2.04.115 Comprehensive Genomic Profiling for Selecting Targeted Cancer Therapies			
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Section:	2.0 Medicine	**Page:**	Page 1 of 27

Policy Statement

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

Note: For individuals enrolled in health plans subject to the Biomarker Testing Law (Health & Safety Code Section 1367.667 and the Insurance Code Section 10123.209), Centers for Medicare & Medicaid Services (CMS) National Coverage Determination (NCD) and Local Coverage Determination (LCD) may also apply. Please refer to the Medicare National and Local Coverage section of this policy, National Coverage Determination (NCD) 90.2 Next Generation Sequencing (NGS), and to MolDX: Next-Generation Sequencing for Solid Tumors for reference.

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

Policy Guidelines

Coding

See the Codes table for details.

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.

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 (RCT), nonrandomized trials, and systematic reviews of these studies. Relevant outcomes are overall survival (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 RCT (SHIVA trial) that used an expanded panel reported no difference in progression free survival (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.

Additional Information
Not applicable.

Related Policies

- Germline and Somatic Biomarker Testing (Including Liquid Biopsy) for Targeted Treatment in Breast Cancer (BRCA1, BRCA2, PIK3CA, Ki-67, RET, BRAF, ESR1, NTRK)
- Germline and Somatic Biomarker Testing (Including Liquid Biopsy) for Targeted Treatment in Prostate Cancer (BRCA1/2, Homologous Recombination Repair Gene Alterations, NTRK Gene Fusion)
- Germline and Somatic Biomarker Testing (Including Liquid Biopsy) for Targeted Treatment in Ovarian Cancer (BRCA1, BRCA2, Homologous Recombination Deficiency, NTRK)
- Somatic Biomarker Testing (Including Liquid Biopsy) for Targeted Treatment in Non-Small-Cell Lung Cancer (EGFR, ALK, BRAF, ROS1, RET, MET, KRAS, NTRK) **(to be published)**
- Genetic Cancer Susceptibility Panels Using Next Generation Sequencing

Benefit Application

Benefit determinations should be based in all cases on the applicable member health services contract language. To the extent there are conflicts between this Medical Policy and the member health services 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 law may prohibit health plans from denying FDA-approved Healthcare Services as investigational or experimental. In these instances, Blue Shield of California may be obligated to determine if these FDA-approved Healthcare Services are Medically Necessary.

Regulatory Status

SB 535
Starting on July 1, 2022 (per CA law SB 535) for commercial plans regulated by the California Department of Managed Healthcare and California Department of Insurance (PPO and HMO), health care service plans and insurers shall not require prior authorization for biomarker testing, including biomarker testing for cancer progression and recurrence, if a member has stage 3 or 4 cancer. Health care service plans and insurers can still do a medical necessity review of a biomarker test and possibly deny coverage after biomarker testing has been completed and a claim is submitted (post service review).

SB 496
SB 496 requires health plans licensed under the Knox-Keene Act ("Plans"), Medi-Cal managed care plans ("MCPS"), and health insurers ("Insurers") to cover biomarker testing for the diagnosis, treatment, appropriate management, or ongoing monitoring of an enrollee's disease or condition to guide treatment decisions, as prescribed. The bill does not require coverage of biomarker testing for screening purposes. Restricted or denied use of biomarker testing for these purposes is subject to

state and federal grievance and appeal processes. Where biomarker testing is deemed medically necessary, Plans and Insurers must ensure that the testing is provided in a way that limits disruptions in care.

Clinical Laboratory Improvement Amendments (CLIA) and FDA Regulatory Overview

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 2. 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.
- ACTOnco (ACT Genomics) received marketing clearance in 2022 (K210017). The next-generation sequencing test is intended to provide information on point mutations, small insertions and deletions, ERBB2 gene amplification, and tumor mutational burden in patients with solid malignant neoplasms.
- xT CDx (Tempus Labs, Inc) is a 648-gene panel that received marketing clearance by the FDA in 2023. The test assesses single nucleotide variants and multi-nucleotide variants as well as insertion and deletion alterations in the included genes as well as microsatelite instability.

