Quantitative imaging tests for non-alcoholic fatty liver disease: which, when and why

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Historically, the medical community has relied on markers of liver fibrosis from a biopsy to direct clinical care decisions in those with non-alcoholic fatty liver disease (NAFLD), as it was previously believed that fibrosis was the most important predictor of poor prognosis and liver related clinical events (1,2). In the last decade, there has been a push to find alternatives to liver biopsy, which is unpopular with both patients and clinicians, unsuitable for repeat measures, and has risks and costs associated with the invasive procedure. Biomarkers from medical imaging have a strong role to play here; they are undeniably liver related, show the whole organ enabling identification of localised disease, and are inherently non-invasive. Radiological approaches are already used clinically to identify liver steatosis for NAFLD diagnosis, including ultrasound for appearance of diffuse hepatic steatosis and quantification of controlled attenuation parameter (CAP) or magnetic resonance imaging (MRI) for measurement of the superior proton density fat fraction (PDFF) (3). Many society guidelines, are also now encouraging the use of non-invasive tests (NITs), including quantitative imaging biomarkers, for staging the degree of liver disease (4-7), although histology is still the recommendation of the American Association for the Study of Liver Diseases (AASLD) and European Association for the Study of the Liver (EASL) for diagnosing non-alcoholic steatohepatitis (NASH), and for those at high risk of advanced fibrosis (8).

An unmet need exists, therefore, to establish care pathways to identify the individuals who are most at-risk of having advanced fibrosis, without relying on histopathology or expensive tests which are unnecessary for the patient's level of risk. The current study by Kaplan *et al.* examined the association between simple, cheap and easily available serum biomarkers and magnetic resonance elastography (MRE) and used the results to propose a fibrosis screening algorithm to separate NAFLD patients with advanced fibrosis from those without. Specifically, they compared the diagnostic accuracy of Fibrosis-4 index (FIB-4) and NAFLD fibrosis score (NFS) to MRE, using a retrospective cohort of patients having undergone MRE evaluation for fibrosis. The authors highlighted that imaging-based testing such as Vibration controlled Transient Elastography (VCTE) and MRE, along with blood-based biomarkers are already being employed as alternatives to a liver biopsy in their clinic. Using fibrosis gradings from MRE as the gold standard, the authors reported the negative predictive value (NPV) and the positive predictive value (PPV) of both FIB-4 and NFS for staging advanced fibrosis. The NPV was acceptable for ruling out significant fibrosis (0.84 FIB-4; 0.89 NFS) but the PPV was only fair for ruling in advanced fibrosis (0.63 FIB-4 and 0.72 NFS). Although the study has some shortcomings around the mismatch between number of groupings in the blood-tests and MRE, as well as delays between blood draw and imaging, these are potentially some of the practical challenges of implementing sequential testing in the real-world. The study highlights the important place for point-of-care assessment, particularly to rule out advanced fibrosis in the clinical algorithm for NAFLD, which the authors rightly suggest is key to ensure correct onward referral for the most at-risk patients and prevent unnecessary further testing when appropriate. This approach, using VCTE rather than MRE following FIB-4

assessment was demonstrated to improve detection of advanced fibrosis in a large individual patient data meta-analysis by the LITMUS (liver investigation: testing marker utility in steatohepatitis) consortium and thus is becoming a widely accepted approach (9). It should be noted however, that in the study by Kaplan *et al.*, there was some discordance between the tests in the rule out for advanced fibrosis; 11% if those with FIB-4 value of less than 1.3 were predicted to have advanced fibrosis by MRE, and this was similarly true for 9.2% of those with NFS values <−1.455. These results suggest that 1 out of 10 patients with advanced fibrosis would be missed by this strategy, which may be highlighting either the insufficiencies in FIB-4 and NFS, or the limitations of MRE. For example, MRE has well reported confounders such as inflammation and iron overload, lacks validation of pre-defined thresholds for use, and the mapping of liver stiffness to fibrosis grading is neither widely accepted nor approved by regulatory agencies. It has also been reported that neither FIB-4 (10) nor MRE (11) are effective biomarkers for detecting the transition from simple steatosis into steatohepatitis, and it should also be acknowledged that the FIB-4 may be particularly misleading in those with concomitant diabetes [prevalence of NAFLD in patients with T2D is >60% (12)] in whom liver biochemistries can be normal (8).

MRE will likely be most useful clinically in the confirmation of advanced fibrosis (5,6,8), for which it has good diagnostic accuracy in the absence of confounders (13). Whilst the authors state that the purpose of the study was not to imply that biopsy should be replaced but instead to determine whether or not patients truly require assessment with MRE, I think it is reasonable to suggest that imaging to confirm advanced fibrosis will have a place in future guidelines.

It has become apparent from large scale patient registries, that even patients with early-stage liver disease are at a much higher risk of clinical outcomes such as cancer and cardiovascular disease than those without liver disease, even in the absence of fibrosis (14). It is therefore important to identify patients in the transition from simple steatosis to the more aggressive NASH. Many of the society guidelines are being updated to reflect this, and whilst histology is still the recommendation of AASLD and EASL, it is clear from studies such as this one, that there is little appetite for using liver biopsy in NAFLD in the real world. Historically, the diagnostic performance of many NASH biomarkers was too poor to be included in clinical algorithms (15). The current blood-based biomarkers for NASH activity such as proteomics-based Somascan (10), NIS-4 (16) and FAST [aspartate aminotransferase (AST) combined with VCTE from ultrasound (17)], however, all have good diagnostic performance for identifying those with NASH. When focussing on imaging, iron-corrected T1 mapping (cT1) is the leading biomarker for NASH (18) and has been recognised for utility in the 'at-risk' population in the recent American Gastroenterological Association (AGA) Practice Update for the diagnosis and Management of Non-alcoholic Fatty Liver Disease in Lean Individuals (6), in the American Association of Clinical Endocrinology (AACE) practice Guideline for the Diagnosis and Management of Non-alcoholic Fatty Liver Disease in Primary Care and Endocrinology Clinical Settings (5) and for differentiating NASH from NAFLD in the Clinical Practice Guideline on NAFLD by the German Society of Gastroenterology, Digestive and Metabolic Diseases (7). This imaging test has an advantage over blood tests in its ability to identify disease in the liver when it is focal or localised, its excellent test-retest performance (19) and its response to change in NASH therapeutic trials (20,21)—one to watch in the NASH biomarkers space.

The future challenge is to establish clinical tools that can accurately risk stratify patients with steatohepatitis with and without fibrosis, that can be also used for monitoring when therapies receive approval; the current challenge is to provide patients the value of knowing about the health of their liver in terms of both fibrosis and disease activity, especially when the responsibility of making lifestyle changes lies entirely with them. Quantitative medical imaging will likely play an integral role in risk stratification of those deemed intermediate risk or indeterminate from other tests and should be considered a reflex test for confirming advanced fibrosis (MRE) and steatohepatitis (cT1) in clinical practice.

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Footnote

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