BlueCross BlueShield Federal Employee Program.

FEP Medical Policy Manual

FEP 2.04.115 Comprehensive Genomic Profiling for Selecting Targeted Cancer Therapies

Annual Effective Policy Date: January 1, 2024

Original Policy Date: June 2014

Related Policies:

2.04.151 - Germline and Somatic Biomarker Testing (Including Liquid Biopsy) for Targeted Treatment and Immunotherapy in Breast Cancer
2.04.155 - Germline and Somatic Biomarker Testing (Including Liquid Biopsy) for Targeted Treatment in Prostate Cancer (BRCA1/2, Homologous Recombination Repair Gene Alterations)
2.04.156 - Germline and Somatic Biomarker Testing (Including Liquid Biopsy) for Targeted Treatment in Ovarian Cancer (BRCA1, BRCA2, Homologous Recombination Deficiency)
2.04.45 - Somatic Biomarker Testing (Including Liquid Biopsy) for Targeted Treatment in Non-Small-Cell Lung Cancer (EGFR, ALK, BRAF, ROS1, RET, MET, KRAS)
2.04.53 - Somatic Biomarker Testing (Including Liquid Biopsy) for Targeted Treatment in Metastatic Colorectal Cancer (KRAS, NRAS, BRAF, and HER2)
2.04.77 - Somatic Genetic Testing to Select Individuals with Melanoma or Glioma for Targeted Therapy (BRAF)
2.04.93 - Genetic Cancer Susceptibility Panels Using Next Generation Sequencing

Comprehensive Genomic Profiling for Selecting Targeted Cancer Therapies

Description

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.

Much of the variability in clinical response may result from genetic variations. Within each broad type of cancer, there may be a large amount of variability in the genetic underpinnings of cancer. Targeted cancer treatment refers to the identification of genetic abnormalities present in the cancer of a particular patient, and the use of drugs that target the specific genetic abnormality. The use of genetic markers allows cancers to be further classified by "pathways" defined at the molecular level. An expanding number of genetic markers have been identified. These may be categorized into 3 classes:[2,] (1) genetic markers that have a direct impact on care for the specific cancer of interest, (2) genetic markers that may be biologically important but are not currently actionable, and (3) genetic markers of uncertain importance.

A smaller number of individual genetic markers fall into the first category (ie, 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 (eg, a panel of several markers for non-small-cell lung cancer). This review also does not address the use of cancer-specific panels that include a few variants. Rather, this review addresses expanded panels that test for many potential variants that do not have established efficacy for the specific cancer in question.

When advanced cancers are tested with expanded molecular panels, most patients are found to have at least 1 potentially pathogenic variant.[3,4,5,] The number of variants varies widely by types of cancers, different variants included in testing, and different testing methods among the available studies. In a study by Schwaederle et al (2015), 439 patients with diverse cancers were tested with a 236-gene panel.[5,] A total of 1813 molecular alterations were identified, and almost all patients (420/439 [96%]) had at least 1 molecular alteration. The median number of alterations per patient was 3, and 85% (372/439) of patients had 2 or more alterations. The most common alterations were in the *TP53* (44%), *KRAS* (16%), and *PIK3CA* (12%) genes.

Some evidence is available on the generalizability of targeted treatment based on a specific variant among cancers that originate from different organs.[2,6,] There are several examples of variant-directed treatment that is effective in 1 type of cancer but ineffective in another. For example, targeted therapy for epidermal growth factor receptor variants have been successful in non-small-cell lung cancer but not in trials of other cancer types. Treatment with tyrosine kinase inhibitors based on variant testing has been effective for renal cell carcinoma but has not demonstrated effectiveness for other cancer types tested. "Basket" studies, in which tumors of various histologic types that share a common genetic variant are treated with a targeted agent, also have been performed. One such study was published by Hyman et al (2015).[7,] In this study, 122 patients with *BRAF* V600 variants in nonmelanoma cancers were treated with vemurafenib. The authors reported that there appeared to be an antitumor activity for some but not all cancers, with the most promising results seen for non-small-cell lung cancer, Erdheim-Chester disease, and Langerhans cell histiocytosis.

OBJECTIVE

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

POLICY STATEMENT

The use of comprehensive genomic profiling for selecting targeted cancer treatment is considered **not medically necessary**.

POLICY GUIDELINES

None

BENEFIT APPLICATION

Experimental or investigational procedures, treatments, drugs, or devices are not covered (See General Exclusion Section of brochure).

Screening (other than the preventive services listed in the brochure) is not covered. Please see Section 6 General exclusions.

Benefits are available for specialized diagnostic genetic testing when it is medically necessary to diagnose and/or manage a patient's existing medical condition. Benefits are not provided for genetic panels when some or all of the tests included in the panel are not covered, are experimental or investigational, or are not medically necessary.

