BlueCross BlueShield of Alabama

Name of Policy:

Expanded Molecular Panel Testing of Cancers to Identify Targeted Therapies

Policy #: 540
Category: Laboratory

Latest Review Date: October 2017
Policy Grade: B

Background/Definitions:

As a general rule, benefits are payable under Blue Cross and Blue Shield of Alabama health plans only in cases of medical necessity and only if services or supplies are not investigational, provided the customer group contracts have such coverage.

The following Association Technology Evaluation Criteria must be met for a service/supply to be considered for coverage:

1. *The technology must have final approval from the appropriate government regulatory bodies;*
2. *The scientific evidence must permit conclusions concerning the effect of the technology on health outcomes;*
3. *The technology must improve the net health outcome;*
4. *The technology must be as beneficial as any established alternatives;*
5. *The improvement must be attainable outside the investigational setting.*

Medical Necessity means that health care services (e.g., procedures, treatments, supplies, devices, equipment, facilities or drugs) that a physician, exercising prudent clinical judgment, would provide to a patient for the purpose of preventing, evaluating, diagnosing or treating an illness, injury or disease or its symptoms, and that are:

1. *In accordance with generally accepted standards of medical practice; and*
2. *Clinically appropriate in terms of type, frequency, extent, site and duration and considered effective for the patient's illness, injury or disease; and*
3. *Not primarily for the convenience of the patient, physician or other health care provider; and*
4. *Not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of that patient's illness, injury or disease.*

Description of Procedure or Service:

There is interest in treating cancers by targeting biological "pathways" that are characterized by specific genetic markers. Genetic panel testing offers the potential to evaluate a large number of genetic markers at a single time to identify treatments that target specific pathways. Some individual markers have established benefit in certain types of cancers; they are not addressed in this evidence review. Rather, this review focuses on "expanded" panels, which are defined as panels that test a wide variety of genetic markers in cancers without regard for whether specific targeted treatment has demonstrated benefit. This approach may result in a treatment different than that usually selected for a patient based on the type of cancer and its stage.

Traditional Therapeutic Approaches to Cancer

Tumor location, grade, stage and the patient's underlying physical condition have traditionally been used in clinical oncology to determine the therapeutic approach to a specific cancer, which could include surgical resection, ionizing radiation, systemic chemotherapy, or combinations thereof. Currently some 100 different types are broadly categorized according to the tissue, organ, or body compartment in which it arises. Most treatment approaches in clinical care were developed and evaluated in studies that recruited subjects and categorized results based on this traditional classification scheme.

This traditional approach to cancer treatment does not reflect the wide diversity of cancer at the molecular level. While treatment by organ type, stage, and grade may demonstrate statistically significant therapeutic efficacy overall, only a subgroup of patients may actually derive clinically significant benefit. It is unusual for a cancer treatment to be effective for all patients treated in a traditional clinical trial. Spear et al analyzed the efficacy of major drugs used to treat several important diseases. They reported heterogeneity of therapeutic responses ranging from a low of 25% for cancer chemotherapeutics, with response rates for most drugs falling in the range of 50% to 75%. The low rate for cancer treatments is indicative of the need for better identification of characteristics associated with treatment response and better targeting of treatment in order to have higher rates of therapeutic responses.

Targeted Cancer Therapy

Much of the variability in clinical response may result from genetic variations. Within each broad type of cancer there may be a large amount of variability in the genetic underpinnings of the cancer. Targeted cancer treatment refers to the identification of genetic abnormalities present in the cancer of a particular patient, and the use of drugs that target the specific genetic abnormality. Using genetic markers, cancers can be further classified by "pathways" defined at the molecular level. An expanding number of genetic markers have been identified. Dienstmann et al categorize these findings into three classes. These are: (1) genetic markers that have a direct impact on care for the specific cancer of interest, (2) genetic markers that may be biologically important but are not currently actionable, and (3) genetic markers of uncertain importance.

