Prior Authorization Review Panel
MCO Policy Submission

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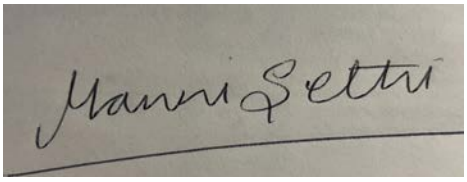
Plan: Keystone First Community Health Choices	**Submission Date**: 7/27/2023
Policy Number: ccp.1466	**Effective Date:** 8/2020 **Revision Date:** July 1, 2023
Policy Name: Molecular analysis for targeted treatment for hepatobiliary cancer	
Type of Submission – Check all that apply: **New Policy** **x 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 analysis for targeted treatment for hepatobiliary cancer

Clinical Policy ID: CCP.1466

Recent review date: 7/2023

Next review date: 11/2024

Policy contains: Biliary tract cancer; biomarker; cholangiocarcinoma; FGFR2; hepatocellular carcinoma; microsatellite instability; NTRK.

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 of targeted therapies is rapidly evolving, molecular analysis for targeted therapy for hepatobiliary cancer is clinically proven and, therefore, may be medically necessary for indications specified in National Comprehensive Cancer Network (2023a, 2023b) clinical practice guidelines and U.S. Food and Drug Administration-approved package labeling for indication and usage. Validated molecular testing should be performed in a Clinical Laboratory Improvement Amendments-approved laboratory or by a U.S. Food and Drug Administration-approved companion diagnostic test (see Appendix).

Molecular analysis for targeted treatment for hepatobiliary cancer is clinically proven and, therefore, may be medically necessary for the following indications, when the testing result will impact treatment provision:

- Neurotrophic tyrosine receptor kinase gene fusion testing to determine eligibility for larotrectinib and entrectinib as subsequent-line therapy in members with hepatobiliary cancer that is unresectable or metastatic or has progressed following primary treatment (National Comprehensive Cancer Network, 2023a, 2023b).
- Microsatellite instability/deficient mismatch repair testing to determine eligibility for pembrolizumab in members with primary biliary tract cancer that is unresectable or metastatic or has progressed following primary treatment (National Comprehensive Cancer Network, 2023a, 2023b).
- For members with microsatellite instability-high/mismatch repair-deficient tumors or a family history suggestive of breast cancer gene-1/2 mutations, germline testing or referral to a genetic counselor is considered medically necessary. Microsatellite instability-high is defined as having at least two of the five

markers of the validated core panel (Boland, 1998) showing instability or more than 30% of markers showing instability in other validated marker panels.

- Fibroblast growth factor receptor 2 fusion or rearrangement testing using FoundationOne® CDx (Foundation Medicine, Inc., Cambridge, Massachusetts) to determine eligibility for pemigatinib (Incyte Corp., Wilmington, Delaware) for the treatment of adults with previously treated, unresectable locally advanced or metastatic cholangiocarcinoma (U.S. Food and Drug Administration, 2021a, 2023).
- Tumor mutational burden to determine eligibility for pembrolizumab for members with unresectable or metastatic solid tumors that have progressed following prior treatment and who have no satisfactory alternative treatment options (National Comprehensive Cancer Network, 2023a, 2023b).
- Tumor mutational burden-high is defined as at least 10 mutations/megabase as determined by the FoundationOne CDx test.

For any determinations of medical necessity for medications, refer to the applicable state-approved pharmacy policy.

Limitations

Other molecular markers for predicting therapeutic response in hepatobiliary cancers are investigational/not clinically proven and not medically necessary.

Molecular testing to determine clinical trial eligibility is investigational/not clinically proven and not medically necessary.

Molecular testing using circulating tumor cells or circulating tumor deoxyribonucleic acid methods (also known as “liquid biopsy”) for predicting therapeutic response in hepatobiliary cancers is investigational/not clinically proven and not medically necessary.

The optimal choice for neurotrophic tyrosine receptor kinase gene fusion testing and microsatellite instability/mismatch repair testing will depend on availability of validated testing modalities and local considerations for each individual laboratory.

