Comprehensive Genomic Profiling for Selecting Targeted Cancer Therapies

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:

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,
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 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.\textsuperscript{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.\textsuperscript{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 \textit{TP53} (44%), \textit{KRAS} (16%), and \textit{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.\textsuperscript{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).\textsuperscript{7} In this study, 122 patients with \textit{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

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

The policies contained in the FEP Medical Policy Manual are developed to assist in administering contractual benefits and do not constitute medical advice. They are not intended to replace or substitute for the independent medical judgment of a practitioner or other health care professional in the treatment of an individual member. The Blue Cross and Blue Shield Association does not intend by the FEP Medical Policy Manual, or by any particular medical policy, to recommend, advocate, encourage or discourage any particular medical technologies. Medical decisions relative to medical technologies are to be made strictly by members/patients in consultation with their health care providers. The conclusion that a particular service or supply is medically necessary does not constitute a representation or warranty that the Blue Cross and Blue Shield Service Benefit Plan covers (or pays for) this service or supply for a particular member.
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.

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>
<thead>
<tr>
<th>Tumor Type</th>
<th>Biomarker(s) Detected</th>
<th>Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-small cell lung cancer (NSCLC)</td>
<td>EGFR exon 19 deletions and EGFR exon 21 L858R alterations</td>
<td>Gilotrif (afatinib), Iressa (gefitinib), Tagrisso (osimertinib), or Tarceva (erlotinib)</td>
</tr>
<tr>
<td></td>
<td>EGFR exon 20 T790M alterations</td>
<td>Tagrisso (osimertinib)</td>
</tr>
<tr>
<td></td>
<td>ALK rearrangements</td>
<td>Alecensa (alectinib), Alunbrig (brigatinib), Xalkori (crizotinib), or Zykadia (ceritinib)</td>
</tr>
<tr>
<td></td>
<td>BRAF V600E</td>
<td>Tafinlar (dabrafenib) in combination with Mekinist (trametinib)</td>
</tr>
<tr>
<td></td>
<td>MET</td>
<td>Tabrecta™ (capmatinib)</td>
</tr>
<tr>
<td>Melanoma</td>
<td>BRAF V600E</td>
<td>Tafinlar (dabrafenib) or Zelboraf (vemurafenib)</td>
</tr>
<tr>
<td></td>
<td>BRAF V600E and V600K</td>
<td>Mekinist (trametinib) or Cotellic (cobimetinib) in combination with Zelboraf (vemurafenib)</td>
</tr>
<tr>
<td>Breast cancer</td>
<td>ERBB2 (HER2) amplification</td>
<td>Herceptin (trastuzumab), Kadcyla (ado-trastuzumabemtansine), or Perjeta (pertuzumab)</td>
</tr>
<tr>
<td></td>
<td>PIK3CA alterations</td>
<td>Piqray (alpelsib)</td>
</tr>
<tr>
<td>Colorectal cancer</td>
<td>KRAS wild-type (absence of mutations in codons 12 and 13)</td>
<td>Erbitux (cetuximab)</td>
</tr>
<tr>
<td></td>
<td>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)</td>
<td>Vectibix (panitumumab)</td>
</tr>
<tr>
<td>Ovarian cancer</td>
<td>BRCA1/2 alterations</td>
<td>Lynparza (olaparib) or Rubraca (rucaparib)</td>
</tr>
<tr>
<td>Cholangiocarcinoma</td>
<td>FGFR2 fusion or other select rearrangements</td>
<td>Pemazyre (pemigatinib) or Truseltiq™ (infigratinib)</td>
</tr>
<tr>
<td>Prostate cancer</td>
<td>Homologous Recombination Repair (HRR) gene alterations</td>
<td>Lynparza (olaparib)</td>
</tr>
<tr>
<td>Solid Tumors</td>
<td>Tumor mutational burden &gt;10 mutations per megabase</td>
<td>Keytruda (pembrolizumab)</td>
</tr>
<tr>
<td></td>
<td>NTRK1/2/3 fusions</td>
<td>Vitrakvi (larotrectinib)</td>
</tr>
</tbody>
</table>

The policies contained in the FEP Medical Policy Manual are developed to assist in administering contractual benefits and do not constitute medical advice. They are not intended to replace or substitute for the independent medical judgment of a practitioner or other health care professional in the treatment of an individual member. The Blue Cross and Blue Shield Association does not intend by the FEP Medical Policy Manual, or by any particular medical policy, to recommend, advocate, encourage or discourage any particular medical technologies. Medical decisions relative to medical technologies are to be made strictly by members/patients in consultation with their health care providers. The conclusion that a particular service or supply is medically necessary does not constitute a representation or warranty that the Blue Cross and Blue Shield Service Benefit Plan covers (or pays for) this service or supply for a particular member.
**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 control 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 randomized controlled trial (SHIVA trial) that used an expanded panel reported no difference in progression free survival (PFS) compared with standard treatment. Additional randomized and nonrandomized trials for drug development, along with systematic reviews of these trials, have compared outcomes in patients who received molecularly targeted treatment with patients who did not. Generally, trials in which therapy was targeted to a gene variant resulted in improved response rates, PFS, and OS compared to patients in trials who did not receive targeted therapy. A major limitation in the relevance of these studies for comprehensive genomic profiling is that treatment in these trials was guided both by the tissue source and the molecular target for drug development, rather than being matched solely by the molecular marker (i.e., basket trials). As a result, these types of studies do not provide evidence of the benefit of broad molecular profiling compared to more limited genetic assessments based on known tumor-specific variants. Basket trials that randomize patients with various tumor types to a strategy of comprehensive genomic profiling followed by targeted treatment are needed, and several are ongoing. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

