2.04.115	Comprehensive Genomic Profiling for Selecting Targeted Cancer Therapies		
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Section:	2.0 Medicine	**Page:**	Page 1 of 24

Policy Statement

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

NOTE: Refer to Appendix A to see the policy statement changes (if any) from the previous version.

Policy Guidelines

Coding

The following PLA codes includes FoundationOne CDx™ (F1CDx):

- **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

The following PLA codes may be used:

- **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.
- **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.
- **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.

The following PLA code is for Praxis (TM) Extended RAS Panel test:

- **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

Effective July 1, 2022, the following CPT code has been ***revised***:

- **0016M**: Oncology (bladder), mRNA, microarray gene expression profiling of 219 genes, utilizing formalin-fixed paraffin-embedded tissue, algorithm reported as molecular subtype (luminal, luminal infiltrated, basal, basal claudin-low, neuroendocrine-like)

The following is a PLA code for MI Cancer Seek™ NGS Analysis:

- **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.

There is a CPT code that may be billed as a companion diagnostic test:

- **0239U**: Targeted genomic sequence analysis panel, solid organ neoplasm, cell-free DNA, analysis of 311 or more genes, interrogation for sequence variants, including substitutions, insertions, deletions, select rearrangements, and copy number variations

The following CPT code represents Guardant360 CDx by Guardant Health. Per the manufacturer, this is a gene sequencing panel approved for use in advanced solid tumor cancer patients to help determine therapeutic options.

- **0242U**: Targeted genomic sequence analysis panel, solid organ neoplasm, cell-free circulating DNA analysis of 55-74 genes, interrogation for sequence variants, gene copy number amplifications, and gene rearrangements

The following CPT code represents Oncotype MAP Pan-Cancer Tissue Test by Paradigm Diagnostics. Per the manufacturer, this is a gene sequencing profile test for solid tumors.

- **0244U**: 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

The following CPT code represents Personal Genome Diagnostics Inc. Per the manufacturer, this test is intended to provide tumor mutation profiling information on somatic alterations, microsatellite instability and tumor mutation.

- **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

Effective January 1, 2022, there is a new CPT code that represents Praxis Somatic Whole Genome Sequencing, Praxis Genomics LLC. Per the manufacturer, this is a gene sequencing panel for oncology. It compares all genes in the genome of normal DNA and malignant cells by Illumina Short Read sequencing.

- **0297U:** Oncology (pan tumor), whole genome sequencing of paired malignant and normal DNA specimens, fresh or formalin-fixed paraffin-embedded (FFPE) tissue, blood or bone marrow, comparative sequence analyses and variant identification

Effective January 1, 2022, there is a new CPT code that represents Praxis Somatic Transcriptome, Praxis Genomics LLC. Per the manufacturer, this is a gene sequencing panel for oncology. It compares all genes in the genome of normal RNA and malignant cells by Illumina Short Read sequencing.

- **0298U:** Oncology (pan tumor), whole transcriptome sequencing of paired malignant and normal RNA specimens, fresh or formalin-fixed paraffin-embedded (FFPE) tissue, blood or bone marrow, comparative sequence analyses and expression level and chimeric transcript identification

Effective January 1, 2022, there is a new CPT code that represents Praxis Somatic Optical Genome Mapping, Praxis Genomics LLC. Per the manufacturer, this is a gene sequencing panel for oncology. It compares all genes in the genome of normal DNA and malignant cells by Bionano Optical genome mapping.

- **0299U:** Oncology (pan tumor), whole genome optical genome mapping of paired malignant and normal DNA specimens, fresh frozen tissue, blood, or bone marrow, comparative structural variant identification

Effective January 1, 2022, there is a new CPT code that represents Praxis Somatic Combined Whole Genome Sequencing and Optical Genome Mapping, Praxis Genomics LLC. Per the manufacturer, this is a gene sequencing panel for oncology. It compares all genes in the

genome of normal DNA and malignant cells by Illumina Short Read sequencing and Optical Genome mapping.

- **0300U:** Oncology (pan tumor), whole genome sequencing and optical genome mapping of paired malignant and normal DNA specimens, fresh tissue, blood, or bone marrow, comparative sequence analyses and variant identification

Effective July 1, 2022, there is a new CPT code that represents Oncomap™ ExTra; Exact Sciences; Genomic Health, Inc. Per the manufacturer, Oncomap™ is a gene sequencing panel designed to match patients to appropriate targeted therapies or clinical trials who have relapsed, refractory, advanced or metastatic tumors.