Next-generation sequencing tests for tumor profiling (e.g., Caris Molecular Intelligence® Tumor Profiling, Caris Life Sciences, Irving, Texas) that have not been approved or cleared by the U.S. Food and Drug Administration are investigational and, therefore, not medically necessary, as their clinical utility has not been established for predicting response to any targeted gene therapy for any cancer type.

Alternative covered services

- Multidisciplinary evaluation to assess liver reserve, comorbidity, and staging (e.g., history and physical, hepatitis panel, liver function panel, cross-sectional imaging, and tumor biopsy).
- Guideline-directed treatment (resection, transplantation, ablative methods, arterially directed therapy, radiation, and systemic therapy).

Background

Primary hepatobiliary cancers are rare but highly lethal tumors of the liver, gallbladder, and biliary tract (National Cancer Institute, 2023a). In 2019 in the United States, there were an estimated 42,030 new cases and 31,780 deaths from liver and intrahepatic bile duct cancer and an estimated 12,360 new cases and 3,960 deaths from gallbladder and other biliary cancers (Siegel, 2019). The prognosis for primary hepatobiliary cancers is generally poor due to the advanced nature of disease at presentation and overall treatment refractoriness.

In adults, malignant primary tumors originating in the liver include hepatocellular carcinoma (90% of cases) and intrahepatic cholangiocarcinoma (National Cancer Institute, 2023a). Among children with primary liver cancer,

hepatoblastoma and, to a far lesser extent, hepatocellular carcinoma are the main histologic subtypes (National Cancer Institute, 2023b). Most primary biliary tract cancers are either adenocarcinomas originating in the epithelium of the gallbladder or extrahepatic cholangiocarcinoma of the perihilar and distal biliary tree (National Cancer Institute, 2023a, 2023b).

The choice of available treatment options depends on histopathology, disease location, disease stage, hepatic functional reserve, and other factors. For patients with localized or recurrent disease and adequate functional hepatic reserve, surgical resection, ablation, and embolization are important treatment options, and some of these patients may be candidates for liver transplantation. In most cases, the tumors are unresectable or cannot be completely removed, and are often refractory to standard chemotherapy and radiation therapy regimens. Disease recurrence is common. For patients with unresectable disease, transarterial embolization, chemotherapy, and palliative therapy are options.

The pathogenetic mechanisms underlying development and progression of hepatobiliary cancers encompass growth factors and receptors, signaling pathways, and transcription factors that promote tumor cell survival, proliferation, and invasion (Marks, 2016; National Cancer Institute, 2023a, 2023b). For advanced disease, targeted therapeutics and immunotherapy options are available. Targeted therapeutics (e.g., multikinase inhibitors, isocitrate dehydrogenase 1 inhibitors, and fibroblast growth factor receptor 2 inhibitors) selectively inhibit the pathways that drive tumor development and growth. Several methods for identifying kinase gene fusions are available, including immunohistochemistry, fluorescence in situ hybridization, and sequencing.

Immunotherapy (e.g., nivolumab or pembrolizumab) blocks immune checkpoint molecules such as programmed death receptor or ligand for tumors with deficient mismatch repair or microsatellite instability-high mutations. Microsatellites are short, repeated nucleotide sequences that are particularly susceptible to errors that may occur when deoxyribonucleic acid is copied in the cell (National Cancer Institute, undated). Microsatellite instability is assessed using either a validated core panel of five microsatellite markers (Boland, 1998) or validated panels containing core plus additional markers. However, there is a lack of consensus on the utility of markers beyond the five designed by Boland (1998). Microsatellite instability is classified as high if at least two of the five markers of the core panel show instability or more than 30% of markers show instability in other marker panels. Next-generation sequencing methods have been used to detect microsatellite instability-high tumor status.

Research applying comprehensive tumor genomic profiling has identified differences in the molecular signatures of hepatocellular carcinoma, intrahepatic cholangiocarcinoma, extrahepatic cholangiocarcinoma, and gallbladder cancer that may have implications for prediction of treatment response of individual patients to particular therapeutic agents (Marks, 2016). The role of molecular diagnostics continues to evolve, as variable genomic alterations are emerging that may affect prognosis and overall disease outcome independent from their therapy selection value.

