Protocol

Expanded Molecular Panel Testing of Cancers to Identify Targeted Therapies

(204115)

Medical Benefit		**Effective Date**: 10/01/18	**Next Review Date**: 07/19
Preauthorization	No	**Review Dates**: 07/15, 07/16, 07/17, 07/18	

This protocol considers this test or procedure investigational. If the physician feels this service is medically necessary, preauthorization is recommended.

The following protocol contains medical necessity criteria that apply for this service. The criteria are also applicable to services provided in the local Medicare Advantage operating area for those members, unless separate Medicare Advantage criteria are indicated. If the criteria are not met, reimbursement will be denied and the patient cannot be billed. Please note that payment for covered services is subject to eligibility and the limitations noted in the patient's contract at the time the services are rendered.

Populations	Interventions	Comparators	Outcomes
Individuals: • With cancers that have not responded to standard therapy	Interventions of interest are: • Testing of tumor tissue with an expanded cancer molecular panel	Comparators of interest are: • Next-line therapy without expanded cancer molecular panel testing	Relevant outcomes include: • Overall survival • Disease-specific survival • Test accuracy • Test validity • Other test performance measures

DESCRIPTION

There is interest in treating cancers by targeting biologic pathways 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. Some individual markers have established benefit in certain types of cancers; they are not addressed in this protocol. Rather, this protocol focuses 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 treatment different from that usually selected for a patient based on the type of cancer and stage.

SUMMARY OF EVIDENCE

For individuals who have cancers that have not responded to standard therapy who receive testing of tumor tissue with an expanded cancer molecular panel, the evidence includes a randomized controlled trial (RCT), nonrandomized trials, and numerous case series. Relevant outcomes are overall survival, disease-specific survival, test accuracy and validity, and other test performance measures. The analytic validity of these panels is likely to be high when next-generation sequencing is used. The clinical validity of the individual variants for particular types of cancer is not easily determined from the published literature. The large number of variants and many types of cancer preclude determination of the clinical validity of the panels as a whole. Some evidence has reported that many of the identified variants are false positives (i.e., not biologically active), after filtering by comparison with matched normal tissue and cancer variant databases. To demonstrate clinical utility, direct evidence from interventional trials, ideally randomized controlled trials, are needed that compare the strategy of targeted treatment based on panel results with standard care. The first such published RCT (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. 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.

POLICY

The use of expanded cancer molecular panels for selecting targeting 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 protocol 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.

MEDICARE ADVANTAGE

For Medicare Advantage Next Generation Sequencing (NGS) as a diagnostic laboratory test is **medically**

necessary when performed in a CLIA-certified laboratory, when ordered by a treating physician and when all of the following requirements are met:

1. Patient has:
   a. either recurrent, relapsed, refractory, metastatic, or advanced stages III or IV cancer; and
   b. either not been previously tested using the same 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
   c. decided to seek further cancer treatment (e.g., therapeutic chemotherapy).
2. The diagnostic laboratory test using NGS must have:
   a. FDA approval or clearance as a companion in vitro diagnostic; and
   b. an FDA approved or cleared indication for use in that patient's cancer; and
   c. results provided to the treating physician for management of the patient using a report template to specify treatment options.

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 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 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 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.[1] 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.

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 the 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. Dienstmann et al (2013) categorized these findings into three classes,[2] which are listed following: (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 RCTs that select patients with the marker and report significant improvements in outcomes with targeted therapy compared with standard therapy. This protocol does not apply to the individual markers that have demonstrated efficacy. According to recent National Comprehensive Cancer Network guidelines,[3] 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 variants (KRAS, NRAS)
  - BRAF c1799T>A
- Non-small-cell lung cancer (NSCLC)
  - EGFR
  - ALK, ROS1
  - KRAS
  - RET
  - MET
- Metastatic melanoma
  - BRAF V600
  - C-KIT
- Ovarian cancer
  - BRCA (germline)
- Chronic myeloid leukemia
  - BRC-ABL
- Gastrointestinal stromal tumors
  - C-KIT.

