Editorial

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iLFT: A big assist in the recognition of liver disease in general practice

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The burden of chronic liver disease worldwide is substantial, with approximately 2 million deaths annually attributed to cirrhosis or hepatocellular carcinoma caused by viral hepatitis, non-alcoholic fatty liver disease (NAFLD), or alcohol-related liver disease (ALD), in addition to other important but less common chronic liver diseases.[1] Despite widespread availability of accurate assays to diagnose viral hepatitis and effective therapies for hepatitis B and C, millions of individuals remain undiagnosed or have limited access to care worldwide. NAFLD is often not recognized in the primary care setting.[2] The prevalence of NAFLD continues to increase with an estimated 1 in 4 adults affected worldwide, of whom approximately 1 in 5 will develop non-alcoholic steatohepatitis (NASH) with potential complications of fibrosis, cirrhosis, and hepatocellular carcinoma.[3] Furthermore, alcohol use is a leading risk factor for death globally in populations aged 15–49 years and remains a leading indication for liver transplantation in the United States and Europe.[4–6] A large proportion of patients with chronic liver disease can be diagnosed based on clinical history and routinely available serum-based and radiologic studies, including multiple non-invasive methods to assess for the presence of significant fibrosis. However, given that general practitioners (GPs) must oversee the care of often complex patients across a wide range of organ systems and chronic diseases, it is challenging to efficiently recognize and evaluate all liver test abnormalities, particularly in the early stages of chronic liver disease. Appropriate recognition of chronic liver diseases may not occur until clinical decompensation with development of advanced disease which leads to substantially increased costs to the healthcare system.[7]

To help improve the recognition of liver disease, Dillon *et al.*[8] devised an innovative algorithm, intelligent liver function testing (iLFT), that provides diagnostic assistance to GPs for the immediate evaluation of abnormal liver tests. This real-world study assessed 6 general practices in the UK using a stepped wedge design to evaluate patients with abnormal liver tests for 6 months under their normal protocol and 6 months with incorporation of the iLFT protocol to assist the GP in establishing a diagnosis of liver disease, in addition to estimating the downstream effects of subsequent referrals to specialists, additional workload required by the GP, and cost effectiveness. Use of iLFT markedly increased the proportion of individuals assigned a diagnosis by the GP for elevated liver tests with 36 of 64 (56%) using iLFT compared to 79 of 490 (16%) patients in the control arm. The results from this study should be interpreted with some caution given that enrollment into the active (iLFT) phase of the protocol in those with elevated liver tests was notably lower than the initial control phase. In addition, a significant number of patients with abnormal liver tests in the control arm (59%) were not rechecked or not investigated further due to subsequent normalization. This likely reflects general clinical practice across the world, as multiple factors are considered when deciding whether to pursue abnormal liver tests. Subtle or minor liver test abnormalities may be deemed clinically insignificant and not worth further evaluation by a GP, whereas the iLFT algorithm was designed to immediately pursue evaluation of laboratory abnormalities. It would be useful to know the specific parameters that triggered further investigation, particularly alanine aminotransferase (ALT) levels, as this may provide further insight into the decisions made by the GPs and may help refine the iLFT algorithm. One guidance document proposed ALT cut-offs of 29 to 33 IU/L for males and 19 to 25 IU/L for females, which was based on higher rates of liver-related mortality with ALT levels above these cut-offs.[9] However, many labs report higher “normal” reference ranges and there is substantial variability in how GPs approach those with ALT levels slightly above these cut-offs.

When hepatologists evaluate individuals with decompensated liver disease, it is not uncommon to find historical data showing abnormal liver chemistries that were not further evaluated during those prior time points. It would be helpful in this real-world study to attain a more granular understanding of why GPs did not choose to further evaluate abnormal test results. As primary care providers are tasked with evaluating multiple organ systems, often with significant time constraints, a marginally abnormal liver test may have simply been a lower priority compared to other issues that need to be addressed. A better understanding of how GPs evaluate abnormal liver tests in the context of other diseases or abnormalities can help provide a foundation to improve algorithms including iLFT and provide feedback to the GP regarding the incorporation of liver chemistry testing into their evaluation. Screening tests for Wilson’s disease, hemochromatosis, and alpha-1 antitrypsin deficiency were included in the iLFT algorithm, though no cases of these disorders were recorded in the final results, which likely reflects the lower prevalence of these disease entities. Indeed,

