Medical Policy

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Title: Comprehensive Genomic Profiling for Selecting Targeted Cancer Therapies

Professional
Original Effective Date: September 5, 2014
Revision Date(s): September 5, 2014; June 23, 2015; January 1, 2016; February 19, 2016; January 20, 2017; November 8, 2017; January 1, 2018; March 28, 2018; July 1, 2018; January 1, 2019; March 5, 2021; May 11, 2021, July 01, 2021
Current Effective Date: March 5, 2021

Institutional
Original Effective Date: September 5, 2014
Revision Date(s): September 5, 2014 June 23, 2015; January 1, 2016; February 19, 2016; January 20, 2017; November 8, 2017; January 1, 2018; March 28, 2018; July 1, 2018; January 1, 2019; March 5, 2021, May 11, 2021, July 01, 2021
Current Effective Date: March 5, 2021

Populations	Interventions	Comparators	Outcomes
Individuals: • With cancer that is being considered for targeted therapy	Interventions of interest are: • Comprehensive genomic profiling of tumor tissue	Comparators of interest are: • Single gene molecular testing	Relevant outcomes include: • Overall survival • Disease-specific survival • Test validity • Other test performance measures

DESCRIPTION

Comprehensive genomic profiling offers the potential to evaluate a large number of genetic markers at a single time to identify cancer treatments that target specific biologic 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 molecular panels that test a wide variety of genetic markers in cancers without regard for whether a specific targeted treatment has demonstrated benefit. This approach may result in treatment different from that usually selected for a patient based on the type and stage of cancer.

OBJECTIVE

The objective of this policy is to determine whether comprehensive genomic profiling improves the net health outcome of individuals with cancer.

BACKGROUND

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 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 they arise. 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 derive clinically significant benefits. It is unusual for cancer treatment to be effective for all patients treated in a traditional clinical trial. Spear et al (2001) analyzed the efficacy of major drugs used to treat several important diseases.[1,] They reported heterogeneity of therapeutic responses, noting a low rate 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 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 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. The use of genetic markers allows cancers to be further classified by "pathways" defined at the molecular level. An expanding number of genetic markers have been identified. These may be categorized into 3 classes[2,] (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). The utility of these markers has been demonstrated by

randomized controlled trials that select patients with the marker and report significant improvements in outcomes with targeted therapy compared with standard therapy. Testing for individual variants with established utility is not covered in this evidence review. In some cases, limited panels may be offered that are specific to 1 type of cancer (e.g., a panel of several markers for non-small-cell lung cancer). This review also does not address the use of cancer-specific panels that include a few variants. Rather, this review addresses 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.[3,4,5,] 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 study by Schwaederle et al (2015), 439 patients with diverse cancers were tested with a 236-gene panel.[5,] A total of 1813 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% (372/439) of patients had 2 or more alterations. The most common alterations were in the *TP53* (44%), *KRAS* (16%), and *PIK3CA* (12%) genes.

Some evidence is available on the generalizability of targeted treatment based on a specific variant among cancers that originate from different organs.[2,6,] There are several examples of variant-directed treatment that is effective in 1 type of cancer but ineffective in another. For example, targeted therapy for epidermal growth factor receptor variants have 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 by Hyman et al (2015).[7,] In this study, 122 patients with *BRAF* V600 variants in nonmelanoma cancers were treated with vemurafenib. The authors reported that there appeared to be an antitumor 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®CDx test (F1CDx)	Foundation Medicine	Solid	NGS
FoundationOne®CDx 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

Test	Manufacturer	Tumor Type	Technology
SmartGenomics™	PathGroup	Solid and hematologic	NGS, cytogenomic array, other technologies
Paradigm Cancer Diagnostic (PcDx™) Panel	Paradigm	Solid	NGS
MSK-IMPACT™	Memorial Sloan Kettering Cancer Center	Solid	NGS
TruSeq® Amplicon Panel		Solid	NGS
TruSight™ Oncology	Illumina	Solid	NGS
Ion AmpliSeq™ Comprehensive Cancer Panel		Solid	NGS
Ion AmpliSeq™ Cancer Hotspot Panel v2	Thermo Fisher Scientific	Solid	NGS
OmniSeq Comprehensive®	OmniSeq	Solid	NGS
Oncomine DX Target Test™	Thermo Fisher Scientific	Solid	NGS

NGS: next-generation sequencing; PCR: polymerase chain reaction.

REGULATORY STATUS

Clinical laboratories may develop and validate tests in-house and market them as a laboratory service; laboratory-developed tests must meet the general regulatory standards of the Clinical Laboratory Improvement Amendments. Laboratories that offer laboratory-developed tests must be licensed by the Clinical Laboratory Improvement Amendments for high-complexity testing.

