PHP_2.04.115	Comprehensive Genomic Profiling for Selecting Targeted Cancer Therapies		
Original Policy Date:	March 1, 2026	**Effective Date:**	March 1, 2026
Section:	2.0 Medicine	**Page:**	Page 1 of 52

State Guidelines

Applicable Medi-Cal guidelines as of the publication of this policy (this guideline supersedes the criteria in the Policy Statement section below):

I. Department of Managed Health Care (DMHC) All Plan Letter (APL) Guideline:
- N/A

II. Department of Health Care Services (DHCS) Provider Manual Guideline:
- TAR and Non-Standard Benefits List: Codes 0001M thru 0999U (tar and non cd0)
- TAR and Non-Standard Benefits List: Codes 80000 thru 89999 (tar and non cd8)
- Pathology: Molecular Pathology (path molec)

Below is an excerpt of the Molecular Pathology guideline language. Please refer to the specific Provider Manual in the link above for the complete guideline.

Biomarker and Pharmacogenetic Testing
Medi-Cal covers medically necessary biomarker and pharmacogenomic testing, as described in the manual section Proprietary Laboratory Analyses (PLA). Medi-Cal may not cover all CPT and HCPCS codes associated with a particular biomarker or pharmacogenomic test. As such, the particular biomarker or pharmacogenomic test code may be covered with an approved Treatment Authorization Request (TAR) if medical necessity is established, as described in the TAR and Non-Benefit: Introduction to List section of the Provider Manual.

Biomarker Testing
Biomarker testing is used to diagnose, treat, manage, or monitor a Medi-Cal member's disease or condition to guide treatment decisions. As defined by Section 14132.09 of the Welfare and Institutions Code, biomarker testing is the analysis of an individual's tissue, blood or other biospecimen for the presence of a biomarker. Biomarker testing includes, but is not limited to, single-analyte tests, multiplex panel tests and whole genome sequencing. Biomarkers are a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes or pharmacologic responses to a specific therapeutic intervention. A biomarker includes, but is not limited to, gene mutations or protein expression. Medically necessary biomarker testing is subject to utilization controls and evidence-based clinical practice guidelines.

When testing for biomarkers, all Medi-Cal providers must ensure that they are provided in a manner that limits disruptions to care. As with all Medi-Cal benefits, restricted or denied use of biomarker testing for the purpose of diagnosis, treatment or ongoing monitoring of any medical condition is subject to Medi-Cal's grievance, appeal and State Fair Hearing processes, as well as any additional processes established specifically for Medi-Cal managed care plans.

Pharmacogenomic Testing
Pharmacogenomic testing is defined as a laboratory genetic testing that includes, but is not limited to, a panel test to identify how a person's genetics may impact the efficacy, toxicity and safety of medications. Medically necessary pharmacogenomic testing is covered subject to utilization controls and evidence-based clinical practice guidelines.

Requirements for CPT codes 81445 and 81455:
A TAR for CPT code 81445 requires documentation of the following criteria:

1. For Somatic Testing:
   - The member has either recurrent, relapsed, refractory, metastatic or advanced stages III or IV cancer, and
   - The member either has not been previously tested using the same Next Generation Sequencing (NGS) test for the same primary diagnosis of cancer or repeat testing using the same NGS test only when a new primary cancer diagnosis is made by the treating physician, and
   - The decision for additional cancer treatment is contingent on the test results.
2. For Germline Testing:
   - Ovarian or breast cancer, and
   - Clinical indication for germline (inherited) testing for hereditary breast or ovarian cancer (i.e., American College of Obstetrician Gynecologists' criteria for further genetic evaluation for hereditary [germline] breast and ovarian cancer), and
   - A risk factor for germline (inherited) breast or ovarian cancer, and (BRCAPRO, Myriad, Claus, Boadicea, or Tyrer Cuzick), and
   - Has not been previously tested with the same germline test using NGS for the same germline genetic content.
3. Independent of the above criteria, either Somatic or Germline testing may be approved if the test is approved by the U.S. Food and Drug Administration (FDA) as a Companion Diagnostic Device, and the decision for additional treatment is contingent on the test results.

- Proprietary Laboratory Analyses (PLA) (prop lab)

Below is an excerpt of the guideline language. Please refer to the specific Provider Manual in the link above for the complete guideline.

Requirements for PLA code 0022U:
A TAR requires documentation of the following criteria:

- Member has a diagnosis of non-small cell lung cancer (NSCLC)
- Treatment is contingent on test results

Requirements for PLA code 0037U:
A TAR requires documentation of the following criteria:

- The member has either recurrent, relapsed, refractory, metastatic or advanced stages III or IV cancer, and
- The member either has not been previously tested using the same Next Generation Sequencing (NGS) test for the same primary diagnosis of cancer or repeat testing using the same NGS test only when a new primary cancer diagnosis is made by the treating physician, and
- The decision for additional cancer treatment is contingent on the test results

Requirements for PLA code 0244U:
A TAR requires documentation of the following criteria:

For Somatic Testing

- The member has either recurrent, relapsed, refractory, metastatic or advanced stages III or IV cancer, and
- The member either has not been previously tested using the same Next Generation Sequencing (NGS) test for the same primary diagnosis of cancer or repeat testing using the same NGS test only when a new primary cancer diagnosis is made by the treating physician, and
- The decision for additional cancer treatment is contingent on the test results.

Requirements for PLA code 0329U:
A TAR requires documentation of the following criteria:
For Somatic Testing

- The member has recurrent, relapsed, refractory, metastatic or advanced stage III or IV cancer, and
- The member either has not been previously tested using the same Next-Generation Sequencing (NGS) test for the same primary diagnosis of cancer or repeat testing using the same NGS test only occurs when a new primary cancer diagnosis is made by the treating physician, and
- The decision for additional cancer treatment is contingent on the test results.

Requirements for PLA code 0334U:
A TAR requires documentation of the following criteria:
For Somatic Testing

- The member has recurrent, relapsed, refractory, metastatic or advanced stage III or IV cancer, and
- The member either has not been previously tested using the same Next-Generation Sequencing (NGS) test for the same primary diagnosis of cancer or repeat testing using the same NGS test only occurs when a new primary cancer diagnosis is made by the treating physician, and
- The decision for additional cancer treatment is contingent on the test results.

Requirements for PLA code 0379U:
A TAR requires documentation of the following criteria:
For Somatic Testing

- The member has recurrent, relapsed, refractory, metastatic or advanced stage III or IV cancer, and
- The member either has not been previously tested using the same Next-Generation Sequencing (NGS) test for the same primary diagnosis of cancer or repeat testing using the same NGS test only occurs when a new primary cancer diagnosis is made by the treating physician, and
- The decision for additional cancer treatment is contingent on the test results.

Requirements for PLA code 0391U:
A TAR requires documentation of the following criteria:
For Somatic Testing

- The member has recurrent, relapsed, refractory, metastatic or advanced stage III or IV cancer, and
- The member either has not been previously tested using the same Next-Generation Sequencing (NGS) test for the same primary diagnosis of cancer or repeat testing using the same NGS test only occurs when a new primary cancer diagnosis is made by the treating physician, and
- The decision for additional cancer treatment is contingent on the test results.

Requirements for PLA code 0473U:
A TAR requires documentation of the following criteria:
For Somatic Testing

- The member has recurrent, relapsed, refractory, metastatic or advanced stage III or IV cancer, and
- The member either has not been previously tested using the same next-generation sequencing (NGS) test for the same primary diagnosis of cancer or repeat testing using the same NGS test only occurs when a new primary cancer diagnosis is made by the treating physician, and
- The decision for additional cancer treatment is contingent on the test results. Independent of the above criteria, somatic testing may be approved if the test is approved by the U.S. Food and Drug Administration (FDA) as a companion diagnostic device, and the decision for additional treatment is contingent on the test results.

III. Department of Health Care Services (DHCS) All Plan Letter (APL) Guideline:

- APL 22-010 – Cancer Biomarker Testing

Below is an excerpt of the guideline language. Please refer to the specific All Plan Letter in the link above for the complete guideline.

For the purposes of this APL, "Biomarker test" is defined as a diagnostic test, single or multigene, of an individual's biospecimen, such as tissue, blood, or other bodily fluids, for DNA or RNA alterations, including phenotypic characteristics of a malignancy, to identify an individual with a subtype of cancer, in order to guide treatment. Biomarkers, also called tumor markers, are substances found in higher-than-normal levels in the cancer itself, or in blood, urine, or tissues of some individuals with cancer. Biomarkers can determine the likelihood some types of cancer will spread. They can also help doctors choose the best treatment.

Medi-Cal managed care health plans (MCPs) are required to cover medically necessary biomarker testing for members with:

- Advanced or metastatic stage 3 or 4 cancer.
- Cancer progression or recurrence in the member with advanced or metastatic stage 3 or 4 cancer.

MCPs are prohibited from imposing prior authorization requirements on biomarker testing that is associated with a federal Food and Drug Administration (FDA)-approved therapy for advanced or metastatic stage 3 or 4 cancer. If the biomarker test is not associated with an FDA-approved cancer therapy for advanced or metastatic stage 3 or 4 cancer, MCPs may still require prior authorization for such testing.

Policy Statement

Any criteria that are not specifically addressed in the above APL and Provider Manuals, please refer to the criteria below.

Tumor Tissue Genetic Testing

I. The use of broad molecular profiling (See Policy Guidelines for definition) for selecting targeted cancer treatment may be considered **medically necessary** when **both** of the following criteria are met:

A. The individual has been diagnosed with recurrent, relapsed, refractory, metastatic, or advanced stages III or IV cancer
B. The genetic test being utilized should follow the parameters laid out in Table 1 (See Policy Guidelines) and the sequencing methodology has received U.S. Food and Drug Administration (FDA) approval or is a validated diagnostic laboratory test, performed in a Clinical Laboratory Improvement Amendments (CLIA) certified laboratory (See Policy Guidelines)

Plasma Genetic Testing When Tissue is Insufficient

II. When using blood-based broad molecular profiling, testing for oncogenic driver variants using liquid biopsy (ctDNA) may be considered **medically necessary** to monitor for resistance mechanisms to targeted therapy or select an FDA-approved targeted therapy for individuals meeting **all** of the following criteria:
   A. The individual has been diagnosed with recurrent, relapsed, refractory, unresectable metastatic, or advanced stages III or IV cancer
   B. The genetic test being utilized should follow the parameters laid out in Table 1 (See Policy Guidelines) and the sequencing methodology has received FDA approval or is a validated diagnostic laboratory test, performed in a Clinical Laboratory Improvement Amendments (CLIA) certified laboratory (See Policy Guidelines)
   C. If no actionable oncogenic driver variants were identified when using tumor tissue samples or if the goal is to identify resistance gene variants upon disease progression following systemic therapy for new treatment decision-making (See Policy Guidelines)
   D. Follow-up tissue-based analysis is planned should no driver variant be identified via plasma testing

Comprehensive Genetic Profiling

III. The use of comprehensive genetic profiling for selecting targeted cancer treatment is considered **investigational** (See Policy Guidelines).
(Per Medi-Cal guidelines and for Medi-Cal members only: comprehensive genetic profiling may be approved based on the criteria listed in the State Guidelines section above.)

