Medical Policy

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***Current Policy Effective Date: 7/1/24**
(See policy history boxes for previous effective dates)

Title: Genetic Testing – NGS of Multiple Genes (Panel) for Solid and Hematolymphoid Malignant Conditions

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Description/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 of cancer, 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 (2001) 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. These may be categorized into three classes[2] (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 (ie, 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. In some cases, limited panels may be offered that are specific to 1 type of cancer (eg, a panel of several markers for non-small-cell lung cancer).

NEXT-GENERATION SEQUENCING

Sequencing technologies have evolved rapidly over the past few years. Semi-automated Sanger sequencing has been used in clinical testing for many years and is still considered the gold standard. However, its limitations include low throughput and high cost, making multigene panels laborious and expensive. Recent technological advancements have radically changed the landscape of medical sequencing. Next-generation sequencing (NGS) technologies utilize clonally amplified or single molecule templates, which are then sequenced in a massively parallel fashion. This increases throughput by several orders of magnitude. Next-generation sequencing technologies are widely adopted in clinical settings.[3] Using next-generation sequencing, large scale investigations, such as The Cancer Genome Atlas, have molecularly characterized many cancers.

MULTIGENE PANEL TESTING

Panel testing with next-generation sequencing (NGS) involves evaluating sequence variants in multiple genes at one time. Multiple commercial companies and medical center laboratories offer genetic testing panels that use NGS methods for cancers. Next-generation sequencing is one of several methods that allow the sequencing of large stretches of DNA. Panel testing is potentially associated with greater efficiencies in the evaluation of genetic diseases; however, it may provide information on genetic variants of uncertain clinical significance or findings that would not lead to changes in patient management.

Limited testing may not reveal all potentially actionable alterations. In addition to DNA-based NGS, other assay types are available to assess single-nucleotide variants, copy-number variation, fusions, insertion-deletions, larger structural variants, and Microsatellite Instability (MSI), such as Immunohistochemistry (IHC), Fluorescence in situ hybridization (FISH), microarray hybridization analysis, RNA-based sequencing, or Polymerase chain reaction (PCR).[4] In tissue-based testing, RNA-based assays are being increasingly used for detection of gene fusions and slicing variants.[5]

TUMOR AGNOSTIC THERAPY

Tumor agnostic therapy or cancer site agnostic therapy uses drugs or other substances to treat cancer based on their genetic and molecular features without regard to the cancer type or where the cancer started in the body. Basket studies are a type of clinical trial that test how well a new drug or other substance works in patients who have different types of cancer that all have the same genetic mutation or biomarker. Basket studies performed during clinical trials emerged as a tool for evaluating biomarker targeted therapies among multiple tumor types with same or similar genomic alterations.[6]

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.

In the United States, genomic sequencing must be performed in Clinical Laboratory Improvement Amendments (CLIA)-certified laboratories. Cross-institutional studies have shown high concordance in mutations reported among different CLIA-certified laboratories in both the solid tumor and hematologic malignancy settings.[7]

U.S. Food & Drug Administration – Companion Diagnostics[8]
A companion diagnostic is a medical device, often an in vitro device, which provides information that is essential for the safe and effective use of a corresponding drug or biological product. The test helps a health care professional determine whether, for a specific patient, a particular therapeutic product's benefits outweigh any potential serious side effects or risks.

Companion diagnostics can:
- identify patients who are most likely to benefit from a particular therapeutic product;
- identify patients likely to be at increased risk for serious side effects as a result of treatment with a particular therapeutic product; or
- monitor response to treatment with a particular therapeutic product for the purpose of adjusting treatment to achieve improved safety or effectiveness.

FDA-Approved Companion Diagnostic Tests
FDA-approved companion diagnostic tests include:
- Tests which are billed with CPT* codes (most laboratories are able to process these)
- Proprietary laboratory analyses (PLA) tests (processed by one specific independent laboratory). Most PLA tests have billing codes that end in "U".
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Information regarding FDA-approved companion diagnostic tests should be obtained from the FDA "List of Cleared or Approved Companion Diagnostic Devices (In Vitro and Imaging Tools)" website. www.fda.gov/medical-devices/in-vitro-diagnostics/list-cleared-or-approved-companion-diagnostic-devices-in-vitro-and-imaging-tools
For accuracy, the reader is advised to access the information directly from the FDA site. (This website is updated frequently)

Medical Policy Statement

Next-generation sequence testing of clinically-actionable genes, through a multiple-gene panel, may be considered established for solid cancers or hematolymphoid cancers for diagnostic and prognostic purposes, and in guiding the selection of appropriate therapeutic options, when criteria are met.

Next-generation sequencing (NGS) of clinically-actionable genes, through a multiple-gene panel may be considered established for metastatic or advanced cancers when criteria are met.

Policies that discuss gene testing for diagnosis and treatment of solid cancers, include the following as of date 10/17/2023

- Circulating Tumor DNA and Circulating Tumor Cells for Selecting Targeted Therapy for Advanced Solid Cancers (Liquid Biopsy)
- Circulating Tumor DNA for Management of Non-Small-Cell Lung Cancer (Liquid Biopsy)
- Genetic Testing – BRAF Mutation in Selecting Melanoma Patients for Targeted Therapy
- Genetic Testing – Molecular Analysis for Targeted Therapy of Non-Small-Cell-Lung Cancer
- Somatic Biomarker Testing (Including liquid biopsy) for targeted treatment and immunotherapy in metastatic colorectal cancer (KRAS, NRAS, BRAF, MMR/MSI, and HER2)
- Somatic Biomarker Testing (including liquid biopsy) for Targeted Treatment and Immunotherapy in Non-Small Cell Lung Cancer (EGFR, ALK, BRAF, ROS1, RET, MET, KRAS, HER2, PD-L1, TMB)

Inclusionary and Exclusionary Guidelines

If there is a medical policy specific to the cancer (type or treatment) and to the appropriate genetic testing, that policy direction supersedes this policy.