In 2017, FoundationOne CDx (Foundation Medicine) received premarket approval by the U.S. Food and Drug Administration (FDA) (P170019) as a companion diagnostic to identify patients who may benefit from treatment with the targeted therapies listed in Table 2. "Additionally, F1CDx is intended to provide tumor mutation profiling to be used by qualified health care professionals in accordance with professional guidelines in oncology for patients with solid malignant neoplasms." FDA product code: PQP

In 2017, the Oncomine DX Target Test (Life Technologies Corp) received premarket approval by the FDA (P160045) to aid in selecting non-small cell lung cancer patients for treatment with approved targeted therapies. FDA product code: PQP

MSK-IMPACT (Memorial Sloan Kettering) received de novo marketing clearance in 2017 (DEN170058). "The test is intended to provide information on somatic mutations (point mutations and small insertions and deletions) and microsatellite instability for use by qualified health care professionals in accordance with professional guidelines, and is not conclusive or prescriptive for labeled use of any specific therapeutic product." FDA product code: PZM

OmniSeq Comprehensive® is approved by the New York State Clinical Laboratory Evaluation Program.

Table 2. Companion Diagnostic Indications for F1CDx

Tumor Type	Biomarker(s) Detected	Therapy
Non-small cell lung cancer (NSCLC)	*EGFR* exon 19 deletions and *EGFR* exon 21 L858R alterations	Gilotrif® (afatinib), Iressa® (gefitinib), Tagrisso® (osimertinib), or Tarceva® (erlotinib)
	EGFR exon 20 T790M alterations	Tagrisso® (osimertinib)
	ALK rearrangements	Alecensa® (alectinib), Xalkori® (crizotinib), or Zykadia® (ceritinib)
	BRAF V600E	Tafinlar® (dabrafenib) in combination with Mekinist® (trametinib)
	MET	Tabrecta(TM) (capmatinib)
Melanoma	*BRAF* V600E	Tafinlar® (dabrafenib) or Zelboraf® (vemurafenib)
	BRAF V600E and V600K	Mekinist® (trametinib) or Cotellic® (cobimetinib) in combination with Zelboraf® (vemurafenib)
Breast cancer	*ERBB2* (HER2) amplification	Herceptin® (trastuzumab), Kadcyla® (ado-trastuzumabemtansine), or Perjeta® (pertuzumab)
	PIK3CA alterations	Piqray® (alpelsib)
Colorectal cancer	*KRAS* wild-type (absence of mutations in codons 12 and 13)	Erbitux® (cetuximab)
	KRAS wild-type (absence of mutations in exons 2, 3, and 4) and NRAS wild type (absence of mutations in exons 2, 3, and 4)	Vectibix® (panitumumab)
Ovarian cancer	*BRCA1/2* alterations	Lynparza® (olaparib) or Rubraca® (rucaparib)
Chaolangiocarcinoma	*FGFR2* fusion or other select rearrangements	Pemazyre(TM) (pemigatinib)
Prostate cancer	Homologous Recombination Repair (HRR) gene alterations	Lynparza® (olaparib)

POLICY

The use of comprehensive genomic profiling for selecting targeted cancer treatment is considered **experimental / investigational**.

Policy Guidelines

Genetics Nomenclature Update

The Human Genome Variation Society nomenclature is used to report information on variants found in DNA and serves as an international standard in DNA diagnostics. It is being implemented for genetic testing medical evidence review updates starting in 2017 (see Table PG1). The Society's nomenclature is recommended by the Human Variome Project, the Human Genome Organization, and by the Human Genome Variation Society itself.

The American College of Medical Genetics and Genomics and the Association for Molecular Pathology standards and guidelines for interpretation of sequence variants represent expert opinion from both organizations, in addition to the College of American Pathologists. These recommendations primarily apply to genetic tests used in clinical laboratories, including genotyping, single genes, panels, exomes, and genomes. Table PG2 shows the recommended standard terminology-"pathogenic," "likely pathogenic," "uncertain significance," "likely benign," and "benign"-to describe variants identified that cause Mendelian disorders.

Table PG1. Nomenclature to Report on Variants Found in DNA

Previous	Updated	Definition
Mutation	Disease-associated variant	Disease-associated change in the DNA sequence
	Variant	Change in the DNA sequence
	Familial variant	Disease-associated variant identified in a proband for use in subsequent targeted genetic testing in first-degree relatives

Table PG2. ACMG-AMP Standards and Guidelines for Variant Classification

Variant Classification	Definition
Pathogenic	Disease-causing change in the DNA sequence
Likely pathogenic	Likely disease-causing change in the DNA sequence
Variant of uncertain significance	Change in DNA sequence with uncertain effects on disease
Likely benign	Likely benign change in the DNA sequence
Benign	Benign change in the DNA sequence

ACMG: American College of Medical Genetics and Genomics; AMP: Association for Molecular Pathology.

RATIONALE

This evidence review has been updated regularly with a literature review of the PubMed database. The most recent literature update was performed through September 14, 2020.

Evidence reviews assess whether a medical test is clinically useful. A useful test provides information to make a clinical management decision that improves the net health outcome. That is, the balance of benefits and harms is better when the test is used to manage the condition than when another test or no test is used to manage the condition.

The first step in assessing a medical test is to formulate the clinical context and purpose of the test. The test must be technically reliable, clinically valid, and clinically useful for that purpose. Evidence reviews assess the evidence on whether a test is clinically valid and clinically useful. Technical reliability is outside the scope of these reviews, and credible information on technical reliability is available from other sources.

