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Molecular diagnostics as the clinical standard in cholangiocarcinoma and hepatocellular carcinoma: a new era of precision oncology

Review based on the proceedings of the OeGHO spring meeting, March 19, 2026, Bregenz

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Summary The management of hepatobiliary malignancies has undergone a profound transformation, shifting from an empiric, uniform systemic approach to an increasingly stratified paradigm of precision oncology. Advances in molecular characterization, particularly through next-generation sequencing (NGS), have identified actionable alterations in a clinically relevant proportion of patients with cholangiocarcinoma (CCC) and are increasingly informing biomarker-driven treatment strategies in hepatocellular carcinoma (HCC). This review summarizes current clinical standards in molecular diagnostics, with a focus on FGFR2 testing, the implications of CTNNB1 mutations for the immune microenvironment, and the emerging role of liquid biopsy in monitoring clonal evolution and therapeutic resistance.

Keywords Cholangiocarcinoma · Biliary tract cancer · Hepatocellular carcinoma · Molecular profile · Targeted therapy

Introduction

For decades, biliary tract cancers (BTC) and hepatocellular carcinoma (HCC) were associated with poor outcomes and limited systemic treatment options. However, as presented at the 2026 OeGHO (*Österreichische Gesellschaft für Hämatologie und Medizinische Onkologie*) meeting in Bregenz, the integration of comprehensive molecular profiling into the early diagnostic work-up has changed clinical decision-making, particularly for patients with advanced BTC. These malignancies are no longer approached as uniform disease entities; rather, they are increasingly classified into molecularly defined subsets with direct therapeutic implications. The current European Society for Medical Oncology (ESMO) guidelines (interim update 2025) recommend upfront molecular profiling for patients with advanced BTC, reflecting the shift toward biomarker-driven therapy as an established clinical standard [1].

Cholangiocarcinoma (CCC): the paradigm of targetable heterogeneity

Intrahepatic cholangiocarcinoma (iCCA) is one of the most molecularly diverse gastrointestinal malignancies. Up to 25% of patients with iCCA harbor potentially actionable genetic alterations, requiring a diagnostic strategy that integrates histopathology, high-quality tissue acquisition, and comprehensive molecular testing [1].

FGFR2 alterations: navigating fusions and rearrangements

The most prominent targets in iCCA are fibroblast growth factor receptor 2 (FGFR2) alterations, identified in approximately 10–15% of cases. A critical diagnostic distinction must be made between fusions and rearrangements.

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- FGFR2 fusions involve the joining of FGFR2 with a partner gene, such as BICC1 or CCDC6, resulting in a chimeric protein that drives constitutive oncogenic signaling.
- FGFR2 rearrangements denote broader structural changes, often detected by break-apart signals on fluorescence in situ hybridization (FISH), which may or may not generate a functional fusion transcript.

The choice of diagnostic modality is clinically relevant. DNA-based next-generation sequencing (NGS) is widely used, but it may fail to detect fusions when breakpoints occur within large, repetitive intronic regions outside the covered target intervals. RNA-based NGS is particularly valuable because it interrogates the spliced transcript, bypasses intronic complexity, and confirms whether a detected rearrangement results in an expressed functional fusion. In comparative series, RNA-based sequencing has identified additional clinically relevant FGFR2 fusions that were missed by DNA-based NGS [2]. Targeted therapy options for advanced/metastatic biliary tract cancer are summarized in Fig. 1.

Resistance mechanisms and the role of liquid biopsy

Although selective FGFR inhibitors such as pemigatinib can produce clinically meaningful responses, acquired resistance is common. Resistance is frequently mediated by secondary FGFR2 kinase-domain mutations, including V565 gatekeeper and N550 molecular-brake alterations, which either reduce drug binding or favor an active kinase conformation [2].

These resistance mechanisms are often polyclonal; distinct metastatic deposits may harbor different secondary mutations. In this setting, liquid biopsy based on circulating free DNA (cfDNA) has a specific clinical advantage. Although plasma assays may be less sensitive than tissue testing for the initial detection of large FGFR2 fusions, they can capture spatial and temporal heterogeneity during therapy, detect emerging resistance clones noninvasively, and support selection of subsequent FGFR-targeted strategies, including covalent inhibitors such as futibatinib [3].

Beyond FGFR: IDH1, BRAF, and HER 2

Other established targets include IDH1 mutations, found in approximately 10% of iCCA cases, for which ivosidenib is a standard treatment option in previously treated disease, and BRAF V600E mutations, which are targetable with combined BRAF/MEK inhibition.