Inclusions:

Hematolymphoid Cancer

Next-generation sequencing (NGS), with a multiple-gene panel test (eg, CPT* code , 81450, 81451, 81455, or 81456), may be considered established when used for diagnostic and prognostic purposes or for guidance in the selection of appropriate targeted FDA therapeutic options for the following conditions:

- Suspected hematolymphoid neoplasms supported by clinical records which reflect an inconclusive diagnosis despite the clinical history, physical examination findings, blood work (eg, CBC with peripheral smear, chromosome analysis)
- Acute Lymphoblastic Leukemia
- Acute Myelogenous Leukemia
- Basophilia
- B-Acute Lymphocytic Leukemia
- B-Cell Non-Hodgkin Lymphoma
- Chronic Lymphocytic Leukemia
- Chronic Myeloid Leukemia
- Chronic Myeloid Proliferative Disease
- Essential Thrombocythemia or Thrombocytosis
- Myelodysplastic Syndrome
- Pancytopenia
- Plasma Cell Dyscrasia
- Pediatric Hematologic Malignancies
- Polycythemia Vera
- Primary Myelofibrosis (PMF), or Pre-PMF, or suspicion for PMF

- T-Acute Lymphocytic Leukemia
- T-Cell Lymphoma, Peripheral

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Solid Cancers

Next-generation sequencing (NGS), with a multiple-gene panel test (eg, CPT* code 81445, 81449, 81455, 81456), may be considered established when used for diagnostic and prognostic purposes or for guidance in the selection of appropriate targeted FDA therapeutic options for any of the following conditions:

- Metastatic cancers
- Inoperable locally advanced cancers
- Refractory cancers
- Recurrent cancers
- When diagnosis cannot be made by histopathologic means alone (eg, sarcomas, neurologic neoplasms, etc.)
- NGS testing for adjuvant therapy in non-advanced cancers may be considered, if consistent with FDA-approved indications

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Tumor Agnostic Therapy

Next-generation sequencing (NGS) with a multiple-gene panel test may be considered established when the following criteria are met

- Adult and pediatric individuals for whom there are no satisfactory options in the treatment of: metastatic or unresectable solid tumors; OR disease progression following prior treatment

NOTE:

Tumor agnostic therapy is established for the following genetic variants:

- *BRAF* V600E or V600K variants
- Mismatch Repair Deficient (dMMR) or Microsatellite Instability-High (MSI-H)
- Tumor mutational burden-high (TMB-H) (≥10 mutations/mega base [mut/Mb])
- Neurotrophic tyrosine receptor kinase (*NTRK* 1/2/3) gene fusion
- Programmed Cell Death ligand 1 (PD-L1)

Proprietary Laboratory Analyses (PLA) Testing

A PLA test is considered **established** when the following criteria are met:

- Biomarker confirmation is required by an FDA-approved or -cleared test prior to initiating treatment (as described in the FDA prescribing label of the therapeutic in the section “Indications and Usage”), AND
- The test is an FDA-approved companion diagnostic

Information regarding FDA-approved companion diagnostic tests should be obtained from the FDA “List of Cleared or Approved Companion Diagnostic Devices (In Vitro and Imaging Tools)” website. www.fda.gov/medical-devices/in-vitro-diagnostics/list-cleared-or-approved-companion-diagnostic-devices-in-vitro-and-imaging-tools

For accuracy, the reader is advised to access the information directly from the FDA site. (This website is updated frequently)

Exclusions:

- Next-generation sequencing, with multiple-gene panel testing (5 to 50 genes; OR 51 or more genes) when the above criteria are not met
- Concurrent ordering of more than one multiple-gene panel test

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CPT/HCPCS Level II Codes *(Note: The inclusion of a code in this list is not a guarantee of coverage. Please refer to the medical policy statement to determine the status of a given procedure.)*

Established codes:

81191	81192	81193	81194	81210	81301
81445	81449	81450	81451	81455	81456
81457	81458	81459	81479*		
0037U	0172U	0022U	0244U	0250U	0334U
0379U					

Other codes (investigational, not medically necessary, etc.):

0048U 0444U

**** Policy criteria must be met. This code is subject to individual review. This code may represent various gene panel tests, eg, BRACAnalysis CDx***

Note: Individual policy criteria determine the coverage status of the CPT/HCPCS code(s) on this policy. Codes listed in this policy may have different coverage positions (such as established or experimental/investigational) in other medical policies.

Rationale:

Evidence reviews assess whether a medical test is clinically useful. A useful test provides information to make a clinical management decision that improves the net health outcome. That is, the balance of benefits and harms is better when the test is used to manage the condition than when another test or no test is used to manage the condition.

The first step in assessing a medical test is to formulate the clinical context and purpose of the test. The test must be technically reliable, clinically valid, and clinically useful for that purpose. Evidence reviews assess the evidence on whether a test is clinically valid and clinically useful. Technical reliability is outside the scope of these reviews, and credible information on technical reliability is available from other sources.

Comprehensive Genomic Profiling of Tumor Tissue

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.

The question addressed in this evidence review is: In individuals with cancer that is being considered for targeted therapy, does the use of comprehensive genomic profiling of tumor tissue improve the net health outcome?

The following PICO was used to select literature to inform this review.

Populations
The relevant population of interest is 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, small and large insertions, and deletions, copy number variants, and fusions in cancer-associated genes by next-generation sequencing 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.

Technically Reliable
Assessment of technical reliability focuses on specific tests and operators and requires review of unpublished and often proprietary information. Review of specific tests, operators, and unpublished data are outside the scope of this evidence review and alternative sources exist. This evidence review focuses on the clinical validity and clinical utility.

Clinical 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 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, 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.

Section Summary: Clinically Validity

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.

Direct Evidence

Direct evidence of clinical utility is provided by studies that have compared health outcomes for patients managed with and without the test. Because these are intervention studies, the preferred evidence would be from randomized controlled trials (RCTs).

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. 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. Overall survival 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.

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 vs standard care, with the first results published in 2015 (Tables 2 and 3).[9,10] 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.