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.

Policy Guidelines

Criteria for Genetic Biomarker Testing for Targeted Therapies

The National Comprehensive Cancer Network (NCCN) provides criteria for when genetic biomarker testing for targeted therapy in individuals with cancer may be appropriate. Updated versions of the criteria are available on the NCCN website.[1]

Genetic Panel Testing

A genetic panel will be defined as a test that simultaneously evaluates multiple genes, as opposed to sequential testing of individual genes. This includes panels performed by next-generation sequencing (NGS), massive parallel sequencing, and chromosomal microarray analysis. The definition of a panel will not include panels that report on gene expression profiling, risk-stratification, or prognostication, which generally do not directly evaluate genetic variants.

Cancer Panels

Genetic panels for cancer can be of several types and may test for either germline and/or somatic variants. Their intended purpose can be for:

- Testing an asymptomatic patient to determine future risk of cancer
- Aid in the diagnosis of certain cancer types and determine the prognosis of the disease
- Therapeutic testing of cancer cells from an affected individual to benefit the individual by directing targeted treatment based on specific somatic variants.

There are variations of panels for use in risk assessment or for directing targeted treatment. For our purposes, we will focus on panels that pertain to detecting gene variants for targeted therapy in advanced or metastatic cancers:

- NGS panels contain multiple variants indicating driver or passenger variants for a specific type of cancer. These panels delineate multiple variants that denote oncogenic drivers that are targetable by one or more therapies. They include somatic variants (some assays may include germline variants) and may be used to guide treatment regimens to determine targeted therapies for individuals who harbor known pathogenic or likely pathogenic variants based on the genetic testing results. An example of this type of panel would be a next-generation sequencing (NGS) assay that test for multiple gene variants associated with non-small cell lung cancer (NSCLC). Additionally, these NGS-based panels have been developed to use both tumor tissue and circulating DNA (ctDNA) biopsies for variant testing.
- NGS panels may test somatic variants with or without germline variants.
- NGS panels are commonly referred to as "*limited*" or "*expanded*" depending on the type and number of variants included in the assay. For our purposes, "limited" NGS panels will refer to NGS assays that are limited to a 50-gene threshold utilized by Current Procedural Terminology (CPT) coding convention (may include RNA-based assays for gene fusions), while "*expanded*" NGS panels will refer to assays that are greater than 50 genes and include both coding and non-coding regions of DNA, microsatellite instability (MSI), tumor mutational burden (TMB), and detects RNA.

Cancer Panel Definitions

- **Comprehensive genetic profiling** will refer to these "*expanded*" panels used to determine appropriate treatment regimens regardless of cancer type.
- **Broad molecular profiling** refers to NGS panels that include all genetic biomarkers that have an NCCN 1 or 2a recommendation regardless of the cancer type with the goal of identifying targeted therapies that provide a net health benefit for individuals with advanced or metastatic cancer.
- **Molecular profiling** refers to "*limited*" gene panels that include genetic biomarkers that have an NCCN 1 or 2A recommendation but are specific to the cancer indication based on the likelihood of discovering a genetic variant that is an oncogenic driver.

NCCN defines broad molecular profiling - "as molecular testing that identifies all biomarkers identified [for a specific cancer indication] in either a single assay or a combination of a limited number of assays, and optimally also identifies emerging biomarkers [for a specific cancer indication]". However, the NCCN does not provide any formal definitions for "comprehensive genetic profiling", "comprehensive germline and somatic profiling", "tumor molecular profiling", "molecular profiling", or "comprehensive molecular profiling" and seemingly uses these terms interchangeably to denote molecular biomarker analysis for pathogenic or likely pathogenic gene fusions and/or variants with the goal of identifying oncogenic driver alterations that have targeted therapies. Thus, this medical policy will instead use the above definitions rather than the NCCN definitions to denote what "profiling" methodology is most appropriate for selecting targeted therapies for molecular biomarkers (Table 1).

Table 1. Genetic Biomarker Indications for Targeted Therapy in Advanced and Metastatic Cancer[1]

Tumor Type	Biomarker(s) Detected	Therapy	NCCN Guideline with 1 or 2A recommendation
Non-small cell lung cancer (NSCLC)[d,e,f]	*EGFR* exon 19 deletions and *EGFR* exon 21 L858R variants	Gilotrif® (afatinib), Iressa® (gefitinib), Tagrisso® (osimertinib), Tarceva® (erlotinib), or Vizimpro® (dacomitinib)	NSCLC v8.2025[1]
	EGFR S768I, L861Q, and/or G719X variants	Gilotrif® (afatinib), Iressa® (gefitinib), Tagrisso® (osimertinib), Tarceva® (erlotinib), or Vizimpro® (dacomitinib)	
	EGFR exon 20 T790M variants	Tagrisso® (osimertinib)	
	EGFR exon 20 insertion variants	Rybrevant® (amivantamb), Exkivity® (mobocertinib)	
	ALK rearrangements	Alecensa® (alectinib), Xalkori® (crizotinib), Alunbrig® (brigatinib), Ensacove® (ensartinib), Lorbrena® (lorlatinib), or Zykadia® (ceritinib)	
	BRAF V600E	Tafinlar® (dabrafenib), Zelboraf® (vemurafenib), Tafinlar® (dabrafenib) in combination with Mekinist® (trametinib), and Braftovi® (encorafenib) in combination with Mektovi® (binimetinib)	
	METex14 skipping variants	Tabrecta™ (capmatinib), Tepmetko (tepotinib), or Xalkori® (crizotinib)	
	KRAS G12C	Krazati® (adagrasib), Lumakras® (sotorasib)	
	RET fusions	Gavreto® (pralsetinib), Retevmo® (selpercatinib)	
	ROS1 fusions	Rozlytrek® (entrectinib), Xalkori® (crizotinib), Ibtrozi® (taletrectinib),or Augtyro® (repotrectinib)	
	NRG1 fusions	Bizengri® (zenocutuzumab-zbco)	
	NTRK1/2/3 gene fusions	Vitrakvi® (larotrectinib), Rozlytrek® (entrectinib), or Augtyro® (repotrectinib)	
	ERBB2 (*HER2*) variants	Enhertu® (fam-trastuzumab deruxtecan-nxki	
	PD-L1 ≥1% and negative for actional molecular biomarkers above	PD-1 or PD-L1[b]	
	PD-L1 <1% and negative for actional molecular biomarkers above	PD-1 or PD-L1[b]	
	High-level *MET* amplification[c]	Tabrecta™ (capmatinib), Tepmetko® (tepotinib), or Xalkori® (crizotinib)	
	FGFR variants	Balversa® (erdafitinib)	
Melanoma (Cutaneous and Uveal)[e,f]	*BRAF* V600E (Cutaneous)	Tafinlar® (dabrafenib), Mekinist (trametinib) or Zelboraf® (vemurafenib)	Melanoma (Cutaneous) v2.2025[2] & Melanoma (Uveal) v1.2025[3]
	BRAF V600E and V600K (Cutaneous)	Braftovi® (encorafenib), Mekinist® (trametinib) or Tecentriq® (atezolizumab) in combination with Cotellic® (cobimetinib) and	

Tumor Type	Biomarker(s) Detected	Therapy	NCCN Guideline with 1 or 2A recommendation
		Zelboraf® (vemurafenib), Cotellic® (cobimetinib) in combination with Zelboraf® (vemurafenib), or Braftovi® (encorafenib) in combination with Mektovi® (binimetinib)	
	*HLA-A*02:01* (Uveal)	Kimmtrak® (tebentafusp-tebn)	
	KIT exon 11 and 13 variants (e.g., W557R, V559D, L576P, K642E)	Gleevec (imatinib), Sutent® (sunitinib), or Tasigna® (nilotinib)	
Breast cancer[e,f]	*ERBB2* (HER2) amplification	Herceptin® (trastuzumab), Kadcyla® (ado-trastuzumabemtansine), Enhertu® (fam-trastuzumab deruxtecan-nxki), or Perjeta® (pertuzumab)	Breast v4.2025[4]
	ESR1 missense variants	Orserdu® (elacestrant)	
	PIK3CA variants	Lynparza® (olaparib), Truqap® (capivasertib) in combination with Faslodex® (fulvestrant), Piqray® (alpelisib), Itovebi® (inavolisib)	
	BRCA1 and BRCA2 variants	Lynparza® (olaparib), Talzenna® (talazoparib)	
	PD-L1 (TNBC) amplification	Keytruda® (pembrolizumab)	
	NTRK1/2/3 gene fusions	Vitrakvi® (larotrectinib), Rozlytrek® (entrectinib)	
	PALB2 variants	Lynparza® (olaparib)	
	MSI-H/dMMR	Keytruda® (pembrolizumab) and Jemperli (dostarlimab-gxly)	
	TMB-H (≥10 mutations per megabase)	Keytruda® (pembrolizumab)	
	RET fusions	Retevmo® (selpercatinib)	
Colorectal cancer[d,e,f]	*BRAF* V600E variant	Braftovi® (encorafenib) or in combination with ERBITUX (cetuximab)	Colon cancer v4.2025[5] & rectal cancer v3.2025[6]
	KRAS wild-type (absence of variants in codons 12 and 13)	Erbitux® (cetuximab)	
	KRAS wild-type (absence of variants in exons 2, 3, and 4) and *NRAS* wild-type (absence of variants in exons 2, 3, and 4)	Vectibix® (panitumumab)	
	ERBB2 (HER2) amplification	Enhertu® (fam-trastuzumab deruxtecan-nxki)	
	KRAS exon 12 and 13 variants	Erbitux® (cetuximab) or Vectibix® (panitumumab)	
	EGFR amplification	Erbitux® (cetuximab) or Vectibix® (panitumumab)	
	KRAS variants (G12A, G12D, G12R, G12C, G12S, G12V, G13D)	Erbitux® (cetuximab) or Vectibix® (panitumumab)	
	KRAS variant G12C	Krazati® (adagrasib) in combination with Erbitux® (cetuximab) or Lumakras® (sotorasib) in combination with Vectibix® (panitumumab)	
	MLH1, PMS2, MSH2 and MSH6	Keytruda® (pembrolizumab), Jemperli® (dostarlimag-gxly)	
	MSI-H/dMMR	Keytruda® (pembrolizumab) and Jemperli (dostarlimab-gxly)	

