ABOUT THE MORPHOGENESIS, DIAGNOSIS AND TREATMENT OF LIVER CIRRHOSIS

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ANNOTATION

Chronic liver disease (CLD) is a neglected epidemic. Cases of early death from this disease are increasing. Along with heart and respiratory diseases, liver diseases are among the top three health problems in Uzbekistan. 50% of patients with CLD are first diagnosed with cirrhosis after emergency care, leading to poor patient outcomes. Traditional care models are based on secondary care when the need is at the community level. Screening patients for the presence of the disease based on population-level risk factors in the community allows early detection of disease when potential reversibility is present.

Innovation in three broad areas is needed to improve clinical care in this area: improving access to diagnostics in the community, integrating diagnostics into primary and secondary care, and using digital health to improve patient care. In this article, we describe how the Integrated Diagnostics for Early Detection of Liver Diseases (ID-LIVER) project, funded by Research and Innovation of Uzbekistan, is developing solutions for a population-level approach to liver disease detection in Uzbekistan. Bringing together NHS organisations, academic partners and commercial organisations, building on the innovation pathways previously established in Nottingham.

The goal is to co-create and implement a commercial solution that integrates multimodal diagnostics through advanced data science to drive growth and disrupt the current inadequate model. It is intended to be widely used within the NHS for the early diagnosis and stratification of liver disease at a population level.

Key words: liver disease, diagnosis, pathway, implementation, team, artificial intelligence.

Relevance. Liver disease is a serious health burden worldwide and is recognized as the main cause of death and morbidity in Uzbekistan. In 2011, for the first time, it was noted that despite improvements in mortality rates in neighboring Europe, deaths from liver disease continued to increase in England (1,8,12). It is the fifth leading cause

of death in Uzbekistan, and since 1970 the standardized mortality rate for liver disease has increased by 400%, in contrast to improvements in mortality rates for other major diseases (2,7,8). In addition, in Uzbekistan, liver disease is the main cause of death in the 30-49 age group (3.10,12).

The prevalence of lifestyle-related liver disease has increased over the past decade with the prevalence of diseases such as non-alcoholic fatty liver disease (NAFLD), a spectrum of diseases in which the liver cells contain excess fat. decreased, estimated to ~20-20. 30% worldwide (4,5,7). Timely diagnosis enables potential reversal of early liver fibrosis with behavioral intervention; 90% of liver diseases are related to lifestyle (5,10). About 50% of patients are diagnosed with liver disease only after emergency hospitalization (6,8,11). Liver diseases are in the first three places in terms of unequal medical care (7,12); The average age of death for people with chronic liver disease (CLD) differs by 9 years from those living in the least well-off Uzbekistan (8,9). In addition, the COVID-19 pandemic has a disproportionate impact on CLD; In a study of 15,000 hospitalized patients, the risk of death (hazard ratio 1.5) was the highest of all chronic diseases (9,12).

Although good at detecting advanced disease, no single diagnostic test is currently available or sufficient to reliably detect and stratify early liver disease. Traditionally, a series of blood tests called "liver function tests" (LFTs) are performed to determine the presence of liver disease. These include enzymes and molecules present when the liver is damaged. These tests are frequently requested but often do not detect liver disease; Up to 20% of LFTs have an abnormal result, but only 1.26% of these patients are subsequently diagnosed with chronic liver disease (10,11). In contrast, liver blood tests may be normal in up to 90% of people with severe liver disease (11).

Other methods for assessing a patient's likelihood of developing liver disease in the community include noninvasive scoring systems such as the patient's blood test results and the age-based FIB4 score, which are widely used in clinical practice (1,2,12). The advanced liver fibrosis (ELF) test can be used to predict the presence of liver fibrosis, but the availability of this test in the UK varies (4,6,13). Fibroscan is a specialized ultrasound examination that provides a quantitative assessment of the degree of scarring or fibrosis in the liver.

Early detection of liver disease in Uzbekistan The Integrated Diagnostics for Early Detection of Liver Disease (ID-LIVER) consortium of NHS clinicians, academics and leaders in the fields of diagnostics and artificial intelligence (AI) is working together to develop solutions for early detection of liver disease is working We have identified three gaps that we believe will improve the detection of early liver disease. The first critical gap is to improve how to detect liver disease at a stage where early intervention can make a difference. A second critical gap is the transition of diagnosis and initial management from hospital-based care to community-based care.

A third critical gap is the focus on diagnosis and intervention at the point of need, based on objective data rather than historical needs. Our hypothesis is that an innovative approach, combined with the expertise required to implement a clinical pathway in the NHS, will help meet these three needs. The novelty of our approach includes both interdisciplinary collaboration and broad disciplinary engagement; It is highlighted by the diversity of partners that span the NHS, two major universities and industry.

