Molecular Panel Testing of Cancers to Identify Targeted Therapies

Currently, there is interest in treating cancers by targeting biological “pathways” that are characterized by specific genetic markers. Genetic panel testing offers the potential to evaluate a large number of genetic markers at a single time to identify treatments that target specific pathways. There are some individual markers that have established benefit in certain types of cancers; these situations are not addressed in this policy. Rather, the focus of this review is on “expanded” panels, which are defined as 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 different treatment than usually selected for a patient based on the type of cancer and its stage.

Background

Tumor location, grade, stage and the patient’s underlying physical condition have traditionally been used in clinical oncology to determine the therapeutic approach to a specific cancer, which could include surgical resection, ionizing radiation, systemic chemotherapy, or combinations thereof. Currently some 100 different types are broadly categorized according to the tissue, organ, or body compartment in which it arises. 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 actually derive clinically significant benefit. It is unusual for a cancer treatment to be effective for all patients treated in a traditional clinical trial. Spear et al analyzed the efficacy of major drugs used to treat several important diseases. They reported heterogeneity of therapeutic responses ranging from a low of 25% for cancer chemotherapeutics to a high of 80% for medications such as COX-2 inhibitors, 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 in order to have higher rates of therapeutic responses.

Much of the variability in clinical response may be a result of genetic variations. Within each broad type of cancer there may be a large amount of variability in the genetic underpinnings of the cancer. Targeted cancer treatment refers to the identification of genetic abnormalities that are present in the cancer of a particular patient, and the use of drugs that target the specific genetic abnormality. Using genetic markers, cancers can be further classified by “pathways” defined at the molecular level. An expanding number of genetic markers have been identified. Dienstmann et al categorize these findings into 3 categories. These are: Genetic markers that have a direct impact on care for the specific cancer of interest, Genetic markers that may be biologically important but are not currently actionable, and Genetic markers of unknown importance.
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There are a smaller number of individual genetic markers that fall into the first category, i.e., have established utility for a particular cancer type. Utility of these markers has generally been demonstrated by randomized controlled trials (RCTs) that select patients with the marker, and report significant improvements in outcomes with targeted therapy compared with standard therapy. This policy does not apply to these individual markers that have demonstrated efficacy. According to recent National Comprehensive Cancer Network (NCCN) guidelines, the following markers have demonstrated utility for predicting treatment response to targeted therapies for the specific cancers listed:

- Breast cancer
  - HER2 (ERBB2)
- Colon cancer
  - RAS mutations (KRAS, NRAS)
  - BRAF c1799T>A
- Non-small-cell lung cancer
  - EGFR
  - ALK/ROS1
  - KRAS
- Metastatic melanoma
  - BRAF v600
- Ovarian cancer
  - BRCA (germline)
- Chronic myeloid leukemia
  - BRC-ABL
- Gastrointestinal stromal tumors
  - KIT

Testing for these individual mutations with established utility will not be covered in this policy. In some cases, limited panels may be offered that are specific to one particular type of cancer, for example a panel of several markers for non-small-cell lung cancer. This policy is also not intended to address the use of these cancer-specific panels that include a few mutations. Rather, the intent is to address expanded panels that test for many potential mutations that do not have established efficacy for the specific cancer in question.

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

Some evidence is available on the generalizability of targeted treatment based on a specific mutation among cancers that originate from different organs. There are several examples of mutation-directed treatment that was effective in 1 type of cancer but not effective in another. For example, targeted therapy for epidermal growth factor receptor (EGFR) mutations has been successful in non-small-cell lung cancer but not in trials of other cancer types. Treatment with tyrosine kinase inhibitors based on mutation 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 mutation are treated with a targeted agent also have been performed. One such study was published in 2015 by Hyman et al. In this study, a total of 122 patients with BRAF V600 mutations in nonmelanoma cancers were treated with vemurafenib. The authors reported that there appeared to be anti-tumor activity for some but not all cancers, with the most promising results seen for non-small cell lung cancer, Erdheim-Chester...
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disease, and Langerhans’-cell histiocytosis.

