt; 3 prostate cores with tumor AND ≤ 50% tumor in any core AND PSA density of &lt; 0.15 ng/mL/g</td>
<td>T1-T2a AND Gleason score ≤ 6 AND PSA ≤ 10 ng/mL</td>
<td>T2b-T2c OR Gleason score = 7 OR PSA 10-20 ng/mL</td>
<td>T3a OR Gleason Score 8-10 OR PSA &gt; 20 ng/mL</td>
</tr>
<tr>
<td><strong>Treatment Options</strong></td>
<td>Active Surveillance RT or Brachy RP (± LND)</td>
<td>Active Surveillance RT or Brachy RP (± LND)</td>
<td>RP (± LND) RT or Brachy ± Adj Horm</td>
<td>RT + Adj Horm RT + Brachy RP + LND ± RT, ADT</td>
</tr>
<tr>
<td><strong>≥ 20 y life expectancy</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>≥ 10 y life expectancy</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>&lt; 10 y life expectancy</strong></td>
<td>Observation</td>
<td>Observation</td>
<td>RT or Brachy ± Adj Horm</td>
<td>N/A</td>
</tr>
</tbody>
</table>

Table 1: NCCN 2014 V2 - Localized Prostate Cancer Risk Stratification and Treatment (PSA – Prostate Specific Antigen; RT – Radiation Therapy; RP – Radical Prostatectomy; LND – lymph node dissection; Adj Horm – Adjuvant Androgen Deprivation)
Use of these stratification and treatment approaches has led to high cure rates for early stage prostate cancer. Yet it is widely accepted that many men are over-treated to achieve the cure rate. In the PIVOT trial men with early prostate cancer, initially randomized to radical prostectomy or observation, showed that over 12 years there was no difference in absolute mortality between the groups. However, this study was hampered by several problems including:

- Only 731 of 5023 eligible patients chose to participate in the study based on randomization criteria.
- In the group randomized to RP: only 85% of the men received definitively therapy (79% surgery; 6% other).
- In the observational group: 10% of the observation group received RP initially and additional 20% eventual received definitive treatment.
- Despite broad inclusion criteria, > 50% of patients had a PSA of <10 (median PSA of 7) and had biopsy proven T1c disease. Although there were a significant number of patients with Gleason score ≥7 (25%), 40% of men were classified initially as being low risk; and 30% were intermediate.

Although subgroups were small, it appears that high-risk groups (including those with PSA > 10) benefitted from RP. Furthermore, there was a trend for the intermediate risk patients to benefit from RP as well. The small number of patients willing to enter the study, and the high rate of crossover (both initially and subsequently) demonstrates the difficulty of doing observation trials in the United States.

**Prolaris™ Prostate Cancer Assay**

**Test Description**

Prolaris™ is an RNA based assay measuring the expression of 31 cell cycle progression (CCP) genes and 15 “housekeeping” genes that act as internal controls and normalization standards in each patient sample. The assay is performed on formalin fixed paraffin-embedded (FFPE) prostate cancer blocks. The assay results are reported as a numerical score along with accompanying interpretive information.

**Test Performance**

The clinical performance of this assay was assessed in several retrospective validation studies. These include two British cohorts of men diagnosed with prostate cancer on biopsy and then treated conservatively; and an additional cohort of men diagnosed by TURP and conservatively managed. Further validation was performed in various other cohorts including men who underwent radical prostatectomy, and men treated with definitive radiotherapy. The Prolaris™ cell cycle progression score (CCP) was found to be an independent and more robust prognostic factor for disease related death than traditional clinicopathologic factors although disease stage and Gleason score consistently portended a more negative prognostic picture.

Due to the difficulty in obtaining prospective data in early prostate cancer (outcomes take decades to develop, hard to accrue patients to a conservatively managed arm in the US), and given the unmet need, clinical utility can be extrapolated from this retrospective data. Doing so is not without shortcomings. It is unclear how the British cohorts were followed or who went on to receive definitive therapy inside the observation groups. The U.K. standard of care for treating these prostate cancer patients is different. In the U.S. conservatively managed patients is not the common occurrence. Furthermore, the long time period to determine outcomes and the lack of tissue specimens make review of a U.S. cohort unlikely if not impossible for many years.
In several of the published cohorts including the conservatively managed patients, multivariate analysis identified CCP score and Gleason score as the only values that consistently identify increased risk of death from prostate cancer. It also should be noted that the cancer related death rate in these retrospective studies of conservatively managed patients was much greater than would be expected in the United States with 19.3% of the patients with the lowest CCP succumbing to disease. Subset analysis suggests that if the patients with higher risk disease (Gleason score > 7; higher stage) had received definitive treatment (like the current standard in the US) the rate succumbing to disease would likely be substantially better.

