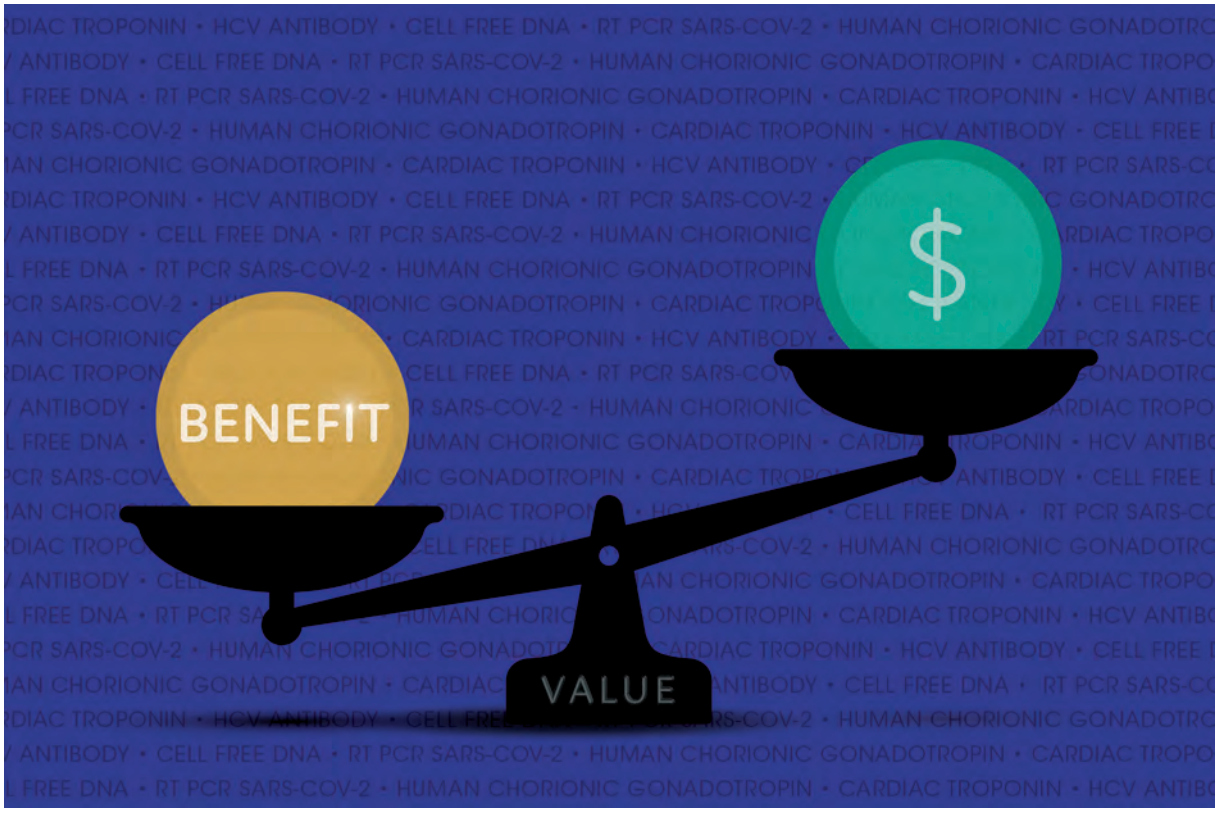
jalm.org

VOLUME 05 | NUMBER 05 | SEPTEMBER 2020

The Journal of APPLIED LABORATORY MEDICINE

An AACC Publication



OXFORD UNIVERSITY PRESS

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ADD-132514-GBL-EN

SPECIAL REPORT

Intelligent Liver Function Testing: Working Smarter to Improve Patient Outcomes in Liver Disease

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Chronic liver disease (CLD) is a significant health problem affecting millions of people worldwide. In Scotland, CLD is a major cause of premature mortality. Liver function tests (LFTs) are a panel of frequently requested blood tests which may indicate liver disease. However, LFTs commonly contain at least one abnormal result, and abnormalities are rarely investigated to the extent recommended by national guidelines. The intelligent Liver Function Testing (iLFT) pathway is a novel, automated system designed to improve early diagnosis of liver disease. Initial abnormal LFT results trigger a cascade of reflexive testing to help identify the cause of any liver dysfunction. Algorithms combine these results with demographic and clinical data (such as patient age, body mass index, and alcohol intake) and fibrosis estimates to produce an electronic diagnosis and management plan. The pilot trial demonstrated that iLFT increased diagnosis of liver disease whilst remaining cost-effective. As such, iLFT has been fully operational across our region (NHS Tayside, Scotland) since August 2018. In the first year, iLFT generated over 2000 diagnoses from 1824 patient samples with an abnormality in the initial LFTs. The majority of these patients could be safely managed in primary care. iLFT allows maximal value to be obtained from liver blood tests across biochemistry, virology, immunology, and hematology with only minor changes to working practices. 'Intelligent', algorithm-led testing pathways break down the barrier between clinical and laboratory medicine and offer solutions to many of the challenges experienced in modern healthcare systems.