A smaller number of individual genetic markers fall into the first category, i.e., have established utility for a particular cancer type. Utility of these markers has generally been demonstrated by randomized controlled trials (RCTs) that select patients with the marker, and report significant improvements in outcomes with targeted therapy compared with standard therapy. This evidence review does not apply to the individual markers that have demonstrated efficacy. According to

recent National Comprehensive Cancer Network (NCCN) guidelines, the following markers have demonstrated utility for predicting treatment response to targeted therapies for the specific cancers listed:

- Breast cancer
  - *HER2 (ERBB2)*
- Colon cancer
  - *RAS* variants *(KRAS, NRAS)*
  - *BRAF* c1799T>A
- Non-small-cell lung cancer (NSCLC)
  - *EGFR*
  - *ALK/ROS1*
  - *KRAS*
  - *RET*
  - *MET*
- Metastatic melanoma
  - *BRAF* v600
  - *KIT*
- Ovarian Cancer
  - *BRCA* (germline)
- Chronic myeloid leukemia
  - *BRC-ABL*
- Gastrointestinal stromal tumors
  - *C-KIT*

Testing for these individual variants with established utility is not covered herein. In some cases, limited panels may be offered that are specific to one type of cancer (e.g., a panel of several markers for non-small-cell lung cancer). This policy is also not intended to address the use of these cancer-specific panels that include a few variants. Rather, the intent is to address expanded panels that test for many potential variants that do not have established efficacy for the specific cancer in question.

When advanced cancers are tested with expanded molecular panels, most patients are found to have at least 1 potentially pathogenic variant. The number of variants varies widely by types of cancers, different variants included in testing, and different testing methods among the available studies. In a 2015 study, 439 patients with diverse cancers were tested with a 236-gene panel. A total of 1,813 molecular alterations were identified, and almost all patients (420/439, 96%) had at least 1 molecular alteration. The median number of alterations per patient was 3, and 85% of patients (372/439) had two or more alterations. The most common alterations were in the genes *TP53* (44%), *KRAS* (16%), and *PIK3CA* (12%).

Some evidence is available on the generalizability of targeted treatment based on a specific variant among cancers that originate from different organs. There are several examples of variant-directed treatment that was effective in one type of cancer but ineffective in another. For example, targeted therapy for epidermal growth factor receptor (*EGFR*) variants has been successful in non-small-cell lung cancer but not in trials of other cancer types. Treatment with tyrosine kinase inhibitors based on variant testing has been effective for renal cell carcinoma, but

has not demonstrated effectiveness for other cancer types tested. "Basket" studies, in which tumors of various histologic types that share a common genetic variant are treated with a targeted agent, also have been performed. One such study was published in 2015 by Hyman et al. In this study, 122 patients with *BRAF* V600 variants in nonmelanoma cancers were treated with vemurafenib. The authors reported that there appeared to be anti-tumor activity for some but not all cancers, with the most promising results seen for non-small cell lung cancer, Erdheim-Chester disease, and Langerhans'-cell histiocytosis.

Expanded Cancer Molecular Panels

Table 1 provides a select list of commercially available expanded cancer molecular panels.

Table 1. Commercially Available Molecular Panels for Solid and Hematologic Tumor Testing

