The EASL–Lancet Liver Commission: protecting the next generation of Europeans against liver disease complications and premature mortality

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Frontpage sentence: **"The liver is a window to the 21st century health of the European population."**

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Abbreviations: See Supplementary Appendix for details.

Methods: See Supplementary Appendix for details.

Word count, Executive summary (after revision): 879

Word count, Main text (after revision): 24,990

Number of references (after revision): 434

Main figures: 20 (and 8 Supplementary Figures)

Main tables: 6 (and 4 Supplementary Tables)

Main box items: 2 (and 2 Supplementary Boxes)

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Executive summary

Liver diseases have become a major health threat across Europe and the face of European hepatology is changing due to the cure and control of chronic viral hepatitis C and B respectively, the increasingly widespread unhealthy use of alcohol, the epidemic of obesity and undiagnosed or untreated liver disease in immigrants. Consequently, Europe is facing a looming syndemic in which socioeconomic and health inequalities combine to adversely affect the prevalence, outcomes and opportunities to receive liver care. In addition, the Covid-19 pandemic has magnified pre-existing challenges to uniform implementation of policies and equity of access to care in Europe, arising from national borders and the cultural and historical heterogeneity of European societies. In following up on work from the Lancet Commission on Liver Disease in the UK and epidemiological studies led by the European Association for the Study of the Liver (EASL), our multidisciplinary Commission, comprising a wide range of public health and medical and nursing specialty groups, along with patient representatives, set out to provide a snapshot of the European landscape on liver diseases, and to propose a framework for the principal actions required to improve liver health in Europe. We believe that a joint European process of thinking, construction of uniform policies and action, implementation and evaluation can serve as a powerful mechanism to improve liver care in Europe and set the way for similar changes globally.

Our analysis resulted in the following key findings:

1) Liver disease is now the second leading cause of years of working life lost in Europe, second only to ischaemic heart disease.

2) The clinical focus in patients with liver disease is oriented towards cirrhosis and its complications, while early and reversible disease stages are frequently disregarded and overlooked.

3) The dissociation between primary and secondary care and the considerable heterogeneity across clinical pathways and inconsistent models of care, cause delays in diagnosis of both rare and common liver diseases.

4) Stigma has a major impact on liver diseases in Europe leading to discrimination, reduction in health-seeking behaviour and reduced allocation of resources, which all result in poor clinical outcomes.

5) Europe has the highest rate of alcohol consumption in the world, which together with ultra-processed food consumption, and high prevalence of obesity are the major drivers of liver-related morbidity and mortality.

6) A lack of consistent and efficient screening and vaccination programs for viral hepatitis combined with high costs of drugs due to variable European reimbursement systems result in reduced access to treatment and delays in elimination programs.

7) Covid-19, alongside imposing delays in diagnostic pathways of liver diseases, has brought overlapping metabolic risk factors and social inequalities into the spotlight as critical barriers to liver health for the next generation of Europeans.

8) Liver diseases are in the main avoidable and/or treatable if measures for prevention and early detection are properly implemented, thus reducing premature morbidity and saving the lives of almost 300,000 people per year across Europe.

Based on these data, we present ten actionable recommendations, half of which are oriented towards health care providers and half of which focus primarily on health policy. A fundamental shift must occur, where health promotion, prevention, proactive case-finding, early identification of progressive liver fibrosis and early treatment of liver diseases replace the current emphasis on the management of end-stage liver disease complications. A considerable focus should be put on underserved and marginalised communities, including the need for early diagnosis and management in children, and we provide proposals on how to better target disadvantaged communities through health promotion, prevention and care using multilevel interventions acting on current barriers to care.

Underlying this transformative shift, we need to enhance awareness of the preventable and treatable nature of many liver diseases. Therapeutic nihilism, which is prevalent in current clinical practice across a range of medical specialities as well as in many patients themselves, has to end. We wish to challenge medical specialty protectionism, and invite a broad range of stakeholders, including primary care, nurses, patients, peers and members of relevant communities, along with medical specialists trained in obesity, diabetes, liver disease, oncology, cardiovascular disease, public health, addictions and infectious diseases, and more, to engagement in an integrated, person-centred liver patient care across classical medical specialty boundaries. This shift includes a revision in how we converse about liver disease and speak with our patients, in order to reappraise disease-related medical nomenclature so as to increase awareness and reduce the social stigmatisation associated with liver disease.

Reimbursement mechanisms and insurance systems must be harmonized to account for patient-centric, multimorbidity models of care across a range of medical specialties, and the World Health Assembly resolution to improve the transparency and fairness of market prices for medicines throughout Europe should be reinforced. Finally, we outline how Europe can move forward with implementation of effective policy action on taxation, food reformulation, product labelling, advertising and availability, similar to that implemented for tobacco, to reduce consumption of alcohol, ultra-processed foods, and foods with added sugar, especially amongst the young. We should utilize the window of opportunity created by Covid-19 to overcome fragmentation and variability of health prevention policies and research across Europe. Through our proposed syndemic approach to liver disease and social-health inequalities in Europe, the liver will serve as a sentinel for improving the overall health of European populations.

A NEW ERA OF EUROPEAN HEPATOLOGY

Liver disease is frequently silent, and ongoing liver injury may result in few overt symptoms and signs until end-stage liver disease has developed. Silent also, is the voice of those with liver disease; liver maladies frequently affect the most vulnerable and unrepresented sectors of society. The decisive silence is the lack of political willingness to implement population-level policies to overcome the social and environmental factors and health inequalities that synergistically drive some of the key causes of liver disease; unhealthy alcohol consumption and obesity. Far beyond the liver, alcohol and ultra-processed foods (UPFs) represent key health challenges in the 21st century, and it is increasingly clear that liver disease acts as a cipher for health and a sentinel for our public health capacity.

Three important factors signal the timeliness for a reconsideration of liver disease and liver disease management.[1,2] The advent of direct acting antiviral (DAA) drugs marked the end of a 30-year translational journey from the discovery of the hepatitis C virus (HCV) as the cause for non-A, non-B hepatitis to a definitive cure.[3] Beyond vaccines, there are only a few examples of such transformative drug developments in medicine, and the importance of discovering the virus was recognized by the award of the 2020 Nobel Prize in Physiology and Medicine.[4] Second, the major adverse impacts of type 2 diabetes and obesity on outcomes during the Covid-19 pandemic have revealed the deleterious effect of poor levels of underlying health and galvanised opinions on the importance of policy interventions to deal with rising population levels of obesity.[5,6] It has also highlighted the need for rapid, at scale point-of-care testing and appropriate vaccination programs for infectious agents, emphasizing in particular existing public health deficits for hepatitis B virus (HBV) and HCV infection.[7] Finally, whilst improvements in medicine have been driven by

specialisation, there is an increasing realization of the importance of multiple linked morbidities and hence the need for multi-disciplinary teams of primary care physicians, nurses, allied health professionals and other specialists to deliver high quality care efficiently.[8] Non-alcohol related fatty liver disease (NAFLD) exemplifies the need for conjoined working between hepatologists, diabetologists, dietitians, cardiologists and general practitioners (GPs).[9,10]

These challenges resonate in European hepatology given changing populations as a result of ageing and a changing demography, as well as immigration from areas with higher exposure to HBV, HCV and hepatitis D virus (hepatitis delta virus, HDV). Europe also has the highest level of alcohol consumption in the world, and more than 50% of end-stage liver disease is due to unhealthy levels of alcohol consumption.[11] The Lancet Commission on liver disease in the UK has provided strong examples of how challenging it is to implement effective regulations and policy measures against obesity and alcohol-related liver disease.[12,13] The European Association for the Study of the Liver (EASL) “Hepahealth” project has also demonstrated significant geographical variability within Europe; some areas have low or decreasing liver-related mortality, whereas in others liver-related mortality remains high and is increasing.[14] Whilst there may be policy or legislative solutions to prevent many liver diseases, these are often met with policy inertia, with governments reluctant to introduce them, largely driven by the actions of vested interest groups,[11] and an absence of public demand for action.[15]

In this Commission report, we will detail the challenges and propose solutions. The realisation that many liver diseases are preventable provides an important opportunity, although this will require concerted efforts to make the case for changes both to the public and to governments. For medical professionals, early identification

of progressive forms of liver disease, at scale, will be clinically important, as will new models of delivering care that incorporate the power of digital healthcare and multi-disciplinary skills. We reinforce the need to work with medical specialties beyond the liver, to increase awareness and recognition in other disciplines. Liver disease is positioned to take on the role as a canary in the coalmine for the health of the next generation of Europeans.

THE BURDEN OF LIVER DISEASE BASED ON A EUROPEAN LANDSCAPE OF RISK FACTORS

Chronic liver disease has a substantial impact on young and middle-aged individuals in their prime working years, with the peak age of death occurring in the late 40's and early 50's. This contrasts with morbidity from smoking-related and other obesity-related illnesses, like lung cancer or type 2 diabetes, respectively, where deaths typically occur in the 60's (**Figure 1**). Consequently WHO data demonstrate that liver disease is now second only to ischaemic heart disease as the leading cause of years of working life lost in Europe (**Figure 2, Supplementary Figure 1**).[16] In fact, on average two-thirds of all potential years of life lost due to mortality from liver diseases are years of working life.[14]

Mining for quality data

Chronic liver disease led to 287,000 deaths in Europe in 2019 (95% confidence interval [CI] 268,000-306,000), of which 63,500 (95% CI 58,916-67,530) were due to primary liver cancer. Liver-related deaths comprised 3% of all deaths in 2019, which is an increase from the 204,000 deaths in 1990 (2.3% of all deaths). These changes equated to a 25% increase in deaths due to chronic liver disease and a 70% increase for primary liver cancer.[17,18] The contrasting changes over time in liver mortality between countries (**Figure 3**) can be captured by categorising them into five groups; stable low, decreasing, stable high, increasing, as well as an intermediate category with no clear trend (**Supplementary Table 1**). Understanding the underlying reasons for this wide variability holds important lessons for Europe and the world beyond.

In establishing a data-driven basis for recommendations in this report, information on the aetiology of liver disease was collected from several sources, with inevitably some inherent strengths and weaknesses. Death certification data collated by the

WHO are known to under-report liver deaths, as in some countries they are derived from interviews with family members.[19] In Europe, alcohol consumption is by far the leading cause of liver-related mortality, but the aetiology of liver disease is frequently not recorded (**Supplementary Figure 2, panel A**) and similar issues arise with the coding of hospital admissions.[20,21] Indeed, in some European countries 80% of liver deaths do not have a recorded aetiology, and ICD-10 classification is known to vary largely between studies.[22] These problems of reported liver-related deaths can also be illustrated by comparing data from England and Wales in a single year (**Supplementary Table 2**). In the modelled Global Burden of Disease (GBD) estimates, the proportions of liver deaths attributed to alcohol were similar to those recorded directly on death certificates, whereas deaths due to NAFLD were 42% higher and for viral hepatitis 7 times higher (**Supplementary Table 2**). An alternate approach taken by the GBD study is to use the cause of death on death records only to classify deaths as due to cirrhosis or liver cancer, and to model what proportion can be attributed to different aetiologies based on the proportions observed in representative cirrhosis and liver cancer case series (**Supplementary Figure 2, panel B**). There is, however, consistency between the WHO and GBD data (**Supplementary Figure 2**), and since GBD modelling probably represents the best resource, data from the 2019 release were analysed for this report.

The scope of this work goes beyond the European Union (EU) and spans the WHO definition of Europe.[23] Due to limitations in available data, our reporting and descriptions are regional for several topics, e.g. accounting for the EU; the EU and the European Economic Area (EEA), also accounting for Switzerland, the UK and/or Russia (when specified); as well as for some examples by data from case studies of single countries or areas. The problem of making a coherent definition of Europe for

all aspects of this report is related to several of the problems the Commission has been mandated to query.

The European landscape of risk factors and liver disease

The progression from a normal liver, through progressive fibrosis, to cirrhosis, liver failure and related complications, and in some cases liver cancer, occurs in response to multiple risk factors and disease mechanisms (**Figure 4**). A shift in diagnostic emphasis towards these final, common pathways of end-stage liver disease has important implications for the simplification of case-finding and patient referral, which should focus on the detection of progressive disease with high risk of complications. It often takes a long time to develop liver disease complications, sometimes decades, and this inherent resilience also means that multiple risk factors acting in synergy should always be considered in progressive liver disease.

Alcohol and liver disease - a dose-related condition at the population-level

Europe has the highest rates of alcohol consumption per capita, the highest prevalence of heavy episodic drinking, and the lowest rates of abstention from alcohol in the world.[11,24] According to GBD modelling alcohol was responsible for around 580,000 deaths in 2019, 6.2% of all deaths, in the WHO European region.[17] Alcohol causes approximately 40% of the 287,000 premature, liver-related deaths in Europe every year, although numbers may be higher.[25] Alcohol-related liver disease is the most frequent liver disease, being responsible for at least 50% of cases of cirrhosis,[24] and is the most common indication for liver transplantation in Europe.[26,27] Despite this, the topic of alcohol-related research is under-represented, amounting to just 5% of all publications in the area of liver disease (2010-2014 assessment). At the large

European and American liver congresses, alcohol-related liver disease represented only 7% and 4%, respectively, of the research presented.[28]

Alcohol-related harm correlates with the volume and pattern of drinking, with epidemiological studies demonstrating an exponential dose-response relationship between alcohol and liver disease.[29] As such, an understanding of the volume and pattern of alcohol consumption across populations and by individuals is essential to better understand alcohol-related liver disease, and to identify the most effectual and cost-effective policies and interventions to prevent and reduce the burden of disease. For most European WHO region countries there is strong relationship between liver mortality rates and population level alcohol consumption (**Figure 5, Panel A**). Some countries, notably Ireland, have lower standardised liver mortality rates than may be expected from population level alcohol consumption, but this may, in part, reflect errors in coding in relation to death certificates. There are a number of European countries with very high levels of liver mortality in relationship to alcohol consumption (**Figure 5, Panel B**). Hungary and Moldova have high levels of recorded alcohol consumption, and also have high levels of unrecorded alcohol consumption,[24] reflected in levels of liver mortality.

The evidence linking liver-related mortality and population alcohol consumption has a critical message for disease prevention - alcohol-related cirrhosis is a dose-related condition at the population-level, and the most effective and cost-effective means to reduce mortality rates from alcohol related liver disease are interventions that reduce population-level alcohol consumption.[30-32]

The European landscape of viral hepatitis

Based on GBD estimates, there were approximately 300 deaths per day due to HBV and HCV in the WHO Europe region in 2019,[17] the majority related to cirrhosis. These GBD estimates indicate that ten of the 53 countries in Europe account for the majority (74%) of the total viral hepatitis burden, while some smaller countries (e.g. Georgia) demonstrate the highest population rates.[7,17] Robust estimates of incidence and prevalence of chronic HBV and HCV infection remain challenging even in countries with well-developed surveillance systems, due to the high frequency of asymptomatic and thus largely undiagnosed infections, the lack of formal screening programs and poor access to diagnostic testing. Therefore epidemic models are often used to infer disease burden and transmission. However, absent or uncertain data underpinning these models poses methodological challenges.[33] A collaborative effort by EASL and the European Centre for Disease Prevention and Control has demonstrated the feasibility of sentinel site surveillance – piloted in three European countries (Bulgaria, Norway and Portugal) – to measure the fraction of cirrhosis and HCC attributed to viral hepatitis and help facilitate country-level monitoring, without which evaluation of the impact of interventions to avert liver disease will be thwarted.[34]

Between 1.6% and 3.1% of the population in Europe are estimated to be infected with hepatitis viruses (15 million with HBV and 14 million with HCV), with prevalences ranging markedly from low (<0.1% for HBV and <0.5% for HCV) in some Western, Northern and Central European countries to high (6-8% for HBV and 3-6% for HCV) in some countries in the eastern part of region.[35,36] The epidemiology of viral hepatitis in the WHO European region thus varies considerably. Of those infected in Europe, a

minority (only 13% with HBV and 31% with HCV) are estimated to have been diagnosed.[36] People who inject drugs (PWID) and prisoners have the highest prevalence for both infections.[37] The prevalence of HCV or HBV is 15 to 50 times higher in PWID than in the general population in European countries with available data, and risks associated with injecting drug use contribute to the majority of new HCV infections in Europe.[38-41] However, transmission due to unsafe procedures inside and outside health care settings continues to play a role in several countries.[42]

The introduction of universal childhood HBV vaccination in the 1990s was a landmark event in hepatology; this intervention has had a marked positive effect on the prevalence of HBV infection in children under the age of 10 years.[43-46] There has also been a documented decrease in hepatocellular carcinoma (HCC) incidence,[47,48] and the HBV vaccine is the first vaccine that has been shown to prevent neoplasia.[49] Although vaccination has reduced the prevalence of HBV in children, vaccination programs will not alleviate the large existing burden of chronic HBV infection in an older generation. Thus many countries, for example Bulgaria and Romania, still have a heavy disease burden in older age cohorts.[50] Furthermore, low endemic countries in Europe with an overall HBV prevalence of nearly 1% among the general population, have rates of HBV infection in foreign born immigrants of up to 5%, contributing to an important fraction of the total number of HBV cases in these countries.[51] The 2030 goal of preventing new cases of chronic HBV in Europe requires widespread birth dose vaccination and additional interventions, including third trimester nucleoside analogue prophylaxis, to prevent mother-to-child transmission from mothers with viraemia.