Tumor Type	Biomarker(s) Detected	Therapy	NCCN Guideline with 1 or 2A recommendation
	TMB-H (≥10 mutations per megabase)	Keytruda® (pembrolizumab)	
	RET fusions	Retevmo® (selpercatinib)	
	NTRK1/2/3 gene fusions	Vitrakvi® (larotrectinib), Rozlytrek® (entrectinib)	
Ovarian, Fallopian Tube, and Primary peritoneal cancer [d,e,g,n]	*BRCA1/2*variants	Lynparza® (olaparib) or Rubraca® (rucaparib)	Ovarian, Fallopian Tube, and Primary peritoneal cancer v3.2025[7]
	FOLR1 protein expression	Elahere® (mirvetuximab soravtansine-gynx)	
	RET fusions	Retevmo® (selpercatinib)	
	NTRK1/2/3 gene fusions	Vitrakvi® (larotrectinib), Rozlytrek® (entrectinib)	
	MSI-H/dMMR	Keytruda® (pembrolizumab) and Jemperli (dostarlimab-gxly)	
	TMB-H (≥10 mutations per megabase)	Keytruda® (pembrolizumab)	
	Homologous recombination deficiency	Lynparza® (olaparib) or Zejula (niraparib)	
Biliary Tract Cancers (BTC)[d,e,f]	*FGFR2* fusions or other select rearrangements	Pemazyre® (pemigatinib) or Truseltiq fgv™ (infigratinib)	BTC v2.2025[8]
	RET fusions	Retevmo® (selpercatinib)	
	NTRK1/2/3 gene fusions[h]	Vitrakvi® (larotrectinib), Rozlytrek® (entrectinib)	
	IDH1 variants	Tibsovo® (ivosidenib)	
	ERBB2 (HER2) amplification	Enhertu® (fam-trastuzumab deruxtecan-nxki)	
	BRAF V600E variant	Braftovi® (encorafenib) or in combination with ERBITUX (cetuximab)	
	KRAS variant G12C	Krazati® (adagrasib) in combination with Erbitux® (cetuximab) or Lumakras® (sotorasib) in combination with Vectibix® (panitumumab)	
	MLH1, PMS2, MSH2 and MSH6	Keytruda® (pembrolizumab), Jemperli® (dostarlimag-gxly)	
	MSI-H/dMMR	Keytruda® (pembrolizumab) and Jemperli (dostarlimab-gxly)	
	TMB-H (≥10 mutations per megabase)	Keytruda® (pembrolizumab)	
Hepatocellular Carcinoma (HCC)	There is no established indication for routine molecular profiling for this indication, but it should be considered on case-by-case basis		HCC v1.2025[9]
Prostate cancer[d,e,f]	*BRCA1/2* variants	Akeega® (niraparib + abiraterone acetate), Rubraca® (rucaparib), Lynparza® (olaparib) alone or in combination with abiraterone	Prostate v2.2026[10]
	ATM variants	Lynparza® (olaparib)	
	Homologous Recombination Repair (HRR) gene variants *(BRCA1, BRCA2, ATM, BARD1, BRIP1, CDK12, CHEK1, CHEK2, FANCL, PALB2, RAD51B, RAD51C, RAD51D* and *RAD54L)*	Lynparza® (olaparib)	
	MLH1, PMS2, MSH2 and MSH6	Keytruda® (pembrolizumab), Jemperli® (dostarlimag-gxly)	
	MSI-H/dMMR (mCRPC only)	Keytruda® (pembrolizumab) and Jemperli (dostarlimab-gxly)	

Tumor Type	Biomarker(s) Detected	Therapy	NCCN Guideline with 1 or 2A recommendation
	TMB-H (≥10 mutations per megabase) (mCRPC only)	Keytruda® (pembrolizumab)	
Pancreatic Adenocarcinoma[e,f]	*ALK* rearrangements	Alecensa® (alectinib), Xalkori® (crizotinib), Alunbrig® (brigatinib), Ensacove® (ensartinib), Lorbrena® (lorlatinib), or Zykadia® (ceritinib)	Pancreatic Adenocarcinoma v2.2025[11]
	NRG1 fusions	Bizengri® (zenocutuzumab-zbco)	
	FGFR2 fusions or other select rearrangements	Pemazyre® (pemigatinib) or Truseltiq fgv™ (infigratinib)	
	RET fusions	Retevmo® (selpercatinib)	
	NTRK1/2/3 gene fusions	Vitrakvi® (larotrectinib), Rozlytrek® (entrectinib)	
	ROS1 fusions	Rozlytrek® (entrectinib), Xalkori® (crizotinib), Ibtrozi® (taletrectinib), or Augtyro® (repotrectinib)	
	PALB2 variants	Lynparza® (olaparib)	
	BRCA1 and BRCA2 variants	Lynparza® (olaparib), Talzenna® (talazoparib)	
	BRAF V600E and V600K	Braftovi® (encorafenib), Mekinist® (trametinib) or Tecentriq® (atezolizumab) in combination with Cotellic® (cobimetinib) and Zelboraf® (vemurafenib), Cotellic® (cobimetinib) in combination with Zelboraf® (vemurafenib), or Braftovi® (encorafenib) in combination with Mektovi® (binimetinib)	
	KRAS exon 12 and 13 variants	Erbitux® (cetuximab) or Vectibix® (panitumumab)	
	KRAS variants (G12A, G12D, G12R, G12C, G12S, G12V, G13D)	Erbitux® (cetuximab) or Vectibix® (panitumumab)	
	KRAS variant G12C	Krazati® (adagrasib) in combination with Erbitux® (cetuximab) or Lumakras® (sotorasib) in combination with Vectibix® (panitumumab)	
	ERBB2 (HER2) amplification	Enhertu® (fam-trastuzumab deruxtecan-nxki)	
	MLH1, PMS2, MSH2 and MSH6	Keytruda® (pembrolizumab), Jemperli® (dostarlimag-gxly)	
	MSI-H/dMMR	Keytruda® (pembrolizumab) and Jemperli (dostarlimab-gxly)	
	TMB-H (≥10 mutations per megabase)	Keytruda® (pembrolizumab)	
Esophageal and Esophagogastric Junction Cancer[e,n]	*RET* fusions	Retevmo® (selpercatinib)	Esophageal and Esophagogastric Junction Cancer v4.2025[12]
	NTRK1/2/3 gene fusions	Vitrakvi® (larotrectinib), Rozlytrek® (entrectinib)	
	BRAF V600E and V600K	Braftovi® (encorafenib), Mekinist® (trametinib) or Tecentriq® (atezolizumab) in combination with Cotellic® (cobimetinib) and Zelboraf® (vemurafenib), Cotellic® (cobimetinib) in combination with Zelboraf® (vemurafenib), or Braftovi® (encorafenib) in	

Tumor Type	Biomarker(s) Detected	Therapy	NCCN Guideline with 1 or 2A recommendation
		combination with Mektovi® (binimetinib)	
	ERBB2 (HER2) amplification	Enhertu® (fam-trastuzumab deruxtecan-nxki)	
	PD-L1 amplification	Keytruda® (pembrolizumab)	
	MLH1, PMS2, MSH2 and MSH6	Keytruda® (pembrolizumab), Jemperli® (dostarlimag-gxly)	
	MSI-H/dMMR	Keytruda® (pembrolizumab) and Jemperli (dostarlimab-gxly)	
	TMB-H (≥10 mutations per megabase)	Keytruda® (pembrolizumab)	
Gastric Cancer[e,n]	*RET* fusions	Retevmo® (selpercatinib)	Gastric Cancer v3.2025[13]
	NTRK1/2/3 gene fusions	Vitrakvi® (larotrectinib), Rozlytrek® (entrectinib)	
	CLDN18 amplification[i]	Vyloy® (zolbetuximab)	
	BRAF V600E and V600K	Braftovi® (encorafenib), Mekinist® (trametinib) or Tecentriq® (atezolizumab) in combination with Cotellic® (cobimetinib) and Zelboraf® (vemurafenib), Cotellic® (cobimetinib) in combination with Zelboraf® (vemurafenib), or Braftovi® (encorafenib) in combination with Mektovi® (binimetinib)	
	PD-L1 amplification	Keytruda® (pembrolizumab)	
	ERBB2 (HER2) amplification	Enhertu® (fam-trastuzumab deruxtecan-nxki)	
	MLH1, PMS2, MSH2 and MSH6	Keytruda® (pembrolizumab), Jemperli® (dostarlimag-gxly)	
	MSI-H/dMMR	Keytruda® (pembrolizumab) and Jemperli (dostarlimab-gxly)	
	TMB-H (≥10 mutations per megabase)	Keytruda® (pembrolizumab)	
Gastrointestinal Stromal Tumors (GIST)[d,e,n]	*PDGFRA* D842V variant	Ayvakit® (Avapritinib)	GIST v1.2025[14]
	PDGFRA variants	Gleevec (imatinib), if imatinib-resistant variants arise use Sutent® (sunitinib), if resistance mounts against sunitinib use Stivarga® (regorafenib), if 3 or more kinase inhibitors have failed use Qinlock (ripertinib)	
	KIT exon 9 variants	Sutent® (sunitinib), if resistance mounts against sunitinib use Stivarga® (regorafenib), if 3 or more kinase inhibitors have failed use Qinlock (ripertinib)	
	KIT exon 11 and 13 variants (e.g., W557R, V559D, L576P, K642E)	Gleevec (imatinib), if imatinib-resistant variants arise use Sutent® (sunitinib), if resistance mounts against sunitinib use Stivarga® (regorafenib), if 3 or more kinase inhibitors have failed use Qinlock (ripertinib)	
	SDH deficiency	Sutent® (sunitinib) or Stivarga® (regorafenib)	

Tumor Type	Biomarker(s) Detected	Therapy	NCCN Guideline with 1 or 2A recommendation
	NTRK1/2/3 gene fusions	Vitrakvi® (larotrectinib), Rozlytrek® (entrectinib)	
	FGFR2 fusions or other select rearrangements	Pemazyre® (pemigatinib) or Truseltiq fgv™ (infigratinib)	
	BRAF V600E and V600K	Braftovi® (encorafenib), Mekinist® (trametinib) or Tecentriq® (atezolizumab) in combination with Cotellic® (cobimetinib) and Zelboraf® (vemurafenib), Cotellic® (cobimetinib) in combination with Zelboraf® (vemurafenib), or Braftovi® (encorafenib) in combination with Mektovi® (binimetinib)	
	NF1 variants	Koselugo® (selumetinib) or Gomekli™ (mirdametinib)	
	MLH1, PMS2, MSH2 and MSH6	Keytruda® (pembrolizumab), Jemperli® (dostarlimag-gxly)	
	MSI-H/dMMR	Keytruda® (pembrolizumab) and Jemperli (dostarlimab-gxly)	
	TMB-H (>10 mutations per megabase)	Keytruda® (pembrolizumab)	
Cervical Cancer[e,f]	*RET* fusions	Retevmo® (selpercatinib)	Cervical Cancer v4.2025[15]
	NTRK1/2/3 gene fusions	Vitrakvi® (larotrectinib), Rozlytrek® (entrectinib)	
	ERBB2 (HER2) amplification	Enhertu® (fam-trastuzumab deruxtecan-nxki)	
	MLH1, PMS2, MSH2 and MSH6	Keytruda® (pembrolizumab), Jemperli® (dostarlimag-gxly)	
	MSI-H/dMMR	Keytruda® (pembrolizumab) and Jemperli (dostarlimab-gxly)	
	TMB-H (>10 mutations per megabase)	Keytruda® (pembrolizumab)	
Neuroendocrine and Adrenal Tumors[e,f]	*RET* fusions	Retevmo® (selpercatinib)	Neuroendocrine and Adrenal Tumors v2.2025[16]
	NTRK1/2/3 gene fusions	Vitrakvi® (larotrectinib), Rozlytrek® (entrectinib)	
	BRAF V600E and V600K variants	Braftovi® (encorafenib), Mekinist® (trametinib) or Tecentriq® (atezolizumab) in combination with Cotellic® (cobimetinib) and Zelboraf® (vemurafenib), Cotellic® (cobimetinib) in combination with Zelboraf® (vemurafenib), or Braftovi® (encorafenib) in combination with Mektovi® (binimetinib), Tafinlar (dabrafenib) in combination with Mekinist® (trametinib)	
	MLH1, PMS2, MSH2 and MSH6	Keytruda® (pembrolizumab), Jemperli® (dostarlimag-gxly)	
	MSI-H/dMMR	Keytruda® (pembrolizumab) and Jemperli (dostarlimab-gxly)	
	TMB-H (>10 mutations per megabase)	Keytruda® (pembrolizumab)	
Ampullary Adenocarcinoma[e,f]	*ALK* rearrangements	Alecensa® (alectinib), Xalkori® (crizotinib), Alunbrig® (brigatinib),	Ampullary Adenocarcinoma

