Molecular analysis for targeted treatment for hepatobiliary cancer

Clinical Policy ID: CCP.1466

Recent review date: 7/2024

Next review date: 11/2025

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

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Coverage policy

Molecular analysis for targeted therapy for hepatobiliary cancer may be medically necessary for the following indications, when the testing result will impact treatment provision (Boland, 1998; National Comprehensive Cancer Network, 2024a, 2024b; U.S. Food and Drug Administration, 2021a, 2024):

- Neurotrophic tyrosine receptor kinase gene fusion testing for larotrectinib and entrectinib eligibility in unresectable, metastatic, or progressive hepatobiliary cancer.
- Microsatellite instability/deficient mismatch repair testing for pembrolizumab eligibility in unresectable, metastatic, or progressive primary biliary tract cancer.
- Germline testing or genetic counselor referral for microsatellite instability-high/mismatch repair-deficient tumors or family history suggestive of BRCA1/2 mutations.

- Fibroblast growth factor receptor 2 fusion or rearrangement testing using FoundationOne® CDx for pemigatinib eligibility in previously treated, unresectable locally advanced or metastatic cholangiocarcinoma.
- Tumor mutational burden testing for pembrolizumab eligibility in unresectable or metastatic solid tumors that have progressed following prior treatment without satisfactory alternative treatment options.

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).

Microsatellite instability-high is defined as having at least two of five markers showing instability in a validated core panel or >30% of markers in other validated panels. Tumor mutational burden-high is defined as ≥10 mutations/megabase 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

Clinical Guidelines

NCCN Guidelines for Biliary Tract Cancers recommend comprehensive molecular profiling for unresectable or metastatic biliary tract cancers due to the presence of clinically relevant molecular alterations. Up to 10-15% of biliary tract cancers may be associated with inherited cancer syndromes, and genetic counseling and potential germline testing are advised for patients diagnosed at a young age, with a strong personal or family cancer history, or with specific mutations identified in tumor testing (National Comprehensive Cancer Network, 2024a) Recommended molecular tests include neurotrophic tyrosine receptor kinase fusions, microsatellite instability-high or mismatch repair deficiency, tumor mutational burden-high, B-Raf proto-oncogene V600E mutations,

fibroblast growth factor receptor 2 fusions, isocitrate dehydrogenase 1 mutations, human epidermal growth factor receptor 2 overexpression, and rearranged during transfection or KRAS mutations. For patients with unresectable disease, molecular testing should guide targeted treatment, with options including systemic therapy, clinical trials, or best supportive care, and potentially radiation therapy (National Comprehensive Cancer Network, 2024a)

In contrast, NCCN Clinical Practice Guidelines for Hepatocellular Carcinoma recommend molecular profiling on a case-by-case basis, particularly for patients with atypical or combined hepatocellular carcinoma-cholangiocarcinoma histology, unusual clinical presentations, or clinical trial enrollment. While hepatocellular carcinoma is associated with various molecular alterations, no treatments currently provide differential benefits for specific molecular subgroups (National Comprehensive Cancer Network, 2024b). The guidelines highlight insufficient evidence for universal germline testing or specific genetic risk assessment criteria in hepatobiliary cancers, and routine testing for microsatellite instability, mismatch repair, tumor mutational burden, or programmed death ligand 1 is not recommended (National Comprehensive Cancer Network, 2024b).

The American Association for the Study of Liver Diseases practice guidelines mention molecular analysis for considering biopsies of liver imaging reporting and data system four and five lesions, but do not provide specific recommendations on when or how to use molecular analysis for targeted treatment of hepatocellular carcinoma (American Association for the Study of Liver Diseases, 2023).

Systematic Reviews and Meta-Analyses

Diagnostic Advancements

Several systematic reviews have provided valuable insights into the molecular aspects of biliary tract cancers, focusing on diagnostics, biomarkers, prognostic markers, and therapeutic targets. One evaluated 58 studies (n = 4701) and highlighted the effectiveness of liquid biopsy methods, such as circulating tumor DNA (ctDNA) and cell-free DNA (cfDNA), in diagnosing biliary tract cancer. These methods showed high concordance with traditional tissue biopsies and emphasized actionable genetic mutations like IDH1, FGFR2, KRAS, and ERBB2, which are crucial for targeted therapy in biliary tract cancer (Lee, 2024).

Building on the theme of diagnostic improvements, a meta-analysis focusing on identifying key molecular markers in hepatobiliary cancers noted limitations of traditional biomarkers like AFP and CA19.9, and proposed volatile organic compounds (VOCs) as promising novel biomarkers. Their meta-analysis included 18 studies (n = 2,296) patients and reported pooled sensitivity and specificity of 0.79 and 0.81, respectively, for VOCs in detecting hepatobiliary cancers. The combined use of VOCs with existing markers significantly improved early detection rates, underscoring the need for improved diagnostic tools for early and accurate cancer detection (Boscoe, 2019).

Prognostic Markers and Treatment Guidance

The prognostic value of molecular markers in patients with resected extrahepatic cholangiocarcinoma has been examined, identifying KRAS and TP53 mutations as significant prognostic markers, with their presence correlating with lower survival rates. This review highlighted the importance of integrating molecular profiling into clinical practice to enhance prognostic assessments and tailor post-surgical treatments effectively (Roos, 2019).