The goal is to have an iterative and integrated solution that crosses the traditional boundaries of primary and secondary care. The need for a comprehensive strategy to combat the burden of liver disease was first highlighted at the national level in 2011, and the first priority on the agenda was to strengthen early detection of liver disease (1, 2). Currently, most UK health care facilities do not have formal methods for diagnosing and treating liver disease. Screening of the general population for liver disease is not recommended by the American Association for the Study of Liver Disease and the European Association for the Study of Liver Disease (10, 12). Local initiatives aimed at early diagnosis of liver diseases among the general population have been implemented with heterogeneous approaches across Uzbekistan. Three established approaches are discussed below.

In Uzbekistan, the Scarred Liver Project (SLP) established a piloted pathway in which a general practitioner (GP) identifies patients for screening for CLD based on risk factors. Initial pilot studies in 2013 focused on risk factors for CLD, and this pathway is also implicated in metabolic and alcohol-related disease etiologies (11, 14). Based on Fibroscan results, patients at high risk of CLD receive additional testing in secondary care, while low-risk patients are discharged with lifestyle counseling. It has been shown to have diagnostic efficiency and cost-effectiveness compared to usual standard of care (13, 14).

Another approach that has been developed is the use of a "reflex" test method, in which further tests are initiated if the initial screening result is abnormal. Dillon et al. described a pathway of "Intelligent LFTs" (iLFTs) initiated in Dundee, Scotland, where abnormal LFT results led to a reflexive cascade of subsequent blood tests. Diagnosis and management advice based on these results is then provided to the GP (12). The ILFTs pathway has been shown to allow primary care management of 75% of abnormal liver blood tests (11). Reflex testing has also been used in the Gwent region of Wales to automatically calculate the ratio of aspartate aminotransferase (AST) and alanine aminotransferase (ALT) to LFT results after abnormal ALT, leading to increased detection of patients with cirrhosis. Community environment (2).

In the regions of Uzbekistan, two-stage stratification methods were established and accepted as routine clinical care. An example of a two-stage pathway in North London is Srivastava et al. Put the “NAFLD pathway” using FIB4 scoring and the ELF

test to stratify patients with a clinical diagnosis of NAFLD or abnormal ALT (12). Patients with a new or established diagnosis of NAFLD are eligible to participate in the program, and patients are stratified for low risk, unclear risk, or high risk for advanced liver fibrosis based on initial FIB4 results. Subsequently, the detection rate of cirrhosis was reported to be threefold compared to those on standard therapy.

The three separate paths have individual strengths and weaknesses. For example, starting with abnormal liver enzymes may miss disease, and focusing on risk factors will strain resources in the short term, even if long-term savings are realized. The ability to replicate and develop these pathways will be critical in a rapidly dynamic NHS landscape.

Collaboration between primary and secondary care was critical to the success of SLPs. As described in the President's Fund's 2019 report, Adopting and Disseminating Innovation in the NHS, the presence of senior clinical champions in primary and secondary care not only enabled co-production of the pathway, but also stakeholder education and problem-solving. was important in doing. inevitable problems that arose in the process of implementation. A shared sense of ownership by both primary and secondary stakeholders facilitated rapid resolution of implementation issues and prevented conflict between participants.

Having a deliberate pilot phase in implementing the project in different geographical locations was important in managing capacity and identifying problems early. This multi-step process required long-term commitment, active participation and negotiation of primary care and clinical champions to secure ongoing funding at each stage of the process. A major obstacle for the project was based on financial budgets that were trapped within operational silos. Long-term health economic arguments were understood by commissioners, but they were limited to focusing on short-term annual budgets. Similar challenges have been highlighted in numerous innovation reports, including a report from the President's Fund, which often cited funding for the transition to clinical care as a key barrier to successful innovation delivery (8).

Early studies of SLPs were conducted in different geographic and socio-ethnic areas and showed similarities in feasibility, engagement, and disease detection. However, an evaluation of the referral pathway found that 30 % of referrals originated from only 5 % of practices (Guha et al., Internal audit - unpublished). These practices are not based on areas of highest disease prevalence, and it has been emphasized that traditionally "hard-to-reach" groups (including disease characteristics and socio-ethnic factors) may need special solutions. Given the need to target areas with high liver-related morbidity and mortality, this study

Transferred to the ID-LIVER program.

