Prior Authorization Review Panel
MCO Policy Submission

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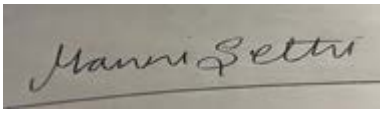
Plan: Keystone First Community HealthChoices	**Submission Date**: 5/1/2024
Policy Number: ccp.1483	**Effective Date:** 5/2021 **Revision Date:** April 1, 2024
Policy Name: Molecular testing for sarcoma	
Type of Submission – Check all that apply: **New Policy** **x Revised Policy*** **Annual Review – No Revisions** **Statewide PDL**	
***All revisions to the policy must be highlighted using track changes throughout the document.** **Please provide any clarifying information for the policy below:** See tracked changes below.	
Name of Authorized Individual (Please type or print): Manni Sethi, MD, MBA, CHCQM	**Signature of Authorized Individual:** 

Keystone First
Community HealthChoices

Molecular testing for sarcoma

Clinical Policy ID: CCP.1483

Recent review date: 4/2024

Next review date: 8/2025

Policy contains: Genetic testing; molecular testing; personalized medicine; sarcoma; targeted therapy.

Keystone First Community HealthChoices has developed clinical policies to assist with making coverage determinations. Keystone First Community HealthChoices' clinical policies are based on guidelines from established industry sources, such as the Centers for Medicare & Medicaid Services (CMS), state regulatory agencies, the American Medical Association (AMA), medical specialty professional societies, and peer-reviewed professional literature. These clinical policies along with other sources, such as plan benefits and state and federal laws and regulatory requirements, including any state- or plan-specific definition of "medically necessary," and the specific facts of the particular situation are considered by Keystone First Community HealthChoices when making coverage determinations. In the event of conflict between this clinical policy and plan benefits and/or state or federal laws and/or regulatory requirements, the plan benefits and/or state and federal laws and/or regulatory requirements shall control. Keystone First Community HealthChoices' clinical policies are for informational purposes only and not intended as medical advice or to direct treatment. Physicians and other health care providers are solely responsible for the treatment decisions for their patients. Keystone First Community HealthChoices' clinical policies are reflective of evidence-based medicine at the time of review. As medical science evolves, Keystone First Community HealthChoices will update its clinical policies as necessary. Keystone First Community HealthChoices' clinical policies are not guarantees of payment.

Coverage policy

As the landscape for targeted therapies is rapidly evolving, the medical necessity of molecular testing in oncology is indicated according to the National Comprehensive Cancer Network clinical practice guidelines and U.S. Food and Drug Administration-approved package labeling for indication and usage.

Molecular testing for sarcoma is clinically proven and, therefore, may be medically necessary as a diagnostic approach (ancillary to microscopic examinations of histologic sections) for any of 59 genetic variants, covering 29 forms of sarcoma, that indicate potential for personalized treatment (National Comprehensive Cancer Network, 2023, 2024). Also see list of variants in the appendix.

Molecular testing is clinically proven and therefore, may be medically necessary for members with metastatic or refractory sarcoma subtypes to determine candidacy for an approved targeted therapy (National Comprehensive Cancer Network, 2023, 2024).

In addition to the list of variants in the appendix, testing for the following molecular variants is clinically proven and therefore, may be medically necessary (National Comprehensive Cancer Network, 2024):

- Susceptible isocitrate dehydrogenase-1 variants by next-generation sequencing or targeted exon sequencing.
- Microsatellite instability-high using polymerase chain reaction testing or mismatch repair deficiency using immunohistochemistry.
- Tumor mutational burden-high status using the FoundationOne CDx (Foundation Medicine, Inc., Cambridge, Massachusetts) molecular test (U.S. Food and Drug Administration, 2023).

Limitations

No limitations were identified during the writing of this policy.

Alternative covered services

No alternative covered services were identified during the writing of this policy.