COMPREHENSIVE GENOMIC PROFILING OF TUMOR TISSUE

Clinical Context and Test Purpose

The purpose of comprehensive genomic profiling in individuals with cancer is to identify somatic variants in tumor tissue to guide treatment decisions with targeted therapies.

The question addressed in this evidence review is: In individuals with cancer that is being considered for targeted therapy, does the use of comprehensive genomic profiling of tumor tissue improve the net health outcome?

The following PICO was used to select literature to inform this review.

Patients

The relevant population of interest are individuals with advanced cancer who have not previously been treated with targeted therapy.

Interventions

The relevant intervention of interest is comprehensive genomic profiling of tumor tissue, including all major types of molecular variants, single nucleotide variants, small and large insertions, and deletions, copy number variants, and fusions in cancer-associated genes by next-generation sequencing technologies. Some tests may also evaluate microsatellite instability and tumor mutation burden.

Comparators

The following practice is currently being used to identify somatic variants in tumor tissue to guide treatment decisions: therapy guided by single-gene testing.

Outcomes

Beneficial outcomes are an increase in progression-free survival (PFS) and overall survival (OS). A beneficial outcome may also be the avoidance of ineffective therapy and its associated harms.

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.

A follow-up to monitor for outcomes varies from several months to several years, depending on the type and stage of cancer.

Technically Reliable
Assessment of technical reliability focuses on specific tests and operators and requires a 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 the clinical validity of expanded panels and comprehensive genomic profiling is incomplete. Because of a large number of variants contained in expanded panels, it is not possible to determine the clinical validity of the panels as a whole. While some variants have a strong association with 1 or a small number of specific malignancies, none has 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 variants 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: Clinically Valid
The clinical validity of the panels as a whole cannot be determined because of the different variants and a large number of potential cancers for which they can be used. Clinical validity would need to be reported for each variant for a particular type of cancer. Because there are hundreds of variants included in the panels and dozens of 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. RCTs 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. OS 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

Molecularly targeted therapy based on tumor molecular profiling vs conventional therapy for advanced cancer (SHIVA trial) was an RCT of treatment directed by cancer variant testing vs standard care, with the first results published in 2015 (see Tables 3 and).[8,9,] 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 3. Summary of Key RCT Characteristics

Study	Countries	Sites	Dates	Participants	Interventions	
					Active	Comparator
Le Tourneau et al (2012, 2015)[8,9,]; SHIVA	France	8		195 patients with any kind of metastatic solid tumor refractory to standard targeted treatment who had a molecular alteration in 1 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.
a Molecular alterations affecting the hormonal pathway were found in 82 (42%) patients; alterations affecting the PI3K/AKT/mTOR pathway were found in 89 (46%) patients; alterations affecting the RAF/MED pathway were found in 24 (12%) patients.
b Variant testing included comprehensive analysis of3 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 4. 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, *PDGFRB*, *FLT-3*	Sorafenib
EGFR	Erlotinib
HER2	Lapatinib and trastuzumab
SRC, *EPHA2*, *LCK*, *YES*	Dasatinib
Estrogen receptor, progesterone receptor	Tamoxifen (or letrozole if contraindications)
Androgen receptor	Abiraterone

Adapted from Le Tourneau et al (2012).[8,]

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 of care group (p=0.41; see Table 5). In the subgroup analysis by molecular pathway, there were no significant differences in PFS between groups.

Table 5. 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)[8,9]; 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

Limitations of the SHIVA trial are shown in Tables 6 and 7. A major limitation of the SHIVA trial is that the population consisted of patients who had failed a targeted treatment.

Table 6. Study Relevance Limitations

Study	Population[a]	Intervention[b]	Comparator[c]	Outcomes[d]	Follow-Up[e]
Le Tourneau et al (2015) SHIVA[8,9]	4. Patients had failed a targeted therapy for their indication		3. Included combination therapy whereas the intervention was single- agent		

The study limitations 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 7. Study Design and Conduct Limitations

Study	Allocation[a]	Blinding[b]	Selective Reporting[d]	Data Completeness[e]	Power[d]	Statistical[f]
Le Tourneau et al (2015) SHIVA [8,9,]		1-3. The study was not blinded and outcomes were assessed by the treating physician				

The study limitations 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 agent (MTA) therapy to treatment at physician's choice (TPC) or vice versa.[10,] The PFS ratio was defined as the PFS on MTA to PFS on TPC 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 on MTA to PFS on TPC 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 might have benefited from the treatment algorithm evaluated in the SHIVA trial.

Systematic Reviews

Systematic reviews compare the outcomes of patients who were enrolled in trials with personalized therapy with those of patients enrolled in non-personalized therapy trials (see Table 8). Schwaederle et al (2015) assessed outcomes in single-agent phase 2 trials, while Jardim et al (2015) evaluated trials for 58 newly approved cancer agents.[11,12,] The results of the meta-analyses are shown in Table 9. Treatment directed by a personalized strategy was associated with an increased response rate, PFS, and OS compared to treatment that was not personalized. While these studies support a strategy of targeted therapy within a specific tumor type, they do not provide evidence that broad genomic profiling is more effective than tumor-specific variant assessment.

