EASL™
The Home of Hepatology

THE DIGITAL INTERNATIONAL LIVER CONGRESS™

27-29 August 2020

CONGRESS REVIEW

CONTENTS

Preface

This report, produced by EASL, summarizes the scientific highlights from Digital ILC 2020 for the international hepatology community. It presents the most impactful and noteworthy contributions to the field of hepatology in 2020, alongside top-line attendance and demographic information showcasing the success of the congress. For healthcare professionals and scientists who were not able to attend, this report provides an overview of the congress experience and the unmissable science presented. For industry and future sponsors, it summarizes the congress experience and demonstrates EASL's ability to adapt to a changing world with innovative formats to maintain delegate engagement and interaction.

More on Digital ILC 2020

EASL HIGHLIGHTS 2019–2020

It has been a pivotal year for EASL, and this video pinpoints the most important achievements and milestones for the society

DIGITAL ILC DAILY NEWS

Dive into the key moments from each day of the congress

Thursday 27th August

Friday 28th August

Saturday 29th August

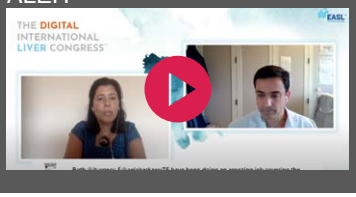
EASL STUDIO

This online broadcast was pivotal in bringing Digital ILC to life. You can now watch our panel's interviews with experts from APASL, AASLD and ALEH

APASL

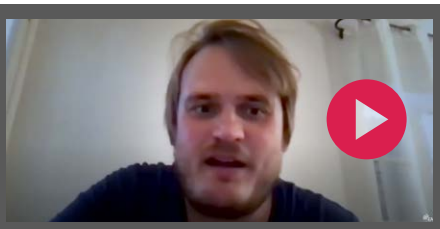
AASLD

ALEH



VOICES FROM THE VIRTUAL FLOOR

Get perspectives from congress participants with our series of interviews on our YouTube channel



EASL TAKEAWAYS

Continuing the education beyond the congress, the EASL Takeaways webcast series takes a retrospective look at the key developments from Digital ILC 2020

TRIBUTE TO PROFESSOR ROGER WILLIAMS

The world of hepatology lost one of its giants this year, and Professor Rajiv Jalan led a moving tribute at the congress

Introduction

The Digital International Liver Congress™ (ILC) 2020 was the 55th annual meeting of the European Association for the Study of the Liver (EASL), and in this unprecedented year transformed by the COVID-19 pandemic, the first to take place entirely online.

COVID-19 has profoundly impacted all aspects of life and healthcare worldwide, including liver disease. Data from the international collaborative EASL-supported COVID-Hep and the SECURE-Cirrhosis registries show a stepwise increase in rates of major adverse outcomes, including death, with increasing severity of liver disease. Mortality rates of 79% have been reported among patients with Child–Pugh C cirrhosis once admitted to intensive care, rising to 90% in patients requiring invasive ventilation.

The pandemic has also radically affected how we – clinicians and researchers, patients and advocates – can interact. EASL rose to this challenge with a wide range of innovative approaches to make Digital ILC 2020 a unique and memorable event. The virtual congress platform and exhibition space allowed delegates to engage with presenters and faculty to explore and discuss the latest clinical developments and scientific breakthroughs. The ground-breaking EASL Studio livestreams brought real-time expert commentary and perspective to the programme and highlighted the close and collaborative international partnerships that exist between EASL and hepatology societies around the world.

As in previous years, the state-of-the-art scientific programme was classified across six topic tracks, allowing delegates the freedom to tailor their congress experience to their specific interests. This year, an additional focus was put on public health and rare liver diseases. Reflecting the excellence of the programme, Digital ILC 2020 was accredited by the European Accreditation Council for Continuing Medical Education with 17 European CME credits.

The learning and innovation continued after the congress. EASL experts have teamed up with renowned colleagues from around the world to launch EASL Takeaways, a series of open-access webcasts available through the EASL Campus discussing selected highlights from a broader perspective. Comprehensive slide decks summarizing the most impactful science from the congress are also available to all registered delegates through the online platform.

The commitment and dedication of our collaborators, speakers, sponsors and delegates have all contributed to making the Digital ILC 2020 a huge success under challenging circumstances. This report highlights their contributions and explores the key scientific and clinical developments shared during the event.

