



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 2018
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. 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	Technology
FoundationOne® test	Foundation Medicine	Solid	NGS
FoundationOne® Heme test	Foundation Medicine	Hematologic	RNA sequencing
OnkoMatch™	GenPath Diagnostics	Solid	Multiplex PCR
GeneTrails® Solid Tumor Panel	Knight Diagnostic Labs	Solid	
Tumor profiling service	Caris Molecular Intelligence through Caris Life Sciences	Solid	Multiple Technologies
SmartGenomics™	PathGroup	Solid and Hematologic	NGS, cytogenomic array, other technologies

Test	Manufacturer	Tumor Type	Technology
Guardant360 panel	Guardant Health	Solid	Digital sequencing
Paradigm Cancer Diagnostic (PcDx™) Panel	Paradigm	Solid	NGS
Memorial Sloan Kettering-Integrated Mutation Profiling of Actionable Cancer Targets	MSK-IMPACT™; Memorial Sloan Kettering Cancer Center	Solid	NGS
TruSeq® Amplicon Panel	Illumina	Solid	NGS
Illumina TruSight™ Tumor	Illumina	Solid	NGS
Ion AmpliSeq™ Comprehensive Cancer Panel	Thermo Fisher Scientific	Solid	NGS
Ion AmpliSeq™ Cancer Hotspot Panel v2	Thermo Fisher Scientific	Solid	NGS
OmniSeq Comprehensive	OmniSeq	Solid	NGS

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 6, 2018.

Evidence reviews assess the clinical evidence to determine whether the use of a technology improves the net health outcome. Broadly defined, health outcomes are length of life, quality of life, and ability to function-including benefits and harms. Every clinical condition has specific outcomes that are important to patients and to managing the course of that condition. Validated outcome measures are necessary to ascertain whether a condition improves or worsens; and whether the magnitude of that change is clinically significant. The net health outcome is a balance of benefits and harms.

To assess whether the evidence is sufficient to draw conclusions about the net health outcome of a technology, 2 domains are examined: the relevance and the quality and credibility. To be relevant, studies must represent one or more intended clinical use of the technology in the intended population and compare an effective and appropriate alternative at a comparable intensity. For some conditions, the alternative will be supportive care or surveillance. The quality and credibility of the evidence depend on study design and conduct, minimizing bias and confounding that can generate incorrect findings. The randomized controlled trial is preferred to assess efficacy; however, in some circumstances, nonrandomized studies may be adequate. Randomized controlled trials are rarely large enough or long enough to capture less common adverse events and long-term effects. Other types of studies can be used for these purposes and to assess generalizability to broader clinical populations and settings of clinical practice.

Expanded Molecular Panel Testing for Cancer

Clinical Context and Test Purpose

The purpose of expanded molecular panel testing in individuals with cancer that 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.

Interventions

The relevant intervention of interest is expanded molecular panel testing.

Comparators

The relevant comparator is therapy guided by single gene testing.

Outcomes

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

Harmful outcomes could occur if ineffective therapy is given based on test results, because there may be adverse events of therapy in the absence of a benefit.

Timing

The time frame for outcomes measures varies from several months to several years, depending on the type and stage of cancer.

Setting

Patients with cancer are actively managed by oncologists.

Technically Reliable

Assessment of technical reliability focuses on specific tests and operators and requires review of unpublished and often proprietary information. Review of specific tests, operators, and unpublished data are outside the scope of this evidence review and alternative sources exist. This evidence review focuses on the clinical validity and clinical utility.

Clinically Valid

A test must detect the presence or absence of a condition, the risk of developing a condition in the future, or treatment response (beneficial or adverse).

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.

Section Summary: 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.

Clinically Useful

A test is clinically useful if the use of the results informs management decisions that improve the net health outcome of care. The net health outcome can be improved if patients receive correct therapy, or more effective therapy, or avoid unnecessary therapy, or avoid unnecessary testing.

Direct Evidence

Direct evidence of clinical utility is provided by studies that have compared health outcomes for patients managed with and without the test. Because these are intervention studies, the preferred evidence would be from randomized controlled trials (RCTs).

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.

Randomized Controlled Trials

SHIVA was an RCT of treatment directed by cancer variant testing vs standard care, with the first results published in 2015 (see Tables 2 and 3). Based on the pattern of abnormalities found, 9 different regimens of established cancer treatments were assigned to the experimental treatment arm. The primary outcome was PFS analyzed by intention to treat. Baseline clinical characteristics and tumor types were similar between groups.

