



Louisiana

Molecular Panel Testing of Cancers to Identify Targeted Therapies

Policy # 00423

Original Effective Date: 07/16/2014

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Based on review of available data, the Company considers the use of expanded cancer mutation panels for selecting targeting cancer treatment to be **investigational**.*

Background/Overview

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. 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 3 classes, 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.

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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 randomized controlled trials that select patients with the marker and report significant improvements in outcomes with targeted therapy compared with standard therapy. This evidence review does not apply to the individual markers that have demonstrated efficacy. According to recent National Comprehensive Cancer Network 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* 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 evidence review. 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 review 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. 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. A total of 1813 molecular alterations were identified, and almost all patients (420/439 [96%]) had at least 1 molecular alteration. The median number

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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 variant among cancers that originate from different organs. 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. 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) | Solid | 315 cancer-related genes and introns from 28 genes | NGS |
| FoundationOne® Heme test (Foundation Medicine, Cambridge, MA) | Hematologic | 406 cancer-related genes and selected introns from 31 genes involved in rearrangements | RNA sequencing |
| OnkoMatch™ (GenPath Diagnostics, Elmwood Park, NJ) | Solid | 68 variants in 14 oncogenes and tumor suppressor genes | Multiplex PCR |
| GeneTrails® Solid Tumor Panel (Knight Diagnostic Labs, Portland, OR) | Solid | 123 genes | |
| Tumor profiling service (Caris Molecular Intelligence through Caris Life Sciences, Irving, TX) | Solid | Up to 56 tumor-associated genes | NGS, IHC, FISH, Sanger sequencing, pyrosequencing, quantitative PCR, fragmentation analysis |
| SmartGenomics™ (PathGroup, Nashville, TN) | Solid and hematologic | 160 genes and 126 gene fusions | NGS, cytogenomic array, other technologies |
| Guardant360 panel (GuardantHealth, Redwood City, CA) | Solid | | Digital sequencing |
| Paradigm Cancer Diagnostic (PcDx™) Panel (Paradigm, Phoenix, AZ) | Solid | 186 alterations | NGS |
| Memorial Sloan Kettering-Integrated Mutation Profiling of Actionable Cancer Targets (MSK-IMPACT™; Memorial Sloan Kettering Cancer Center, New York, NY) | Solid | 341 cancer-associated genes | NGS |
| TruSeq® Amplicon Panel (Illumina, San Diego, CA) | Solid | 48 cancer-related genes | NGS |
| Illumina TruSight™ Tumor (Illumina, San Diego, CA) | Solid | 26 cancer-related genes | NGS |

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

FDA or Other Governmental Regulatory Approval

U.S. Food and Drug Administration (FDA)

On November 30, 2017, the Food and Drug Administration granted marketing approval to the FoundationOne CDx (F1CDx, Foundation Medicine, Inc.), a next generation sequencing (NGS) based in vitro diagnostic (IVD) to detect genetic mutations in 324 genes and two genomic signatures in any solid tumor type.

The test can also identify which patients with non-small cell lung cancer (NSCLC), melanoma, breast cancer, colorectal cancer, or ovarian cancer may benefit from 15 different FDA-approved targeted treatment options.

Centers for Medicare and Medicaid Services (CMS)

The Centers for Medicare & Medicaid Services (CMS) has determined that Next Generation Sequencing (NGS) as a diagnostic laboratory test is reasonable and necessary and covered nationally, when performed in a CLIA-certified laboratory, when ordered by a treating physician and when all of the following requirements are met:

- Patient has either recurrent, relapsed, refractory, metastatic, or advanced stages III or IV cancer; and 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
- Patient has decided to seek further cancer treatment (e.g., therapeutic chemotherapy).
- The diagnostic laboratory test using NGS must have:
 - o FDA approval or clearance as a companion in vitro diagnostic; and
 - o an FDA approved or cleared indication for use in that patient's cancer; and
 - o results provided to the treating physician for management of the patient using a report template to specify treatment options.