Test (Manufacturer)	Tumor Type	No. of Genes Tested	Technology
FoundationOne® test (Foundation Medicine, Cambridge, MA)	Solid	315 cancer-related genes and introns from 28 genes	NGS
FoundationOne® Heme test (Foundation Medicine, Cambridge, MA)	Hematologic	406 cancer-related genes and selected introns from 31 genes involved in rearrangements	RNA sequencing
OnkoMatch™ (GenPath Diagnostics, Elmwood Park, NJ)	Solid	68 variants in 14 oncogenes and tumor suppressor genes	Multiplex PCR
GeneTrails® Solid Tumor Panel (Knight Diagnostic Labs, Portland, OR)	Solid	123 genes	
Tumor profiling service (Caris Molecular Intelligence through Caris Life Sciences, Irving, TX)	Solid	Up to 56 tumor-associated genes	NGS, IHC, FISH, Sanger sequencing, pyrosequencing, quantitative PCR, fragmentation analysis
SmartGenomics™ (PathGroup, Nashville, TN)	Solid and hematologic	160 genes and 126 gene fusions	NGS, cytogenomic array, other technologies
Guardant360 panel (GuardantHealth, Redwood City, CA)[14]	Solid		Digital sequencing
Paradigm Cancer Diagnostic (PcDx™) Panel (Paradigm, Phoenix, AZ)	Solid	186 alterations	NGS
Memorial Sloan Kettering-Integrated Mutation Profiling of Actionable Cancer Targets (MSK-IMPACT™; Memorial Sloan Kettering Cancer Center, New York, NY)	Solid	341 cancer-associated genes	NGS
TruSeq® Amplicon Panel (Illumina, San Diego, CA)	Solid	48 cancer-related genes	NGS
Illumina TruSight™ Tumor (Illumina, San Diego, CA)	Solid	26 cancer-related genes	NGS
Ion AmpliSeq™ Comprehensive Cancer Panel (Thermo Fisher Scientific, Waltham, MA)	Solid	>400 cancer-related genes and tumor suppressor genes	NGS
Ion AmpliSeq™ Cancer Hotspot	Solid	"Hotspot" regions of 50	NGS

Test (Manufacturer)	Tumor Type	No. of Genes Tested	Technology
Panel v2 (Thermo Fisher Scientific, Waltham, MA)		cancer-related and tumor suppressor genes	

FISH: fluorescence in situ hybridization; IHC: immunohistochemistry; NGS: next-generation sequencing; PCR: polymerase chain reaction

Policy:

The use of expanded cancer molecular panels as a method to guide the selection of therapeutic agents for malignant tumors/targeting cancer treatment does not meet Blue Cross and Blue Shield of Alabama's medical criteria for coverage and is considered **investigational**.

Blue Cross and Blue Shield of Alabama does not approve or deny procedures, services, testing, or equipment for our members. Our decisions concern coverage only. The decision of whether or not to have a certain test, treatment or procedure is one made between the physician and his/her patient. Blue Cross and Blue Shield of Alabama administers benefits based on the member's contract and corporate medical policies. Physicians should always exercise their best medical judgment in providing the care they feel is most appropriate for their patients. Needed care should not be delayed or refused because of a coverage determination.

Key Points:

The most recent literature review was updated through August 23, 2017.

The evaluation of a genetic test focuses on three main principles: (1) analytic validity (technical accuracy of the test in detecting a variant that is present or in excluding a variant that is absent); (2) clinical validity (diagnostic performance of the test [sensitivity, specificity, positive and negative predictive values] in detecting clinical disease); and (3) clinical utility (how the results of the diagnostic test will be used to change management of the patient and whether these changes in management lead to clinically important improvements in health outcomes).

Expanded Molecular Panel Testing for Cancer

Clinical Context and Test Purpose

The purpose of expanded molecular panel testing in individuals with cancer that has not responded to standard therapy is to identify somatic variants in tumor tissue to guide treatment decisions with targeted therapies for specific somatic variants.

The question addressed in this evidence review is: In individuals with cancer that has not responded to standard therapy, does the use of expanded molecular panel testing improve health outcomes?

The following PICOTS were used to select literature to inform this review.

Patients
The relevant population of interest includes individuals with cancer that has not responded to standard therapy.

Interventions
The relevant intervention of interest is expanded molecular panel testing.

Comparators
The relevant comparator of interest is next-line therapy without expanded molecular panel testing.

Outcomes
The beneficial outcomes of interest include progression-free survival (PFS) and overall survival (OS).

Timing
The time frame for outcomes measures varies from several months to several years.

Setting
Patients with cancer are actively managed by oncologists.