Findings

We identified two systematic reviews (Boscoe, 2019; Roos, 2019), one National Comprehensive Cancer Network (2020) evidence-based guideline, one narrative review of liquid biopsy techniques (Ye, 2019), three cohort studies of comprehensive molecular profiling (Cancer Genome Atlas Research Network, 2017; Lowery, 2018; Shibata, 2018), and no economic analyses for this policy. We also considered product labelling and regulatory requirements for companion diagnostics and targeted therapeutics for hepatobiliary carcinoma (U.S. Food and Drug Administration, 2020a, 2020b).

The evidence highlights the substantial research into identifying the molecular signatures of hepatobiliary cancers. Multiple molecular mutations have been implicated in hepatobiliary cancers and provide the basis for determining clinical trial eligibility and targeted treatment development, but relatively few molecular tests currently provide clinically actionable information for prognosis, diagnosis, or predicting treatment response.

Of emerging interest is the potential value of liquid biopsy methods that analyze circulating tumor cells and circulating tumor deoxyribonucleic acid shed from primary and metastatic tumors into the blood. This collection of tests attempts to overcome the limitations of tissue sampling by providing real-time, noninvasive genetic profiling of primary and metastatic tumors and dynamically tracking therapeutic response and tumor burden. However, the technology platforms for liquid biopsy vary, and testing methods require standardization and validation before the technology can be endorsed for routine use in guiding therapy provision or monitoring tumor burden (Ye, 2019).

The following molecular tests are validated predictors of treatment response in hepatobiliary cancers:

- Neurotrophic tyrosine receptor kinase gene fusion testing to determine eligibility for larotrectinib and entrectinib as subsequent-line therapy in patients with hepatobiliary cancer that is unresectable or metastatic or has progressed following primary treatment (National Comprehensive Cancer Network, 2020). A U.S. Food and Drug Administration-approved (2020a) companion diagnostic is not currently available.
- Microsatellite instability/mismatch repair testing to determine eligibility for the programmed death receptor-1 blockade drug pembrolizumab in patients with primary biliary tract cancer that is unresectable or metastatic or has progressed following primary treatment (National Comprehensive Cancer Network, 2020).
- The FoundationOne CDx test for detection of fibroblast growth factor receptor 2 fusion or rearrangement, to determine candidacy for the new kinase inhibitor pemigatinib for treatment of adults with previously treated, unresectable, locally advanced or metastatic cholangiocarcinoma (U.S. Food and Drug Administration, 2020a, 2020b).

Hepatocellular carcinoma

The Cancer Genome Atlas Research Network (2017) applied several integrated genomic platforms from a large set of participants (n = 363 total cases) with hepatocellular carcinoma. The findings from 196 participants confirmed frequent mutations in: 1) the telomerase reverse transcriptase promoter region associated with regulating cell survival; 2) tumor protein p53, one of the most frequently mutated genes in cancer; 3) catenin beta 1, which is a member of the wingless and Int-1 signaling pathway that mediates cell growth and differentiation; and 4) combinations of infrequent alterations in other cancer pathways.

Shibata (2018) reviewed the results of the above cohort and two other large cohorts from Japan and France to identify the major driver genes in hepatocellular carcinoma across ethnically diverse populations. They confirmed tumor protein p53, catenin beta 1, and telomerase reverse transcriptase as the core driver genes. These findings suggest multiple agents that specifically attack different identified targets may be needed to effectively treat all or most hepatocellular carcinoma subtypes.

The National Comprehensive Cancer Network (2020) recommends the multikinase inhibitors sorafenib and lenvatinib as first-line targeted treatments for patients with advanced disease, but the molecular targets responsible for their therapeutic effect are not known. In limited cases, larotrectinib and entrectinib may be offered as first-line systemic therapies for patients with neurotrophic tyrosine receptor kinase gene fusion-positive hepatocellular carcinoma. Testing for neurotrophic tyrosine receptor kinase gene fusions is conducted using next-generation sequencing. Several subsequent-line therapy options are available for patients with disease progression following systemic therapy, including other multikinase inhibitors and programmed death receptor-1 immune checkpoint inhibitors.