The overall disease burden of HDV co-infection in HBV patients is declining in Europe following the introduction of HBV vaccination programs. The current

prevalence of anti-HDV is approximately 3% among young individuals and PWID (of those positive for HBsAg), reflecting the positive impact of HBV vaccination and harm reduction programs. Still, high rates of HDV are observed in older individuals of countries such as Romania and Moldova where HDV infection is endemic. Currently, immigrants from countries with high HDV prevalence are responsible of the majority of new cases of HDV.[52] Co-infection with HDV results in more rapid progression to cirrhosis and HCC.[53] Specific therapies are under development, just approved, or on the horizon.[54]

Based on the presence of anti-HCV antibodies or on surveys conducted in selected populations, two-thirds of the HCV infected persons in Europe live in eastern regions.[7,55] The incidence of HCV-related cirrhosis, HCC and liver transplantation for end-stage liver disease due to HCV infection is declining due to scale-up treatment with highly effective DAA therapies.[56,57] Within four years of the introduction of DAAs in Scotland, major reductions in new presentations of decompensated cirrhosis (67% fall), HCC (69% fall) and associated deaths (49% fall) were observed among those with chronic HCV.[56,58] The prevalence of chronic HCV is estimated to have declined, perhaps by as much as one third, in many Western European countries such as France, Spain, Italy, and UK over the last 5 years, based on estimates of available data and the size of at risk populations, although these estimates are dependent upon imperfect models utilizing incomplete surveillance data to track progress.[59] While it is difficult to measure incidence directly (because of asymptomatic infections and suboptimal surveillance programs) it has been suggested that the incidence of HCV infection has remained relatively stable over the past five years. Currently, transmission through injection drug use accounts for 84% (95% credibility interval 57%-94%) of HCV new infections in Europe.[41]

Hepatitis E virus (HEV) infection is an important cause of acute viral hepatitis with an increasing incidence. It is underreported though, as the majority of HEV infections are asymptomatic and only 20 European countries actively monitor HEV infection, rendering it difficult to gauge the true incidence. Most cases of acute HEV occur in men older than 50 years, are caused by genotype 3, are food-borne and are usually self-limiting.[60] However, it is increasingly recognized that in immunosuppressed individuals or those with pre-existing liver disease, HEV infection can progress to chronic disease.[61]

An epidemic on the rise - metabolic liver disease in Europe

NAFLD is becoming a leading cause of liver-related mortality in Europe and is predicted to become the leading cause of end-stage liver disease in Europe unless dramatic action is taken.[62-64] Indeed, NAFLD is already the most common liver disease worldwide, affecting as much as a quarter of the global adult population with a prevalence in Europe of 23.7% (95% CI, 16.1%-33.5%).[65] For people with NAFLD, the development of non-alcohol related steatohepatitis (NASH), characterized by the presence of fat together with signs of inflammation, marks the first step of progression towards advancing stages of liver fibrosis.[66] Modelling of the disease burden in France, UK, Germany, Italy and Spain along with China, Japan and the US shows that the burden of advanced liver disease due to NAFLD will more than double during 2016–2030.[63,67] Modelling also suggests that the annual predicted economic burden of NAFLD in Europe will be more than €35 billion in direct costs and a further €200 billion in societal costs.[68]

NAFLD is an often neglected but integral component of metabolic disturbances in people with obesity and type 2 diabetes. The prevalence of NAFLD is very high in

people with obesity or severe obesity in whom it is 75%-92% and over 90%, respectively.[69] The prevalence of NAFLD was 59.7% (95%CI 54.3-64.9) in a meta-analysis of 24 observational studies including a total of 35,599 patients with type 2 diabetes.[70] In another study the prevalence of biopsy-proven NASH among people with type 2 diabetes was 37.3% (95% CI 24.70–50.02%) of whom 17% (95% CI 7.29–34.86%) had significant fibrosis (more than stage F2, in a classification from F0; no fibrosis to F4; cirrhosis).[71] These data rank NAFLD as a major non-communicable disease (NCD), which we will elaborate below.

The burden of NASH in the WHO European region in 2019, the prevalence of NASH-related cirrhosis and liver cancer and resulting estimated years lived with disability indicate that NASH affects the lives of hundreds of thousands of Europeans (**Table 1**). The latest GBD estimates of the age-standardised death rate from NASH-related cirrhosis in the WHO European region was 1.4 (1.0–1.9) per 100,000 in 1990 and increased slightly to 1.5 (1.1–2.1) per 100,000 in 2019. Greater increases are noted in the prevalence, incidence and mortality of NASH-related liver cancer (**Figure 6**). In the past three decades, the age-standardized prevalence rate of liver cancer due to NASH has almost doubled.

Furthermore, a purely liver-centric view does not encompass the multisystem and multidisciplinary implications of NAFLD. Indeed, NAFLD is just one facet of a systemic disease that confers substantially increased morbidity and mortality on those patients who are affected and where the most common causes of death are cardiovascular disease (~40% of the total deaths), followed by extra-hepatic cancers (~20%) and liver-related complications (~10%).[72-75]

Primary liver cancer – a prototype case for screening

In 2020 primary liver cancer was the sixth most common tumour in terms of incidence and the third most lethal tumour in terms of mortality.[76] HCC accounts for more than 80% of all primary liver cancers. Cholangiocarcinoma (CCA), arising from the bile duct epithelium, and although rarer, confers an even poorer prognosis due to late diagnosis.[77,78] Only 20% of CCA patients are eligible for surgical resection, with 5-year survival of less than 10% for all patients.

Within Europe around 87,000 new cases of HCC were diagnosed in 2020, resulting in an average age-standardized annual incidence rate of 5.2 per 100,000 person-years. During the same year (2020) around 78,000 persons died in Europe as a consequence of liver cancer. Driven by differences in aetiology and other factors, the incidence in Northern Europe is around half (12,000 cases per year) that of Central and Eastern, Southern and Western Europe (24,000 to 26,000 cases per year).[76] Whilst often a sequel and accompaniment of cirrhosis from a variety of aetiologies, NAFLD-related liver cancer stands out by increasingly being seen even in patients without cirrhosis.[79,80]

The mortality-to-incidence ratio (MIR) measures the lethality of a tumour, such that for the most lethal tumour, mortality would equal incidence resulting in an MIR of 100%. In comparison to prostate cancer, with high curability and a MIR of 20%, the MIR of HCC is 91% worldwide, ranking it as the third most lethal tumour globally.[76] The average number of years of life lost due to HCC compared to a reference population of the same age-class was estimated as 7.9 years, although reassuringly the number of years of life lost has declined from 12.6 years in 1986-1999, to 10.7 years in 2000-2006 and now to 7.9 years. This may reflect advances in HCC diagnosis and management but also the occurrence at later stages in life where

comparative life expectancy is shorter.[81] Indeed, the average age of onset and death have risen over the years and are now about 68 years and 71 years, respectively, with the loss of life span closely related to the age of diagnosis. Patients diagnosed with HCC younger than 60 years may lose an average of 15.5 years of life, whereas those diagnosed after 75 years may only lose 4.5 years.

Detection of HCC at earlier stages would reduce mortality to a maximum of 5 years of life lost, regardless of age at diagnosis, but unfortunately more than 60% of HCC patients in Europe are diagnosed at intermediate or advanced stages.[81,82] This is in contrast to Japan, where more than 60% of these patients are diagnosed at earlier stages,[83] making a strong case for surveillance for HCC in Europe.

The complex and costly care of rare liver diseases

While most of paediatric liver diseases fall into the definitions of rare disease (prevalence less than 1/2,000), in adult care the main aetiologies of rare liver diseases are autoimmune liver diseases, i.e. primary biliary cholangitis (PBC), autoimmune hepatitis (AIH) and primary sclerosing cholangitis (PSC), as well as genetic metabolic liver diseases such as Wilson's disease or alpha-1 antitrypsin deficiency and hemochromatosis. Rare liver tumours, polycystic liver disease and other structural and vascular liver diseases also fall into this category.[84] Despite their rarity, these liver diseases account for a disproportionate number of patients in liver transplant programmes, reflecting the significant unmet need with regards to effective medical therapies. In the European Transplant Registry, rare diseases (PBC, PSC, AIH, biliary atresia, Budd Chiari syndrome and Wilson's disease) cumulatively accounted for 20.7%, 21.8% and 22.6% of liver transplants in 2015, 2016 and 2017, respectively.[85]

The young age of presentation of many rare liver diseases poses a significant challenge for patients and health systems as do the ongoing healthcare costs. One example is PSC, which typically presents in persons of 30-40 years of age. There is no approved medical therapy for PSC and most patients require a liver transplant 15-20 years after presentation.[86] There is significant comorbidity, as inflammatory bowel disease (IBD) occurs in up to 80% of people with PSC, and a high subsequent risk of developing CCA and other cancers. The complex care required in the management of PSC patients even before liver transplantation is costly, with data from the Netherlands estimating the annual costs per patient at around €12.000, which would translate to more than €600 million each year across Europe, exemplifying how, despite their rarity, rare liver diseases are important drivers of health care costs due to their significant morbidity, young age at onset and chronicity. Furthermore, lower quality of life, significant early mortality as well as loss of quality adjusted life years (QALYs) add to the high disease burden.

Recent medical and surgical advances mean that children and young adults with rare liver disease mostly survive with good quality of life into adulthood.[87-90] This requires appropriate transition from paediatric to adult care, with the growing liver transplant population representing a patient group in itself. One example is biliary atresia, which is the single most common cause of neonatal liver disease with an incidence of 1:19.000 newborns (about 270 new cases/year in Europe), and which is the most frequent indication for liver transplantation in children.[87,88] Only 25% of all biliary atresia patients reach adulthood with their native liver, and 45% of the 600 paediatric liver transplants per year in Europe are for biliary atresia. Calculated on the basis of the Diagnostic Related Grouping (DRG) system, a patient with biliary atresia having a good outcome costs about 27.000€ within their first 10 years of life. In contrast, the

costs for a patient with an unfavourable course and early transplantation are eleven times higher.[91,92] Early diagnosis and cost-saving therapies can be achieved by establishing effective case-finding procedures, standardized treatment protocols and centralization of patients to high-volume paediatric liver units.[93]

Drug development and the bottleneck of drug-induced liver injury (DILI)

DILI is the main cause of pre- and post-marketing withdrawal of drugs,[94] and of great regulatory concern. This results from the inherent hepatic metabolism and catabolism of a wide range of compounds,[95,96] From a clinical perspective, DILI is an extremely challenging condition due to the myriad of drugs used in clinical practice, the large number of herbs and dietary supplements with hepatotoxic potential, as well as the variable clinical presentation, spanning most pathological liver manifestations from fatty liver, inflammatory and cholestatic features, to severe, acute liver failure with high mortality.[97] Specific biomarkers are missing,[98] and diagnosis often relies on exclusion of other liver diseases and careful patient history review.

The true prevalence of DILI in Europe is hard to assess.[98] The first prospective population-based study on DILI came from France in the late 1990s and found an annual incidence of 13.9 patients per 100,000.[99] The Spanish Hepatotoxicity Registry started as a cooperative network of clinicians and researchers interested in DILI, and published their 20 years' experience in 2021,[100] which showed that anti-infectives were the most common cause, and were responsible for up to 40% of DILI cases. The most common cause of acute liver failure is acetaminophen (paracetamol). Causes are variable throughout Europe with high numbers of acetaminophen in the UK (43%) and Scandinavia (17%) but much lower numbers in Spain (2%) and France

(7%).[101] This variability is poorly understood, but may be related to over-the-counter availability in different countries.

The overlapping risk landscape of Covid-19 and liver diseases

In part due to the Covid-19 pandemic, obesity is now recognised as a 'metabolic disease risk factor' in infectious diseases beyond its traditionally accepted link with other diseases such as type 2 diabetes and cardiovascular disease. Obesity on the other hand, is increasingly recognised as a chronic disease itself.[102] Obesity has been repeatedly shown to lead to poorer outcomes in the form of respiratory failure and mortality in Covid-19;[103] notably this metabolic link partly explains variations in Covid-19 associated mortality across different ethnic and socioeconomic groups, in part mirroring differences in obesity and type 2 diabetes prevalence according to ethnicity but also deprivation.[104-107]

A meta-analysis has also shown that NAFLD was associated with a two-fold risk for severe COVID-19, independent of obesity although these findings need further confirmation and elucidation.[108,109] The Covid-19 pandemic provides a significant opportunity to heighten current awareness of metabolic risk factors, raise public awareness of the risk of obesity-related conditions, and to drive policy action to reduce the prevalence and improve treatment of obesity.

Synergies and the multiplicative harm of liver disease risk factors

The risk factors for liver disease are multiplicative, interacting and amplifying one another, rather than merely additive. A considerable portion of negative outcomes due to both unhealthy alcohol use and liver disease are due to their interactions with other factors, including socio-economic status.[110] Whilst having obesity with related

co-morbidity and unhealthy alcohol consumption each separately increase the risk of liver disease, the combination of these risk factors leads synergistically to even greater liver damage.[111,112] Being obese makes alcohol consumption far more dangerous; a BMI of >35 kg/m^2 doubles the hepatotoxicity of alcohol.[111] In a large study, concomitant metabolic syndrome increased the 10-year risk for advanced liver disease from 0.3% to 1.4% for moderate alcohol consumption and from 0.8% to 2.4% for unhealthy alcohol consumption.[113] The two risk factors coexist in European countries (**Figure 7, Panel A**), and grouping together countries which have both high alcohol consumption and high obesity prevalence reveals a greater liver-related mortality compared to countries with only one risk factor or none (**Figure 7, Panel B**). Genetic modifiers act in a similar way, with milder alpha1-antitrypsin genetic variation not leading to liver disease *per se*, while it may enhance susceptibility to progressive forms of other liver diseases as well as HCC.[114]

There are also important liver synergies between alcohol consumption and viral hepatitis. Unhealthy alcohol consumption increases the risk of mortality from co-existent HCV infection;[115] in Scotland the alcohol-attributable fraction for cirrhosis in people with HCV is between 30% and 50%.[116,117] The question of attributable risk for liver disease is however problematic as a result of the poor quality both of coding aetiology and of the underlying data, as discussed above. The fraction of liver disease without a coded aetiology varies considerably by country (from 8.5% in Finland to 97% in Bulgaria), taking into account the missing data on aetiology, the proportion of alcohol-related liver disease in Europe is likely to be between 50% and 80%.[25]

Smoking may combine synergistically with other risk factors to accelerate liver disease progression.[118-120] Heavy smoking (40 pack-years and over) and moderate drinking (80-210g/week) led to an 85% increased chance of having NAFLD compared to subjects who neither smoked nor drank alcohol.[121] More clinically significant is the association between smoking and progression to fibrosis in NAFLD patients;[122,123] a large cohort study consisting of persons with type-2 diabetes reported that smoking was associated with a 60% increased risk for severe liver disease (defined as a diagnosis of HCC, cirrhosis, decompensation, liver failure and/or death due to liver disease).[124] Finally, smoking is also an important risk factor for HCC,[125,126] with a meta-analysis showing a 50% increased risk for current smokers (independent of alcohol consumption) compared with never smokers.[127] There are liver synergies between alcohol and smoking such that the combination results in an approximately 7-fold increase in HCC risk.[111] There is also a strong link with health inequality; in the study cited above 30% of manual workers were smokers and consumed unhealthy amounts of alcohol compared with 15% of non-manual workers.[111]

Unhealthy diet is a fourth synergistic risk factor, increasing the burden of liver disease and other chronic diseases. Many European countries have seen a dramatic increase in the consumption of UPFs, which are often characterized by low nutritional quality, high energy density and presence of additives. Common examples are carbonated drinks, packaged snacks, breakfast cereals, instant sauces and many ready to heat products.[128,129] In the 10 countries participating in the European Prospective Investigation into Cancer and Nutrition (EPIC) study, processed foods contributed between 61% and 80% of mean energy intake.[130] The average content of protein, fibre, vitamins and minerals in the diet decreases significantly across quintiles of the

energy contribution of UPFs, whilst carbohydrate, added sugar, and saturated fat content increase.[131] UPFs contribute most of the energy intake from added sugars, the content of added sugars being 5-fold higher than in unprocessed or minimally processed foods.[132] In the UK National Diet and Nutrition Survey (2008–2014), UPFs accounted for 56.8% of total energy intake and 64.7% of total free sugars in the diet, with 61.3% of participants exceeding the recommended limit of 10% energy from free sugars.[133] Several studies across a range of populations have shown an association between the dietary share of UPFs and the risk of mortality and various diet-related chronic diseases including obesity, type 2 diabetes, cardiovascular disease, cancer and NAFLD.[134-140]

Concurrent obesity, type II diabetes and NAFLD may inhibit the reversal of liver fibrosis after curative HCV therapy, and patients cured of their HCV infection thus require monitoring and a holistic treatment approach if there is ongoing risk of NAFLD.[141] The synergistic nature of liver disease risk factors, and both the significantly greater harm this predisposes people to and the socioeconomic patterning of the risk behaviours that drive them, have major implications for policy. As discussed later, it is thus important to address social determinants of health that drive relevant inequalities, and factors including price, availability and marketing across all harmful commodities in concert.