The potential usefulness of this test is that it allows physicians to determine which patients with early prostate cancer are candidates for active surveillance or observation and are more likely to have a good outcome without needing to receive definitive treatment.

Criteria for Coverage
The Prolaris™ assay is covered only when the following clinical conditions are met:

- Needle biopsy with localized adenocarcinoma of prostate (no clinical evidence of metastasis or lymph node involvement), and
- FFPE prostate biopsy specimen with at least 0.5 mm of cancer length, and
- Patient Stage as defined by the one of the following:
  - Very Low Risk Disease (T1c AND Gleason Score ≤ 6 AND PSA ≤ 10 ng/mL AND <3 prostate cores with tumor AND ≤ 50% cancer in any core AND PSA density of <0.15 ng/mL/g) OR
  - Low Risk Disease (T1-T2a AND Gleason Score ≤ 6 AND PSA ≤ 10 ng/mL), and
- Patient has an estimated life expectancy of greater than or equal to 10 years, and
- Patient is a candidate for and is considering conservative therapy and yet and would be eligible for definitive therapy (radical prostatectomy, radiation therapy or brachytherapy), and
- Result will be used to determine treatment between definitive therapy and conservative management, and
- Patient has not received pelvic radiation or androgen deprivation therapy prior to the biopsy, and
- Test is ordered by a physician certified in the Myriad Prolaris™ Certification and Training Registry (CTR), and
- Patient is monitored for disease progression according to established standard of care, and
- Physician must report the development of prostate cancer metastasis or prostate cancer deaths in patients not treated definitively who were deemed low risk by the assay.

Certification and Training Registry (CTR) Program
Because of the complicated nature of management decisions utilizing the Prolaris™ assay and the potential for adverse harm to patients if the test is not used appropriately, testing must be furnished only by physicians who are enrolled in a MolDx approved Myriad Prolaris™ CTR program. This serves to assure the appropriate selection of patients, compliance with management decisions and stringent follow up to ensure the benefits of the test outweigh its risks. As part of this requirement Myriad will provide to the MolDX Contractor reports every 6 months in a mutually agreed upon format.
Important Note: Please also review local carrier Web sites in addition to the Medicare Coverage database on the Centers for Medicare and Medicaid Services’ Website.

DEFINITIONS

Genetic Testing: A type of test that is used to determine the presence or absence of a specific gene, set of genes, genetic mutations or duplications, to help diagnose a disease, screen for specific health conditions, predict course of disease, identify and create more effective and targeted cancer therapies, and for other purposes.

Indels: Short insertions and deletions of the genome

Mutation: An alternation in a DNA sequence.

Next-Generation Sequencing: Sequencing technologies, such as massively parallel sequencing and microarray analysis that allow rapid sequencing of large numbers of segments of DNA.

DESCRIPTION OF SERVICES

Non-small cell lung cancer (NSCLC) is responsible for approximately 85% of all lung cancer types and includes predominantly adenocarcinomas and squamous cell carcinomas. Treatment options include surgery, radiation, and chemotherapy, depending on an individual’s medical condition and disease stage. Although cytotoxic chemotherapy is a standard treatment approach, targeted therapies based on genetic alterations in the tumor may be appropriate in select patients. Identifying mutations in oncogenes associated with NSCLC may help clinicians determine which patients are more likely to benefit from a particular targeted therapy. These oncogenes include epidermal growth factor receptor (EGFR), Kirsten rat sarcoma (KRAS), anaplastic lymphoma kinase (ALK), human epidermal growth factor receptor 2 (HER2) mutations and RET rearrangements. Mutations in the EGFR, KRAS, and ALK oncogenes are generally almost always mutually exclusive, meaning that mutations of only one of the three genes occur within any individual tumor (NCCN, 2016).