FDA REGULATORY STATUS

Table 1 provides a select list of commercially available expanded cancer molecular panels.

Table 1. Commercially Available Molecular Panels for Solid and Hematologic Tumor Testing

Test	Manufacturer	Tumor Type	Technology
FoundationOne®CDx test (F1CDx)	Foundation Medicine	Solid	NGS
FoundationOne® Heme test	Foundation Medicine	Hematologic	RNA sequencing
OnkoMatch™	GenPath Diagnostics	Solid	Multiplex PCR
GeneTrails® Solid Tumor Panel	Knight Diagnostic Labs	Solid	
Tumor profiling service	Caris Molecular Intelligence through Caris Life Sciences	Solid	Multiple technologies
SmartGenomics™	PathGroup	Solid and hematologic	NGS, cytogenomic array, other technologies
Paradigm Cancer Diagnostic (PcDx™) Panel	Paradigm	Solid	NGS
MSK-IMPACT™	Memorial Sloan Kettering Cancer Center	Solid	NGS
TruSeq® Amplicon Panel		Solid	NGS
TruSight™ Oncology	Illumina	Solid	NGS
Ion AmpliSeq™ Comprehensive Cancer Panel		Solid	NGS
Ion AmpliSeq™ Cancer Hotspot Panel v2	Thermo Fisher Scientific	Solid	NGS
OmniSeq Comprehensive®	OmniSeq	Solid	NGS
Oncomine DX Target Test™	Thermo Fisher Scientific	Solid	NGS
Omics Core(SM)	NantHealth	Solid	WES
PGDx elio tissue complete™	Personal Genome Diagnostics	Solid	NGS
NYU Langone Genome PACT assay	NYU Langone Medical Center	Solid	NGS
ACTOnco	ACT Genomics	Solid	NGS

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

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.

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

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

Table 2. Companion Diagnostic Indications for F1CDx[1]

Tumor Type	Biomarker(s) Detected	Therapy
Non-small cell lung cancer (NSCLC)	*EGFR* exon 19 deletions and *EGFR* exon 21 L858R alterations	Gilotrif (afatinib), Iressa (gefitinib), Tagrisso (osimertinib), or Tarceva (erlotinib), Vizimpro (dacomitinib)
	EGFR exon 20 T790M alterations	Tagrisso (osimertinib)
	*EGFR e*xon 20 insertion mutations	Rybrevant (amivantamb), Exkivity (mobocertinib)
	ALK rearrangements	Alecensa (alectinib), Xalkori (crizotinib), or Zykadia (ceritinib)
	BRAF V600E	Tafinlar (dabrafenib) in combination with Mekinist (trametinib)
	MET	Tabrecta™ (capmatinib)
	KRAS G12C	Krazati (adagrasib), Lumakras (sotorasib)
	RET fusions	Gavreto (pralsetinib), Retevmo (selpercatinib)
	ROS1 fusions	Rozlytrek (entrectinib)
Melanoma	*BRAF* V600E	Tafinlar (dabrafenib), Mekinist (trametinib)or Zelboraf (vemurafenib)
	BRAF V600E and V600K	Braftovi (encorafenib), Mekinist (trametinib) or Tecentriq (atezolizumab) in combination with Cotellic (cobimetinib) and Zelboraf (vemurafenib)

Breast cancer	*ERBB2* (HER2) amplification	Herceptin (trastuzumab), Kadcyla (ado-trastuzumabemtansine), Enhertu (fam-trastuzumab deruxtecan-nxki), or Perjeta (pertuzumab)
	ESR1 missense mutations	Orserdu (elacestrant)
	PIK3CA alterations	Lynparza (olaparib)
Colorectal cancer	*BRAF* V600E	Braftovi (encorafenib)
	KRAS wild-type (absence of mutations in codons 12 and 13)	Erbitux (cetuximab)
	KRAS wild-type (absence of mutations in exons 2, 3, and 4) and NRAS wild type (absence of mutations in exons 2, 3, and 4)	Vectibix (panitumumab)
Ovarian cancer	*BRCA1/2* alterations	Lynparza (olaparib) or Rubraca (rucaparib)
	FOLR1 protein expression	Elahere (mirvetuximab soravtansine-gynx)
Cholangiocarcinoma	*FGFR2* fusion or other select rearrangements	Pemazyre (pemigatinib) or Truseltiq fgv™ (infigratinib)
	IDH1 sngle nucleotide variants	Tibsovo (ivosidenib)
Prostate cancer	*BRCA1/2* alterations	AKEEGA (niraparib + abiraterone acetate), Rubraca (rucaparib), Lynparza (olaparib)
	Homologous Recombination Repair (HRR) gene alterations	Lynparza (olaparib)
Solid Tumors	Tumor mutational burden >10 mutations per megabase	Keytruda (pembrolizumab)
	Microsatellite instability-high (MSI-H)	Keytruda (pembrolizumab)
	NTRK1/2/3 fusions	lVitrakvi (larotrectinib) or Rozlytrek (entrectinib)

F1CDx: FoundationOne Companion Diagnostic.