Key policy deficits as risk factors for liver disease

Covid-19 has demonstrated the need for public health action and the direct links which exist between population-level interventions, inequalities, and mortality.[142,143] Arguments often made to oppose such interventions have been refuted by the constant publishing of numbers in news media showing their effectiveness in real-time.[144,145] With regards to alcohol, the evidence for equitable public health policies is remarkably consistent, summarised by the WHO as 'best buys': tax increases on alcohol containing beverages, comprehensive restrictions and bans on alcohol marketing and restrictions to the availability of retailed alcohol.[31]

In Russia, alcohol control policies led to a dramatic fall in alcohol related mortality, with 1.2 million lives saved over the 5 years since inception of the policy,[146] although sadly subsequent relaxation of these policies led to a rapid rise in mortality rates (**Supplementary Figure 3**). The maximal impact on all-cause mortality occurred within two years which, given that cirrhosis develops over many years, may seem surprising, but in practice people with liver disease frequently die as a result of acute decompensation related to recent drinking.[147] The most recent population-level policies, i.e. increased taxation and a minimum sales price on alcohol, have resulted in a significant reduction in all-cause mortality of 39% in men and 36% in woman.[148]

Modelling the impact of health policy on liver disease mortality and morbidity

The Organisation for Economic Co-operation and Development (OECD) has developed a micro-simulation model to examine the relative merit of policies for NCDs. Their model consolidates previous OECD modelling work into a single

platform to produce a comprehensive set of key behavioural and physiological risks.[149] As part of this Commission the OECD performed several specific analyses of liver metrics from the Strategic Public Health Planning for NCDs (SPHeP-NCDs) model in selected European countries ("EU27+5"; i.e. CHE, ISL, GBR, NOR, RUS) for the period 2020 to 2050 (see **Supplementary Methods** for details).[149] The modelling comprised two parts, one examining the burden of liver disease and the second relative effectiveness of health policies.

The OECD model was able to differentiate for the first time between various aetiologies of liver disease. Every year, and across the 32 countries included in the analysis, modelling found liver disease to be responsible for about 200,000 premature deaths, which is in line with the GBD estimates (**Figure 8**). Furthermore, it projects healthy life expectancy to be 0.4 to 1.3 years lower over the next 30 years due to liver diseases, with 46% of the reduction due to alcohol consumption and 28% due to obesity (**Supplementary Figure 4)**. On average, every year, 10.5 million life years and 8.7 million healthy live years are lost in the EU27 + 5 due to liver disease. The average annual health expenditure for liver disease in the EU 27 + countries is €4.3 billion (**Supplementary Figure 5**) and the impact of liver disease on the economy of the same group of countries lead to the loss of the equivalent of 5 million full time workers per year.

The opportunity for financial gains from policy implementation

The OECD modelling also calculated the relative impact of health policies on liver disease outcome metrics including years of life lost, disability adjusted life years and health expenditure and increased labour force productivity due to a healthier and more productive workforce. The most effective measure to improve population health

was food reformulation - which entails a 20% calorie reduction for food high in sugar, salt, calories and saturated fats, following the implementation of a comprehensive package of interventions – closely followed by alcohol price policies (i.e. taxation and minimum unit pricing, MUP; **Figure 9, Panel A**). The potential economic gain from implementation of all the seven policies included in the analysis amounted to more than €31 billion, of which 30% was related to a reduction of health expenditure and 70% to increased labour force productivity (**Figure 9, Panel B**). At the population level, the yearly benefits in terms of life years and DALYS was more than 1.4 million and 2.2 million, respectively, across the 32 countries included in the analysis. Furthermore, food reformulation, tax increases and a MUP for alcohol have implementation costs that are lower than the corresponding benefits in reduced health expenditure and increased labour force productivity. Alcohol taxes also generate revenues.

An economic modelling analysis undertaken for this Commission (**Figure 10**), adapting a published global model,[150] indicated HCV elimination in Europe will not be achieved without scale-up of testing, treatment, and prevention interventions (see **Supplementary Methods** for details). HCV elimination requires very high coverage of testing (reaching 100% diagnosis by 2030, and 59% treated) and expanded harm reduction (40% oral substitution treatment [OST] and 50% needle syringe programmes [NSP] among PWID). The elimination scenario was estimated to cost €38.6 billion between 2020 and 2030 (€15.0 billion for testing, €17.8 billion for treatment, and €5.8 billion for healthcare related to HCV disease) plus €14.9 billion for broader harm reduction services. Compared to the status-quo, this was an additional €18.9 billion investment in HCV services and €11.1 billion for harm reduction over 10 years. A substantial and sustained investment in harm reduction, alongside investments in HCV

testing and treatment, is important and has broader benefits than HCV elimination – including HIV prevention and reduction in overdoses and other non-HCV injecting related disease – thus improving the investment case beyond that estimated here.

Achieving elimination was estimated to lead to productivity gains between 2020 and 2030 due to lower rates of absenteeism (HCV-related sick days) and presenteeism (people attending the workplace but being less productive as a result of their illness), and fewer premature deaths (**Figure 10, Panel B**). Hence, the elimination package was estimated to be cost-saving by 2033 with a net economic benefit of €95 billion by 2050 (**Figure 10, Panel C**). If the cost of DAAs was €5,000 rather than €2,000 this would add four years to the time required for the program to become cost saving, highlighting the importance of negotiating for affordable DAA pricing. Another critical component to achieve HCV elimination is movement of treatment from the tertiary to the primary care/community settings to help ensure that countries have capacity to treat the increased numbers required. Also, there is increasing evidence that providing treatment in primary care/community settings increases retention in the care cascade and is cost saving compared to tertiary settings.[151-154]

INEQUALITIES AND THE NEXT GENERATION OF LIVER DISEASE PATIENTS

Liver diseases are intertwined with social and health inequalities. Socially disadvantaged groups and underserved communities are disproportionately impacted by liver disease for a multitude of reasons including exposure to unhealthy physical, social and economic environments; cultural factors; low levels of agency to adapt behaviours,[155] mental health issues, and use of food, drugs or alcohol to respond to psychosocial stress, as well as immigration, and refugees escaping from areas of high prevalence of viral hepatitis. Mortality from alcohol-related liver disease is substantially greater for disadvantaged socio-economic classes, particularly for younger patients, resulting in major health inequalities.[156] For example, in the UK, more deprived areas have a higher rate of liver disease mortality (**Figure 11**), e.g. rates in Blackpool (42.7 per 100,000 population) being over five times higher than rates in Eden (8.2 per 100,000 population). On a European scale, the wide variation in liver transplant rates throughout Europe reflects inequalities in access to a liver transplantation program as much as variation in liver disease prevalence (**Supplementary Figure 6**).

Lower socio-economic status is also associated with higher prevalence of liver disease risk factors. There are several pathways to explain how different factors interact at the individual and population level to generate inequities that influence the health status of women and men in a given population: discriminatory values, norms, practices and behaviours in relation to health within households and communities, differential exposures and vulnerabilities to disease, disability and injuries, biases in health systems and biased health research.[157]

For example, substantial differences exist in Europe concerning the proportion of adults with overweight or obesity in terms of region, sex and socio-economic background.[158] These differences are much more marked in women than in men, as regards both socio-economic status and education level. The prevalence of both obesity and diabetes is higher among adults with lower socioeconomic status in 2017, indicated by lower household economic capacity in most European countries (**Figure 12**). It has been suggested that low income and food-insecurity may be related to increased prevalence of NAFLD and advanced liver fibrosis, most probably because food insecurity is related to the affordability of energy-dense, high-fat, high-sugar UPFs.[159]

Children – the next generation of patients with liver disease

Childhood obesity and NAFLD represent a “second wave” of metabolic liver disease that will hit Europe over the coming decades. It is important both because of its direct impact of overweight and obesity in childhood, but also the tracking of childhood obesity into adulthood and through the life course. Present day adults in middle age with NAFLD are from a generation that was mostly normal weight in childhood, whereas many of today’s children risk spending the majority of their lives overweight. There is a growing appreciation that NAFLD is an early-onset condition that is likely to increase future liver-related complications, and it is now the most rapidly increasing reason for referral to paediatric hepatology centres. Evidence both from specialist liver centres and at a population level shows that children and young people with obesity have increased liver-related mortality later in life.[160,161]

Socioeconomic inequalities and childhood obesity

There is a particularly strong link between family socioeconomic inequalities and obesity. In England the prevalence of childhood obesity more than doubles between the least deprived and the most deprived deciles of socioeconomic status, and these inequalities are growing.[162] The Health Behaviour in School-aged Children (HBSC) survey highlights sex-related and socioeconomic inequalities among adolescents aged 11, 13 and 15 years. The 2017/2018 survey report presents data from over 220,000 young people in 45 countries and regions in Europe and Canada; one in five adolescents (21%) were overweight or obese.[163] The difference in the prevalence of obesity between the most and least affluent has grown substantially between 2014 and 2018 in most countries, with strong social inequalities being observed such that more affluent boys and girls were less likely to be overweight or obese. Of note, the prevalence of overweight and obesity increased in up to a third of countries/regions between 2014 and 2018. There are differences in prevalence of childhood obesity between countries in Europe, with increasing prevalence as one moves from north to south within the region.[164]

There is wide variation in children's diets across Europe, with a high prevalence of unhealthy dietary patterns,[165] including lower daily fruit and vegetable intake and higher added sugar intake among the least affluent. Half of adolescents eat neither fruit nor vegetables daily (**Figure 13**), whereas a larger portion of adolescents from more affluent families ate fruit and vegetables every day. Overall, one in six (16%) adolescents consumed sugar-sweetened beverages every day, with boys more likely to report daily soft-drink consumption than girls (18% and 14%, respectively) across all ages in most countries/regions. Soft-drink consumption was associated with family

affluence amongst both girls than boys (**Figure 13**). Physical activity is related to affluence, and in 2018, only 19% of adolescents achieve the recommended 60 minutes of moderate-to-vigorous physical activity daily. Physical activity participation was lower among adolescents from low-affluence families.[163]

New marketing modalities and public health responses

Children in Europe are regularly exposed to marketing that promotes UPFs and high-energy drinks, including saturated fats, trans-fatty acids, added sugar (refined sugars: sucrose, fructose and high fructose corn syrup incorporated into food and beverages[166]) or salt. Such targeting of children and adolescents by food and beverage commercials, and in particular those embedded in children's TV programmes, electronic media, including video games, DVDs etc., as well as social media such as Instagram®, TikTok® and Youtube®, has been demonstrated to drive consumption of high-calorie and low-nutrient beverages and foods.[167] Sugar-sweetened beverages (SSBs) are one of the largest sources of added sugar and an important contributor of calories with few, if any, other nutrients.[168,169] Consequently, SSB consumption is now one of the leading causes of childhood and adult obesity and associated NAFLD.[168-172]

Considering the role that social disadvantages play on the onset and persistence of obesity and associated liver disease in children (and adults), it is essential both to address the underlying social determinants of health and to adopt population-level strategies that modify the environmental drivers of behavioural risk factors, in order equitably to relieve the human and financial costs associated with the economic, social and health consequences of childhood obesity.[173] Public health prevention and health promotion initiatives that address the environmental and commercial drivers of

risk factors such unhealthy diets, physical inactivity and unhealthy alcohol consumption are important for achieving equitable outcomes. These include interventions such as taxes on sugar sweetened drinks, that have been successfully imposed in a growing number of countries around the world, and several cities within the USA.[174] Actions that target individuals, especially those that require high levels of personal agency to take effect, risk widening already stark inequalities in ways that population level action on structural factors and social determinants of health may not.[175]

Inequalities resulting from European drug pricing policies: the HCV case

Healthcare systems in Europe generally finance antiviral drugs for HCV through public funding, or via mandatory health insurance. Access limitations, that initially restricted treatment to those with advanced disease, have been removed in many European countries.[7] Competition and price negotiations have driven costs down from the extremely high initial list prices (tens of thousands of Euros), thus reducing the expenditure required in high- and middle-income countries. However, because of the large numbers of patients infected with HCV, the costs of treatment nonetheless continue to pose significant budgetary impacts in Europe. The vast majority (48/53) of countries in Europe fall into the World Bank upper middle income and high-income category; for many particularly upper middle income countries, for example Albania, Armenia, Bosnia and Herzegovina, Bulgaria, Montenegro, North Macedonia, Romania, Serbia and Turkmenistan there is no public data as to whether they have state aided or insurance funded treatment.

Generic HCV drugs are not generally available in Europe due to patent or licensing restrictions. The current cost of a generic HCV cure in some middle-income and low-

income countries in other continents is less than 50 Euros. In Switzerland, the law may allow any individual to import generic medicines for personal use provided the imported quantity is small and for personal consumption.[176] Some distrust of imported generics exists, in part because of poor knowledge of the approval process for generic drugs and fear of substandard drugs being utilised. WHO prequalification, however, ensures that prequalified drugs meet globally recognised standards.[177] This lack of licensed generics puts large areas of Europe in a financial dilemma with regards to HCV elimination, as a mere function of the current pricing regulations.

List prices for licenced HCV treatments are published, however, the prices actually paid are not publicly available.[178] Prices are arrived at by negotiations on a country by country basis and these negotiations in turn depend upon budget allocations but also target treatment numbers and the consequent revenue stream guaranteed to the originators (e.g. in the UK). Harmonisation of pricing will improve transparency and enhance treatment strategies. Furthermore, there are countries like Germany where more than 100 insurance companies cover antiviral costs, leading to high cost and low transparency. In general, countries within Europe are paying lower prices than the list prices through tender competition and negotiation leverage, but these prices are unknown to the public.

Impact of Covid-19 on the burden of liver disease

The response of European countries to the Covid-19 pandemic has varied considerably, demonstrating an underlying variability in public health capacity and policy making. Notably the Covid-19 pandemic has disproportionately affected vulnerable communities in Europe, including immigrants, worsening inequalities.[179,180] Furthermore, since there is an intimate interplay of food insecurity,

malnutrition and obesity and advanced liver disease with Covid-19 vulnerability,[6] the pandemic has placed a spotlight on the urgent need to prevent obesity and improve diet quality in Europe; Covid-19 has magnified disparities and exacerbated these vulnerabilities.[181] Poor social conditions, highly prevalent in people at risk of liver disease, also increase the risk of Covid-19 acquisition and associated negative outcomes, as well as amplify stigma towards these groups.[182-184] In many ways the pandemic has exposed flaws in public health; a post pandemic Europe needs to adopt policies designed to harmonize and share resources. Pooled procurement across countries, sharing of best commissioning practices, and support for generic use of drugs (HCV therapy included) would help reduce inequalities across countries in Europe.

Lockdowns have led to further weight gain in many people as a result of reduction in physical activity, unhealthy eating, and psychosocial factors (e.g. boredom, anxiety and depression).[185] Ongoing efforts from health professionals and policymakers to improve the nutritional value of European food, have been opposed by the food industry, and a number of food companies have increased their advertising and marketing of unhealthy foods and drinks during the Covid-19 pandemic.[186]

Covid-19 has threatened WHO viral hepatitis elimination aims, with severe disruption to testing and other service provisions.[187] Modelling of the impact of delays in viral hepatitis elimination programs due to Covid-19 suggests that globally a “1-year delay” scenario would result in 44,800 excess HCCs and 72,300 excess liver-related deaths, relative to a “no delay” scenario over the next 10 years.[188] Similar models in Italy and the UK project a substantial increase in numbers of cases of advanced liver disease and deaths from HCV-related liver disease, particularly in patients with advanced fibrosis or cirrhosis.[189]

The burden of untreated viral hepatitis is substantial. Prior to the pandemic, a minority of those infected in Europe had been diagnosed (between 15-55% of HBV, and 11-80% of HCV), while treatment among those diagnosed was as low as 5%.[36,190] However, diagnostic rates exceed 70% in a few countries, such as France where long established risk-based population-based screening has been adopted.[191,192] Less than half of EU/EEA countries, which responded to a 2017 survey, had dedicated HBV or HCV testing guidance (29% and 48%, respectively).[193] Access to HBV DNA diagnostic testing remains a key barrier to identifying levels of viremia mandating treatment. This situation leads to a proportion of individuals with chronic hepatitis presenting late with advanced cirrhosis or HCC.[194] The implementation of wider at scale testing approaches across Europe, mandated by public health infrastructures should be employed.

Widespread implementation of mass Covid-19 testing has shown that, with political will and investment, population-level screening of priority groups is feasible. These lessons can and should be applied in the context of viral hepatitis and can be useful to design and strengthen strategies to scale-up testing and treatment. Covid-19 has disrupted existing hepatitis elimination programs across the cascade of care at a critical juncture, with only 9 years left towards WHO target elimination goals. Quarantine and social distancing for Covid-19 have affected screening, diagnosis, treatment and harm reduction programs. The Covid-19 pandemic has limited the access to hospitals and community clinics for diagnosis and treatment; deferring HCV treatment became an almost universal practice at peaks of the epidemic. Moreover, the incidence of viral hepatitis may be increased by reducing the activity of harm reduction centres.[195]

PWID and the incarcerated are key populations in viral hepatitis elimination programs. The Covid-19 pandemic has impacted greatly on these vulnerable populations in terms of reduced access to HCV testing, diagnosis and treatment, but also to harm reduction programs (needle and syringe programs and opioid agonist therapy) and critical medical services hindering the progress towards HCV elimination.[196,197] Social distancing and quarantine during Covid-19 has increased isolation experienced by vulnerable populations, exacerbating the already substantial harms they face, including stigma and discrimination, overdose risk, comorbidities, precarious housing, poverty, and domestic violence. Now more than ever these populations require timely access to harm reduction and blood-borne virus services to prevent HCV (re)-infection as well as other harms associated with injection drug use.