Medicare Administrative Contractors (MACs) may determine coverage of other Next Generation Sequencing (NGS) as a diagnostic laboratory test for patients with cancer only when the test is performed in a CLIA-certified laboratory, ordered by a treating physician and the patient has:

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- either recurrent, relapsed, refractory, metastatic, or advanced stages III or IV cancer; and
- 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
- decided to seek further cancer treatment (e.g., therapeutic chemotherapy).

Rationale/Source

The evaluation of a genetic test focuses on 3 main principles: (1) analytic validity (technical accuracy of the test in detecting a variant that is present or in excluding a variant that is absent); (2) clinical validity (diagnostic performance of the test [sensitivity, specificity, positive and negative predictive values] in detecting clinical disease); and (3) clinical utility (how the results of the diagnostic test will be used to change management of the patient and whether these changes in management lead to clinically important improvements in health outcomes).

EXPANDED MOLECULAR PANEL TESTING FOR CANCER

Clinical Context and Test Purpose

The purpose of expanded molecular panel testing in individuals with cancer that has not responded to standard therapy is to identify somatic variants in tumor tissue to guide treatment decisions with targeted therapies for specific somatic variants.

The question addressed in this evidence review is: In individuals with cancer that has not responded to standard therapy, does the use of expanded molecular panel testing improve health outcomes?

The following PICOTS were used to select literature to inform this review.

Patients

The relevant population of interest includes individuals with cancer that has not responded to standard therapy.

Interventions

The relevant intervention of interest is expanded molecular panel testing.

Comparators

The relevant comparator of interest is next-line therapy without expanded molecular panel testing.

Outcomes

The beneficial outcomes of interest include progression-free survival (PFS) and overall survival (OS).

Timing

The time frame for outcomes measures varies from several months to several years.

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Setting

Patients with cancer are actively managed by oncologists.

Analytic Validity

No published studies were identified that evaluated the analytic validity of these panels. The panels are performed primarily by next-generation sequencing, which has a high analytic validity. Some panels supplement next-generation sequencing with additional testing methods, such as polymerase chain reaction, for intronic regions included as components of the panel. Polymerase chain reaction is considered to have an analytic validity of more than 95%.

Information on analytic validity of the FoundationOne test was reported on the Foundation website. This site states that the test's analytic sensitivity is greater than 99% for base substitutions at a mutant allele frequency of 5% or more, 98% for indels at a mutant allele frequency of 10% or more, less than 95% for copy number alterations. It also reports an analytic specificity of more than 99%.

Clinical Validity

The clinical validity of the panels as a whole cannot be determined because of the different variants and large number of potential cancers for which they can be used. Clinical validity would need to be reported for each variant for a particular type of cancer. Because there are hundreds of variants included in the panels and dozens of cancer types, evaluation of the individual clinical validity for each pairing is beyond the scope of this review.

A major concern with clinical validity is differentiating variants that drive cancer growth from genetic variants that are not clinically important. It is expected that variants of uncertain significance will be very frequent with panels that include several hundred markers.

Comparison of cancer variants with matched normal tissue can provide evidence about whether variants are truly somatic cancer variants or whether they are incidental variants that do not have meaningful biologic activity. Jones et al (2015) performed comprehensive variant testing on 815 pairs of tumor tissue and matched normal tissue from patients with 15 different tumor types. Each sample was analyzed by both targeted sequencing and whole exome sequencing. A total of 105,672 somatic alterations were identified. After filtering for variants present in normal tissue, there was an average of 4.34 variants per patient on targeted analysis and 135-variants per patient on whole exome sequencing. After additional filtering using the COSMIC (Catalog of Somatic Mutations in Cancer) database, the authors estimated that 38% of the variants identified by targeted analysis were true positives, and 62% were false positives; on whole exome analysis, 10% of variants were true positives, and 90% were false positives.

Section Summary: Clinical Validity

The evidence on the clinical validity of expanded panels is incomplete. Because of the large number of variants contained in expanded panels, it is not possible to determine clinical validity for the panels as a whole. While some variants have a strong association with one or a small number of specific malignancies, none has demonstrated high clinical validity across a wide variety of cancers. Some have reported that,

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after filtering variants by comparison with matched normal tissue and cancer variants databases, most identified variants are found to be false positives. Thus, it is likely that clinical validity will need to be determined for each variant and each type of cancer individually.