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some studies have suggested focused initial evaluation of liver tests with subsequent comprehensive evaluation only if no etiology is found.[10]

Fibrosis is the most important determinant of liver-related mortality.[11–13] The use of iLFT allowed GPs to determine whether hepatobiliary disease was associated with fibrosis. Only 1 patient in the control group was given a hepatobiliary diagnosis with fibrosis by the GP, whereas 22 of 64 individuals in the iLFT group were assigned a diagnosis of hepatobiliary disease (ALD or NAFLD) which specified the presence or absence of fibrosis. Incorporation of fibrosis scores (FIB-4 and NAFLD fibrosis score) into the iLFT algorithm allowed the GP to recognize this important characterization of hepatobiliary disease. In a typical encounter, GPs do not often look for the presence or absence of fibrosis, as was demonstrated in this real-world report, and access to testing for fibrosis such as elastography is not routinely available in primary care practices. The ability to be alerted to the presence of significant fibrosis can help tailor care, particularly for patients with suspected NAFLD and ALD. Patients with a benign evaluation by the GP, including the assessment of insignificant fibrosis, can be directed toward lifestyle modifications; whereas those with advanced fibrosis can be referred immediately for specialist evaluation. This is particularly important given the increasing prevalence of NAFLD worldwide that would overwhelm specialty clinics if all patients with NAFLD were referred. This algorithm can be a cost-effective tool to help GPs identify those who truly require prompt specialist referral.

Longitudinal use of an algorithm such as iLFT may provide another practical role for this type of technology. The GP may use the initial iLFT assessment as a baseline to determine the presence of liver disease requiring further evaluation. If no actionable liver disease is identified, then the GP may use components of iLFT such as FIB-4 or NAFLD fibrosis score in follow-up evaluations and refer to a specialist if there is subsequent progression of liver disease. The use of iLFT was associated with a greater number of pre and post diagnosis visits to the GP, and inevitably the number of referrals to secondary care increased significantly (OR = 8.44). However, lack of referral in the control group was at least partly due to lack of further evaluation even in the setting of abnormal liver tests. The iLFT algorithm was widely accepted by GPs with only 13% expressing concern that their workload was increased; of note, this result could be different if iLFT had been used more frequently in the study arm. As expected, there was a small incremental cost per diagnosis, but this was offset by significant savings from the predicted lifetime cost benefit due to earlier detection of disease. These benefits are particularly applicable for patients with NAFLD and ALD who are often not identified until severe or decompensated disease has already developed. Indeed, in the health economic analysis, iLFT proved cost-effective across a wide range of willingness to pay thresholds including the UK threshold of £30,000 per QALY.

What refinements could be made to iLFT? Given that Wilson's disease, hemochromatosis, and alpha-1 antitrypsin deficiency are much less common conditions, one could consider removing them from the algorithm and assessing them only if the initial evaluation is unrevealing and liver chemistry abnormalities persist on subsequent testing. Care must be taken to ensure that primary care providers are comfortable interpreting both the FIB-4 index and NAFLD fibrosis score.[14,15] Incorporation of serologies that demonstrate protective antibodies for hepatitis A and B would help identify those needing vaccination if chronic liver disease is identified. With the increasing use of potent targeted immune and cytotoxic therapies for a variety of chronic inflammatory and oncologic disorders, it is important to identify those who are HBsAg positive or anti-HBc positive, as these individuals will be at risk of hepatitis B reactivation if such therapies are administered. iLFT is a promising glimpse into the future and a welcome tool for primary care providers who can incorporate data derived from this algorithm to help identify patients who already have or are at risk of significant liver disease. Early recognition of liver disease with appropriate referrals by our primary care providers will be an essential step in reducing morbidity and mortality worldwide.

Conflicts of interest

Paul Kwo: *Grant support*: Assembly, BMS, Gilead, Allergan, AbbVie, La Jolla. *Advisory board*: AbbVie, BMS, Gilead, Dova, Eisai, Shionogi, Conatus, Merck, Mallinckrodt, Surrozen, Ferring, Quest, Durect, Edigene. *Shareholder*: Durect. *DSMB.* Janssen, Durect.

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Supplementary data

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Author names in bold designate shared co-first authorship

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