**Supplemental Information**

Practice Guidelines and Position Statements

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

National Comprehensive Cancer Network

The National Comprehensive Cancer Network (NCCN) guidelines do not contain recommendations for the general strategy of testing a tumor for a wide range of variants. The guidelines do contain recommendations for specific genetic testing for individual cancers, based on situations where there is a known mutation-drug combination that has demonstrated benefits for that specific tumor type. Some examples of recommendations for testing of common solid tumors are listed below:

Breast cancer

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

Colon

- 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

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

Cutaneous Melanoma

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

**Ovarian cancer**
- **BRCA 1/2, NTRK**, tumor mutational burden, microsatellite instability and mismatch repair.

**Chronic myeloid leukemia**
- **BCR-ABL1**.

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

**Esophageal and esophagogastric junction cancer**
- **HER2**, microsatellite instability, **NTRK gene fusions**.

**Bladder cancer**
- **FGFR**.

**Soft Tissue Sarcomas**
- **NTRK fusions**.

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

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

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

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

**Central nervous system cancers**
- **NTRK, HER2, BRAF, EGFR, MET, ALK, ROS1**.

---

**College of American Pathologists et al**

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

In 2018, the American Society of Clinical Oncology affirmed the majority of these guidelines. The Society guidelines also recommended BRAF testing on all patients with advanced lung adenocarcinoma.

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, 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.

REFERENCES


The policies contained in the FEP Medical Policy Manual are developed to assist in administering contractual benefits and do not constitute medical advice. They are not intended to replace or substitute for the independent medical judgment of a practitioner or other health care professional in the treatment of an individual member. The Blue Cross and Blue Shield Association does not intend by the FEP Medical Policy Manual, or by any particular medical policy, to recommend, advocate, encourage or discourage any particular medical technologies. Medical decisions relative to medical technologies are to be made strictly by members/patients in consultation with their health care providers. The conclusion that a particular service or supply is medically necessary does not constitute a representation or warranty that the Blue Cross and Blue Shield Service Benefit Plan covers (or pays for) this service or supply for a particular member.

The policies contained in the FEP Medical Policy Manual are developed to assist in administering contractual benefits and do not constitute medical advice. They are not intended to replace or substitute for the independent medical judgment of a practitioner or other health care professional in the treatment of an individual member. The Blue Cross and Blue Shield Association does not intend by the FEP Medical Policy Manual, or by any particular medical policy, to recommend, advocate, encourage or discourage any particular medical technologies. Medical decisions relative to medical technologies are to be made strictly by members/patients in consultation with their health care providers. The conclusion that a particular service or supply is medically necessary does not constitute a representation or warranty that the Blue Cross and Blue Shield Service Benefit Plan covers (or pays for) this service or supply for a particular member.
## POLICY HISTORY - THIS POLICY WAS APPROVED BY THE FEP® PHARMACY AND MEDICAL POLICY COMMITTEE ACCORDING TO THE HISTORY BELOW:

<table>
<thead>
<tr>
<th>Date</th>
<th>Action</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>June 2014</td>
<td>New policy</td>
<td>New policy- The use of expanded mutation panels to direct targeted treatment is considered investigational.</td>
</tr>
<tr>
<td>June 2015</td>
<td>Replace policy</td>
<td>Policy updated with literature review. References 6-10 added, and references 19-22 updated. No change to policy statement</td>
</tr>
<tr>
<td>March 2017</td>
<td>Replace policy</td>
<td>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.</td>
</tr>
<tr>
<td>December 2018</td>
<td>Replace policy</td>
<td>Policy updated with literature review through August 6, 2018; references 21-22 added; references 13-20 updated; some references removed. Policy statement unchanged.</td>
</tr>
<tr>
<td>June 2019</td>
<td>Replace policy</td>
<td>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.</td>
</tr>
<tr>
<td>December 2019</td>
<td>Replace policy</td>
<td>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.</td>
</tr>
<tr>
<td>December 2020</td>
<td>Replace policy</td>
<td>Policy updated with literature review through September 14, 2020; no references added. Policy statement unchanged.</td>
</tr>
<tr>
<td>December 2021</td>
<td>Replace policy</td>
<td>Policy updated with literature review through August 26, 2021; references added. Policy statement unchanged.</td>
</tr>
</tbody>
</table>