Clinical Utility

The most direct way to demonstrate clinical utility is through controlled trials that compare a strategy of cancer variant testing followed by targeted treatment with a standard treatment strategy without variant testing. Randomized trials are necessary to control for selection bias in treatment decisions, because clinicians may select candidates for variant testing based on clinical, demographic, and other factors. Outcomes of these trials would be the morbidity and mortality associated with cancer and cancer treatment. OS is most important; cancer-related survival and/or PFS may be acceptable surrogates. A quality-of-life measurement may also be important if study designs allow for treatments with different toxicities in the experimental and control groups.

Systematic Reviews

Schwaederle et al published a meta-analysis of studies comparing personalized treatment with nonpersonalized treatment in 2015. Their definition of personalized treatment was driven by a biomarker, which could be genetic or nongenetic. Therefore, this analysis not only included studies of matched vs unmatched treatment based on genetic markers, but also included studies that personalized treatment based on nongenetic markers. A total of 111 arms of identified trials received personalized treatment, and they were compared with 529 arms that received nonpersonalized treatment. On random-effects meta-analysis, the personalized treatment group had a higher response rate (31% vs 10.5%, $p < 0.001$), and a longer PFS (5.9 months vs 2.7 months, $p < 0.001$) compared with the nonpersonalized treatment group. Another meta-analysis (2015) by this group compared outcomes from 44 FDA-regulated drug trials that used a personalized treatment approach to 68 trials that used a nonpersonalized approach to cancer treatment. Response rates were significantly higher in the personalized treatment trials (48%) than in the nonpersonalized approach (23%; $p < 0.001$). PFS was 8.3 months in the personalized treatment trials compared with 5.5 months in the nonpersonalized approach ($p < 0.001$). For trials that used a personalized treatment strategy, OS was significantly longer (19.3 months) than in trials that did not (13.5 months, $p = 0.01$). Personalized treatment in these studies was based on various biomarkers, both genetic and nongenetic.

Randomized Controlled Trials

SHIVA was a randomized controlled trial of treatment directed by cancer variant testing vs standard care, with the first results published in 2015. In this study, 195 patients with a variety of advanced cancers refractory to standard treatment were enrolled from 8 academic centers in France. Variant testing included comprehensive analysis of 3 molecular pathways (hormone receptor pathway, PI3K/AKT/mTOR pathway, RAF/MEK pathway) performed by targeted next-generation sequencing, analysis of copy number variations, and hormone expression by immunohistochemistry. Based on the pattern of abnormalities found, 9 different regimens of established cancer treatments were assigned to the experimental treatment arm (see Table 2). The primary outcome was PFS analyzed by intention to treat.

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Table 2. Treatment Algorithm for Experimental Arm, From the SHIVA Trial

| Molecular Abnormalities | Molecularly Targeted Agent |
|--|---|
| <i>KIT, ABL, RET</i> | Imatinib |
| <i>AKT, mTORC1/2, PTEN, PI3K</i> | Everolimus |
| <i>BRAFV600E</i> | Vemurafenib |
| <i>PDGFRA, PDGFRB, FLT-3</i> | Sorafenib |
| <i>EGFR</i> | Erlotinib |
| <i>HER2</i> | Lapatinib and trastuzumab |
| <i>SRC, EPHA2, LCK, YES</i> | Dasatinib |
| Estrogen receptor, progesterone receptor | Tamoxifen (or letrozole if contraindications) |
| Androgen receptor | Abiraterone |

Ninety-nine patients were randomized to the targeted treatment group, and 96 to standard care. Baseline clinical characteristics and tumor types were similar between groups. Molecular alterations affecting the hormonal pathway were found in 82 (42%) of 195 patients; alterations affecting the PI3K/AKT/mTOR pathway were found in 89 (46%) of 195 patients; and alterations affecting the RAF/MED pathway were found in 24 (12%) of 195 patients. After a median follow-up of 11.3 months, the median PFS was 2.3 months (95% confidence interval [CI], 1.7 of 3.8 months) in the targeted treatment group vs 2.0 months (95% CI, 1.7 of 2.7 months) in the standard care group (hazard ratio, 0.88; 95% CI, 0.65 of 1.19, p=0.41). Objective responses were reported for 4 (4.1%) of 98 assessable patients in the targeted treatment group vs 3 (3.4%) of 89 assessable patients in the standard care group. In subgroup analysis by molecular pathway, there were no significant differences in PFS between groups.