- **0329U:** Oncology (neoplasia), exome and transcriptome sequence analysis for sequence variants, gene copy number amplifications and deletions, gene rearrangements, microsatellite instability and tumor mutational burden utilizing DNA and RNA from tumor with DNA from normal blood or saliva for subtraction, report of clinically significant mutation(s) with therapy associations

Effective July 1, 2022, there is a new CPT code that represents Augusta Hematology Optical Genome Mapping; Bionano genomics; Per the manufacturer this test is indicated for the evaluation of individuals with hematological malignancies, such myeloid and lymphoid cancers.

- **0331U:** Oncology (hematolymphoid neoplasia), optical genome mapping for copy number alterations and gene rearrangements utilizing DNA from blood or bone marrow, report of clinically significant alternations

If a panel meets the requirements for one of the specific CPT codes for targeted genomic sequence analysis panel (81445-81455), the code may be reported for the test.

If the panel does not meet the requirements for a CPT panel code, any specific variant listed in codes 81200-81409 would be reported using those codes, and the other variants in the panel not specifically listed would be reported with 1 unit of the unlisted molecular pathology code 81479.

As an example of coding that might be used, GenPath recommends the following CPT codes in its test catalog for OnkoMatch Tumor Genotyping (with the number of units indicated in parentheses):

- 81210 (1)
- 81235 (1)
- 81275 (1)
- 81323 (1)

For OnkoMatch Tumor Genotyping + for Lung, GenPath recommends the following CPT codes:

- 81210 (1)
- 81235 (1)
- 81275 (1)
- 81323 (1)
- 88368 (2)
- 88381 (1)

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.

Related Policies

- Genetic Cancer Susceptibility Panels Using Next Generation Sequencing
- Molecular Analysis for Targeted Therapy or Immunotherapy of Non-Small-Cell Lung Cancer

Benefit Application

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control. 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.

Some state or federal mandates (e.g., Federal Employee Program [FEP]) prohibits plans from denying Food and Drug Administration (FDA)-approved technologies as investigational. In these instances, plans may have to consider the coverage eligibility of FDA-approved technologies on the basis of medical necessity alone.

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.

FoundationOne CDx (Foundation Medicine) initially received premarket approval by the U.S. Food and Drug Administration (FDA) (P170019) in 2017. It is intended as a companion diagnostic to identify patients who may benefit from treatment with the targeted therapies listed in Table 1. The approval is both tumor type and biomarker specific, and does not extend to all of the components included in the FoundationOne CDx product. The test is intended to identify patients who may benefit from treatment with targeted therapies in accordance with approved therapeutic product labeling. "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

Subsequent marketing clearance through the FDA's 510(k) process (FDA product code PZM) include the following:

- Omics Core (NantHealth) received marketing clearance in 2019 (K190661). The test is intended to provide information on somatic mutations (point mutations and small insertions and deletions) and tumor mutational burden.
- PGDx elio tissue complete (Personal Genome Diagnostics) received marketing clearance in 2020 (K192063). PGDx elio tissue complete is "intended to provide tumor mutation profiling information on somatic alterations (SNVs [single nucleotide variants],

small insertions and deletions, one amplification and 4 translocations), microsatellite instability and tumor mutation burden (TMB)".
- The NYU Langone Genome PACT assay (NYU Langone Medical Center) is a 607-gene panel that received marketing clearance by the FDA in 2021 (K202304). The test assesses somatic point mutations, insertions and deletions smaller than 35 base pairs.

The intended use is by qualified health care professionals in accordance with professional guidelines for oncology, and not prescriptive for use of any specific therapeutic product.

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

Table 1. 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), Alunbrig® (brigatinib), Xalkori® (crizotinib), or Zykadia® (ceritinib)
	BRAF V600E	Tafinlar® (dabrafenib) in combination with Mekinist® (trametinib)
	MET	Tabrecta(™) (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)
Cholangiocarcinoma	*FGFR2* fusion or other select rearrangements	Pemazyre® (pemigatinib) or Truseltiq(™) (infigratinib)
Prostate cancer	Homologous Recombination Repair (HRR) gene alterations	Lynparza® (olaparib)
Solid Tumors	Tumor mutational burden ≥10 mutations per megabase	Keytruda® (pembrolizumab)
	NTRK1/2/3 fusions	Vitrakvi® (larotrectinib)

Rationale

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

Table 2. 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
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
Omics Core(SM)	NantHealth	Solid	WES
PGDx elio tissue complete™	Personal Genome Diagnostics	Solid	NGS
NYU Langone Genome PACT assay	NYU Langone Medical Center	Solid	NGS

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

Literature Review

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.