Background

Sarcoma is a composite of various cancers that develop in the soft tissue or bone. Soft tissue sarcoma is more common among adults, while bone sarcoma is more common among children. In 2023, the American Cancer Society estimates 13,590 new cases of soft tissue sarcomas and 3,970 new cases of bone sarcoma diagnosed in the United States. The most prevalent subtypes of soft tissue sarcoma are undifferentiated pleomorphic sarcoma (previously called malignant fibrous histiocytoma), liposarcoma, and leiomyosarcoma, while osteosarcoma, chondrosarcoma, and Ewing's sarcoma are the most common bone sarcoma subtypes (American Cancer Society, 2023a, 2023b).

Known risk factors for sarcoma include (American Cancer Society, 2018):

- Radiation given to treat other cancers.
- Damaged lymph systems.
- Exposure to certain chemicals.
- Certain family cancer syndromes caused by genetic defects, including neurofibromatosis (also known as von Recklinghausen disease), Gardner syndrome, Li-Fraumeni syndrome, retinoblastoma, Werner syndrome, Gorlin syndrome, and tuberous sclerosis.

Sarcomas are rare and heterogeneous often with overlapping morphologic and immunohistochemical findings, and misdiagnosis can occur. Microscopic examination of histologic sections is essential for diagnosing sarcoma. Ancillary techniques used to support histologic diagnosis include immunohistochemistry, classic cytogenics, electron microscopy, and molecular genetic testing (National Comprehensive Cancer Network, 2023).

Interest in advanced molecular testing has emerged for its potential to improve prognosis, diagnosis, and treatment management, as many soft tissue sarcoma subtypes are associated with characteristic genetic variants, e.g., single base pair substitutions, deletions, amplifications, and translocations. In a study of 384 sarcoma patients in French referral centers (2009 – 2012), molecular testing modified diagnosis in 14% of the cases, altering primary care and patient management in 12% (Italiano, 2016).

Several targeted treatments are available for certain histologic subtypes of advance or metastatic soft tissue sarcoma. Most are tyrosine kinase inhibitors, other than oralatumab (platelet-derived growth factor) and tazemetostat (enhancer of zeste homolog 2). Tumor-agnostic treatments approved for solid tumors, such as neurotrophic receptor tyrosine kinase inhibitors and immune checkpoint inhibitors, may be used (American Society of Clinical Oncology, 2022). In 2022, the U.S. Food and Drug Administration approved one immune checkpoint inhibitor, atezolizumab (Genentech, Inc., San Francisco, California), for treatment of unresectable or metastatic alveolar soft part sarcoma (U.S. Food and Drug Administration, 2022).

Several kinase inhibitors are available to treat primary bone cancer subtypes, such as chordomas that have metastasized or recurred after treatment (American Cancer Society, 2021). One immune checkpoint inhibitor, pembrolizumab (Merck & Co., Inc., Rahway, New Jersey), may be used for patients with no satisfactory alternative treatment options and with advanced or metastatic solid tumors exhibiting either:

- Microsatellite instability-high using polymerase chain reaction testing or mismatch repair deficiency using immunohistochemistry.
- Tumor mutational burden-high (≥ 10 mutations/megabase) using a U.S. Food and Drug Administration-approved molecular test. The FoundationOne CDx (Foundation Medicine, Inc., Cambridge, Massachusetts) has been approved for this indication (U.S. Food and Drug Administration, 2023).

Findings

The National Comprehensive Cancer Network guideline on soft tissue sarcoma declares ancillary techniques such as molecular genetic testing to be "useful in support of morphological diagnoses," and says that "sarcoma diagnosis should be carried out by pathologists who have access to these ancillary methods." The guideline lists 29 types of sarcoma tumors, along with 59 genetic aberrations (see appendix), each with one or more genes involved that may be useful in personalized treatment. The guideline notes that most molecular testing applies (National Comprehensive Cancer Network, 2023):

- Fluorescence in situ hybridization.
- Polymerase chain reaction methods.
- Next-generation sequencing-based methods.

Choice of methods will depend on the individual tumor and clinical need. The Network further notes that next-generation sequencing should not replace expert pathology review, as it only rarely results in a diagnosis change following expert review (National Comprehensive Cancer Network, 2023).