A 2017 crossover analysis of the SHIVA trial evaluated the PFS ratio from patients who failed standard of care therapy and crossed over from molecularly targeted agents (MTA) therapy to treatment at physician's choice (TPC) or vice versa. The PFS ratio was defined as the PFS on MTA (PFSMTA) to PFS on TPC (PFSTPC) in patients who crossed over. Of the 95 patients who crossed over, 70 patients crossed over from the TPC to MTA arm while 25 patients crossed over from MTA to TPC arm. In the TPC to MTA crossover arm, 26 (37%) of patients and 15 (61%) of patients in the MTA to TPC arm had a PFSMTA/PFSTPC ratio greater than 1.3. The post hoc analysis of the SHIVA trial has limitations because it only evaluated a subset of patients from the original clinical trial but used each patient as his/her control by using the PFS ratio. The analysis would suggest that patients may have benefited from the treatment algorithm evaluated in the SHIVA trial.

Nonrandomized Controlled Trials

Numerous nonrandomized studies have been published that use some type of control. Some of these studies had a prospective, interventional design. In 2016, Wheler et al reported a prospective comparative trial of patients who had failed standard treatment and had been referred to their tertiary center for admission into phase 1 trials. Comprehensive molecular profiling (FoundationOne tumor panel) was performed on 339 patients, of whom 122 went onto a phase 1 therapy that was matched to their genetic profile; based on physician evaluation of additional information, 66 patients went onto a phase 1 trial not matched to their genetic profile. Table 3 summarizes study results; there was a significant benefit on time to treatment failure and a trend for an increased percentage of patients with stable disease and median OS in

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patients matched to their genetic profile. When exploratory analysis divided patients into groups that had high matching results or low matching results (number of molecular matches per patient divided by the number of molecular alterations per patient), the percentage of patients with stable disease and the median time to failure (TTF) were significantly better in the high-match group. Median OS did not differ significantly between groups. Notably, those patients had failed multiple prior therapies (median, 4) and had a number (median, 5; range, 1-14) of gene alterations in the tumors. For comparison, response rates in phase 1 trials with treatment-resistant tumors are typically 5% to 10%.

Table 3. Survival Outcomes After Genetic Profile-Based Therapy

| Group | N | % SD (95% CI) | Median TTF (95% CI), mo | Median OS (95% CI), mo |
|------------|-----|---------------|----------------------------|------------------------|
| Matched | 122 | 19 | 2.8 (2.1 to 3.5) | 9.3 (7.3 to 11.3) |
| Unmatched | 66 | 8 | 1.9 (1.5 to 2.3) | 7.2 (4.9 to 9.5) |
| p | | 0.061 | 0.001 | 0.087 |
| High match | 92 | 22 | 3.4 (2.6 to 4.2) | 9.3 (7.3 to 11.3) |
| Low match | 90 | 9 | 1.9 (1.6 to 2.2) | 7.5 (5.0 to 10.0) |
| p | | 0.028 | <0.001 | 0.121 |

Adapted from Wheler et al (2016).

CI: confidence interval; OS: overall survival; SD: stable disease \geq 6 mo; TTF: time to failure.

Another type of study compares patients matched to targeted treatment with patients not matched. In this type of study, all patients undergo comprehensive genetic testing, but only a subset is matched to targeted therapy. Patients who are not matched continue to receive standard care.