Matching resources with changing demand has become a major obstacle as lifestyle-related risk factors increase. Finding effective triage tests, especially in the

context of normal liver enzyme tests, has been difficult. Thus, the need for fine-tuning the diagnostic pathway is clear; An attractive approach is to explore new tests or hypothesis-free approaches (such as machine learning techniques) in future iterations.

Active implementation of health technologies

ID-LIVER project

Integrated Diagnostics for Early Detection of Liver Disease, or ID-LIVER, is a new consortium focused on early detection of liver disease. We aim to use machine learning algorithms to integrate patient and diagnostic data from multiple sources to develop a model to identify patients at high risk of progression to clinically significant disease. These individuals can then be targeted for interventions to reduce this risk, with the potential to improve health outcomes and costs. The project is funded by the UK Government's Innovate UK Industrial Strategy Challenge Fund, which is providing £2.5m, and a £2m cash match from industry partners. It represents a collaboration between clinical and academic colleagues at the University of Manchester, the University of Manchester NHS Foundation Trust, the University of Nottingham and Nottingham University Hospitals NHS Trust, as well as major industry partners GE Healthcare and Roche Diagnostics.

The clinical care pathway established in Uzbekistan was developed in collaboration with the Integrated Care System (ICS) and Primary Care Networks (PCNs) to create a pathway that facilitates primary and secondary care needs. New liver assessment clinics are blurring the traditional paradigm of primary and secondary care. Early involvement of panel members and having clinical champions in primary and secondary care were important factors in the SLP (Lessons from the Scarred Liver Project). The ID-LIVER team proactively considered factors at each stage of the patient journey, from identification to investigation, that not only improve efficiency but also ensure equity of access (Improving Equity in Healthcare Delivery).

Improving health care equity

The geographic location of clinical interactions for liver assessment clinics is an ongoing discussion for ID-LIVER. The goal of working with the Sollis Clarity health analytics platform is to understand the context of population health. In collaboration with primary care organizations such as ICSs and PCNs, we can begin to understand where risk profiles for liver disease lie geographically through disease 'heat maps' and then establish new community liver assessment clinics in these areas. Clinics may be ranked based on high disease burden, disproportionate liver mortality, or liver-related outcomes. This is aimed at eliminating routing bias and improving the equity of the service provided.

Patient and community engagement organization Vocal has launched an open discussion with various patient groups in Manchester with risk factors for liver disease. Involving "hard-to-reach" patient groups in patient design aims to increase access to

services and is an important part of improving equity of care. Identifying "at risk" patients using digital search tools.

With limited resources in the current NHS, patient identification for further clinical trials is a pressing issue. GP practices are being screened using North West EHEALTH's FARSITE (Feasibility and Recruitment System for Trial Effectiveness) technology to facilitate the identification of patients with risk factors for CLD.

It is a centrally managed profiling tool that identifies whether a patient has risk factors from de-identified records. All patients with risk factors for liver disease documented in their records can be contacted directly by GP written communication, which is an important factor in implementing a GDPR compliant pathway design. Critically, once optimized, this technology requires very little input from busy clinical and operational staff, and the pace of invitations can be controlled to match the capacity of the individual assessment clinic.

After an initial search of Uzbekistan's central practices (serving ~900,000 people), FARSITE identified 2,005 patients with three or more risk factors who had never been screened for liver disease. Another 55, 286 have one or more risk factors for liver disease. This shows how important the potential target population is for research even in a small geographic area. Thus, the project provides a proof of concept if digital search tools can be integrated into clinical pathways of care. Importantly, this provides a mechanism to identify patients with a burden of risk factors but who are not stratified for CLD, and there is a disparity in practices.

Providing diagnostic services to those at high risk of liver disease

Optimizing the delivery of resources to individuals at greatest risk of liver-related outcomes is critical in a financially constrained model. It is important to identify those with advanced or early liver disease and those at high risk of developing the disease. We are using an AI approach to solve this so that differentiation can be done on a larger scale than previously defined paths. In collaboration with Jiva.ai, a company specializing in predictive analytics using artificial intelligence, we are developing an algorithmic tool to predict the risk of clinically significant liver disease. Putative biomarkers are prospectively validated and incorporated into AI modeling.

Improving clinician acceptance

There are many electronic patient record systems around the country that often do not interact with other systems in place in health care facilities. Collecting and managing the multiple streams of data required in patient care is often difficult. As a tool to solve this problem, a new clinical interface, a cloud-based platform, is being developed together with Roche diagnostics. Ideally, this would be accessible to all healthcare professionals involved in the patient's diagnostic pathway, from nurse practitioners to consultant hepatologists, reducing duplication and ensuring consistency.

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