Table 8. Meta-analysis Characteristics

Study	Dates	Trials	Participants	N	Design
Schwaederle et al (2015)[11,]	2010 - 2012	570 (641 arms)	Adult patients with any type of advanced cancer	32,149 (8,078 personalized and 24,071 non-personalized)	Single-agent phase 2 trials
Jardim et al)2015)[12,]		57 RCTs 55 non-RCTs			58 newly approved cancer agents

RCT: randomized controlled trial.

Table 9. Meta-analysis Results

Study	Median Response Rate	Relative Response Rate (95% CI)	Median Progression-Free Survival	Median Overall Survival	Treatment-related Mortality% (95% CI)
Schwaederle et al (2015)[11,]	% (95% CI)		Months (95% CI)	Months (95% CI)	
Total N	31,994		24,489	21,817	
Targeted therapy	31.0 (26.8 to 35.6)		5.9 (5.4 to 6.3)	13.7 (11.1 to 16.4)	1.52 (1.23 to 1.87)
Non-targeted therapy	10.5 (9.6 to 1.5a)		2.7 (2.6 to 2.9)	8.9 (8.3 to 9.3)	2.26 (2.04 to 2.49)
p-Value	<0.001		<0.001	<0.001	<0.001
Jardim et al (2015)[12,]	% (95% CI)		Months (IQR)	Months (IQR)	
Targeted	48 (42 to 55)		8.3 (5)	19.3 (17)	
Non-targeted	23 (20 to 27)		5.5 (5)	13.5 (8)	
p-Value	<0.01		0.002	0.04	
		Hazard ratio compared to control arm	Hazard ratio compared to control arm	Hazard ratio compared to control arm	
Targeted		3.82 (2.51 to 5.82)	0.41 (0.33 to 0.51)	0.71 (0.61 to 0.83)	
Non-targeted		2.08 (1.76 to 2.47)	0.59 (0.53 to 0.65)	0.81 (0.77 to 0.85)	
p-Value		0.03	<0.001	0.07	NS

CI: confidence interval; IQR: interquartile range; NS: reported as not significant.
a This may be a typographical error in the publication.

Nonrandomized Controlled Trials

Nonrandomized studies have been published that use some type of control. These studies are summarized in a review by Zimmer et al (2019).[13,] Some of these studies had a prospective, interventional design.[14,] 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 1 of the "targeted" drugs could be more effective than standard treatment whether or not patients were matched.

One of the largest studies of molecular targeting in phase 1 trials was the Initiative for Molecular Profiling and Advanced Cancer Therapy (IMPACT) study, reported by Tsimberidou (2017) from the MD Anderson Cancer Center.[15,] Patients with advanced cancer who underwent comprehensive genomic profiling were treated with matched targeted therapy when available (see Table 10). Out of 1,436 patients who underwent genomic profiling, 1,170 (82.1%) had 1 or more mutations, of which 637 were actionable. The most frequent alterations were estrogen receptor overexpression, and variants in TP53, KRAS, PTEN, PIK3CA, and BRAF. Comparison of outcomes in patients who received matched and unmatched therapies are shown in Table 11. The group that had matched therapy had a higher response rate (11% vs 5%), longer PFS (3.4 vs 2.9 mo), and longer OS (8.4 vs 7.3 mo). In addition to the general limitations of this type of study design, limitations in relevance and design and conduct are shown in Tables 12 and 13. Note that a randomized trial from this center that will compare matched to unmatched therapy (IMPACT 2) is ongoing with completion expected in early 2020 (see Table 12)

Table 10. Summary of Key Nonrandomized Trials OR Observational Comparative Study Characteristics

Study	Study Type	Country	Dates	Participants	Treatment1	Treatment2	Follow-Up
Tsimberidou et al (2017)[15,] IMPACT	Database Review	U.S.	2012-2013	1,436 patients with advanced cancer	Matched therapy (n=390)	Unmatched therapy (n=247)	

Table 11. Summary of Key Nonrandomized Trials OR Observational Comparative Study Results

Study	Complete or Partial Response	Progression-Free Survival mo	Overall Survival mo
Tsimberidou et al (2017)[15], IMPACT	N	N	N
Matched	11%	3.4	8.4
Unmatched	5%	2.9	7.3
p-Value	0.010	0.002	0.041
Hazard Ratio (95% CI)		0.81 (0.69 to 0.96)	0.84 (0.71 to 0.99)
p-Value		0.015	0.041

CI: confidence interval; Diff: difference; HR: hazard ratio;; OR: odds ratio; RR: relative risk; SD: standard deviation.
[1] Include number analyzed, association in each group and measure of association (absolute or relative) with CI.

Table 12. Study Relevance Limitations

Study	Population[a]	Intervention[b]	Comparator[c]	Outcomes[d]	Follow-Up[e]
Tsimberidou et al (2017)[15], IMPACT	4. The population consisted of patients who had failed guideline-based treatments and were enrolled in phase 1 clinical trials	4. Treatment was based on both genetic variants and tumor types.	2.The study was in the context of phase 1 trials and efficacy of the treatments is uncertain.		