An individual study of this type is Tsimberidou et al (2012). In it, patients with advanced or metastatic cancer refractory to standard therapy underwent molecular profiling. Polymerase chain reaction-based targeted sequencing was used to assess variants in 10 cancer genes. Loss of *PTEN* was determined using immunohistochemistry, and anaplastic lymphoma kinase (*ALK*) translocation was assessed using fluorescence in situ hybridization. Of 1144 patients, 460 had a molecular aberration based on this panel of tests. From this group of 460 patients, 211 were given “matched” treatment and 141 were given nonmatched treatment. The principal analysis presented was of a subgroup of the 460 patients who had only 1 molecular aberration (n=379). Patients were enrolled in 1 of 51 phase 1 clinical trials of experimental agents. It was not stated how patients were assigned to matched or unmatched therapy, or how a particular therapy was considered a match or not. In the list of trials in which patients were enrolled, it appears that many of the investigational agents were inhibitors of specific kinases, and thus a patient with a particular aberration of that kinase would probably be considered a match for that agent.

Among the 175 patients treated with matched therapy, the overall response rate was 27%. Among the 116 patients treated with nonmatched therapy, the response rate was 5% (p<0.001 for the difference in response rates). The median TTF was 5.2 months for patients on matched therapy and 2.2 months for those on nonmatched therapy (p<0.001). At a median 15-month follow-up, survival was 13.4 months vs 9.0 months (p=0.017) in favor of matched therapy. Due to small numbers, individual molecular aberrations

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could not be analyzed, but some sensitivity analyses, excluding certain aberrations, demonstrated that the results were robust, with the exclusion of certain groups.

Section Summary: Clinical Utility

Clinical utility has not been demonstrated for the use of expanded molecular panels to direct targeted cancer treatment. One published randomized controlled trial (SHIVA trial) used an expanded panel in this way and reported no difference in PFS compared with standard treatment. Nonrandomized studies have compared patients who received matched treatment with patients who did not, and have reported that outcomes are superior in patients receiving matched treatment. However, there are potential issues with this design that could compromise the validity of comparing these 2 populations. They include the following: (1) differences in clinical and demographic factors, (2) differences in the severity of disease or prognosis of disease (i.e., patients with more undifferentiated anaplastic cancers might be less likely to express genetic markers), and (3) differences in the treatments received. It is possible that one of the “targeted” drugs could be more effective than standard treatment whether or not patients were matched. As a result, these types of nonrandomized studies do not provide definitive evidence of treatment efficacy. Further controlled trials are needed that randomize patients to a treatment strategy of variant testing followed by targeted treatment vs standard care.

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, nonrandomized trials, and numerous case series. Relevant outcomes are OS, 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 randomized controlled trial (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.

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References

1. Blue Cross and Blue Shield Association, Medical Policy Reference Manual, "Molecular Panel Testing of Cancers to Identify Targeted Therapies", 2.04.115, 10:2017.
2. U.S. Food and Drug Administration (FDA), "FDA grants marketing approval to FoundationOne CDx in vitro diagnostic", <https://www.fda.gov/Drugs/InformationOnDrugs/ApprovedDrugs/ucm587387.htm>, 12/01/2017.
3. Centers for Medicare and Medicaid Services (CMS), Decision Memorandum <http://www.cms.hhs.gov/mcmd/viewdecision> retrieved 3/16/2018.
4. Spear BB, Heath-Chiozzi M, Huff J. Clinical application of pharmacogenetics. *Trends Mol Med*. May 2001;7(5):201-204. PMID 11325631
5. 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
6. National Comprehensive Cancer Network. NCCN Biomarkers Compendium. <http://www.nccn.org/professionals/biomarkers/default.asp>.
7. 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*. 2015 Aug 15;21(16):3631-9. PMID 25567908
8. 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
9. 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
10. 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
11. 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
12. FoundationOne Web Site. About FoundationOne. 2014; <http://www.foundationone.com/learn.php#2>.
13. GenPath®. OnkoMatch: Rapid Tumor Genotyping in Solid Tumors. <https://www.genpathdiagnostics.com/wp-content/uploads/2012/01/OnkoMatch.pdf>.
14. Laboratories KD. GeneTrails Solid Tumor Genotyping Panel. 2015; <http://www.knightdxlabs.com/home/test-details?id=GeneTrails+Solid+Tumor+Genotyping+Panel>.
15. PathGroup SmartGenomics. SmartGenomics: 35 Gene Solid Tumor NGS and aCGH. <http://www.pathgroup.com/smartgenomics-35-gene-solid-tumor-ngs-and-acgh/>. Accessed October 3, 2016.
16. GuardantHealth I. Guardant360 test. 2015; <http://www.guardanthealth.com/guardant360/>.
17. Paradigm Web Site. Next Generation Cancer Diagnostics:About PcDx. <http://www.paradigmdx.org/pcdx/about/>.
18. 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
19. Illumina Inc. TruSeq Amplicon - Cancer Panel. http://www.illumina.com/products/truseq_amplicon_cancer_panel.ilmn. Illumina Inc. TruSight Tumor 26. http://www.illumina.com/content/dam/illumina-marketing/documents/products/datasheets/datasheet_trusight_tumor.pdf.
20. Life Technologies. Cancer Genomics Data Analysis - Compendia Bioscience Products. 2014; <https://www.lifetechnologies.com/us/en/home/life-science/cancer-research/cancer-genomics/cancer-genomics-data-analysis-compendia-bioscience.html>.
21. FoundationOne Web Site. Technical Information and Test Overview. 2014; http://www.foundationone.com/docs/FoundationOne_tech-info-and-overview.pdf. Accessed January 21, 2015.
22. 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
23. 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
24. 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). PMID 26378224

