MASSACHUSETTS

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Medical Policy

Expanded Molecular Panel Testing of Cancers to Identify Targeted Therapies

Table of Contents

Policy Number: 790

BCBSA Reference Number: N/A

NCD/LCD:

- Local Coverage Determination (LCD): Genomic Sequence Analysis Panels in the Treatment of Non-Small Cell Lung Cancer (L36376)
- Local Coverage Determination (LCD): Genomic Sequence Analysis Panels in the Treatment of Acute Myelogenous Leukemia (AML) (L36926)
- Local Coverage Determination (LCD): Genomic Sequence Analysis Panels in the Treatment of Hematolymphoid Diseases (L37606)

Related Policies

- AIM Genetic Testing Management Program, #954
- AIM Genetic Testing Management Program CPT and HCPCS Codes, #957

Policy[1]

Commercial Members: Managed Care (HMO and POS), PPO, and Indemnity Medicare HMO Blue℠ and Medicare PPO Blue℠ Members

The use of a NGS cancer mutation panel including analyses of the genes for solid tumors or for hematologic malignancies is considered **MEDICALLY NECESSARY** for selecting targeted cancer treatment in specific cancer types as indicated in Tables 1a and 1b respectively.

The use of a NGS cancer mutation panel may also be considered **MEDICALLY NECESSARY** to exclude the use of ineffective targeted therapies, to select alternative treatment modalities, to determine suitability for directing patients toward promising investigational therapies, or to establish a definitive diagnosis when other diagnostic approaches yield ambiguous results.

Repeat testing may be required in the setting of patients who have clinically progressed per standardized professional guidelines after therapy or, in the case of myeloid diseases, for periodic monitoring of disease response no more frequently than once per six months.

Tumor tissue genomic panels are **INVESTIGATIONAL** for all other indications not listed above.

Table 1a. Conditions for which Solid Tumor NGS Panel Testing is MEDICALLY NECESSARY

Disease for Which Test is Covered	Additional Requirements
B-Cell NHL	Diagnostic, Prognostic, Monitoring
Bladder Urothelial Carcinoma	Stage IV or recurrent or unresectable
Breast	Stage IV or refractory or recurrent
Cholangiocarcinoma	Stage IV or recurrent or unresectable
Colorectal Cancer	Stage IV or recurrent or unresectable
Endometrial Carcinoma	Stage IV or recurrent or unresectable
GI Stromal Tumor	Any stage
Glioma	Diagnostic, Prognostic, Monitoring
Medulloblastoma	Diagnostic, Prognostic, Monitoring
Melanoma	Stage IIIB, IIIC, IV or recurrent or unresectable
Meningioma	Grade 2 to 4 (only recurrent or unresectable)
Neuroblastoma	Any stage
Non-Small Cell Lung Cancer	Stage IIIB, IV or recurrent
Ovarian	Relapsed or refractory advanced (stage II or higher), non-mucinous ovarian cancer being considered for PARP inhibitor therapy
Pancreatic Tumors	Diagnostic, Prognostic
Pediatric Tumors	Patient age under 21 years
Prostate	Metastatic castration-resistant
Rare Tumors	Less than 5,000/year in US; Metastatic or recurrent or unresectable
Stomach/Esophageal Cancer	Stage IV or recurrent or unresectable
T-Cell NHL	Diagnostic, Prognostic
Thyroid Cancer	Stage IV or recurrent or unresectable
Unknown Primary	May be used for Diagnosis or Therapeutic Decision Making

Table 1b. Conditions for which Hematologic Malignancy NGS Panel Testing or is MEDICALLY NECESSARY

Disease for Which Test is Covered	Purpose/Use of Test
Acute Myeloid Leukemia	Diagnostic, Prognostic, Therapeutic, Monitoring
B-ALL	Diagnostic, Prognostic, Monitoring
B-Cell NHL/ Plasma Cell Dyscrasia	Diagnostic, Prognostic, Monitoring
Myelodysplasia	Diagnostic, Prognostic, Monitoring
Myeloproliferative Diseases	Diagnostic, Prognostic, Therapeutic, Monitoring

Pediatric Hematologic Malignancies	Patient age under 21 years
T-ALL	Diagnostic, Prognostic, Monitoring
T-Cell NHL	Diagnostic, Prognostic

Testing for other types of cancers is considered **INVESTIGATIONAL**.