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 2. Companion Diagnostic Indications for F1CDx[1]

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), Vizimpro® (dacomitinib)
	EGFR exon 20 T790M alterations	Tagrisso® (osimertinib)
	EGFR exon 20 insertion mutations	Rybrevant® (amivantamb), Exkivity® (mobocertinib)
	ALK rearrangements	Alecensa® (alectinib), Xalkori® (crizotinib), or Zykadia® (ceritinib)
	BRAF V600E	Tafinlar® (dabrafenib) in combination with Mekinist® (trametinib)
	MET	Tabrecta™ (capmatinib)
	KRAS G12C	Krazati® (adagrasib), Lumakras® (sotorasib)
	RET fusions	Gavreto® (pralsetinib), Retevmo® (selpercatinib)
	ROS1 fusions	Rozlytrek® (entrectinib)
Melanoma	*BRAF* V600E	Tafinlar® (dabrafenib), Mekinist (trametinib)or Zelboraf® (vemurafenib)
	BRAF V600E and V600K	Braftovi® (encorafenib), Mekinist® (trametinib) or Tecentriq® (atezolizumab) in combination with Cotellic® (cobimetinib) and Zelboraf® (vemurafenib)
	*HLA-A*02:01*	Kimmtrak® (tebentafusp-tebn)
Breast cancer	*ERBB2* (HER2) amplification	Herceptin® (trastuzumab), Kadcyla® (ado-trastuzumabemtansine), Enhertu® (fam-trastuzumab deruxtecan-nxki), or Perjeta® (pertuzumab)
	ESR1 missense mutations	Orserdu® (elacestrant)
	PIK3CA alterations	Lynparza® (olaparib), Truqap® (capivasertib) in combination with Faslodex® (fulvestrant), Piqray® (alpelisib)
Colorectal cancer	*BRAF* V600E	Braftovi® (encorafenib)
	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)
	FOLR1 protein expression	Elahere® (mirvetuximab soravtansine-gynx)
Cholangiocarcinoma	*FGFR2* fusion or other select rearrangements	Pemazyre® (pemigatinib) or Truseltiq fgv™ (infigratinib)
	IDH1 single nucleotide variants	Tibsovo® (ivosidenib)
Prostate cancer	*BRCA1/2* alterations	Akeega® (niraparib + abiraterone acetate), Rubraca® (rucaparib), Lynparza® (olaparib)
	Homologous Recombination Repair (HRR) gene alterations	Lynparza® (olaparib)

Tumor Type	Biomarker(s) Detected	Therapy
Solid Tumors	Tumor mutational burden ≥10 mutations per megabase	Keytruda® (pembrolizumab)
	Microsatellite instability-high (MSI-H)	Keytruda® (pembrolizumab)
	NTRK1/2/3 fusions	Vitrakvi® (larotrectinib) or Rozlytrek® (entrectinib)
	MLH1, PMS2, MSH2 and MSH6	Keytruda® (pembrolizumab), Jemperli® (dostarlimag-gxly)
	RET fusions	Retevmo® (selpercatinib)

F1CDx: FoundationOne Companion Diagnostic.
[1] An updated list of FDA-cleared or -approved companion diagnostic devices is available at https://www.fda.gov/medical-devices/in-vitro-diagnostics/list-cleared-or-approved-companion-diagnostic-devices-in-vitro-and-imaging-tools.

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 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® 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

Test	Manufacturer	Tumor Type	Technology
NYU Langone Genome PACT assay	NYU Langone Medical Center	Solid	NGS
ACTOnco	ACT Genomics	Solid	NGS
xT CDx	Tempus Labs, Inc.	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 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

For the evaluation of clinical validity of comprehensive genomic profiling for selecting targeted cancer therapies, studies that meet the following eligibility criteria were considered:

- Reported on the accuracy of the marketed version of the technology (including any algorithms used to calculate scores)
- Included a suitable reference standard
- Patient/sample clinical characteristics were described
- Patient/sample selection criteria were described.

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.