Testing for these individual variants with established utility is not covered in this protocol. In some cases, limited panels may be offered that are specific to one type of cancer (e.g., a panel of several markers for NSCLC). This protocol is also not intended to address the use of cancer-specific panels that include a few variants. Rather, the intent is to address 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 one potentially pathogenic variant.[4-6] 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 2015 study, 439 patients with diverse cancers were tested with a 236-gene panel.[6] A total of 1813 molecular alterations were identified, and almost all patients (420/439 [96%]) had at least one molecular alteration. The median number of alterations

per patient was three, and 85% of patients (372/439) had two 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 variant among cancers that originate from different organs.[2, 3, 7] There are several examples of variant-directed treatment that was effective in one type of cancer but ineffective in another. For example, targeted therapy for epidermal growth factor receptor (EGFR) variants has been successful in NSCLC 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 in 2015 by Hyman et al.[8] In this study, 122 patients with BRAF V600 variants in nonmelanoma cancers were treated with vemurafenib. The authors reported that there appeared to be antitumor activity for some but not all cancers, with the most promising results seen for NSCLC, 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 1. Commercially Available Molecular Panels for Solid and Hematologic Tumor Testing

Test (Manufacturer)	Tumor Type	No. of Genes Tested	Technology
FoundationOne® test (Foundation Medicine, Cambridge, MA)[9]	Solid	315 cancer-related genes and introns from 28 genes	NGS
FoundationOne® Heme test (Foundation Medicine, Cambridge, MA)[9]	Hematologic	406 cancer-related genes and selected introns from 31 genes involved in rearrangements	RNA sequencing
OnkoMatch™ (GenPath Diagnostics, Elmwood Park, NJ)[10]	Solid	68 variants in 14 oncogenes and tumor suppressor genes	Multiplex PCR
GeneTrails® Solid Tumor Panel (Knight Diagnostic Labs, Portland, OR)[11]	Solid	123 genes	
Tumor profiling service (Caris Molecular Intelligence through Caris Life Sciences, Irving, TX)[12]	Solid	Up to 56 tumor-associated genes	NGS, IHC, FISH, Sanger sequencing, pyrosequencing, quantitative PCR, fragmentation analysis
SmartGenomics™ (PathGroup, Nashville, TN)[13]	Solid and hematologic	160 genes and 126 gene fusions	NGS, cytogenomic array, other technologies
Guardant360 panel (GuardantHealth, Redwood City, CA)[14]	Solid		Digital sequencing
Paradigm Cancer Diagnostic (PcDx™) Panel (Paradigm, Phoenix, AZ)[15]	Solid	186 alterations	NGS
Memorial Sloan Kettering-Integrated Mutation Profiling of Actionable Cancer Targets (MSK-IMPACT™; Memorial Sloan Kettering Cancer Center, New York, NY)[16]	Solid	341 cancer-associated genes	NGS
TruSeq® Amplicon Panel (Illumina, San Diego, CA)[17]	Solid	48 cancer-related genes	NGS
Illumina TruSight™ Tumor	Solid	26 cancer-related genes	NGS

Test (Manufacturer)	Tumor Type	No. of Genes Tested	Technology
(Illumina, San Diego, CA)[18]			
Ion AmpliSeq™ Comprehensive Cancer Panel (Thermo Fisher Scientific, Waltham, MA) [19]	Solid	> 400 cancer-related genes and tumor suppressor genes	NGS
Ion AmpliSeq™ Cancer Hotspot Panel v2 (Thermo Fisher Scientific, Waltham, MA)[19]	Solid	"Hotspot" regions of 50 cancer-related and tumor suppressor genes	NGS

FISH: fluorescence in situ hybridization; IHC: immunohistochemistry; NGS: next-generation sequencing; PCR: polymerase chain reaction.

REGULATORY STATUS

Clinical laboratories may develop and validate tests in-house and market them as a laboratory service; laboratory-developed tests (LDTs) must meet the general regulatory standards of the Clinical Laboratory Improvement Amendments (CLIA). Laboratories that offer LDTs must be licensed by the CLIA for high-complexity testing. To date, the U.S. Food and Drug Administration has chosen not to require any regulatory review of this test.

RELATED PROTOCOLS

General Approach to Evaluating the Utility of Genetic Panels

Genetic Cancer Susceptibility Panels Using Next-Generation Sequencing

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Services that are the subject of a clinical trial do not meet our Technology Assessment Protocol criteria and are considered investigational. *For explanation of experimental and investigational, please refer to the Technology Assessment Protocol.*

It is expected that only appropriate and medically necessary services will be rendered. We reserve the right to conduct prepayment and postpayment reviews to assess the medical appropriateness of the above-referenced procedures. **Some of this protocol may not pertain to the patients you provide care to, as it may relate to products that are not available in your geographic area.**

REFERENCES

We are not responsible for the continuing viability of web site addresses that may be listed in any references below.