Analytic Validity
No published studies were identified that evaluated the analytic validity of these panels. The panels are performed primarily by next-generation sequencing, which has a high analytic validity. Some panels supplement the next-generation sequencing with additional testing methods, such as polymerase chain reaction (PCR), for intronic regions that are included as components of the panel. PCR is generally considered to have an analytic validity of more than 95%.

Information on analytic validity of the FoundationOne test was reported on the Foundation website. This site states that the analytic sensitivity is greater than 99% for base substitutions at a mutant allele frequency of 5% or more, 98% for indels at a mutant allele frequency of 10% or more, less than 95% for copy number alterations. It also reports an analytic specificity of more than 99%.

Clinical Validity
The clinical validity of the panels as a whole cannot be determined because of the many different variants and the large number of potential cancers for which they can be used. Clinical validity would need to be reported for each specific variant for a particular type of cancer. Because there are hundreds of different variants included in the panels and dozens of different cancer types, evaluation of the individual clinical validity for each pairing is beyond the scope of this review.

A major concern with clinical validity is differentiating variants that drive cancer growth from genetic variants that are not clinically important. It is expected that variants of uncertain significance will be very frequent with use of panels that include several hundred markers.

Comparison of cancer variants with matched normal tissue can provide evidence about whether variants are truly somatic cancer variants or whether they are incidental variants that do not have meaningful biologic activity. Jones et al performed comprehensive variant testing on 815 pairs of tumor tissue and matched normal tissue from patients with 15 different tumor types. Each sample was analyzed by both targeted sequencing and whole exome sequencing. A total of 105,672 somatic alterations were identified. After filtering for variants that were present in normal tissue, there were an average of 4.34 variants per patient on targeted analysis and 135 variants per patient on whole exome sequencing. After additional filtering using the COSMIC (Catalog of Somatic Mutations in Cancer) database, the authors estimated that 38% of the variants identified by targeted analysis were true positives and 62% were false positives; on whole exome analysis, 10% of variants were true positive and 90% were false positives.

Section Summary: Clinical Validity

The evidence on clinical validity of expanded panels is incomplete. Because of the large number of variants contained in expanded panels, it is not possible to determine clinical validity for the panels as whole. While some variants have a strong association with one or a small number of specific malignancies, none have demonstrated high clinical validity across a wide variety of cancers. Some have reported that after filtering variants by comparison with matched normal tissue and cancer variant databases, most identified variants are found to be false positives. Thus, it is likely that clinical validity will need to be determined for each variant and each type of cancer individually.

Clinical Utility

The most direct way to demonstrate clinical utility is through controlled trials that compare a strategy of cancer variant testing followed by targeted treatment with a standard treatment strategy without variant testing. Randomized trials are necessary to control for selection bias in treatment decisions, because clinicians may select candidates for variant testing based on clinical, demographic, and other factors. Outcomes of these trials would be the morbidity and mortality associated with cancer and cancer treatment. Overall survival is most important; cancer-related survival and/or PFS may be acceptable surrogates. A quality-of-life measurement may also be important if study designs allow for treatments with different toxicities in the experimental and control groups.

Systematic Reviews

Schwaederle et al published a meta-analysis of studies comparing personalized treatment with non-personalized treatment in 2015. Their definition of personalized treatment was driven by a biomarker, which could be genetic or nongenetic. Therefore, this analysis not only included studies of matched vs unmatched treatment based on genetic markers, but also included studies that personalized treatment based on nongenetic markers. A total of 111 arms of identified trials received personalized treatment, and they were compared with 529 arms that received non-personalized treatment. On random-effects meta-analysis, the personalized treatment group had a higher response rate (31% vs 10.5%, $p<0.001$), and a longer PFS (5.9 months vs 2.7 months,

p<0.001) compared with the non-personalized treatment group. Another meta-analysis (2015) by this group compared outcomes from 44 Food and Drug Administration-regulated drug trials that used a personalized treatment approach to 68 trials that used a non-personalized approach to cancer treatment. Response rates were significantly higher in the personalized treatment trials (48%) than in the non-personalized approach (23%; p<0.001). PFS was 8.3 months in the personalized treatment trials compared with 5.5 months in the non-personalized approach (p<0.001). For trials that used a personalized treatment strategy, OS was significantly longer (19.3 months) than in trials that did not (13.5 months, p=0.01). Personalized treatment in these studies was based on various biomarkers, both genetic and nongenetic.