The study limitations 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 13. Study Design and Conduct Limitations

Study	Allocation[a]	Blinding[b]	Selective Reporting[d]	Data Completeness[e]	Power[d]	Statistical[f]
Tsimberidou et al (2017)[15], IMPACT	1. Not randomized	1-3. No blinding				

The study limitations 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.

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.

Because the clinical validity of expanded cancer molecular panel testing to identify somatic variants to guide targeted treatment therapies has not been established, the chain of evidence supporting the clinical utility of panel testing cannot be constructed.

Section Summary: Clinically Useful

Evidence on targeted therapy for the treatment of various cancers includes an RCT, systematic reviews of phase 1, 2 and 3 trials, and a database review. The 1 published RCT (SHIVA trial) that used an expanded panel reported no difference in PFS compared with standard treatment. Additional randomized and nonrandomized trials for drug development, along with systematic reviews of these trials, have compared outcomes in patients who received molecularly targeted treatment with patients who did not. Generally, trials in which therapy was targeted to a gene variant resulted in improved response rates, PFS, and OS compared to patients in trials who did not receive targeted therapy. A major limitation in the relevance of these studies for comprehensive genomic profiling (CGP) is that treatment in these trials was guided both by the tissue source and the molecular target for drug development, rather than being matched solely by the molecular marker (i.e., basket trials). As a result, these types of studies do not provide evidence of the benefit of broad molecular profiling compared to limited genetic assessment based on known tumor-specific variants. Therefore, the clinical utility has not been demonstrated for the use of expanded molecular panels to direct targeted cancer treatment. RCTs that randomize patients with various tumor types to a strategy of CGP followed by targeted treatment are ongoing.

Summary of Evidence

For individuals who have advanced cancer that is being considered for targeted therapy who receive comprehensive genomic profiling of tumor tissue, the evidence includes a randomized controlled trial, nonrandomized trials, and systematic reviews of these studies. Relevant outcomes are overall survival, disease-specific survival, test validity, and quality of life. A large number of variants and many types of cancer preclude determination of the clinical validity of the panels as a whole, and clinical utility has not been demonstrated for the use of expanded molecular panels to direct targeted cancer treatment. The 1 published randomized controlled trial (SHIVA trial) that used an expanded panel reported no difference in progression-free survival compared with standard treatment. Additional randomized and nonrandomized trials for drug development, along with systematic reviews of these trials, have compared outcomes in patients who received molecularly targeted treatment with patients who did not. Generally, trials in which

therapy was targeted to a gene variant resulted in improved response rates, progression-free survival, and overall survival compared to patients in trials who did not receive targeted therapy. A major limitation in the relevance of these studies for comprehensive genomic profiling is that treatment in these trials was guided both by the tissue source and the molecular target for drug development, rather than being matched solely by the molecular marker (i.e., basket trials). As a result, these types of studies do not provide evidence of the benefit of broad molecular profiling compared to more limited genetic assessments based on known tumor-specific variants. Basket trials that randomize patients with various tumor types to a strategy of comprehensive genomic profiling followed by targeted treatment are needed, and several are ongoing. The evidence is insufficient to determine the effects of the technology on health outcomes.

SUPPLEMENTAL INFORMATION

Practice Guidelines and Position Statements

The National Comprehensive Cancer Network 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 recommendations for testing of common solid tumors are listed below:

Breast cancer[16,]

- *HER2* testing for all new primary or newly metastatic breast cancers, *BRCA1/2, PIK3CA, NTRK* fusions, microsatellite instability and mismatch repair.

Colon cancer[17,]

- *KRAS, NRAS*, and *BRAF* mutation testing, *HER2* amplification, *NTRK* fusions and microsatellite instability or mismatch repair testing for patients with metastatic colon cancer.

Non-small-cell lung cancer[18,]

- *EGFR*, *ALK*, *ROS1, BRAF, MET exon 14, RET, KRAS,* and *NTRK* fusions.

Cutaneous Melanoma[19,]

- *BRAF, NRAS, KIT*
- Uncommon mutations with next-generation sequencing are *ALK, ROS, and NTRK* fusions

Ovarian cancer[20,]

- *BRCA 1/2, NTRK,* microsatellite instability and mismatch repair

Chronic myeloid leukemia[21,]

- *BCR-ABL1*

Gastric cancer[22,]

- *HER2,* microsatellite instability, *NTRK* gene fusions
- *CDH1* for hereditary cancer predisposition syndromes.