Populations

The relevant population of interest is 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.

Study Selection Criteria
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 one 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.

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.

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 controlled trials (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.

Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs;
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.

Review of Evidence

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 versus standard care, with the first results published in 2015 (see Tables 3, 4, and 5).[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 therapies 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 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 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 versus 2.0 months in the standard of care group (p=.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 (2012, 2015)[8,9]; SHIVA				
N	195	195		
Targeted therapy	2.3 (1.7 to 3.8)	13 (7 to 20)	36 (36)	7 (7)

Study	PFS (95% CI), mo	PFS at 6 mo, % (95% CI)	Adverse Events, n (%)	
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-value	.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 (2012, 2015) [8,9]; SHIVA	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[c]	Data Completeness[d]	Power[e]	Statistical[f]
Le Tourneau et al (2012, 2015) [8,9]; SHIVA		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 suggests 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 1.5[a])		2.7 (2.6 to 2.9)	8.9 (8.3 to 9.3)	2.26 (2.04 to 2.49)
p-value	<.001		<.001	<.001	<.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	<.01		.002	.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		.03	<.001	.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 one 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 et al (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 1436 patients who underwent genomic profiling, 1170 (82.1%) had 1 or more variants , 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 months), and longer OS (8.4 vs. 7.3 months). 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 2024 (see Table 14)

Table 10. Summary of Key Nonrandomized Trial Study Characteristics

Study	Study Type	Country	Dates	Participants	Treatment1	Treatment2	Follow-Up
Tsimberidou et al (2017)[15] IMPACT	Database Review	U.S.	2012-2013	1436 patients with advanced cancer	Matched therapy (n=390)	Unmatched therapy (n=247)	

Table 11. Summary of Key Nonrandomized Trial 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	.010	.002	.041
Hazard Ratio (95% CI)		0.81 (0.69 to 0.96)	0.84 (0.71 to 0.99)
p-value		.015	.041

CI: confidence interval; HR: hazard ratio;;.

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	2.The study was in the context of phase 1 trials and efficacy		

Study	Population[a]	Intervention[b]	Comparator[c]	Outcomes[d]	Follow-Up[e]
		variants and tumor types.	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.

Non-Comparative Studies

NCI-MATCH is a master basket trial protocol in which tumors of various types are sequenced and patients assigned to targeted treatment based on the molecular alteration.[16] A total of 6391 patients were enrolled across 1117 clinical sites between 2015 and 2017 and underwent tumor sequencing. Patients had received a median of 3 lines of prior therapy. Common tumors comprised 37.5% of the total; the remainder had less common tumor histologies. Sequencing included 143 genes, of which approximately 40% of alterations were considered actionable, and 18% of patients were assigned to 30 treatment subprotocols. The majority of alterations identified in the 143 gene panel were either not actionable or led to experimental treatments in clinical trials. Response to treatments in the subprotocols are being reported and will provide preliminary evidence on tumor agnostic treatments.[17,18] Co-alterations discovered in NCI-MATCH have also led to a new biomarker-selected combination therapy trial by the National Cancer Institute, NCI-COMBOMATCH. Controlled basket trials that compare tumor-agnostic treatment based on a molecular marker with standard treatments are ongoing (see Table 14).

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 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 comprehensive genomic profiling 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 an RCT , nonrandomized trials, and systematic reviews of these studies. Relevant outcomes are OS, 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 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 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 that the technology results in an improvement in the net health outcome.

Supplemental Information

The purpose of the following information is to provide reference material. Inclusion does not imply endorsement or alignment with the evidence review conclusions.

Practice Guidelines and Position Statements

Guidelines or position statements will be considered for inclusion in 'Supplemental Information' if they were issued by, or jointly by, a US professional society, an international society with US representation, or National Institute for Health and Care Excellence (NICE). Priority will be given to guidelines that are informed by a systematic review, include strength of evidence ratings, and include a description of management of conflict of interest.