1. Spear BB, Heath-Chiozzi M, Huff J. Clinical application of pharmacogenetics. Trends Mol Med. May 2001; 7(5):201-204. PMID 11325631
2. Dienstmann R, Rodon J, Barretina J, et al. Genomic medicine frontier in human solid tumors: prospects and challenges. J Clin Oncol. May 20 2013;31(15):1874-1884. PMID 23589551
3. National Comprehensive Cancer Network (NCCN). NCCN Biomarkers Compendium. https://www.nccn.org/professionals/biomarkers/default.aspx. Accessed August 23, 2017.
4. Drilon A, Wang L, Arcila ME, et al. Broad, hybrid capture-based next-generation sequencing identifies actionable genomic alterations in lung adenocarcinomas otherwise negative for such alterations by other genomic testing approaches. Clin Cancer Res. Aug 15 2015;21(16):3631-3639. PMID 25567908

5. Johnson DB, Dahlman KH, Knol J, et al. Enabling a genetically informed approach to cancer medicine: a retrospective evaluation of the impact of comprehensive tumor profiling using a targeted next-generation sequencing panel. Oncologist. Jun 2014;19(6):616-622. PMID 24797823
6. Schwaederle M, Daniels GA, Piccioni DE, et al. On the road to precision cancer medicine: analysis of genomic biomarker actionability in 439 patients. Mol Cancer Ther. Jun 2015;14(6):1488-1494. PMID 25852059
7. O'Brien CP, Taylor SE, O'Leary JJ, et al. Molecular testing in oncology: Problems, pitfalls and progress. Lung Cancer. Mar 2014;83(3):309-315. PMID 24472389
8. Hyman DM, Puzanov I, Subbiah V, et al. Vemurafenib in multiple nonmelanoma cancers with BRAF V600 mutations. N Engl J Med. Aug 20 2015;373(8):726-736. PMID 26287849
9. FoundationOne Web Site. FoundationOne for Solid Tumors. http://foundationone.com/order.php#2. Accessed August 23, 2017.
10. GenPath®. OnkoMatch: Rapid Tumor Genotyping in Solid Tumors. https://www.genpathdiagnostics.com/wp-content/uploads/2012/01/OnkoMatch.pdf. Accessed August 23, 2017.
11. Knight Diagnostic Laboratories. GeneTrails Solid Tumor Genotyping Panel. 2015; http://www.knightdxlabs.com/home/test-details?id=GeneTrails+Solid+Tumor+Genotyping+Panel. Accessed August 23, 2017.
12. Caris Life Sciences. Caris Molecular Intelligence: Evidence-Based Tumor Profiling Service. http://www.carismolecularintelligence.com/targeting_cancer. Accessed August 23, 2017.
13. PathGroup SmartGenomics. SmartGenomics™. http://www.pathgroup.com/oncology/smartgenomics/. Accessed August 23, 2017.
14. GuardantHealth I. Guardant360 Know Cancer. http://www.guardanthealth.com/guardant360/. Accessed October 3, 2016.
15. Paradigm Web Site. Next Generation Cancer Diagnostics: About PcDx. http://www.paradigmdx.org/pcdx/about/. Accessed August 23, 2017.
16. Cheng DT, Mitchell TN, Zehir A, et al. Memorial Sloan Kettering-Integrated Mutation Profiling of Actionable Cancer Targets (MSK-IMPACT): a hybridization capture-based next-generation sequencing clinical assay for solid tumor molecular oncology. J Mol Diagn. May 2015;17(3):251-264. PMID 25801821
17. Illumina Inc. TruSeq Amplicon - Cancer Panel. http://www.illumina.com/products/truseq_amplicon_cancer_panel.ilmn. Accessed August 23, 2017.
18. Illumina Inc. TruSight Tumor 26. http://www.illumina.com/content/dam/illumina-marketing/documents/products/datasheets/datasheet_trusight_tumor.pdf. Accessed August 23, 2017.
19. Life Technologies. Cancer Genomics Data Analysis - Compendia Bioscience Products. https://www.lifetechnologies.com/us/en/home/life-science/cancer-research/cancer-genomics/cancer-genomics-data-analysis-compendia-bioscience.html. Accessed October 3, 2016.
20. FoundationOne. Technical Information and Test Overview. http://www.foundationone.com/docs/FoundationOne_tech-info-and-overview.pdf. Accessed August 23, 2017.
21. Jones S, Anagnostou V, Lytle K, et al. Personalized genomic analyses for cancer mutation discovery and interpretation. Sci Transl Med. Apr 15 2015;7(283):283ra253. PMID 25877891
22. Schwaederle M, Zhao M, Lee JJ, et al. Impact of precision medicine in diverse cancers: a meta-analysis of phase II clinical trials. J Clin Oncol. Nov 10 2015;33(32):3817-3825. PMID 26304871
23. Jardim DL, Schwaederle M, Wei C, et al. Impact of a biomarker-based strategy on oncology drug development: a meta-analysis of clinical trials leading to FDA approval. J Natl Cancer Inst. Nov 2015;107(11):djv253. PMID 26378224
24. Le Tourneau C, Kamal M, Tredan O, et al. Designs and challenges for personalized medicine studies in oncology: focus on the SHIVA trial. Target Oncol. Dec 2012;7(4):253-265. PMID 23161020

