Comprehensive Genomic Profiling for Selecting Targeted Cancer Therapies

Medical Policy #: 02.04.63
Original Effective Date: September 2016
Reviewed: September 2022
Revised: September 2022

DESCRIPTION

Comprehensive genomic profiling offers the potential to evaluate a large number of genetic markers at a single time to identify cancer treatments that target specific biologic pathways. This review focuses on "expanded" panels, which are defined as molecular panels that test a wide variety of genetic markers in cancers without regard for whether a specific targeted treatment has demonstrated benefit. This approach may result in treatment different from that usually selected for a patient based on the type and stage of cancer.

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

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 benefits. It is unusual for 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 cancer. Targeted cancer treatment refers to the identification of genetic abnormalities present in the cancer of a particular patient, and the use of drugs that target the specific genetic abnormality. The use of genetic markers allows cancers to be further classified by "pathways" defined at the molecular level. An expanding number of genetic markers have been identified. These may be categorized into 3 classes (1) genetic markers that have a direct impact on care for the specific cancer of interest, (2) genetic markers that may be biologically important but are not currently actionable, 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 randomized controlled trials that select patients with the marker and report significant improvements in outcomes with targeted therapy compared with standard therapy. Testing for individual variants with established utility is not covered in this evidence review. In some cases, limited panels may be offered that are specific to 1 type of cancer (e.g., a panel of several markers for non-small-cell lung cancer). This review also does not address the use of cancer-specific panels that include a few variants. Rather, this review addresses expanded panels that test for many potential variants that do not have established efficacy for the specific cancer in question.

Note: *In some cases, limited panels may be offered that are specific to 1 type of cancer (e.g., a panel of several markers for non-small-cell lung cancer see medical policy 02.04.78 Molecular Analysis for Targeted Therapy of Non-Small Cell Lung Cancer).*

When advanced cancers are tested with expanded molecular panels, most patients are found to have at least 1 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.

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 is effective in 1 type of cancer but ineffective in another. For example, targeted therapy for epidermal growth factor receptor variants have been successful in non-small-cell lung cancer but not in trials of other cancer types. Treatment with tyrosine kinase inhibitors based on variant testing has been effective for renal cell carcinoma but has not demonstrated effectiveness for other cancer types tested. "Basket" studies, in which tumors of various histologic types that share a common genetic variant are treated with a targeted agent, also have been performed.

Expanded Cancer Molecular Panels

Commercially Available Molecular Panels for Solid and Hematologic Tumor Testing

Test	Manufacturer	Tumor Type	Technology
Breast Next: Analyzes 17 genetic variants. Assists with medical management and treatment.	Ambry Genetics	Solid	NGS
ColoNext; Analyzes 17 genetic variants. Assists with medical management and treatment.	Ambry Genetics	Solid	NGS
COLONSEQ/COLONSEQPlus: This test is intended to be used as a disease specific solid tumor panel to aid the oncologist in prioritizing standard of care therapy choices for their patients with Colorectal Cancer.	Med Fusion	Solid	NGS
DarwinOncoTarget: patient-derived tumor sample to identify aberrantly activated proteins for which a clinically relevant targeted inhibitor already exists and to match tumor-specific dependencies with clinically relevant drugs.	DarwinHealth	Solid	Transcriptome sequencing (RNASeq)
Decipher Bladder TURBT: Measures the molecular profile of bladder	Veracyte, Inc	Solid	NGS

cancer using gene expression analysis (209 genes) from transurethral resected bladder cancer specimens. It was developed in bladder cancer patients with muscle-invasive disease who face the question of immediate cystectomy or systemic treatment in the neoadjuvant setting prior to cystectomy. The assay results are reported as one of five molecular subtypes (Luminal, Luminal-Infiltrated, Basal, Basal Claudin Low or Neuroendocrine-like), each of which has distinct biological composition, clinical behavior and predicted benefit from NAC.			
FoundationOne®CDx test (F1CDx): is a next generation sequencing based in vitro diagnostic device for detection of substitutions, insertion, and deletion alterations (indels), and copy number alterations (CNAs) in 324 genes and select gene rearrangements, as well as genomic signatures including microsatellite instability (MSI) and tumor mutational burden (TMB) using DNA isolated from formalin-fixed paraffin embedded (FFPE) tumor tissue specimens. The test is intended as a companion diagnostic to identify patients who may benefit from treatment with targeted therapies.	Foundation Medicine	Solid	NGS
FoundationOne®CDx Heme test: 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	Foundation Medicine	Hematologic	RNA sequencing