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 versus 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,] A total of 195 patients were enrolled with metastatic solid tumors, which were refractory to standard therapy with a median number of 3 previous lines of therapy (range 2 to 5). Participants had a median age of 61 years in the molecularly targeted group (n=99) and 63 years of age in the standard of care group based on the

treating physicians' choice. The most common tumor types were breast adenocarcinoma, ovarian cancer, lung cancer, colorectal cancer, cervical cancer, and head and neck squamous cell carcinoma; all other tumor types occurred in less than 5% of participants in each group. 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)
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[d]	Data Completeness[e]	Power[d]	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. Twenty-six (37%) patients in the TPC to MTA crossover arm and 15 (61%) 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 their own 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*. A 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
HR (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 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.

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.[17,18,19,] 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).

TAPUR is an ongoing phase II, prospective, non-randomized, open-label basket study that evaluates the antitumor activity of targeted agents in individuals who have advanced cancers and have genomic alterations that are targets for these drugs and was initiated in March of 2016 (NCT02693535).[20,] The American Society of Clinical Oncology (ASCO) designed and led the trial and matched patients' tumor genomic alternations to US Food and Drug Administration-approved, commercially available, targeted anticancer agents. The primary endpoint of the study is the rate of disease control, defined as a complete response or partial response at 8 weeks or later or stable disease at 16 weeks after study treatment; secondary endpoints included PFS, OS, and safety.

Enrollment was initially limited to 10 individuals per cohort and participants were followed for 16 weeks or more. Enrollment is stopped if 2 or fewer participants have a successful outcome, but if ≥ 2 participants have a successful outcome, the cohort is expanded to enroll an additional 18 participants. As of August 2023, 21 cohorts have had positive findings, and there are currently 14 treatments being investigated in expanded cohorts for multiple indications after showing initial treatment success.

The Drug Rediscovery Protocol (DRUP) is a prospective, non-randomized clinical trial that aims to describe the safety and efficacy of commercially available anticancer agents that are targeted to actionable genomic or protein expression variants (NCT02925234).[21,] Patients are enrolled in separate cohorts based on tumor histology and were matched to off-label targeted molecular therapies or immunotherapies. The study's primary endpoint is a complete response, partial response, or stable disease at ≥16 weeks. A total of 1145 participants with cancer were screened, and 500 initiated therapies with one of 25 drugs and had evaluable outcomes. Approximately a third of participants (33%), including those with rare cancers (n=164), experienced a clinical benefit. These patients with rare cancers were more likely to have inactivating *CDKN2A* or activating *BRAF* mutations (P≦.001) when compared to individuals with non-rare cancers and were found to have higher rates of clinical benefit when treated with small-molecular inhibitors that target *BRAF* when compared versus the non-rare cancer subgroup.

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 a randomized controlled trial (RCT), nonrandomized trials, and systematic reviews of these studies. Relevant outcomes are overall survival (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 RCT (SHIVA trial) that used an expanded panel reported no difference in progression free survival (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.

American Society of Clinical Oncology

In 2022, the American Society of Clinical Oncology (ASCO) published a provisional clinical opinion based on informal consensus in the absence of a formal systematic review on the appropriate use of tumor genomic testing in patients with metastatic or advanced solid tumors.[22,] The opinion notes the following:

PCO 1.1. Genomic testing should be performed for patients with metastatic or advanced solid tumors with adequate performance status in the following 2 clinical scenarios:

- When there are genomic biomarker–linked therapies approved by regulatory agencies for their cancer.
- When considering a treatment for which there are specific genomic biomarker-based contraindications or exclusions (strength of recommendation: strong).

PCO 1.2.1. For patients with metastatic or advanced solid tumors, genomic testing using multigene genomic sequencing is preferred whenever patients are eligible for a genomic biomarker–linked therapy that a regulatory agency has approved (strength of recommendation: moderate).

PCO 1.2.2. Multigene panel–based genomic testing should be used whenever more than one genomic biomarker is linked to a regulatory agency–approved therapy (strength of recommendation: strong).

PCO 2.1. Mismatch repair deficiency status (dMMR) should be evaluated on patients with metastatic or advanced solid tumors who are candidates for immunotherapy. There are multiple approaches, including using large multigene panel-based testing to assess microsatellite instability (MSI).