INTRODUCTION

The incidence and prevalence of chronic liver disease (CLD) has been rising continuously over the past few decades. Globally, liver disease results in approximately 2 million deaths per year, as a result of both liver cirrhosis (around 1 million) and viral hepatitis and hepatocellular carcinoma (HCC) (around 1 million) *(1)*. Cirrhosis and liver cancer together accounted for 3.5% of all worldwide mortality in 2018, compared with 3% in 2000. This approximation is likely a significant underestimate, given the lack of accurate mortality information in many developing countries, including those in

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Received April 14, 2020; accepted June 18, 2020.
DOI: 10.1093/jalm/jfaa109

ADD-132514-GBL-EN

which there is a significant burden of viral hepatitis-related deaths *(1, 2)*.

Worldwide, liver disease risk and prevalence varies with gender, ethnicity, and socio-economic status. Latin America & Caribbean and Middle East & North Africa are the regions with the highest percentage of deaths due to liver disease, and the absolute number of deaths is highest in South Asia and East Asia & Pacific *(3)*.

The Scottish Public Health Observatory (ScotPHO) estimates that liver disease accounted for 16.3 deaths per 100 000 population in Scotland in 2018 *(4)*. Liver disease is the leading cause of death in the 35–49 age group, and the third leading cause of death in individuals under 65 years of age *(5)*. In addition, deaths from HCC have risen by two-thirds in the past 10 years, now ranking as the 9th most common cancer death, and occur almost exclusively in patients with chronic liver disease.

The three most common causes of liver disease in the western world and industrialized countries are nonalcoholic fatty liver disease (NAFLD), alcohol-related liver disease (ARLD), and viral hepatitis. These three etiologies account for 90% of chronic liver disease. All three are preventable, and chronic hepatitis C is now curable. Globally, this pattern varies. For example, in China and other Asian countries, hepatitis B virus remains among the leading causes of death *(6)*.

It is estimated that around a third of adults in the UK have the early stages of NAFLD. Therefore, diagnosing liver disease earlier could provide a window of opportunity to prevent the progression to fibrosis and cirrhosis, and thus reduce the current and future burden on healthcare systems *(5)*.

Liver Function Tests

The primary method of screening for liver disease is by analyzing a panel of blood markers referred to as liver function tests (LFTs). Such a panel will typically include liver enzymes such as alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST), markers of hepatocyte injury; bilirubin, a marker of parenchymal liver disease or biliary obstruction; and alkaline phosphatase (ALP), which can be a marker of biliary disease and cholestasis, but which is also produced by bone, intestine, and placenta. As well as NAFLD, ARLD, and viral hepatitis, there are a number of other causes of elevated (abnormal) LFTs, including autoimmune illnesses, biliary diseases, systemic illness, drug reactions, and infective hepatitis. The etiology of liver disease can be identified by a further cascade of specific blood tests known as a serological liver screen. The presence or absence of liver fibrosis or cirrhosis can be assessed using various noninvasive scoring systems [e.g., NAFLD fibrosis score and Fibrosis-4 (FIB-4) index] or the use of transient elastography, but the gold standard of diagnosis is a liver biopsy.

The number of LFTs requested in primary care has risen dramatically in recent years, almost doubling between 2002 and 2010 in the UK *(7)*. Around 20% of such LFTs have at least one elevated marker *(8)*. However, patients continue to present to liver clinics and acute medical admission units with end stage liver disease, even in cases in which the abnormal LFTs have been present for a number of years, suggesting there is a window for intervention to prevent progression from early liver disease to chronic liver disease that is being missed.

The Abnormal Liver Function Investigations Evaluation (ALFIE) study from Tayside in Scotland examined the consequences of incidental abnormal LFTs in primary care between 1989 and 2003. This study examined 95 977 patients who had LFTs checked a total of 364 194 times. 21.7% of patients had at least one abnormal liver enzyme, and 1090 (1.14%) went on to develop chronic liver disease within the timeframe of follow up (median 3.7 years) *(8)*.