Table 2. Summary of Key RCT Characteristics

Study	Countries	Sites	Dates	Participants	Interventions	
					Active	Comparator
Le Tourneau et al (2012, 2015)[9,10] SHIVA	France	8		195 patients with any kind of metastatic solid tumor refractory to standard targeted treatment who had a molecular alteration in 1 of three molecular pathways[a]	99 off-label therapy based on variant testing by NGS[b]	96 standard care

NGS: next-generation sequencing

[a] Molecular alterations affecting the hormonal pathway were found in 82 (42%) patients; alterations affecting the PI3K/AKT/mTOR pathway were found in 89 (46%) patients; and alterations affecting the RAF/MED pathway were found in 24 (12%) patients.

[b] 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.

Table 3. Treatment Algorithm for Experimental Arm From the SHIVA Trial

Molecular Abnormalities	Molecularly Targeted Agent
KIT, *ABL*, *RET*	Imatinib
AKT, mTORC1/2, *PTEN*, *PI3K*	Everolimus
BRAF V600E	Vemurafenib
PDGFRA, *PDGFRB*, *FLT-3*	Sorafenib
EGFR	Erlotinib
HER2	Lapatinib and trastuzumab
SRC, *EPHA2*, *LCK*, *YES*	Dasatinib
Estrogen receptor, progesterone receptor	Tamoxifen (or letrozole if contraindications)
Androgen receptor	Abiraterone

Adapted from Le Tourneau et al (2012)[8]

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; Table 4). In the subgroup analysis by molecular pathway, there were no significant differences in PFS between groups.

Table 4. Summary of Key RCT Results

Study	PFS (95% CI), mo	PFS at 6 mo % (95% CI)	Adverse Events, n (%)	
			Grade 3	Grade 4
Le Tourneau et al (2015)[9,10]; SHIVA				
N	195	195		
Targeted therapy	2.3 (1.7 to 3.8)	13 (7 to 20)	36 (36)	7 (7)
Standard care	2.0 (1.7 to 2.7)	11 (6 to 19)	28 (31)	4 (4)
HR (95% CI)	0.88 (0.65 to 1.19)			
p	0.41			

CI: confidence interval; HR: hazard ratio; PFS: progression-free survival

Limitations of the SHIVA trial are shown in Tables 5 and 6. A major limitation of the SHIVA trial is that the population consisted of patients who had failed a targeted treatment.

Table 5. Relevance Limitations

Study	Population[a]	Intervention[b]	Comparator[c]	Outcomes[d]	Follow-Up[e]
Le Tourneau et al (2015) SHIVA[9,10]	4. Patients had failed a targeted therapy for their indication		3. Included combination therapy whereas the intervention was single-agent		

The study limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.
[a] Population key: 1. Intended use population unclear; 2. Clinical context is unclear; 3. Study population is unclear; 4. Study population not representative of intended use.
[b] Intervention key: 1. Not clearly defined; 2. Version used unclear; 3. Delivery not similar intensity as comparator; 4.Not the intervention of interest.
[c] Comparator key: 1. Not clearly defined; 2. Not standard or optimal; 3. Delivery not similar intensity as intervention; 4. Not delivered effectively.
[d] Outcomes key: 1. Key health outcomes not addressed; 2. Physiologic measures, not validated surrogates; 3. No CONSORT reporting of harms; 4. Not establish and validated measurements; 5. Clinical significant difference not prespecified; 6. Clinical significant difference not supported.
[e] Follow-Up key: 1. Not sufficient duration for benefit; 2. Not sufficient duration for harms.

Table 6. Study Design and Conduct Limitations

Study	Allocation[a]	Blinding[b]	Selective Reporting[c]	Data Completeness[d]	Power[e]	Statistical[f]

Le Tourneau et al (2015) SHIVA[9,10]		1-3. The study was not blinded and outcomes were assessed by the treating physician				

The study limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.
[a] Allocation key: 1. Participants not randomly allocated; 2. Allocation not concealed; 3. Allocation concealment unclear; 4. Inadequate control for selection bias.
[b] Blinding key: 1. Not blinded to treatment assignment; 2. Not blinded outcome assessment; 3. Outcome assessed by treating physician.
[c] Selective Reporting key: 1. Not registered; 2. Evidence of selective reporting; 3. Evidence of selective publication.
[d] Data Completeness key: 1. High loss to follow-up or missing data; 2. Inadequate handling of missing data; 3.High number of crossovers; 4. Inadequate handling of crossovers; 5. Inappropriate exclusions; 6. Not intent to treat analysis (per protocol for noninferiority trials).
[e] Power key: 1. Power calculations not reported; 2. Power not calculated for primary outcome; 3. Power not based on clinically important difference.
[f] Statistical key: 1. Analysis is not appropriate for outcome type: (a) continuous; (b) binary; (c) time to event; 2. Analysis is not appropriate for multiple observations per patient; 3. Confidence intervals and/or p values not reported; 4. Comparative treatment effects not calculated.

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.[11] 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 would suggest that patients might have benefited from the treatment algorithm evaluated in the SHIVA trial.

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 (Table 8). 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.[14,15] The results of the meta-analyses are shown in Table 9. 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.

Table 7. Meta-analysis Characteristics

Study	Dates	Trials	Participants	N	Design
Schwaederle et al (2015)[14]	2010 - 2012	570 (641 arms)	Adult patients with any type of advanced cancer	32,149 (8,078 personalized and 24,071 non-personalized)	Single-agent phase 2 trials
Jardim et al (2015)[15]		57 RCTs 55 non-RCTs			58 newly approved cancer agents