Randomized Controlled Trials

The SHIVA trial was a randomized controlled trial of treatment directed by cancer variant testing versus standard care, with the first results published in 2015. In this study, 195 patients with a variety of advanced cancers refractory to standard treatment were enrolled from eight academic centers in France. Variant testing included comprehensive analysis for three molecular pathways, (hormone receptor pathway, PI3K/AKT/mTOR pathway, RAF/MEK pathway) performed by targeted next-generation sequencing, analysis of copy number variations, and hormone expression by immunochemistry. Based on the pattern of abnormalities found, nine different regimens of established cancer treatments were assigned to the experimental treatment arm (see Table 2). The primary outcome was PFS analyzed by intention-to-treat.

Table 2. Treatment Algorithm for Experimental Arm, From the SHIVA Trial

Molecular Abnormalities	Molecularly Targeted Agent
KIT, *ABL*, *RET*	Imatinib
AKT, mTORC1/2, *PTEN*, *PI3K*	Everolimus
BRAF V600E	Vemurafenib
PDGFRA/B, *FLT-3*	Sorafenib
EGFR	Erlotinib
HER-2	Lapatinib and trastuzumab
SRC, *EPHA2*, *LCK*, *YES*	Dasatinib
Estrogen receptor, progesterone receptor	Tamoxifen (or letrozole if contraindications)
Androgen receptor	Abiraterone

Ninety-nine patients were randomized to the targeted treatment group and 96 to standard care. Baseline clinical characteristics and tumor types were similar between groups. Molecular alterations affecting the hormonal pathway were found in 82 (42%) of 195 patients, alterations affecting the PI3K/AKT/mTOR pathway were found in 89 (46%) of 195 patients, and alterations affecting the RAF/MED pathway were found in 24 (12%) of 195 patients. After a median follow-up of 11.3 months, the median progression-free survival was 2.3 months (95% Cl 1.7 of 3.8 months) in the targeted treatment group versus 2.0 months (95% Cl 1.7-2.7 months) in the standard care group (hazard ratio 0.88, 95% Cl 0.65 of 1.19, p=0.41). Objective responses were reported for 4 (4.1%) of 98 assessable patients in the targeted treatment group versus 3 (3.4%) of 89 assessable patients in the standard care group. In subgroup analysis by molecular pathway, there were no significant differences in PFS between groups.

A 2017 crossover analysis of the SHIVA trial evaluated the PFS ratio from patients who failed standard of care therapy and crossed over from molecularly targeted agents (MTA) therapy to

treatment at physician's choice (TPC) or vice versa. The PFS ratio was defined as the PFS on MTA (PFSMTA) to PFS on TPC (PFSTPC) in patients who crossed over. Of the 95 patients who crossed over, 70 patients crossed over from the TPC to MTA arm while 25 patients crossed over from MTA to TPC arm. In the TPC to MTA crossover arm, 26 (37%) of patients and 15 (61%) of patients in the MTA to TPC arm had a PFSMTA/PFSTPC ratio greater than 1.3. The post hoc analysis of the SHIVA trial has limitations because it only evaluated a subset of patients from the original clinical trial but used each patient as his/her control by using the PFS ratio. The analysis would suggest that patients may have benefited from the treatment algorithm evaluated in the SHIVA trial.