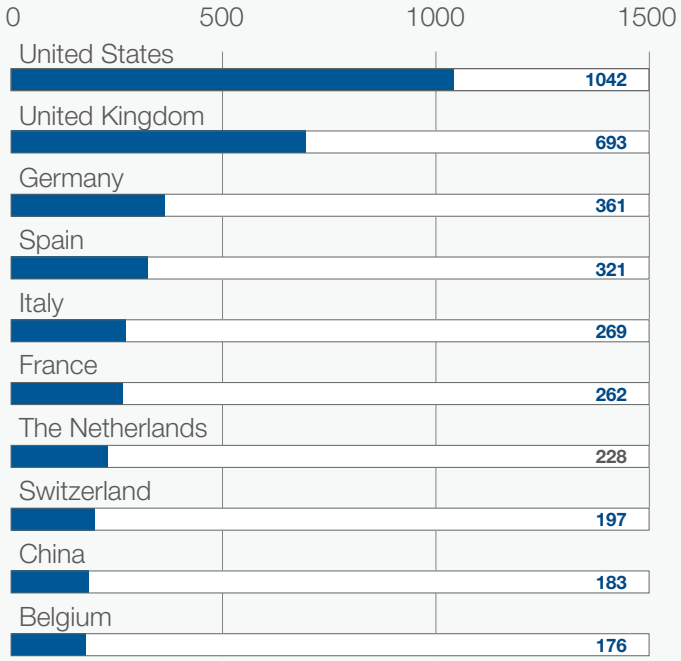
Digital ILC 2020 in numbers

7,389
ONLINE PARTICIPANTS

114
COUNTRIES REPRESENTED

315
FACULTY FROM 23 COUNTRIES

Top 10 participating countries



2,703
ABSTRACT SUBMISSIONS
1,670 ACCEPTANCES
FROM **65** COUNTRIES

94
SESSIONS

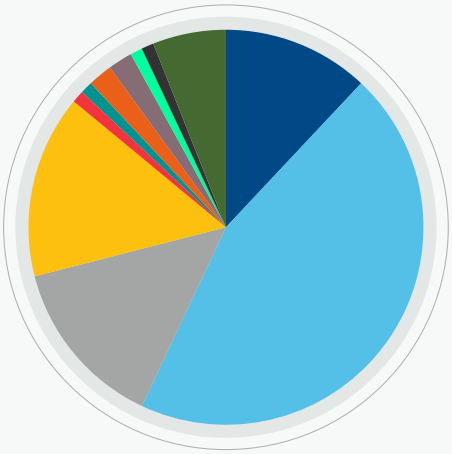
178
ORAL PRESENTATIONS WITH LIVE Q&A

1,439
E-POSTERS

108
VIDEO POSTERS

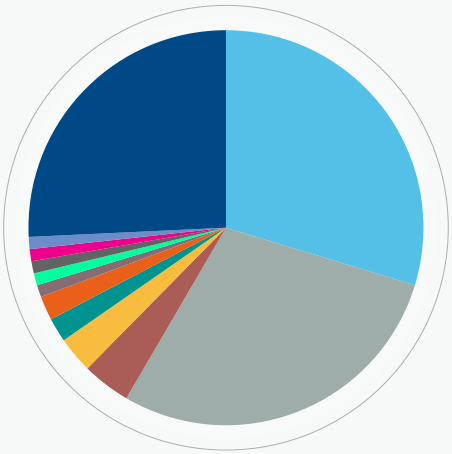
Delegate profiles

PROFESSIONAL ROLES



- Administration/organization employees, **2%**
- Allied health professional, **1%**
- Basic researcher, **12%**
- Clinical practitioner/ medical doctor, **45%**
- Clinical researcher, **14%**
- Industry/corporate professional, **15%**
- Nurse,**1%**
- Nurse practitioner,**1%**
- Fellow, **2%**
- Patient, **1%**
- Other, **6%**

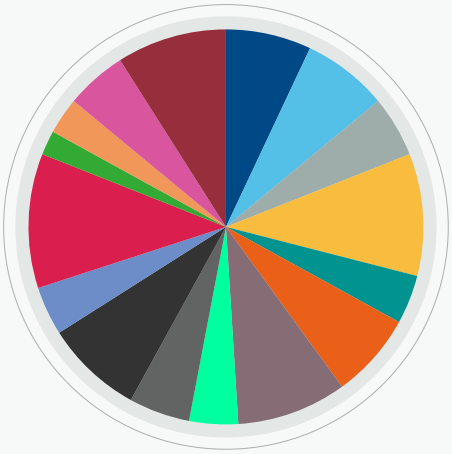
SPECIALTIES



- Allied health professionals and other*, **26%**
- Epidemiology/statistics, **1%**
- Endocrinology, **1%**
- General practitioner, **3%**
- Hepatology/gastroenterology, **30%**
- Hepatology, **29%**
- Immunology, **2%**
- Infectiology, **4%**
- Oncology, **1%**
- Pathology, **1%**
- Pharmacology, **1%**
- Virology, **2%**