Tumor Type	Biomarker(s) Detected	Therapy	NCCN Guideline with 1 or 2A recommendation
		Ensacove® (ensartinib), Lorbrena® (lorlatinib), or Zykadia® (ceritinib)	v2.2025[17]
	NRG1 fusions	Bizengri® (zenocutuzumab-zbco)	
	FGFR2 fusions or other select rearrangements	Pemazyre® (pemigatinib) or Truseltiq fgv™ (infigratinib)	
	RET fusions	Retevmo® (selpercatinib)	
	NTRK1/2/3 gene fusions	Vitrakvi® (larotrectinib), Rozlytrek® (entrectinib)	
	ROS1 fusions	Rozlytrek® (entrectinib), Xalkori® (crizotinib), Ibtrozi® (taletrectinib), or Augtyro® (repotrectinib)	
	PALB2 variants	Lynparza® (olaparib)	
	BRCA1 and BRCA2 variants	Lynparza® (olaparib), Talzenna® (talazoparib)	
	BRAF V600E and V600K	Braftovi® (encorafenib), Mekinist® (trametinib) or Tecentriq® (atezolizumab) in combination with Cotellic® (cobimetinib) and Zelboraf® (vemurafenib), Cotellic® (cobimetinib) in combination with Zelboraf® (vemurafenib), or Braftovi® (encorafenib) in combination with Mektovi® (binimetinib)	
	KRAS exon 12 and 13 variants	Erbitux® (cetuximab) or Vectibix® (panitumumab)	
	KRAS variants (G12A, G12D, G12R, G12C, G12S, G12V, G13D)	Erbitux® (cetuximab) or Vectibix® (panitumumab)	
	KRAS variant G12C	Krazati® (adagrasib) in combination with Erbitux® (cetuximab) or Lumakras® (sotorasib) in combination with Vectibix® (panitumumab)	
	ERBB2 (HER2) amplification	Enhertu® (fam-trastuzumab deruxtecan-nxki)	
	MLH1, PMS2, MSH2 and MSH6	Keytruda® (pembrolizumab), Jemperli® (dostarlimag-gxly)	
	MSI-H/dMMR	Keytruda® (pembrolizumab) and Jemperli (dostarlimab-gxly)	
	TMB-H (>10 mutations per megabase)	Keytruda® (pembrolizumab)	
Occult Primary (CUP)[e,f]	*ALK* rearrangements	Alecensa® (alectinib), Xalkori® (crizotinib), Alunbrig® (brigatinib), Ensacove® (ensartinib), Lorbrena® (lorlatinib), or Zykadia® (ceritinib)	Occult Primary (CUP) v2.2025[18]
	NRG1 fusions	Bizengri® (zenocutuzumab-zbco)	
	FGFR2 fusions or other select rearrangements	Pemazyre® (pemigatinib) or Truseltiq fgv™ (infigratinib)	
	RET fusions	Retevmo® (selpercatinib)	
	NTRK1/2/3 gene fusions	Vitrakvi® (larotrectinib), Rozlytrek® (entrectinib)	
	ROS1 fusions	Rozlytrek® (entrectinib), Xalkori® (crizotinib), Ibtrozi® (taletrectinib), or Augtyro® (repotrectinib)	
	MSI-H/dMMR	Keytruda® (pembrolizumab) and Jemperli (dostarlimab-gxly)	

Tumor Type	Biomarker(s) Detected	Therapy	NCCN Guideline with 1 or 2A recommendation
Small Cell Lung Cancers (SCLC)[e,f]	Broad molecular profiling via blood, tissue, or both can be considered in rare cases- particularly for individuals with extensive stage/relapsed SCLC who do not smoke tobacco, lightly smoke, have remote smoking history, or have diagnostic or therapeutic dilemma, or at time of relapse.		SCLC v2.2026[19]
Uterine Neoplasms[e,f,j]	*NTRK1/2/3* gene fusions	Vitrakvi® (larotrectinib), Rozlytrek® (entrectinib)	Uterine Neoplasms v3.2025[20]
	RET fusions	Retevmo® (selpercatinib)	
	ALK rearrangements	Alecensa® (alectinib), Xalkori® (crizotinib), Alunbrig® (brigatinib), Ensacove® (ensartinib), Lorbrena® (lorlatinib), or Zykadia® (ceritinib)	
	BRCA1 and BRCA2 variants	Lynparza® (olaparib), Talzenna® (talazoparib)	
	ERBB2 (HER2) amplification	Enhertu® (fam-trastuzumab deruxtecan-nxki)	
	MLH1, PMS2, MSH2 and MSH6	Keytruda® (pembrolizumab), Jemperli® (dostarlimag-gxly)	
	MSI-H/dMMR	Keytruda® (pembrolizumab) and Jemperli (dostarlimab-gxly)	
	TMB-H (>10 mutations per megabase)	Keytruda® (pembrolizumab)	
Acute Lymphoblastic Leukemia (ALL; including pediatric individuals)[f,l]	*BCR-ABL1* fusion[k]	Gleevec (imatinib), Scemblix® (asciminib), Bosulif® (bosutinib), Sprycel® (dasatinib), Tasigna® (nilotinib), or Iclusig® (ponatinib)	ALL v2.2025[21]
Acute Myeloid Leukemia (AML)[m,n]	*FLT3* variants	Xospata® (gilteritinib)	AML v1.2026[22]
	FLT3 internal tandem duplication variant	Vanflyta® (quizartinib), Xospata® (gilteritinib)	
	IDH1 variants	Tibsovo® (ivosidenib), Rezlidhia™ (olutasidenib), or Voranigo® (vorasidenib)	
	IDH2 variants	Idhifa® (enasidenib) or Voranigo® (vorasidenib)	
	KMT2A rearrangements	Revuforj (revumenib)	
Bone Cancer[f]	MLH1, PMS2, MSH2 and MSH6	Keytruda® (pembrolizumab), Jemperli® (dostarlimag-gxly)	Bone Cancer v1.2026[23]
	MSI-H/dMMR	Keytruda® (pembrolizumab) and Jemperli (dostarlimab-gxly)	
	TMB-H (>10 mutations per megabase)	Keytruda® (pembrolizumab)	
Central Nervous System (CNS) Cancers (including pediatric patients)[n]	*IDH1* variants (R132C, R132G, R132H, R132L, and R132S)	Voranigo® (vorasidenib)	CNS Cancers v2.2025[24]
	IDH2 variants (*R172M,* R172K, R172W, R172S, and R172G)		
Head and Neck Cancers (Non-nasopharyngeal only if not a very advanced form of cancer)[f]	*FGFR2* fusions or other select rearrangements	Pemazyre® (pemigatinib) or Truseltiq fgv™ (infigratinib)	Head and neck v5.2025[25]
	FGFR2 or FGFR3 variants	Balversa® (erdafitinib)	
	ERBB2 (HER2) amplification	Enhertu® (fam-trastuzumab deruxtecan-nxki)	
	PD-L1[o]	Keytruda® (pembrolizumab)	
	MSI-H/dMMR	Keytruda® (pembrolizumab) and Jemperli (dostarlimab-gxly)	
	TMB-H (>10 mutations per megabase)	Keytruda® (pembrolizumab) or	
	TP53	Venclexta™ (venetoclax)	

Tumor Type	Biomarker(s) Detected	Therapy	NCCN Guideline with 1 or 2A recommendation
Mesothelioma (Pleural and Peritoneal)[f]	*RET* fusions	Retevmo® (selpercatinib)	Mesothelioma Pleural v.2.2025[26] and Peritoneal v.2.2025[27]
	NTRK1/2/3 gene fusions	Vitrakvi® (larotrectinib), Rozlytrek® (entrectinib)	
	MLH1, PMS2, MSH2 and MSH6	Keytruda® (pembrolizumab), Jemperli® (dostarlimag-gxly)	
	MSI-H/dMMR	Keytruda® (pembrolizumab) and Jemperli (dostarlimab-gxly)	
	TMB-H (>10 mutations per megabase)	Keytruda® (pembrolizumab)	
Histiocytic Neoplasms[f]	*RET* fusions	Retevmo® (selpercatinib)	Histiocytic Neoplasms v1.2025[28]
	NTRK1/2/3 gene fusions	Vitrakvi® (larotrectinib), Rozlytrek® (entrectinib)	
	ALK rearrangements	Alecensa® (alectinib), Xalkori® (crizotinib), Alunbrig® (brigatinib), Ensacove® (ensartinib), Lorbrena® (lorlatinib), or Zykadia® (ceritinib)	
	CSF1R variants	Turalio® (pexidartinib)	
	PIK3CA	Rapamune (sirolimus) or Afinitor (everolimus)	
	BRAF V600E and V600K	Braftovi® (encorafenib), Mekinist® (trametinib) or Tecentriq® (atezolizumab) in combination with Cotellic® (cobimetinib) and Zelboraf® (vemurafenib), Cotellic® (cobimetinib) in combination with Zelboraf® (vemurafenib), or Braftovi® (encorafenib) in combination with Mektovi® (binimetinib)	
	KRAS exon 12 and 13 variants	Erbitux® (cetuximab) or Vectibix® (panitumumab)	
	KRAS variants (G12A, G12D, G12R, G12C, G12S, G12V, G13D)	Erbitux® (cetuximab) or Vectibix® (panitumumab)	
	KRAS variant G12C	Krazati® (adagrasib) in combination with Erbitux® (cetuximab) or Lumakras® (sotorasib) in combination with Vectibix® (panitumumab)	
	KRAS wild-type (absence of mutations variants in codons 12 and 13)	Erbitux® (cetuximab)	
	KRAS wild-type (absence of mutations variants in exons 2, 3, and 4) and *NRAS* wild-type (absence of mutations variants in exons 2, 3, and 4)	Vectibix® (panitumumab)	
	MLH1, PMS2, MSH2 and MSH6	Keytruda® (pembrolizumab), Jemperli® (dostarlimag-gxly)	
	MSI-H/dMMR	Keytruda® (pembrolizumab) and Jemperli (dostarlimab-gxly)	
	TMB-H (>10 mutations per megabase)	Keytruda® (pembrolizumab) or	
Neuroblastoma[n]	*ALK* rearrangements	Alecensa® (alectinib), Xalkori® (crizotinib), Alunbrig® (brigatinib), Ensacove® (ensartinib), Lorbrena® (lorlatinib), or Zykadia® (ceritinib)	Neuroblastoma v1.2025[29]