The Covid-19 pandemic has also brought with it physical and social restrictions that may create environments that lead to increased alcohol consumption. In England, the year of the pandemic saw sustained higher purchasing of alcohol compared to previous years, and this increase mainly occurred among those with an unhealthy alcohol intake prior to the pandemic.[198] Over the same period, England saw a consistent increase in alcohol related liver deaths throughout 2020, independent of the rise/fall/rise in Covid-19 related deaths.[199] This change in liver deaths is entirely consistent with increases in alcohol consumption predominantly impacting on those with the highest alcohol intake. The case for action for liver disease is even stronger as a result.

STIGMA AND DISCRIMINATION EXACERBATE INEQUALITIES FOR LIVER DISEASE PATIENTS

Stigma is a socially constructed phenomenon involving the devaluation of one group by another on the basis of a recognised or perceived difference. People with, or at risk of developing, liver disease frequently belong to highly stigmatised groups. These include individuals with obesity, people with alcohol use disorders, PWID, people who are incarcerated, immigrants, and men who have sex with men (MSM). There are several types of stigma (**Figure 14**), including public stigma (mainly associated with stereotypes), structural stigma (e.g. when at the policy level a negative "labelling" nomenclature is used or specific groups have less access to health and social services) [200] and healthcare staff stigma (exerted by healthcare professionals and often a result of stereotyping), which collectively can result in exclusion and discrimination and generate self-stigma (when a person internalises stigma). This can ultimately result in lower disease awareness and subsequently worse outcomes due to late diagnosis.

Stigma is a public health, medical and ethical issue, [201] being a consequence of health inequalities as well as a key driver in perpetuating them. Stigmatising attitudes towards people with liver disease occur frequently in the general population, as there is a widespread assumption that these diseases are self-induced coupled with an implicit linking of alcohol-related behaviours to many liver diseases, even those unrelated to alcohol use. Further, there is a form of spill-over of this stigma to people with liver diseases which are completely unrelated to an individual's lifestyle and behaviour, and in an informal survey performed by patient representatives in this Commission amongst 1,078 adult people with autoimmune liver diseases across

Europe, approximately 40% regularly faced assumptions that their liver disease was related to unhealthy alcohol consumption.

Stigma in the healthcare setting: manifestations, consequences and possible interventions

Stigma can take many forms, including stigmatising language, direct abuse, and discriminatory treatment against individuals. The manifestations of stigma in healthcare settings have been investigated in many domains and include denial of care, provision of sub-standard care, as well as physical and verbal abuse but also more indirect practices, such as making some patients wait longer or task-shifting their care to less experienced colleagues.[202] In many Eastern European countries, for example, people with ongoing or past substance use have been excluded from HCV treatment.[203]

Within the healthcare system, individuals who experience stigma may internalise stigma and feel a loss of self-efficacy as well as mistrust in the healthcare system, which may negatively impact health-seeking behaviour[204] and result in stigma avoidance strategies, including delaying seeking care, seeking care elsewhere, not disclosing alcohol or drug use, and downplaying pain.[205,206] Ultimately, stigmatisation may lead to poorer health outcomes, which can worsen social inequalities by negatively affecting employment, social relationships and educational opportunities.[201]

There are four main categories of interventions to address public and healthcare stigma:[207] providing factual information to counter prejudices and stereotypes through education campaigns or training; protest (public attempts to suppress

stigmatising attitudes or negative representation of the stigmatised group); “social contact” approaches, in which opinion leaders from stigmatised groups describe their condition and experience via video or live sessions to combat stereotypes and increase empathy; and the involvement of services led by peers to fight against labelling and care avoidance, by e.g. helping engage people in care.

Campaigns to increase knowledge about stigmatised populations or to challenge stereotypes, have generally shown limited impact and may even generate negative effects in terms of stigma and healthcare seeking.[208] An infamous example of detrimental effects of a campaign related to mental health and occurred during the “Decade of the Brain” (1990-2000) which labelled addiction as a brain disease.[209,210] This strategy implied that recovery is not possible and discouraged people who use drugs to seek care. A meta-analysis showed that both education and, even more, social contact programmes, may be more effective in reducing public stigma in adults and adolescents,[211] especially if multi-target.[212 213] A review of interventions for decreasing stigmatizing behaviour of healthcare staff concluded that educational interventions resulted in improved attitudes towards stigmatised groups,[214] especially if they also rely on multi-form social contact.[215] Reduction of self-stigma is essential to reduce label avoidance, and interventions conducted by peers or community members have been shown to be effective in increasing empowerment, reducing self-stigma and facilitating engagement in the different steps of the cascade of care.[207]

Stigma towards women with liver diseases, including self-stigma, results in unacceptable delayed screening and access to liver disease care. Recent research has demonstrated that among PWID with HCV infection, women were less likely to receive DAAs.[216] Moreover, since model of end-stage liver disease (MELD) score

values are underestimated in women, they also experience lower chances for liver transplantation.[217-219] Among people with obesity, women are more likely to report experiences of stigma and discrimination[220,221] and gender differences have been found in the occurrence of obesity-associated disease conditions.[222] This deeper experience of stigma and discrimination among women with obesity is known to increase self-stigma and results in reduced access to and quality of healthcare[223]. These consequences may also be exacerbated by the prevalence of lower socio-economic status of women with obesity with respect to men. In fact, in comparison to individuals with the highest incomes, women and men in the lowest income group in Europe are 90% and 50%, respectively, more likely to have obesity, increasing gender-specific social inequalities.[224]

Special features of stigma in children and the elderly

Children and adolescents with obesity are particularly susceptible to multiple sources of weight stigma, notably in healthcare, school, and traditional or social media. “Obesogenic” behaviours among children overlap with social conditions and are tightly related to old (parental education and income), but also new, socioeconomic risk factors such as limited social network, immigrant status or family structure. This suggests that interventions to change behaviours in children need to comprehensively address social inequalities and stigma effects.[173] Furthermore, there is a need to raise awareness of this issue.[225-228] It has been suggested that this failure to recognize and treat obesity as a chronic disease is at the heart of stigma and this failure represents a major obstacle to seeking adequate medical management and prevention of obesity-related consequences.[102,223]

Parents of children with obesity point out the need for a radical change of terms to avoid stigmatisation of children and use terms like unhealthy body weight instead of obesity.[229] Childhood and adolescence are clearly two critical periods for individuals with obesity as they can experience weight-based victimisation through bullying.[230] This situation, amplified by stigmatisation on social media, highlights the need for greater support from parents and paediatricians alongside stronger school and social policies.[173] In an informal query made by this Commission to paediatric liver disease specialists at 62 centres in 25 countries of the ERN RARE LIVER,[84] 50% of clinicians caring for children with liver disease felt that stigma related to liver disease was a major issue for their patients.

As people with chronic liver disease may not only age with a chronic condition but also suffer from accelerating aging [231,232], when seeking care they may experience an additional layer of stigma in health settings that is related to age: so-called “ageism”. This consists of stigmatizing attitudes from healthcare staff, resulting from interactions of stereotypes, prejudice and discrimination towards older individuals affected by aging-related morbidities.[233]”A recent review also highlighted that ageism led to significantly worse health outcomes and that its impact is higher in less educated elderly people[234]. More specifically, a multi-country study conducted in European countries also showed that there was a gradient in ageism as its levels rose from north-west versus south-east Europe.[235]. Effective interventions to reduce ageism are feasible and inexpensive and rely on both education and intergenerational social contact.[236]

The language of liver disease

Stigmatising language, referring especially to alcohol or substance use, or excess weight and obesity, can lead to health practitioners reducing people to their condition rather than recognising their full personhood and distinct medical needs. For example, people with opioid use disorders were for years named ‘abusers’ or ‘addicts’, terms linked to “offences”,[237] which conveys a moralistic interpretation that individuals ‘choose’ to have such a disease. In addition to presupposing personal responsibility for illness, this framing can also elicit bias and discriminatory behaviours and reinforce negative stereotypes towards people with these conditions. ‘People-first language’,[238] in which the words referring to the individual are placed before words describing their behaviours or conditions (e.g. people who inject drugs, people with alcohol use disorder, people with obesity etc.) should be universally adopted.[239]

Stigmatising language is interwoven into everyday clinical management of people with liver disease also through nomenclature. Some efforts have been made to adjust liver disease nomenclature to reduce stigma burden in liver disease patients. In 2015, a name change of ‘primary biliary cirrhosis’ to ‘primary biliary cholangitis' was made,[240] and in 2018 the EASL Clinical Practice Guidelines for the management of alcohol-related liver disease[241] suggested alternative terminology to be used throughout the guideline to reduce stigmatising language. There have been similar discussions suggesting that NAFLD might be changed to metabolic dysfunction-associated fatty liver disease (MAFLD) [242-246], which was in part driven by the assumption that “non-alcoholic” in NAFLD was stigmatising.[247,248] Initial research has now provided early data that such a name change can improve awareness.[249,250] In this Commission we call for a deep and comprehensive revision of potentially stigmatising nomenclature related to liver disease, including those of addiction and

obesity-related language. A priority in these nomenclature changes (see below) is to align with terminology proposed by affected communities, both patient groups and at-risk groups.

MOVING FROM TREATMENT OF COMPLICATIONS TO CASE FINDING, SCREENING AND PREVENTION

Unfortunately, a diagnosis of cirrhosis is often only made after an individual has developed complications of end-stage liver disease when the scope for intervention is markedly reduced. The UK Lancet Commission on Liver Disease identified that more than two thirds of hospitalized patients had not previously been referred to a liver clinic.[12] Analysis of data derived from the "CIRRUS" cohort demonstrated that earlier referral of patients to a liver clinic was associated with longer survival compared to those patients admitted as an acute emergency (**Figure 15**).[251] Cirrhosis is the result of progressive scarring or fibrosis over many years or decades, the process being silent, with no early signs or symptoms in most cases. It is iniquitous that a medical diagnosis in the 21st century is still made only at such late stages. Early detection is an essential prerequisite for more effective therapy and interventions to prevent progression to cirrhosis.[252]

Case finding or screening for cirrhosis in Europe is variable and inconsistent with low levels of knowledge amongst many health care professionals managing patient groups at high risk of liver disease. For people with type 2 diabetes, there is an established awareness of the risks of cardiovascular disease, chronic kidney disease and diabetic retinopathy,[253] yet there is less awareness of diabetes-related or obesity-related progressive liver fibrosis,[254,255] and there are few examples of systematic case finding for liver fibrosis and cirrhosis. Specific therapeutic options for NAFLD are soon to arrive from several ongoing phase III randomized controlled trials, and case finding will soon be needed for providing medical therapy, as well as behavioural interventions.[256]

Alcohol-related liver disease is particularly neglected: out of a cohort of 466 people with alcohol-related cirrhosis, only 24% were diagnosed at the stage of compensated cirrhosis.[257] Moreover it has been clearly shown that late diagnosis of chronic liver disease was associated with aetiology; the odds of a late diagnosis were 12 times higher for an individual with alcohol-related liver disease vs viral hepatitis.[258] These results point towards the crucial importance of early diagnosis as interventions become less effective and more expensive when people with unhealthy alcohol consumption have already developed cirrhosis.[30,259]

From this perspective, the range of targets of existing liver-related case finding programmes appears too narrow. HCC surveillance in patients with cirrhosis has shown potential benefits in observational studies.[260] HBV screening has been recommended for immigrant populations from endemic countries.[23].[261,262] Many centres have protocols to survey for oesophageal varices in people with cirrhosis.[263] In Germany HBV (HBsAg) and HCV (anti-HCV) testing in high-risk populations is now covered by the health care system. Organizations such as the German Liver Foundation are advocating for an even broader implementation of liver testing, by universal alanine aminotransferase (ALT) screening as part of the national “Check-Up-35” programme. In this German funding mechanisms, as much as clinical need and scientific evidence are crucial determinants for screening opportunities and clinical management.

The first step of investigation of potential liver disease is commonly based on serum liver enzyme levels as part of generic liver blood panels, often called liver function tests or liver blood tests (LBTs).[264] LBTs are elevated in people with hepatitis, and historically have played important roles in the detection of inflammatory liver diseases including viral and autoimmune hepatitis. However, LBTs interpreted in isolation are not good

correlates or predictors of advanced liver fibrosis or cirrhosis. If we are to reduce liver-related mortality resulting from progressive fibrosis we must improve the identification of people with this type of disease behaviour before they present with advanced disease and the ominous consequences of hepatic decompensation. As an illustration, the majority of people with undetected cirrhosis in the community have normal ALT.[265] In a community-based study in the UK 60% of people with newly diagnosed liver fibrosis on biopsy had a normal ALT level and 91% of those with undetected cirrhosis had an ALT level within the normal range.[266,267] Similarly, in a population-based study from Catalonia, Spain, almost 75% of subjects with liver fibrosis, mostly due to NAFLD, as assessed by increased liver stiffness using transient elastography, had normal ALT levels.[268] A significant responsibility and opportunity resides with hepatologists in generating and communicate simple testing strategies, in keeping with the simplicity of haemoglobin A1c (HbA1c) in diabetes management or estimated glomerular filtration rate (eGFR) to guide chronic kidney disease management.[269]

There is now evidence to support such strategies; the multi-centre Optimising Delivery of Healthcare Intervention (ODHIN) randomized controlled trial in over 120 different locations throughout Catalonia in Spain, UK, the Netherlands, Poland, and Sweden has demonstrated the benefit of providing primary health-care units with training, support, and financial reimbursement for delivering AUDIT-C based screening and advice to screen for alcohol consumption.[270] Countries across Europe should rise to this challenge to increase the wide-scale roll-out of a standardized LBT with implicit assessment of liver fibrosis, coupled with automated, laboratory reflex testing and clinical follow-up, and similar research is urgently needed for other liver disease areas. The current late diagnosis of liver disease comes at a cost over and above the loss of

life years, including as it does the large costs of managing complications of end-stage liver disease.

The relevance of scaled up testing for health-care costs is also evident in rare liver diseases. Only two European countries have systematic national screening programmes for neonatal liver disease (Switzerland and France initiated stool colour charts to alert parents to altered stool colour). As noted above, achieving good outcomes for people with biliary atresia generates major savings in treatment costs. Extrapolated from the basis of 2700 patients/10 years in Europe, and a 30% survival rate for those with their native liver, the financial expenses for patients with unfavourable outcomes alone, are conservatively estimated beyond half a billion Euros.[91,92] This scenario could be improved by 10%, if early diagnosis and timely therapy could be achieved.

Screening for liver fibrosis as a strategy for early detection of progressive liver disease in the community setting

To reduce the burden of liver disease from alcohol and NAFLD, hepatologists, general practitioners (GPs), specialist nurses or community health staff, including pharmacists, who are in contact with people at risk or patients with liver disease will need to revise their strategies, and rather focus on case finding of people at risk of progressive forms of liver disease and premature death, and distinguishing progressive from more benign, less rapidly progressive disease, at an early stage. The mechanisms required to do this already exist for the most part as there are cheap, simple tests for advanced liver fibrosis and cirrhosis, including a range of

algorithms to calculate fibrosis risk from LBTs (**Supplementary Table 3**), with a high degree of accuracy.[271-273]

These non-invasive tests can be used in conjunction with more specific fibrosis tests based on combinations of circulating fibrosis markers or transient elastography.[274] Elastography also has a role in identifying people with portal hypertension who need primary variceal prophylaxis and follow-up.[275,276] A fundamental flaw in current practice is that such non-invasive fibrosis tests will only be performed once liver disease is already identified, and hence frequently not in people with low or normal serum ALT levels. One algorithm examined more than 500,000 anonymised hospital records and found that the data required to detect cirrhosis was previously available in 96% of subjects who went on to have a first admission with a serious liver event.[251]

Similar fibrosis screening protocols have been subjected to clinical studies such as "The Scarred Liver project" in the UK which screened 920 subjects in the community with risk factors for liver disease.[266,277] Among preselected people on a risk factor basis who were identified with increased liver stiffness (assessed by transient elastography), 72% had normal LBTs and would be missed by traditional investigation algorithms. Subsequently this diagnostic pathway has been locally adapted.[278] Other models of case finding were tested in the "LOCATE" study which found greater effectiveness in case identification in the arm based on nurse-led risk-factor identification with portable elastography assessment and referral to primary care than for regular care.[265] Two research nurses with portable elastography equipment were able to detect and stage as many new cases of progressive liver disease as five consultants in a year. Critical to the success of this diagnostic

pathway was engagement and promotion by a local GP, such that it is now in widespread use with almost as many liver fibrosis serum tests being requested by GPs as by hepatologists.[279]

In another screening project performed in the metropolitan area of Barcelona (Spain), out of 3,076 subjects aged 18-75 years recruited randomly from the general population, without known liver diseases, 3.6% had transient elastography values of more than 9.2 kPa, values highly suggestive of significant liver fibrosis (F2 stage or greater). The most common aetiology of liver disease in this cohort was NAFLD, followed by alcohol-related liver disease. This project proposed a screening algorithm to identify silent liver fibrosis in the population based on assessment of risk factors of liver diseases and measurement of fatty liver index (FLI). Presence of risk factors of liver diseases together with a FLI value greater than 60 identified 92.5% of subjects who had high probability of liver fibrosis as assessed by a liver stiffness measurement more than 9.2 kPa in the overall population.[268]

These examples provide strong support for implementation of proactive testing for liver fibrosis as the critical tool for progressive liver disease case finding. Research should be part of such an implementation, e.g. to define optimal target populations, type of tests or algorithms to be used, pathways of referral, and long-term impact of screening on liver-related mortality. In this regard, a large European study which will include 40,000 subjects in 8 countries is underway to evaluate screening strategies for chronic liver diseases.[280] The results of this study will help determine the most useful case-finding strategies according to specific countries and health systems. Two such strategies have been evaluated and showed a good cost-effectiveness

profile.[281,282] Nevertheless, more information is needed with respect to cost-effectiveness evaluation of screening strategies in different countries and health systems, accounting for local variability in prevalence of various liver diseases.

