FEP 2.04.115 Expanded Molecular Panel Testing of Cancers to Identify Targeted Therapies

Effective Date: January 15, 2019

Related Policies: None

Expanded Molecular Panel Testing of Cancers to Identify Targeted Therapies

Description

Genetic panel testing 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 specific targeted treatment has demonstrated benefit. This approach may result in a treatment different from that usually selected for a patient based on the type and stage of cancer.

OBJECTIVE

The objective of this evidence review is to determine whether molecular panel testing improves the net health outcome of individuals with cancer.

POLICY STATEMENT

The use of expanded cancer molecular panels for selecting targeted cancer treatment is considered **investigational**.

POLICY GUIDELINES

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 patients 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.

BENEFIT APPLICATION

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.

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

FDA REGULATORY STATUS

Expanded Cancer Molecular Panels

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

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

Test	Manufacturer	Tumor Type	Technology
FoundationOne® test	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	

Test	Manufacturer	Tumor Type	Technology
Tumor profiling service	Caris Molecular Intelligence through Caris Life Sciences	Solid	Multiple technologies
SmartGenomics™	PathGroup	Solid and hematologic	NGS, cytogenomic array, other technologies
Guardant360 panel	GuardantHealth	Solid	Digital sequencing
Paradigm Cancer Diagnostic (PcDx™) Panel	Paradigm	Solid	NGS
Memorial Sloan Kettering-Integrated Mutation Profiling of Actionable Cancer Targets	MSK-IMPACT™; Memorial Sloan Kettering Cancer Center	Solid	NGS
TruSeq® Amplicon Panel		Solid	NGS
Illumina TruSight™ Tumor	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

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

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. To date, the U.S. Food and Drug Administration has chosen not to require any regulatory review of this test.

RATIONALE

Summary of Evidence

For individuals who have a cancer that is being considered for targeted therapy who receive testing of tumor tissue with an expanded cancer molecular panel, the evidence includes an RCT, nonrandomized trials, and numerous case series. Relevant outcomes are overall survival, 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. To demonstrate clinical utility, direct evidence from interventional trials, ideally RCTs, are needed that compare the strategy of targeted treatment based on panel results with standard care. The first such published RCT, molecularly targeted therapy based on tumour molecular profiling vs conventional therapy for advanced cancer, (the SHIVA trial) reported that there was no difference in PFS when panels were used in this way. Some nonrandomized comparative studies, comparing matched treatment with nonmatched treatment, have reported that outcomes are superior for patients receiving matched treatment. However, these studies are inadequate to determine treatment efficacy, because the populations with matched and unmatched cancers may differ on several important clinical and prognostic variables. Also, there is potential for harm if ineffective therapy is given based on test results, because there may be adverse events of therapy in the absence of a benefit. The evidence is insufficient to determine the effects of the technology on health outcomes.

SUPPLEMENTAL INFORMATION

Practice Guidelines and Position Statements

The National Comprehensive Cancer Network 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[13]
  - *HER2* testing, when specific criteria are met.
- Colon cancer[14]
  - *KRAS, NRAS*, and *BRAF* testing for patients with metastatic colon cancer.
- Non-small-cell lung cancer[15]
  - *KRAS*, *EGFR*, *ALK*, and *ROS1* as part of broad molecular profiling to minimize wasting of tissue.
- Melanoma[16]
  - *BRAF* V600 testing for patients with metastatic disease
  - *KIT* in the appropriate clinical setting for patients with metastatic disease
- Ovarian cancer[17]
  - *BRCA*
- Chronic myelogenous leukemia[18]
  - *BCR-ABL1*
- Gastric cancer[19]
  - *CDH1* for hereditary cancer predisposition syndromes.
- Bladder cancer[20]
  - Comprehensive molecular profiling for advanced disease.

College of American Pathologists et al

The College of American Pathologists and 2 other associations (2018) updated their joint guidelines on molecular testing of patients with non-small-cell lung cancer.[21] 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

The American Society of Clinical Oncology (2018) affirmed the majority of these guidelines. The Society guidelines also recommended *BRAF* testing on all patients with advanced lung adenocarcinoma.[22]

U.S. Preventive Services Task Force Recommendations

Not applicable.

Medicare National Coverage

There is no national coverage determination (NCD). In the absence of an NCD, coverage decisions are left to the discretion of local Medicare carriers.

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POLICY HISTORY

Date	Action	Description
June 2014	New Policy	New policy- The use of expanded mutation panels to direct targeted treatment is considered investigational.
June 2015	Update Policy	Policy updated with literature review. References 6-10 added, and references 19-22 updated. No change to policy statement.
March 2017	Update 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	Update 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	Update Policy	Policy updated with literature review through August 6, 2018; references 21-22 added; references 13-20 updated; some references removed. Policy statement unchanged.