Consider the prevalence of dMMR and/or MSI-H status in individual tumor types when making this decision (strength of recommendation: strong).

PCO 2.2. When tumor mutational burden (TMB) may influence the decision to use immunotherapy, testing should be performed with either large multigene panels with validated TMB testing or whole-exome analysis (strength of recommendation: strong).

PCO 4.1. Genomic testing should be considered to determine candidacy for tumor-agnostic therapies in patients with metastatic or advanced solid tumors without approved genomic biomarker–linked therapies (strength of recommendation: moderate).

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.[23,] 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.

National Comprehensive Cancer Network

The National Comprehensive Cancer Network (NCCN) guidelines 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[24,]

- *HER2* testing for all new primary or newly metastatic breast cancers, *BRCA1/2, ESR1, PIK3CA*, *NTRK* fusions, *RET* fusions, microsatellite instability and mismatch repair, and tumor mutational burden.

Colon cancer[25,]

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

Non-small-cell lung cancer[26,]

- *EGFR*, *ALK*, *ROS1, BRAF, MET exon 14, RET, KRAS, HER2,* and *NTRK* fusions.

Cutaneous melanoma[27,]

- *BRAF, NRAS, KIT.*
- Uncommon mutations with next-generation sequencing are *ALK, ROS1, NTRK,* and *BRAF* fusions.

Ovarian cancer[28,]

- *BRCA 1/2, BRAF, NTRK, HER2, HRD, RET*, *FRα,* tumor mutational burden, microsatellite instability and mismatch repair.

Pancreatic cancer[29,]

- *ALK, NRG1, NTRK, ROS1, FGRF2, RET, BRAF, BRCA1/2, HER2, KRAS, PALB2*, mismatch repair deficiency, microsatellite instability, or tumor mutational burden.

Prostate cancer[30,]

- *BRCA1, BRCA2, ATM, ATR, PALB2, FANCA, MLH1, MRE11A, NBN, RAD51, CHEK2, CDK12,* microsatellite instability, tumor mutational burden, and mismatch repair deficiency.

Updated recommendations for testing of solid tumors can be accessed at https://www.nccn.org/guidelines.

U.S. Preventive Services Task Force Recommendations

Not applicable.

Medicare National and Local 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 (National Coverage Determination [NCD] 90.2 Next Generation Sequencing). 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.

Local coverage guidance for California is provided by the Molecular Diagnostic Services Program (MolDx) in the document MolDX: Next-Generation Sequencing for Solid Tumors and the associated Billing and Coding: MolDX: Next-Generation Sequencing for Solid Tumors.
MolDx states that all the following must be present for coverage eligibility:

- As per NCD 90.2, this test is reasonable and necessary when:
  - the patient has either:
    - Recurrent cancer
    - Relapsed cancer
    - Refractory cancer
    - Metastatic cancer
    - Advanced cancer (stages III or IV)
  - AND has not been previously tested by the same test for the same genetic content
  - AND is seeking further treatment
- The test has satisfactorily completed a TA by MolDX for the stated indications of the test
- The assay performed includes at *least* the minimum genes and genomic positions required for the identification of clinically relevant FDA-approved therapies with a companion diagnostic biomarker as well as other biomarkers known to be necessary for clinical decision making for its intended use that can be reasonably detected by the test. Because these genes and variants will change as the literature and drug indications evolve, they are listed separately in associated documents such as the MolDX TA forms.

The following PLA Codes are included in MolDx Billing and Coding article for Next Generation Sequencing for Solid Tumors:

Code	Description	TEST NAME
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	Oncotype MAP™ PanCancer Tissue Test.
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	PGDx elio™ tissue complete
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	Oncomap™ ExTra
0334U	ONCOLOGY (SOLID ORGAN), TARGETED GENOMIC SEQUENCE ANALYSIS, FORMALIN-FIXED PARAFFINEMBEDDED (FFPE) TUMOR TISSUE, DNA	Guardant360 TissueNext™