Biliary tract cancers

Biliary tract cancers are currently classified by anatomical origin. Results from the Cancer Genome Atlas Research Network and systematic reviews show that these cancers are genetically diverse with driver mutations

identified among distinct anatomic and clinical subtypes, which may be prognostic biomarkers or predictive of treatment response. Overlap in mutation profiles occurred across biliary tract cancer types but overlap occurred least frequently between intrahepatic cholangiocarcinoma and gallbladder carcinoma (Boscoe, 2019; Lowery, 2018; Roos, 2019).

In patients with biliary tract tumors that are unresectable or metastatic or have progressed following primary treatment, the National Comprehensive Cancer Network (2020) recommends: 1) microsatellite instability-high/deficient mismatch repair testing to determine candidacy for the programmed death receptor-1 blockade drug pembrolizumab; and 2) neurotrophic tyrosine receptor kinase gene fusion testing to assess candidacy for entrectinib or larotrectinib therapy.

Under an accelerated approval process, the U.S. Food and Drug Administration (2020b) approved a new kinase inhibitor pemigatinib for the treatment of adults with previously treated, unresectable locally advanced or metastatic cholangiocarcinoma. In a single-arm trial of 107 participants, pemigatinib demonstrated a clinical benefit in terms of an overall response rate of 36% (95% confidence interval 27% to 45%) and median duration of response of 9.1 months (95% confidence interval 6.0 months to 14.5 months). Patient selection for the clinical trial was based on the presence of a fibroblast growth factor receptor 2 fusion or rearrangement detected by the FoundationOne CDx companion diagnostic for this indication (U.S. Food and Drug Administration, 2020a).

Several other molecular markers are used to determine clinical trial eligibility. As yet, their diagnostic, prognostic, and therapeutic value is uncertain and will continue to evolve as actionable targeted treatments emerge.

In 2021, we updated the references related to the U.S. Food and Drug Administration and National Cancer Institute. We added the following indication to coverage:

- Tumor mutational burden testing to determine eligibility for pembrolizumab for the treatment of adult and pediatric patients with unresectable or metastatic tumor mutational burden-high (defined as at least 10 mutations/megabase) solid tumors, as determined by a U.S. Food and Drug Administration-approved test, that have progressed following prior treatment and who have no satisfactory alternative treatment options (National Comprehensive Cancer Network, 2021). The FoundationOne CDx test has been approved for this indication (U.S. Food and Drug Administration, 2021b).

In 2022, we updated the references related to the National Comprehensive Care Network (2022), U.S. Food and Drug Administration (2021a, 2021b, 2022) and the National Cancer Institute (2021, 2022a, 2022b, 2022c).

In 2023, we updated references for the National Cancer Institute (2022, 2023a, 2023b, undated), National Comprehensive Cancer Network (2023a, 2023b), and U.S. Food and Drug Administration (2023).

We added a systematic review of 73 studies that analyzed molecular biomarkers of cholangiocarcinoma. Results showed PI3K (Phosphoinositide 3-kinases)/ERK/Akt (AKT serine/threonine kinase 1)/mTOR (mammalian target of rapamycin) signaling pathway and HER2 (Human epidermal growth factor receptor 2) and EGFR (Epidermal Growth Factor Receptor) pathways are the most potential targets for cholangiocarcinoma treatment (Idris, 2023).

We also added a meta-analysis that revealed the KRAS mutation is commonly found in cholangiocellular carcinoma but is also strongly associated with more aggressive tumors and lower survival rates, making it a potential indicator leading to targeted treatments (Procopio, 2022).

References

On April 21, 2023, 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 "cholangiocarcinoma" (MeSH), "biliary tract neoplasms" (MeSH), and "molecular diagnostic techniques" (MeSH). 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.

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Policy updates

7/2020: initial review date and clinical policy effective date: 8/2020

7/2021: Policy references updated. Coverage modified.

7/2022: Policy references updated.

7/2023: Policy references updated.