rearrangements resulting from gene fusion.			
Guardant360 Tissue Next™: Is a tissue biopsy test that offers comprehensive genomic profiling to find actionable information when tissue testing is appropriate. This comprehensive panel includes 84 genes, 20 amplification genes, and 12 fusion genes. Also includes PD-L1 status if ordered. MSI status qualitative result. TMB status mutations per megabase.	Guardant Health, Inc.	Solid	NGS
GeneTrails® Solid Tumor Panel: 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.	Knight Diagnostic Labs	Solid	NGS
Ion AmpliSeq™ Cancer Hotspot Panel v2: Analyzes the "hotspot" regions of 50 cancer-related and tumor suppressor genes.	Thermo Fisher Scientific	Solid	NGS
Ion AmpliSeq™: Comprehensive Cancer Panel: analyzes more than 400 cancer-related genes and tumor suppressor genes.	Thermo Fisher Scientific	Solid	NGS
MI Cancer Seek: Comprehensive tumor profiling approach to assess DNA, RNA and Proteins reveals the	Caris Life Sciences	Solid	NGS

highest quality molecular blueprint to guide more precise and individualized treatment decisions that is proven to extend overall survival.			
MiProfile/MiTumorSeek/Molecular Intelligence Service: MI Profile is a multi-platform, solid tumor biomarker analysis for therapeutic decision support and clinical trials matching.	Caris Life Sciences	Solid	NGS
MSK-IMPACT™: Consists of 341 cancer associated genes. It is a hybridization capture- based NGS assay that 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.	Memorial Sloan Kettering Cancer Center	Solid	NGS
NeoType Cancer Profiles: Three large pan-tumor profiles and 25 targeted cancer-specific profiles. Comprehensive summary of results that includes diagnostic, prognostic, therapeutic and clinical trials information. Can be used in all phases of clinical trials and appropriate as a companion diagnostic.	Neo Genomics	Solid and hematologic	NGS
NexCourse Complete: Is a multi-gene molecular profiling assay covering genes implicated in the pathogenesis of solid and/or hematological malignancies. The results may provide insight into the pathobiology of the malignancy, aid in risk assessment, and identify potential therapeutic options and clinical trials based on molecular drivers.	Neo Genomics	Solid and hematologic	NGS
NYU Langone Genome PACT assay: Is a 607-gene panel that assesses	NYU Langone Medical Center	Solid	NGS

somatic point mutations, insertions, and deletions smaller than 35 base pairs			
Omics Core(SM): The test is intended to provide information on somatic mutations (point mutations and small insertions and deletions) and tumor mutational burden.	NantHealth	Soid	WES
OmniSeq Comprehensive®: Is a next-generation molecular sequencing assay that tests tumor DNA and RNA, identifying somatic variants in 144 genes said to guide cancer therapeutic management	OmniSeq	Solid	NGS
Oncomine DX Target Test™:Next generation sequencing (NGS in vitro diagnostic test for cholangiocarcinoma delivering multiple biomarker results for multiple targeted therapies.	Thermo Fisher Scientific	Solid	NGS
Oncomap Test: comprehensive tumor profiling (257 gene panel) to aid therapy selection for patients with advanced, metastatic, refractory, relapsed or recurrent cancer.	Exact Sciences, Inc.	Solid	NGS and broad array of immuno-histochemical stains and panels
Oncomap ExTra Test: Compare genes in both tumor (somatic) and normal (germline) DNA to understand the changes to the patient's genomic profile and outline an optimal therapeutic treatment plan. Conditions that may benefit from this approach include treatment of advanced, refractory, rare of aggressive cancers.	Exact Sciences, Inc.	Solid	WES
OnkoMatch: 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,	GenPath Diagnostics	Solid	Multiplex PCR