Birmingham and Lambeth Liver Evaluation Testing Strategies (BALLETS) was a prospective

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study of patients with incidentally abnormal LFTs in primary care *(7)*. 1118 patients with abnormal LFTs were followed up by way of a full serological liver screen and ultrasound scan, as well as recording their BMI (body mass index), weekly alcohol intake, and features of the metabolic syndrome. NAFLD accounted for 26.4% of cases with abnormal LFTs, and alcohol-related liver disease accounted for 25.3% of cases. Of the NAFLD cases, 7.6% of patients had a high NAFLD Fibrosis Score (NFS), indicating a likelihood of having advanced fibrosis or cirrhosis, and a further 35.2% of patients had an indeterminate NFS, which recommends further disease assessment in secondary care *(9)*. This study, alongside the ALFIE study, indicates there is a significant number of patients with chronic liver disease with no clinical signs who could easily be identified at opportune moments.

ALT Upper Limit of Normal

In the ALFIE study, elevated transaminases (ALT and/or AST) were associated with a diagnosis of liver disease *(8)*. However, the value of the upper limit of normal (ULN) of ALT is subject to much debate. The value is known to be affected by BMI and age, validated in a study from Korea involving over 1000 potential liver donors, which proposed a ULN of 33 U/L for men and 25 U/L for women *(10)*. A European study involving 6835 blood donors with normal BMI and no history of liver disease identified an ULN of 30 U/L for men and 19 U/L for women *(11)*, while an American study as part of the National Health and Nutrition Examination Survey (NHANES) between 1999–2002 and 2005–2008 identified 29 U/L for men and 22 U/L for women *(12)*. Despite this, many laboratories continue to routinely use significantly higher ULN for ALT, usually 55 U/L, without discrimination between males and females. Using a lower ALT may allow the earlier detection of chronic liver disease, but it is unclear how this would impact service delivery. In addition, it is unclear if those with an ALT value of <55 U/L would require any intervention from healthcare services, and so detection of an 'abnormality'may not add any clinically relevant information.

Primary Care Management of Abnormal LFTs and the Introduction of the ELF Test

The management of abnormal LFTs by general practitioners (GPs) is variable, despite the presence of national guidelines *(13)*. Some abnormalities are ignored, some patients undergo extensive investigation, and some are referred to secondary care. Such guidelines recommend different pathways based on the pattern of LFT abnormality, including the drawing of various further blood samples, calculation of noninvasive fibrosis scores, and ultrasound imaging. Liver biopsy is defined as the gold standard in the diagnosis of chronic liver disease. However, it is expensive and has notable intra-observer variability *(14)*. In addition, Bravo et al. reported a hospitalization rate of up to 1%–3% following percutaneous liver biopsy with complications such as pain, vasovagal hypotension, and less commonly, bleeding, sepsis, and injury to surrounding organs *(15)*. There is also a small but significant risk of death; a large study (n = 61 187) in the UK found the 7-day all-cause mortality following liver biopsy to be 0.2%, and the mortality directly related to the biopsy procedure to be 0.01% *(16)*. On account of this, several noninvasive approaches to diagnose or exclude advanced liver disease confidently have been suggested.

The Enhanced Liver Fibrosis (ELF) score is a blood test measuring three molecules—hyaluronic acid, procollagen III amino-terminal peptide, and tissue inhibitor of matrix metalloproteinase 1—involved in the metabolism of the liver matrix. Elevated serum levels of these analytes represent increased turnover of the extracellular matrix and have been shown to correlate with various stages of liver fibrosis and cirrhosis *(17)*. ELF has been incorporated into the National Institute

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for Health and Care Excellence (NICE) guidelines for the diagnosis of NAFLD *(18)*. Higher scores are associated with increased risk of liver-associated adverse events such as decompensated chronic liver disease and liver-related mortality *(19)*. Despite featuring in several sets of clinical guidelines, including those published by NICE and the British Society of Gastroenterology *(13, 18)*, the ELF test is not routinely used in clinical practice and indeed is limited to very few centers in the United Kingdom. However, it appears to carry the potential to provide a reliable marker of liver fibrosis and could eliminate the need for transient elastography (which requires a secondary care clinic appointment) or liver biopsy.

The ALFIE study found that 50% of patients with abnormal LFTs underwent no further investigative testing *(8)*, and the BALLETS study found a significant number of patients with abnormal LFTs were at risk of advanced fibrosis and/or cirrhosis *(7)*. The workload on primary care is already substantial, and, despite clear guidelines for the management of abnormal LFTs *(13)*, patients in whom lifestyle interventions can make a difference go undiagnosed. As a result, an automated, real-time diagnostic tool—intelligent liver function testing (iLFT)—was developed to diagnose liver disease earlier and to provide management plans for GPs.

The aim of iLFT was to improve the diagnosis of liver disease. Referrers (GPs) provide information on BMI, the presence or absence of diabetes mellitus, and alcohol intake. In the case of any abnormality in initial LFTs, iLFT would automatically cascade into performing all of the recommended blood tests indicated in guidelines, such as viral serology, biochemistry testing, and immunology serology. The results are combined with the information provided by the GP and noninvasive fibrosis scoring systems to provide an automated, real-time diagnosis. This diagnosis, with an associated management plan (including whether the patient requires specialist review), would be communicated back to the GP.