Inclusion of any additional genes in the panel is considered **INVESTIGATIONAL**.

Medicare HMO Blue[SM] and Medicare PPO Blue[SM] Members

Medical necessity criteria and coding guidance for **Medicare Advantage members living in Massachusetts** can be found through the links below.

Local Coverage Determinations (LCDs) for National Government Services, Inc.

Local Coverage Determination (LCD): Genomic Sequence Analysis Panels in the Treatment of Non-Small Cell Lung Cancer (L36376)

Local Coverage Determination (LCD): Genomic Sequence Analysis Panels in the Treatment of Acute Myelogenous Leukemia (AML) (L36926)

Local Coverage Determination (LCD): Genomic Sequence Analysis Panels in the Treatment of Hematolymphoid Diseases (L37606)

Note: To review the specific LCD, please remember to click "accept" on the CMS licensing agreement at the bottom of the CMS webpage.

For medical necessity criteria and coding guidance for **Medicare Advantage members living outside of Massachusetts**, please see the Centers for Medicare and Medicaid Services website at https://www.cms.gov for information regarding your specific jurisdiction.

Prior Authorization Information

Inpatient

- For services described in this policy, precertification/preauthorization **IS REQUIRED** for all products if the procedure is performed **inpatient**.

Outpatient

- For services described in this policy, see below for products where prior authorization **might be required** if the procedure is performed **outpatient**.

	Outpatient
Commercial Managed Care (HMO and POS) **Commercial PPO and Indemnity**	The requirements of BCBSMA Genetic Testing Management Program require prior authorization via AIM Specialty Health. These requirements are member-specific: Please verify member eligibility and requirements through **Online Services** by logging onto **Provider Central**. Refer to our ***Quick Tip*** for an overview of pre-certification and prior authorization requirements. Ordering clinicians should request prior authorization from **AIM Specialty Health**. **AIM's ProviderPortal**[SM] registration is required or call 1-866-745-1783 (when applicable).

Medicare HMO Blue **Medicare PPO Blue**	Prior authorization through AIM Specialty Health is not required for Medicare Advantage products. Please see the appropriate National Coverage Determination (NCD) or Local Coverage Determination (LCD) through the **CMS website** for specific genetic testing guidelines.

CPT Codes / HCPCS Codes / ICD Codes

Inclusion or exclusion of a code does not constitute or imply member coverage or provider reimbursement. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage as it applies to an individual member.

Providers should report all services using the most up-to-date industry-standard procedure, revenue, and diagnosis codes, including modifiers where applicable.

The following codes are included below for informational purposes only; this is not an all-inclusive list.

The above medical necessity criteria MUST be met for the following codes to be covered for Commercial Members: Managed Care (HMO and POS), PPO, Indemnity, Medicare HMO Blue and Medicare PPO Blue:

CPT Codes

CPT codes:	Code Description
81445	Targeted genomic sequence analysis panel, solid organ neoplasm, DNA analysis, and RNA analysis when performed, 5-50 genes (eg, ALK, BRAF, CDKN2A, EGFR, ERBB2, KIT, KRAS, NRAS, MET, PDGFRA, PDGFRB, PGR, PIK3CA, PTEN, RET), interrogation for sequence variants and copy number variants or rearrangements, if performed
81450	Targeted genomic sequence analysis panel, hematolymphoid neoplasm or disorder, DNA analysis, and RNA analysis when performed, 5-50 genes (eg, BRAF, CEBPA, DNMT3A, EZH2, FLT3, IDH1, IDH2, JAK2, KRAS, KIT, MLL, NRAS, NPM1, NOTCH1), interrogation for sequence variants, and copy number variants or rearrangements, or isoform expression or mRNA expression levels, if performed
81455	Targeted genomic sequence analysis panel, solid organ or hematolymphoid neoplasm, DNA analysis, and RNA analysis when performed, 51 or greater genes (eg, ALK, BRAF, CDKN2A, CEBPA, DNMT3A, EGFR, ERBB2, EZH2, FLT3, IDH1, IDH2, JAK2, KIT, KRAS, MLL, NPM1, NRAS, MET, NOTCH1, PDGFRA, PDGFRB, PGR, PIK3CA, PTEN, RET), interrogation for sequence variants and copy number variants or rearrangements, if performed
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