Tumor Type	Biomarker(s) Detected	Therapy	NCCN Guideline with 1 or 2A recommendation
Penile Cancer[f]	*ALK* rearrangements	Alecensa® (alectinib), Xalkori® (crizotinib), Alunbrig® (brigatinib), Ensacove® (ensartinib), Lorbrena® (lorlatinib), or Zykadia® (ceritinib)	Penile Cancer v2.2025[30]
	RET fusions	Retevmo® (selpercatinib)	
	NTRK1/2/3 gene fusions	Vitrakvi® (larotrectinib), Rozlytrek® (entrectinib)	
	MLH1, PMS2, MSH2 and MSH6	Keytruda® (pembrolizumab), Jemperli® (dostarlimag-gxly)	
	MSI-H/dMMR	Keytruda® (pembrolizumab) and Jemperli (dostarlimab-gxly)	
	TMB-H (>10 mutations per megabase)	Keytruda® (pembrolizumab)	
Small Bowel Adenocarcinoma[f]	*RET* fusions	Retevmo® (selpercatinib)	Small Bowel Adenocarcinoma v1.2025[31]
	NTRK1/2/3 gene fusions	Vitrakvi® (larotrectinib), Rozlytrek® (entrectinib)	
	BRAF V600E and V600K	Braftovi® (encorafenib), Mekinist® (trametinib) or Tecentriq® (atezolizumab) in combination with Cotellic® (cobimetinib) and Zelboraf® (vemurafenib), Cotellic® (cobimetinib) in combination with Zelboraf® (vemurafenib), or Braftovi® (encorafenib) in combination with Mektovi® (binimetinib)	
	KRAS exon 12 and 13 variants	Erbitux® (cetuximab) or Vectibix® (panitumumab)	
	KRAS variants (G12A, G12D, G12R, G12C, G12S, G12V, G13D)	Erbitux® (cetuximab) or Vectibix® (panitumumab)	
	KRAS variant G12C	Krazati® (adagrasib) in combination with Erbitux® (cetuximab) or Lumakras® (sotorasib) in combination with Vectibix® (panitumumab)	
	KRAS wild-type (absence of mutations variants in codons 12 and 13)	Erbitux® (cetuximab)	
	KRAS wild-type (absence of mutations variants in exons 2, 3, and 4) and *NRAS* wild-type (absence of mutations variants in exons 2, 3, and 4)	Vectibix® (panitumumab)	
	ERBB2 (HER2) amplification	Enhertu® (fam-trastuzumab deruxtecan-nxki)	
	MSI-H/dMMR	Keytruda® (pembrolizumab) and Jemperli (dostarlimab-gxly)	
	TMB-H (>10 mutations per megabase)	Keytruda® (pembrolizumab)	
Testicular Cancer[f]	MSI-H	Keytruda® (pembrolizumab) and Jemperli (dostarlimab-gxly)	Testicular Cancer v2.2025[14]
	TMB-H (>10 mutations per megabase)	Keytruda® (pembrolizumab)	
Vaginal Cancer[f]	*RET* fusions	Retevmo® (selpercatinib)	Vaginal Cancer v5.2025[31]
	NTRK1/2/3 gene fusions	Vitrakvi® (larotrectinib), Rozlytrek® (entrectinib)	
	PD-L1[o]		

Tumor Type	Biomarker(s) Detected	Therapy	NCCN Guideline with 1 or 2A recommendation
	MSI-H	Keytruda® (pembrolizumab) and Jemperli (dostarlimab-gxly)	
	TMB-H (>10 mutations per megabase)	Keytruda® (pembrolizumab)	
Vulvar Cancer (squamous cell carcinoma and adenocarcinoma)[f]	*NTRK1/2/3* gene fusions	Vitrakvi® (larotrectinib), Rozlytrek® (entrectinib)	Vulvar Cancer v1.2025[32]
	MSI-H/dMMR	Keytruda® (pembrolizumab) and Jemperli (dostarlimab-gxly)	
	TMB-H (>10 mutations per megabase)	Keytruda® (pembrolizumab)	
Other Solid Tumors[f]	TMB-H (≥10 mutations per megabase)	Keytruda® (pembrolizumab)	NA
	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)	

CNV: copy number variants; CUP: cancer of unknown primary; dMMR: deficient mismatch repair; FDA: Food and Drug Administration; MSI-H: microsatellite instability-high; NA: not available; NCCN: national comprehensive cancer network; TMB-H: tumor mutational burden-high; TNBC: triple-negative breast cancer; TP53: tumor protein 53; 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.

[a] Comprehensive genetic profiling (CGP) by NGS panels may be used to identify molecular biomarkers for targeted therapy but is not considered medically necessary as standard genetic profiling is sufficient to detect actionable oncogenic variants for targeted therapy.

[b] Contraindications for treatment with PD-1/PD-L1 inhibitors may include active or previously documented autoimmune disease and/or current use of immunosuppressive agents; some oncogenic drivers (i.e., *EGFR* exon 19 deletions or L858R; *ALK*, *RET*, or *ROS1* rearrangements) have been shown to be associated with less benefit from PD-1/PD-L1 inhibitors.

[c] The definition of high-level *MET amplification* is evolving and may differ according to the assayed used for testing. For NGS-based results, a copy number ≥10 is consistent with high-level *MET* amplification. In individuals with NSCLC with *EGFR* variants who develop high-level *MET* amplifications, administration of these agents with continuation of Osimertinib is acceptable.

[d] For any individual with disease progression while on targeted therapy, histological transformation is a possible mechanism of resistance. Tissue biopsy of progression lesion(s) should be considered to evaluate morphology and biomarker analysis (see Policy Guidelines). If the intent of concurrent testing is to follow an individual over time to monitor for resistance variants, then consideration could be given to doing liquid biopsy at diagnosis with the tissue biopsy to make sure that mutations that are going to be followed longitudinally can be detected by the liquid biopsy. Comprehensive genetic profiling offers an informative approach to examining potential mechanisms of resistance, which may require more than one biopsy and different biopsy samples over the course of an individual patient's treatment regimen.

[e] Studies have demonstrated that ctDNA testing has very high specificity and is only recommended in advanced/metastatic disease setting. Tumor heterogeneity may be more accurately reflected by ctDNA NGS assays with certain variants being more readily detected through this methodology (see Policy Guidelines).

[f] Broad genomic profiling (CGP) by NGS for pathogenic or likely pathogenic gene fusions and/or variants with the goal of identifying actionable oncogenic driver variants that are able to be treated with targeted therapy is recommended by the NCCN. For CUP, an initial determination of histology must be made before CGP can be performed.

[g] More comprehensive somatic genetic testing may be particularly important in low-grad serous carcinoma and other less common histologies with limited approved therapeutic options.

[h] Multigene NGS testing, preferably with a transcriptome-based approach, is the preferred assay given the rarity of *NTRK* fusions in biliary tract cancers.

[i] IHC staining demonstrates 75% viable tumor cells (% TC) demonstrating moderate to strong membrane CLDN18.2 staining (2+ or 3+ intensity) above background. RNA NGS-based assays that demonstrate equivalent

expression profiles may be used.
[j] NCCN encourages CGP via a validated and/or FDA-approved assay in the initial evaluation of uterine neoplasms to help facilitate cancer diagnosis (*POLE* variants, MSI-H, and CNV for TP53).
[k] Contraindicated variants for tyrosine kinase inhibitors for Philadelphia chromosome positive cancers: asciminib (A337T, P465S, M244V, or F359V/I/C); bosutinib (T315I, V229L, G250E, or F317L); dasatinib (T315I/A, F317L/V/I/C, or V299L); nilotinib (T315I, Y253H, E255K/V, F359V/C/I, or G250E); ponatinib (none).
[l] For relapsed/refectory disease comprehensive molecular characterization and minimal residual disease (MRD) assessment, if not previously done, is recommended by NCCN. MRD quantification to detect fusion genes or clonal rearrangements in immunoglobulin or T-cell receptor loci via FDA-approved NGS-based assays are preferred by NCCN.
[m] At the time of relapse or progression, molecular profiling is recommended and should be performed if not done at diagnosis, or repeated to determine clonal evolution.
[n] NCCN encourages molecular profiling via a validated and/or FDA-approved assay because if a driver variant (e.g., *BRAF* V600E or *NTRK* fusion) is detected, it may be reasonable to treat with a targeted therapy on a compassionate use basis (See Related Policies on genetic testing for targeted therapies).
[o] Combined positive score (CPS) ≥ 1, ≥ 10, or tumor proportion score (TPS) ≥ 1% in concordance with the prescribing information on the FDA label.

Repeat Genetic Testing
Selection of a panel and decision to retest that includes additional genes beyond the minimal sets should be based on considerations such as age at presentation, family cancer phenotype(s), and personal and family history of cancer, as well as patient and provider preference. Furthermore, germline genetic testing typically does not need to be repeated in an individual's lifetime, however, repeating a panel test is supported if the testing technology has advanced in the interim and/or there is evidence to support that the technology has been updated since the last use of the technology.

There may be utility in repeated testing of gene variants for determining targeted therapy or immunotherapy in individuals with advanced and/or metastatic cancer, as tumor molecular profiles may change with subsequent treatments and re-evaluation may be considered at time of cancer progression for treatment decision-making. The American Society of Clinical Oncology (ASCO) currently suggests repeat genomic testing for individuals on targeted therapy with suspected acquired resistance, especially if choice of next-line therapy would be guided. The ASCO guidance is not tumor specific, and it cautions to consider clinical utility (Chakravarty et al, 2022; PMID 35175857).

Repeat Genetic Testing in the Setting of Disease Progression on Targeted Therapy
Individuals who are undergoing targeted therapy for cancer and experience progressive disease after or while on treatment may have tumor(s) that undergo histologic transformation or develop molecular mechanisms of resistance to these targeted therapies. Re-testing of tumor biopsy that is actively progressing while exposed to targeted therapy can shed light on appropriate next therapeutic steps. Additionally, broad genetic profiling offers an informative approach to examining potential mechanisms of resistance, which may require more than one biopsy and different biopsy samples over the course of an individual patient's treatment regimen. Assay methodology selection can impact the ability to identify subclonal events in this setting.