DEVELOPMENT OF THE ILFT PATHWAY

Minimum Diagnostic Criteria

The initial development phase of the iLFT pathway required formulation of minimum diagnostic criteria for liver disease of various etiologies. These criteria were created by an expert group of hepatologists using Delphi methodology, with the aim to produce an algorithm which would allow patients to be stratified into three groups: 1) patients with early liver disease who can safely be managed in primary care (such as patients with uncomplicated NAFLD or ARLD); 2) patients in whom the diagnosis is unclear, but liver screen and fibrosis markers do not indicate liver disease and there is no evidence of fibrosis; and 3) patients with advanced liver disease or a liver diagnosis requiring specialist hepatology input (for example, any case of autoimmune hepatitis, or ARLD with evidence of fibrosis/cirrhosis). Patients could therefore be efficiently triaged, with groups 1 and 2 remaining in primary care for follow-up, and group 3 receiving a recommendation of specialist liver service referral *(20)*.

With the vision of iLFT in mind, the only data available to the hepatologists were limited patient demographics and characteristics (patient age, BMI, alcohol intake, and presence of metabolic syndrome), results of a predefined liver etiology screen, and calculated fibrosis scores (FIB-4 index and NFS). The criteria were designed to 'fail safe', with indeterminate fibrosis scores or presence of autoantibodies triggering referral to secondary care.

Validation of Diagnostic Criteria

The criteria were validated by comparing the suggested diagnosis and referral recommendation (primary versus secondary care) using the minimum diagnostic criteria against the 'gold standard' opinion of an expert hepatologist who had reviewed the patient in an outpatient clinic.

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The study population comprised 323 patients who had been reviewed in liver clinics in 3 Scottish tertiary referral hospitals. Referral recommendation agreement between the criteria and expert opinion was seen in 91.3% of cases, and 23 of the 28 incorrect referral recommendations 'failed safe' to secondary care. Diagnostic agreement was seen in 82.4% of cases. Of the 323 patients, all of whom had been seen in secondary care as per current practice, over a third could have been followed up safely in primary care without being seen in the liver clinic *(20)*.

Laboratory Automation, Reconfiguration, and IT Programming

Following development of the minimum diagnostic criteria, the next challenge was to employ the existing functionality within our automated laboratory system to allow these criteria to be applied in real-time as assay results were generated.

The Ninewells Blood Sciences Core Laboratory had undergone a significant upgrade in 2012 with the installation of Aptio® Automation technology (Siemens Healthcare Diagnostics Inc.). The hematology, clinical chemistry, and immunoassay systems were therefore linked by the track to various other units including the input/output, centrifugation, and refrigerated storage modules. This functionality was already utilized routinely by aematology and biochemistry for reflex, reflective and add-on testing, but for iLFT required virology to move from batched testing of hepatitis serology to real-time flow analysis.

iLFT required reprogramming of both the order communications software and Laboratory Information Management System (LIMS). Electronic requesting via the order communications software [Sunquest ICE v7.0.5 (Sunquest Information Systems)] is key to the function of iLFT as it allows transfer of clinical information (alcohol intake, BMI, and presence of metabolic syndrome) into the LIMS in such a way that it can be manipulated as data. Additionally, patient demographics such as age can be extracted automatically for use in the algorithms and calculated fibrosis scores, reducing the required data input from the requesting clinician. The order communications system prompts the requestor to take 3 blood samples—2 serum separator tubes for biochemistry, virology, and immunology analyses, and a potassium-ethylenediaminetetraacetic acid (K-EDTA) sample for hematology analysis.

On arrival at the laboratory the samples are processed and loaded onto the automated track system as per standard laboratory protocols. The iLFT pathway initially triggers analysis of the locally agreed liver panel (albumin, bilirubin, ALP, and ALT), plus gamma-glutamyl transferase (GGT). If the results of the initial analyses fall within predefined reference ranges, no further analysis is performed and the results are issued to the primary care physician. However, if results for the initial measurands exceed these ranges, additional tests cascade to produce the agreed liver disease etiology screen as per the algorithms shown in Fig. 1.