A guideline developed by Cancer Care Ontario's Program in Evidence-Based Care and the Sarcoma Disease Site Group includes three strong recommendations for molecular testing (Yao, 2020):

- MDM2 amplification by fluorescence in situ hybridization, as a sensitive and specific test to differentiate patients with atypical lipomatous tumor/well-differentiated liposarcoma, or dedifferentiated liposarcoma from lipoma or other STS in the differential diagnosis.
- SS18 (SYT) break-apart by FISH or SS18-SSX (SYT-SSX) fusion by reverse transcription-polymerase chain reaction is recommended, as a sensitive and specific test to differentiate patients with synovial sarcoma from other sarcomas.
- CTNNB1 S45F mutation by polymerase chain reaction, as a prognostic factor for poor recurrence-free survival in patients with desmoid tumors.

The guideline also includes 14 recommendations, nine qualified statements, and seven "no recommendations" (Yao, 2020).

A panel of experts notes that research has identified chromosomal translocations involving the NTRK1, NTRK2, and NTRK3 genes (TRK fusions) in pediatric cancers, including undifferentiated sarcomas. As selective TRK inhibitors, such as larotrectinib, which had a 75% response rate across children and adults with TRK fusion cancers, may be appropriate treatment, the group recommends screening these pediatric tumors for presence of TRK fusions, by fluorescence in situ hybridization or immunohistochemistry (Albert, 2019).

A systematic review/meta-analysis of 70 studies, covering 13 subtypes of soft tissue sarcomas, showed that:

- The test of detecting MDM2 amplification by fluorescence in situ hybridization was accurate in differentiating atypical lipomatous tumor/well-differentiated liposarcoma/dedifferentiated liposarcoma from:

    - Benign tumors (n = 971, sensitivity = 95%, specificity = 100%).
    - Other soft tissue sarcomas (n = 347; sensitivity = 99%, specificity = 90%).
- The test of detecting SS18-SSX fusion by reverse transcription polymerase chain reaction was accurate in differentiating synovial sarcoma from other soft tissue sarcomas (n = 532; sensitivity = 93%, specificity = 99%).
- Presence of a CTNNB1 S45F mutation detected by polymerase chain reaction was a risk factor for reduced recurrence-free survival in desmoid tumors (n = 418) (Kandel, 2018).

A systematic review/meta-analysis of 32 case-control studies (n = 15,336) analyzed 24 single nucleotide variants in 14 genes. Twelve variants in CTLA-4, IL-8, MDM2, PRCKG, RECQL5, TNF-a, TP53, XRCC3, and VEGF correlated with osteosarcoma risk. Authors view the study as a powerful tool for tracking the most viable genes for osteosarcoma (Wang, 2018).

In a meta-analysis of seven studies (n = 1,404), potential association of ERCC1 and ERCC2 polymorphisms with osteosarcoma survival prognosis after chemotherapy showed no significant association under dominant, recessive, or allelic models for rs11615, (*P* = .235, *P* = .095, *P* = .165), rs13181 (*P* = .801, *P* = .944, *P* = .870), and rs1799793 (*P* = .322, *P* = .750, *P* = .450) (Liu, 2018).

A meta-analysis of 12 studies (n = 491) of primary osteosarcoma in children showed the loss of the retinoblastoma-1 gene function results in a 62% increase in mortality (*P* = .0006), an increase in metastasis (*P* = .0004), and a reduction in the histological response of osteosarcoma to chemotherapy (*P* = .038). The findings indicate alterations may serve as a prognostic marker for the management of osteosarcoma patients (Ren, 2017).

A systematic review/meta-analysis of 10 studies (n = 902) of persons with synovial sarcoma reviewed the prognostic value of testing for the SS18-SSX fusion gene, and found:

- Overall survival or disease-specific survival showed predictive value was not significant (*P* = .29).
- Presence of SS18-SSX1 may indicate a lower progression-free or metastasis-free survival probability than that of SS18-SSX2 (borderline significant at *P* = .09) (Kubo, 2015).