Table 2. Summary of Key RCT Characteristics

Study; Trial	Countries	Sites	Dates	Participants	Interventions	
					Active	Comparator
Le Tourneau et al (2015); SHIVA	France	8		195 patients with any kind of metastatic solid tumor refractory to standard targeted treatment who had a molecular alteration in one of 3 molecular pathways ^a	99 off-label therapy based on variant testing by NGS ^b	96 standard care

NGS: next-generation sequencing; RCT: randomized controlled trial.

^aMolecular alterations affecting the hormonal pathway were found in 82 (42%) patients; alterations affecting the PI3K/AKT/mTOR pathway were found in 89 (46%) patients; and alterations affecting the RAF/MED pathway were found in 24 (12%) patients.

^bVariant testing included comprehensive analysis of 3 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 immunohistochemistry.

Table 3. Treatment Algorithm for Experimental Arm, From the SHIVA Trial

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

Adapted from Le Tourneau et al (2012)

After a median follow-up of 11.3 months, the median PFS was 2.3 months in the targeted treatment group vs 2.0 months in the standard care group (p=0.41; see Table 4). In subgroup analysis by molecular pathway, there were no significant differences in PFS between groups.

Table 4. Summary of Key RCT Results

Study	PFS (95% CI), mo	PFS at 6 mo (95% CI)	Adverse Events, n (%)	
			Grade 3	Grade 4
Le Tourneau et al (2015) ; SHIVA				
N	195	195		
Targeted Therapy	2.3 (1.7 to 3.8)	13 (7 to 20)	36 (36)	7 (7)
Standard care	2.0 (1.7 to 2.7)	11 (6 to 19)	28 (31)	4 (4)
HR (95% CI)	0.88 (0.65 to 1.19)			
p	0.41			

CI: confidence interval; HR: hazard ratio; PFS: progression-free survival; RCT: randomized controlled trial

The purpose of the gaps tables (see Tables 5 and 6) is to display notable gaps identified in each study. This information is synthesized as a summary of the body of evidence following each table and provides the conclusions on the sufficiency of evidence supporting the position statement.

Table 5. Relevance Gaps

Study	Population ^a	Intervention ^b	Comparator ^c	Outcomes ^d	Follow-Up ^e
Le Tourneau et al (2015)	4. Patients had failed a targeted therapy for their indication				

The evidence gaps stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.

^a Population key: 1. Intended use population unclear; 2. Clinical context is unclear; 3. Study population is unclear; 4. Study population not representative of intended use.

^b Intervention key: 1. Not clearly defined; 2. Version used unclear; 3. Delivery not similar intensity as comparator; 4. Not the intervention of interest.

^c Comparator key: 1. Not clearly defined; 2. Not standard or optimal; 3. Delivery not similar intensity as intervention; 4. Not delivered effectively.

^d Outcomes key: 1. Key health outcomes not addressed; 2. Physiologic measures, not validated surrogates; 3. No CONSORT reporting of harms; 4. Not establish and validated measurements; 5. Clinical significant difference not prespecified; 6. Clinical significant difference not supported.

^e Follow-Up key: 1. Not sufficient duration for benefit; 2. Not sufficient duration for harms

Table 6. Study Design and Conduct Gaps

Study	Allocation ^a	Blinding ^b	Selective Reporting ^d	Data Completeness ^e	Power ^d	Statistical ^f
Le Tourneau et al (2015)		1.-3. The study was not blinded and outcomes were assessed by the treating physician				

The evidence gaps stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.

^a Allocation key: 1. Participants not randomly allocated; 2. Allocation not concealed; 3. Allocation concealment unclear; 4. Inadequate control for selection bias.

^b Blinding key: 1. Not blinded to treatment assignment; 2. Not blinded outcome assessment; 3. Outcome assessed by treating physician.

^c Selective Reporting key: 1. Not registered; 2. Evidence of selective reporting; 3. Evidence of selective publication.

^d Data Completeness key: 1. High loss to follow-up or missing data; 2. Inadequate handling of missing data; 3. High number of crossovers; 4. Inadequate handling of crossovers; 5. Inappropriate exclusions; 6. Not intent to treat analysis (per protocol for noninferiority trials).

^e Power key: 1. Power calculations not reported; 2. Power not calculated for primary outcome; 3. Power not based on clinically important difference.

^f Statistical key: 1. Analysis is not appropriate for outcome type: (a) continuous; (b) binary; (c) time to event; 2. Analysis is not appropriate for multiple observations per patient; 3. Confidence intervals and/or p values not reported; 4. Comparative treatment effects not calculated.

