

# MOLECULAR PROFILING TO GUIDE CANCER TREATMENT

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Table of Contents	Page
<a href="#">INSTRUCTIONS FOR USE</a> .....	1
<a href="#">CONDITIONS OF COVERAGE</a> .....	1
<a href="#">BENEFIT CONSIDERATIONS</a> .....	2
<a href="#">COVERAGE RATIONALE</a> .....	2
<a href="#">DEFINITIONS</a> .....	2
<a href="#">APPLICABLE CODES</a> .....	2
<a href="#">DESCRIPTION OF SERVICES</a> .....	3
<a href="#">CLINICAL EVIDENCE</a> .....	4
<a href="#">U.S. FOOD AND DRUG ADMINISTRATION</a> .....	6
<a href="#">REFERENCES</a> .....	6
<a href="#">POLICY HISTORY/REVISION INFORMATION</a> .....	7

Related Policies
<ul style="list-style-type: none"> <li><a href="#">Gene Expression Tests</a></li> <li><a href="#">Chemosensitivity and Chemoresistance Assays in Cancer</a></li> </ul>

## INSTRUCTIONS FOR USE

This Clinical Policy provides assistance in interpreting Oxford benefit plans. Unless otherwise stated, Oxford policies do not apply to Medicare Advantage members. Oxford reserves the right, in its sole discretion, to modify its policies as necessary. This Clinical Policy is provided for informational purposes. It does not constitute medical advice. The term Oxford includes Oxford Health Plans, LLC and all of its subsidiaries as appropriate for these policies.

When deciding coverage, the member specific benefit plan document must be referenced. The terms of the member specific benefit plan document [e.g., Certificate of Coverage (COC), Schedule of Benefits (SOB), and/or Summary Plan Description (SPD)] may differ greatly from the standard benefit plan upon which this Clinical Policy is based. In the event of a conflict, the member specific benefit plan document supersedes this Clinical Policy. All reviewers must first identify member eligibility, any federal or state regulatory requirements, and the member specific benefit plan coverage prior to use of this Clinical Policy. Other Policies may apply.

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.

## CONDITIONS OF COVERAGE

Applicable Lines of Business/ Products	This policy applies to Oxford Commercial plan membership.
Benefit Type	General benefits package
Referral Required (Does not apply to non-gatekeeper products)	No
Authorization Required (Precertification always required for inpatient admission)	Yes
Precertification with Medical Director Review Required	Yes <sup>1</sup>
Applicable Site(s) of Service (If site of service is not listed, Medical Director review is required)	Laboratory
Special Considerations	<sup>1</sup> Precertification with review by a Medical Director or their designee is required.

## BENEFIT CONSIDERATIONS

Before using this policy, please check the member specific benefit plan document and any federal or state mandates, if applicable.

### **Essential Health Benefits for Individual and Small Group**

For plan years beginning on or after January 1, 2014, the Affordable Care Act of 2010 (ACA) requires fully insured non-grandfathered individual and small group plans (inside and outside of Exchanges) to provide coverage for ten categories of Essential Health Benefits ("EHBs"). Large group plans (both self-funded and fully insured), and small group ASO plans, are not subject to the requirement to offer coverage for EHBs. However, if such plans choose to provide coverage for benefits which are deemed EHBs, the ACA requires all dollar limits on those benefits to be removed on all Grandfathered and Non-Grandfathered plans. The determination of which benefits constitute EHBs is made on a state by state basis. As such, when using this policy, it is important to refer to the member specific benefit plan document to determine benefit coverage.

## COVERAGE RATIONALE

### **Molecular profiling using multiplex or next generation sequencing (NGS) technology is proven and medically necessary for guiding systemic chemotherapy in patients with metastatic stage IV non-small cell lung cancer (NSCLC) when both of 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**

See the National Comprehensive Cancer Network (NCCN) Clinical Practice Guideline for Non-Small Cell Lung Cancer, available at [www.nccn.org](http://www.nccn.org), for updates regarding oncogenes used in molecular profile testing for NSCLC. (Accessed April 21, 2016)

- **The laboratory providing molecular profiling testing services must be approved by the New York State Department of Health for performing the molecular profile test.**

See the following web site for a list of clinical laboratories holding a New York State Department of Health permit in the category of oncology molecular and cellular tumor markers:

<http://www.wadsworth.org/labcert/lep/CategoryPermitLinks/CategoryListing.htm> (Accessed April 21, 2016)

### **Molecular profiling using multiplex or NGS technology is unproven and 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.

