MEDICAL POLICY

MEDICAL POLICY DETAILS	
Medical Policy Title	**MOLECULAR PANEL TESTING OF TUMOR TISSUE TO IDENTIFY TARGETED THERAPIES FOR CANCERS (Excluding NSCLC and CRC)**
Policy Number	**2.02.51**
Category	**Laboratory Tests**
Effective Date	**12/21/17**
Revised Date	**12/21/18, 10/17/19**
Product Disclaimer	• *If a product excludes coverage for a service, it is not covered, and medical policy criteria do not apply.* • *If a commercial product (including an Essential Plan product) or a Medicaid product covers a specific service, medical policy criteria apply to the benefit.* • *If a Medicare product covers a specific service, and there is no national or local Medicare coverage decision for the service, medical policy criteria apply to the benefit.*

POLICY STATEMENT

I. Based on our criteria and assessment of the peer-reviewed literature, molecular panel testing to identify targeted cancer treatment is considered ***investigational***.

Refer to Corporate Medical Policy2.02.35 Molecular Analysis for Targeted Therapy of Non-Small Cell Lung Cancer (NSCLC)

Refer to Corporate Medical Policy2.02.41 Genotyping- RAS Mutation Analysis (KRAS/NRAS) in Metastatic Colorectal Cancer (CRC)

POLICY GUIDELINES

I. The Foundation One® CDx™ (Cambridge MA) panel includes sequencing of more than 300 cancer-related genes and select introns from another 25 genes as well as genomic signatures including microsatellite instability (MSI) and tumor mutational burden (TMB) using DNA isolated from formalin-fixed paraffin embedded (FFPE) tumor tissue specimens. Indications for testing include solid tumors of non-small cell lung cancer (NSCLC), colorectal cancer, breast, ovarian and melanoma. Typical turnaround time for testing is two weeks. FDA approval of the FoundationOne CDx™ was granted November 2017.

II. The Comprehensive Genomic Profiling Plus, (Caris Life Sciences, Irving, TX) panel uses multiple tumor profiling technologies to decode cancer such as immunohistochemistry (IHC), *in situ* hybridization, next-generation sequencing (NGS), Sanger sequencing, Pyro sequencing (PyroSeq), and fragment analysis (FA/Frag. analysis). Turnaround time for testing is 10-14 days.

III. The OmniSeq℠ Comprehensive panel test is a next-generation molecular sequencing assay that tests tumor DNA and RNA, identifying somatic variants in 144 genes to guide cancer therapeutic management. Test turnaround time is 10-15 days.

IV. The Federal Employee Health Benefit Program (FEHBP/FEP) requires that procedures, devices or laboratory tests approved by the U.S. Food and Drug Administration (FDA) may not be considered investigational and thus these procedures, devices or laboratory tests may be assessed only on the basis of their medical necessity.

DESCRIPTION

According to the Precision Medicine Initiative, precision medicine is "an emerging approach for disease treatment and prevention that takes into account individual variability in genes, environment, and lifestyle for each person. Precision medicine includes understanding how variations in our genes influence our health. Research has been directed to understand molecular variations in tumors from different cancer types so that drugs used to treat the tumors are “targeted” or directed to inhibit the function of the molecular alteration. The goal of precision medicine is to maximize efficiency

and minimize side effects of therapy. Some success has been achieved with the use of EGFR or ALK inhibitors in specific subtypes of non-small cell lung cancer and BRAF/MEK inhibitors in BRAFV600E-positive melanomas. However the benefits have not always translated for these same molecular variations in other cancers.

Molecular panel tests evaluate between 140-300 genes in tumor tissue for which there are only a small number of FDA-approved targeted therapy options. Molecular panel testing may be used to determine off-label drug therapy or whether or not a patient may be eligible for a clinical trial.

Currently molecular panel testing is limited to larger academic centers with only a small number of patients receiving testing. Of those patients with testing, only a small number will experience clinical utility (have a targeted therapy identified) and an even smaller number will experience clinical benefit.

RATIONALE

The ACCE framework is used to evaluate genetic tests which includes collecting, evaluating, interpreting, and reporting data about DNA (and related) testing for disorders with a genetic component in a format that allows policy makers to have access to up-to-date and reliable information for decision making. Elements of the frame include evaluation of the tests' analytic validity, clinical validity, clinical utility and associated ethical, legal and social implications. Studies published to evaluate the analytic validity of molecular panels for targeted therapy are lacking. However the panels are mainly performed using next-generation sequencing (NGS), which has a high analytic validity. As described in the Guidelines section of this policy, some of the tests utilize additional testing methods (e.g., IHC, Sanger sequencing) which also have high analytical validity.