Reconsidering LBTs and making a choice for a fibrosis algorithm

The concept of LBTs, or also “liver blood tests” or “hepatic biochemistries”, holds no uniform interpretation. A new analysis performed for this Commission evaluated the performance of traditional LBTs as predictors of future serious liver events (SLE) in 400,000 patients.[251] Areas Under the Curve (AUC) for the results prior to the first serious liver event for ALT (AUC 0.63, 95% CI 0.61-0,66) and alkaline phosphatase (ALP; AUC 0.70, 95% CI 0.68-0.71) performed relatively poorly, with the best performing single test being gamma-glutamyl transferase (GGT; AUC 0.79, 95% CI 0.78-0.80). The AUC for a maximum GGT result was higher (0.83, 95% CI 0.82-0.84) within the clinically useful range, but not as high as one of the dedicated fibrosis algorithms (AUC 0.91, 95% CI 0.90-0.91) (**Figure 16)**.

Serum GGT level is frequently elevated in conjunction with excessive alcohol consumption. However, an elevated GGT level has been shown to identify both alcohol and non-alcohol related liver disease. Serum levels of GGT were higher in people with an alcohol risk: the serious liver event prediction cut off of GGT was higher at 126 IU/L in alcohol risk patients compared with 79 IU/L in non-alcohol risk patients and 82 IU/L in people with type 2 diabetes. GGT is the best single liver enzyme for predicting a future liver event providing the correct cut-off values are used (**Supplementary Figure 7**). In fact, the insurance industry already commonly uses

GGT as a cost effective marker to exclude clients at risk for liver-related morbidity and mortality.

Algorithms of liver blood tests in liver fibrosis

In the UK, NICE as part of its cirrhosis guidelines stated that normal LBTs should not be used to exclude significant liver disease and recommended transient elastography to diagnose cirrhosis in people with known alcohol-related liver disease, i.e. men regularly drinking >50 cl alcohol / week and women drinking > 35 cl, and in people with chronic HCV infection.[283] These guidelines also recommended specific liver fibrosis markers in the form of the enhanced liver fibrosis (ELF) test to stage fibrosis in people with NAFLD, and again cautioned against interpreting normal LBTs to exclude severe liver disease. However, the converse should be highlighted: abnormal LBT's should not be disregarded.

The problem is that primary care and also many secondary care settings throughout Europe do not in general have access to either a validated serum fibrosis test (e.g. the enhanced liver fibrosis test; ELF®), transient elastography or other specialized fibrosis tests. They do however have access to routine LBTs, which allows the application of fibrosis assessment algorithms with useful accuracy.[264,284] However, the wide range of liver fibrosis testing algorithms illustrated in **Supplementary Table 3,** with varying expert opinions over which to choose, potentially undermines confidence and results in inertia and neglect by non-specialist clinicians. The UK Lancet Liver Commission made a recommendation for the AST / ALT ratio, which has not perhaps stood the test of time and generally performs poorly in comparison to FIB4, APRI, Forns index and CIRRUS algorithms.

For clarity this Commission has decided to recommend the FIB4 algorithm for European implementation (at this point in time), whilst accepting that other algorithms including APRI, Forns index and CIRRUS algorithms, are also accurate. FIB4 can be calculated by the baseline parameters described in **Supplementary Table 4**. On-line calculators are readily and freely available,[285] and there are numerous examples of locally adopted referral pathways using FIB4.[286] It needs to be emphasized that some population-based cohort studies demonstrated that the reliability of FIB-4 for assessing significant liver fibrosis is far from perfect.[268] Whilst fibrosis measurement tools and algorithms are thus still evolving, we should not delay in communicating a clear and coherent recommendation for how to proceed at this point in time.

Challenges of putting primary care pathways into practice

We cannot assume that primary care can or will automatically take on a major responsibility for people with liver diseases; the transfer of this workload to primary care practicioners faces significant barriers (**Supplementary Box 1**), given that primary care in many European countries report unmanageable, underfunded workloads with inadequate capacity and restricted access to secondary care support.[287] **Box 1** gives examples of challenges to the roll-out of liver disease initiatives in primary care in selected European countries. Challenges arise at every step, particularly regarding the financial justification for any initial investment in screening strategies. Scaled-up testing and case finding impact across biochemistry, haematology and radiology, over and above that of hepatology and gastroenterology per se; all of which may have separate funding allocations, geographical restrictions and competing priorities of their own. Additionally, decision-making mechanisms for

adopting new tests and pathways or for adopting IT solutions (such as embedding FIB4 algorithm within a primary care computer system) may be locally or regionally rather than nationally determined, creating further challenges to standardisation when many more decision-making panels and committees need to be involved. Successful change and investment will require evidence of benefit, cost-benefit, strong advocacy and partnered working within integrated care systems. The role of primary care regarding liver health is, as yet, unclear and undefined, reflecting the lack of incentivisation, and inconsistent access to testing and referral.[277] Without understanding and addressing simple but common barriers (**Supplementary Box 1**), progress to engage primary care will stall.

Barriers extend to those commissioning and investing in new services and infrastructure too. The timescales for demonstrating beneficial outcomes or cost savings from liver disease prevention may be longer than the typical time-span of a commissioning cycle, so that further investment may be hard to justify if an inappropriate requirement to demonstrate within-cycle cost saving has been imposed. This process is further perversely hampered if budgets are held in separate silos for primary and secondary care: primary care commissioners will be disincentivised to commit primary care investment that generates more work in primary care but if benefits are only evident in reduced secondary care workload. The issue of capacity becomes a self-fulfilling problem of successful initiatives. The waiting times for transient elastography through the Scarred Liver project rapidly escalated from six weeks to many months as local GPs became familiar and confident in referring through the pathway.[266,277]

The need for a greater role of primary care in the early detection of cirrhosis in individuals who are otherwise asymptomatic has been underlined by research.[268] In a survey of Italian family doctors, the general understanding of NAFLD was low.[288] Furthermore, whilst management of cirrhosis in primary care is critical and the majority of GPs see people with cirrhosis in their practice, only a minority assume responsibility for HCC surveillance and their knowledge of current complex modalities of treatment of HCC is understandably limited. Screening for unhealthy alcohol use in primary care is infrequent and physicians who practise it are also those recognising that controlled drinking should be a key therapeutic goal.[289] Three overarching themes emerge in GPs' perceptions of their patients with cirrhosis: the complexity of comorbid medical, psychiatric, and substance issues; the importance of patient self-management; and challenges surrounding specialty care involvement and co-management of cirrhosis.[290] Although GPs feel they bring important skills to bear, care coordination in particular, they generally prefer to defer liver disease management to specialists.[289] There is a significant opportunity in bridging this gap between primary and secondary care for people with liver diseases, but simplified and clear protocols and revenue streams to demarcate joined-up care and maintenance treatment, are required.

A number of gaps should thus be filled in the area of early detection of liver fibrosis in primary care, the most important being a) increasing awareness and understanding of liver diseases among primary care physicians and nurses; b) implementation of algorithms for early detection of liver fibrosis that could be easily applied to different primary care settings; and c) improving interaction between primary care and hospital

care for an easy and rapid referral of subjects with suspicion of liver fibrosis to be assessed in specialized settings.

The experience from HCC surveillance

All international guidelines recommend surveillance of high-risk populations for HCC with a view to early diagnosis, so that potentially curative therapy can be offered.[291] In Europe, the population to be screened are those people with cirrhosis, the method of surveillance being ultrasound scanning. However, there are limitations of ultrasound surveillance, particularly in people with obesity – an increasing percentage of the European HCC population. A meta-analysis of 32 major surveillance studies involving over 13,000 patients showed that the sensitivity of liver ultrasound was less than 50% for early HCC.[292] The addition of the biomarker alpha-fetoprotein (AFP) slightly improved this figure to more than 60%. Inevitably, some of the benefit from HCC screening is related to lead-time bias, but where the impact of lead-time bias has been examined in detail the benefit on survival from surveillance is still very significant.[293,294]

In most European centres, HCC surveillance falls under the responsibility of secondary care. Although the adherence to HCC surveillance programs in Europe in a published meta-analysis was 70%, higher than in other regions of the world,[295] the true adherence is heterogeneous. The sheer load of patients with compensated cirrhosis undergoing regular ultrasonography can overload health care systems (both the gastroenterology/hepatology and radiology departments of hospitals as well as outpatient specialist clinic). This Commission analysed an international cohort of 5901 patients including 2599 from Japan, 1356 from United Kingdom, 834 from

Spain, and 1112 from China (**Figure 17**). While Japan has a formal surveillance program, surveillance is only performed “ad hoc” in the two European countries based on individual physicians’ recommendations, and no surveillance at all was current practice in China. This “gradient” of surveillance intensity was reflected in patient outcomes. Median overall survival was 47.2 months in Japan, 22.3 months in Europe, and 7.2 months in China. The proportion of patients accessing potentially curative therapies such as resection, transplantation or percutaneous ablation was 71% in Japan, 35% in Europe, and 16% in China (**Figure 17**).

A CALL FOR ACTION TO IMPROVE EUROPEAN LIVER HEALTH

A vicious circle is apparent, where the increasing pressures of socio-demographic factors and unhealthy behaviours are amplified by health systems, and the early diagnosis of preventable and treatable liver disease is hampered by short-comings in effective case-finding mechanisms, barriers associated with the stigma of liver diseases, social inequalities and a general lack of attention and political will. Unless appropriate action is taken, negative trends already apparent in some countries (e.g. UK, Finland and Bulgaria), with an increasing prevalence of liver disease, may extend throughout Europe. The close relationship between risk factors for liver disease, social inequalities and general health, means that these developments are likely to reflect general health trends of our European population far into the 21st century. The strong link with health-related behaviours also represents an opportunity; there is a great potential to prevent liver disease from developing, especially if at risk groups are identified early and effectively targeted for intervention.

Necessary actions will impact significantly on the way we organise health policies, health services and the language we use when we converse about patients from marginalised segments of our heterogeneous and changing European population. How successful we are in bringing about changes for people with liver diseases will reflect how successful we are in advancing European health in general. This will include a response to commercial forces working through rapidly evolving digital media, a shift in health systems from emphasising complications of end-stage liver disease to emphasising early diagnosis and management, especially in children who will soon be growing into the European working population – in whom liver diseases currently make the biggest impact. As the Covid-19 pandemic has posed a stress-test to our health systems throughout 2020 and 2021, liver diseases will continue to serve

as a sentinel for our capacity to deal with European health challenges over the next 2-3 decades. We should pay careful attention to this “canary in the coalmine”.

The EASL-Lancet Commission has used the data in this report to lay out a long-term vision for liver health in Europe (**Table 3),** with several panels of key actionable recommendations outlining how to move forward using these vision-oriented directions. The set of recommendations were selected by the Commission due to their potential to reduce not only the burden of liver disease in Europe, but the proportion of this burden which is attributable to social inequalities. Each recommendation is matched with a set of potential barriers and corresponding example actions for implementation. Whilst the first five recommendations mainly target healthcare staff, community members and patients, and the last five are mainly conceived for policy makers, most recommendations require multi-level interventions and are thus not stratified according to target audience. Many of our recommendations require deep national and international health policy changes to overcome the current environmental effects which are fuelling liver diseases in Europe. In the remainder of this section we will discuss how to proceed, and the obstacles we will need to overcome, on the basis of details given in **Table 3**.

Focusing on early disease detection and primary care to bring about transformative change

Case finding, health promotion and long-term management are core roles for primary care,[296] whose effectiveness can be enhanced by the involvement of specialised nurses and community members. There is significant overlap between the behavioural support as well as the disease monitoring relevant to people with liver disease and other metabolic conditions. Transformative change is challenging not

only due to the diverse multidisciplinary workforce that potentially impact upon liver outcomes, but also by a wide array of health delivery systems and reimbursement mechanisms across Europe. Whilst educational steps to increase awareness and prioritisation of liver health will ultimately support improved care, in order for exemplary practice to become a feasible reality, change should first be facilitated by addressing many of the underlying drivers of healthcare delivery – such as standardisation of the 'liver blood test panel' (**Supplementary Table 4**), awareness/access to fibrosis algorithms (**Supplementary Table 3**) and developing models of multimorbidity care that incorporate liver health review alongside review of the 'metabolic basket' of shared co-morbidities that are already commonly treated in primary care. [297,298] Initiatives to promote standardisation of testing and care across Europe (including new digital health solutions) would help with economic arguments in countries where reimbursement mechanisms are a limiting factor in liver testing.[299] It is important to note that economic cost/benefit analysis is another challenging area when considering the patient with multimorbid-associated liver disease risk for whom the burden of care becomes increasingly relevant but features little in economic modelling, despite studies showing improvements in the people's lived experience of disease.[300]

Liver diseases related to unhealthy alcohol use and obesity are potentially preventable if the process of progressive fibrosis is detected and effective intervention to arrest progression is applied. There are potential 'economies of conversation' where the same behavioural advice and multidisciplinary management applies across several disease areas, generating further economies of shared testing, care review and delivery of behavioural interventions. Liver disease

prevention should be included in these conversations, as part of a focus on multimorbidity and integrated, person-centred care,[297,298,300] rather than medical specialty boundaries.

Overcoming barriers to primary care involvement in liver diseases

Enhanced primary care and specialist nurse engagement with simple care pathways focused on the detection and staging of progressive liver fibrosis will potentially pick up more patients in time to intervene, reduce worry and inconvenience from unnecessary referrals and lead to efficiency savings from improved quality of referrals to secondary care.[301,302] Involvement of peers or community members can be a viable solution for reaching and self-empowering people with liver disease and ensure adequate linkage to care.[303,304]

Cardiovascular disease is generally well managed in primary care, and supported by well-evidenced care pathways and extensive secondary care resources. Consequently, mortality rates are decreasing throughout Europe (**Figure 2**). The picture for liver diseases could not be more different though, and a significant responsibility resides with the specialism of hepatology in providing similarly coherent guidance. The prevalence of liver disease is variable and can be highly concentrated with dense foci of unhealthy alcohol use and PWID.[305] Elsewhere liver diseases form a smaller proportion of a primary care workload, with large variability between different countries in Europe. Thus, a nuanced, but mutually beneficial approach is needed; primary care health professionals with competing workloads could usefully recognise that focusing on liver disease and its interwoven relationship with other

common metabolic co-morbidities like obesity and type 2 diabetes is relevant, feasible and worthwhile[306], whilst hepatology will help in communicating stream-lined diagnostic and management algorithms. Whilst LBTs are widely carried out in relation to co-morbidity monitoring, confidence in managing incidental findings is low, with evidence of *ad hoc*, repeat testing (rather than appropriate further investigation) of minor abnormalities being the norm.[307]

We propose to focus on identifying people on the common pathway of progressive liver fibrosis, which will require a more balanced approach than the current, almost exclusive, focus on “abnormal LBTs”, which should be abandoned. Some people with elevated LBTs do have clinically significant liver disease, but for the majority of people with mild elevations in LBTs and people at risk the fundamental change needed is to focus early assessments on an evaluation of liver fibrosis. This Commission thus pragmatically recommends screening using first the FIB4 score followed by transient elastography or validated serum fibrosis tests intrinsic to liver disease testing (**Figure 18)**. In areas where these new pragmatic care pathways have been introduced such as “The Scarred Liver project” the experience has been positive for patients and clinicians, with projected longer-term health-economic benefits.[278]

Importantly, these apparently simple solutions will require significant system change, including investments in laboratory or elastography (ultrasound and magnetic resonance-based), with automated and digital response systems, in addition to actions by the individual primary care worker. We call for international consensus on these systems on the part of professional medical associations, and the

establishment of multidisciplinary working groups to push for change across these organisations as well as co-ordinating advocacy directed at policy and health service funders to generate change. Agreement over the structure of revised services will then open up a route to developing an as yet absent, international framework for education in liver disease tailored to primary care, starting and pioneered in Europe.

Models of care in established liver disease – accounting for multimorbidity

A common barrier to optimal care is a delivery system that is often fragmented, lacks clinical informatics capabilities, duplicates services, holds an emphasis on traditional medical specialty boundaries rather than patient needs, and is poorly designed for the coordinated delivery of chronic care in people with multiple co-morbidities. From the physician's perspective, integrated care for people with multiple morbidities and chronic diseases warrants multidisciplinary approaches, and bridging of traditional boundaries between medical specialties. From the patient perspective, multimorbidity models of care serve the same purpose, and may lead to better integration and improved coordination of services. The widely recognized chronic care model (CCM) is a patient-centred, evidence-based, proactive framework,[8] that has been adopted and implemented for many NCDs, including type 2 diabetes, hypertension and cardiovascular disease,[308-310] and which applies to both of these perspectives.