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

RATIONALE

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 (ie, basket trials). As a result, these types of studies do not provide evidence of the benefit of broad molecular profiling compared to more limited genetic assessments based on known tumor-specific variants. Basket trials that randomize patients with various tumor types to a strategy of comprehensive genomic profiling followed

by targeted treatment are needed, and several are ongoing. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

SUPPLEMENTAL INFORMATION

Practice Guidelines and Position Statements

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

American Society of Clinical Oncology

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

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

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

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

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

PCO 2.1. Mismatch repair deficiency status (dMMR) should be evaluated on patients with metastatic or advanced solid tumors who are candidates for immunotherapy. There are multiple approaches, including using large multigene panel-based testing to assess microsatellite instability (MSI). Consider the prevalence of dMMR and/or MSI-H status in individual tumor types when making this decision (strength of recommendation: strong).

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

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

College of American Pathologists et al

In 2018, the College of American Pathologists, International Association for the Study of Lung Cancer, and the Association for Molecular Pathology updated their joint guidelines on molecular testing of patients with non-small-cell lung cancer.[23,] The groups gave a strong recommendation for *EGFR, ALK*, and *ROS1* testing. Based on expert consensus opinion *KRAS* was recommended as a single gene test if *EGFR, ALK*, and *ROS1* were negative. Tests that were not recommended for single gene testing outside of a clinical trial were *BRAF, RET, ERBB2 (HER2)*, and *MET*, although these genes should be tested if included in a panel.

National Comprehensive Cancer Network

The National Comprehensive Cancer Network (NCCN) guidelines contain recommendations for specific genetic testing for individual cancers, based on situations where there is a known mutation-drug combination that has demonstrated benefits for that specific tumor type. Some examples of recommendations for testing of common solid tumors are listed below:

Breast cancer[24,]

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

Colon cancer[25],

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

Non-small-cell lung cancer[26],

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

Cutaneous melanoma[27],

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

Ovarian cancer[28],

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

Pancreatic cancer[29],

- *ALK, NRG1, NTRK, ROS1, FGRF2, RET, BRAF, BRCA1/2, HER2, KRAS, PALB2*, mismatch repair deficiency.

Prostate cancer[30],

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

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

U.S. Preventive Services Task Force Recommendations

Not applicable.

Medicare National 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.

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POLICY HISTORY - THIS POLICY WAS APPROVED BY THE FEP® PHARMACY AND MEDICAL POLICY COMMITTEE ACCORDING TO THE HISTORY BELOW:

Date	Action	Description
June 2014	New policy	New policy- The use of expanded mutation panels to direct targeted treatment is considered investigational.
June 2015	Replace policy	Policy updated with literature review. References 6- 10 added, and references 19-22 updated. No change to policy statement
March 2017	Replace policy	Policy updated with literature review through August 29, 2016; references 24, 26, and 35-36 added, references 3, and 28-33 updated. Policy statement unchanged.
December 2017	Replace policy	Policy updated with literature review through August 23, 2017; reference 26 added, references 3, 9-13, 15, 17-20, 29- 34, 36 and 38 updated. "Mutation, changed to "molecular, in the Policy-statement otherwise unchanged.
December 2018	Replace policy	Policy updated with literature review through August 6, 2018; references 21-22 added; references 13-20 updated; some references removed. Policy statement unchanged.
June 2019	Replace policy	Policy updated to add related policies: 2.04.93, 2.04.45, and 2.04.77 and updated the name of the FoundationOne CDx test.
December 2019	Replace policy	Policy updated with literature review through September 4, 2019, references added. Language in policy statement changed from "expanded cancer molecular panels" to "comprehensive genomic profiling"; "investigational" changed to "not medically necessary"; the intent of the policy is unchanged. Title changed to Comprehensive Genomic Profiling for Selecting Targeted Cancer Therapies.
December 2020	Replace policy	Policy updated with literature review through September 14, 2020; no references added. Policy statement unchanged.
December 2021	Replace policy	Policy updated with literature review through August 26, 2021; references added. Policy statement unchanged.
December 2022	Replace policy	Policy updated with literature review through September 28, 2022; references added. Related policies updated. Policy statement unchanged.
December 2023	Replace policy	Policy updated with literature review through September 6, 2023; references added. Policy statement unchanged.