Description

Advances in cancer care over the past two decades have shown improved outcomes, as compared to conventional cytototoxic chemotherapies, when treatment targets biological "pathways" that are characterized by specific genetic markers. Genetic testing offers the potential to evaluate molecular markers that identify the specific pathways that should be targeted in each patient's cancer. For some cancers, specific genetic tests are standard-of-care determinants for FDA-approved targeted therapies and are incorporated into professional practice guidelines from the National Comprehensive Cancer Network (NCCN). For other cancers, genetic tests are used to exclude the use of a targeted therapy and shift the focus of treatment instead towards other modalities. In still other cancers, genetic tests are used to indicate suitability for treatment with an investigational agent, as an alternative to an ineffective traditional therapy that is expected to have marginal, if any, benefit. Finally, genetic testing of cancer samples can be used to establish a definitive diagnosis or for stratification into risk-based treatment groups.

While individual gene tests have proven utility in these contexts, recent technical advances, in particular "next generation" or "massively parallel" sequencing (NGS), have enabled the simultaneous assessment of these markers in a single assay run. For patients, physicians, and laboratories, the advantages of the NGS panel tests are (1) more efficient use of limited samples, (2) more rapid time to a completed set of results, (3) more efficient resource utilization compared to performing multiple individual tests, (4) better ability to rapidly incorporate new genes into a panel in order to support clinical decision making since evidence in the field is rapidly evolving, and (5) identification of unexpected clinically actionable mutations that are not customarily associated with the tissue type of the tumor.

NGS-based genetic panels that test for a large number of cancer-associated mutations are commercially available and implemented currently as laboratory-developed tests (LDTs) offered primarily by academic centers and commercial laboratories. Clinical validity and clinical utility have been established for a number of individual genes and sets of genes in specific cancer types, based primarily upon single gene companion diagnostic assays. In this regard, NGS panels are a valid and useful technical means to efficiently combine multiple individually valid single gene tests, in defined clinical contexts where those single gene tests are also valid and useful. A growing body of evidence supports the use of expanded panel testing in selected tumor types. The evidence shows that for selected tumors, expanded panel testing reveals “driver mutations”, (mutations that activate signaling pathways which cause uncontrolled tumor cell growth) for which there are known and/or investigational drugs that will improve outcomes in patients with these tumors in comparison to conventional cytotoxic therapy.

RATIONALE

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

Analytic Validity

Multiple studies have demonstrated the analytic accuracy of next generation sequencing to be greater than 99%. Initial demonstration and ongoing maintenance of analytic validity is a legal requirement for clinical laboratories operating under the Clinical Laboratories Information Act (CLIA). Laboratories that perform NGS panels must possess valid CLIA certification and must be prepared to provide documentation of their certification status, CLIA inspection reports, and performance in proficiency testing (PT) programs, if requested. Testing in non-CLIA laboratories is not appropriate.

Clinical Validity of Expanded Tumor Genomic Profiling

The goal of genomic test panels in cancer is to identify molecular genetic alterations that, in the appropriate context, provide clinical benefit, either in terms of establishing a diagnosis, selecting a molecularly-targeted therapy, or determining prognosis in a way that has a tangible patient impact, such as influencing therapeutic decisions such as whether or not to undergo a bone marrow transplant, a high intensity chemotherapeutic or radiotherapy regimen, surgical procedures, or palliative care. These classes of alterations are collective considered "actionable" in terms of their clinical potential. While different studies have used different definitions and "tier"-based classification schemes for actionability, several studies have shown that genomic sequencing panels afford the ability to detect actionable mutations in a high percentage of patients within diverse cancer populations. Diagnostic sensitivity for actionable alterations has ranged from 30% to 90%, depending on the population studied.[1-6] Clinical experience with the panels addressed in this medical policy indicates that actionable mutations are found in 58.5% of tested tumors (personal communication from Brigham and Women’s Laboratory for Molecular Diagnostics).[7]

Clinical Utility of Expanded Tumor Genomic Profiling

Research over the past 20 years has clearly demonstrated that cancer is caused by mutations in one or more genes in a cell that result in overriding the normal mechanisms that inhibit growth and reproduction of the cell and cause the cell to divide and multiply despite the signals in the cell’s environment that

should inhibit its growth and division. The association between specific mutations (often know as driver mutations) in particular genes and cancer has been well established through conventional technologies including Sanger sequencing, genotyping, PCR, and others. The mechanism of action of these "driver mutations" has been confirmed by the in vitro, in vivo, and clinical efficacy of compounds that serve as inhibitors in the altered signaling pathways of cancer cells. Many "targeted therapies" (therapeutic compounds that have inhibitory properties in the signaling pathways known to be driving uncontrolled growth and division due to a particular mutation) have been approved by the FDA for treatment of different cancers that contain the driver mutation associated with the effective therapeutic compound. The outcomes of targeted therapies have been impressive in comparison to conventional cytotoxic chemotherapy particularly when effective cytotoxic regimens have failed.