The Sustainable Development Goal (SDG) target 3.4 is to reduce premature mortality from NCDs by a third by 2030 relative to 2015 levels.[311] Reducing liver related mortality has the potential to make a major contribution to achieving this goal, but it faces a number of fundamental barriers. The first barrier is the widespread perception that liver diseases do not belong to the domain of NCDs. This is a flawed perspective

likely resulting from the past focus on the global burden of viral hepatitis rather than that of the growing non-communicable forms of liver diseases resulting from NAFLD, alcohol and various autoimmune and vascular aetiologies which predominate in Europe and to which more than 80% of European liver transplants are attributable (**Figure 19**). The second is that cirrhosis is listed among non-NCD causes of death, in contrast to cardiovascular diseases, chronic respiratory diseases and diabetes. However, there is a large body of evidence on the burden of end-stage liver disease due to NAFLD in people with NCDs, particularly in high-risk groups such as people with obesity and type 2 diabetes. It is notable that neither the Lancet Commission on type 2 diabetes, [312] nor a large review of overweight in 195 countries, mention liver-related complications, including, NAFLD, cirrhosis or HCC.[313] This misperception should be changed and underscores the urgency to modernising liver disease pathways and investment in holistic services to avoid overlooking the risk of cirrhosis and HCC in people with metabolic syndrome, obesity and type 2 diabetes. Liver-related morbidity is one of the possible outcomes in a wider risk scenario, as exemplified by NAFLD, obesity and type 2 diabetes.[308,309]

Non-communicable liver diseases and the chronic care model (CCM)

The CCM model addresses six aspects of care delivery: organizational support, community-linking, self-management support, decision support, delivery systems design and clinical information systems.[8,308] In liver disease, there is some experience from the model in late-stage liver disease, e.g. for the long-term management of cirrhosis, as the “end-stage NCD” of all liver disease aetiologies, to increase integration with multidisciplinary services in primary care, district hospital liver units and specialist centres.[12] In an Italian study, use of a structured CCM model

for patients discharged from hospital with ascites showed it significantly reduced 30-day readmissions (from 42% to 15%), 12-month readmissions (from 71% to 46%) and 12-month mortality (from 46% to 23%) whilst achieving a 46% reduction in health-care costs.[314] We propose that an adapted CCM is applied at the early stages of liver disease, as part of a proactive practice starting from primary care, promoting education and empowerment of individuals at risk of NCDs, with selective referral to hospital for further diagnosis and establishing of treatment only for severe, complex or rare cases.

In many cases, lethal outcomes from Covid-19 have occurred on a substrate of NCDs, many of them shared and fostered by NAFLD. Nevertheless, NAFLD is barely mentioned in international and national guidelines on NCDs, and is missing in the WHO webpage on obesity complications.[315] Complex diseases and multiple needs of individuals with metabolically driven NCDs require stratification of the competing and often co-occurring risks (cardiovascular disease, diabetes, chronic kidney disease and liver disease) that needs to be addressed.[75] This allows the delivery of integrated interdisciplinary management with ongoing support to individuals with multiple comorbidities, liver disease included, and their associated complex needs. That the pathological processes of metabolic liver disease are intertwined with Covid-19 severity underscores the urgent need to modernise liver disease pathways and increase investment in holistic services which includes liver disease perspectives.[316]

Many CCM programmes already exist across a spectrum of different NCDs, both at the level of general hospitals and specialist centres. To maximize efficacy, these should be integrated in a wider, comprehensive CCM model, which includes primary care and a liver perspective. Effective and durable achievements are not feasible if

addressing only a single disease or cause of morbidity and mortality. It is time to include liver diseases within the spectrum of NCDs related to metabolic disorders by creating platforms for collaborative work –including non-communicable liver diseases, which will enhance the collective efforts of multiple actors across diverse medical specialties and sectors of research and health care, with the patient at the centre of their own care needs.

Merging CCMs, liver diseases included, into integrated and data-driven multimorbidity care also gives the opportunity to create a synergy of research and action. Systematic data collection in CCMs can help to establish a multidisciplinary register for providing the information required to stratify risk, identify needs, personalise care and treat multiple targets. Unified data management systems can support research based on this type of 360° patient knowledge and transform the care of NCDs. Several of the needs require simple technological solutions, like automated responsive testing ("reflex testing") rather than repeat testing. The effective reshaping of existing CCMs to provide integrated care requires on one hand the engagement of nurses and non-medical personnel with relevant knowledge and skills, and on the other the use of technology to improve accessibility and interactions.

Nurse led care for people with established liver disease

Specialist liver nurses may play an integral part in case-finding and the care of people with liver disease and bridge gaps between clinicians and patients, and between primary and hospital care. They also may play an important role, both in community and hospital settings, in providing health education to patients and families and stimulating the engagement of patients in their own care, aspects that

are barely present in the current care for people with liver disease. Benchmarked standards for different roles in nursing will need to be developed for skills, knowledge, and competencies. To our knowledge, the UK Royal College of Nurse guidance on “Caring for people with liver disease: a competence framework for nursing” is the only available document in Europe that describes the professional standards for nurses when caring for people with liver disease.[317] In this model, the key role of nurses would be to actively co-ordinate and promote liver services across the appropriate care pathway. Embedding more knowledge of liver diseases throughout training of nurses and doctors will improve consideration of liver care by the wider healthcare team when caring for people with associated co-morbid conditions.

The role of specialist liver nurses in the care of people with cirrhosis has been proposed by the “LiverHope” nursing project, a task force of nurses from different European liver units with expertise in people with cirrhosis working in a EU funded Horizon 2020 project.[318] The project has identified specific activities of nursing care for inpatients and outpatients with cirrhosis and their specific complications,[319] and should bring valuable model experience for the further implementation of nurse led models for people with liver diseases in Europe.

The nurse led model also holds relevance for the aforementioned gaps in paediatric and transition care. In the above mentioned informal query among 62 paediatric centres from 25 countries in Europe, more than 80% had full diagnostic facilities, more than 70% had specialised multidisciplinary teams and 30/62 centres provided liver transplantation. The main weaknesses were a lack of family support (51%) and organised transition services from paediatric to adult care (<60%). A global framework document is necessary at the EU level and should include skills and

competencies of specialist liver nurses both at the community and also specialized settings and how they are best incorporated into care pathways. Methods of attaining the competencies/skills will be country-specific and we as commissioners strongly advise the use of this document as a starting point for reshaping the role of nurses in liver services across Europe.

Pathways of care in established and advanced liver disease

Cirrhosis should be considered a distinct, complex and severe disease that represents the final stage for any aetiology within the spectrum of chronic liver diseases (**Figure 4**). People with cirrhosis are sometimes diagnosed before the development of complications, a phase known as compensated cirrhosis, but are unfortunately most commonly diagnosed after development of such complications, known as decompensated cirrhosis.[320,321] Although mortality due to cirrhosis has decreased over the past three decades in Europe,[322,323] the burden of decompensated cirrhosis has in fact increased. In addition, current indications for liver transplantation in cirrhosis are changing, with a steady rise in people with NAFLD and a significant drop in those with HCV infection,[26] indicating a shift in the burden of specific aetiologies of cirrhosis. The changing landscape of cirrhosis in Europe requires an urgent assessment and action plan to adapt the care of patients with cirrhosis to the changes in underlying aetiology.

Traditional care pathways for cirrhosis predominantly involve hospital-based care and provide marginal survival benefits at very high costs. Major disparities exist between countries in terms of access to care, models of co-management of people with cirrhosis and integration of nurses. Currently, some countries almost exclusively delegate its management to specialized units in hospitals, whilst in others primary

care plays an integral, collaborative role. However, pathways linking primary and secondary care are ill-defined and underdeveloped in many countries throughout Europe. The complexity of cirrhosis, with its various, potentially severe complications and diverse aetiologies, may be in part responsible for the difficulty in establishing good collaboration between primary and secondary care. This Commission strongly urges for a shift towards a flexible yet uniform model of task distribution on the management of cirrhosis between primary or secondary care (**Table 4**).

GPs and nurses working in primary care may intervene in four fundamental areas: detection of cirrhosis; behaviour and risk factor modification; screening programs in compensated cirrhosis; and palliative care in advanced disease.[324] The diagnosis of asymptomatic compensated cirrhosis in the primary care setting relies heavily on the recognition of risk factors and follow-up with appropriate investigations. The potential impact of primary care in the management of alcohol and metabolic risk factors may become important upon implementation of adequate training. The role of primary care in the co-management of people with cirrhosis such as for HCC surveillance requires further research. As technological advances increasingly allow electronic case finding and intervention delivery for relevant liver disease risks, the importance of careful coding in the primary care record of both risk factors and established diagnostic terms cannot be overstated.[325] Amongst the multiple barriers to broadening the role of primary care (**Supplementary Box 1**), the lack of clear and consistent guidance on how to choose amongst the spectrum of fibrosis algorithms proposed throughout literature should be an easy fix (**Supplementary Table 3, Figure 18**). From the patient perspective, the lack of simplified guidance adds to the feeling of discrimination and the complexity of the healthcare pathways as main barriers to engagement in liver disease care.[326] In one qualitative study, the presence

of national guidelines, combined with clear flowcharts or computer prompts, increased the confidence of primary care workers in their diagnostic capabilities.[327]

The issue of end-of-life care in advanced liver disease is an area upon which much can be improved. An international systematic review on the perspective of patients, their caregivers and healthcare professionals, highlighted important issues in the patient's limited understanding of the disease and in the provider's difficulties in communicating information.[328] Primary care plays a fundamental role in end-of-life care,[329-331] yet also face multiple challenges, including complexity of symptom management, complex social circumstances and lack of any confidence in having discussions about prognosis and future care preference.[324,328]

By redefining roles of primary and secondary care in management of people with cirrhosis, the attention of hospital care can be paid to complex cases. Indeed, the subset of patients with cirrhosis who develop complications represent an important amount of the workload of the overall hospital care, both for the day hospital and the inpatient wards. This is related to the high prevalence of the disease, the variety of complications patients may develop, and the frequent recurrence of these complications, particularly hepatic encephalopathy, ascites, and bacterial infections. In a study from Catalonia in Spain, the overall cost associated with care of people with cirrhosis during 1 year represented 1.8% of the total annual budget of the healthcare system; moreover, 35% of the costs were related to hospitalizations.[332] Reports from Germany, Portugal, Scotland, and Denmark confirmed a very high frequency of hospitalizations of people with cirrhosis and the same may be true for other European countries,[333-336] underscoring the relevance of the proposed task distribution.

Moreover, hospital readmissions are very common due to the recurrent nature of complications of cirrhosis. In fact, cirrhosis has one of the highest rates of early readmissions among different medical conditions, including cancers.[337] Several factors associated with high risk of readmission have been reported, which makes it possible to identify people with higher risk of readmission.[338,339] Several reports indicate that either use of planned care for specific complications, such as large-volume paracentesis for refractory ascites, or a quality improvement program based on electronic decision support reduce readmission rates in people with cirrhosis.[340,341] Increasing the collaboration between primary and hospital care may reduce the high rate of hospital admissions of people with cirrhosis and help improve quality of life of these patients.

The application of multidisciplinary approaches in specific areas

The treatment of liver cancer is complex and costly, interdisciplinary and involves therapies that are rarely used for other tumours (such as liver transplantation, percutaneous ablation or intra-arterial therapies), while systemic therapy plays a limited although increasing role. As with other complex medical conditions, the ideal way of providing optimal therapy is through a multidisciplinary team (MDT). In practice, access to care in networks of MDTs is difficult and inequalities are perceived by participating physicians (**Supplementary Box 2**). The MDT for liver cancer should involve at least the 'core' involved specialties (hepatology, liver transplant surgery, diagnostic and interventional radiology, medical oncology, and pathology), and discuss all patients irrespective of staging or liver function status. When liver transplant surgery or interventional radiology is not available in smaller centres, the participation of specialists from other hospitals should be secured, for instance using telemedicine participation, or digital conferencing.

Despite a significant part of the European population being affected by rare liver diseases, healthcare systems in many European countries are not set up adequately to provide high-quality care.[342,343] Multidisciplinary services provided to many of these patients, for instance those with PSC and biliary atresia as discussed above, and in particular specialized surgical procedures, demonstrate enhanced quality of care associated with centralisation of care services that lead to elevated case loads. Outcomes following the Kasai procedure in biliary atresia are significantly better in centres performing a higher case load (five or more cases per year) vs. low volume centres.[87,336,344,345] The EU has recognized the challenges and need for action and thus supported the implementation of a European Reference Network for rare liver diseases in both adults and children (ERN RARE LIVER).[84,346] However, at the time of implementation of the ERN, only 50% of children with biliary atresia in the EU were being cared for in ERN RARE LIVER certified centres. Furthermore, European countries that are not EU members are excluded from being full members of this program. We believe the program should be more inclusive across the whole of Europe, and holds an important model example for harmonization of health systems in Europe, far beyond the topic of rare diseases.[347]

Opportunities of telemedicine and new pathways of care

The changes to healthcare delivery systems triggered and demanded by the Covid-19 pandemic provide a unique opportunity to improve liver disease care.[348] Change is now the norm and all clinical practices are being reviewed, adapted and modernised, reflecting the necessity to streamline care and use technology to optimise outcomes. There has been a major shift towards remote working, using phone, text messages, video-calls and much wider triaging of patients before, or instead of, face-to-face assessment.[349]

The move to telemedicine has facilitated remote delivery of care, allowing increased access to care for those in isolated environments as well as those currently fearful of attending clinics. All these opportunities should be used to foster a digital framework of multidisciplinary care for liver diseases under the guidance of scientific societies. From a governmental standpoint, this means allocation of sufficient financial resources for integration of these models in existing digital health-care platforms and investment in artificial intelligence (AI) driven remote health system to integrate the entire continuum of care. At the interface between primary and secondary care, telemedicine has also reduced hospital out-patient appointments as secondary care assessment has shifted significantly to remote assessment, with increased use of 'Advice and Guidance' to respond to referrals (whereby consultants write back to GP requests for advice rather than taking over responsibility of the referral).[350] However the stopgap use of telemedicine and its impact on health inequalities is yet to be evaluated as reduced face-to-face assessment is likely to have differential positive and negative effects across different groups.

Responding to stigma and discrimination

Reducing stigma and discrimination towards individuals at risk of liver diseases cannot be achieved without a combination of interventions targeting the multiple layers of stigma, in particular stigma in healthcare settings, structural stigma and self-stigma (**Figure 14**).[351] Such multi-level anti-stigma interventions are needed to reduce delayed consultation and care avoidance, and ensure optimal and timely prevention and care of people concerned by liver disease. For children with obesity, multi-level interventions tackling environmental and commercial determinants of obesity alongside addressing associated comorbidities, stigma and social disparities,[173] while promoting comprehensive packages of healthcare and

involvement of associations of parents, have the potential to counteract the growing childhood obesity epidemic.[352]

At the healthcare level, education and social contact interventions in the training of medical and nurse students should be implemented, as well as social contact interventions led by peers or community members to healthcare staff. For all liver diseases, as stigma is an issue, healthcare services should offer disclosure support to people unable to disclose their disease or behaviours. In particular for HBV and HCV, testing guidelines should put forth how to increase testing and treatment in high-risk groups such as sex workers, homeless people, MSM, PWID and immigrant populations.

To fight against self-stigma, there is a wide and increasing spectrum of multi-targeting interventions, combining objectives of promoting self-esteem and self-efficacy, empowerment from support from peers or the community, education to discard stereotypes, increased social and coping skills and encouragement of treatment engagement.[353] Many of these interventions can be incorporated in treatment education programmes (e.g. also including nutrition or harm reduction strategies) and delivered by peers or healthcare staff other than physicians.[354]

Health policy-makers and clinicians must encourage stigmatised populations concerned by liver disease to get tested and identify innovative entry points for screening and treatment in settings beyond specialty care, such as primary care, prisons and community sites. In a post-Covid-19 era of economic restraints, the involvement of peers or use of community services, e.g. needle and syringe exchange services for people who inject drugs, parents' associations for children with obesity, immigrant community settings etc., can significantly reduce costs and create

novel and trusted entry points for prevention and care. Peers and community members can provide education on prevention, facilitate case-finding, promote early diagnosis, fight against label avoidance and act as navigators to ensure linkage to care,[355] thereby preventing dangerous delays or discontinuation of care, which disproportionately contribute to the current burden of liver disease in Europe.

It is the opinion of this Commission that the guiding principle should be that restrictions on access to liver care based on behaviours should be minimized or absent. Restrictions based on alcohol or drug use abstinence or weight reduction can be regarded as a type of structural stigma and discrimination which is likely to leave the most socially vulnerable behind and increase the burden of liver disease in the most socially deprived groups. For HCV and HBV, the introduction of point of care testing and oral antiviral drugs warrants appropriate care for all groups. Thus, removing all stigmatising barriers and obstacles to diagnosis and treatment, including insistence on abstinence from substance or alcohol use is obligatory. As elaborated below, treatment restrictions must not be imposed. Treatment deferral should only be advised by providers when it is necessary to ensure the safety of individuals. For alcohol and obesity the case is more complex, as exemplified by liver transplantation. For alcohol-related liver disease, prolonged abstinence (3-6 months) is a key criterion for acceptance to European liver transplant waiting lists. The notion that liver transplantation for patients who did not remain abstinent during the pre-transplant period does not appear to affect long-term survival despite higher risk of relapse [356], has to be balanced against donor perceptions and local availability of management programs for avoiding relapse to harmful alcohol use after transplantation. In the field of NAFLD/NASH, severe obesity is generally a contraindication for liver

transplantation because of higher risk of complications. It therefore becomes essential to reduce harms from both obesity and muscle wasting before and after transplantation through the delivery of comprehensive interventions combining specific nutritional approaches and/or exercise [357].Concerning structural stigma, a key step is to change all stigmatising nomenclature, as we propose in this Commission (see **Table 5)**. Words matter. Names matter. Stigmatising terminology, even if used unintentionally, can have devastating consequences for those affected by such terms, including reduced healthcare seeking behaviour. It is the strong opinion of this Commission that the entire liver health vocabulary requires a language revision to amend stigmatising terms, wherever they may be used, e.g. in clinical guidelines, ICD codes, strategies and action plans as well as reports and conference session titles. Therefore, in **Table 5**, we have listed potentially stigmatising terms commonly used in the liver field and how they have been revised, e.g., by EASL in its clinical practice guidelines, or might be revised moving forward.