It is difficult to determine the clinical validity of the molecular panels because of the different mutations and the large number of potential cancers for which they can be used. Testing each gene in the panel for each of the cancer types would require extensive research potentially taking many years to complete. Consequently the evidence on clinical validity of the molecular panels is insufficient to make any recommendations.

The evidence for clinical utility of molecular panel testing to direct targeted therapies in cancer patients has been conflicting. The SHIVA study, a randomized, open-label phase 2 trial, randomized patients with any kind of metastatic solid tumor refractory to standard of care (Le Tourneau, et al (2015)) to matched molecularly targeted treatment based on one of three molecular pathways (hormone receptor, PI3K/AKT/mTOR, RAF/MEK) (experimental group) or treatment at physician's choice (control group). At median follow-up of 11.3 months, Median progression-free survival was similar for both groups. Grade 3–4 adverse events were slightly higher in the experimental group. The authors concluded progression-free survival was not improved with the use of molecularly targeted agents outside their indications compared with treatment at physician's choice in heavily pretreated patients with cancer. Off -label use of molecularly targeted agents should be encouraged in clinical trials to assess predictive biomarkers of efficacy. the IMPACT study (2007), a phase I study at the University of Texas MD Anderson Cancer Center that assessed whether molecular analysis of advanced cancer and targeted therapy would be associated with improved clinical outcomes. Of the 1144 patients analyzed, 40.2% had one or more molecular aberration in their tumor. The patients with 1 aberration and matched therapy had a higher overall response rate (27%) compared to those patients who without matched therapy (5%). Patients with matched therapy had longer time-to-treatment failure (5.2 mos) and longer survival (13.4 mos) compared to those without matched therapy (2.2 mos and 9.0 mos, respectively). The author reports the IMPACT2 study (2014) which is a randomized study evaluating molecular profiling and targeted agents which includes clinical trials with immunotherapy, targeted therapy, and other therapeutic strategies designed for specific patients is underway. Studies have been limited by the small number of patients that have received molecularly targeted therapy and the small number of patients that have derived benefit from it.

The National Comprehensive Cancer Network (NCCN) guidelines do not contain recommendations for the general strategy of testing a tumor for a wide range of mutations. However there are specific genetic testing guidelines for individual cancers, based on situations where there is a known mutation-drug combination that has demonstrated benefits for that specific tumor type (e.g., NSCLC, ovarian cancer, colorectal cancer, and melanoma).

CODES

- *Eligibility for reimbursement is based upon the benefits set forth in the member's subscriber contract.*
- *CODES MAY NOT BE COVERED UNDER ALL CIRCUMSTANCES. PLEASE READ THE POLICY AND GUIDELINES STATEMENTS CAREFULLY.*
- *Codes may not be all inclusive as the AMA and CMS code updates may occur more frequently than policy updates.*

CPT Codes

Code	Description
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
81445	Targeted genomic sequence analysis panel, solid organ neoplasm, DNA analysis, and RNA analysis when performed, 5-50 genes (eg, 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 analysis, and RNA analysis when performed, 51 or greater genes (eg, 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
0037U **(E/I)**	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 (e.g., FoundationOne CDx™ (F1CDx)
0154U	FGFR3 (fibroblast growth factor receptor 3) gene analysis (ie, p.R248C [c.742C>T], p.S249C [c.746C>G], p.G370C [c.1108G>T], p.Y373C [c.1118A>G], FGFR3-TACC3v1, and FGFR3-TACC3v3) (therascreen® FGFR RGQ RT-PCR Kit, QIAGEN, QIAGEN GmbH) (effective 1/1/2020)

HCPCS Codes

Code	Description
No specific code(s)	

ICD10 Codes

Code	Description
C18.0-C21.8	Malignant neoplasm of colon, rectosigmoid junction, rectum, and anus and anal canal (code range)
C25.0-C25.9	Malignant neoplasm of pancreas (code range)
C34.10 - C34.12	Malignant neoplasm of upper lobe, bronchus or lung (code range)
C34.30-C34.32	Malignant neoplasm of lower lobe, bronchus or lung (code range)
C34.80-C34.82	Malignant neoplasm of overlapping sites of bronchus and lung (code range)
C34.90-C34.92	Malignant neoplasm of unspecified part of bronchus or lung (code range)
C50.011-C50.929	Malignant neoplasm of breast (code range)
C56.1-C56.9	Malignant neoplasm of ovary (code range)
C61	Malignant neoplasm of prostate
C78.5	Secondary malignant neoplasm of large intestine and rectum
C79.60-C79.62	Secondary malignant neoplasm of ovary (code range)
C79.81	Secondary malignant neoplasm of breast
D05.00-D05.02	Lobular carcinoma in situ of breast (code range)
D05.10-D05.12	Intraductal carcinoma in situ of breast (code range)
D05.80-D05.92	Carcinoma in situ of breast, specified, unspecified (code range)
D07.30-D07.39	Carcinoma in situ of other and unspecified female genital organs (code range)
D40.0	Neoplasm of uncertain behavior of prostate

REFERENCES

Au TH, et al. Personalized and precision medicine: integrating genomics into treatment decisions in gastrointestinal malignancies. J Gastrointest Oncol 2017;8(3):387-404.