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Louisiana

Molecular Panel Testing of Cancers to Identify Targeted Therapies

Policy # 00423

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25. 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
26. 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
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. American Society for Clinical Oncology. Targeted Agent and Profiling Utilization Registry Study. 2015; <http://www.asco.org/practice-research/targeted-agent-and-profiling-utilization-registry-study>. Accessed October 1, 2015.

Policy History

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07/10/2014 Medical Policy Committee review

07/16/2014 Medical Policy Implementation Committee approval. New policy.

06/04/2015 Medical Policy Committee review

06/17/2015 Medical Policy Implementation Committee approval. Updated rationale and references. No change in coverage.

08/03/2015 Coding update: ICD10 Diagnosis code section added; ICD9 Procedure code section removed.

06/02/2016 Medical Policy Committee review

06/20/2016 Medical Policy Implementation Committee approval. Coverage eligibility unchanged.

01/01/2017 Coding update: Removing ICD-9 Diagnosis Codes

06/01/2017 Medical Policy Committee review

06/21/2017 Medical Policy Implementation Committee approval. Coverage eligibility unchanged.

04/01/2018 Coding update

06/07/2018 Medical Policy Committee review

06/20/2018 Medical Policy Implementation Committee approval. Coverage eligibility unchanged.

07/01/2018 Coding update

Next Scheduled Review Date: 06/2019

Coding

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Procedural Terminology which contains the complete and most current listing of CPT codes and descriptive terms. Applicable FARS/DFARS apply.

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Codes used to identify services associated with this policy may include (but may not be limited to) the following:

| Code Type | Code |
|------------------|--|
| CPT | 81272, 81311, 81314, 81455 , 81479 Code added eff 4/1/18: 0037U Code added eff 7/1/18: 0048U |
| HCPCS | No codes |
| ICD-10 Diagnosis | All related diagnoses |

*Investigational – A medical treatment, procedure, drug, device, or biological product is Investigational if the effectiveness has not been clearly tested and it has not been incorporated into standard medical practice. Any determination we make that a medical treatment, procedure, drug, device, or biological product is Investigational will be based on a consideration of the following:

- A. Whether the medical treatment, procedure, drug, device, or biological product can be lawfully marketed without approval of the U.S. Food and Drug Administration (FDA) and whether such approval has been granted at the time the medical treatment, procedure, drug, device, or biological product is sought to be furnished; or
- B. Whether the medical treatment, procedure, drug, device, or biological product requires further studies or clinical trials to determine its maximum tolerated dose, toxicity, safety, effectiveness, or effectiveness as compared with the standard means of treatment or diagnosis, must improve health outcomes, according to the consensus of opinion among experts as shown by reliable evidence, including:
 - 1. Consultation with the Blue Cross and Blue Shield Association technology assessment program (TEC) or other nonaffiliated technology evaluation center(s);
 - 2. Credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community; or
 - 3. Reference to federal regulations.

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