However, in spite of an important revision in 2018 of terminology for alcohol-related liver disease,[241] none of the proposed terms have been implemented in the upcoming ICD-11 to be launched in 2022. WHO needs to be made aware of the potential for their current and upcoming nomenclature to increase stigma. In line with the efforts of affected communities, we encourage the use of “people first” language which focuses on the person, rather than their ailment or diagnosis, thus emphasising the dignity of the individual. As noted below, describing someone as a person who injects drugs rather than an injecting drug user helps reduce the stigma associated with injecting drug use.

We do not claim that the revised terminology in **Table 5** will remove all structural stigma of liver disease nomenclature. The suggestions are intended to inform a

deeper, global conversation that medical associations, patient groups, and representatives of affected communities need to initiate in the coming year in order to address and agree on new destigmatising language. National language differences throughout Europe will need to be accounted for, and we hope that our proposals may serve as a blueprint for the desirable direction of travel for these activities. A complete removal of potentially stigmatising terms, like “fat” and “alcohol” from liver disease nomenclature although desirable, may be considered unlikely to happen, as etiologic and histopathologic terms have a strong historical base within hepatology, including for non-stigmatised areas (e.g. autoimmune hepatitis, viral hepatitis, DILI), but we need to strive towards their appropriate implementation. Furthermore, while some names of liver diseases may not be inherently stigmatised, their transmission routes and the populations most at risk are, for example injecting drug use and PWID with regards to chronic HCV infection. While we do not wish to overstate its importance, we believe that the health of millions depends on urgently addressing how we converse about our patients and their diseases.

Helping European children navigate a rapidly developing marketing ecosystem

The strongest evidence for the impact of marketing comes from reviews of longitudinal and cohort studies of children, which consistently report that exposure to alcohol marketing increases the risk that children will start to drink alcohol, or if they already drink, will consume greater quantities.[358-361] In 2018, the EU Audio-Visual Media Services Directive (AVMSD) implemented regulation on advertising for foods high in fat, salt and sodium, and sugars, and has strengthened the “Country of Origin Principle”, rules for video sharing platforms, better protection of minors, and strengthened provisions to protect children from inappropriate audio-visual

commercial communications.[362] Currently, however, the AVMSD does not account for alcohol advertising. There is strong evidence to support policies that reduce children's exposure to marketing, with those of complete and partial marketing bans being most effective.[30]

Children, young people and vulnerable groups are the most susceptible to marketing messages and need to be protected from the marketing of both alcohol and UPFs, as well as high fat, sugar and salt foods (so called HFSS foods). Current systems of self-regulation are ineffective, and transparent monitoring and reporting by public health agencies is required to ensure consistent enforcement and accountability.[363] Most European countries have marketing regulation policies to protect the youngest and most vulnerable segments of the population ranging from complete bans to light-touch self-regulation – 63% of European countries have statutory regulation, 34% have self-regulation and 3% have co-regulation.[364]

The 2011 Alcohol act in Norway prohibits the marketing of alcohol almost entirely and has wide public and political support.[365] Lithuania implemented a similar legislation in 2018 which includes a total ban on alcohol advertising with only minor exemptions such as a logo of producers in sales areas.[366] In a compromise with industry, the Irish Public Health Bill from 2019 has key components for regulation to protect children such as limits to the placement of adverts near schools or at public transport stops or stations, and alcohol adverts cannot be shown in cinemas showing films to those below the age of 18 years. A similar compromise in France is the measure called the "Loi Evin",[367] where alcohol marketing required action on both the advertising media used and the messages transmitted. The existence of these compromises shows that commercial forces remain strong.

The marketing landscape is rapidly evolving with the emergence of digital marketing. WHO reports that marketing on mobile phones increased from US$20 billion in 2013 to $200 billion in 2018.[368] Digital marketing spend now exceeds television spend in many countries and is highly focused and largely immune from scrutiny. WHO has uncovered a rapidly evolving and complex digital marketing ecosystem, whereby individual “ad impressions” are traded within obscure interactions between networks of competing delivery agencies. The absence of reliable sources of age verification data means that exposure of children to the marketing of unhealthy products is not prevented. The WHO have proposed a range of technological solutions under the banner of ‘CLICK’, an acronym derived from: Comprehend the digital marketing environment, Landscape of campaigns, Investigate exposure, Capture on screen and Knowledge sharing. The intention of these measures is for policymakers to start to understand and map the digital marketing environment, leading to transparency around the actual levels of exposure of children to individual brands, and formal regulation of the digital ecosystem.

The principle that marketing bans work was first established for tobacco and framed into global law with the WHO Framework Convention on Tobacco Control (WHO FCTC).[369] Commercial operators are highly skilled at evading partial regulations; in an article subtitled “Marketing with the lights out”; the various evasion methods include: sponsorship, surrogate brand extensions, clothes branding, product placement, cross border tourism, innovative packaging and imaginative uses of direct digital communications.[370] This Commission strongly believes that the only effective solution will be a complete ban on all forms of alcohol marketing, including digital marketing, in keeping with SDG target 3.5 on addressing the prevention and treatment of harmful use of alcohol.

Labelling regulation is also relevant. A well-known prototype example comes from Chile, where legal restrictions were imposed from 2016 providing firm restrictions to marketing and labeling.[371] The law constrains cartoon food packaging, prevents educational institutions from offering unhealthy products, limits TV marketing, prohibits promotional toys and forces producers to place black warning signs in their packaging in case they exceed the established limits of total sugar, saturated fats or sodium. This approach has already resulted in a significant reduction in the content of sugar, saturated fats and salt.[372] The quest for Europe will not be as easy, as the most powerful food lobbies reach deeply and have a long history of influencing policy making. Nonetheless, Europe needs the same type of leadership in a much more politically complex setting, accounting for the point that EU member states alone do not represent the whole of Europe.

The relationship between media use, family dynamics, and school environments on a child's likelihood to be overweight or obese is an area of research with a paucity of empirical evidence. However, the limited evidence for health literacy programs cognition, attitudes, and behaviours suggests a need for both better designed studies and more effective interventions.[373] Once obesity occurs it is very difficult to reverse it: in long-term randomised controlled trials, the greatest weight reduction occurs within the first 6 months of diets followed by weight regain in most people.[374,375] Hence a focus on prevention at the earlier stages of life such as childhood has greater potential impact.

However, this is not the sole reason for targeting school children. In a given environment, food, transport, land use and urban environments are macro-systems that in turn influence the intermediate systems in which people interact, mainly schools, workplaces and community spaces. The latter, in turn, influence micro-

systems such as families and social groups, changing their behavioural patterns. A change in micro-intermediate environment is easier to be carried out and can have sustainable and measurable targets, while providing a starting point for a change in macro-system from inside (“think globally, act locally”). As of today, over 50% of the world population lives in cities with more than 500.000 inhabitants, and two thirds of people with type 2 diabetes live in urban areas, with an increased risk of NCDs (“urban diabetes”). Making cities and human settlements inclusive, safe, resilient and sustainable (SDG 11) has the potential to reduce inequalities (SDG 10.2) and to reduce the prevalence of NCDs, including NAFLD.

Children represent the crossroads between families and schools (micro-and intermediate systems) and community policies, where actions to improve children’s health are generally well supported by public opinion. In addition to their role as pupils receiving education in schools, children may have a role in promoting sustainable changes within local communities. For example, fostering specific education programmes involving academia, local governments, schools, children and their families, may help knowledge to be translated into action by children themselves, encouraged to be “teachers” to other children and to their families. These programmes should be age-specific, with a special focus on adolescence as a period of flux in relation to health-related behaviour) and should engage all people across the socioeconomic spectrum.

Whilst educational programs in overcoming obesity are unlikely to be effective as interventions on their own,[173,373] there are studies reporting the effectiveness of parent-based interventions on healthy eating and active behaviours in pre-school children.[376] A systematic review that included 19 studies found that school-based interventions for obesity prevention and promotion of physical activity and fitness

have the potential to be more effective if they prioritise physical activity.[377] A Cochrane review showed that physical activity intervention designed for childhood weight management exhibited benefits on mathematics achievement,[378] executive function and working memory while only multicomponent interventions focusing on both physical activity and healthy diet in children with obesity could deliver benefits in general school achievement.[378]

Similarly to the treatment approach in other chronic diseases, healthcare providers should discuss the broader picture of complications with their liver disease patients; the message should be that risk reduction of end-stage liver disease, liver cancer, diabetes and cardiovascular disease, is possible. These messages and supportive information and education can also be delivered through patient groups and associations. In a cross-sectional study among 146 NAFLD patients, a healthier nutritional behaviour was associated with higher patient understanding of NAFLD.[379] A qualitative study [380] highlights the important role of healthcare providers as educators on the significance of NAFLD (in itself and in the broader context of the metabolic syndrome) and its potential to regress; teaching healthy eating skills and enhancing confidence in the benefits of diet, [381]. Among 3,822 persons with NAFLD (Fatty Liver Index ≥ 30) from the US National Health and Nutrition Examination Survey (2001-2014) only 53.9% of people with NAFLD intended to lose weight even though over 95% had overweight or obesity. Notably, amongst those who tried to lose weight ≤10% (lower rates among men) attended weight loss programs [382]. Education make an important contribution but is insufficient on its own; it should be one aspect of a broad package of measures that include comprehensive, accessible and affordable car, and the creation of healthy environments.

Viral hepatitis elimination in Europe

The World Health Assembly has promulgated a strategy for the elimination of viral hepatitis as a component of the 2030 Agenda for Sustainable Development. The aim is to reduce annual deaths from viral hepatitis by 65% and new infections by 90%, thus saving 7.1 million lives globally by 2030. To achieve these goals, two age-dependent interventions are key: prevention of neonatal and childhood infection by HBV vaccination and secondly, prevention of cirrhosis and HCC in adults, by appropriate diagnosis and treatment. Only a few high-income countries in Europe are projected to meet the WHO HCV mortality targets by 2030 (France, Germany, Iceland, Italy Spain, Sweden, Switzerland and the United Kingdom)[188]; others are not expected to meet these targets with 9 years remaining. Current status for key indicators of progress is listed in **Table 6**.

The WHO viral hepatitis elimination aims are however achievable. Prevention of incident chronic HBV infection is being attained by universal birth dose HBV immunization, and appropriate treatment in HBsAg-positive mothers in the third trimester of pregnancy to prevent mother-to-child transmission; substantial progress has been made.[383] Almost all countries in the WHO European Region (92%) have successfully implemented universal childhood HBV immunization programs with excellent coverage of three doses of HBV vaccine (at least 90%). However, some low endemic countries (e.g. Denmark, Finland, Iceland and Sweden) have not implemented a universal vaccination program and rely on selective immunization of people at high risk of HBV infection. This Commission recommends that all European countries implement universal childhood HBV vaccination and monitor its compliance particularly in newborns of marginalized populations or immigrants. The revised WHO recommendations to prevent mother to child transmission mandate testing for HBsAg

and HBV DNA to identify mothers with viraemia requiring care, and can be linked to clustered family screening.[384] Screening of pregnant women for HCV in addition to HIV and HBV offers a unique means to identify young women with chronic hepatitis and provide timely treatment.[385] Universal birth dose vaccination is an imperative (a first dose of hepatitis B vaccine preferably within 24 hours of birth to all infants, followed by two or three doses to complete immunization), and HBV vaccination coverage among high-risk populations, such as prisoners, PWID, MSM and sex workers require amplification.

Highly effective antiviral agents against HBV and HCV have the potential to dramatically reduce morbidity and mortality.[56] In Western Europe, where surveillance data have documented a decline in prevalence of HCV and a reduction in admission for the consequences of chronic viral hepatitis, substantial progress has been made towards the WHO elimination targets. However, surveillance data to track progress is in much of Europe, which presents an obstacle to determining gains. In order to realise the promise of antiviral therapy to further reduce incidence, collaborative and innovative stakeholder partnerships are needed to devise new strategies to raise awareness, scale-up test and treat strategies in community-based settings, and increase access to harm reduction services (e.g. oral substitution therapy and needle syringe exchange programmes).

As expected, a higher prevalence of chronic HBV has been observed in immigrant populations from endemic regions including sub-Saharan Africa and the Middle East. The majority of immigrants with HBV or HCV are not aware of their status. The continued influx of immigrants, refugees and asylum seekers to Europe poses health challenges but also provides an opportunity for health gain. The majority of them are younger than 35 years old. Proactive testing and treatment for chronic viral hepatitis

provide an important opportunity to ensure entry to health care systems in their country of adoption,[386] and may contribute to an increase of their health awareness, work productivity and social assimilation.[387] In the pursuit of universal access to healthcare for all immigrants, European nations need to adopt unified policies to testing and treatment for viral hepatitis of newly arrived immigrants, including those undocumented.[388]

European countries with universal health coverage such as Spain, France, and the UK have made progress by developing national plans outlining agreed elimination goals, strategies to achieve those goals, and indicators to track progress. Similarly, Georgia has an ambitious national HCV elimination plan, with surveillance and modeling undertaken to assess interim progress.[389] These existing national plans can be adapted to assist the modeling and development of surveillance strategies and well-funded action plans in several eastern European countries, Russia and some former Soviet republics, which have still not prioritized viral hepatitis as a public health threat. Numerous cost-effective and economic analyses have underpinned viral hepatitis policies, including screening in pregnancy, [390,391] technology assessments for DAA therapy, [392] investment frameworks for finding and treating viral hepatitis, [393] vaccination, [150,394] pricing, [395] and scaling up prevention test and treat efforts. [396,397]

Treatment as prevention is pivotal but can only be achieved by pro-active outreach and widespread test-and-treat approaches. We propose reducing costs and improving access to treatment by enhancing transparency and universal disclosure of antiviral pricing within Europe. This wouldhighlight discrepancies, in contrast to the current concealment of national prices, behind national protective procurement dealings that cite “commercial sensitivities”. Lower pricing would incentivize the

evaluation of greater treatment access, resulting in net benefit to originators and to public health elimination strategies (**Box 2**).

Injecting drug use is the main driver of HCV transmission in Europe,[41] highlighting the importance of PWID-targeted interventions. Substantial investment in harm reduction services is needed, , and all restrictions to harm reduction programs should be lifted. New initiatives to assist surveillance of viral hepatitis in PWID,[398] and to reduce the punitive stigmatisation of PWID are required. Improving the currently suboptimal coverage and inadequate provision of needle exchange and opioid substitution therapy programs is crucial to reducing the incidence of HCV infection and improving HCV treatment uptake.[399-402] Peer workers programs to navigate vulnerable individuals toward test-and-treat programs are invaluable adjuncts.

Micro-elimination is a strategic approach to eliminating HCV in particular groups, which can be expanded to reduce national incidence and even global prevalence.[403,404] It proposes targeting specific sub-populations with an elevated HCV prevalence or geographic settings for HCV elimination. Sub-populations of interest may include those most marginalised, such as PWID or prisoners, or others such as those co-infected with HIV, people with haemophilia and patients on chronic dialysis. The four key components defining micro-elimination are having a plan, achievable time-bound targets, a multi-stakeholder process, and ongoing monitoring, all in line with the WHO Global Health Sector Strategy. Examples of micro-elimination programs in progress include testing and treatment for HCV in HIV infected MSM,[405] and testing in prisons.[406,407] However, micro-elimination of HCV has had limited success in many countries, and national data reporting the effect of micro-elimination in Europe is limited. Micro-elimination is more difficult to apply in HBV infection, but

universal vaccination, testing and treatment have reduced the expected mortality from HBV in regional initiatives in large target populations.[408]

Thus current levels of diagnosis and treatment demand a challenging expansion to meet WHO HCV elimination targets.[409] All archaic treatment restrictions should be lifted. A large number of patients require diagnosis and assessment which have become more challenging as historical treatment groups shrunk in high-income countries. Quality linkage programs should be put in place to ensure reflex testing for HCV RNA and appropriate linkage to care. Prison testing should provide an opportunity for opt out testing. Widespread regular testing of HIV positive MSM and HIV negative MSM for HCV in conjunction with HIV pre-exposure prophylaxis programs is required to ensure early detection of de novo and recurrent infection in those engaging in high risk activities. Testing high risk groups alone, however, will not satisfactorily diagnose 90% of all viral infections and initiatives to find all adults are required – hence our proposal to link viral hepatitis testing to current Covid-19 surveillance programs (**Table 3**).

Defragmentation of the European policy landscape – "One Europe"

The changes to health systems, testing and treatment, research priorities and health policy suggested throughout this Commission report should be implemented without fragmentation at a pan-European level.[410,411] Within the EU, the idea of a biomedical advanced research and development agency (BARDA), or an European Health Emergency Response Authority (HERA), has been debated in the European Commission since early autumn 2020, and is currently on a path towards establishing end of 2021.[412] Whilst focusing on responses to cross-border infectious threats and

emergencies, inspired by the Covid-19 pandemic, the concept of unified and coordinated approaches "...across the whole value chain and develop strategic investments for research, development, manufacturing, deployment, distribution and use of medical countermeasures"[412] holds considerable relevance also for non-infectious risks, NCDs and the liver disease syndemic included. Whilst the Lancet Commission on Liver the Disease in the UK has provided important model examples on policy interventions at a single country level,[12] we have throughout this report demonstrated the benefits that would result from taking a pan-European perspective to similar interventions.[410,411,413] The policies that regulate consumption patterns of products involved in liver disease development, UPFs, alcohol and added sugar included, are crucial prototypes for this principle point,[13] and in urgent need of anchoring at a broader, European level similar to that of policies to control tobacco use.