Code	Description	TEST NAME
	ANALYSIS, 84 OR MORE GENES, INTERROGATION FOR SEQUENCE VARIANTS, GENE COPY NUMBER AMPLIFICATIONS, GENE REARRANGEMENTS, MICROSATELLITE INSTABILITY AND TUMOR MUTATIONAL BURDEN	
0379U	TARGETED GENOMIC SEQUENCE ANALYSIS PANEL, SOLID ORGAN NEOPLASM, DNA (523 GENES) AND RNA (55 GENES) BY NEXT-GENERATION SEQUENCING, INTERROGATION FOR SEQUENCE VARIANTS, GENE COPY NUMBER AMPLIFICATIONS, GENE REARRANGEMENTS, MICROSATELLITE INSTABILITY, AND TUMOR MUTATIONAL BURDEN	Solid Tumor Expanded Panel
0391U	ONCOLOGY (SOLID TUMOR), DNA AND RNA BY NEXT-GENERATION SEQUENCING, UTILIZING FORMALIN-FIXED PARAFFIN-EMBEDDED (FFPE) TISSUE, 437 GENES, INTERPRETIVE REPORT FOR SINGLE NUCLEOTIDE VARIANTS, SPLICE-SITE VARIANTS, INSERTIONS/DELETIONS, COPY NUMBER ALTERATIONS, GENE FUSIONS, TUMOR MUTATIONAL BURDEN, AND MICROSATELLITE INSTABILITY, WITH ALGORITHM QUANTIFYING IMMUNOTHERAPY RESPONSE SCORE	Strata Select™
0543U	ONCOLOGY (SOLID TUMOR), NEXT-GENERATION SEQUENCING OF DNA FROM FORMALIN-FIXED PARAFFIN-EMBEDDED (FFPE) TISSUE OF 517 GENES, INTERROGATION FOR SINGLE-NUCLEOTIDE VARIANTS, MULTI-NUCLEOTIDE VARIANTS, INSERTIONS AND DELETIONS FROM DNA, FUSIONS IN 24 GENES AND SPLICE VARIANTS IN 1 GENE FROM RNA, AND TUMOR MUTATION BURDEN	TruSight™ Oncology Comprehensive

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			
			(unknown status)
NCT04111107	Precision Medicine for Patients With Identified Actionable Mutations at Wake Forest Baptist Comprehensive Cancer Center (WFBCCC): A Pragmatic Trial	337	Jun 2024 (terminated)
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)	3641	Dec 2025
NCT02152254[a]	Randomized Study Evaluating Molecular Profiling and Targeted Agents in Metastatic Cancer: Initiative for Molecular Profiling and Advanced Cancer Therapy (IMPACT 2)	1362	Dec 2024
NCT05554341	A ComboMATCH Treatment Trial ComboMATCH Treatment Trial E4: Nilotinib and Paclitaxel in Patients With Prior Taxane-Treated Solid Tumors	40	Jul 2025
NCT05525858[a]	KOrean Precision Medicine Networking Group Study of MOlecular Profiling Guided Therapy Based on Genomic Alterations in Advanced Solid Tumors II (KOSMOSII)	1000	Sep 2025
NCT02465060	Molecular Analysis for Therapy Choice (MATCH)	6452	Dec 2025
NCT05058937[a]	A Study to Examine the Clinical Value of Comprehensive Genomic Profiling Performed by Belgian NGS Laboratories: a Belgian Precision Study of the BSMO in Collaboration With	936	May 2026