The logic for the iLFT algorithms is programmed in the LIMS [CliniSys LabCentre v1.13 (CliniSys Solutions Ltd.)]. The LIMS communicates with the analysers and Aptio® Automation via middleware [CentraLink® Data Management System v16.0.3.1 (Siemens Healthcare Diagnostics Inc.]. This bidirectional flow of data allows reflexive addition of tests from across the laboratory specialties, with the sample being directed between analyzers in real-time as required.

iLFT Assays

The automated analyses for the iLFT pathway are performed on the ADVIA® 2400 Clinical Chemistry System [ALT, ALP, total bilirubin, albumin, GGT, iron, c-reactive protein (CRP)], Dimension Vista® 1500 System (alpha-1 antitrypsin, AST, direct bilirubin, ferritin, haptoglobin), ADVIA Centaur® XP Immunoassay System (hepatitis B surface antigen, hepatitis C IgG antibody) and

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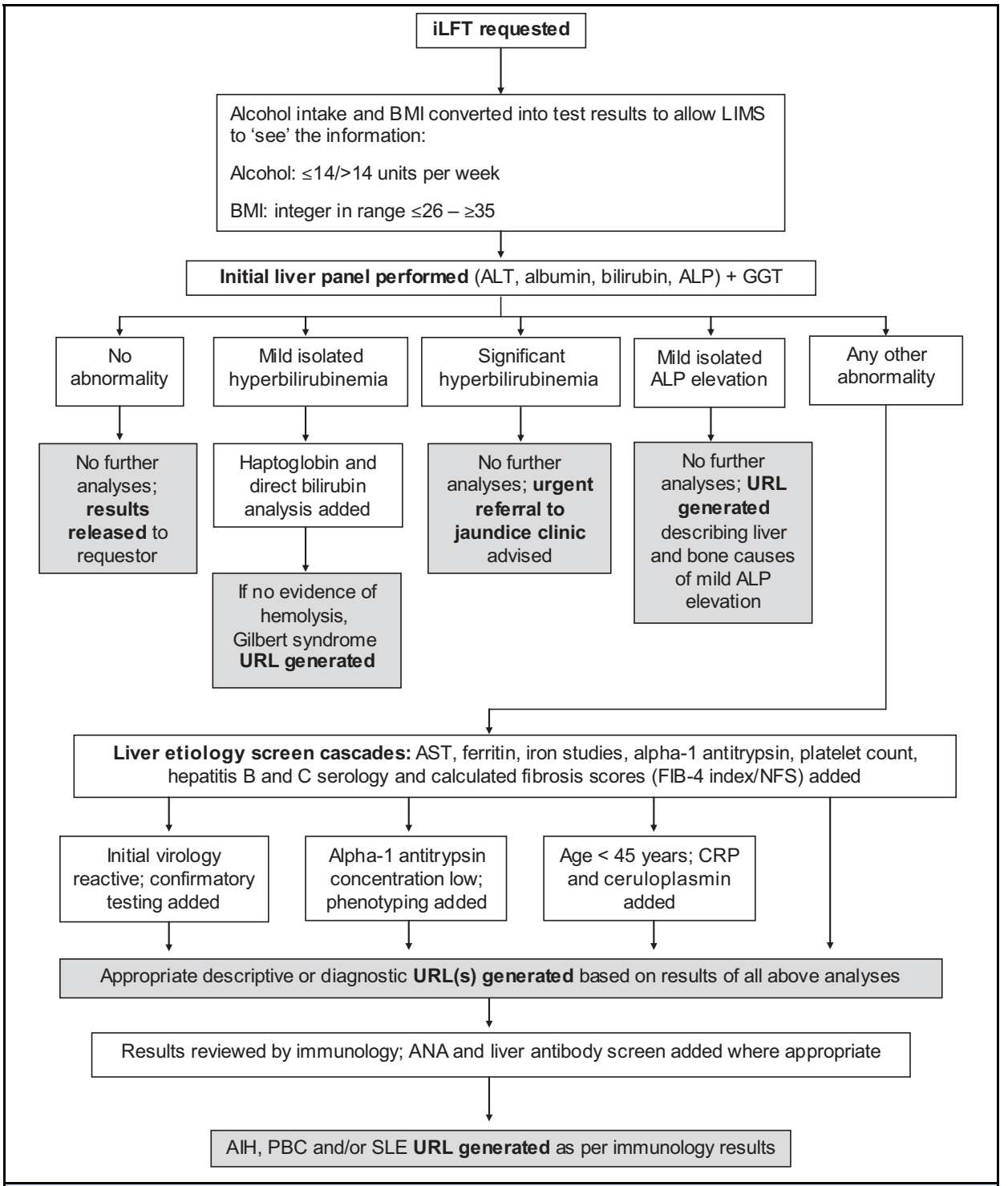

Fig. 1. Flow diagram illustrating the basic algorithms used in the iLFT pathway.

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ADVIA® 2120i Hematology System (platelet count) (all Siemens Healthcare Diagnostics Inc.). Where indicated, liver antibody screening is performed by indirect immunofluorescence on rat triple block tissue using QUANTALyser® 2 (Inova Diagnostics Inc.) and microscopy. Anti-nuclear antibody (ANA) testing (also by indirect immunofluorescence) is performed on HEp-2 slides. Ceruloplasmin and alpha-1 antitrypsin phenotyping are sent away to referral centers as per our standard laboratory protocol.