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."			
OncoSignal: The OncoSignal test uses an advanced molecular and bioinformatics system to measure mRNA expression patterns and calculate the specific activity of seven key oncogenic driver signal pathways. The pathways include ER (estrogen receptor), AR (androgen receptor), PI3K (Phosphoinositide 3-Kinase), HH (Hedgehog pathway), NOTCH (notch signal pathways), TGFbeta (transforming growth factor receptor beta), and MAPK (mitogen activated protein kinase). The pathways measure key oncogenic drivers of numerous distinct cancer types including but not limited to breast cancer, prostate cancer, ovarian cancer, colon cancer, lymphoma and more.	Protean Bio-Diagnostics	Solid and hematologic	Measure mRNA expression patterns
OvaNext: Analyzes 25 genes associated with hereditary ovarian, uterine, and breast cancer. Assists with medical management and treatment.	Ambry Genetics	Solid	NGS
Paradigm Cancer Diagnostic (PcDx™) Panel: Evaluates more than 500 genetic "targets." Targets include point mutations, deletions, CNVs, fusions, mRNA expression, and	Paradigm	Solid	NGS

protein expression. The test is intended for patients with a wide variety of cancers refractory to standard care.			
PGDx elio tissue complete™: is intended to provide tumor mutation profiling information on somatic alterations (SNVs [single nucleotide variants], small insertions and deletions, one amplification and 4 translocations), microsatellite instability and tumor mutation burden (TMB).	Personal Genome Diagnostics	Solid	NGS
SmartGenomics™: 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.	PathGroup	Solid and hematologic	NGS, cytogenomic array, other technologies
Target Now Molecular Profiling Test: molecular profiling service is designed for patients with solid tumors (including breast, colon, lung, pancreatic and ovarian cancers) where there is significant uncertainty in the most effective course of action. Utilized to predict a tumour's response to a specific therapy, or the likelihood of tumor recurrence.	Caris Life Sciences	Solid	NGS
Tempus xT: Targeted panel of 648 genes that tests tumor DNA and RNA to guide cancer therapeutic management.	Tempus	Solid	NGS
TruSeq® Amplicon Panel: Analyzes 48 cancer-related genes by next-generation sequencing.	Illumina	Solid	NGS
TruSight™ Oncology: Analyzes 26 cancer-related genes associated with solid tumors.	Illumina	Solid	NGS
Tumor profiling service: Offers tumor profiling services that allow	Caris Life Sciences	Solid	Multiple technologies

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.			
50SEQ: Cancer Gene Mutation Panel for the identification of mutations in 50 cancer-related genes facilitating the detection of actionable and targetable mutations in lung, colorectal, thyroid, brain and skin cancer (melanoma) for appropriate diagnosis, prognosis and selection of therapy. The panel will also identify relevant genes that may have implications for enrollment of the patient in clinical trials.	Thermo Fisher Scientific	Solid	NGS

Clinical Context and Test Purpose
The purpose of comprehensive genomic profiling in individuals with cancer is to identify somatic variants in tumor tissue to guide treatment decisions with targeted therapies.

Populations
The relevant population of interest are individuals with advanced cancer who have not previously been treated with targeted therapy.

Interventions
The relevant intervention of interest is comprehensive genomic profiling of tumor tissue, including all major types of molecular variants, single nucleotide variants (SNVs), small and large insertions, and deletions, copy number variants, and fusions in cancer-associated genes by next-generation sequencing (NGS) technologies. Some tests may also evaluate microsatellite instability and tumor mutation burden.

Comparators
The following practice is currently being used to identify somatic variants in tumor tissue to guide treatment decisions: therapy guided by single-gene testing.

Outcomes
Beneficial outcomes are an increase in progression-free survival (PFS) and overall survival (OS). A beneficial outcome may also be the avoidance of ineffective therapy and its associated harms.

Harmful outcomes could occur if ineffective therapy is given based on test results, because there may be adverse events of therapy in the absence of a benefit.

A follow-up to monitor for outcomes varies from several months to several years, depending on the type and stage of cancer.