Esophageal and esophogastric junction cancer[23,]

- *HER2,* microsatellite instability, *NTRK* gene fusions

Bladder cancer[24,]

- *FGFR*

Soft Tissue Sarcomas[25,]

- *NTRK* fusions

Pancreatic cancer[26,]

- *ALK, NRG1, NTRK, ROS1, BRAF, BRCA1/2, HER2, KRAS, PALB2*, mismatch repair deficiency

Prostate cancer[27,]
- *BRCA1, BRCA2, ATM, PALB2, FANCA, RAD51D, CHEK2, CDK12,* microsatellite instability and mismatch repair

Hepatobiliary cancer[28,]
- *NTRK, FGFR2, IDH1,* microsatellite instability and mismatch repair

Uterine cancer[29,]
- *NTRK,* microsatellite instability and tumor mutational burden

Central nervous system cancers[30,]
- *NTRK, HER2, BRAF, ALK, ROS1*

College of American Pathologists et al

In 2018, the College of American Pathologists, International Association for the Study of Lung Cancer, and the Association for Molecular Pathology updated their joint guidelines on molecular testing of patients with non-small-cell lung cancer.[31,] 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.[32,]

U.S. Preventive Services Task Force Recommendations

Not applicable.

Ongoing and Unpublished Clinical Trials

Some currently ongoing and unpublished trials that might influence this review are listed in Table 14.

Table 14. Summary of Key Trials

NCT No.	Trial Name	Planned Enrollment	Completion Date
Ongoing			
NCT02272595	A Study to Select Rational Therapeutics Based on the Analysis of Matched Tumor and Normal Biopsies in Subjects with Advanced Malignancies	200	Nov 2020
NCT02693535[a]	TAPUR: Testing the Use of U.S. Food and Drug Administration (FDA) Approved Drugs That Target a Specific Abnormality in a Tumor Gene in People with Advanced Stage Cancer (TAPUR)	3279	Dec 2023
NCT02152254	Randomized Study Evaluating Molecular Profiling and Targeted Agents in Metastatic Cancer: Initiative for Molecular Profiling and Advanced Cancer Therapy (IMPACT 2)	1362	Dec 2024

NCT No.	Trial Name	Planned Enrollment	Completion Date
NCT02299999[a]	Evaluation of the Efficacy of High Throughput Genome Analysis as a Therapeutic Decision Tool for Patients with Metastatic Breast Cancer (SAFIR02_Breast)	1460	Dec 2022
NCT02465060	Molecular Analysis for Therapy Choice (MATCH)	6452	Jun 2022
NCT02645149[a]	Molecular Profiling and Matched Targeted Therapy for Patients with Metastatic Melanoma	1000	Sep 2022
NCT02029001	A 2 period, Multicenter, Randomized, Open-label, Phase II Study Evaluating the Clinical Benefit of a Maintenance Treatment Targeting Tumor Molecular Alterations in Patients with Progressive Locally advanced or Metastatic Solid Tumors (MOST plus)	560	Oct 2022
NCT02925234	A Dutch National Study on Behalf of the CPCT to Facilitate Patient Access to Commercially Available, Targeted Anti-cancer Drugs to Determine the Potential Efficacy in Treatment of Advanced Cancers with a Known Molecular Profile (DRUP Trial)	950	Dec 2022
NCT03784014	Molecular Profiling of Advanced Soft-tissue Sarcomas. A Phase III Study	960	Oct 2024

NCT: national clinical trial.
[a] Industry-sponsored or co-sponsored.

CODING

The following codes for treatment and procedures applicable to this policy are included below for informational purposes. This may not be a comprehensive list of procedure codes applicable to this policy.

Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

The code(s) listed below are medically necessary ONLY if the procedure is performed according to the "Policy" section of this document.

CPT/HCPCS

81445-	Targeted genomic sequence analysis panel, solid organ or hematolymphoid neoplasm, DNA analysis, and RNA analysis when performed, 51 or greater genes (e.g., ALK, BRAF, CDKN2A, CEBPA, DNMT3A, EGFR, ERBB2, EZH2, FLT3, IDH1, IDH2, JAK2, KIT, KRAS, MLL, NPM1, NRAS, MET, NOTCH1, PDGFRA, PDGFRB, PGR, PIK3CA, PTEN, RET), interrogation for sequence variants and copy number variants or rearrangements, if performed
81450	Targeted genomic sequence analysis panel, hematolymphoid neoplasm or disorder, DNA analysis, and RNA analysis when performed, 5-50 genes (e.g., BRAF, CEBPA, DNMT3A, EZH2, FLT3, IDH1, IDH2, JAK2, KRAS, KIT, MLL, NRAS, NPM1, NOTCH1),