## 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.

## 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 may apply.

CPT Code	Description
81445	Targeted genomic sequence analysis panel, solid organ neoplasm, DNA analysis, and RNA analysis when performed, 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.
81450	Targeted genomic sequence analysis panel, hematolymphoid neoplasm or disorder, DNA analysis, 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.
81455	Targeted genomic sequence analysis panel, solid organ or hematolymphoid neoplasm, DNA analysis, 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.
81599	Unlisted multianalyte assay with algorithmic analysis

*CPT® is a registered trademark of the American Medical Association*

ICD-10 Diagnosis Code	Description
C34.00	Malignant neoplasm of unspecified main bronchus
C34.01	Malignant neoplasm of right main bronchus
C34.02	Malignant neoplasm of left main bronchus
C34.10	Malignant neoplasm of upper lobe, unspecified bronchus or lung
C34.11	Malignant neoplasm of upper lobe, right bronchus or lung
C34.12	Malignant neoplasm of upper lobe, left bronchus or lung
C34.2	Malignant neoplasm of middle lobe, bronchus or lung
C34.30	Malignant neoplasm of lower lobe, unspecified bronchus or lung
C34.31	Malignant neoplasm of lower lobe, right bronchus or lung
C34.32	Malignant neoplasm of lower lobe, left bronchus or lung
C34.80	Malignant neoplasm of overlapping sites of unspecified bronchus and lung
C34.81	Malignant neoplasm of overlapping sites of right bronchus and lung
C34.82	Malignant neoplasm of overlapping sites of left bronchus and lung
C34.90	Malignant neoplasm of unspecified part of unspecified bronchus or lung
C34.91	Malignant neoplasm of unspecified part of right bronchus or lung
C34.92	Malignant neoplasm of unspecified part of left bronchus or lung

## 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 Web site for more information: <http://www.wadsworth.org/regulatory/clep>. (Accessed April 8, 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  $\leq 15$  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 = 2), and CCDC6-RET. 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  $\leq 15$  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-regarding 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., Vignot et al., 2015; Miura et al., 2014)
- Head and neck cancer (Chung et al., 2015)
- Melanoma (Wheler et al., 2015; Hutchinson 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>. (Accessed April 21, 2016)

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The foregoing Oxford policy has been adapted from an existing UnitedHealthcare national policy that was researched, developed and approved by UnitedHealthcare Medical Technology Assessment Committee. [2016T0576C]

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## POLICY HISTORY/REVISION INFORMATION

Date	Action/Description
08/01/2016	<ul style="list-style-type: none"> <li>• Reformatted and reorganized policy; transferred content to new template</li> <li>• Updated/clarified coverage rationale:               <ul style="list-style-type: none"> <li>○ Replaced language indicating "molecular profiling using multiplex or next generation sequencing (NGS) technology is proven and medically necessary to guide systemic chemotherapy in patients with metastatic stage IV non-small cell lung cancer (NSCLC) when used to test <i>only</i> for epidermal growth factor receptor (EGFR) mutations, human epidermal growth factor receptor 2 (HER2) mutations, RET rearrangements, and anaplastic lymphoma kinase (ALK) gene arrangements" with "molecular profiling using multiplex or next</li> </ul> </li> </ul>

Date	Action/Description
	<p>generation sequencing (NGS) technology is proven and medically necessary <i>for guiding</i> systemic chemotherapy in patients with metastatic stage IV non-small cell lung cancer (NSCLC) when used 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”</p> <ul style="list-style-type: none"> <li>○ Replaced language indicating “molecular profiling using multiplex or NGS technology is unproven and not medically necessary <i>when the listed criteria are not met</i>” with “molecular profiling using multiplex or NGS technology is unproven and not medically necessary <i>for all other indications [not listed as proven/medically necessary]</i>”</li> <li>• Updated definitions: <ul style="list-style-type: none"> <li>○ Revised definition of “genetic testing”</li> <li>○ Removed definition of “molecular profiling”</li> </ul> </li> <li>• Updated supporting information to reflect the most current clinical evidence and references</li> <li>• Archived previous policy version CANCER 038.2 T2</li> </ul>