Study Selection Criteria

Clinically Valid
A test must detect the presence or absence of a condition, the risk of developing a condition in the future, or treatment response (beneficial or adverse).

The evidence on the clinical validity of expanded panels and comprehensive genomic profiling is incomplete. Because of a large number of variants contained in expanded panels, it is not possible to determine the clinical validity of the panels as a whole. While some variants have a strong association with 1 or a small number of specific malignancies, none has demonstrated high clinical validity across a wide variety of cancers. Some have reported that, after filtering variants by comparison with matched normal tissue and cancer variants databases, most identified variants are found to be false positives.

The clinical validity of the panels as a whole cannot be determined because of the different variants and a 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.

Clinically Useful
A test is clinically useful if the use of the results informs management decisions that improve the net health outcome of care. The net health outcome can be improved if patients receive correct therapy, or more effective therapy, or avoid unnecessary therapy, or avoid unnecessary testing.

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 controlled trials (RCTs) 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.

Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for randomized controlled trials (RCTs);
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.

Review of Evidence

Randomized Controlled Trials

Molecularly targeted therapy based on tumor molecular profiling vs conventional therapy for advanced cancer (SHIVA trial) was an RCT of treatment directed by cancer variant testing versus standard care. Based on the pattern of abnormalities found, 9 different regimens of established cancer treatments were assigned to the experimental treatment arm. The primary outcome was PFS analyzed by intention to treat. Baseline clinical characteristics and tumor types were similar between groups. After a median follow-up of 11.3 months, the median PFS was 2.3 months in the targeted treatment group versus 2.0 months in the standard of care group (p=.41). In the subgroup analysis by molecular pathway, there were no significant differences in PFS between groups. A major limitation of the SHIVA trial is that the population consisted of patients who had failed a targeted treatment.

A crossover analysis of the SHIVA trial by Belin et al (2017) evaluated the PFS ratio from patients who failed standard of care therapy and crossed over from molecularly targeted agent (MTA) therapy to treatment at physician's choice (TPC) or vice versa. The PFS ratio was defined as the PFS on MTA to PFS on TPC 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 PFS on MTA to PFS on TPC 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 suggests that patients might have benefited from the treatment algorithm evaluated in the SHIVA trial.

Nonrandomized Controlled Trials

Nonrandomized studies have been published that use some type of control. These studies are summarized in a review by Zimmer et al (2019). Some of these studies had a

prospective, interventional design. 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. These studies 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 (ie, 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.

One of the largest studies of molecular targeting in phase 1 trials was the Initiative for Molecular Profiling and Advanced Cancer Therapy (IMPACT) study, reported by Tsimberidou et al (2017) from the MD Anderson Cancer Center. Patients with advanced cancer who underwent comprehensive genomic profiling were treated with matched targeted therapy when available. Out of 1436 patients who underwent genomic profiling, 1170 (82.1%) had 1 or more variants, of which 637 were actionable. The most frequent alterations were estrogen receptor overexpression, and variants in *TP53*, *KRAS*, *PTEN*, *PIK3CA*, and *BRAF*. The group that had matched therapy had a higher response rate (11% vs. 5%), longer PFS (3.4 vs. 2.9 months), and longer OS (8.4 vs. 7.3 months). Note that a randomized trial from this center that will compare matched to unmatched therapy (IMPACT 2) is ongoing with completion expected in 2024.

Non-Comparative Studies

NCI-MATCH is a master basket trial protocol in which tumors of various types are sequenced and patients assigned to targeted treatment based on the molecular alteration. A total of 6391 patients were enrolled across 1117 clinical sites between 2015 and 2017 and underwent tumor sequencing. Patients had received a median of 3 lines of prior therapy. Common tumors comprised 37.5% of the total; the remainder had less common tumor histologies. Sequencing included 143 genes, of which approximately 40% of alterations were considered actionable, and 18% of patients were assigned to 30 treatment subprotocols. The majority of alterations identified in the 143 gene panel were either not actionable or led to experimental treatments in clinical trials. Response to treatments in the subprotocols are being reported and will provide preliminary evidence on tumor agnostic treatments. Co-alterations discovered in NCI-MATCH have also led to a new biomarker-selected combination therapy trial by the National Cancer Institute, NCI-COMBOMATCH. Controlled basket trials that compare tumor-agnostic treatment based on a molecular marker with standard treatments are ongoing