*Includes allied health professionals, corporate attendees and physicians of other specialties

AREA OF INTEREST



- Alcoholic liver disease, **7%**
- Autoimmune and chronic cholestatic liver diseases, **7%**
- Basic and translational science, **5%**
- Cirrhosis and complications, **10%**
- Drug-induced liver injury, **4%**
- Fibrosis, **7%**
- General hepatology, **9%**
- Imaging and interventional, **4%**
- Liver transplantation/ surgery, **5%**
- Liver tumours, **8%**
- Molecular and cellular biology, **4%**
- NAFLD/NASH, **11%**
- Paediatric hepatology, **2%**
- Public health, **3%**
- Rare diseases of the liver, **5%**
- Viral hepatitis, **9%**

Media highlights

The Digital ILC 2020 media coverage featured a wide range of scientific advances across the field of hepatology throughout the 3-day digital event, including the encouraging progress in clinical trials of multiple novel therapies for hepatitis B virus (HBV), hepatitis D virus (HDV) infection, non-alcoholic steatohepatitis (NASH), and hepatocellular carcinoma (HCC). New models to identify advanced liver disease in patients with diabetes and to predict HCC following hepatitis C virus (HCV) treatment were also presented, along with new evidence to support early use of transjugular intrahepatic portosystemic shunts (TIPS) in patients with cirrhosis and acute variceal bleeding (AVB). Additionally, the problem of liver donor shortages was addressed by studies investigating a new add-on treatment to improve transplant-free survival in primary biliary cholangitis, and the enzymatic mechanisms behind liver regeneration. The press briefing highlighted two studies of particular significance to patient outcomes.

FAECAL MICROBIAL TRANSPLANT CAN SIGNIFICANTLY REDUCE ALCOHOL-RELATED LIVER DISEASE AND CANCER RISK

The key role of microbial biodiversity in the gut was highlighted. In a pilot, double-blind, placebo-controlled, randomized clinical trial, faecal microbial transplant (FMT) from healthy individuals was shown to reduce alcohol cravings and improve quality of life in 20 patients with alcohol use disorder and liver cirrhosis, who had made several unsuccessful attempts to give up alcohol.

The results, observed 15 days after treatment, were further supported by a corresponding significant increase in microbiota diversity in FMT patients compared with baseline. In particular, higher relative abundances of *Odoribacter, Alistipes*, and *Roseburia*, suggesting improvements in metabolic function, were reported.

In chronic alcohol use, imbalances in gut microbiota are thought to arise due to increases in reactive oxygen species that cause intestinal inflammation, leading to increased gut permeability. The consequent translocation of gut bacterial DNA and endotoxins to the liver is believed to induce pro-inflammatory toll-like receptor 4 (TLR4) signalling pathways associated with hepatocarcinogenesis. By manipulating gut microbiota to reduce alcohol cravings, FMT shows substantial promise in improving outcomes.

Dr Jasmohan S Bajaj of McGuire VA Medical Center, USA, who presented the study, added that *"The relative abundance of short-chain fatty acid-producing bacteria identified in patients with higher diversity after FMT demonstrates that altering the gut–brain axis is a potential avenue to alleviating alcohol use disorder in those with cirrhosis."*

PRIORITIZING PATIENTS USING MELD-Na COULD REDUCE LIVER TRANSPLANT (LT) WAITING-LIST DEATHS IN EUROPE

Prioritizing patients for LT using the Model for End-stage Liver Disease Sodium (MELD-Na) score, instead of the more commonly used MELD score, could increase the chances of high-risk patients receiving a transplant and reduce the risk of dying while on the transplant waiting list. Although MELD has been very successful in prioritizing patients, it does not accurately reflect the risk of death in patients with hyponatraemia, which is an important predictor of mortality in patients listed for LT.

According to the results of a large retrospective study of 5,223 patients across Europe with end-stage liver disease allocated for LT between 2007 and 2018, MELD-Na-based allocation has the potential to reduce 90-day waiting list mortality by almost 5% versus MELD. The research was carried out by Eurotransplant, a non-profit international collaboration responsible for the allocation of donor organs in Austria, Belgium, Croatia, Germany, Hungary, Luxembourg, the Netherlands, and Slovenia.

Globally, there is a shortage of liver grafts, and the prevalence of cirrhosis is increasing. We need methods that better predict mortality and improve prioritization of patients for LT.

Scientific programme highlights

GENERAL HEPATOLOGY

The General Hepatology track explored the most important advances relevant to healthcare professionals and scientists with an interest in liver disease. Key sessions explored how to bring hepatology into the primary care setting, the role of society in improving general liver health, and the pros and cons of screening in the general population. As well as a dedicated session on COVID-19 and the liver, there was a focus on managing liver disease in vulnerable groups, including pregnant women and adolescents.