NCT No.	Trial Name	Planned Enrollment	Completion Date
	the Cancer Centre - Belgian Approach for Local Laboratory Extensive Tumor Testing (BALLETT)		
NCT05554367	A ComboMATCH Treatment Trial: Palbociclib and Binimetinib in RAS-Mutant Cancers	199	Aug 2026
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)	1550	Dec 2027
NCT03784014	Molecular Profiling of Advanced Soft-tissue Sarcomas. A Phase III Study (MULTISARC)	960	Oct 2024
NCT04589845[a]	Tumor-Agnostic Precision Immunooncology and Somatic Targeting Rational for You (TAPISTRY) Phase II Platform Trial	770	Sep 2032
NCT05906407	COGNITION: Comprehensive Assessment of Clinical Features, Genomics and Further Molecular Markers to Identify Patients With Early Breast Cancer for Enrolment on Marker Driven Trials (Molecular Diagnostic Platform)	2000	Dec 2028
NCT05652569	Comprehensive Assessment of Clinical Features and Biomarkers to Identify Patients With Advanced or Metastatic Breast Cancer for Marker Driven Trials in Humans (CATCH)	5000	Dec 2030
NCT05695638	Proseq Cancer: A Prospective Study of Comprehensive Genomic Profiling in Patients With Incurable Cancer in Search for Targeted Treatment	3000	May 2035
Unpublished			
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	170	Nov 2022
NCT05385081	PREcision Medicine in Cancer in Odense, Denmark (PRECODE) Feasibility of Genomic Profiling and Frequency of Genomic Matched Treatment in Solid Tumors With no Treatment Options (PRECODE)	900	Dec 2023
NCT04111107	Precision Medicine for Patients With Identified Actionable Mutations at Wake Forest Baptist Comprehensive Cancer Center (WFBCCC): A Pragmatic Trial	337	Jun 2024 (terminated)

NCT: national clinical trial.

[a] Industry-sponsored or co-sponsored.

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Documentation for Clinical Review

- No records required

Coding

The list of codes in this Medical Policy is intended as a general reference and may not cover all codes. Inclusion or exclusion of a code(s) does not constitute or imply member coverage or provider reimbursement policy.

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
	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)
	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 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)
	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])

Type	Code	Description
	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
	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
	0288U	Oncology (lung), mRNA, quantitative PCR analysis of 11 genes (BAG1, BRCA1, CDC6, CDK2AP1, ERBB3, FUT3, IL11, LCK, RND3, SH3BGR, WNT3A) and 3 reference genes (ESD, TBP, YAP1), formalin-fixed paraffin-embedded (FFPE) tumor tissue, algorithmic interpretation reported as a recurrence risk score
	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
	0334U	Oncology (solid organ), targeted genomic sequence analysis, formalin-fixed paraffin-embedded (FFPE) tumor tissue, DNA analysis, 84 or more genes, interrogation for sequence variants, gene copy number amplifications, gene rearrangements, microsatellite instability and tumor mutational burden
	0379U	Targeted genomic sequence analysis panel, solid organ neoplasm, DNA (523 genes) and RNA (55 genes) by next-generation sequencing, interrogation for sequence variants, gene copy number amplifications, gene rearrangements, microsatellite instability, and tumor mutational burden
	0391U	Oncology (solid tumor), DNA and RNA by next-generation sequencing, utilizing formalin-fixed paraffin-embedded (FFPE) tissue, 437 genes, interpretive report for single nucleotide variants, splice-site variants, insertions/deletions, copy number alterations, gene fusions, tumor mutational burden, and microsatellite instability, with algorithm quantifying immunotherapy response score
	0422U	Oncology (pan-solid tumor), analysis of DNA biomarker response to anti-cancer therapy using cell-free circulating DNA, biomarker comparison to a previous baseline pre-treatment cell-free circulating

Type	Code	Description
		DNA analysis using next-generation sequencing, algorithm reported as a quantitative change from baseline, including specific alterations, if appropriate
	0444U	Oncology (solid organ neoplasia), targeted genomic sequence analysis panel of 361 genes, interrogation for gene fusions, translocations, or other rearrangements, using DNA from formalin-fixed paraffin-embedded (FFPE) tumor tissue, report of clinically significant variant(s)
	0473U	Oncology (solid tumor), next-generation sequencing (NGS) of DNA from formalin-fixed paraffin-embedded (FFPE) tissue with comparative sequence analysis from a matched normal specimen (blood or saliva), 648 genes, interrogation for sequence variants, insertion and deletion alterations, copy number variants, rearrangements, microsatellite instability, and tumor-mutation burden
	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
	81449	Solid organ neoplasm, genomic sequence analysis panel, 5-50 genes, interrogation for sequence variants and copy number variants or rearrangements, if performed; RNA analysis
	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
	81451	Hematolymphoid neoplasm or disorder, genomic sequence analysis panel, 5-50 genes, interrogation for sequence variants, and copy number variants or rearrangements, or isoform expression or mRNA expression levels, if performed; RNA analysis
	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
	81456	Solid organ or hematolymphoid neoplasm or disorder, 51 or greater genes, genomic sequence analysis panel, interrogation for sequence variants and copy number variants or rearrangements, or isoform expression or mRNA expression levels, if performed; RNA analysis
	81479	Unlisted molecular pathology procedure
	81599	Unlisted multianalyte assay with algorithmic analysis
	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
11/01/2022	Coding update
12/01/2022	Annual review. Policy statement, guidelines and literature updated.
10/01/2025	Policy reactivated. Previously archived from 06/01/2023 to 09/30/2025