National Comprehensive Cancer Network

The 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 recommendations for testing of common solid tumors are listed below:

Breast cancer[19.]
- *HER2* testing for all new primary or newly metastatic breast cancers, *BRCA1/2, PIK3CA, NTRK* fusions, microsatilite instability and mismatch repair.

Colon[20.]
- *KRAS, NRAS*, and *BRAF* mutation testing, *HER2* amplification, *NTRK* fusion and microsatellite instability or mismatch repair testing for patients with metastatic colon cancer.

Non-small-cell lung cancer[21.]
- *EGFR*, *ALK*, *ROS1, BRAF, MET exon 14, RET, KRAS,* and *NTRK* fusions.

Cutaneous Melanoma[22.]
- *BRAF, NRAS, KIT.*
- Uncommon mutations with next-generation sequencing are *ALK, ROS, and NTRK* fusions

Ovarian cancer[23.]
- *BRCA 1/2, NTRK,* tumor mutational burden, microsatalite instability and mismatch repair.

Chronic myeloid leukemia[24.]
- *BCR-ABL1.*

Gastric cancer[25.]
- *HER2,* microsatellite instability or mismatch repair, *NTRK* gene fusions.
- *CDH1* for hereditary cancer predisposition syndromes.

Esophageal and esophogastric junction cancer[26.]
- *HER2,* microsatellite instability, *NTRK* gene fusions.

Bladder cancer[27.]
- *FGFR.*

Soft Tissue Sarcomas[28.]
- *NTRK* fusions.

Pancreatic cancer[29.]
- *ALK, NRG1, NTRK, ROS1, BRAF, BRCA1/2, HER2, KRAS, PALB2*, mismatch repair deficiency.

Prostate cancer[30.]
- *BRCA1, BRCA2, ATM, PALB2, FANCA, RAD51, CHEK2, CDK12,* microsatellite instability and mismatch repair.

Hepatobiliary cancer[31.]
- *NTRK, FGFR2, IDH1, BRAF-V600E,* microsatellite instability and mismatch repair.

Uterine cancer[32.]
- *NTRK,* mismatch repair, microsatellite instability and tumor mutational burden.

Central nervous system cancers[33.]
- *NTRK, HER2, BRAF, EGFR, MET, 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.[34.] 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.[35.]

U.S. Preventive Services Task Force Recommendations

Not applicable.

Medicare National Coverage

The Centers for Medicare and Medicaid Services will cover diagnostic testing with next-generation sequencing for beneficiaries with recurrent, relapsed, refractory, metastatic cancer, or advanced stages III or IV cancer if the beneficiary has not been previously tested using the same next-generation sequencing test, unless a new primary cancer diagnosis is made by the treating physician, and if the patient has decided to seek further cancer treatment (CAG-00450N). The test must have a U.S. Food and Drug Administration approved or cleared indication as an in vitro diagnostic, with results and treatment options provided to the treating physician for patient management.

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			
NCT03084757	SHIVA02 - Evaluation of the Efficacy of Targeted Therapy Based on Tumor Molecular Profiling in Patients With Advanced Cancer Using Each Patient as Its Own Control	370	Nov 2022
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)	3581	Dec 2024
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
NCT02465060	Molecular Analysis for Therapy Choice (MATCH)	6452	Jun 2022
NCT02645149[a]	Molecular Profiling and Matched Targeted Therapy for Patients With Metastatic Melanoma (MatchMel)	1000	Dec 2028
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 2026
NCT02925234[a]	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.

References

1. Spear BB, Heath-Chiozzi M, Huff J. Clinical application of pharmacogenetics. Trends Mol Med. May 2001; 7(5): 201-4. PMID 11325631