A meta-analysis of 13 studies (n = 703) observed that high p53 expression correlated with poor overall survival and disease-free survival in osteosarcoma and Ewing's sarcoma, each significant at P < .001 (Jiang, 2013).

A meta-analysis of 225 patients with rhabdomyosarcoma (non-metastatic) from two studies found those who were PAX3/FOXO1 positive had a significantly poorer (*P* < .001) outcome three years after treatment compared with both alveolar-negative and PAX7/FOXO1-positive patients (Missiaglia, 2012).

In 2022, we updated the references and added new medical necessity criteria based on a National Comprehensive Cancer Network guideline (2021) for primary bone cancer. The new guideline recommends comprehensive genetic profiling with a validated or U.S. Food and Drug Administration-approved assay to identify targeted therapy opportunities for various metastatic bone sarcoma subtypes. Multiple genetic variants are implicated in bone sarcoma, many of which overlap with the genetic variants found in soft tissue sarcoma (see appendix). In addition, the following molecular tests are recommended for targeted therapy provision for primary bone sarcoma:

- Testing for susceptible isocitrate dehydrogenase-1 mutations by next-generation sequencing or targeted exon sequencing to assess candidacy for ivosidenib.
- Testing for microsatellite instability-high using polymerase chain reaction testing or mismatch repair deficiency using immunohistochemistry to inform the use of pembrolizumab.

- Testing for tumor mutational burden-high status to inform the use of pembrolizumab in patients with unresectable or metastatic disease solid tumors that have progressed following prior treatment and who have no satisfactory treatment alternatives.

In 2023, we updated the references, including National Comprehensive Cancer Network guidelines, and added no new relevant studies to the policy. No policy changes are warranted.

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References

On February 7, 2024, we searched PubMed and the databases of the Cochrane Library, the U.K. National Health Services Centre for Reviews and Dissemination, the Agency for Healthcare Research and Quality, and the Centers for Medicare & Medicaid Services. Search terms were “genetic testing,” “molecular testing,” “sarcoma” (MeSH), “molecular diagnostic techniques” (MeSH), “personalized medicine,” “sarcoma,” and “targeted therapy.” We included the best available evidence according to established evidence hierarchies (typically systematic reviews, meta-analyses, and full economic analyses, where available) and professional guidelines based on such evidence and clinical expertise.

Albert CM, Davis JL, Federman N, Casanova M, Laetsch TW. TRK fusion cancers in children: A clinical review and recommendations for screening. *J Clin Oncol*. 2019;37(6):513-524. Doi: 10.1200/JCO.18.00573.

American Cancer Society. Risk factors for soft tissue sarcomas. https://www.cancer.org/cancer/soft-tissue-sarcoma/causes-risks-prevention/risk-factors.html. Last revised April 6, 2018.

American Cancer Society. Key statistics about bone cancer. https://www.cancer.org/cancer/types/bone-cancer/about/key-statistics.html. Published 2023. (a)

American Cancer Society. Key statistics for soft tissue sarcomas. https://www.cancer.org/cancer/types/soft-tissue-sarcoma/about/key-statistics.html . Published 2023. (b)

American Society of Clinical Oncology. https://www.cancer.net/cancer-types/sarcomas-soft-tissue/types-treatment. Approved June 2022.

American Cancer Society. Targeted therapy and other drugs for bone cancer. https://www.cancer.org/cancer/bone-cancer/treating/targeted-therapy.html. Last revised June 17, 2021.

Italiano A, Di Maguro ID, Rapp J, et al. Clinical effect of molecular methods in sarcoma diagnosis. (GENSARC): A prospective, multicentre, observational study. *Lancet Oncol*. 2016;17(4):532-538. Doi: 10.1016/S1470-2045(15)00583-5.

Jiang L, Tao C, He A. Prognostic significance of p53 expression in malignant bone tumors: A meta-analysis. *Tumour Biol*. 2013;34(2):1037-1043. Doi: 10.1007/s13277-012-0643-5.

Kandel RA, Yao X, Dickson BC, et al. Molecular analyses in the diagnosis and prediction of prognosis in non-GIST soft tissue sarcomas: A systematic review and meta-analysis. *Cancer Treat Rev*. 2018;66:74-81. Doi: 10.1016/j.ctrv.2018.04.005.