RCT: randomized clinical trial

Table 8. Meta-analysis Results

Study	Median Response Rate	Relative Response Rate (95% CI)	Median Progression-Free Survival	Median Overall Survival	Treatment-related Mortality% (95% CI)
Schwaederle et al (2015)[14]	% (95% CI)		Months (95% CI)	Months (95% CI)	
Total N	31,994		24,489	21,817	
Targeted therapy	31.0 (26.8 to 35.6)		5.9 (5.4 to 6.3)	13.7 (11.1 to 16.4)	1.52 (1.23 to 1.87)
Non-targeted therapy	10.5 (9.6 to 1.5a)		2.7 (2.6 to 2.9)	8.9 (8.3 to 9.3)	2.26 (2.04 to 2.49)
p-Value	<0.001		<0.001	<0.001	<0.001
Jardim et al (2015)[14]	% (95% CI)		Months (IQR)	Months (IQR)	
Targeted	48 (42 to 55)		8.3 (5)	19.3 (17)	
Non-targeted	23 (20 to 27)		5.5 (5)	13.5 (8)	
p-Value	<0.01		0.002	0.04	
		Hazard ratio compared to control arm	Hazard ratio compared to control arm	Hazard ratio compared to control arm	
Targeted		3.82 (2.51 to 5.82)	0.41 (0.33 to 0.51)	0.71 (0.61 to 0.83)	
Non-targeted		2.08 (1.76 to 2.47)	0.59 (0.53 to 0.65)	0.81 (0.77 to 0.85)	
p-Value		0.03	<0.001	0.07	NS

CI: confidence interval; IQR interquartile range; NS: reported as not significant

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).[16] Some of these studies had a prospective, interventional design.[17] Another type of study compared 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 two 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 (2017) from the MD Anderson Cancer Center.[17] Patients with advanced cancer who underwent comprehensive genomic profiling were treated with matched targeted therapy when available (see Table 9). Out of 1,436 patients who underwent genomic profiling, 1,170 (82.1%) had one or more mutations, of which 637 were actionable. The most frequent alterations were estrogen receptor overexpression, and variants in TP53, KRAS, PTEN, PIK3CA, and BRAF. Comparison of outcomes in patients who received matched and unmatched therapies are shown in Table 10. The group that had matched therapy had a higher response rate (11% vs 5%), longer PFS (3.4 vs 2.9 mo), and longer OS (8.4 vs 7.3 mo). In addition to the general limitations of this type of study design, limitations in relevance and design and conduct are

shown in Tables 11 and 12. Note that a randomized trial from this center that will compare matched to unmatched therapy (IMPACT 2) is ongoing with completion expected in early 2020 (Table 11).

Table 9. Summary of Key Nonrandomized Trials OR Observational Comparative Study Characteristics

Study	Study Type	Country	Dates	Participants	Treatment1	Treatment2	Follow-Up
Tsimberidou et al (2017)[17], IMPACT	Database review	U.S.	2012-2013	1,436 patients with advanced cancer	Matched Therapy (n=390)	Unmatched Therapy (n=247)	

Table 10. Summary of Key Nonrandomized Trials OR Observational Comparative Study Results

Study	Complete or Partial Response	Progression-Free Survival mo	Overall Survival mo		
Tsimberidou et al (2017)[18] IMPACT	N	N	N		
Matched	11%	3.4	8.4		
Unmatched	5%	2.9	7.3		
p-Value	0.010	0.002	0.041		
Hazard Ratio (95% CI)					
p-Value		0.015	0.041		

CI: confidence interval; Diff: difference; HR: hazard ratio;; OR: odds ratio; RR: relative risk; SD: standard deviation.
1 Include number analyzed, association in each group and measure of association (absolute or relative) with CI.

Table 11. Relevance Limitations

Study	Population[a]	Intervention[b]	Comparator[c]	Outcomes[d]	Follow-Up[e]
Tsimberidou et al (2017)[18] IMPACT	4. The population consisted of patients who had failed guideline-based treatments and were enrolled in phase 1 clinical trials	4. Treatment was based on both genetic variants and tumor types.	2. The study was in the context of phase 1 trials and efficacy of the treatments is uncertain		

The study limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.
[a] Population key: 1. Intended use population unclear; 2. Clinical context is unclear; 3. Study population is unclear; 4. Study population not representative of intended use.
[b] Intervention key: 1. Not clearly defined; 2. Version used unclear; 3. Delivery not similar intensity as comparator; 4.Not the intervention of interest.
[c] Comparator key: 1. Not clearly defined; 2. Not standard or optimal; 3. Delivery not similar intensity as intervention; 4. Not delivered effectively.
[d] Outcomes key: 1. Key health outcomes not addressed; 2. Physiologic measures, not validated surrogates; 3. No CONSORT reporting of harms; 4. Not establish and validated measurements; 5. Clinical significant difference not prespecified; 6. Clinical significant difference not supported.
[e] Follow-Up key: 1. Not sufficient duration for benefit; 2. Not sufficient duration for harms.

Table 12. Study Design and Conduct Limitations

Study	Allocation[a]	Blinding[b]	Selective Reporting[c]	Data Completeness[d]	Power[e]	Statistical[f]
Tsimberidou et al (2017)[18] IMPACT	1. Not randomized	1.-3. No blinding				

The study limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.
[a] Allocation key: 1. Participants not randomly allocated; 2. Allocation not concealed; 3. Allocation concealment unclear; 4. Inadequate control for selection bias.
[b] Blinding key: 1. Not blinded to treatment assignment; 2. Not blinded outcome assessment; 3. Outcome assessed by treating physician.
[c] Selective Reporting key: 1. Not registered; 2. Evidence of selective reporting; 3. Evidence of selective publication.
[d] Data Completeness key: 1. High loss to follow-up or missing data; 2. Inadequate handling of missing data; 3.High number of crossovers; 4. Inadequate handling of crossovers; 5. Inappropriate exclusions; 6. Not intent to treat analysis (per protocol for noninferiority trials).

[e] Power key: 1. Power calculations not reported; 2. Power not calculated for primary outcome; 3. Power not based on clinically important difference.
[f] Statistical key: Analysis is not appropriate for outcome type: (a) continuous; (b) binary; (c) time to event; 2. Analysis is not appropriate for multiple observations per patient; 3. Confidence intervals and/or p values not reported; 4.Comparative treatment effects not calculated.

Chain of Evidence

Indirect evidence on clinical utility rests on clinical validity. If the evidence is insufficient to demonstrate test performance, no inferences can be made about clinical utility.

Because the clinical validity of expanded cancer molecular panel testing to identify somatic variants to guide targeted treatment therapies has not been established, the chain of evidence supporting the clinical utility of panel testing cannot be constructed.