2. Dienstmann R, Rodon J, Barretina J, et al. Genomic medicine frontier in human solid tumors: prospects and challenges. J Clin Oncol. May 20 2013; 31(15): 1874-84. PMID 23589551
3. 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. Aug 15 2015; 21(16): 3631-9. PMID 25567908
4. 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): 616-22. PMID 24797823
5. 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): 1488-94. PMID 25852059
6. O'Brien CP, Taylor SE, O'Leary JJ, et al. Molecular testing in oncology: problems, pitfalls and progress. Lung Cancer. Mar 2014; 83(3): 309-15. PMID 24472389
7. 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): 726-36. PMID 26287849
8. 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. Dec 2012; 7(4): 253-65. PMID 23161020
9. 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, randomised, controlled phase 2 trial. Lancet Oncol. Oct 2015; 16(13): 1324-34. PMID 26342236
10. 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. PMID 27993804
11. 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): 3817-25. PMID 26304871
12. Jardim DL, Fontes Jardim DL, Schwaederle M, 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). PMID 26378224
13. Zimmer K, Kocher F, Spizzo G, et al. Treatment According to Molecular Profiling in Relapsed/Refractory Cancer Patients: A Review Focusing on Latest Profiling Studies. Comput Struct Biotechnol J. 2019; 17: 447-453. PMID 31007870
14. Wheler JJ, Janku F, Naing A, et al. Cancer Therapy Directed by Comprehensive Genomic Profiling: A Single Center Study. Cancer Res. Jul 01 2016; 76(13): 3690-701. PMID 27197177
15. Tsimberidou AM, Hong DS, Ye Y, et al. Initiative for Molecular Profiling and Advanced Cancer Therapy (IMPACT): An MD Anderson Precision Medicine Study. JCO Precis Oncol. 2017; 2017. PMID 29082359
16. Murciano-Goroff YR, Drilon A, Stadler ZK. The NCI-MATCH: A National, Collaborative Precision Oncology Trial for Diverse Tumor Histologies. Cancer Cell. Jan 11 2021; 39(1): 22-24. PMID 33434511
17. Kalinsky K, Hong F, McCourt CK, et al. Effect of Capivasertib in Patients With an AKT1 E17K-Mutated Tumor: NCI-MATCH Subprotocol EAY131-Y Nonrandomized Trial. JAMA Oncol. Feb 01 2021; 7(2): 271-278. PMID 33377972
18. Salama AKS, Li S, Macrae ER, et al. Dabrafenib and Trametinib in Patients With Tumors With BRAF V600E Mutations: Results of the NCI-MATCH Trial Subprotocol H. J Clin Oncol. Nov 20 2020; 38(33): 3895-3904. PMID 32758030
19. National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Breast Cancer. Version 7.2021

https://www.nccn.org/professionals/physician_gls/pdf/breast.pdf. Accessed August 20, 2021.
20. National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Colon Cancer. Version 2.2021. https://www.nccn.org/professionals/physician_gls/pdf/colon.pdf. Accessed August 21, 2021.
21. National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Non-Small Cell Lung Cancer. Version 5.2021. https://www.nccn.org/professionals/physician_gls/pdf/nscl.pdf. Accessed August 22, 2021.
22. National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Cutaneous Melanoma. Version 2.2021. https://www.nccn.org/professionals/physician_gls/pdf/cutaneous_melanoma.pdf. August 23, 2021.
23. National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Ovarian Cancer. Version 2.2021. https://www.nccn.org/professionals/physician_gls/pdf/ovarian.pdf. Accessed August 24, 2021.
24. National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Chronic Myeloid Leukemia. Version 1.2022. https://www.nccn.org/professionals/physician_gls/pdf/cml.pdf. Accessed August 25, 2021.
25. National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Gastric Cancer. Version 4.2021. https://www.nccn.org/professionals/physician_gls/pdf/gastric.pdf. Accessed August 26, 2021.
26. National Comprehensive Cancer Network (NCCN) NCCN Clinical Practice Guidelines in Oncology: Esophageal and Esophagogastric Junction Cancers. Version 4.2021. https://www.nccn.org/professionals/physician_gls/pdf/esophageal.pdf. Accessed August 27, 2021
27. National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Bladder Cancer. Version 4.2021. https://www.nccn.org/professionals/physician_gls/pdf/bladder.pdf. Accessed August 28, 2021.
28. National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Soft-Tissue Sarcoma. Version 2.2021. https://www.nccn.org/professionals/physician_gls/pdf/sarcoma.pdf. Accessed August 29, 2021.
29. National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Pancreatic Adenocarcinoma. Version 2:2021. https://www.nccn.org/professionals/physician_gls/pdf/pancreatic.pdf. Accessed August 30, 2021.
30. National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology: Prostate Cancer. Version 2.2021. https://www.nccn.org/professionals/physician_gls/pdf/prostate.pdf. Accessed August 15, 2021.
31. National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Hepatobiliary Cancers. Version 4.2021. https://www.nccn.org/professionals/physician_gls/pdf/hepatobiliary.pdf. Accessed August 16, 2021.
32. National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Uterine Neoplasms. Volume 3.2021. https://www.nccn.org/professionals/physician_gls/pdf/uterine.pdf. Accessed August 17, 2021.
33. National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology:Central Nervous System Cancers. Version 1.2021.

https://www.nccn.org/professionals/physician_gls/pdf/cns.pdf. Accessed August 18, 2021.
34. 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. PMID 29396253
35. 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. PMID 29401004
36. Blue Cross Blue Shield Association. Medical Policy Reference Manual, No. 2.04.115 (October 2021).