Reporting of results

The results of the assays are combined with the clinical details and demographics in the algorithms to produce one or more URLs that link to PDF files. These files provide a definitive or descriptive diagnosis and a further investigation and/or management plan for the primary care physician to follow. A recommendation as to whether referral to secondary care is appropriate is clearly stated. Using centrally-hosted PDF files allows the latest guidance and advice to be incorporated into the plans in a contemporaneous manner.

The main challenge was reprogramming our LIMS to allow it to report an active URL, but this was overcome with the help of Clinisys. The iLFT report is structured in a way that it can be easily read in a variety of different clinical software packages, or via a paper report. A short auto-comment summarizing the diagnosis and management plan is always included. Extensive end-to-end testing was required to cover every foreseeable scenario including reporting of all of the possible algorithm outcomes, and how to deal with missing laboratory, clinical, or demographic data.

RESULTS

Pilot Trial

A pilot study took place in the Tayside region of Scotland from September 2015 to November 2016. Six group General Practices (family doctors) were selected to ensure a mix of urban and rural patients. Inclusion criteria were people aged 18–75 for whom the GP requested LFTs. Exclusion criteria were jaundice, preexisting liver disease, previously known abnormal LFTs, or LFTs being performed for monitoring of a specific side effect of a drug or treatment.

A stepped wedge design was used with all six practices receiving iLFT as an intervention. A control population was derived from all patients in the practices who fulfilled the inclusion and exclusion criteria for 6 months prior to the intervention in each practice.

For all patients requiring LFTs, GPs could request iLFT instead of standard LFTs, simply by entering the BMI, diabetes status, and alcohol intake of the patient. If the components of the LFT results were abnormal based on NHS Tayside limits, the automated cascade of reflex tests was performed as described above. The report and 1 of 31 management plans were then made available to the GP in real time for action. The study team then reviewed each patient's notes 6 months after the intervention to assess the diagnosis recorded by the GP who had received the management plan from the iLFT result.

There were 490 patients in the control group and 229 patients in the intervention group. In the latter group, 64 (27.9%) patients had abnormal LFTs. GPs were able to ignore or adjust the iLFT diagnosis in favor of their own clinical diagnosis. iLFT supported the GP diagnosis in 67% of cases. However, the rate of liver disease diagnosis increased by 43% using iLFT ($P < 0.0002$) compared with controls. The number of nurse visits and blood requests did not increase. Referrals to hepatology specialist clinics were increased with an odds ratio of 8.44 (95% CI 1.99–35.73), in keeping with an increased detection of advanced liver disease.

A within-trial analysis assessed the cost effectiveness of iLFT. There is an incremental cost per

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correct diagnosis of £284. However, there is a cost saving of £3216 per patient lifetime with 0.021 quality-adjusted life year (QALY) gain, confirmed using a 1000 iteration Monte Carlo probabilistic analysis.

In a survey, 21 of the 23 GPs involved in the trial felt that iLFT reduced their workload and were positive about the project.

Real-World Data

Following the successful trial, iLFT went 'live' in Tayside in August 2018.

Requests were received for 2362 iLFT cascades in the 1 year from launch. A total of 160 (6.8%) were rejected due to missing clinical details such as alcohol history, or because the patient had had iLFT performed within the past 12 months. Normal LFTs were present in 378 (16%) cases and thus iLFT did not cascade. There were 1824 (77.2%) requests with at least 1 abnormal liver enzyme, resulting in iLFT cascade and 2013 diagnostic outcomes. Patients may have more than 1 diagnostic outcome if, for example, they have high levels of alcohol intake and also have positive hepatitis C virology, which would result in 2 separate management plans being sent to the GP.

The most common outcome was isolated ALT elevation without fibrosis (23.5%), followed by alcohol-related liver disease without fibrosis (14.7%) and nonalcoholic fatty liver disease with fibrosis (9.4%). The frequency of each outcome is shown in Fig. 2.

iLFT recommended patients be referred to secondary care in 509 (25.3%) outcomes (of which 393 (77.2%) were for further assessment of fibrosis only), with 1504 (74.7%) recommending primary care management.