A crossover analysis of the SHIVA trial by Belin et al (2017) 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 PFS MTA/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 nonrandomized studies have been published that use some type of control. Some of these studies had a prospective, interventional design. 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. These studies 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 2 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.

Chain of Evidence

Indirect evidence on clinical utility rests on clinical validity. If the evidence is insufficient to demonstrate test performance, no inferences can be made about clinical utility.

Section Summary: Clinically Useful

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 cancer that is being considered for targeted 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 below:

- 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], and *ROS1* as part of broad molecular profiling to minimize wasting of tissue.

- Melanoma
 - *BRAF* V600 testing for patients with metastatic disease
 - *KIT* in the appropriate clinical setting for patients with metastatic disease
- Ovarian cancer
 - *BRCA*
- Chronic myelogenous leukemia
 - *BCR-ALB1*
- Gastric cancer
 - CDH1 for hereditary cancer predisposition syndromes
- Bladder cancer
 - Comprehensive molecular profiling for advanced disease

College of American Pathologists et al

The College of American Pathologists and 2 other associations updated their joint guidelines on molecular testing of patients with non-small-cell lung cancer in 2018. The groups gave a strong recommendation for EGFR, ALK, and ROS1 testing. Based on expert consensus opinion KRAS was recommended as a single gene test if EGFR, ALK, and ROS1 were negative. Tests that were not recommended for single gene testing outside of a clinical trial were BRAF, RET, ERBB2 (HER2), and MET, although these genes should be tested if included in a panel.

American Society of Clinical Oncology

In 2018, the American Society of Clinical Oncology affirmed the majority of these guidelines. The Society guidelines also recommended BRAF testing on all patients with advanced lung adenocarcinoma.

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) |
| 0037U | Targeted genomic sequence analysis, solid organ neoplasm, DNA analysis of 324 genes, interrogation for sequence variants, gene copy number amplifications, gene rearrangements, microsatellite instability and tumor mutational burden (Effective 4/01/2018) |

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.

References:

1. American Society for Clinical Oncology. Targeted Agent and Profiling Utilization Registry Study. 2017; www.asco.org/practice-research/targeted-agent-and-profiling-utilization-registry-study. Accessed August 23, 2017.
2. Belin L, Kamal M, Mauborgne C, et al. Randomized phase II trial comparing molecularly targeted therapy based on tumor molecular profiling versus conventional therapy in patients with refractory cancer: cross-over analysis from the SHIVA trial. *Ann Oncol*. Mar 01 2017; 28(3):590-596.
3. Caris Life Sciences. Caris Molecular Intelligence. 2015; www.carislifesciences.com/physicians/.
4. Caris Life Sciences. Caris Molecular Intelligence: Evidence-Based Tumor Profiling Service. www.carismoleculairintelligence.com/targeting_cancer. Accessed August 23, 2017
5. Cheng DT, Mitchell TN, Zehir A, et al. Memorial Sloan Kettering-Integrated Mutation Profiling of Actionable Cancer Targets (MSK-IMPACT): a hybridization capture-based next-generation sequencing clinical assay for solid tumor molecular oncology. *J Mol Diagn*. May 2015; 17(3):251-264.
6. Demetri GD, Benjamin RS, Blanke CD, et al. NCCN Task Force report: management of patients with gastrointestinal stromal tumor (GIST)--update of the NCCN clinical practice guidelines. *J Natl Compr Canc Netw*. Jul 2007; 5 Suppl 2:S1-29; quiz S30.
7. Dienstmann R, Rodon J, Barretina J et al. Genomic medicine frontier in human solid tumors: prospects and challenges. *J Clin Oncol* 2013; 31(15):1874-1884.
8. Dienstmann R, Serpico D, Rodon J et al. Molecular profiling of patients with colorectal cancer and matched targeted therapy in phase I clinical trials. *Mol Cancer Ther*. May 2012; 11(9):2062-2071.
9. Doroshow JH. Selecting systemic cancer therapy one patient at a time: is there a role for molecular profiling of individual patients with advanced solid tumors? *J Clin Oncol*. 2010; 28(33):4869-4871.
10. Drilon A, Wang L, Arcila ME, et al. Broad, hybrid capture-based next-generation sequencing identifies actionable genomic alterations in lung adenocarcinomas otherwise negative for such alterations by other genomic testing approaches. *Clin Cancer Res*. Jan 7 2015
11. FoundationOne Web Site. About FoundationOne. www.foundationone.com/learn.php#2. Accessed August 23, 2017.
12. FoundationOne Web Site. Technical Information and Test Overview. 2014. Available online at: www.foundationone.com/docs/FoundationOne_tech-info-and-overview.pdf. Accessed August 23, 2017.
13. Garber K. Ready or not: personal tumor profiling tests take off. *J Natl Cancer Inst*. 2011; 103(2):84-86.
14. GenPath Oncology. OnkoMatch™ tumor genotyping. 2014; www.genpathdiagnostics.com/oncology/onkomatch/. Accessed August 23, 2017.