Documentation for Clinical Review

- No records required

Coding

This Policy relates only to the services or supplies described herein. Benefits may vary according to product design; therefore, contract language should be reviewed before applying the terms of the Policy.

The following codes are included below for informational purposes. Inclusion or exclusion of a code(s) does not constitute or imply member coverage or provider reimbursement policy. Policy Statements are intended to provide member coverage information and may include the use of some codes for clarity. The Policy Guidelines section may also provide additional information for how to interpret the Policy Statements and to provide coding guidance in some cases.

Type	Code	Description
CPT®	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
	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)
	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)
	0016M	Oncology (bladder), mRNA, microarray gene expression profiling of 219 genes, utilizing formalin-fixed paraffin-embedded tissue, algorithm reported as molecular subtype (luminal, luminal infiltrated, basal, basal claudin-low, neuroendocrine-like) ***(Code revision effective 7/1/2022)***
	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
	0022U	Targeted genomic sequence analysis panel, non-small cell lung neoplasia, DNA and RNA analysis, 23 genes, interrogation for

Type	Code	Description
		sequence variants and rearrangements, reported as presence/absence of variants and associated therapy(ies) to consider
	0036U	Exome (i.e., somatic mutations), paired formalin-fixed paraffin-embedded tumor tissue and normal specimen, sequence analyses
	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
	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)
	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)
	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])
	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])
	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])
	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
	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
	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
	0239U	Targeted genomic sequence analysis panel, solid organ neoplasm, cell-free DNA, analysis of 311 or more genes, interrogation for sequence variants, including substitutions, insertions, deletions, select rearrangements, and copy number variations)
	0242U	Targeted genomic sequence analysis panel, solid organ neoplasm, cell-free circulating DNA analysis of 55-74 genes, interrogation for

Type	Code	Description
		sequence variants, gene copy number amplifications, and gene rearrangements
	0244U	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
	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
	0297U	Oncology (pan tumor), whole genome sequencing of paired malignant and normal DNA specimens, fresh or formalin-fixed paraffin-embedded (FFPE) tissue, blood or bone marrow, comparative sequence analyses and variant identification ***(Code effective 1/1/2022)***
	0298U	Oncology (pan tumor), whole transcriptome sequencing of paired malignant and normal RNA specimens, fresh or formalin-fixed paraffin-embedded (FFPE) tissue, blood or bone marrow, comparative sequence analyses and expression level and chimeric transcript identification ***(Code effective 1/1/2022)***
	0299U	Oncology (pan tumor), whole genome optical genome mapping of paired malignant and normal DNA specimens, fresh frozen tissue, blood, or bone marrow, comparative structural variant identification ***(Code effective 1/1/2022)***
	0300U	Oncology (pan tumor), whole genome sequencing and optical genome mapping of paired malignant and normal DNA specimens, fresh tissue, blood, or bone marrow, comparative sequence analyses and variant identification ***(Code effective 1/1/2022)***
	0329U	Oncology (neoplasia), exome and transcriptome sequence analysis for sequence variants, gene copy number amplifications and deletions, gene rearrangements, microsatellite instability and tumor mutational burden utilizing DNA and RNA from tumor with DNA from normal blood or saliva for subtraction, report of clinically significant mutation(s) with therapy associations ***(Code effective 7/1/2022)***
	0331U	Oncology (hematolymphoid neoplasia), optical genome mapping for copy number alterations and gene rearrangements utilizing DNA from blood or bone marrow, report of clinically significant alternations ***(Code effective 7/1/2022)***
	81445	Targeted genomic sequence analysis panel, solid organ neoplasm, DNA analysis, and RNA analysis when performed, 5-50 genes (e.g., ALK, BRAF, CDKN2A, EGFR, ERBB2, KIT, KRAS, NRAS, MET, PDGFRA, PDGFRB, PGR, PIK3CA, PTEN, RET), interrogation for sequence variants and copy number variants or rearrangements, if performed
	81450	Targeted genomic sequence analysis panel, hematolymphoid neoplasm or disorder, DNA analysis, and RNA analysis when performed, 5-50 genes (e.g., BRAF, CEBPA, DNMT3A, EZH2, FLT3, IDH1, IDH2, JAK2, KRAS, KIT, MLL, NRAS, NPM1, NOTCH1), interrogation for sequence variants, and copy number variants or rearrangements, or isoform expression or mRNA expression levels, if performed
	81455	Targeted genomic sequence analysis panel, solid organ or hematolymphoid neoplasm, DNA analysis, and RNA analysis when performed, 51 or greater genes (e.g., ALK, BRAF, CDKN2A, CEBPA,