Non-Randomized Controlled Trials

Numerous non-randomized studies have been published that use some type of a control. Some of these studies have a prospective, interventional design. In 2016, Wheler et al reported a prospective comparative trial of patients who had failed standard treatment and had been referred to their tertiary center for admission into Phase I trials. Comprehensive molecular profiling (Foundation One tumor panel) was performed on 339 patients, of whom 122 went on to a Phase I therapy that was matched to their genetic profile, and based on physician evaluation of additional information, 66 patients went on to a Phase I trial that was not matched to their genetic profile. Table 3 summarizes study results; there was a significant benefit on time to treatment failure and a trend for an increased percentage of patients with stable disease and median OS in patients matched to their genetic profile. When exploratory analysis divided patients into groups that had high matching results or low matching results (number of molecular matches per patient divided by the number of molecular alterations per patient), the percentage of patients with stable disease and the median time to failure were significantly better in the high match group. Median OS did not differ significantly between groups. Notably, those patients who had failed multiple prior therapies (median of 4) and had a number (median 5, range, 1-14) of gene alterations in the tumors. For comparison, response rates in Phase I trials with treatment-resistant tumors are typically 5% to10%.

Table 3. Survival Outcomes After Genetic Profile-Based Therapy

Group	N	% SD (95% CI)	Median TTF (95% CI)	Median OS (95% CI)
Matched	122	19%	2.8 (2.1 to 3.5)	9.3 (7.3 to 11.3)
Unmatched	66	8%	1.9 (1.5 to 2.3)	7.2 (4.9 to 9.5)
p		0.061	0.001	0.087
High match	92	22%	3.4 (2.6 to 4.2)	9.3 (7.3 to 11.3)
Low match	90	9%	1.9 (1.6 to 2.2)	7.5 (5.0 to 10.0)
p		0.028	<0.001	0.121

Adapted from Wheler et al (2016).
CI: confidence interval; OS: overall survival; SD: stable disease ≥6 mo; TTF: time to failure.

Another type of study compares patients matched to targeted treatment with patients not matched. In this type of study, all patients undergo comprehensive genetic testing, but only a subset is matched to targeted therapy. Patients who are not matched continue to receive standard care.

An individual study of this type is Tsimberidou et al (2012). In it, patients with advanced or metastatic cancer refractory to standard therapy underwent molecular profiling. Polymerase chain reaction-based targeted sequencing was used to assess variants in ten cancer genes. Loss of

PTEN was determined using immunohistochemistry, and anaplastic lymphoma kinase (*ALK*) translocation was assessed using fluorescence in situ hybridization. Of 1144 patients, 460 had a molecular aberration based on this panel of tests. From this group of 460 patients, 211 were given "matched" treatment and 141 were given non-matched treatment. The principal analysis presented was of a subgroup of the 460 patients who had only one molecular aberration (n=379). Patients were enrolled in 1 of 51 Phase 1 clinical trials of experimental agents. It was not stated how patients were assigned to matched or unmatched therapy, or how a particular therapy was considered a match or not. In the list of trials in which patients were enrolled, it appears that many of the investigational agents were inhibitors of specific kinases, and thus a patient with a particular aberration of that kinase would probably be considered a match for that agent.

Among the 175 patients who were treated with matched therapy, the overall response rate was 27%. Among the 116 patients treated with non-matched therapy, the response rate was 5% ($p<0.001$ for the difference in response rates). The median time-to-failure was 5.2 months for patients on matched therapy versus 2.2 months for those on non-matched therapy ($p<0.001$). At a median 15-month follow-up, survival was 13.4 months versus 9.0 months ($p=0.017$) in favor of matched therapy. Due to small numbers, individual molecular aberrations could not be analyzed, but some sensitivity analyses excluding certain aberrations, demonstrated that the results were robust, with the exclusion of certain groups.

