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Non-invasive tests fail to ensure therapeutic precision for resmetirom in MASLD

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The approval of resmetirom in 2024 as the first pharmacological therapy for metabolic dysfunction-associated steatohepatitis (MASH) resolution and fibrosis regression represents a paradigm shift in MASH management. Yet, the shift from histology-based clinical trials to real-world prescribing based on non-invasive tests (NITs) raises concerns regarding the accuracy, efficacy, and economic impact of current eligibility algorithms.[1] The study by Kaya et al.,[2] presented in this issue of Hepatology Forum, provides a timely and important evaluation of how NITs perform in clinical practice when identifying appropriate candidates for resmetirom therapy.

Using a biopsy-confirmed cohort of 266 Turkish patients with MASLD from the national NAFLD biobank, the authors examined two widely proposed diagnostic strategies, CAP+LSM and CAP+-FAST, to identify MASH patients with F2–F3 fibrosis, the target group defined in the pivotal MAESTRO trials.[3,4] Their results are striking: both algorithms underdiagnosed over 60% of biopsy-eligible patients and simultaneously overdiagnosed ~40% of those who did not meet histologic criteria. The agreement between NITs and biopsies, as measured by Cohen's kappa, was poor (0.128 for LSM; 0.101 for FAST), highlighting that the tests do not provide reliable diagnostic results.

These findings carry several important implications. First, they confirm that NIT-based algorithms lack the necessary specificity and sensitivity to replace liver biopsy when it comes to therapeutic decision-making in MASH. Second, they highlight an economic risk, especially for middle-income countries such as Türkiye. If current NIT strategies were applied to a population with MASLD prevalence rates as high as up to 50%, a significant proportion of patients could be exposed to unnecessary treatment, while many eligible candidates might remain untreated.[5,6]

Given that resmetirom therapy is projected to cost more than $300,000 per patient over a lifetime, these inaccuracies could lead to large-scale inefficiencies in healthcare spending, especially in publicly funded systems. More importantly, overprescription may expose patients without significant fibrosis to drug-related risks with little to no clinical benefit, whereas underprescription may delay treatment in those with progressive disease.

The strength of the study by Kaya et al.[2] lies in its real-world design and its use of histology as the reference standard. Unlike clinical trials, which often enroll selected patient populations in tightly controlled settings, this analysis reflects the complexity and heterogeneity of clinical practice. Other promising non-invasive strategies, such as ELF, MEFIB, MAST, and MR Elastography, were not evaluated in this study and may offer better discriminatory performance in future validation cohorts. However, as this study clarifies, the proposed NITs are not currently suitable for guiding resmetirom prescription without confirmation via histology.

In light of this data, what should clinicians and policymakers do? Until alternative strategies are validated, liver biopsy should remain a prerequisite before prescribing resmetirom. This is especially true in countries where drug access is regulated by public health insurance systems.

In conclusion, the study by Kaya et al.[2] provides a persuasive case for a more cautious, biopsy-centered approach to resmetirom prescription. As we try to expand MASH treatment, we should be careful not to choose convenience over accuracy or cost-effectiveness. This study reminds us that precision medicine must start with an accurate diagnosis.

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