Concurrent Somatic Liquid-Based and Tissue-Based Genetic Testing
Liquid biopsy testing uses blood samples and assesses cancer DNA and non-cancer DNA in the same blood sample. The goal is to identify options for genetic-informed treatment. Some providers will order a liquid biopsy test and a tissue biopsy test at the same time to hasten time to treatment. If the intent of concurrent testing is to follow an individual over time to monitor for resistance variants, then consideration could be given to doing liquid biopsy at diagnosis with the tissue biopsy to make sure that mutations that are going to be followed longitudinally can be detected by the liquid biopsy. Tissue-based assays have greater sensitivity for some variants, but ctDNA may reflect tumor heterogeneity more accurately. If one specimen is negative for actionable biomarkers, testing an alternative specimen can be considered. Studies have demonstrated ctDNA and tissue testing to

have very high specificity. Both ctDNA and tissue testing have appreciable false-negative rates, supporting the complementarity of these approaches, and data support complementary testing to reduce turnaround time and increase yield of targetable alteration detection. Neither tissue-based nor blood-based genetic profiling is 100% sensitive due to biological and technological factors. The only way to achieve 100% sensitivity for actionable biomarkers is to perform testing on both tissue and liquid, when possible. Some NGS-based assays that leverage plasma for liquid biopsies (ctDNA) include a measure of tumor fraction (TF), which can aid in identification of low ctDNA concentration. Liquid biopsy samples with low TF, especially <1%, should be interpreted with caution. NGS assays have varying sensitivities at low TF. Additional sampling form current tumor sample or future plasm can be considered.

Recommended Testing Strategies

Individuals who meet criteria for genetic testing as outlined in the policy statements above should be tested for the variants specified.

- When tumor tissue is available, use of tissue for testing of any/all variants and biomarkers outlined in this policy is recommended, but is not required in all situations. In certain situations, including low availability of tumor tissue or tumor type whereby tumor biopsy is difficult to obtain such as with lung cancer, circulating tumor DNA testing (liquid biopsy) may be an option.

Genetics Nomenclature Update

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

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

Table PG1. Nomenclature to Report on Variants Found in DNA

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

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

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

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

Genetic Counseling

Genetic counseling is primarily aimed at individuals who are at risk for inherited disorders, and experts recommend formal genetic counseling in most cases when genetic testing for an inherited

condition is considered. The interpretation of the results of genetic tests and the understanding of risk factors can be very difficult and complex. Therefore, genetic counseling will assist individuals in understanding the possible benefits and harms of genetic testing, including the possible impact of the information on the individual's family. Genetic counseling may alter the utilization of genetic testing substantially and may reduce inappropriate testing. Genetic counseling should be performed by an individual with experience and expertise in genetic medicine and genetic testing methods.

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

- Genetic Biomarker Testing (Including Liquid Biopsy) for Targeted Treatment in Advanced Cancer

Benefit Application

Blue Shield of California Promise Health Plan is contracted with L.A. Care Health Plan for Los Angeles County and the Department of Health Care Services for San Diego County to provide Medi-Cal health benefits to its Medi-Cal recipients. In order to provide the best health care services and practices, Blue Shield of California Promise Health Plan has an extensive network of Medi-Cal primary care providers and specialists. Recognizing the rich diversity of its membership, our providers are given training and educational materials to assist in understanding the health needs of their patients as it could be affected by a member's cultural heritage.

The benefit designs associated with the Blue Shield of California Promise Medi-Cal plans are described in the Member Handbook (also called Evidence of Coverage).

Regulatory Status

Cal. Health & Safety Code § 1367.665 and Insurance Code Section 10123.20
California laws that prohibit health plans and insurers from requiring prior authorization for biomarker testing for advanced or metastatic stage 3 or 4 cancer, and cancer progression or recurrence.

Cal. Health & Safety Code §1367.667, Insurance Code Section 10123.209, and Welfare and Institutions Code 14132.09
California laws that require 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.

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 microsatellite instability.
- Guardant360CDx (Guardant) is a 74-gene panel that received marketing clearance by the FDA in 2020, 2021, 2022, and 2023. The test is a high throughput hybridization-based capture technology for detection of single nucleotide variants (SNVs), insertions and deletions (indels) in 55 genes, copy number amplifications (CNAs) in two (2) genes, and fusions in four (4) genes using circulating cell-free DNA (cfDNA). Guardant360 utilizes ctDNA and epigenomic NGS-based assay, which includes 739 genes, MSI, tumor mutational burden (TMB), and promoter methylation for treatment selection.

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.

Health Equity Statement

Blue Shield of California Promise Health Plan's mission is to transform its health care delivery system into one that is worthy of families and friends. Blue Shield of California Promise Health Plan seeks to advance health equity in support of achieving Blue Shield of California Promise Health Plan's mission.

Blue Shield of California Promise Health Plan ensures all Covered Services are available and accessible to all members regardless of sex, race, color, religion, ancestry, national origin, ethnic group identification, age, mental disability, physical disability, medical condition, genetic information, marital status, gender, gender identity, or sexual orientation, or identification with any other persons or groups defined in Penal Code section 422.56, and that all Covered Services are provided in a culturally and linguistically appropriate manner.

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, some100 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.[33] 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.

New Sequencing Technologies

New genetic technology, such as NGS and chromosomal microarray, has led to the ability to examine many genes simultaneously.[34] This in turn has resulted in a proliferation of genetic panels. Panels using next-generation technology are currently widely available, covering a broad range of conditions related to inherited disorders, cancer, and reproductive testing.[35,36,37] These panels are intuitively attractive to use in clinical care because they can analyze multiple genes more quickly and may lead to greater efficiency in the workup of genetic disorders. It is also possible that newer technology can be performed more cheaply than direct sequencing, although this may not be true in all cases.

Newer sequencing techniques were initially associated with higher error rates than direct sequencing.[38] While there are limited published data directly comparing the accuracy of NGS with direct sequencing, several publications have reported that the concordance between NGS and Sanger sequencing is greater than 99% for cancer susceptibility testing,[39] inherited disorders,[40] and hereditary hearing loss.[41] Another potential pitfall is the easy availability of a multitude of genetic information, much of which has uncertain clinical consequences. Variants of uncertain significance are found commonly and in greater numbers with NGS than with direct sequencing.[42,43]

The intended use for these panels is variable, For example, for the diagnosis of hereditary disorders, a clinical diagnosis may be already established, and genetic testing is performed to determine whether this is a hereditary condition, and/or to determine the specific variant present. In other cases, there is a clinical syndrome (phenotype) with a broad number of potential diagnoses, and genetic testing is used to make a specific diagnosis. For cancer panels, there are also different intended uses. Some panels may be intended to determine whether a known cancer is part of a hereditary cancer syndrome. Other panels may include somatic variants in a tumor biopsy specimen that may help identify a cancer type or subtype and/or help select the best treatment.

There is no standardization to the makeup of genetic panels. Panel composition is variable, and different commercial products for the same condition may test a different set of genes. The makeup of the panels is determined by the specific lab that developed the test. Also, the composition of any

individual panel is likely to change over time, as new variants are discovered and added to existing panels.

Despite the variability in the intended use and composition of panels, there are a finite number of broad panel types that can be identified and categorized. Once categorized, specific criteria on the utility of the panel can be developed for each category. One difficulty with this approach is that the distinction between the different categories, and the distinction between the intended uses of the panels, may not be clear. Some panels will have features or intended uses that overlap among the different categories.

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:[44] (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.[45,46,47] 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.[47] 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.[44,48] 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).[49] 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 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® 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
ACTOnco	ACT Genomics	Solid	NGS
xT CDx	Tempus Labs, Inc.	Solid	NGS
Guardant360CDx™	Guardant	Solid	NGS
Guardant360	Guardant	Solid	NGS
PredicineATLAS™	Predicine	Solid	NGS
PredicineCARE™	Predicine	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 genetic 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 genetic 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 genetic 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 genetic 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

Systematic Reviews

Kazmi et al (2025) conducted a systematic review and meta-analysis to evaluate the benefits and harms of using comprehensive genetic profiling (CGP) via next-generation sequencing (NGS) for matched targeted therapies in individuals with advanced cancers from randomized controlled trials (35 studies; N=9819).[50] Outcomes of interest were progression-free survival (PFS), overall survival (OS), overall response rates (ORR), serious (grade 3 or 4) adverse events (AEs) and quality of life (QOL). The meta-analysis compared matched targeted therapy (MTT) with and without standard-of-care (SOC) to SOC treatment, non-matched targeted therapies, or no treatment (best supportive care). MTT compared with standard systemic therapy reduced the risk of disease progression by 34% (hazard ratio [HR]: 0.66, 95% confidence interval [CI]: 0.59 to 0.74), however, there was no significant difference in the risk of death (HR: 0.85, 95% CI: 0.75 to 0.97) with limited evidence to suggest an improved QOL for the MTT patients. MTT in combination with SOC compared to SOC alone decreased the risk of disease progression by 39% (HR: 0.61, 95% CI: 0.53 to 0.70) and risk of death by 21% (HR: 0.79, 95% CI: 0.70 to 0.89) but had limiting evidence to demonstrate an improved QOL. MTT versus non-matched targeted therapy exhibited a reduction in the risk of disease progression by 24% (HR: 0.76, 95% CI: 0.64 to 0.89) and risk of death by 25% (HR: 0.75, 95% CI: 0.65 to 0.86). MTT compared to best supportive care reduced the risk of disease progression by 61% % (HR: 0.37, 95% CI: 0.28 to 0.50) but no clear evidence to suggest a difference in OS between the groups. The overall risk of bias was judged low for eight studies, unclear for two studies, and the remaining 27 studies were high risk. MTT guided by NGS for individuals with advanced cancer slows down cancer progression compared to standard therapies, however, there is limited evidence to suggest that it prolongs overall survival, improves the quality of life or increases adverse events.

Zerdes et al (2025) performed systematic review and meta-analysis on data compiled from real-world evidence (144 studies; N=54,739) to investigate the applicability and clinical impact of GCP in individuals with metastatic cancer.[51] For individuals treated with NGS-guided therapy, the pooled median PFS was 4.41 months (95% CI: 3.71 to 5.24; 35 studies) and OS was 13.14 months (95% CI: 9.56 to 18.06; 16 studies) for all cancer types. CGP-guided treatment was correlated with statically significant increase in ORR (Odds ratio [OR]: 2.75; 95% CI: 1.84 to 4.13; 16 studies, n=1109), PFS (pooled HR: 0.63; 95% CI: 0.56 to 0.70; 18 studies, n=3269), and OS (pooled HR: 0.60; 95% CI: 0.51 to 0.70; 21 studies, n=2772) when compared to conventional treatment. Despite these promising results, the

authors note there was a low certainty of evidence, mainly due to clinical heterogeneity and low internal validity of eligible studies.

Limaye et al (2025) carried out a systematic review on the clinical utility of GCP from randomized clinical trials (RCT), non-randomized, and observational studies (14 studies; N=35,975) encompassing all cancer types and different therapeutic interventions using OS and PFS as the primary outcome.[52] Targeted therapy that was based on genomically matched scores and/or molecular tumor board (MTB) recommendations enhanced OS, PFS, and yielded better clinical outcomes when compared to standard chemotherapy or physician's choice regimens (Table 3 and 4). Improved OS and PFS were reported when CGP guided treatment decisions, but its clinical utility varied among cancer types. Furthermore, while most of the studies in this review incorporated CGP testing during the study, the actual treatment based on CGP testing was limited to subgroup analysis only, which were limited by low sample size, statistical insignificance, and heterogeneity in the matching scores.