**Expanded cancer mutation panels**

The FoundationOne™ test (Foundation Medicine Inc., Cambridge, MA) is a targeted mutation panel intended for use with solid tumors. It analyzes 236 cancer-related genes and 47 introns from an additional 19 genes using next-generation sequencing technology. The test identifies a number of types of mutations, including base substitutions, duplications/deletions, copy number variations, and rearrangements. The test can be performed on a surgical biopsy or a needle biopsy of a solid tumor that contains at least 40 μm of tissue, 20% of which must be malignant material.

FoundationOne Heme test (Foundation Medicine Inc., Cambridge, MA) is a similar panel that is intended for use in hematologic malignancies. It analyzes 405 cancer-related genes and selected introns from an additional 31 genes. In addition, RNA sequencing of 265 genes is done to test for common rearrangements resulting from gene fusion.

OnkoMatch (GenPath Diagnostics) is a polymerase chain reaction (PCR)–based gene panel that detects 68 mutations (single nucleotide polymorphisms) in 14 oncogenes and tumor suppressor genes that are associated with solid tumors (AKT1, APC, BRAF, CTNNB1 [beta-catenin], EGFR, IDH1, KIT, KRAS, MAP2K1, NOTCH1, NRAS, PIK3CA, PTEN, TP53). The product brochure (available on the manufacturer website) states that OnkoMatch is intended for use in patients with lung, breast, colon, gastrointestinal, pancreatic, head and neck, ovarian, or thyroid cancers, or melanoma. Test developers recommend its use “to support diagnostic and treatment decisions and to facilitate clinical trial enrollment.” GenPath also lists OnkoMatch Plus for Lung and OnkoMatch Plus for ALK-Negative Lung in its test catalog.

The GeneTrails Solid Tumor Panel (Knight Diagnostic Labs, Portland OR) consists of 37 genes that are known to have mutations in solid tumors. Of the 37 mutations, 20 have known targetable treatments based on the presence or absence of mutations, and 17 have mutations that might indicate eligibility for ongoing clinical trials. According to the manufacturer, this test is intended toward patients with adenocarcinomas (colon, small intestine, stomach, esophagus), squamous cell carcinomas (lung, head, neck, esophagus, cervix), BRAF-negative melanomas, cholangiocarcinoma, and carcinomas of the endometrium, ovaries, salivary glands, urothelium, and adrenal cortices.

Caris Life Sciences (Irving, TX) offers tumor profiling services that allow analysis of up to 56 tumor associated genes. According to the manufacturer’s website, panels with specific genes are not listed, but customized panels are available according to the patients’ clinical information and cancer type. The panels use a variety of technologies, including NGS, immunohistochemistry, fluorescence in situ hybridization, Sanger sequencing, pyrosequencing, quantitative PCR, and fragmentation analysis.

SmartGenomics (PathGroup, Brentwood TN) offers testing of up to 62 cancer-associated genes using a combination of NGS, cytogenomic array and other technologies. It is intended for use in a wide variety of solid and hematologic tumors to identify targeted treatments and also to assess eligibility for clinical trials.

The Guardant360 panel (GuardantHealth, Redwood City, CA) analyzes 68 genes associated with solid tumors. It is intended to be used for a wide variety of solid tumors. This panel uses novel technology of analyzing cell-free DNA present in the circulating blood rather than analyzing a tumor sample. The manufacturer’s website refers to “digital sequencing” using information technology, but there is a lack of published studies that evaluate the analytic validity of this technique.

The Paradigm Cancer Diagnostic (PcDx) Panel (Paradigm, Ann Arbor, MI) is a NGS-based panel that evaluates more than 500 genetic “targets.” Targets include point mutations, deletions, CNVs, fusions, mRNA expression, and protein expression. The test is intended for patients with a wide variety of cancers refractory to standard care.

The Memorial Sloan Kettering-Integrated Mutation Profiling of Actionable Cancer Targets (MSK-IMPACT) consists of 341 cancer associated genes. It is a hybridization capture-based NGS assay that
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detects mutations, CNVs, and structural rearrangements. This test offers paired analysis of tumor tissue with matched normal tissue to determine whether mutations are truly somatic cancer mutations.

A number of other targeted panels appear to be primarily marketed to researchers. Some of these are listed next:

- Illumina Inc. (San Diego, CA) offers several cancer panels. The TruSeq® Amplicon Panel analyzes 48 cancer-related genes by next-generation sequencing. The Illumina TruSight™ Tumor panel analyzes 26 cancer-related genes associated with solid tumors.
- Life technologies Inc. offers several variations of their Ion AmpliSeq™ panels intended for use in cancer. The Ion AmpliSeq Comprehensive Cancer Panel analyzes more than 400 cancer-related genes and tumor suppressor genes. The Ion AmpliSeq Cancer Hotspot Panel v2 analyzes the “hotspot” regions of 50 cancer-related and tumor suppressor genes.