Section Summary: Clinically Useful

Evidence on targeted therapy for the treatment of various cancers includes an RCT, systematic reviews of phase 1, 2 and 3 trials, and a database review. The one published RCT (SHIVA trial) that used an expanded panel reported no difference in 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, PFS, and 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 (CGP) 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 (ie, basket trials). As a result, these types of studies do not provide evidence of the benefit of broad molecular profiling compared to limited genetic assessment based on known tumor-specific variants. RCTs that randomize patients with various tumor types to a strategy of CGP followed by targeted treatment are ongoing.

SUMMARY OF EVIDENCE

Next generation sequencing (NGS) panel testing is medically necessary for diagnosis, prognosis (for the purposes of therapeutic decision-making), and direction of targeted therapy for a broad range of neoplasms. According to the 2022 American Society of Clinical Oncology (ASCO) Provisional Clinical Opinions: Somatic Genomic Testing in Patients with Metastatic or Advanced Solid Cancer, there are numerous therapies that are FDA-approved for specific molecular alterations affecting specific neoplasms. ASCO defines multi-gene panel testing as the testing of 50 or more genes. This testing is identified as clinically useful in the recommendation of appropriate FDA treatment options. Use of multi-panel testing should be considered as part of the evaluation for an approved genomic biomarker linked therapy within the patient's tumor tissue type. Multi-panel gene testing is the most efficient use of testing limited tumor tissue as it allows the simultaneous testing of several approved therapeutic targets. If more than one biomarker therapy is being considered for an individual's specific cancer type, multi-gene panel testing is the most efficient in tissue preservation.[7]

Supplemental Information

National Comprehensive Cancer Network® (NCCN Guidelines®)

Category 1 or 2A Recommendations

The National Comprehensive Cancer Network® (NCCN Guidelines®) do not contain recommendations for the general strategy of testing a tumor for a wide range of variants. The guidelines 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 gene testing of common solid tumors are listed below.

Cancer Type and Gene Testing Recommendations – Not a Comprehensive List

Type of Cancer	Genes
Breast Cancer	
DCIS	ESR1
Invasive Breast Cancer	BRCA1, BRCA2, ESR1, PGR, ERBB2, MKI67, CD274, PIK3CA, NTRK1/2/3, MLH1, MSH2, MSH6, PMS2, MSI, TMB, CEACAM5, MUC1
Inflammatory BC	ESR1, PGR, ERBB2
Bladder Cancer	FGFR2, FGFR3, CD274, MLH1, MSH2, MSH6, PMS2, MSI
Central Nervous System Cancers	
Adult Gliomas	ATRX, BRAF, IDH1, IDH2, MGMT, TERT, H3-3A, H3C2
Chronic Myeloid Leukemia	ABL1, BCR, ASXL1, BCOR, BRAF, CALR, CBL, CEBPA, CSF3R, DNMT3A, ETV6, EZH2, FLT3, GATA2, IDH1, IDH2, JAK2, KIT, KMT2A, KRAS, MPL, NPM1, NRAS, PHF6, PTPN11, RUNX1, SF3B1, SH2B3, SMC1A, SMC3, SRSF2, STAG2, TET2, TP53, U2AF1, WT1, ZRSR2
Colon Cancer	CEACAM5, KRAS, NRAS, MLH1, MSH2, MSH6, PMS2. MSI, BRAF, ERBB2, NTRK1/2/3
Esophageal Cancer	ERBB2, CD274, MLH1, MSH2, MSH6, PMS2, NTRK1/2/3
Gastric Cancer	ERBB2, MLH1, MSH2, MSH6, PMS2, CD274, NTRK1/2/3, CDH1
Gastrointestinal Stromal Tumors	KIT, PDGFRA, BRAF, NF1, SDHB, ANO1, CD34, FGFR1, NTRK1/2/3
Hepatobiliary Cancer	
HCC	AFP, NTRK1/2/3
Intrahepatic Carcinoma	CEACAM5, AFP, MLH1, MSH2, MSH6, PMS2, BRCA1, BRCA2, BRAF, ERBB2, FGFR2, IDH1, NTRK1/2/3, RET
Melanoma, Cutaneous	BRAF, KIT, CDKN2A, MLANA, SOX10, PRAME, LDHA, LDHB, LDHC, PDPN
Non-Small Cell Lung Cancer	EGFR, KRAS, MET, NTRK1/2/3, RET, ALK, CALB2, KRT5, KRT6A, KRT6B, PDPN, WT1. CEACAM5, CLDN4, EPCAM, FUT4, NAPSA, NKX2-1, CHGA, INSM1, NCAM1, SYP, TP63, ROS1, BRAF, ERBB2, CD274, NUTM1, CDX2, ESR1, GATA3, NKX3-1, PAX2, PAX8, PGR, PIP, SCGB2A2, TG
Ovarian Cancer	AFP, CGB4, INHA, LDHA, LDHB, LDHC, CEACAM5, MUC16, BRCA1, BRCA2, MLH1, MSH2, MSH6, PMS2, HRD, MSI, TMB, NTRK1/2/3 fusion

Pancreatic Cancer	ALK, BRAF, BRCA1, BRCA2, ERBB2, FGFR2, KRAS, MLH1, MSH2, MSH6, NRG1, NTRK1, NTRK2, NTRK3, PALB2, PMS2, RET, ROS1
Prostate Cancer	KLK3, ATM, BRCA1, BRCA2, CHEK2, HOXB13, MLH1, MSH2, MSH6, PALB2, PMS2, BARD1, BRIP1, CDK12, CHEK1, FANCA, FANCL, PPP2R2A, RAD51B, RAD51C, RAD51D, RAD54L, AR
Soft Tissue Sarcoma	
Well-Differentiated Liposarcoma	CDK4, GLI1, HMGA2, MDM2, TSPAN31
Uterine Cancer	
Endometrial Carcinoma	MLH1, MSH2, MSH6, PMS2, ESR1, MUC16, NTRK1/2/3, POLE, TP53

(This information is based on a search of the NCCN Biomarkers Compendium® on 10/06/2022.[19])

Government Regulations
National:

There is no national coverage determination (NCD) for molecular panel testing of cancers to identify targeted therapies.