Section Summary: Clinical Utility

Clinical utility has not been demonstrated for the use of expanded molecular panels to direct targeted cancer treatment. One published randomized controlled trial (SHIVA trial) used an expanded panel in this way and reported no difference in PFS compared with standard treatment. Nonrandomized studies have compared patients who received matched treatment with patients who did not, and have reported that outcomes are superior in patients receiving matched treatment. However, there are potential issues with this design that could compromise the validity of comparing these two populations. They include the following: (1) differences in clinical and demographic factors, (2) differences in the severity of disease or prognosis of disease (i.e., patients with more undifferentiated anaplastic cancers might be less likely to express genetic markers), and (3) differences in the treatments received. It is possible that one of the "targeted" drugs could be more effective than standard treatment whether or not patients were matched. As a result, these types of nonrandomized studies do not provide definitive evidence of treatment efficacy. Further controlled trials are needed that randomize patients to a treatment strategy of variant testing followed by targeted treatment vs standard care.

Summary of Evidence

For individuals who have cancers that have not responded to standard therapy who receive testing of tumor tissue with an expanded cancer molecular panel, the evidence includes a randomized controlled trial, nonrandomized trials, and numerous case series. Relevant outcomes are overall survival, disease-specific survival, test accuracy and validity, and other test performance measures. The analytic validity of these panels is likely to be high when next-generation sequencing is used. The clinical validity of the individual variants for particular types of cancer is not easily determined from the published literature. The large number of variants and many types of cancer preclude determination of the clinical validity of the panels as a whole. Some evidence has reported that many of the identified variants are false positives (i.e., not

biologically active), after filtering by comparison with matched normal tissue and cancer variant databases. To demonstrate clinical utility, direct evidence from interventional trials, ideally randomized controlled trials are needed that compare the strategy of targeted treatment based on panel results with standard care. The first such published randomized controlled trial (the SHIVA trial) reported that there was no difference in progression-free survival when panels were used in this way. Some nonrandomized comparative studies, comparing matched treatment with non-matched treatment, have reported that outcomes are superior for patients receiving matched treatment. However, these studies are inadequate to determine treatment efficacy, because the populations with matched and unmatched cancers may differ on several important clinical and prognostic variables. Also, there is potential for harm if ineffective therapy is given based on test results, because there may be adverse events of therapy in the absence of a benefit. The evidence is insufficient to determine the effects of the technology on health outcomes.

Practice Guidelines and Position Statements

National Comprehensive Cancer Network

NCCN guidelines do not contain recommendations for the general strategy of testing a tumor for a wide range of variants. The guidelines do contain recommendations for specific genetic testing for individual cancers, based on situations where there is a known mutation-drug combination that has demonstrated benefits for that specific tumor type. Some examples of their recommendations for common solid tumors are listed next:

- Breast cancer
  - *HER2* testing, when specific criteria are met.
- Colon cancer
  - *KRAS*, *NRAS* and *BRAF* testing for patients with metastatic colon cancer.
- Non-small-cell lung cancer
  - *KRAS*, *EGFR* [epidermal growth factor receptor] and *ALK* [anaplastic lymphoma kinase] testing for patients with metastatic adenocarcinoma
  - Consider *EGFR* and *ALK* testing especially in never smokers, mixed histology, or small biopsy specimen
  - Strongly endorses broader molecular profiling to identify rare driver mutations (*HER2*, *BRAF V600E*, *ROS1*, and *RET* gene rearrangements, and *MET* amplification or *MET* exon skipping)
- Melanoma
  - *BRAF* V600 testing for patients with metastatic disease
  - Activating *C-KIT* variants for patients with metastatic disease
- Ovarian cancer
  - *BRCA*
- Chronic myelogenous leukemia
  - *BCR-ACL*
- Gastrointestinal stromal tumors
  - *C-KIT*
- Bladder cancer
  - Comprehensive molecular profiling for advanced disease

U.S. Preventive Services Task Force Recommendations

Not applicable.