15. GenPath®. Test catalog. www.genpathdiagnostics.com/oncology/test-catalog/?type=by_test.
16. Gerlinger M, Rowan AJ, Horswell S, et al. Intratumor heterogeneity and branched evolution revealed by multiregion sequencing. *N Engl J Med*. 2012; 366(10):883-892.
17. GuardantHealth I. Guardant360 Know Cancer. www.guardanthealth.com/guardant360/.
18. Hyman DM, Puzanov I, Subbiah V, et al. Vemurafenib in Multiple Nonmelanoma Cancers with BRAF V600 Mutations. *N Engl J Med*. Aug 20 2015; 373(8):726-736.
19. Illumina Inc. TruSight Tumor 26. www.illumina.com/content/dam/illumina-marketing/documents/products/datasheets/datasheet_trusight_tumor.pdf. Accessed August 23, 2017.
20. Illumina IWP. TruSeq Amplicon - Cancer Panel. 2014. www.illumina.com/products/truseq_amplicon_cancer_panel.ilmn. Accessed August 23, 2017.
21. Ioannidis JPA. Is Molecular Profiling Ready for Use in Clinical Decision Making? *The Oncologist* 2007; 12:301-311.
22. Jardim DL, Schwaederle M, Wei C, et al. Impact of a Biomarker-Based Strategy on Oncology Drug Development: A Meta-analysis of Clinical Trials Leading to FDA Approval. *J Natl Cancer Inst*. Nov 2015; 107(11).
23. Johnson DB, Dahlman KH, Knol J, et al. Enabling a genetically informed approach to cancer medicine: a retrospective evaluation of the impact of comprehensive tumor profiling using a targeted next-generation sequencing panel. *Oncologist*. Jun 2014; 19(6):616-622.
24. Jones S, Anagnostou V, Lytle K, et al. Personalized genomic analyses for cancer mutation discovery and interpretation. *Sci Transl Med*. Apr 15 2015; 7(283):283ra253.
25. Kalemkerian GP, Narula N, Kennedy EB, et al. Molecular Testing Guideline for the Selection of Patients With Lung Cancer for Treatment With Targeted Tyrosine Kinase Inhibitors: American Society of Clinical Oncology Endorsement of the College of American Pathologists/International Association for the Study of Lung Cancer/Association for Molecular Pathology Clinical Practice Guideline Update. *J Clin Oncol*. Mar 20 2018;36(9):911-919.
26. Knight Diagnostic Laboratories. GeneTrails Solid Tumor Genotyping Panel. 2015; www.knightdxlabs.com/home/test-details?id=GeneTrails+Solid+Tumor+Genotyping+Panel.
27. Laboratories KD. GeneTrails Solid Tumor Genotyping Panel. 2015; www.knightdxlabs.com/home/testdetails?id=GeneTrails+Solid+Tumor+Genotyping+Panel. Accessed August 23, 2017.
28. Le Tourneau C, Delord JP, Goncalves A, 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*. Oct 2015; 16(13):1324-1334.
29. Le Tourneau C, Kamal M, Tredan O et al. Designs and challenges for personalized medicine studies in oncology: focus on the SHIVA trial. *Target Oncol* 2012; 7(4):253-265.
30. Life Technologies. Cancer Genomics Data Analysis - Compendia Bioscience Products. 2014. Available online at: www.lifetechnologies.com/us/en/home/life-science/cancer-

research/cancer-genomics/cancer-genomics-data-analysis-compedia-bioscience.html.
Accessed October 3, 2016.