National Coverage Determination (NCD) for Next Generation Sequencing (NGS) (90.2)
Effective date of this version: 1/27/2020; Implementation date: 11/13/2020[20]

Item/Service Description
A. General
Clinical laboratory diagnostic tests can include tests that, for example, predict the risk associated with one or more genetic variations. In addition, in vitro companion diagnostic laboratory tests provide a report of test results of genetic variations and are essential for the safe and effective use of a corresponding therapeutic product. Next Generation Sequencing (NGS) is one technique that can measure one or more genetic variations as a laboratory diagnostic test, such as when used as a companion in vitro diagnostic test.

This National Coverage Determination (NCD) is only applicable to diagnostic lab tests using NGS for somatic (acquired) and germline (inherited) cancer. Medicare Administrative Contractors (MACs) may determine coverage of diagnostic lab tests using NGS for RNA sequencing and protein analysis.

Indications and Limitations of Coverage
B. Nationally Covered Indications
1. Somatic (Acquired) Cancer

Effective for services performed on or after March 16, 2018, 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 Clinical Laboratory Improvement Amendments (CLIA)-certified laboratory, when ordered by a treating physician, and when all of the following requirements are met:

a. Patient has:
   i. either recurrent, relapsed, refractory, metastatic, or advanced stage III or IV cancer; and

ii. not been previously tested with the same test using NGS for the same cancer genetic content, and
iii. decided to seek further cancer treatment (e.g., therapeutic chemotherapy).

b. The diagnostic laboratory test using NGS must have:
i. Food & Drug Administration (FDA) approval or clearance as a companion in vitro diagnostic; and,
ii. an FDA-approved or -cleared indication for use in that patient's cancer; and,
iii. results provided to the treating physician for management of the patient using a report template to specify treatment options.

2. Germline (Inherited) Cancer

Effective for services performed on or after January 27, 2020, CMS has determined that NGS as a diagnostic laboratory test is reasonable and necessary and covered nationally for patients with germline (inherited) cancer, when performed in a CLIA-certified laboratory, when ordered by a treating physician and when all of the following requirements are met:

a. Patient has:
i. ovarian or breast cancer; and,
ii. a clinical indication for germline (inherited) testing for hereditary breast or ovarian cancer; and,
iii. a risk factor for germline (inherited) breast or ovarian cancer; and
iv. not been previously tested with the same germline test using NGS for the same germline genetic content.

b. The diagnostic laboratory test using NGS must have all of the following:
i. FDA-approval or clearance; and,
ii. results provided to the treating physician for management of the patient using a report template to specify treatment options.

C. Nationally Non-Covered Indications

1. Somatic (Acquired) Cancer

Effective for services performed on or after March 16, 2018, NGS as a diagnostic laboratory test for patients with cancer are non-covered if the cancer patient does not meet the criteria noted in section B.1. above.

D. Other

1. Somatic (Acquired) Cancer

Effective for services performed on or after March 16, 2018, Medicare Administrative Contractors (MACs) may determine coverage of NGS as a diagnostic laboratory test for patients with advanced cancer only when the test is performed in a CLIA-certified laboratory, when ordered by a treating physician, and when the patient has:

a) either recurrent, relapsed, refractory, metastatic, or advanced stages III or IV cancer; and,
b) not been previously tested with the same test using NGS for the same cancer genetic content, and
c) decided to seek further cancer treatment (e.g., therapeutic chemotherapy).

2. Germline (Inherited) Cancer

Effective for services performed on or after January 27, 2020, MACs may determine coverage of NGS as a diagnostic laboratory test for patients with germline (inherited) cancer only when the test is performed in a CLIA-certified laboratory, when ordered by a treating physician, when

results are provided to the treating physician for management of the patient and when the patient has:

a) any cancer diagnosis; and,
b) a clinical indication for germline (inherited) testing of hereditary cancers; and,
c) a risk factor for germline (inherited) cancer; and,
d) not been previously tested with the same germline test using NGS for the same germline genetic content.

Local:

Wisconsin Physicians Service Insurance Corporation
Local Coverage Determination (LCD): MolDX: Next-Generation Sequencing for Solid Tumors (L38158)
Original effective date for services performed on or after 02/09/2020
Revision effective date for services performed on or after 06/08/2023

Coverage Indications, Limitations, and/or Medical Necessity
This policy describes and clarifies coverage for Lab-Developed Tests (LDTs), FDA-cleared, and FDA-approved clinical laboratory tests utilizing Next-Generation Sequencing (NGS) in cancer as allowable under the National Coverage Determination (NCD) 90.2, under section D describing Medicare Administrative Contractor (MAC) discretion for coverage. This policy's scope is specific for solid tumor testing, and is exclusive of hematologic malignancies, circulating tumor DNA testing (ctDNA), and other cancer-related uses of NGS, such as germline testing in/for patients with cancer.

Criteria for Coverage
All the following must be present for coverage eligibility:

- As per NCD 90.2, this test is reasonable and necessary when:
  - the patient has either:
    - Recurrent cancer
    - Relapsed cancer
    - Refractory cancer
    - Metastatic cancer
    - Advanced cancer (stages III or IV)
  - AND has not been previously tested by the same test with the same primary diagnosis
  - AND is seeking further treatment
- The test has satisfactorily completed a TA by MolDX for the stated indications of the test
- The assay performed includes at *least* the minimum genes and genomic positions required for the identification of clinically relevant FDA-approved therapies with a companion diagnostic biomarker as well as other biomarkers known to be necessary for clinical decision making for its intended use that can be reasonably detected by the test. Because these genes and variants will change as the literature and drug indications evolve, they are listed separately in associated documents such as the MolDX TA forms.