HER2 (ERBB2) is another clinically relevant target, particularly in gallbladder carcinoma and extrahepatic cholangiocarcinoma. The absence of a universally standardized HER2 immunohistochemistry scor-

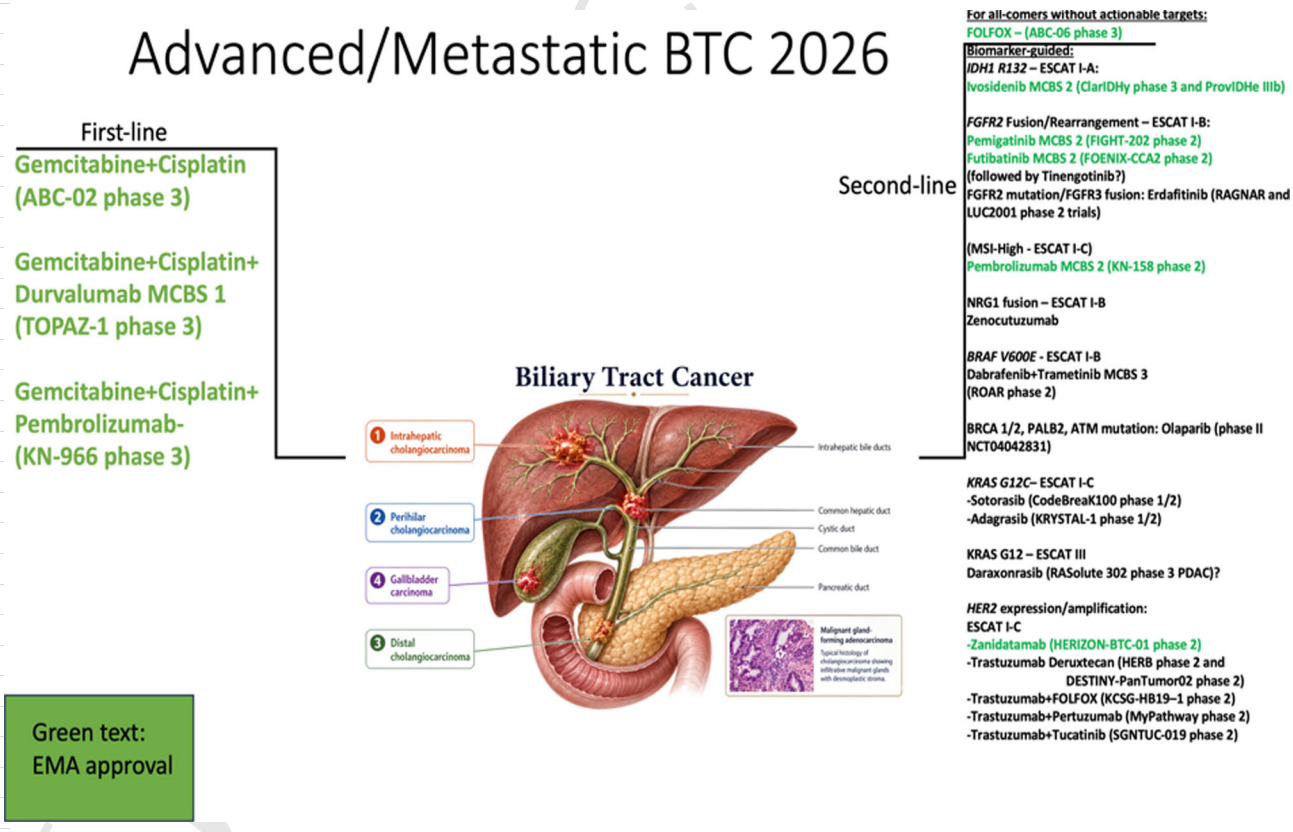

Fig. 1 Targeted therapy options for advanced/metastatic biliary tract cancer. Copyright Hossein Taghizadeh—image created with ChatGPT 5.5 and Canva

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ing system for BTC, analogous to those used in breast or gastric cancer, remains a diagnostic challenge. Nevertheless, pivotal trials such as HERIZON-BTC-01 with zanidatamab have demonstrated durable responses in pretreated HER2-positive BTC, supporting incorporation of HER2 testing into comprehensive molecular assessment [1].