Complementing these findings, another meta-analysis revealed that KRAS mutations are common in cholangiocarcinoma and are significantly associated with more aggressive tumor behavior and poorer survival rates. This study synthesized data from multiple cohorts and suggested that targeting KRAS mutations could be a viable strategy for developing new therapeutic approaches, as these mutations are linked to resistance to conventional treatments and worse prognosis (Procopio, 2022). Both studies underscore the critical role of molecular profiling in predicting disease outcomes and customizing post-surgical treatments to improve patient prognosis.

Therapeutic Targets and Pathways

An extensive evaluation of molecular targets and signaling pathways in cholangiocarcinoma identified the PI3K/ERK/Akt/mTOR and HER2/EGFR pathways as particularly promising for developing targeted therapies. This review, which analyzed 73 studies, emphasized the potential of these pathways to regulate critical processes like cell proliferation, apoptosis, and metastasis, which are central to cancer progression. The suggestion that combination therapies targeting these pathways could offer synergistic effects and lead to improved therapeutic outcomes for cholangiocarcinoma patients highlights the potential for more effective treatments (Idris, 2023).

Large-Scale Genomic Studies

The Cancer Genome Atlas Research Network (2017): This large-scale genomic analysis of hepatocellular carcinoma involved 363 cases and used integrated genomic platforms to identify frequent mutations in key genes such as TERT, TP53, and CTNNB1. The findings suggested multiple potential targets for therapeutic intervention and underscored the heterogeneity of hepatocellular carcinoma at the molecular level, highlighting the necessity for targeted treatment approaches tailored to specific genetic alterations.

Building on the Networks findings, this study compared genomic data from diverse populations, confirming the presence of core driver mutations in TP53, CTNNB1, and TERT across different ethnic groups. The analysis identified additional mutations and pathways for therapeutic exploitation, emphasizing the global applicability of genomic data in developing effective treatments for hepatocellular carcinoma (Shibata, 2018).

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).

In 2024, we updated references for the National Comprehensive Cancer Network (2024a, 2024b), and added new clinical guidelines from the American Association for the Study of Liver Diseases (2023) and U.S. Food and Drug Administration (2024). We also reorganized and condensed the findings section and added a new systematic review (Lee, 2024). In addition, we added an Appendix with U.S. Food and Drug Administration approved diagnostic tests.

References

On June 5, 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 “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.

7/2024: Policy references updated.

Appendix

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.

Approved Companion Diagnostic Tests as of May 2024 are:

1. FoundationOne CDx (Foundation Medicine, Inc.)

- Indication: Cholangiocarcinoma - Tissue
- Therapeutic: Pemazyre (pemigatinib) NDA 213736
- Target: FGFR2
- Genetic Alterations: FGFR2 fusions and select rearrangements
- FDA Approval: P170019/S013 (04/17/2020)

2. FoundationOne CDx (Foundation Medicine, Inc.)

- - Indication: Metastatic Castrate Resistant Prostate Cancer (mCRPC) - Tissue
- - Therapeutic: Lynparza (olaparib) NDA 208558
- - Target: Homologous recombination repair (HRR) genes

- - Genetic Alterations: BRCA1, BRCA2, ATM, BARD1, BRIP1, CDK12, CHEK1, CHEK2, FANCL, PALB2, RAD51B, RAD51C, RAD51D and RAD54L alterations
- - FDA Approval: P170019/S015 (05/19/2020)

3. FoundationOne CDx (Foundation Medicine, Inc.)

- - Indication: Prostate Cancer - Tissue
- - Therapeutic: AKEEGA (niraparib + abiraterone acetate) NDA 216793
- - Target: BRCA1 and BRCA2
- - Genetic Alterations: BRCA1 and BRCA2 alterations
- - FDA Approval: P170019/S042 (08/11/2023)

4. HER2 FISH pharmDx Kit (Dako Denmark A/S)

- Indication: Gastric and Gastroesophageal Cancer - Tissue
- Therapeutic: Herceptin (trastuzumab) BLA 103792
- Target: ERBB2 (HER2)
- Genetic Alterations: HER-2/neu (ERBB2) gene amplification
- FDA Approval: P040005/S005 (10/20/2010)

5. HercepTest (Dako Denmark A/S)

- Indication: Gastric and Gastroesophageal Cancer - Tissue
- Therapeutic: Herceptin (trastuzumab) BLA 103792
- Target: ERBB2 (HER2)
- Genetic Alterations: HER-2 protein overexpression
- FDA Approval: P980018/S010 (10/20/2010)

6. Oncomine Dx Target Test (Life Technologies Corporation)

- Indication: Cholangiocarcinoma - Tissue
- Therapeutic: Tibsovo (ivosidenib) NDA 211192
- Target: IDH1
- Genetic Alterations: Single nucleotide variants
- FDA Approval: P160045/S028 (08/25/2021)

7. PD-L1 IHC 22C3 pharmDx (Dako North America, Inc.)

- Indication: Gastric or Gastroesophageal Junction (GEJ) Adenocarcinoma - Tissue
- Therapeutic: Keytruda (pembrolizumab) BLA 125514
- Target: PD-L1
- Genetic Alterations: PD-L1 protein expression
- FDA Approval: P150013/S027 (11/07/2023)

Source: U.S. Food and Drug Administration (2024).