Type	Code	Description
		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
HCPCS	None	

Policy History

This section provides a chronological history of the activities, updates and changes that have occurred with this Medical Policy.

Effective Date	Action
09/30/2015	BCBSA Medical Policy adoption
02/01/2016	Coding update
09/01/2016	Policy title change from Molecular Panel Testing of Cancers to Identify Targeted Therapies Policy revision without position change
12/01/2016	Policy revision without position change
12/01/2017	Policy revision without position change
05/01/2018	Coding update
12/01/2018	Policy revision without position change
08/01/2019	Administrative update
12/16/2019	Policy title change from Expanded Molecular Panel Testing of Cancers to Identify Targeted Therapies Policy revision without position change Coding update
12/01/2020	Annual review. No change to policy statement. Literature review updated. Coding update.
01/01/2021	Coding update
06/01/2021	Coding update
08/01/2021	Coding update
12/01/2021	Annual review. No change to policy statement. Policy guidelines and literature updated.
02/01/2022	Coding update
08/01/2022	Coding update

Definitions of Decision Determinations

Medically Necessary: Services that are Medically Necessary include only those which have been established as safe and effective, are furnished under generally accepted professional standards to treat illness, injury or medical condition, and which, as determined by Blue Shield, are: (a) consistent with Blue Shield medical policy; (b) consistent with the symptoms or diagnosis; (c) not furnished primarily for the convenience of the patient, the attending Physician or other provider; (d) furnished at the most appropriate level which can be provided safely and effectively to the patient; and (e) 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 the Member's illness, injury, or disease.

Investigational/Experimental: A treatment, procedure, or drug is investigational when it has not been recognized as safe and effective for use in treating the particular condition in accordance with generally accepted professional medical standards. This includes services where approval by the federal or state governmental is required prior to use, but has not yet been granted.

Split Evaluation: Blue Shield of California/Blue Shield of California Life & Health Insurance Company (Blue Shield) policy review can result in a split evaluation, where a treatment, procedure, or drug will be considered to be investigational for certain indications or conditions, but will be deemed safe and effective for other indications or conditions, and therefore potentially medically necessary in those instances.

Prior Authorization Requirements (as applicable to your plan)

Within five days before the actual date of service, the provider must confirm with Blue Shield that the member's health plan coverage is still in effect. Blue Shield reserves the right to revoke an authorization prior to services being rendered based on cancellation of the member's eligibility. Final determination of benefits will be made after review of the claim for limitations or exclusions.

Questions regarding the applicability of this policy should be directed to the Prior Authorization Department at (800) 541-6652, or the Transplant Case Management Department at (800) 637-2066 ext. 3507708 or visit the provider portal at www.blueshieldca.com/provider.

Disclaimer: This medical policy is a guide in evaluating the medical necessity of a particular service or treatment. Blue Shield of California may consider published peer-reviewed scientific literature, national guidelines, and local standards of practice in developing its medical policy. Federal and state law, as well as contract language, including definitions and specific contract provisions/exclusions, take precedence over medical policy and must be considered first in determining covered services. Member contracts may differ in their benefits. Blue Shield reserves the right to review and update policies as appropriate.

Appendix A

POLICY STATEMENT (No changes)	
BEFORE	**AFTER**
Comprehensive Genomic Profiling for Selecting Targeted Cancer Therapies 2.04.115 **Policy Statement:** The use of comprehensive genomic profiling for selecting targeted cancer treatment is considered **investigational**.	**Comprehensive Genomic Profiling for Selecting Targeted Cancer Therapies 2.04.115** **Policy Statement:** The use of comprehensive genomic profiling for selecting targeted cancer treatment is considered **investigational**.