Within the WHO European region there is an inverse relation between the price of alcohol and liver mortality rates (**Figure 20)**, supporting the health benefits of harmonizing alcohol taxes.[14] For instance, in Finland, rapid increases in liver mortality occurred when Estonia joined the EU and import controls were relaxed, leading to an influx of cheap alcohol, but a subsequent increase in alcohol tax and changes in alcohol availability reduced consumption and consequently liver mortality.[25] Since 1980, UK liver death rates have increased by a factor of four, closely tracking changes in affordability of alcohol (**Supplementary Figure 8**) demonstrating the responsiveness of liver mortality to relatively small changes in alcohol taxation.[414] These country level experiences should inspire the establishing of European standards for policy measures to control associated health threats.

Various types of price regulation and taxation strategy have been shown to be effective and cost-effective,[415,416] and the social policy experiment of MUP in Scotland reinforces its effectiveness, especially in terms of reducing health inequalities.[15] The evidence for MUP is robust and comes from several sources;[30,417] e.g. a series of natural experiments and modelling studies across the UK, Ireland, the Czech Republic and Germany which were able to estimate the longer-term effects of a MUP policy.[32,418-420] Taken together, these studies consistently demonstrate that a MUP is effective at reducing alcohol consumption, hospital admissions, deaths, criminal offences, and workplace absence. By effectively targeting the cheap alcohol that is purchased by those with the highest alcohol intake, MUP results in the greatest health and social gains for the least affluent groups.

Legal challenges, led by the alcohol industry, have been turned down by unanimous verdicts from the European Court of Justice and the UK Supreme Court that both judged MUP to be more effective than comparable measures because it is targeted at those with the highest alcohol intake, and geared towards reducing health inequalities.[421] Natural experiments in MUP underway in Scotland, Ireland and the Russian Federation will provide more data on the impact of such measures, and influence policy in Europe.

Other effective policies to reduce alcohol consumption and alcohol-related harm include marketing regulations and ideally a complete marketing ban, like those seen in Norway and Lithuania, with the effectiveness of marketing regulation reducing as any advertising ban moves from a complete ban, covering print and non-print media and online, to a partial ban, that may include only one media type. Our Commission believes that the EU should step up to this challenge, and impose pan-European regulations to all forms of alcohol marketing, expanding on the AVMSD and building

on the experiences from other areas of pan-European legislation, such as the General Data Protection Regulation (GDPR).

Taxation for added sugar and UPFs is currently being implemented in some European countries,[422] and this Commission strongly recommends that these efforts are harmonised across Europe. SSB levies are the most prominent and there is consistent evidence regarding the beneficial impact on reducing consumption in several policy evaluations.[17,18] Multinational corporations hold a significant resistance to adapt to national social and political requirements. This resistance can only be overcome by coordinated actions across countries. Proposed policies certainly do not only impact liver health, hence, their widespread adoption should be a priority in new EU legislation over the next decade. Tobacco regulations exemplify how the combination of strict taxations, packaging and advertisement control lead to reductions in disease-specific incidence and premature mortality. In plain words, European countries should address unhealthy foods and drinks with the same, uniform approach.

The WHO has recommended ‘Best Buys’; evidence-based policies for tackling the drivers of NCDs, and one of the most recommended measures is mandatory front-of-pack labelling. This is an important policy tool for countries to help consumers make healthier food choices and to reduce intake of total energy intake, sugar, sodium and saturated fat.[423-425] Voluntary food labelling schemes, currently present in many European countries, are insufficient resulting in a lack of adherence from food manufacturers. Countries that do have food labelling policies employ different schemes and regulations, resulting in inconsistency across the continent and confusion. The implementation of a European-wide mandatory government-led, simple, informative, based on the latest scientific research and guidelines and uniform front-of-pack labelling approach would help to encourage consumers reduce

their intake of ultra-processed foods (and in turn saturated fat, sugar and salt). WHO guidelines and recommendations also state that labelling should be accompanied by supporting initiatives to aid implementation by the industry and public.[423] In addition a formal and comprehensive policy monitoring and evaluation programmes are needed across Europe to assess impact, such as purchasing and consumption changes, nutritional knowledge in consumers and potential health benefits as well as the extent to which food manufacturers reformulate their products to become healthier to avoid unfavourable nutritional labelling.

Reformulation to reduce sugar content in food or labelling to reduce purchase of high sugar foods can have a great impact on NAFLD prevention as suggested from clinical studies, and also as strongly supported by our analysis of the OECD data (see above). Food labelling alone is unlikely to be sufficiently effective without an accompanying impact on food reformulation, making collaboration with the food industry imperative. In controlled trials, reduced sugar consumption amongst children led to a regression of NAFLD within a short time (weeks),[426,427] whereas inaction leads to situations in infants where at the age of 1 year those consuming more than two sugar-containing beverage servings per day were three times more likely to develop NAFLD at age 10 years compared to those with less than one serving/day. The association was independent of BMI, and the association was strongest amongst children from mothers with a lower level of educational attainment.[172]

All measures to target obesity will have a major beneficial effect in preventing NAFLD development and related complications, but will require concerted efforts if they are to be successful. A WHO meta-analysis of 11 systematic reviews on the effectiveness of fiscal policies to reduce body weight, improve diet and prevent chronic diseases

(including NCDs) concluded that the strongest evidence to date was for SSB levies, reducing consumption by 20-50%.[428] A national study,[429] modelled on a 20% levy on SSB in the UK, estimated that it would prevent 3.7 million cases of obesity and 25,498 cases of BMI-related disease over the next 10 years (2015-2025). These examples should set clear important directions for European health policy going forward, supporting at a European level the work of previous Lancet Commissions.[12,13,15,430]

FUTURE PERSPECTIVES

Over the last decades hepatology has been transformed from a field of therapeutic nihilism to one with some of the greatest successes in modern medicine including a vaccine against cancer (in the form of HCC as a complication to HBV) and the first chronic viral infection to be cured by medical therapy with oral drugs – HCV. Whilst such developments will certainly help address part of the burden of liver diseases in Europe there are problems still to be resolved. A major emerging challenge is that any improvement in diagnosis and care of liver disease and associated comorbidities will not be successful in reducing the burden of liver disease mortality if it is not accompanied by an effort to target the most disadvantaged communities.

We will have to keep moving the focus towards health promotion and the prevention of liver diseases and also diagnose these conditions at much earlier stages, so as to prevent the development of end stage liver disease with its costly and life-threatening complications (**Figure 5**). Here primary care and community health care settings have a crucial role to playin outreach, referring and filtering patients with benign or irrelevant abnormities in LBTs from patients at risk of progressive fibrosis, aided by technology in promoting streamlined care, automated investigation in response to mild abnormalities and increased access to second line – and second generation – fibrosis testing.

There will continue to be a huge unmet need for healthcare professionals looking after people with liver disease, and only a minority of these will be hepatologists. The health burden caused by liver diseases will only be ameliorated if this challenge is taken as a multidisciplinary task and with the involvement of communities, which are the most concerned with liver disease. Enabling primary care to identify patients, at risk of, and with liver disease and to implement proposed algorithms for fibrosis

screening will be critical. The gastroenterologist when taking care of IBD patients must keep an eye on the bile ducts and should not miss PSC. The endocrinologist should not miss NAFLD and should be aware that people with type 2 diabetes have significantly increased risk of advancing liver fibrosis and HCC. The oncologist should be aware of metastatic liver disease and be knowledgeable of DILI caused by the anti-cancer drugs, in particular when using check-point inhibitors. The haematologist should not miss haemochromatosis and think of cirrhosis when patients present with thrombocytopenia. The neurologist should refer any patient with Wilson's disease to the hepatologist and should not miss hepatic encephalopathy. And importantly, the close relationship between liver disease and mental health warrant attention as psychiatric disorders (e.g. depression) are highly prevalent in people with liver disease and strongly affect engagement in care.[431] If all disciplines work together and are pro-actively seek to intervene at early disease stages the burden of liver disease complications will decline. Specialty protectionism should be challenged – it should be considered as appropriate that the diabetologist may manage people with NALFD and an oncologist the patient with liver cancer. Our priority should be to ensure that people with liver disease access the best care, not the terms of our profession. This will require the development of interdisciplinary and multi-professional teams focusing on patient-centred training and care, and which should supported by electronic systems and the developing telemedicine tools. However, this also requires a change in the way health care is funded and reimbursed, which is principally a political problem, and without which health inequalities will remain a major challenge.

The multidisciplinary composition of this Commission, nurses and patients included, reflects the orientation which is needed to overcome many of the barriers highlighted for our recommendations (**Table 3**). Responsibilities reside at multiple levels, and

messages provided throughout this document holds a diverse target audience. More than anything, we wish for the document to serve as a resource base for all those wishing to improve the conditions for liver disease patients, including politicians, physicians, nurses and the patients themselves, and to prevent the many premature deaths occurring throughout Europe every year. Due to restrictions of space and time, many topics warrant in depth work and further investigations in the future, those related to health inequalities and multidisciplinary care most of all. Some of this work may reside with the team responsible for this report, while some of the ensuing work warrants considerations for separate Commissions and academic research projects. The work explicitly should to account for gender-related differences in risk factors, protective/aggravating effects of sexual hormones, and variances linked to genetics physiological differences between men and women to achieve truly individualized management for patients at risk of liver disease.[432]

There are many stakeholders within the health-care system to involve in the follow-up of this report, including both primary and secondary care, their involvement requires coordination and integration. We believe EASL needs to step up to this responsibility, and continue its outreach to other learned societies (e.g. European Association for the Study of Diabetes [EASD] and European Association for the Study of Obesity [EASO][433]) in forming the necessary partnerships, versus primary care and nurses in particular, and promote interdisciplinary and team-based work. Disease competition and positioning of roles and responsibilities throughout the care cascade for people with liver disease should belong in the past, and patient needs and the patient voice should be the nucleus around which health systems and health-care amendments should be built. Patient organisations, as those participating in this Commission may help in bridging some of the gaps. Monitoring of impact remains an integral part to

these future steps, and the major gaps in data surrounding liver diseases must be overcome as a centrally important part of this monitoring.

With the ageing European population, the incidence of HCC will continue to grow and early diagnosis is critical to enable curative treatment. The promising developments of new HCC medical therapies will improve survival even for people at advanced stages of disease. A particular future challenge is CCA, which is on the rise in Europe and in many parts of the world. Gene sequencing of tumour tissue leading to targeted molecular and personalized therapies has provided some hope for CCA patients, and general improvements in medical oncology, immunotherapy included, is slowly being applied also to these liver cancers. Liver surgery will continue to evolve, with minimal invasive procedures being widely used to treat curable liver cancers. Whilst regenerative medicine is likely to provide opportunities in people with end-stage and acute liver failure, only the future will tell if the dream of artificial liver systems for long-term organ replacement will finally become reality. In the future, we will see cellular and stem cell therapies in a variety of forms, representing this shift.

The emphasis of this Commission report has been on the working age population and young Europeans. We nevertheless face an era where European populations are ageing more than any other region in the world.[434] Due to changing demographics, a decreasing working age population has to support health care for an increasing population of retired people suffering from costly chronic diseases, including chronic liver diseases and their complications. This will increasingly challenge health care systems throughout Europe and may also contribute to stigmatization of older people.

The field of liver transplantation itself will change dramatically, as organ shortage will likely become more of an issue. More than 150,000 liver transplants have been performed in Europe since the start of the programs in the early 1980's, and more than 100,000 of these patients are still alive. The age of donors and recipients will continuously increase, leading to an acceleration of fibrosis progression in the transplanted livers. The technique of orthotopic liver transplantation has not changed over the past decades, nor has immunosuppression with all its current side effects. Donations after cardiac arrest is a topic predominantly driven by hepatology, and developments in live donor transplant, auxiliary transplants, machine perfusion and liver support devices are likely to expand opportunities in end-stage liver disease management. Finally, in orthotopic liver transplantation long-term tolerance must be sought by weaning of toxic immunosuppressive drugs and development of strategies for personalization of immunosuppression.

We are likely to see an increased attention to the role of toxic exposures in the development of liver diseases, drugs and occupational hazards included.[435] DILI as a medical example will further increase in prevalence as the number of drugs developed will continuously grow. Every seven years the number of compounds produced by the chemical industry doubles, and most of them are metabolized by the liver, creating the potential for acute, subacute or chronic DILI. We will certainly see new entities of DILI in the future as we have recently seen by the advent of immune mediated drug induced liver disease caused by modern biologicals used in many disciplines, including oncology, rheumatology, gastroenterology, neurology and dermatology.

Most of all, this Commission report has aimed to demonstrate how liver health is a window to the general health challenges of Europe in the 21st century. The risk

factors for liver disease; alcohol, obesity and intravenous drug use reflect behaviours and conditions that are the consequence of both unhealthy environments and social inequalities. Addressing these problems requires bold and extensive public health responses, but these measures are often opposed by commercial interests which prioritise the financial health of their shareholders and employees over the health of the European population.

The Covid-19 pandemic has exposed the weaknesses of European health systems, which are ill-equipped to fight such public health challenges. Europe's public health response to Covid-19, as for other threats, has been dominated by wide variations and a lack of coordination. This Commission calls for a different kind of European response; integrated, co-ordinated, and effective. As we recover from the Covid-19 pandemic we must seize the opportunity to improve the health of our populations. Changing the ways we address the risk factors for liver disease could function as a sentinel for the health of the European population, increasing solidarity and unity across all EU member states and the entire European region.

Acknowledgements

We dedicate this work to the memory of Prof. Roger Williams, in following up on his tireless efforts for the UK Lancet Commission on Liver Disease. The opinions expressed and arguments employed herein are solely those of the authors and do not necessarily reflect the official views of the Organisation for Economic Co-operation and Development (OECD) or of its member countries. We thank Christian Kuschel for HCV economic model development work. We thank Commissioners Angelos Hatzakis, Greece, and Marina Maevskaya, Russia, for useful discussions. We thank Neil Guha for helpful input to the primary care sections. We thank Nikolai Pushkarev (epha.org) and Peter Rice for helpful discussions on the recommendations of the Commission. We thank medical illustrator Kari Toverud for graphical assistance in developing figures 4, 14 and 18. We thank Ansgar Lohse for helpful discussions on the role of European Reference Network for rare liver diseases (ERN RARE LIVER) for patients with rare liver diseases. We thank Vincent Karam and the European Liver Transplant Registry (www.eltr.org) for providing detailed output when requested. We thank Sofia Blomqvist, Margaret Walker, Frauke Degenhardt and Marit Mæhle Grimsrud for technical assistance. We thank the EASL office (www.easl.eu) for support in organizing the physical meetings of the Commission and in administering the many formal and informal surveys performed. We thank Sabine Kleinert for invaluable supervision. We thank Camila Picchio, Adam Palayew and Danielle Guy for input to early drafts of stigma-related report sections. JVL acknowledges support to ISGlobal from the Spanish Ministry of Science, Innovation and Universities through the 'Centro de Excelencia Severo Ochoa 2019–2023' Programme (CEX2018-000806-S) and from the Government of Catalonia through the CERCA Programme. This paper uses data from SHARE Wave 7 (DOIs: 10.6103/SHARE.w7.711), see Börsch-Supan et al. (2013) for methodological details. The SHARE data collection has been funded by the European Commission through FP5 (QLK6-CT-2001-00360), FP6 (SHARE-I3: RII-CT-2006-062193, COMPARE: CIT5-CT-2005-028857, SHARELIFE: CIT4-CT-2006-028812), FP7 (SHARE-PREP: GA N°211909, SHARE-LEAP: GA N°227822, SHARE M4: GA N°261982, DASISH: GA N°283646) and Horizon 2020 (SHARE-DEV3: GA N°676536, SHARE-COHESION: GA N°870628, SERISS: GA N°654221, SSHOC: GA N°823782) and by DG Employment, Social Affairs & Inclusion. Additional funding from the German Ministry of Education and Research, the Max Planck Society for the Advancement of Science, the U.S. National Institute on Aging (U01_AG09740-13S2, P01_AG005842, P01_AG08291, P30_AG12815, R21_AG025169, Y1-AG-4553-01, IAG_BSR06-11, OGHA_04-064, HHSN271201300071C) and from various national funding sources is gratefully acknowledged (see www.share-project.org). PC acknowledges support by the French National Agency for HIV, hepatitis and emerging infectious diseases research (ANRS / EMERGING INFECTIOUS DISEASES). We thank Prof. Yossi Harel-Fisch; Head of The Israeli HBSC (Health Behavior in School-Aged Children) research program, School of Education, Bar Ilan University, Ramat Gan 5290002, Israel, and Dr. Riki Tesler- Department of Health System Management, Faculty of Health Science, Ariel University, Ariel 407000, Israel for their help in providing HBSC data and their support in analysis of these data. We thank Carina Ferreira-Borges and co-workers for approval to reprint Supplementary Figure 3.

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Declarations of potential conflicts of interest

EB, PB, RB, MB, MC, HCP, GD, NF, RF, PG, IG, SJH, THK, JVL, AL, CL, MPM, GM, NKM, MN, CYP, BS, CS, NSc, MSB., ES and CT declared potential conflicts of interests. For details, see full ICMJE declaration of the individual authors. The other authors declared no conflicts of interest.

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