CONCLUSIONS

iLFT offers significant benefits to all the specialties involved in the diagnosis of liver disease. A recent survey of 100 local GPs showed that 98% would recommend iLFT to a colleague. More GPs continue to adopt the new iLFT test, with uptake in the Tayside region still showing exponential increase as of January 2020. iLFT also benefits hepatologists because patients referred to clinic following iLFT already have their liver screen results and calculated fibrosis scores available, saving time and clinic venipuncture. Anecdotally, hepatologists now feel that they are seeing the right patient group in clinic—those in which they can offer valuable management, advice, and follow-up. The pilot data indicate that iLFT is cost-effective and will therefore benefit the health system more widely. Of course, longer-term data collection is required to confirm this. Finally, iLFT benefits patients in multiple ways: it increases overall diagnosis, allows diagnosis earlier in the disease course, and with long-term follow-up is expected to show some increase in QALYs.

However, the development of the iLFT pathway has not been without limitations and challenges. Despite the appropriate rate of secondary care referral recommended by iLFT, the fact that abnormal LFTs are now being fully investigated in line with national guidance has led to an increased demand for liver clinic appointments. A significant proportion of patients who receive a recommendation of secondary care referral do so because of indeterminate fibrosis scores (those between the 'rule out' and 'rule in' thresholds). In this indeterminate group we are currently investigating whether incorporation of the ELF score into the iLFT algorithm could help further stratify patients by risk of fibrosis, thus reducing unnecessary referral. A similar approach has been used by Srivastava et al. in the Camden and Islington NAFLD pathway and has been shown to be safe and effective *(21)*.

It has been challenging to engage with local GPs at the extent necessary for this study, which is understandable given the immense pressures on their time. We have provided education sessions

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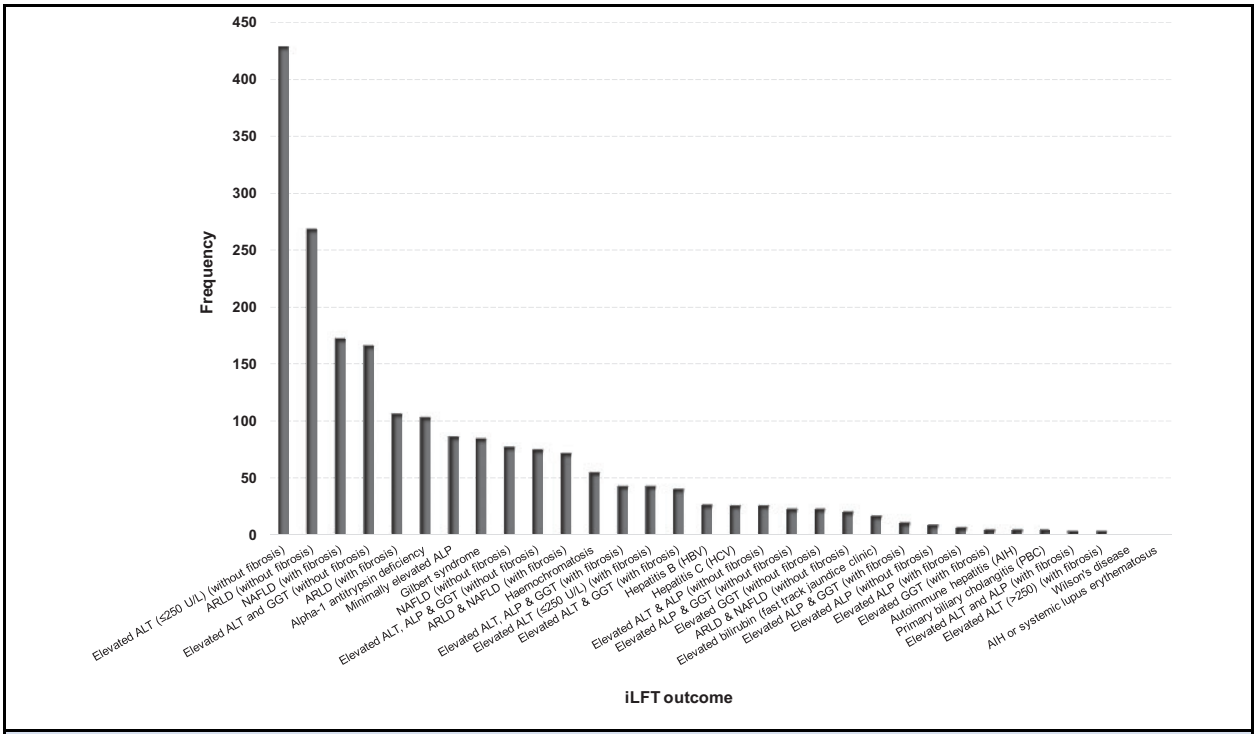

Fig. 2. Chart demonstrating the frequency of the iLFT outcomes generated by 1824 samples with an abnormality in the initial liver tests.

locally to help GPs make best use of the pathway, but are still finding that a significant number are not requesting iLFT in the target group—i.e., as the first set of liver tests in a patient with suspected liver disease—and are instead using it as a follow-up test after an initial set of abnormal LFTs. More structured education would also help us to emphasize the importance of the accuracy of the data they enter (as with almost all laboratory testing, the quality of what is put in increases the usefulness of the results generated) and help to reduce requests with missing data or samples. Finally, it is important that the requestors understand the limitations of iLFT. Whilst it has been shown to have high accuracy in referral recommendation and good accuracy in diagnosis, it is purely algorithm-driven, and as with all laboratory data, should be interpreted in the clinical context.