Typically, a limited number of driver mutations are associated with a cancer of a particular tissue-type. In practice, when a cancer of a particular tissue type is identified, analyses of the commonly associated genes are run to determine if the particular tumor has an "actionable mutation", that is, a driver mutation against which a drug is known to be effective in controlling the progression of the disease. With the ability to identify new compounds that are active in inhibiting different pathways, there has been a rapid expansion of drugs (targeted therapies) that are effective against tumors with different driver mutations.

As next generation sequencing technology has been introduced into clinical practice, it has become more effective and efficient to analyze tumor tissue-associated genes concurrently as a panel rather than sequencing each individual gene separately. Evidence supporting the use of somatic cancer panels for the management of patients is rapidly progressing. Retrospective analysis of phase I molecularly targeted trials at a single cancer center has indicated improved response rates, progression-free survival and overall survival in patients whose tumors were genotyped and matched to a targeted agent.[8] Looking across cancer centers, the multi-institutional Lung Cancer Mutation Consortium demonstrated improved patient outcomes for patients with advanced lung cancers when a panel of molecular biomarkers were assessed and used to guide treatment decisions.[9] An unexpected benefit of concurrently analyzing many genes for mutations is the discoveries that mutations are found that are not typically associated with the cancer's tissue-type, yet are known to be driver mutations in a different tissue-type.[10-13] Treating these cancers with a drug (targeted therapy) known to be active in the unexpected driver pathway has led to significantly improved outcomes.

There is documentation in the clinical literature that each of the genes included in this panel has clinical utility in one of the following ways:

- The mutation is a driver mutation that causes the uncontrolled growth and proliferation of the tumor cells and that by finding the mutation, a targeted therapy that is effective in slowing the growth of the cancer is available.
- The mutation indicates that a targeted therapy selected on the basis of a different (driver) mutation will be ineffective.
- The mutation is characteristic of a cancer whose origin cannot be determined by histologic and immunochemical means and helps make the diagnosis.
- The mutation may indicate prognosis that influences treatment unrelated to targeted therapies, such as decisions around bone marrow transplantation, high-intensity or low-intensity chemotherapy or radiation therapy, surgery, or palliation.

In addition to identifying mutations that are known to be associated with particular tumor tissue types, the panel provides additional clinical utility by identifying mutations in a particular tumor specimen that are not typically associated with that tissue type but may be the actual driver mutation of that specimen. This gives the oncologist the option of treating the patient with a targeted therapy that would otherwise not have been available to this patient. Tables 2a and 2b provide examples of genetic panels that meet the clinical intent of this policy.

Table 2a. Genes and analyses included in NGS Solid Tumor Panel

Gene	Hotspots	All exons	Copy number	Fusions	Gene	Hotspots	All exons	Copy number	Fusions
AKT1	H				MDM2			C	
ALK	H			F	MET	H		C	F
APC		E	C		MLH1		E		
ARID1A		E			MSH2		E		
ATM		E			MSH6		E		
BRAF	H			F	MYC			C	
BRCA1		E			MYCN			C	
BRCA2		E			NF1		E	C	
CCND1	H		C		NOTCH1	H			
CCNE1			C		NRAS	H			
CDH1		E			NTRK1		E		F
CDK4	H		C		NTRK2		E		F
CDKN2A		E	C		NTRK3		E		F
CTNNB1	H				PALB2		E		
DDR2		E			PDGFRA	H			
EGFR	H		C	F	PIK3CA	H		C	
ERBB2	H		C	F	PIK3R1		E		
ERBB3		E			PMS2		E		
ESR1	H			F	PTCH		E	C	
FGFR1	H		C	F	PTEN		E	C	
FGFR2	H		C	F	RB1		E	C	
FGFR3	H		C	F	RELA				F
GATA3		E			RET	H			F
GLI2		E	C		ROS1		E		F
GNA11	H				SMAD2		E		
GNAQ	H				SMAD4		E		
GNAS	H				SMARCA4		E		
HRAS	H				SMARCB1			C	
IDH1	H				SMO	H			
IDH2	H				STAG2		E		
KIT	H				STK11		E	C	
KRAS	H		C		SUFU		E	C	
MAP2K1	H				TP53		E	C	