Definitions of Decision Determinations

Healthcare Services: For the purpose of this Medical Policy, Healthcare Services means procedures, treatments, supplies, devices, and equipment.

Medically Necessary: Healthcare 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 of California, are: (a) consistent with Blue Shield of California 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 member; 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 or Experimental: Healthcare Services which do not meet ALL of the following five (5) elements are considered investigational or experimental:

A. The technology must have final approval from the appropriate government regulatory bodies.

- This criterion applies to drugs, biological products, devices and any other product or procedure that must have final approval to market from the U.S. Food and Drug Administration ("FDA") or any other federal governmental body with authority to regulate the use of the technology.
- Any approval that is granted as an interim step in the FDA's or any other federal governmental body's regulatory process is not sufficient.
- The indications for which the technology is approved need not be the same as those which Blue Shield of California is evaluating.

B. The scientific evidence must permit conclusions concerning the effect of the technology on health outcomes.
   - The evidence should consist of well-designed and well-conducted investigations published in peer-reviewed journals. The quality of the body of studies and the consistency of the results are considered in evaluating the evidence.
   - The evidence should demonstrate that the technology can measure or alter the physiological changes related to a disease, injury, illness, or condition. In addition, there should be evidence, or a convincing argument based on established medical facts that such measurement or alteration affects health outcomes.

C. The technology must improve the net health outcome.
   - The technology's beneficial effects on health outcomes should outweigh any harmful effects on health outcomes.

D. The technology must be as beneficial as any established alternatives.
   - The technology should improve the net health outcome as much as, or more than, established alternatives.

E. The improvement must be attainable outside the investigational setting.
   - When used under the usual conditions of medical practice, the technology should be reasonably expected to satisfy Criteria C and D.

Feedback

Blue Shield of California is interested in receiving feedback relative to developing, adopting, and reviewing criteria for medical policy. Any licensed practitioner who is contracted with Blue Shield of California or Blue Shield of California Promise Health Plan is welcome to provide comments, suggestions, or concerns. Our internal policy committees will receive and take your comments into consideration. Our medical policies are available to view or download at www.blueshieldca.com/provider.

For medical policy feedback, please send comments to: MedPolicy@blueshieldca.com

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: 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 member health services contract language, including definitions and specific contract provisions/exclusions, take precedence over medical policy and must be considered first in determining covered services. Member health services contracts may differ in their benefits. Blue Shield reserves the right to review and update policies as appropriate.

Appendix A

POLICY STATEMENT	
BEFORE	AFTER Blue font: Verbiage Changes/Additions
Reactivated Policy **Policy Statement:** N/A	**Comprehensive Genomic Profiling for Selecting Targeted Cancer Therapies 2.04.115** **Policy Statement:** I. The use of comprehensive genomic profiling for selecting targeted cancer treatment is considered **investigational**. Note: For individuals enrolled in health plans subject to the Biomarker Testing Law (Health & Safety Code Section 1367.667 and the Insurance Code Section 10123.209), Centers for Medicare & Medicaid Services (CMS) National Coverage Determination (NCD) and Local Coverage Determination (LCD) may also apply. Please refer to the Medicare National and Local Coverage section of this policy, National Coverage Determination (NCD) 90.2 Next Generation Sequencing (NGS), and to MolDX: Next-Generation Sequencing for Solid Tumors for reference.