Systematic Reviews

Systematic reviews compare the outcomes of patients who were enrolled in trials with personalized therapy with those of patients enrolled in non-personalized therapy trials. Schwaederle et al (2015) assessed outcomes in single-agent phase 2 trials, while

Jardim et al (2015) evaluated trials for 58 newly approved cancer agents. Treatment directed by a personalized strategy was associated with an increased response rate, PFS, and OS compared to treatment that was not personalized. While these studies support a strategy of targeted therapy within a specific tumor type, they do not provide evidence that broad genomic profiling is more effective than tumor-specific variant assessment.

Summary of Evidence

For individuals who have advanced cancer that is being considered for targeted therapy who receive comprehensive genomic profiling (expanded genetic panel testing) of tumor tissue, the evidence includes a randomized controlled trial, nonrandomized trials, and systematic reviews of these studies. A large number of variants and many types of cancer preclude determination of the clinical validity of the panels as a whole, and clinical utility has not been demonstrated for the use of expanded molecular panels to direct targeted cancer treatment. The 1 published randomized controlled trial (SHIVA trial) that used an expanded panel reported no difference in progression-free survival (PFS) compared with standard treatment. Additional randomized and nonrandomized trials for drug development, along with systematic reviews of these trials, have compared outcomes in patients who received molecularly targeted treatment with patients who did not. Generally, trials in which therapy was targeted to a gene variant resulted in improved response rates, progression-free survival (PFS), and overall survival (OS) compared to patients in trials who did not receive targeted therapy. A major limitation in the relevance of these studies for comprehensive genomic profiling is that treatment in these trials was guided both by the tissue source and the molecular target for drug development, rather than being matched solely by the molecular marker (i.e., basket trials). As a result, these types of studies do not provide evidence of the benefit of broad molecular profiling compared to more limited genetic assessments based on known tumor-specific variants. Basket trials that randomize patients with various tumor types to a strategy of comprehensive genomic profiling followed by targeted treatment are needed, and several are ongoing. The evidence is insufficient to determine the effects of the technology on health outcomes.

Professional Guidelines and Position Statements

National Comprehensive Cancer Network (NCCN)

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:

Bladder Cancer

- FGFR.

Breast Cancer

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

Central Nervous System Cancers

- NTRK, HER2, BRAF, EGFR, MLT, ALK, ROS1.

Colon Cancer

- KRAS, NRAS, and BRAF mutation testing, HER2 amplification, NTRK fusions and microsatellite instability or mismatch repair testing for patients with metastatic colon cancer.

Cutaneous Melanoma

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

Esophageal and Esophagogastric Junction Cancer

- HER2, microsatellite instability, NTRK gene fusions.

Gastric Cancer

- HER2, microsatellite instability, NTRK gene fusions
- CDH1 for hereditary cancer predisposition syndromes.

Hepatobiliary Cancer

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

Ovarian Cancer

- BRCA 1/2, NTRK, microsatellite instability and mismatch repair.

Pancreatic Adenocarcinoma

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

Prostate Cancer

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

Soft Tissue Sarcomas

- NTRK fusions.

Uterine Cancer

- NTRK, microsatellite instability and tumor mutational burden.

Regulatory Status
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.

The FDA has approved more than 50 companion diagnostic devices to detect mutations in 12 different genes for the targeted treatment of cancer. Methodologies include immunohistochemistry, real-time or multiplex PCR, FISH, and next generation sequencing.

The FDA has also approved additional nucleic acid- based tests for cancer, not specifically as companion diagnostics. The U.S. Food and Drug Administration (FDA) currently do not require approval for any expanded genetic panels tests. Because of the large number of mutations contained in expanded panels, it is not possible to determine clinical validity for the panels as a whole.