Situations in which Test should not be used or coverage is denied:
The test in question will be non-covered if:

- It does not fulfill all the criteria set forth in the NCD 90.2 as stated above
- Another CGP test was performed on the same tumor specimen (specimen obtained on the same date of service)
- A Technical Assessment is not completed satisfactorily by MolDX for new tests

- For tests that are currently covered but a TA submission has not been made, providers must submit complete TA materials by February 10th, 2020 or coverage will be denied

Wisconsin Physicians Service Insurance Corporation
Local Coverage Article: Billing and Coding: MolDX: Next-Generation Sequencing for Solid Tumors (A57858)
Original Effective Date 02/09/2020
Revision Effective Date 07/01/2023

Group 1 Codes: 81445, 81449,81479, 0244U, 0250U, 0329U,0334U,0379U,0391U

Wisconsin Physicians Service Insurance Corporation
Local Coverage Article: Billing and Coding: MolDX: Next-Generation Sequencing Lab-Developed Tests for Myeloid Malignancies and Suspected Myeloid Malignancies (A57878)
Original Effective Date 02/09/2020
Revision Effective Date 01/01/2023

Group 1 Codes: 81450, 81451,81479

Wisconsin Physicians Service Insurance Corporation
Local Coverage Article: MolDX: Targeted and Comprehensive Genomic Profile Next Generation Sequencing Testing in Cancer (A55197)
Original effective date: 02/16/2017
Revision effective date: 06/01/2023

Targeted Tumor Panels
Targeted Next-Generation Sequencing (NGS) panels are hereby defined as tests that identify somatic alterations known to occur in certain regions (i.e., 'hotspots') within specific genes of interest for cancer management (i.e., diagnosis, selection of molecularly targeted therapies, prognosis in a context where prognostic classification is essential for treatment selection). Generally, these NGS panels can detect single nucleotide variants (SNVs) and small insertions or deletions (INDELs) within these regions. These alterations typically represent response or lack of response to corresponding targeted cancer therapies. The hotspot test should include relevant regions in the genes required for companion diagnostic testing and/or known to be necessary for proper patient management.

Comprehensive Genomic Profile (CGP) Testing
CGP refers to NGS-based molecular assays that provide additional insight beyond individual gene hotspots; these assays seek to describe the genomic makeup of a tumor and can help identify underlying mechanisms of disease to guide clinical decision making. These tests include not only mutations in individual relevant genes, but also patterns of mutations across related genes in established cancer pathways and often include an assessment of overall mutational burden. These tests typically involve sequencing of entire exonic regions of genes of interest (within a comprehensive gene panel or whole exome sequencing), and may also include selected intronic regions. CGP can detect multiple types of molecular alterations (i.e., SNVs, small and large INDELs, copy number alterations (CNAs), structural variants (SVs), and splice-site variants) in a single assay. Patterns of mutations seen across multiple genes may be used to infer clinically relevant etiologies, such as DNA mismatch repair deficiency and microsatellite instability, and total mutational load/burden (TMB) may be determined. CGP testing may also include RNA sequencing to detect structural variations, such as translocations

or large deletions, and to detect functional splicing mutations. CGP is not defined as a targeted panel by MolDX.
[See A57858 and A57878 for codes]

Wisconsin Physicians Service Insurance Corporation
Local Coverage Article: Billing and Coding: MolDX: Molecular Diagnostic Tests (MDT) (A57772)
Original Effective Date 11/01/2019
Revision Effective Date 07/01/23

Group 1 codes: 0037U, 0244U, 0250U, 0329U are listed as well as other codes.

Wisconsin Physicians Service Insurance Corporation
Local Coverage Determination (LCD): MolDX: Next-Generation Sequencing Lab-Developed Tests for Myeloid Malignancies and Suspected Myeloid Malignancies (L38176)
Original effective date for services performed on or after 02/09/2020
Revision effective date for services performed on or after 07/01/2022

Coverage Indications, Limitations, and/or Medical Necessity
This policy describes and clarifies coverage for Lab-Developed Tests (LDTs) and Food and Drug Administration (FDA)-approved or cleared clinical laboratory tests utilizing Next-Generation Sequencing (NGS) in cancer as allowable under the National Coverage Determination (NCD) 90.2, under section D describing Medicare Administrative Contractor (MAC) discretion for coverage, as well as for use of NGS in suspected myeloid neoplasms. This policy's scope is specific for myeloid malignancies and suspected malignancies, and is exclusive of solid tumor testing, circulating tumor DNA (ctDNA) testing, and other cancer-related uses of NGS, such as in germline testing.

Criteria for Coverage
The following must be present for coverage eligibility:
- For tests that are specifically indicated in patients whom are known to have a myeloid malignancy at the time of testing, NCD 90.2 applies
- The patient has a diagnosis of AML, MDS, or MPN. AML, MDS, and MPN are herein classified as refractory and/or metastatic cancers and fulfill the NCD 90.2 criteria.
- The test has satisfactorily completed a TA by MolDX for the stated indications of the test.
- The assay performed includes *at least* the minimum genes and positions indicated for its intended use, as described in an associated coverage Article and found in the TA forms.
- For patients that do not have a diagnosis of a myeloid malignancy, where one is suspected, the patient must have an undefined cytopenia for greater than 4 months, other possible causes have been reasonably excluded.
- Testing is performed on bone marrow biopsies, bone marrow aspirates, bone marrow clots, peripheral blood samples, or extramedullary sites suspected of harboring a myeloid malignancy.

Situations in which Test should not be used or coverage is denied:
The test in question will be non-covered if:
- A Technical Assessment has not been satisfactorily completed by MolDX. For tests that are currently covered but a TA submission has not been made, providers must submit complete TA materials by February 10th, 2020 or coverage will be denied.

- Another NGS test was performed on the same surgical specimen/ blood draw (specimen obtained on the same date of service).
- Testing falls within scope of NCD 90.2 and has been tested with the same test for the same primary tumor.

(The above Medicare information is current as of the review date for this policy. However, the coverage issues and policies maintained by the Centers for Medicare & Medicare Services [CMS, formerly HCFA] are updated and/or revised periodically. Therefore, the most current CMS information may not be contained in this document. For the most current information, the reader should contact an official Medicare source.)