					TSC1		E	C	
					TSC2		E	C	

Table 2b. Genes and analyses included in Hematologic Malignancy NGS Panel

Gene	Hotspots	All exons	Copy number	Gene	Hotspots	All exons	Copy number
ABL1		E		JAK2	H		
ASXL1		E		KIT	H		
ATM		E	C	KRAS	H		
BCL6			C	MAP2K1	H		
BCOR		E		MPL	H		
BRAF	H			MYD88	H		
CALR	H			NOTCH1		E	
CBL	H			NOTCH2		E	
CBLB		E	C	NPM1	H		
CEBPA		E		NRAS	H		
CHEK2	H			PDGFRA	H		
CREBBP	H			PTEN		E	C
CSF3R	H			RB1		E	C
CXCR4		E		RUNX1		E	
DNMT3A	H			SETBP1	H		
EZH2	H			SF3B1	H		
FBXW7	H			SRSF2	H		
FLT3	H			STAT3	H		
GATA2	H			TET2		E	
GATA3	H			TP53		E	C
IDH1	H			U2AF1	H		
IDH2	H			WT1		E	
IKZF1			C	ZRSR2		E	

The quantity of DNA obtained from a sample of tumor tissue can frequently be a limiting factor in obtaining an accurate and complete analysis. It can also limit the ability to repeat the genomic analysis on the same piece of tumor tissue. As evidence emerges that mutations in genes on the panel in cancers in which the mutations are not typically found are susceptible to new compounds, the presence of these mutations in a particular patient's tumor has already been established, avoiding the need to re-run the specimen.

The turn-around time of one large genomic analysis is shorter than multiple analyses, and can result in earlier treatment.

Summary

Tumor marker genomic analysis has been shown to reliably identify driver mutations that initiate proliferation of tumor cells. Expanded molecular panel testing provides the information needed for targeted cancer therapies and also increases efficiencies by providing a large amount of data in a short amount of time. Clinical outcomes can be directly impacted in certain cancers when particular driver mutations are known and treatment can be tailored appropriately. Therefore, expanded molecular panel testing is considered medically necessary for specific genetic panels where the identified tumor markers have known treatment options.

Policy History

Date	Action
4/2019	Policy revised to indicate coverage for pancreatic tumors and metastatic castration-resistant prostate cancer added under table 1a. ATM, PALB2, MLH1, PMS2, MSH2 genes added under solid tumor panel table 2a. MAP3K1, MDM4, ERBB4 genes removed from solid tumor panel table 2a. Pediatric tumor testing under 1a and pediatric hematologic malignancy testing under table 1b revised to age 21. References added. Effective 4/1/2019.
12/2018	Policy clarified to indicate coverage for pediatric tumors under table 2a and pediatric hematologic malignancies under table 2b.
10/2018	Clarified coding information.
9/2018	Clarified coding information.
8/2018	Local Coverage Determination (LCD): Genomic Sequence Analysis Panels in the Treatment of Hematolymphoid Diseases (L37606) added. Effective date 8/1/2018.
4/2018	Clarified coding information.
3/2018	Diagnostic Exchange (DEX) registration requirement removed.
10/2017	Clarified coding information.
1/2017	Glioblastoma and Medulloblastoma indications clarified. Effective 1/1/2017.
8/2016	Table 2a. Solid Tumor NGS Panel Testing clarified to include B- Cell NHL and T-Cell NHL. Clarified coding information.
7/2016	New medical policy describing medically necessary and investigational indications. Effective 7/1/2016.

Information Pertaining to All Blue Cross Blue Shield Medical Policies

Click on any of the following terms to access the relevant information:
Medical Policy Terms of Use
Managed Care Guidelines
Indemnity/PPO Guidelines
Clinical Exception Process
Medical Technology Assessment Guidelines

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Endnotes

[1] Based on expert opinion