Subsequent marketing clearance through the FDA's 510(k) process (FDA product code PZM) include the following:

- Omics Core (NantHealth) received marketing clearance in 2019 (K190661). The test is intended to provide information on somatic mutations (point mutations and small insertions and deletions) and tumor mutational burden.
- PGDx elio tissue complete (Personal Genome Diagnostics) received marketing clearance in 2020 (K192063). PGDx elio tissue complete is "intended to provide tumor mutation profiling information on somatic alterations (SNVs [single nucleotide variants], small insertions and deletions, one amplification and 4 translocations), microsatellite instability and tumor mutation burden (TMB)".
- The NYU Langone Genome PACT assay (NYU Langone Medical Center) is a 607-gene panel that received marketing clearance by the FDA in 2021 (K202304). The test assesses somatic point mutations, insertions and deletions smaller than 35 base pairs.

In November 2017 the FDA approved the marketing of the MSK-IMPACT assay as a qualitative in vitro diagnostic test that uses targeted next generation sequencing of formalin-fixed paraffin-embedded tumor tissue matched with normal specimens from patients with solid malignant neoplasms to detect tumor gene alterations in a broad multi gene panel. The test is intended to provide information on somatic mutations (point mutations and small insertions and deletions) and microsatellite instability for use by qualified health care professionals in accordance with professional guidelines and is not conclusive or prescriptive for labeled use of any specific therapeutic product. MSK-IMPACT is a single-site assay performed at Memorial Sloan Kettering Cancer Center.

On November 30, 2017, the FDA approved FoundationOne CDx™ (F1CDx) as a next generation sequencing based in vitro diagnostic device for detection of substitutions, insertion, and deletion alterations (indels), and copy number alterations (CNAs) in 324

genes and select gene rearrangements, as well as genomic signatures including microsatellite instability (MSI) and tumor mutational burden (TMB) using DNA isolated from formalin-fixed paraffin embedded (FFPE) tumor tissue specimens. The test is intended as a companion diagnostic to identify patients who may benefit from treatment with the targeted therapies in accordance with the approved therapeutic product labeling. Additionally, F1CDx is intended to provide tumor mutation profiling to be used by qualified health care professionals in accordance with professional guidelines in oncology for patients with solid malignant neoplasms. The F1CDx assay is a single-site assay performed at Foundation Medicine, Inc.

PRIOR APPROVAL

Not applicable.

POLICY

Note: This policy does not apply to the testing related in the below medical policies, see each specific medical policy for information regarding genetic testing for applicable oncologic indications related to those medical policies.

See related medical policies:

- 02.04.73 Analysis of MGMT Promoter Methylation
- 02.04.16 Circulating Tumor DNA and Circulating Tumor Cells for Cancer Management (Liquid Biopsies)
- 02.04.55 Epidermal Growth Factor Receptor (EGFR) Mutation Analysis Excluding Non-Small Cell Lung Cancer
- 02.04.20 KRAS/NRAS and BRAF Mutation Analysis
- 02.04.78 Molecular Analysis (Including Liquid Biopsy) for Targeted Therapy or Immunotherapy of Non-Small Cell Lung Cancer

In individuals with cancer to identify genetic variants in tumor tissue to guide treatment decisions with targeted therapies using comprehensive genomic profiling, including but not limited to the following, is considered **investigational** because the evidence is insufficient in determining the technology improves net health outcomes to include changes in clinical management**:**

- 50SEQ
- BreastNext (0102U)
- COLONSEQ/COLONSEQPlus
- ColoNext (0101U)
- DarwinOncoTarget/DarwinOnco Treat (0019U)
- Decipher Bladder TURBT (0016M)
- FoundationOne ® CDx (0037U)