Related Policies

General Approach to Evaluating the Utility of Genetic Panels
Genetic Cancer Susceptibility Panels Using Next Generation Sequencing

***Note: This Medical Policy is complex and technical. For questions concerning the technical language and/or specific clinical indications for its use, please consult your physician.

Policy

Molecular panel testing of cancers to identify targeted therapy is considered investigational for all applications. BCBSNC does not provide coverage for investigational services or procedures.

Benefits Application

This medical policy relates only to the services or supplies described herein. Please refer to the Member's Benefit Booklet for availability of benefits. Member's benefits may vary according to benefit design; therefore member benefit language should be reviewed before applying the terms of this medical policy.

When Molecular Panel Testing of Cancers to Identify Targeted Therapies is covered

Not applicable.

When Molecular Panel Testing of Cancers to Identify Targeted Therapies is not covered

The use of expanded cancer mutation panels for selecting targeting cancer treatment is considered investigational.

Policy Guidelines

Genetic panels that test for a large number of cancer-associated mutations are commercially available. These expanded panels are intended for use in patients with cancer for whom a specific targeted therapy based on mutation analysis is not available. The evidence for the use of expanded mutation panels to direct targeted cancer treatment includes 1randomized controlled trial (RCT), several nonrandomized trials, and numerous case series. Relevant outcomes are overall survival, disease-specific survival, test accuracy and validity, and other test performance measures.
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The analytic validity of these panels is likely to be high when next generation sequencing is used. The clinical validity of the individual mutations for particular types of cancer is not easily obtained from the available published literature. The large number of mutations and many different types of cancer preclude determination of clinical validity for the panels as a whole. Some evidence reports that many of the identified mutations are false positives (i.e., not biologically active), after filtering by comparison with matched normal tissue and cancer mutation databases.

To demonstrate clinical utility, RCTs are needed that compare the strategy of targeted treatment based on panel results with standard care. The first such RCT published, the SHIVA trial, reported that there was no difference in progression-free survival 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. No such trials have currently been published. The available literature on clinical utility consists of a small number of uncontrolled studies, and nonrandomized controlled trials that use imperfect comparators. This evidence is not sufficient to make any conclusions on clinical utility. In addition, there is potential for harm if ineffective therapy is given based on test results, because there may be adverse effects of therapy in absence of a benefit.

Billing/Coding/Physician Documentation Information

This policy may apply to the following codes. Inclusion of a code in this section does not guarantee that it will be reimbursed. For further information on reimbursement guidelines, please see Administrative Policies on the Blue Cross Blue Shield of North Carolina web site at www.bcbsnc.com. They are listed in the Category Search on the Medical Policy search page.

Applicable codes: 81311, 81445, 81450, 81455

BCBSNC may request medical records for determination of medical necessity. When medical records are requested, letters of support and/or explanation are often useful, but are not sufficient documentation unless all specific information needed to make a medical necessity determination is included.

Scientific Background and Reference Sources

Senior Medical Director – 4/2014


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Policy Implementation/Update Information

5/13/14  New policy. “The use of expanded cancer mutation panels for selecting targeting cancer treatment is considered investigational.” Senior Medical Director review 4/18/2014.(btw)

9/9/14  Specialty matched consultant advisory panel review 8/26/2014. No change to policy statement. (lpr)

12/30/14 Added CPT codes 81445,81450,81455 to the Billing/Coding section for effective date 1/1/2015. (lpr)

10/1/15 Reference added. Updated Description section. Under NCCN guidelines in Description section, added RAS mutations (KRAS, NRAS) under colon cancer, and KRAS under non-small cell lung cancer. Specialty Matched Consultant Advisory Panel review 8/26/2015. No change to policy statement. (lpr)

11/24/15 Updated the description and policy guidelines sections. Removed the regulatory section. Reference added. No change to policy statement. (lpr)

12/30/15 Added CPT code 81311 to Billing/Coding section for effective date 1/1/2016. (lpr)

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