31. Lindeman NI, Cagle PT, Aisner DL, et al. Updated Molecular Testing Guideline for the Selection of Lung Cancer Patients for Treatment With Targeted Tyrosine Kinase Inhibitors: Guideline From the College of American Pathologists, the International Association for the Study of Lung Cancer, and the Association for Molecular Pathology. *J Thorac Oncol.* Mar 2018;13(3):323-358.
32. National Cancer Institute. Press Release: NCI launches trial to assess the utility of genetic sequencing to improve patient outcomes, 1/30/2014. 2014. Available online at: www.cancer.gov/newscenter/newsfromnci/2014/MPACTlaunch.
33. National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Bladder Cancer Version 5.2017. www.nccn.org/professionals/physician_gls/pdf/bladder.pdf.
34. National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Breast Cancer. Version 2.2017. www.nccn.org/professionals/physician_gls/pdf/breast.pdf.
35. National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Chronic Myelogenous Leukemia. Version 1.2018. www.nccn.org/professionals/physician_gls/pdf/cml.pdf.
36. National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Colon Cancer. Version 2.2017. www.nccn.org/professionals/physician_gls/pdf/colon.pdf.
37. National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Melanoma. Version 1.2017. www.nccn.org/professionals/physician_gls/pdf/melanoma.pdf.
38. National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Non-Small Cell Lung Cancer. Version 9.2017. www.nccn.org/professionals/physician_gls/pdf/nscl.pdf.
39. National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Ovarian Cancer. Version 3.2017. www.nccn.org/professionals/physician_gls/pdf/ovarian.pdf.
40. National Comprehensive Cancer Network. NCCN Biomarkers Compendium. Available online at: www.nccn.org/professionals/biomarkers/default.asp.
41. O'Brien CP, Taylor SE, O'Leary JJ et al. Molecular testing in oncology: Problems, pitfalls and progress. *Lung Cancer* 2014; 83(3):309-315.
42. Pal SK, Agarwal N, Boorjian SA, et al. National Comprehensive Cancer Network Recommendations on Molecular Profiling of Advanced Bladder Cancer. *J Clin Oncol.* Sep 20 2016; 34(27):3346-3348.
43. Paradigm Web Site. Next Generation Cancer Diagnostics: About PcDx. [//www.paradigmdx.org/pcdx/about/](http://www.paradigmdx.org/pcdx/about/).
44. Pathgroup SmartGenomics. Advance Oncogenomic diagnostics. 2015; www.pathgroup.com/smartgenomics-35-gene-solid-tumor-ngs-and-acgh/.
45. PathGroup SmartGenomics. SmartGenomics: 35 Gene Solid Tumor NGS and aCGH. www.pathgroup.com/smartgenomics-35-gene-solid-tumor-ngs-and-acgh/

46. Schwaederle M, Daniels GA, Piccioni DE, et al. On the Road to Precision Cancer Medicine: Analysis of Genomic Biomarker Actionability in 439 Patients. *Mol Cancer Ther.* Jun 2015; 14(6):1488-1494.
47. Schwaederle M, Zhao M, Lee JJ, et al. Impact of Precision Medicine in Diverse Cancers: A Meta-Analysis of Phase II Clinical Trials. *J Clin Oncol.* Nov 10 2015; 33(32):3817-3825.
48. Spear BB, Heath-Chiozzi M, Huff J. Clinical application of pharmacogenetics. *Trends Mol Med* 2001; 7(5):201-204.
49. Tsimberidou AM, Iskander NG, Hong DS et al. Personalized medicine in a phase I clinical trials program: the MD Anderson Cancer Center initiative. *Clin Cancer Res* 2012; 18(22):6373-6383.
50. Von Hoff DD, Stephenson JJ Jr., Rosen P, et al. Pilot study using molecular profiling of patients' tumors to find potential targets and select treatments for their refractory cancers. *J Clin Oncol.* 2010; 28(33):4877-4883.
51. Wheler JJ, Janku F, Naing A, et al. Cancer Therapy Directed by Comprehensive Genomic Profiling: A Single Center Study. *Cancer Res.* Jul 1 2016; 76(13):3690-3701.

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.

Medical Policy Panel, October 2018

Medical Policy Group, October 2018 (9): 2018 Updates to Description, Key Points, References. Added code 0037U to current coding. No change to policy statement.

This medical policy is not an authorization, certification, explanation of benefits, or a contract. Eligibility and benefits are determined on a case-by-case basis according to the terms of the member's plan in effect as of the date services are rendered. All medical policies are based on (i) research of current medical literature and (ii) review of common medical practices in the treatment and diagnosis of disease as of the date hereof. Physicians and other providers are solely responsible for all aspects of medical care and treatment, including the type, quality, and levels of care and treatment.

This policy is intended to be used for adjudication of claims (including pre-admission certification, pre-determinations, and pre-procedure review) in Blue Cross and Blue Shield's administration of plan contracts.