Key Words:

AmpliSeq™, BioSpeciFx, Caris Life Sciences, EndoGene, FoundationOne™, FoundationOne Heme test, Ion AmpliSeq ™, Ion AmpliSeq Cancer Hotspot Panel, Ion Ampliseq Comprehensive Cancer Panel, gene expression assay, GeneKey, GeneTrails Sequencing Solid Tumor Panel, Guardant360 Panel, IntelliGEN, Kay's Array, Memorial Sloan Kettering Integrated Mutation Profiling of Actionable Cancer Targets, MSK-IMPACT, Molecular Intelligence, Molecular tumor profiling, OncInsights, OnkoMatch, OvaGene, OvariGene, Paradigm Cancer Diagnostic Panel, PcDx, SmartGenomics, Target Now, TruSeq®, TruSight™

Approved by Governing Bodies:

Clinical laboratories may develop and validate tests in-house and market them as a laboratory service; laboratory-developed tests (LDTs) must meet the general regulatory standards of the Clinical Laboratory Improvement Act (CLIA). Laboratories that offer LDTs must be licensed by CLIA for high-complexity testing. To date, the U.S. Food and Drug Administration has chosen not to require any regulatory review of this test.

Benefit Application:

Coverage is subject to member's specific benefits. Group specific policy will supersede this policy when applicable.
ITS: Home Policy provisions apply.
FEP: Special benefit consideration may apply. Refer to member's benefit plan. FEP does not consider investigational if FDA approved and will be reviewed for medical necessity.

Current Coding:

CPT Codes:

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 **(Effective 01/01/2015)**
81450	Targeted genomic sequence analysis panel, hematolymphoid neoplasm or disorder, DNA analysis, and RNA analysis when performed, 5-50 genes (eg, 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 **(Effective 01/01/2015)**
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 **(Effective 01/01/2015)**
0019U	Oncology, RNA, gene expression by whole transcriptome sequencing, formalin-fixed paraffin embedded tissue or fresh frozen tissue, predictive algorithm reported as potential targets for therapeutic agents **(Effective 10/01/2017)**

Previous Coding:

There are no specific codes for molecular profile testing. If the specific gene being analyzed is listed in CPT codes **81161-81355** or **81400-81408**, the specific CPT code would be reported. If the specific gene being analyzed is not listed in the more specific CPT codes, unlisted code **81479** would be reported. The unlisted code would be reported once to represent all of the unlisted genes being analyzed in the profile.

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Policy History:

Medical Policy Group, October 2013 **(1):** New policy
Medical Policy Administration Committee, October 2013
Available for comment October 4 through November 18, 2013
Medical Policy Panel, March, 2014
Medical Policy Group, March 2014 **(1):** Update to Title, Description, Key Points and References; no change to policy statement
Medical Policy Group, November 2014 **(4):** 2015 Annual Coding update; Added codes 81445, 81450, and 81455 to current coding; Added Previous coding section
Medical Policy Group, March 2015 **(1)**: Update to Key Words and Governing Bodies; no change to policy statement
Medical Policy Panel, April 2015
Medical Policy Group, May 2015 **(3)**: 2015 Updates to Description, Key Points, Key Words, & References; moved panel-specific information out from under Governing Bodies to Description; no change in policy statement
Medical Policy Panel, October 2015
Medical Policy Group, October 2015 **(3)**: Updates to Title, Description, Key Points, Key Words, & References; no change in policy statement
Medical Policy Group, November 2015: 2016 Annual Coding Update. Revised CPT codes 81445, 81450, and 81455.
Medical Policy Panel, October 2016
Medical Policy Group, November 2016 **(3)**: 2016 Updates to Description, Key Points, & References; no change in policy statement.

Medical Policy Panel, October 2017
Medical Policy Group, October 2017 **(3):** 2017 Updates to Description, Key Points & References. Edits made to policy section but no change in policy statement intent.
Medical Policy Group, October 2017: Quarterly Coding Update. Added CPT code 0019U to Current Coding.
Medical Policy Group, March 2017: Quarterly Coding Update, April 2018. Added new CPT code 0037U to Current Coding.
Medical Policy Group, June 2018: Removed CPT code 0037U from this policy and added to MP# 532.
