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Evolving Concepts in Liver Pathology (Part I): Application to Liver Biopsy Interpretation of Liver Neoplasia

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It is with great pleasure that we present this special issue on *Evolving Concepts in Liver Pathology: Application to Liver Biopsy Interpretation*. Liver pathology remains a cornerstone of clinical decision-making, providing critical guidance for diagnosis, prognosis, and treatment across a broad spectrum of liver diseases. Over recent years, profound advances in molecular biology, histologic classification, and diagnostic technologies have transformed how we approach liver biopsy interpretation. The 9 invited articles in this issue collectively reflect the dynamism and complexity of modern liver pathology—from rare pediatric malignancies in Part I to metabolic disorders and the nuances of drug-induced injury in Part II.

A central theme weaving through this collection is the integration of molecular insights with traditional histomorphology, reshaping diagnostic frameworks across both neoplastic and nonneoplastic liver diseases. In their comprehensive review, Jiao, Saxena, and Morotti revisit hepatoblastoma, the most common pediatric liver malignancy, highlighting its histologic heterogeneity and evolving molecular classifications. Their discussion of the Children's Hepatic tumors International Collaboration (CHIC) risk stratification underscores how combined clinical, histologic, and molecular data refine prognostication and guide therapy, exemplifying the precision medicine paradigm now taking root in pediatric liver oncology.

Similarly, Zheng, Haw, and Wang provide a state-of-the-art update on hepatocellular carcinoma (HCC), where the discovery of driver mutations such as *TERT* promoter, *CTNNB1*, and *TP53* has enhanced diagnostic precision and prognostic stratification. Their emphasis on distinct histologic subtypes and the challenging differential diagnosis between HCC and precursor lesions underlines the necessity of comprehensive morpho-molecular integration, especially when interpreting limited biopsy samples. The article exemplifies the movement toward diagnostic granularity, where molecular markers augment, rather than replace, expert histologic evaluation.

Expanding beyond hepatocellular tumors, Liang and Chopra focus on preneoplastic and neoplastic biliary diseases, describing evolving concepts in biliary intraepithelial neoplasia, intraductal papillary neoplasms, and emerging variants of cholangiocarcinoma. Their description of novel entities such as the cholangioblastic variant with its unique *NIBPL--NACCI* fusion highlights how molecular discoveries drive nomenclature refinement and diagnostic criteria, with direct clinical implications for prognosis and treatment.

This theme continues in Mannan and Szeto's review of other primary epithelial liver neoplasms, where rare but aggressive tumors like combined hepatocellular-cholangiocarcinoma (cHCC-CCA), intermediate cell carcinoma and combined HCC and neuroendocrine carcinoma pose distinct diagnostic challenges. This article emphasizes the critical role of morphologic assessment supported by immunohistochemistry, reminding us that accurate tumor classification remains a key prognostic and therapeutic determinant.

Part II of this special issue also addresses critical nonneoplastic liver diseases, underscoring the breadth of liver pathology practice. Myoteri, Sakellariou, and Tiniakos review autoimmune hepatitis (AIH), an immune-mediated chronic disease whose diagnosis relies heavily on histologic features such as lymphoplasmacytic portal infiltrates and interface hepatitis. Their discussion of new consensus criteria from the International Autoimmune Hepatitis Pathology Group exemplifies how standardization of histopathologic criteria can improve diagnostic accuracy and clinical care.

It is not uncommon for liver biopsies to show normal or near-normal histologic findings, which can present significant diagnostic challenges for pathologists and lead to frustration for treating physicians. In their article, Du and Wang explore rare metabolic, storage, and inclusion

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disorders that may look near-normal on liver biopsies, challenging pathologists to recognize subtle abnormalities in the context of clinical and laboratory data. This article importantly highlights the limits of morphology alone and the value of an integrated multidisciplinary approach.

Memon and Saxena's review of molecular advances in cholestatic liver diseases further illustrates the expanding role of genetic testing in liver pathology. The identification of mutations in genes such as *JAG1*, *ATP8B1*, and *ABCB11* has revolutionized the understanding and diagnosis of inherited cholestatic disorders, while also shedding light on mechanisms underlying drug-induced cholestasis. This molecular perspective complements prior discussions of biopsy interpretation, highlighting the increasing necessity for pathologists to incorporate genetic data into their diagnostic algorithms.

On a more common yet evolving front, Jiao and Zhang present current concepts in steatotic liver disease, reviewing new nomenclature frameworks such as metabolic dysfunction-associated steatotic liver disease (MASLD) and alcohol-associated subtypes. Their discussion of histologic features, grading systems, and the emerging role of digital pathology emphasizes the ongoing modernization of liver biopsy interpretation in this highly prevalent disease group.

Finally, Parrack and Zhao provide a timely review of drug-induced liver injury (DILI), a frequent cause of liver pathology marked by a wide morphologic spectrum. Their emphasis on the diagnostic challenge posed by variable histologic presentations, the importance of clinical correlation, and the evolving injury patterns associated with novel

therapeutics such as immune checkpoint inhibitors serves as an important reminder of the dynamic nature of liver pathology in an era of rapid pharmaceutical innovation.

Taken together, this special issue encapsulates the current state and future trajectory of liver pathology. Several key messages emerge:

- Morphology remains foundational but is increasingly complemented by molecular and genetic data, enabling more precise classification, risk stratification, and prognostication.
- Recognition of rare, variant, and emerging entities continues to grow, requiring pathologists to stay current with evolving nomenclature and diagnostic criteria.
- Integration of clinical, radiologic, and laboratory data is essential, particularly in challenging cases with subtle or overlapping histologic features.
- Technological advances such as digital pathology and comprehensive genetic panels are poised to further enhance diagnostic accuracy and reproducibility.
- The field is moving toward precision diagnostics tailored to individual tumor biology and patient context, a paradigm reflected across pediatric and adult diseases, neoplastic and non-neoplastic alike.

We thank the distinguished authors for their outstanding contributions and invite readers to explore this rich collection, which we hope will serve as a practical and conceptual guide for pathologists, hepatologists, and clinicians involved in the complex diagnosis and management of liver diseases.