25. Le Tourneau C, Delord JP, Goncalves A, et al. Molecularly targeted therapy based on tumour molecular profiling versus conventional therapy for advanced cancer (SHIVA): a multicentre, open-label, proof-of-concept, randomised, controlled phase 2 trial. Lancet Oncol. Oct 2015;16(13):1324-1334. PMID 26342236
26. Belin L, Kamal M, Mauborgne C, et al. Randomized phase II trial comparing molecularly targeted therapy based on tumor molecular profiling versus conventional therapy in patients with refractory cancer: cross-over analysis from the SHIVA trial. Ann Oncol. Mar 01 2017;28(3):590-596. PMID 27993804
27. Wheler JJ, Janku F, Naing A, et al. Cancer therapy directed by comprehensive genomic profiling: a single center study. Cancer Res. Jul 1 2016;76(13):3690-3701. PMID 27197177
28. Tsimberidou AM, Iskander NG, Hong DS, et al. Personalized medicine in a phase I clinical trials program: the MD Anderson Cancer Center initiative. Clin Cancer Res. Nov 15 2012;18(22):6373-6383. PMID 22966018
29. National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Breast Cancer. Version 2.2017 https://www.nccn.org/professionals/physician_gls/pdf/breast.pdf. Accessed August 23, 2017.
30. National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Colon Cancer. Version 2.2017. https://www.nccn.org/professionals/physician_gls/pdf/colon.pdf. Accessed August 23, 2017.
31. National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Non-Small Cell Lung Cancer. Version 9.2017. https://www.nccn.org/professionals/physician_gls/pdf/nscl.pdf. Accessed September 28, 2017.
32. National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Melanoma. Version 1.2017. https://www.nccn.org/professionals/physician_gls/pdf/melanoma.pdf. Accessed August 23, 2017.
33. National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Ovarian Cancer. Version 3.2017. https://www.nccn.org/professionals/physician_gls/pdf/ovarian.pdf. Accessed August 30, 2017.
34. National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Chronic Myelogenous Leukemia. Version 1.2018. https://www.nccn.org/professionals/physician_gls/pdf/cml.pdf. Accessed August 23, 2017.
35. Demetri GD, Benjamin RS, Blanke CD, et al. NCCN Task Force report: management of patients with gastrointestinal stromal tumor (GIST)--update of the NCCN clinical practice guidelines. J Natl Compr Canc Netw. Jul 2007;5(Suppl 2):S1-29; quiz S30. PMID 17624289
36. National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Bladder Cancer. Version 5.2017. https://www.nccn.org/professionals/physician_gls/pdf/bladder.pdf. Accessed August 23, 2017.
37. Pal SK, Agarwal N, Boorjian SA, et al. National Comprehensive Cancer Network recommendations on molecular profiling of advanced bladder cancer. J Clin Oncol. Sep 20 2016;34(27):3346-3348. PMID 27458279
38. National Coverage Analysis (NCA) Decision Memo for Next Generation Sequencing (NGS) for Medicare Beneficiaries with Advanced Cancer (CAG-00450N), 03/16/2018.