BlueCross BlueShield Association. Expanded molecular panel testing of cancers to identify targeted therapies. Medical Policy Reference Manual Policy #2.04.115. 2018 Oct 10.

Coyne G, et al. Defining precision: the precision medicine initiative trials NCI-IMPACT and NCI-MATCH. Curr Probl Cancer 2017; 41(3):182-194.

Deverka P, et al. Generating and evaluating evidence of the clinical utility of molecular diagnostic tests in oncology. Genet Med 2016 Aug;18(8):780-787.

Hilal T, et al. Comprehensive genomic profiling in routine clinical practice leads to a low rate of benefit from genotype-directed therapy. BMC Cancer 2017 Aug 30;17(1):602.

Kieler M, et al. Interim analysis of a real-world precision medicine platform for molecular profiling of metastatic or advanced cancers: MONDTI. ESMO Open 2019 Jul 17;4(4):e000538.

Lee DH. Practical issues of biomarker-assisted targeted therapy in precision medicine and immune-oncology era. ESMO Open 2018 Jun12;3(Suppl 1):e000379.

Le Tourneau C, et al. Molecularly targeted therapy based on tumour molecular profiling versus conventional therapy for advanced cancer (SHIVA): a multicentre, open-label, proof-of-concept, randomized controlled phase 2 trial. Lancet Oncol 2015 Oct;16(13):1324-1334.

Liang X, et al. Targeted next-generation sequencing identifies clinically relevant somatic mutations in a large cohort of inflammatory breast cancer. Breast Cancer Res 2018 Aug 7;20(1):88.

McCrea EM, et al. Precision medicine applications in prostate cancer. Ther Adv Med Oncol 2018;10(1):1-13.

Mohapatra SS, et al. Precision medicine for CRC patients in the veteran population: state-of-the-art, challenges and research directions. Dig Dis Sci 2018 May;63(5):1123-1138.

Salgado R, et al. Societal challenges of precision medicine: bringing order to chaos. Eur J Cancer 2017 Aug 30:84:325-334.

Santa-Maria CA, et al. Impact of tissue-based genomic profiling on clinical decision making in the management of patients with metastatic breast cancer at academic centers. Breast Cancer Res Treat 2017 Nov;166(1):179-184.

Thewes B, et al. Fear of cancer recurrence in an era of personalized medicine. J Clin Oncol. 2017 Oct 10;35(29):3275-3278.

Tsimberidou AM. Initiative for molecular profiling and advanced cancer therapy and challenges in the implementation of precision medicine. Curr Probl Cancer 2017 May - Jun;41(3):176-181.

Vivot A, et al. Pharmacogenomic biomarkers as inclusion criteria in clinical trials of oncology-targeted drugs: a mapping of ClinicalTrials.gov. Genet Med. 2016 Aug;18(8):796-805.

Weinberg BA, et al. Molecular profiling of biliary cancers reveals distinct molecular alterations and potential therapeutic targets. J Gastrointest Oncol 2019;10(4):652-662.

Zhu J, et al. Clinical utility of FoundationOne tissue molecular profiling in men with metastatic prostate cancer. Urol Oncol 2019 Jul 18 [Epub ahead of print].

*Key Article

KEY WORDS

Molecular Panel Testing, Targeted Therapy, Foundation One, Caris Life Sciences, OmniSeq, PyroSeq

CMS COVERAGE FOR MEDICARE PRODUCT MEMBERS

There is a Decision Memo for Next Generation Sequencing (NGS) for Medicare Beneficiaries with Advanced Cancer. Please refer to the following LCD website for Medicare Members:

https://www.cms.gov/medicare-coverage-database/details/nca-decision-memo.aspx?NCAId=290&bc=AAAAAAAAACAA&&utm_campaign=FoundationOne%20CDx&utm_source=hs_email&utm_medium=email&utm_content=61525882&_hsenc=p2ANqtz-_RlYQJUaVsqZ4Mg0L3KyI-D3c8sEtU-RkxTdCGIMf5qy6Qq-SAqTqlVvcS_hLXWFSG6cDEeCAAQLqbistIEakGsrAl5A&_hsmi=61525882

There is currently a Local Coverage Determination (LCD) for Molecular Pathology Procedures**.** Please refer to the following LCD website for Medicare Members: https://www.cms.gov/medicare-coverage-database/details/lcd-details.aspx?LCDId=35000&ver=131&CntrctrSelected=298*1&Cntrctr=298&s=41&DocType=Active&bc=AAgAAAQBAAAA&