Related Policies

- Genetic Cancer Susceptibility Panels Using Next Generation Sequencing
  - Circulating Tumor DNA and Circulating Tumor Cells for Selecting Targeted Therapy for Advanced Solid Cancers (Liquid Biopsy)
  - Circulating Tumor DNA for Management of Non-Small-Cell Lung Cancer (Liquid Biopsy)
  - Genetic Testing – BRAF Mutation in Selecting Melanoma Patients for Targeted Therapy
  - Genetic Testing – Molecular Markers in Fine Needle Aspirates (FNA) of the Thyroid
  - Genetic Testing for Lynch Syndrome
  - Genetic Testing for BRCA1 or BRCA2 for Hereditary Breast/Ovarian Cancer Syndrome and Other High Risk Cancer
  - Somatic Biomarker Testing (Including liquid biopsy) for targeted treatment and immunotherapy in metastatic colorectal cancer (KRAS, NRAS, BRAF, MMR/MSI, and HER2)
  - Somatic Biomarker Testing (including liquid biopsy) for Targeted Treatment and Immunotherapy in Non-Small Cell Lung Cancer (EGFR, ALK, BRAF, ROS1, RET, MET, KRAS, HER2, PD-L1, TMB)

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22. Wisconsin Physicians Service Insurance Corporation. Local Coverage Article: MolDX: Targeted and Comprehensive Genomic Profile Next Generation Sequencing Testing in Cancer (A55197). Original effective date: 02/16/2017. Revision effective date: 06/01/2023
23. Wisconsin Physicians Service Insurance Corporation. Local Coverage Article: Billing and Coding: MolDX: Molecular Diagnostic Tests (MDT) (A57772). Original Effective Date 11/01/2019. Revision Effective Date 07/01/2023.
24. Wisconsin Physicians Service Insurance Corporation. Local Coverage Determination (LCD): MolDX: Next-Generation Sequencing Lab-Developed Tests for Myeloid Malignancies and Suspected Myeloid Malignancies (L38176). Original effective date for services performed on or after 02/09/2020; Revision effective date for services performed on or after 06/01/2023.

The articles reviewed in this research include those obtained in an Internet based literature search for relevant medical references through 9/1/23, the date the research was completed.

Joint BCBSM/BCN Medical Policy History

Policy Effective Date	BCBSM Signature Date	BCN Signature Date	Comments
3/1/15	12/9/14	12/29/14	Joint policy established
7/1/16	4/19/16	4/19/16	Routine maintenance
7/1/17	4/18/17	4/18/17	Routine maintenance Added unlisted procedure code 81479 References and rationale updated Medicare information updated
7/1/18	4/17/18	4/17/18	Routine maintenance Removed codes 81460 and 81465 Updated Medicare information, rationale and references
7/1/19	6/21/19		Procedure codes 81445 and 81450 changed to established for specified indications Updated body, rationale and references Updated Medicare information Medicaid section deleted
7/1/20	5/29/20		Routine maintenance Title changed from “Genetic Testing Expanded Molecular Panel Testing of Cancers to Identify Targeted Therapies” to “Genetic Testing - NGS Testing of Multiple Genes (Panel) to Identify Targeted Cancer Therapy” Added E/I statement for panels over 50 genes; updated Medicare: LCDs/articles related to NGS Solid Tumors and Myeloid Malignancies; added to inclusions: MPD, MDS, urothelial cancer.
7/1/21	4/20/21		Routine maintenance References to Guardant360 removed
	4/19/22		Title changed to: GT – Next-Generation Sequencing of Multiple Genes (Panel) for Malignant Conditions. Approved policy not published due to ongoing discussion

			related to covered conditions and criteria.
	8/16/22		Policy reviewed and tabled.
1/1/23	12/6/22		Policy updates to background, regulatory, medical policy statement, inclusions, exclusions and rationale. Coverage provided for testing of 5-50 genes, and 51 or greater genes. 0037U, 0172U, 81479, 81210 added to EST section of policy
1/1/24	10/18/23		Routine Maintenance (jf) Vendor Managed: NA • Edits made to the description, inclusions and medical policy statement • Added codes 81449,81451, 81456,0022U, 0244U,0250U,0334U,0379U as EST. • Added ref: 4 and 5 • Removed ref: 9, 10 • Added Solid and Hematolymphoid into the title • Title from Genetic Testing – NGS of Multiple Genes (Panel) for Malignant Conditions Changed to Genetic Testing – NGS of Multiple Genes (Panel) for Solid and Hematolymphoid Malignant Conditions.
7/1/24	4/16/24		Vendor Managed: NA • Per 2024 CPT code Update: (jf) Add 81457, 81458 and 81459 as Payable/EST codes effective 1/1/24 • Nomenclature updates on codes Revised to reflect current practice in genomic sequencing technology for somatic mutation and cancer treatment. 81445,81450,81451,81455 • PLA 1 QTR Update • Add 0444U Aventa FusionPlus as E/I to policy.

			• Add 0048U MSK-IMPACT (Integrated Mutation Profiling of Actionable Cancer Targets), Memorial Sloan Kettering Cancer Center] E/I to policy.

Next Review Date: 4th Qtr, 2024

BLUE CARE NETWORK BENEFIT COVERAGE
POLICY: GENETIC TESTING – NGS OF MULTIPLE GENES (PANEL) FOR SOLID AND HEMATOLYMPHOID MALIGNANT CONDITIONS

I. Coverage Determination:

Commercial HMO (includes Self-Funded groups unless otherwise specified)	Covered; criteria apply
BCNA (Medicare Advantage)	See the Government Regulations section.
BCN65 (Medicare Complementary)	Coinsurance covered if primary Medicare covers the service.

II. Administrative Guidelines:

- The member's contract must be active at the time the service is rendered.
- Coverage is based on each member's certificate and is not guaranteed. Please consult the individual member's certificate for details. Additional information regarding coverage or benefits may also be obtained through customer or provider inquiry services at BCN.
- The service must be authorized by the member's PCP except for Self-Referral Option (SRO) members seeking Tier 2 coverage.
- Services must be performed by a BCN-contracted provider, if available, except for Self-Referral Option (SRO) members seeking Tier 2 coverage.
- Payment is based on BCN payment rules, individual certificate and certificate riders.
- Appropriate copayments will apply. Refer to certificate and applicable riders for detailed information.
- CPT - HCPCS codes are used for descriptive purposes only and are not a guarantee of coverage.