Labaki et al (2025) evaluated clinical studies that assessed molecularly directed therapies (MDT) in the management of individuals with cancers of unknown primary (CUP), as compared to empiric treatment, and performed a meta-analysis using OS and PFS as the endpoints.[53] Only 1 study (Krämer et al [2024]) used CGP methodology to determine what targeted therapy individuals with CUP received with the results presented in Table 3 and 4. Of note, the study was a randomized phase 2 clinical trial that enrolled 436 individuals with 326 patients receiving targeted therapy as a result of CGP and 110 patients receiving empirical chemotherapy.

Table 3. Clinical Utility of Comprehensive Genetic Profiling for Improving Overall Survival in Patients with Advanced Cancers

Study	Treatment Arms		mOS	HR, 95% CI	p value
Schwaederle et al (2016)[54]	Matching score > 0.2	Matching score < 0.2	15.7 (matching score >0.2) vs 10.6 (matching score <0.2)	NR, 13.1 to 18.3	.04
Lee et al (2019)[55]	Matched therapy	Conventional 2L therapy	9.8 (matched) vs 6.9 (conventional)	0.58, 0.45 to 0.76	<.0001
Steuten et al (2019)[56]	Targeted therapy	Non-targeted treatment	2.31 (targeted) vs 1.73 (non-targeted)	NR, 0.31 to 4.12y (targeted) vs 0.28 to 3.59y (non-targeted)	NR
Singal et al (2019)[57]	Targeted therapy	Non-targeted treatment	18.6 (targeted) vs 11.4 (non-targeted)	NR, 15.2 to 21.7 (targeted) vs 9.7 to 12.5 (non-targeted)	<.001
Kato et al (2020)[58]	MTB recommendation therapy	Physician chosen therapy	NR	0.69, 0.49 to 0.98	.036
Stahler et al (2020)[59]	*SMAD4* wild-type tumors	*SMAD4*-mutated tumors	NR	0.59, 0.34 to 1.01	>.05
Catenacci et al (2021)[60]	Targeted immunotherapy plus chemotherapy	Historical controls	15.7 (targeted) vs 9 (controls)	NR, 13.4 to 17.7 (targeted) vs 4.6 to 20.3 (non-targeted)	.05
Krämer et al (2024)[61]	Targeted therapy	chemotherapy	14.7 (targeted therapy) vs 11.0 (chemotherapy)	0.82, 0.62 to 1.09	0.18

HR: hazard ratio; mOS: median overall survival; MTB: molecular tumor board; NR: not reported; SMAD4: mothers against decapentaplegic homolog 4; 2L: second line;

Table 4. Clinical Utility of Comprehensive Genetic Profiling for Improving Progression-free Survival in Patients with Advanced Cancers

Study	Treatment Arms		mPFS (mos)	HR, 95% CI	p value
Hortobagyi et al (2016)[62]	Everolimus	Placebo	7.0 (Everolimus) vs 4.0 (placebo)	NR, 6.7 to 8.5 (Everolimus) vs 2.6 to 4.2 (placebo)	NR

Study	Treatment Arms		mPFS (mos)	HR, 95% CI	p value
Schwaederle et al (2016)[54]	Matching score > 0.2	Matching score < 0.2	4.0 (matching score >0.2) vs 3.0 (matching score <0.2)	NR	.039
Massard et al (2017)[63]	Matched therapy (PFS2)	Prior therapy (PFS1)	PFS2/PFS1 ratio was > 1.3	NR, 26% to 39%	NR
Coleman et al (2017)[64]	*BRCA*-mutant carcinoma	Placebo	16.6 (*BRCA*) vs 5.4 (placebo)	13.4 to 22.9 (*BRCA*) vs 3.4 to 6.7 (placebo)	<.0001
Lee et al (2019)[55]	Matched therapy	Conventional 2L therapy	5.7 (matched) vs 3.7 (conventional)	NR	<.0001
Sicklick et al (2019)[65]	High-matching score	Low-matching score	6.5 (high-match) vs 3.1 (low-match) mos	NR, 0.31 to 4.12y (targeted) vs 0.28 to 3.59y (non-targeted)	NR
Tuxen et al (2019)[66]	Targeted therapy (PFS2)	Most recent treatment (PFS1)	PFS2/PFS1 ratio was > 1.3 in 32% of all patients	NR, 23% to 42%	NR
Kato et al (2020)[58]	MTB recommendation treatment	Physican chosen regimen	NR	0.63, 0.50 to 0.80	<.001
Sultova et al (2021)[67]	Targeted immunotherapy plus hormone therapy	Recommended treatment (PFS1)	PFS2/PFS1 ratio ≥ 1.3 in 9/16 patients (56%, 9% of all patients)	NR	NR
Hlevnjak et al (2021)[68]	Targeted immunotherapy plus hormone therapy	Recommended treatment (PFS1)	PFS2/PFS1 ratio ≥ 1.3 in 30% of all patients	NR	NR
Krämer et al (2024)[61]	Targeted therapy	chemotherapy	6.1 (targeted therapy) vs 4.4 (chemotherapy)	0.72, 0.56 to 0.92	.0079

HR: hazard ratio; MTB: molecular tumor board; NR: not reported; PFS: progression-free survival, PFS1: PFS under immediate previous treatment line; PFS2: PFS under MTB-recommended treatment; 2L: second line.

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.69,[70] 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 genetic profiling is more effective than tumor-specific variant assessment.

Table 5. Meta-Analysis Characteristics

Study	Dates	Trials	Participants	N	Design
Schwaederle et al (2015)[69]	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)[70]		57 RCTs 55 non-RCTs			58 newly approved cancer agents

RCT: randomized controlled trial.

Table 6. 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)[69]	% (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)[70]	% (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.

Randomized Controlled Trials

Randomized controlled trials (RCT) have been published that compare molecular profiling techniques to assess the utility of detecting actionable gene variants in advanced or metastatic cancers. One of these studies used molecular biomarker analysis as an exploratory endpoint during a phase III trial to evaluate the benefit of two different treatment regimens[71], another study was examining the utility of CGP by liquid biopsies to tailor treatment for individuals with refectory metastatic colorectal cancer (CRC)72, the last study was assessing the potential benefit of using larger "*expanded*" gene panels versus smaller "limited" gene panels in identifying actionable gene variants.73 These studies have reported that outcomes are better in patients receiving targeted therapy. However, there are potential limitations with these designs that could compromise the validity these studies, which 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.

Trédan et al (2025) examined molecular alterations via an "*expanded*" panel of 324-cancer genes (Foundation OneCDX [F1CDX]) or a "*limited*" panel of 87-genes of single-nucleotide and copy number variants, which were subsequently reviewed by a molecular tumor board to identify actionable gene variants.[73] Significantly more actionable gene variants were identified using CGP assays (51.65) versus the "limited" panel (36.9%; p<.001), but no differences in clinical outcomes were observed.

Ciardiello et al (2025) evaluated if CGP by liquid biopsy could identify individuals with refractory metastatic CRC who would be suitable for anti-EGFR rechallenge therapy.[72] Ultimately, the findings uncovered the complexity and heterogeneity of genomic profiles for CRC, but CGP was able to identify actionable gene variants that can be targeted with new therapy regimens or resistance

variants that were suitable for anti-EGFR re-challenge therapies, albeit in a relatively small number of patients.

Kopetz et al (2024) conducted a RCT with a prespecified exploratory biomarker analysis to characterized genomic and transcriptomic correlates of clinical outcomes and acquired resistance mechanisms in response to two different treatment regimens (encorafenib + cetuximab with or without binimetinib).71 Tumors with higher immune signatures showed a trend towards increased OS benefit with encorafenib + binimetinib + cetuximab. Additionally, unique molecular signatures arose as a result from receiving either of the two treatments suggesting insights into the biology of response and resistance to MAPK-pathway-targeted therapy.

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 7, 8, and 9).[74,75] 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 7. Summary of Key RCT Characteristics

Study	Countries	Sites	Dates	Participants	Interventions	
					Active	Comparator
Le Tourneau et al (2012, 2015)[74,75]; 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 8. 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).[74]

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 9). In the subgroup analysis by molecular pathway, there were no significant differences in PFS between groups.

Table 9. 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)[74,75]; 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 10 and 11. A major limitation of the SHIVA trial is that the population consisted of patients who had failed a targeted treatment.

Table 10. Study Relevance Limitations

Study	Population[a]	Intervention[b]	Comparator[c]	Outcomes[d]	Follow-Up[e]
Le Tourneau et al (2012, 2015)[74,75]; 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 11. 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)[74,75]; 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.[76] 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.

Nonrandomized Controlled Trials

Nonrandomized studies have been published that use some type of control.[77] Some of these studies had a prospective, interventional design.[78] 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. Another study used a different approach, where comprehensive genetic testing was performed to identify actionable gene variants for targeted therapies and was compared to an *in silico* 50-gene panel for the same purpose.[79] Furthermore, this study assessed overall survival of patients receiving targeted therapy versus chemotherapy. 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.[80] Patients with advanced cancer who underwent comprehensive genetic profiling were treated with matched targeted therapy when available (see Table 12). 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 13. 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 14 and 15. 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 16).

Table 12. Summary of Key Nonrandomized Trial Study Characteristics

Study	Study Type	Country	Dates	Participants	Treatment 1	Treatment 2	Follow-Up
Tsimberidou et al (2017)[80] IMPACT	Database Review	U.S.	2012-2013	1436 patients with advanced cancer	Matched therapy (n=390)	Unmatched therapy (n=247)	

Table 13. Summary of Key Nonrandomized Trial Study Results

Study	Complete or Partial Response	Progression-Free Survival, mo	Overall Survival, mo
Tsimberidou et al (2017)[80] 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 14. Study Relevance Limitations

Study	Population[a]	Intervention[b]	Comparator[c]	Outcomes[d]	Follow-Up[e]
Tsimberidou et al (2017)[80] 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 15. Study Design and Conduct Limitations

Study	Allocation[a]	Blinding[b]	Selective Reporting[d]	Data Completeness[e]	Power[d]	Statistical[f]
Tsimberidou et al (2017)[80] 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

Copenhagen Prospective Personalized Oncology (CoPPO) is a prospective, single-center, single-arm open label phase I trial assessing comprehensive genetic profiling in patients with advanced solid tumors (N=2147).[81] Genetic data was reviewed and discussed by a multidisciplinary tumor board and actionable alterations were classified according to the European Society for Medical Oncology Scale for Clinical Actionability of molecular Targets (ESCAT). If a patient had an actionable variant, they were treated with a therapy regimen matched to their genomic profile. At least one actionable target was identified in 57% of patients with at least 24% of these patients receiving matched targeted therapy. In total, 274 targeted treatment regimens were initiated, and 259 treatments were evaluable with an overall response (OR) rate of 25% (95% confidence interval 0.20% to 0.30%). Patients treated with an actionable target classified as ESCAT I/II had a median progression-free survival (PFS) of 5.02 months (95% confidence interval [CI]: 4.07 to 6.36 months) versus 2.26 months (95% CI: 1.84 to 2.79 months) for ESCAT III/IV. Similarly, the median overall survival (OS) was 10.49 months (95% CI: 8.56 to 13.80 months) for ESCAT I/II versus 6.66 months (95% CI: 5.34 to 7.32 months) for ESCAT III/IV. Notable limitations, include but are not limited to, actionable genomic variants were defined retrospectively, differences in clinical and demographic factors, 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 differences in the treatments received, ultimately underscoring the heterogeneity of this clinical design.