The development of the iLFT pathway has required adaptations to overcome issues as they have arisen, such as autorejection of incomplete requests and duplicate request evaluation. Given this, we now have a slightly more complex collection of algorithms and logic which could be streamlined if we were to start the project again. This experience is invaluable when helping other laboratories to implement their own version of the iLFT pathway. We have multiple enquiries from groups around the world, who are now progressing with iLFT in their own centers at varying rates. Barriers to roll-out primarily comprise IT issues (lack of a standardized LIMS or order communications package), organizational issues in both laboratory and hepatology services, as well as the configuration of laboratory automation in individual sites.

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We believe that the success of iLFT is centered on its utilization of existing technologies and processes in a novel way, and on its true multi-disciplinary reflexive testing approach. These allow the expertise of hepatology, clinical biochemistry, virology, immunology, and hematology to combine to generate a clear, practical report that assists GPs to investigate potential liver disease in line with guidelines. The general approach used in iLFT, namely the combination of demographic and clinical information with blood test results, lends itself to various other clinical problems. One such avenue is in the investigation, diagnosis, and management of the various causes of anemia.

iLFT helps to break down the barrier we often find between clinical and laboratory medicine, and uses information from both to increase diagnosis and improve patient outcomes. We have been proud to receive accolades from leading healthcare organizations across medicine, including the Royal College of Physicians (London), Royal College of Pathologists, and a UNIVANTS of Healthcare Excellence award. Our health service continues to require cost-, time- and personnel-efficient approaches to deal with the ever-increasing workload, and intelligent testing pathways such as iLFT hold the promise of forming part of the solution.

Nonstandard Abbreviations: CLD, chronic liver disease; HCC, hepatocellular carcinoma; S cotPHO, Scottish Public Health Observatory; NAFLD, non-alcoholic fatty liver disease; ARLD, alcohol-related liver disease; LFTs, liver function tests; ALT, alanine aminotransferase; AST, aspartate aminotransferase; ALP, alkaline phosphatase; FIB-4, Fibrosis-4; ALFIE, Abnormal Liver Function Investigations Evaluation; BALLETS, Birmingham and Lambeth Liver Evaluation Testing Strategies; BMI, body mass index; NFS, NAFLD Fibrosis Score; ULN, upper limit of normal; NHANES, National Health and Nutrition Examination Survey; GP, General Practitioner; ELF, Enhanced Liver Fibrosis; NICE, National Institute for Health and Care Excellence; iLFT, intelligent liver function testing; LIMS, Laboratory Information Management System; K-EDTA, potassium-ethylenediaminetetraacetic acid; GGT, gamma-glutamyl transferase; CRP, c-reactive protein; ANA, anti-nuclear antibody; URL, uniform resource locator; PDF, portable document format; NHS, National Health Service; QALY, quality-adjusted life year.

Author Contributions: *All authors confirmed they have contributed to the intellectual content of this paper and have met the following 4 requirements: (a) significant contributions to the conception and design, acquisition of data, or analysis and interpretation of data; (b) drafting or revising the article for intellectual content; (c) final approval of the published article; and (d) agreement to be accountable for all aspects of the article thus ensuring that questions related to the accuracy or integrity of any part of the article are appropriately investigated and resolved*.

I. Macpherson, statistical analysis; J.H. Nobes, statistical analysis, administrative support; E. Furrie, administrative support, provision of study material or patients.

Authors' Disclosures or Potential Conflicts of Interest: *Upon manuscript submission, all authors completed the author disclosure form. Disclosures and/or potential conflicts of interest:* **Employment or Leadership:** I. Macpherson, NHS Tayside. **Consultant or Advisory Role:** None declared. **Stock Ownership:** None declared. **Honoraria:** E. Dow, Siemens, Abbott. **Research Funding:** The development was funded by a research grant from the CSO Scottish Government. **Expert Testimony:** None declared. **Patents:** None declared. **Other Remuneration:** E. Dow, Siemens, Abbott.

Role of Sponsor: The funding organizations played no role in the design of study, choice of enrolled patients, review and interpretation of data, preparation of manuscript, or final approval of manuscript.

Acknowledgments: Mr Ian Kennedy, all our biomedical scientists and medical laboratory assistants, and local GPs.

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ADD-132514-GBL-EN