	interrogation for sequence variants, and copy number variants or rearrangements, or isoform expression or mRNA expression levels, if performed
81455	Targeted genomic sequence analysis panel, solid organ or hematolymphoid neoplasm, DNA analysis, and RNA analysis when performed, 51 or greater genes (e.g., ALK, BRAF, CDKN2A, CEBPA, DNMT3A, EGFR, ERBB2, EZH2, FLT3, IDH1, IDH2, JAK2, KIT, KRAS, MLL, NPM1, NRAS, MET, NOTCH1, PDGFRA, PDGFRB, PGR, PIK3CA, PTEN, RET), interrogation for sequence variants and copy number variants or rearrangements, if performed
88342	Immunohistochemistry or immunocytochemistry, per specimen; initial single antibody stain procedure
88381	Microdissection (i.e., sample preparation of microscopically identified target); manual
0013U	Oncology (solid organ neoplasia), gene rearrangement detection by whole genome next-generation sequencing, DNA, fresh or frozen tissue or cells, report of specific gene rearrangement(s). This PLA code is for MatePair Targeted Rearrangements, Oncology, developed by the Mayo Clinic Laboratories
0014U	Hematology (hematolymphoid neoplasia), gene rearrangement detection by whole genome next-generation sequencing, DNA, whole blood or bone marrow, report of specific gene rearrangement(s). This PLA code is for MatePair Targeted Rearrangements, Hematologic, developed by the Mayo Clinic Laboratories
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. This PLA code is for the OncoTarget™/OncoTreat™ developed at the Columbia University Department of Pathology and Cell Biology for Darwin Health™,
0022U	Targeted genomic sequence analysis panel, non-small cell lung neoplasia, DNA and RNA analysis, 23 genes, interrogation for sequence variants and rearrangements, reported as presence/absence of variants and associated therapy(ies) to consider. This PLA code is for the Oncomine™ Dx Target Test from Thermo Fisher Scientific
0036U	Exome (i.e., somatic mutations); paired formalin fixed paraffin embedded tumor tissue and normal specimen, sequence analyses. This PLA code is for the EXaCT-1 whole exome sequencing (WES) test from the Lab of Oncology-Molecular Detection, Weill Cornell Medicine-Clinical Genomics Laboratory
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. This PLA code is for the FoundationOne CDx™ (F1CDx®) test, a companion diagnostic (CDx) from Foundation Medicine, Inc
0048U	Oncology (solid organ neoplasia), DNA, targeted sequencing of protein-coding exons of 468 cancer-associated genes, including interrogation for somatic mutations and microsatellite instability, matched with normal specimens, utilizing formalin-fixed paraffin-embedded tumor tissue, report of clinically significant mutation(s). This PLA code is for the MSK-IMPACT™ (Integrated Mutation Profiling of Actionable Cancer Targets), Memorial Sloan Kettering Cancer Center
0056U	Hematology (acute myelogenous leukemia), DNA, whole genome next-generation sequencing to detect gene rearrangement(s), blood or bone marrow, report of specific gene rearrangement(s). This PLA code is for the MatePair Acute Myeloid Leukemia Panel developed by Mayo Clinic

0101U	Hereditary colon cancer disorders (e.g., Lynch syndrome, PTEN hamartoma syndrome, Cowden syndrome, familial adenomatosis polyposis), genomic sequence analysis panel utilizing a combination of NGS, Sanger, MLPA, and array CGH, with MRNA analytics to resolve variants of unknown significance when indicated (15 genes [sequencing and deletion/duplication], EPCAM and GREM1 [deletion/duplication only]). This PLA code is for the ColoNext® test from Ambry Genetics®,
0102U	Hereditary breast cancer-related disorders (e.g., hereditary breast cancer, hereditary ovarian cancer, hereditary endometrial cancer), genomic sequence analysis panel utilizing a combination of NGS, Sanger, MLPA, and array CGH, with MRNA analytics to resolve variants of unknown significance when indicated (17 genes [sequencing and deletion/duplication]). This PLA code is for the BreastNext® test from Ambry Genetics®
0103U	Hereditary ovarian cancer (e.g., hereditary ovarian cancer, hereditary endometrial cancer), genomic sequence analysis panel utilizing a combination of NGS, Sanger, MLPA, and array CGH, with MRNA analytics to resolve variants of unknown significance when indicated (24 genes [sequencing and deletion/duplication], EPCAM [deletion/duplication only]). This PLA code is for the OvaNext® test from Ambry Genetics®
0111U	Oncology (colon cancer), targeted KRAS (codons 12, 13 and 61) and NRAS (codons 12, 13 and 61) gene analysis utilizing formalin-fixed paraffin-embedded tissue. This PLA code is for the Praxis (TM) Extended RAS Panel by Illumina.
0174U	Oncology (solid tumor), mass spectrometric 30-protein targets, formalin-fixed, paraffin-embedded tissue, prognostic and predictive algorithm reported as likely, unlikely or uncertain benefit of 39 chemotherapy and targeted therapeutic oncology agents, This PLA code is OncoOnimisDx (eff 07/01/2020)
0211U	Oncology (pan-tumor), DNA and RNA by next-generation sequencing, utilizing formalin-fixed paraffin-embedded tissue, interpretative report for single nucleotide variants, copy number alterations, tumor mutational burden, and microsatellite instability, with therapy association. This PLA code is for MI Cancer Seek™ NGS Analysis, Caris MPI d/b/a Caris Life Sciences (eff 10/01/2020)
0224U	Oncology (solid organ), DNA, comprehensive genomic profiling, 257 genes, interrogation for single nucleotide variants, insertions/deletions, copy number alterations, gene rearrangements, tumor mutational burden and microsatellite instability, utilizing formalin-fixed paraffin embedded tumor tissue (eff 4/1/21)
0250U	Oncology (solid organ neoplasm), targeted genomic sequence DNA analysis of 505 genes, interrogation for somatic alterations (SNVs [single nucleotide variant], small insertions and deletions, one amplification, and four translocations), microsatellite instability and tumor-mutation burden
0006M	Oncology (hepatic), mRNA expression levels of 161 genes, utilizing fresh hepatocellular carcinoma tumor tissue, with alpha-fetoprotein level, algorithm reported as a risk classifier. This MAAA code is for the HeproDX™, GoPath Laboratories, LLC
0016M	Oncology (bladder), mRNA, microarray gene expression profiling of 209 genes, utilizing formalin fixed paraffin-embedded tissue, algorithm reported as molecular subtype (luminal, luminal infiltrated, basal, basal claudin-low, neuroendocrine-like. This MAAA code is for the Decipher Bladder TURBT® (new effective 10/1/2020)