- FoundationOne® Heme test
- Guardant360 Tissue Next (0334U)
- GeneTrails® Solid Tumor Panel
- Illumina TruSight Tumor
- Ion AmpliSeq™ Comprehensive Cancer Panel
- Ion AmpliSeq™ Cancer Hotspot Panel v2
- MSK-IMPACT™ (Memorial Sloan Kettering-Integrated Mutation Profiling of Actionable Cancer Targets) (0048U)
- MiProfile/MiTumorSeek/Molecular Intelligence Service
- MI Cancer Seek (0211U)
- NeoType Cancer Profiles
- NexCourse Complete
- NYU Langone Genome PACT assay
- Omics Core(SM)
- OmniSeq Target®/OmniSeq Comprehensive®
- Oncomap Test
- Oncomap ExTra Test (0329U)
- Oncomine DX Target Test for cholangiocarcinoma
- OncoSignal (0262U)
- OnkoMatch
- Oncotype MAP™ Pan-Cancer Tissue Test, Paradigm Diagnostics (0244U)
- OvaNext (0103U)
- Paradigm Cancer Diagnostic (PcDx™) Panel
- PGDx elio tissue complete™ (0250U)
- SmartGenomics™
- Target Now Molecular Profiling Test
- Tempus xT
- Thyroid GuidePx
- TruSeq Panels
- TruSight™ Oncology
- Tumor profiling service (Caris Molecular Intelligence through Caris Life Sciences)

PROCEDURE CODES AND BILLING GUIDELINES

To report provider services, use appropriate CPT* codes, Alpha Numeric (HCPCS level 2) codes, Revenue codes, and/or ICD diagnosis codes.

- 81455 Targeted genomic sequence analysis panel, solid organ or hematolymphoid neoplasm or disorder, 51 or greater genes (e.g., ALK, BRAF, CDKN2A, CEBPA, DNMT3A, EGFR, ERBB2, EZH2, FLT3, IDH1, IDH2, JAK2, KIT, KRAS, MET, MLL, NOTCH1, NPM1, NRAS, PDGFRA, PDGFRB, PGR, PIK3CA, PTEN, RET), interrogation for sequence variants and copy number variants or

rearrangements, or isoform expression or mRNA expression levels, if performed; DNA analysis or combined DNA and RNA analysis

- 81456 Targeted genomic sequence analysis panel, solid organ or hematolymphoid neoplasm or disorder, 51 or greater genes (e.g., ALK, BRAF, CDKN2A, CEBPA, DNMT3A, EGFR, ERBB2, EZH2, FLT3, IDH1, IDH2, JAK2, KIT, KRAS, MET, MLL, NOTCH1, NPM1, NRAS, PDGFRA, PDGFRB, PGR, PIK3CA, PTEN, RET), interrogation for sequence variants and copy number variants or rearrangements, or isoform expression or mRNA expression levels, if performed; RNA analysis
- 81479 Unlisted molecular pathology procedure
- 0016M Oncology (bladder), mRNA, microarray gene expression profiling of 219 genes, utilizing formalinfixed paraffin-embedded tissue, algorithm reported as molecular subtype (luminal, luminal infiltrated, basal, basal claudin-low, neuroendocrine-like) (Decipher Bladder TURBT)
- 0019U Oncology, RNA, gene expression by whole transcriptome sequencing, formalin-fixed paraffin embedded tissue or fresh frozen tissue, predictive algorithm reported as potential targets for therapeutic agents. This PLA code is for the OncoTarget™/OncoTreat™ developed at the Columbia University Department of Pathology and Cell Biology for Darwin Health™
- 0037U Targeted genomic sequence analysis, solid organ neoplasm, DNA analysis of 324 genes, interrogation for sequence variants, gene copy number amplifications, gene rearrangements, microsatellite instability and tumor mutational burden (FoundationOne CDx [F1CDx])
- 0048U Oncology (solid organ neoplasia), DNA, targeted sequencing of protein-coding exons of 468 cancer-associated genes, including interrogation for somatic mutations and microsatellite instability, matched with normal specimens, utilizing formalin-fixed paraffin-embedded tumor tissue, report of clinically significant mutation(s) (MSK-IMPACT [Integrated Mutation Profiling of Actionable Cancer Targets], Memorial Sloan Kettering Cancer Center)
- 0101U Hereditary colon cancer disorders (e.g., Lynch syndrome, PTEN hamartoma syndrome, Cowden syndrome, familial adenomatosis polyposis), genomic sequence analysis panel utilizing a combination of NGS, Sanger, MLPA, and array CGH, with MRNA analytics to resolve variants of unknown significance when indicated (15 genes [sequencing and deletion/duplication], EPCAM and GREM1 [deletion/duplication only]). This PLA code is for the ColoNext® test from Ambry Genetics®,
- 0102U Hereditary breast cancer-related disorders (e.g., hereditary breast cancer, hereditary ovarian cancer, hereditary endometrial cancer), genomic sequence analysis panel utilizing a combination of NGS, Sanger, MLPA, and array CGH, with MRNA analytics to resolve variants of unknown significance when indicated (17 genes [sequencing and deletion/duplication]). This PLA code is for the BreastNext® test from Ambry Genetics®
- 0103U Hereditary ovarian cancer (e.g., hereditary ovarian cancer, hereditary endometrial cancer), genomic sequence analysis panel utilizing a combination of NGS, Sanger, MLPA, and array CGH, with MRNA analytics to resolve variants of