Molecular profiling can identify the mutations associated with targeted therapy response or resistance. As a result, predictive molecular profiling is being used more frequently in clinical practice to guide cancer treatment, thereby increasing the likelihood that patients may benefit from selected treatment (NCCN, 2016). Next-generation sequencing (NGS) broadly describes the various DNA sequencing technologies that allow rapid sequencing of large DNA segments, including entire genomes. NGS has led to the advent of genetic testing that incorporate broad panels, which analyze multiple genes for multiple mutations at the same time. Examples of NGS include massively parallel sequencing and microarray analysis.

In particular, the FoundationOne® test or assay (Foundation Medicine, Inc.) uses parallel DNA sequencing to identify alterations and rearrangements in solid tumor cancers using NGS. In general, the FoundationOne test is intended to identify molecular growth drivers of cancers and help physicians identify appropriate and effective targeted cancer therapies in patients diagnosed with cancer. According to the manufacturer, the test “is designed to interrogate the entire coding sequence of 315 cancer-related genes plus introns from 28 genes often rearranged or altered in cancer.” NGS can be
performed on double stranded DNA from specimens obtained via surgical or needle biopsy. Test results are provided in a report that identifies various gene alterations. The report also includes an interpretation of the findings and information about potentially relevant targeted therapies and clinical trials to inform clinical treatment decisions. The complete list of genes identified by the FoundationOne assay are listed on the company website. (FoundationOne, 2015).

New York became the first state to establish a licensure program for laboratories performing clinical testing. Public Health Law established the Clinical Laboratory Reference System to promote the public health and safety by requiring the licensure of clinical laboratories and by requiring that the performance of all procedures performed by clinical laboratories meet minimum standards accepted and approved by the department. The Clinical Laboratory Reference System is administered by the New York State Department of Health’s public health laboratory, the Wadsworth Center. Mandated activities include collaborative research, method development and test approval, and inspection and proficiency testing to ensure that laboratory services provided meet performance standards for good patient care. See the following website for more information: http://wadsworth.org/regulatory/clep (Accessed July 2016).

**CLINICAL EVIDENCE**

**Non-small Cell Lung Cancer (NSCLC)**

Frampton and colleagues (2013) conducted an analytical and clinical validation study to evaluate massively parallel DNA sequencing using the FoundationOne assay to characterize base substitutions, indels, copy number alterations, and selected fusions across 287 cancer-related genes from routine formalin-fixed and paraffin-embedded (FFPE) clinical specimens. The authors implemented a validation strategy with reference samples of pooled cell lines that modeled key drivers of test accuracy, including mutant allele frequency, indel length and amplitude of copy change. Test sensitivity achieved was 95% to 99% across alteration types, with high specificity (positive predictive value [PPV] >99%). The authors confirmed accuracy using 249 FFPE cancer specimens characterized by established assays. Application of the test to 2,221 clinical cases revealed clinically actionable alterations in 76% of tumors, three times the number of actionable alterations detected by current diagnostic tests. This study did not evaluate the clinical utility of such findings in improving care and outcome of patients by tailoring treatments or predicting response to treatment. Hence, it is important to note that the clinical utility of genomic profiling using massively parallel DNA sequencing remains unknown. In addition, study authors colleagues did not categorize the data regarding sensitivity, specificity, and positive predictive value (PPV) by cancer type, so it is not clear how well the test performed among patients with NSCLC.

Drilon et al. (2015) identified 31 patients with lung adenocarcinoma with a ≤ 15 pack-year smoking history whose tumors previously tested "negative" for alterations in 11 genes (mutations in EGFR, ERBB2, KRAS, NRAS, Braf, MAP2K1, PIK3CA, and AKT1 and fusions involving ALK, ROS1, and RET) via multiple non-NGS methods. A broad, hybrid-capture–based NGS assay (FoundationOne) was performed (4,557 exons of 287 cancer-related genes and 47 introns of 19 genes frequently rearranged in solid tumors). A genomic alteration with a corresponding targeted therapeutic based on the National Comprehensive Cancer Network (NCCN) guidelines for non–small cell lung cancer (NSCLC) was found in 26% (n = 8 of 31) of patients. The drivers identified in tumors from these 8 patients were EGFR G719A, BRAF V600E, SOCS5-ALK, HIP1-ALK, CD74-ROS1, KIF5B-RET (n
Molecular Profiling to Guide Cancer Treatment

Six of these patients went on to receive targeted therapy. The authors noted that the reasons for non-detection of these genomic alterations via non-NGS testing can be varied such as lower sensitivity, complex rearrangements undetectable by standard FISH, and, possibly, heterogeneity between different tumor biopsies or sites. They concluded that broad, hybrid capture-based NGS assays have the potential to uncover clinically actionable genomic alterations in never smokers or ≤15 pack-year smokers whose lung adenocarcinomas do not harbor a potential driver via non-NGS testing.