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.82 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.83,[84,85] 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).86 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).[87] 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 include RCTs, systematic reviews, nonrandomized trials, non-comparative studies, and a database review. A published RCT (SHIVA trial) that used an expanded panel reported no difference in PFS compared with standard treatment. Furthermore, a well conducted systematic review by Cochrane (Kazmi et al 2025) did not demonstrate a net health benefit for individuals (N=9,819) subjected to matched targeted therapies based on comprehensive genetic profiling. Additionally, randomized and nonrandomized trials for drug development, along with systematic reviews , 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 genetic 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 comprehensive 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 genetic 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 randomized controlled trials (RCT), nonrandomized trials, and systematic reviews. 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. A well conducted systematic review by Cochrane (Kazmi et al 2025) did not demonstrate a net health benefit for individuals (N=9,819) subjected to matched targeted therapies based on comprehensive genetic profiling. Additional randomized and nonrandomized trials for drug development, along with other systematic reviews, 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 comprehensive 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 U.S. professional society, an international society with U.S. 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.[88] 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 2022, the College of American Pathologists, Association for Molecular Pathology, and Fight Colorectal Cancer collaborated on a joint evidence-based clinical guideline on "Mismatch Repair and Microsatellite Instability Testing for Immune Checkpoint Inhibitor Therapy" to help pathologists optimize testing methods to better identify and evaluate patients with cancer who may be eligible for immunotherapies known as checkpoint inhibitors.[89] The following are strong recommendations:

- "For patients with CRC being considered for immune checkpoint inhibitor therapy, pathologists should use MMR-IHC and/or MSI by PCR for the detection of DNA MMR defects.

Although MMR-IHC or MSI by PCR are preferred, pathologists may use a validated MSI by NGS assay for the detection of DNA MMR defects.
- For patients with gastroesophageal and small bowel cancer being considered for immune checkpoint inhibitor therapy, pathologists should use MMR-IHC and/or MSI by PCR over MSI by NGS for the detection of DNA MMR defects.
- For patients with endometrial cancer being considered for immune checkpoint inhibitor therapy, pathologists should use MMR-IHC over MSI by PCR or NGS for the detection of DNA MMR defects
- For all cancer patients being considered for immune checkpoint inhibitor therapy based upon defective MMR, pathologists should NOT use TMB as a surrogate for the detection of DNA MMR defects. If a tumor is identified as TMB-high, pathologists may perform IHC and/or MSI by PCR to determine if high TMB is secondary to MMR deficiency."

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.90 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[4]
- *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[5]
- *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[1]
- *EGFR*, *ALK, ROS1, BRAF, MET exon 14, RET, KRAS, HER2,* and *NTRK* fusions.

Cutaneous melanoma[2]
- *BRAF, NRAS, KIT.*
- Uncommon mutations with next-generation sequencing are *ALK, ROS1, NTRK*, and *BRAF* fusions.

Ovarian cancer[7]
- *BRCA 1/2, BRAF, NTRK, HER2, HRD, RET, FR*α*,* tumor mutational burden, microsatellite instability and mismatch repair.

Pancreatic cancer[11]
- *ALK, NRG1, NTRK, ROS1, FGRF2, RET, BRAF, BRCA1/2, HER2, KRAS, PALB2*, mismatch repair deficiency, microsatellite instability, or tumor mutational burden.

Prostate cancer[10]
- *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 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.

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	Oncomap™ ExTra

Code	Description	TEST NAME
	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 PARAFFINEMBEDDED (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	Guardant360 TissueNext™
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 16. Summary of Key Trials+

NCT No.	Trial Name	Planned Enrollment	Completion Date
Ongoing			
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

NCT No.	Trial Name	Planned Enrollment	Completion Date
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 the Cancer Centre - Belgian Approach for Local Laboratory Extensive Tumor Testing (BALLETT)	936	May 2026
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

Please provide the following documentation:

- History and physical and/or consultation notes including:
  - Clinical findings (i.e., pertinent symptoms and duration)

- Family history, if applicable
- Reason for procedure/test, when applicable
- Pertinent past procedural and surgical history
- Past and present diagnostic testing and results
- Prior conservative treatments, duration, and response
- Treatment plan (i.e., surgical intervention)

- Radiology report(s) and interpretation (i.e., MRI, CT, PET)
- Other pertinent multidisciplinary notes/reports: (i.e., psychological or psychiatric evaluation, physical therapy, multidisciplinary pain management), when applicable

Post Service (in addition to the above, please include the following):

- Results/reports of tests performed

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 ***(Includes OncoTarget/OncoTreat, Columbia University Department of Pathology and Cell Biology, Darwin Health)***
	0022U	Targeted genomic sequence analysis panel, non-small cell lung neoplasia, DNA and RNA analysis, 23 genes, interrogation for sequence variants and rearrangements, reported as presence/absence of variants and associated therapy(ies) to consider ***(Includes Oncomine™ Dx Target Test, Thermo Fisher Scientific)***
	0036U	Exome (i.e., somatic mutations), paired formalin-fixed paraffin-embedded tumor tissue and normal specimen, sequence analyses ***(Includes EXaCT-1 Whole Exome Testing, Lab of Oncology-Molecular Detection, Weill Cornell Medicine-Clinical Genomics Laboratory)***
	0037U	Targeted genomic sequence analysis, solid organ neoplasm, DNA analysis of 324 genes, interrogation for sequence variants, gene copy number amplifications, gene rearrangements, microsatellite instability and tumor mutational burden ***(Includes FoundationOne CDx™ (F1CDx), Foundation Medicine, Inc)***
	0048U	Oncology (solid organ neoplasia), DNA, targeted sequencing of protein-coding exons of 468 cancer-associated genes, including interrogation for somatic mutations and microsatellite instability, matched with normal specimens, utilizing formalin-fixed paraffin-embedded tumor tissue, report of clinically significant mutation(s)

Type	Code	Description
		(Includes MSK-IMPACT (Integrated Mutation Profiling of Actionable Cancer Targets), Memorial Sloan Kettering Cancer Center)
	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 ***(Includes Praxis™ Extended RAS Panel, Illumina)***
	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 ***(Includes MI Cancer Seek™ - NGS Analysis, Caris MPI d/b/a Caris Life Sciences)***
	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 ***(Includes Oncotype MAP™ Pan-Cancer Tissue Test, Paradigm Diagnostics, Inc)***
	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 ***(Includes PGDx elio™ tissue complete, Personal Genome Diagnostics, Inc)***
	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 ***(Includes RiskReveal™, Razor Genomics)***
	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 ***(Includes Praxis Somatic Whole Genome Sequencing, Praxis Genomics LLC)***
	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 ***(Includes Oncomap™ ExTra, Exact Sciences, Inc, Genomic Health Inc)***
	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 ***(Includes Guardant360® Tissue, Guardant Health, Inc)***

Type	Code	Description
	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 ***(Includes Solid Tumor Expanded Panel, Quest Diagnostics®)***
	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 ***(Includes Strata Select™, Strata Oncology, Inc)***
	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 DNA analysis using next-generation sequencing, algorithm reported as a quantitative change from baseline, including specific alterations, if appropriate ***(Includes Guardant360 Response™, Guardant Health, Inc)***
	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) ***(Includes Aventa FusionPlus™, Aventa Genomics, LLC)***
	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 ***(Includes xT CDx, Tempus AI, Inc)***
	0586U	Oncology, mRNA, gene expression profiling of 216 genes (204 targeted and 12 housekeeping genes), RNA expression analysis, formalin-fixed paraffin-embedded (FFPE) tissue, quantitative, reported as log2 ratio per gene. ***(Includes RNA Salah Targeted Expression Panel, Moffitt Cancer Center Advanced Diagnostics Laboratory, Laboratory Developed Test)*** ***(Code effective 10/01/2025)***
	0592U	Oncology (hematolymphoid neoplasms), DNA, targeted genomic sequence of 417 genes, interrogation for gene fusions, translocations, rearrangements, utilizing formalin-fixed paraffin-embedded (FFPE) tumor tissue, results report clinically significant variant(s) ***(Includes Aventa Lymphoma, Aventa Genomics, LLC)*** ***(Code effective 10/01/2025)***
	0597U	Oncology (breast), RNA expression profiling of 329 genes by targeted next-generation sequencing and 20 proteins by multiplex immunofluorescence, formalin-fixed paraffin-embedded (FFPE) tissue, algorithmic analyses to determine tumor-recurrence risk score ***(Includes AidaBreast™, PreludeDx™, Prelude Corporation)*** (***Code effective 10/01/2025)***

Type	Code	Description
	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
03/01/2026	New policy.

Definitions of Decision Determinations

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

Medically Necessary or **Medical Necessity** means reasonable and necessary services to protect life, to prevent significant illness or significant disability, or alleviate severe pain through the diagnosis or treatment of disease, illness, or injury, as required under W&I section 14059.5(a) and 22 CCR section 51303(a). Medically Necessary services must include services necessary to achieve age-appropriate growth and development, and attain, maintain, or regain functional capacity.

For Members less than 21 years of age, a service is Medically Necessary if it meets the Early and Periodic Screening, Diagnostic, and Treatment (EPSDT) standard of Medical Necessity set forth in 42 USC section 1396d(r)(5), as required by W&I sections 14059.5(b) and 14132(v). Without limitation, Medically Necessary services for Members less than 21 years of age include all services necessary to achieve or maintain age-appropriate growth and development, attain, regain or maintain functional capacity, or improve, support, or maintain the Member's current health condition. Contractor must determine Medical Necessity on a case-by-case basis, taking into account the individual needs of the Child.

Criteria Determining Experimental/Investigational Status
In making a determination that any procedure, treatment, therapy, drug, biological product, facility, equipment, device, or supply is "experimental or investigational" by the Plan, the Plan shall refer to evidence from the national medical community, which may include one or more of the following sources:

1. Evidence from national medical organizations, such as the National Centers of Health Service Research.
2. Peer-reviewed medical and scientific literature.
3. Publications from organizations, such as the American Medical Association (AMA).
4. Professionals, specialists, and experts.
5. Written protocols and consent forms used by the proposed treating facility or other facility administering substantially the same drug, device, or medical treatment.
6. An expert physician panel selected by one of two organizations, the Managed Care Ombudsman Program of the Medical Care Management Corporation or the Department of Managed Health Care.

Feedback

Blue Shield of California Promise Health Plan 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 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/en/bsp/providers.

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

Questions regarding the applicability of this policy should be directed to the Blue Shield of California Promise Health Plan Prior Authorization Department at (800) 468-9935, or the Complex Case Management Department at (855) 699-5557 (TTY 711) for San Diego County and (800) 605-2556 (TTY 711) for Los Angeles County or visit the provider portal at www.blueshieldca.com/en/bsp/providers.

Disclaimer: Blue Shield of California Promise Health Plan 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 of California Promise Health Plan reserves the right to review and update policies as appropriate.