unknown significance when indicated (24 genes [sequencing and deletion/duplication], EPCAM [deletion/duplication only]). This PLA code is for the OvaNext® test from Ambry Genetics®

- 0174U Oncology (solid tumor), mass spectrometric 30 protein targets, formalin-fixed paraffin-embedded tissue, prognostic and predictive algorithm reported as likely, unlikely, or uncertain benefit of 39 chemotherapy and targeted therapeutic oncology agents (OncoOmicDx)
- 0211U Oncology (pan-tumor), DNA and RNA by next-generation sequencing, utilizing formalin-fixed paraffin-embedded tissue, interpretative report for single nucleotide variants, copy number alterations, tumor mutational burden, and microsatellite instability, with therapy association (MI Cancer Seek)
- 0250U Oncology (solid organ neoplasm), targeted genomic sequence DNA analysis of 505 genes, interrogation for somatic alterations (SNVs [single nucleotide variant], small insertions and deletions, one amplification, and four translocations), microsatellite instability and tumor-mutation burden- PGDx elioTM tissue complete, Personal Genome Diagnostics, Inc.
- 0262U Oncology (solid tumor), gene expression profiling by real-time RT-PCR of 7 gene pathways (ER, AR, PI3K, MAPK, HH, TGFB, Notch), formalin-fixed paraffin-embedded (FFPE), algorithm reported as gene pathway activity score (OncoSignal)
- 0244U Oncology (solid organ), DNA, comprehensive genomic profiling, 257 genes, interrogation for single-nucleotide variants, insertions/deletions, copy number alterations, gene rearrangements, tumor-mutational burden and microsatellite instability, utilizing formalin-fixed paraffin embedded tumor tissue (Oncotype MAP Pan-Cancer Tissue Test by Paradigm Diagnostics embedded tumor tissue)
- 0329U Oncology (neoplasia), exome and transcriptome sequence analysis for sequence variants, gene copy number amplifications and deletions, gene rearrangements, microsatellite instability and tumor mutational burden utilizing DNA and RNA from tumor with DNA from normal blood or saliva for subtraction, report of clinically significant mutation(s) with therapy associations (Oncomap^{TM} ExTra, Exact Sciences, Inc.)
- 0334U Oncology (solid organ) targeted genomic sequence analysis, formalin-fixed paraffin embedded (FFEP) tumor tissue, DNA analysis, 84 or more genes, interrogation for sequence variants, gene copy number amplifications, gene rearrangements, microsatellite instability and tumor mutational burden (Guardant360 Tissue Next)
- 0362U Oncology (papillary thyroid cancer), gene-expression profiling via targeted hybrid capture–enrichment RNA sequencing of 82 content genes and 10 housekeeping genes, formalin-fixed paraffin embedded (FFPE) tissue, algorithm reported as one of three molecular subtypes (Thyroid GuidePX)

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POLICY HISTORY

Date	Reason	Action
September 2022	Annual Review	Policy Revised
November 2021	Interim Review	Policy Revised
September 2021	Annual Review	Policy Revised
November 2020	Interim Review	Policy Revised
September 2020	Annual Review	Policy Revised
September 2019	Annual Review	Policy Revised
September 2018	Annual Review	Policy Revised
September 2017	Annual Review	Policy Revised
September 2016	New Policy	New Policy

New information or technology that would be relevant for Wellmark to consider when this policy is next reviewed may be submitted to:

Wellmark Blue Cross and Blue Shield
Medical Policy Analyst
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