The National Comprehensive Cancer Network (NCCN) guidelines for NSCLC (NCCN, 2016) strongly endorse the use of broad molecular profiling to detect certain rare mutations using multiplex or NGS. The guidelines specifically report that “EGFR and ALK testing be conducted as part of broad molecular profiling.” The NCCN Panel states that such testing would ensure that patients receive the most effective available targeted treatment for NSCLC (NCCN, 2016).

A National Institute for Health and Care Excellence (NICE) guidance document for epidermal growth factor receptor tyrosine kinase (EGFR-TK) mutation testing in adults with locally advanced or metastatic non-small-cell lung cancer states that there is insufficient evidence to make a recommendation on next generation sequencing for EGFR-TK mutations. NICE noted that research is currently being conducted on this method to evaluate panels of lung cancer genes. Study authors concluded that NGS is likely to be an important method for identifying EGFR-TK mutations in the future (NICE, 2013).

Professional Societies
Conclusions of other leading experts and well-regarded research organizations regarding the value of the NGS technology as a method of genomic profiling are uncertain regarding the use of molecular profiling to match NSCLC patients to appropriate cancer therapies.

American College of Chest Physicians (ACCP)
In an evidence-based clinical practice guideline for the diagnosis and management of lung cancer, the ACCP states that the epidemiology of lung cancer is an active field. According to the ACCP, researchers in the area of molecular epidemiology are making advances in the identification of biomarkers of risk and for early detection, although these are not yet mature enough for clinical application (Detterbeck et al., 2013).

Other Cancers
Molecular profiling has many theoretical clinical applications in the field of oncology. Published clinical studies have addressed the use of molecular profiling for the following:

- Adrenocortical cancer (Ross et al., 2014a)
- Breast cancer (Ganesan et al., 2014; Wheler et al., 2014)
- Gastric and gastrointestinal cancer (Ali et al., 2015, Vignot et al., 2015; Miura et al., 2014)
- Head and neck cancer (Chung et al., 2015)
- Melanoma (Wheler et al., 2015; Hutchison et al., 2013)
- Ovarian cancer (Ross et al., 2013)
- Pancreatic cancer (Chmielecki et al., 2014; Chantrill et al., 2015)
- Prostate cancer (Beltran et al., 2013)
- Unknown primary cancer site (Ross et al., 2015; Gatalica et al., 2014)
• Urothelial carcinoma (Ross et al., 2014b; Millis et al., 2015)

There is insufficient published evidence to support the use of molecular profiling for these cancers. The main evidence deficiencies for molecular profiling for these cancers are insufficient data on analytical validity, clinical validity, and clinical utility. Published studies evaluating molecular profiling for these conditions are mainly case reports or case series with a limited number of patients.

Johnson et al. (2014) retrospectively assessed demographics, next-generation sequencing (NGS) results, and therapies received for patients undergoing targeted NGS using the FoundationOne test. Co-primary endpoints were the percentage of patients with targeted therapy options uncovered by mutational profiling and the percentage who received genotype-directed therapy.

Samples from 103 patients were tested; most frequently breast carcinoma (26%), head and neck cancers (23%), and melanoma (10%). Most patients (83%) were found to harbor potentially actionable genetic alterations, involving cell-cycle regulation (44%), phosphatidylinositol 3-kinase-AKT (31%), and mitogen-activated protein kinase (19%) pathways. With median follow-up of 4.1 months, 21% received genotype-directed treatments, most in clinical trials (61%), leading to significant benefit in several cases. The most common reasons for not receiving genotype-directed therapy were selection of standard therapy (35%) and clinical deterioration (13%). The authors concluded that mutational profiling using a targeted NGS panel identified potentially actionable alterations in a majority of advanced cancer patients. The assay identified additional therapeutic options and facilitated clinical trial enrollment. According to the authors, there are many unanswered questions regarding implementation of this technology. First, based on this study, some patients with potentially actionable alterations did not respond to genotype-directed therapy, highlighting the still underdeveloped understanding of the pathophysiologic implications of many genetic alterations. Second, the most appropriate indications for obtaining targeted NGS are not yet clear. Third, randomized studies in the future will need to assess whether targeted NGS improves overall outcomes.