Kubo T, Shimose S, Fukumori J, Furuta T, Ochi M. Prognostic value of SS18-SSX fusion type in synovial sarcoma: Systematic review and meta-analysis. *Springerplus*. 2015;4:375. Doi: 10.1186/s40064-015-1168-3.

Liu D, Liu X. Genetic polymorphisms of ERCC-1 and ERCC-2 are not prognostic markers in osteosarcoma patients with chemotherapy: A meta-analysis in Chinese population. *Medicine (Baltimore)*. 2018;97(49):e13358. Doi: 10.1097/MD.0000000000013358.

Missiaglia E, Williamson D, Chisholm J, et al. PAX3/FOXO1 fusion gene status is the key prognostic molecular marker in rhabdomyosarcoma and significantly improves current risk stratification. *J Clin Oncol*. 2012;30(14):1670-31677. Doi: 10.1200/JCO.2011.38.5591.

National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology. (NCCN Guidelines®). Bone cancer. Version 1.2024. www.nccn.org. Updated August 7, 2023.

National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology. (NCCN Guidelines®). Soft tissue sarcoma. Version 3. 2023. www.nccn.org. Updated December 12, 2023.

Ren W, Gu G. Prognostic implications of RB1 tumour suppressor gene alterations in the clinical outcome of human osteosarcoma: A meta-analysis. *Eur J Cancer Care (Engl)*. 2017;26(1). Doi: 10.1111/ecc.12401.

U.S. Food and Drug Administration. List of cleared or approved companion diagnostic devices (in vitro and imaging tools). https://www.fda.gov/medical-devices/in-vitro-diagnostics/list-cleared-or-approved-companion-diagnostic-devices-in-vitro-and-imaging-tools. Content current as of December 21, 2023.

U.S. Food and Drug Administration. TECENTRIQ® (atezolizumab) injection, for intravenous use. Product label. Initial U.S. Approval: 2016 https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/761034s047lbl.pdf. Recent change December 2022.

Wang X, Liu Z. Systematic meta-analysis of genetic variants associated with osteosarcoma susceptibility. *Medicine (Baltimore)*. 2018;97(38):e12525. Doi: 10.1097/MD.0000000000012525.

Yao X, Ghert M, Dickson BC, et al. An evidence-based guideline on the application of molecular testing in the diagnosis, prediction of prognosis, and selection of therapy in non-GIST soft tissue sarcomas. *Cancer Treat Rev*. 2020;85:101987. Doi: 10.1016/j.ctrv.2020.101987.

Policy updates

4/2021: initial review date and clinical policy effective date: 5/2021

4/2022: Policy references updated. Coverage modified.

4/2023: Policy references updated.

4/2024: Policy references updated.

Appendix

Recurrent Genetic Aberrations in Sarcoma

TUMOR	ABERRATION	GENE(S) INVOLVED
<u>Malignant Round Cell Tumors</u>		
Alveolar rhabdomyosarcoma	t(2;13) (q35:q14) t(1;13) (p36:q14) t(X;2) (q13:q35)	PAX3::FOX01 PAX7::FOX01 PAX3::AFX
Desmoplastic small round cell tumor	t(11;22) (p13:q12)	EWSR1::WT1
Embryonal rhabdomyosarcoma	Complex alterations	MYOD1, KRAS, HRAS, TP53, NF1,