Hepatocellular carcinoma: from histology and imaging to immunobiology

For many years, the diagnosis of hepatocellular carcinoma (HCC) in clinical practice was commonly confirmed by ultrasound- or computed tomography (CT)-guided biopsy when imaging was not diagnostic or when histology was required. In contemporary practice, noninvasive imaging criteria, including LI-RADS, permit an imaging-based diagnosis in appropriately selected patients at risk of HCC, particularly when lesions meet LI-RADS 5 criteria. Thus, an imaging-only diagnosis is a relatively recent and context-dependent standard rather than a historical default. Nevertheless, the increasing use of immunotherapy and the development of molecular biomarkers of response and resistance have made histological and molecular analysis increasingly relevant for treatment selection, clinical trial enrollment, and translational research.

The CTNNB1 dichotomy: strong vs. weak activators

The Wnt/beta–catenin pathway, particularly mutations in CTNNB1, is altered in 15–40% of HCC cases. Recent evidence highlighted in Bregenz suggests that the type and functional strength of CTNNB1 mutation contribute to the tumor immune phenotype.

- Strong CTNNB1 mutations: These involve the beta-TrCP docking motif (D32-S37) or T41. They result in high-level Wnt/beta–catenin activation and are associated with an immune-excluded, “cold” tumor microenvironment, reduced T-cell infiltration, and primary resistance to immune checkpoint inhibitor (ICI)-based regimens, including atezolizumab/bevacizumab.
- Weak CTNNB1 mutations: Mutations at S45 produce lower levels of Wnt/beta–catenin activation and appear to preserve a higher degree of immune-cell infiltration.

This distinction is clinically relevant. It suggests that CTNNB1-mutated HCC should not be considered a homogeneous ICI-resistant category; rather, patients with strong Wnt/beta–catenin activation may require alternative or combination strategies, including investigational approaches that pair Wnt-pathway inhibition with immune checkpoint blockade [4].

New targets: the FGFR4/FGF19 axis

Further development is also focused on the FGFR4 pathway, which can be activated by overexpression of its ligand FGF19 in approximately 30% of HCCs. Selective FGFR4 inhibitors such as irpagratinib are being investigated, including in phase 2 studies in combination with atezolizumab (NCT05441475). This development underscores the need for molecular testing to identify FGF19 overexpression, FGF19 amplification, or FGFR4 pathway activation as the field moves toward more personalized second- and later-line therapy in HCC [5].

Integrating molecular diagnostics into clinical practice

The implementation of these standards requires a multidisciplinary pathway. The molecular tumor board has become a core component of gastrointestinal oncology, bringing together medical oncologists, pathologists, radiologists, molecular biologists, and bioinformaticians to interpret complex NGS reports and translate them into treatment recommendations.

The diagnostic workflow in 2026:

- Tissue biopsy: Required for CCC to confirm histology and enable RNA/DNA NGS; in HCC, biopsy should be considered when imaging is inconclusive, when histology is clinically required, or when tissue is needed for molecular characterization, clinical trial eligibility, or translational biomarker analyses.
- Upfront comprehensive profiling: Large DNA/RNA panels should include FGFR2, with RNA-based fusion testing or RNA reflex testing, IDH1, BRAF, HER2/ERBB2, MSI/MMR status, and TMB where clinically appropriate.
- Sequential liquid biopsy: At progression on targeted therapy, cfDNA analysis can identify resistance mutations and inform subsequent treatment selection.

Conclusion and future perspectives

The transition of molecular diagnostics from a predominantly research-based approach to a clinical standard has altered the trajectory of hepatobiliary oncology. In cholangiocarcinoma (CCC), the focus has shifted toward more accurate detection of actionable fusions and toward management of polyclonal resistance. In hepatocellular carcinoma (HCC), the suspected diagnosis will continue to rely primarily on imaging in eligible patients, but the field is moving beyond imaging-based diagnosis and empiric treatment toward biologically informed treatment selection, including characterization of genetic drivers of immune evasion and emerging actionable targets.

Looking ahead, integration of artificial intelligence in pathology and radiology, together with refined multi-omic liquid biopsy approaches, may further improve the ability to deliver the right treatment to

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the right patient at the right time. For oncologists, the message from Bregenz 2026 is clear: precision diagnostics is no longer an adjunct to therapy; it is the foundation of modern treatment decision-making in hepatobiliary malignancies.

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Data availability All data supporting the findings of this work are included in the article.

Declarations

Conflict of interest H. Taghizadeh declares that he has no competing interests.

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