Kato et al. (2015) investigated the clinical correlates of CDK4/6 and CDKN2A/B abnormalities in diverse malignancies. Patients with various cancers who underwent molecular profiling by targeted next generation sequencing (Foundation Medicine; 182 or 236 cancer-related genes) were reviewed. Of 347 patients analyzed, 79 (22.8%) had aberrant CDK 4/6 or CDKN2A/B. Only TP53 mutations occurred more frequently than those in CDK elements. Aberrations were most frequent in glioblastomas (21/26 patients; 81%) and least frequent in colorectal cancers (0/26 patients). Aberrant CDK elements were independently associated with EGFR and ARID1A gene abnormalities. CDK aberrations were associated with poor overall survival. In multivariate analysis, PTEN and TP53 aberrations were independently associated with poorer survival; CDK aberrations showed a trend toward worse survival. There was also a trend toward worse progression-free survival (PFS) with platinum-containing regimens in patients with abnormal CDK elements (3.5 versus 5.0 months). In conclusion, aberrations in the CDK pathway were some of the most common in cancer and independently associated with EGFR and ARID1A alterations. Patients with abnormal CDK pathway genes showed a trend toward poorer survival, as well as worse PFS on platinum-containing regimens. According to the authors, further investigation of the prognostic and predictive impact of CDK alterations across cancers is warranted. This study was limited because it was performed retrospectively in a single institution with a relatively limited number of patients.
In a technology report for multiple molecular testing of cancers to identify targeted therapies, the Blue Cross Blue Shield Association (BCBSA) stated that the use of multiple molecular testing to assist in making treatment decisions for cancer patients is rapidly evolving. Strong evidence of clinical effectiveness of this approach is not available, and a number of issues remain to be solved, particularly patient selection. According to the report, different approaches may be taken to the interpretation of multiple molecular marker panels. Clinical trials to determine the effectiveness of this approach will be challenging to complete (BCBSA TEC, 2013).

### U.S. FOOD AND DRUG ADMINISTRATION (FDA)

Commercially available laboratory-developed genomic profile panel tests are not subject to FDA approval. Laboratories that perform genomic profile tests are regulated under the Clinical Laboratory Improvement Amendments (CLIA) Act of 1988. More information is available at: [http://www.fda.gov/medicaldevices/deviceregulationandguidance/ivdregulatoryassistance/ucm124105.htm](http://www.fda.gov/medicaldevices/deviceregulationandguidance/ivdregulatoryassistance/ucm124105.htm) (Accessed July 2016)

### APPLICABLE CODES

The following list(s) of procedure and/or diagnosis codes is provided for reference purposes only and may not be all inclusive. Listing of a code in this policy does not imply that the service described by the code is a covered or non-covered health service. Benefit coverage for health services is determined by the member specific benefit plan document and applicable laws that may require coverage for a specific service. The inclusion of a code does not imply any right to reimbursement or guarantee claim payment. Other Policies and Coverage Determination Guidelines may apply.

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<td>Targeted genomic sequence analysis panel, solid organ neoplasm, DNA analysis, 5-50 genes (eg, ALK, BRAF, CDKN2A, EGFR, ERBB2, KIT, KRAS, NRAS, MET, PDGFR, PDGFRB, PGR, PIK3CA, PTEN, RET), interrogation for sequence variants and copy number variants or rearrangements, if performed</td>
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*CPT® is a registered trademark of the American Medical Association*
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REFERENCES


ECRI Institute. Product Brief. FoundationOne (Foundation Medicine, Inc.) Genomic Profiling Test for Guiding Targeted Therapy for Cancer. August 2014.


**PROTOCOL HISTORY/REVISION INFORMATION**

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The foregoing Health Plan of Nevada/Sierra Health & Life Health Operations protocol has been adopted from an existing UnitedHealthcare coverage determination guideline that was researched, developed and approved by the UnitedHealthcare Coverage Determination Committee.