For tests without specific panel codes bill the panel with unlisted codes 81599 or 81479

ICD-10 Diagnoses

Experimental / Investigational for all diagnoses related to this medical policy.

REVISIONS

09-05-2014	Policy added to the bcbsks.com web site on August 6, 2014.
06-23-2015	Updated Description section.
	Updated Rationale section.
	In Coding section: ▪ Added CPT codes 81246, 81287, 81288, 81313, 81370, 81371, 81372, 81373, 81374, 81375, 81376, 81377, 81378, 81379, 81380, 81381, 81382, 81383, 81445, 81450, 81455, 88368, 88381.
	Updated References section.
01-01-2016	In Coding section: ▪ Added CPT code: 81162 ▪ Updated nomenclature to CPT codes: 81210, 81275, 81355, 81405, 81445, 81450, 81455.
02-19-2016	Revised title from, "Molecular Panel Testing of Cancers to Identify Targeted Therapies."
	Updated Description section.
	In Policy section: ▪ In Policy language, revised "targeting" to "targeted" to read, "The use of expanded cancer mutation panels for selecting targeted cancer treatment is considered experimental / investigational." ▪ Added Policy Guidelines.
	Updated Rationale section.
	Updated References section.
	Added Appendix section.
01-20-2017	Updated Description section.
	In Policy section: ▪ Removed Policy Guidelines.
	Updated Rationale section.
	In Coding section: ▪ Added CPT codes: 81161, 81218, 81219, 81272, 81273, 81276, 81311, 81314, 81400, 81401, 81402, 81403, 81404. ▪ Removed CPT codes: 81280, 81281, 81282 *(Termed codes, effective December 31, 2016).*
	Updated References section.
11-08-2017	Updated Description section.
	In Policy section: ▪ Removed "mutation" and added "molecular" to read, "The use of expanded cancer molecular panels for selecting targeting cancer treatment is considered experimental / investigational."
	Updated Rationale section.
	Updated References section.
01-01-2018	In Coding section: ▪ Revised nomenclature to CPT code: 81257.
03-28-2018	In Coding section: ▪ Added CPT code: 0037U.
07-01-2018	In Coding section:

	▪ Added CPT code: 0050U.
	Updated References section.
01-01-2019	Updated Description section.
	Updated Rationale section.
	In Coding section: ▪ Revised nomenclature to CPT codes: 81162, 81212, 81215, 81216, 81217, 81244, 81287. ▪ Removed deleted CPT codes: 81211, 81213, 81214.
	Updated References section.
	Removed Appendix section.
03-05-2021	Updated Description section
	In Policy Section: ▪ Deleted: "expanded cancer molecular panels" ▪ Added: "comprehensive genomic profiling"
	Updated Rationale section
	In Coding section: ▪ Deleted CPT/ HPCS: 81161; 81162; 81200; 81201; 81202; 81203; 81205; 81206; 81207; 81208; 81209; 81210; 81212; 81215; 81216; 81217; 81218; 81219; 81220; 81221; 81222; 81223; 81224; 81225; 81226; 81227; 81228; 81229; 81235; 81240; 81241; 81242; 81243; 81244; 81245; 81246; 81250; 81251; 81252; 81253; 81254; 81255; 81256; 81257; 81260; 81261; 81262; 81263; 81264; 81265; 81266; 81267; 81268; 81270; 81272; 81273; 81275; 81276; 81287; 81288; 81290; 81291; 81292; 81293; 81294; 81295; 81296; 81297; 81298; 81299; 81300; 81301; 81302; 81303; 81304; 81310; 81311; 81313; 81314; 81315; 81316; 81317; 81318; 81319; 81321; 81322; 81323; 81325; 81326; 81331; 81332; 81340; 81341; 81342; 81350; 81355; 81370; 81371; 81372; 81373; 81374; 81375; 81376; 81377; 81378; 81379; 81380; 81381; 81382; 81383; 81400; 81402; 81403; 81404; 81405; 81406; 81407; 81408; 81445; 81450; 007U; 005OU ▪ Added CPC/HCPCS: 81445; 88342; 88381; 0013U; 0014U; 0019U; 0022U; 0036U; 0037U; 0048U; 0056U; 0101U; 0102U; 0103U; 0111U; 0174U; 0211U; 0006M; 0016M
	Updated References section
05-11-2021	In Coding section: ▪ Added code: 0224U.
07-01-2021	In Coding section: ▪ Added code: 0250U (effective 07-01-2021).

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