		NRAS, PIK3CA, FBXW7, FGFR4, BCOR
Ewing sarcoma/peripheral neuroectodermal tumor	t(11;22) (q24:q12) t(21;22) (q22:q12) t(2;22) (q33:q12) t(7;22) (q22:q12) t(17;22) (q12:q12) inv(22) (q12q:q12) t(16;21) (p11:q22)	EWSR1::FLI1 EWSR1::ERG EWSR1::FEV EWSR1::ETV1 EWSR1::E1AF EWSR1::ZSG FUS::ERG
Undifferentiated round cell sarcoma	t(4;19) (q35:q13); or t(10;19) (q26:q13) inv(X)p11 (4p11.22)	CIC::DUX BCOR::CCNB
<u>Lipomatous Tumors</u>		
Atypical lipomatous tumor/ well-differentiated liposarcoma (ALT-WDLS)	Supernumery ring chromosomes; giant marker chromosomes	Amplification of region 12q14-16, including MDM2, CDK4, HMGA2, SAS, GLI
Differentiated liposarcoma	Same as for ALT-WDLS	Same as for ALT::WDLS
Myxoid/round cell liposarcoma	t(12;16) (q13:p11) t(12;22) (q13:q12)	FUS::DDIT3 EWSR1::DDIT3
Pleomorphic liposarcoma	Complex alterations	Unknown
<u>Other Sarcomas</u>		
Alveolar soft part sarcoma	der(17) t(X:17) (p11:q26)	ASPL::TFE3
Angiomatoid fibrous histiocytoma	t(12;22) (q13:q12) t(2;22) (q33:q12) t(12;16) (q13:q11)	EWSR1::ATF1 EWSR1::CREB1 FUS::ATF1
Clear cell sarcoma	t(12;22) (q13:q12) t(2;22) (q33:q12)	EWSR1::ATF1 EWSR1::CREB1
Congenital/infantile fibrosarcoma	t(12;15) (q13:q25)	ETV6::NTRK3
Dermatofibrosarcoma protuberans	t(17;22) (q21:q13) and derivative ring chromosomes	COL1A1::PDGFB
Desmoid fibromatosis	Trisomy 8 or 20; loss of 5q21	CTNNB1 or APC mutations
High-grade endometrial stromal sarcoma	t(10;17) (q22:p13) t(x;22) (p11:q13)	YWHAE::NUTM2 ZC3H7B::BCOR

Epithelioid hemangioendothelioma	t(1;13) (p36:q25) t(X;11) (q22:p11,23)	WWTR1::CAMTA1 YAP1::TFP3
<u>Other Sarcomas</u>		
Epithelioid sarcoma	Inactivation, deletion, or mutation of IN1 (SMARCB-1)	IN1 (SMARCB-1)
Extrarenal rhabdoid tumor	Inactivation of IN1 (SMARCB-1)	IN1 (SMARCB-1)
Extraskeletal myxoid Chrondrosarcoma	t(9;22) (q22:q12) t(9;17) (q22:q11) t(9;15) (q22:q21) t(3;9) (q11:q22)	EWSR1::NR4A3 TAF2N::NR4A3 TCF12::NR4A3 TFG::NR4A3
Sporadic and familial GIST Carney-Stratakis syndrome (gastric GIST and paraganglioma)	Activating kinase mutations Krebs cycle mutations	KIT or PDGFRA Germline or SDH subunit mutations
Inflammatory myofibroblastic tumor	t(1;2) (q22:p23) t(2;19) (p23:p13) t(2;17) (q23:p23) t(2;2) (q23:p13) t(2;11) (q23:p15) inv(2) (p23:q35)	TPM3::ALK TPM4::ALK CTLC::ALK RANBP2::ALK CARS::ALK ATIC::ALK ETV6::NTRK3 TFG::ROS1
Leiomyosarcoma	Complex alterations	Unknown
Low-grade fibromyxoid sarcoma	t(7;16) (q33:p11) t(11;16) (p11:p11)	FUS::CREB3L2 FUS::CREB3L1
Malignant peripheral nerve sheath tumor		NF1, CDKN2A and EED or SUZ12
Mesenchymal chondrosarcoma	t(8;8) (q13:q21)	HEY1::NCOA2
Solitary fibrous tumor	inv(12) (q12:q13)	NAB2::STAT6
Synovial sarcoma	t(X;18) (p11:q11) t(X;18) (p11:q11) t(X;18) (p11:q11)	SS1B::SSX1 SS1B::SSX2 SS1B::SSX4
Tenosynovial giant cell tumor/ pigmented villonodular synovitis	CSF1 rearrangements	Multiple

Source: National Comprehensive Cancer Network (2023, 2024).