THE CRITICAL ROLE OF PRIMARY CARE IN IDENTIFYING PATIENTS WITH ADVANCED LIVER DISEASE

It is a sobering thought that, despite advances in therapy, the prevalence of advanced liver disease and its associated mortality continue to increase. Thus, it is more important than ever to identify patients with advanced liver disease and engage them in the healthcare system before their situation becomes critical.

To improve the recognition of patients with significant liver disease, a 2016 proof-of-concept study, commissioned by the Wales Liver Plan in the UK, used reflex aspartate aminotransferase (AST) testing in 17,700 patients who presented with elevated alanine aminotransferase (ALT) in a primary care setting. The introduction of reflex AST testing led to a significant increase in new diagnoses of cirrhosis among patients who attended their follow-up appointments. Despite this, the study showed that many patients with abnormal liver function tests were not referred, and patient attendance was poor; of the 2,117 patients with an AST:ALT ratio >1, only 750 were referred from primary care, of whom ~40% failed to attend their liver ultrasound appointments.

These findings suggest that both compliance among general practitioners with referral pathways and community access to non-invasive testing need to improve in order to increase rates of detection of advanced liver disease in the general population.

MANAGING PREGNANCY IN PATIENTS WITH LIVER DISEASE

The latest advances in research into managing pregnancy across the spectrum of liver disease were presented at Digital ILC 2020. A case-based session designed to reflect the everyday challenges faced by doctors managing liver disease during pregnancy discussed approaches that are directly transferable to routine clinical practice. This interactive session also provided the audience with the opportunity to share insights and ask questions of the expert panel.

Among women with autoimmune hepatitis (AIH) of childbearing age, there is a clear need to initiate discussions on family planning in a timely manner. In addition, it is critical to aim for minimal adjustment of standard immunosuppressive therapy during pregnancy in order to minimize the risk of adverse birth outcomes and disease flare.

Given the increasing number of women with liver cirrhosis who want to get pregnant, it is also critical to invest in pre-pregnancy counselling and assessment of portal hypertension in this population, as risk scores can be extremely valuable in informing management decisions and devising delivery plans.

This session discussed the latest research into the use of ursodeoxycholic acid (UDCA) in patients with intrahepatic cholestasis or high HBV viral load who are considering pregnancy. There is a linear association between high maternal levels of HBV DNA and the risk of mother-to-child transmission (MTCT). Thus, the use of tenofovir disoproxil fumarate in the third trimester should be mandatory in pregnant women with HBV DNA levels >200,000 IU. Additionally, amniocentesis should be avoided because of the increased risk of MTCT.

ADVANCES IN UNDERSTANDING OF SURVIVAL IN LIVER TRANSPLANTATION

Analysis from the prospective multicentric European Liver Transplant Registry between 1998 and 2017 has revealed a greatly increased risk of death within 5 years among patients who underwent LT for autoimmune hepatitis versus those receiving LT for other autoimmune liver diseases or alcohol-related cirrhosis. After 5 years, the prognosis of patients after AIH-LT improved considerably compared with the other groups.

The relatively poor survival in the first 5 years was attributed to increased incidence of early lethal infections, particularly fungal infections. All deaths from fungal infections in patients with AIH-LT occurred within the first year of follow-up. It was also observed that patients receiving a donation from a living donor showed decreased survival compared with donation after brain death.

THE ROLE OF TELOMERES AND GENETIC INSTABILITY IN LIVER-RELATED DISEASES

Investigations into the impact of rare hereditary telomere-related gene mutations provided new insight into their role in the development of liver abnormalities. These mutations reduce the length of telomeres and induce genetic instability and early cell ageing, and their impact on liver disease was characterized in 132 patients in a retrospective analysis of cases referred to 25 tertiary pneumology, haematology, or hepatology centres in France between 2004 and 2019.

Analysis of liver involvement, as well as survival, identified a number of abnormalities including vascular porto-sinusoidal disease, advanced fibrosis/cirrhosis, and NASH in 35%, 19%, and 13% of patients, respectively, with 12 patients requiring LT. In a multivariate analysis, a fibrosis-4 (FIB-4) score of ≥3.25 and other factors in liver disease – including excessive alcohol consumption, presence of hepatitis B surface antigen, metabolic syndrome, body mass index (BMI) >25 kg/m^2, and ferritin >1,000 µg/L – independently predicted LT or death.

Despite the frequency of liver involvement, with heterogeneous histological lesions, few patients were found to be symptomatic. As a consequence, knowledge of the risk factors that may lead to liver disease will be of great benefit in patients with telomere-related mutations.

Metabolism, alcohol and toxicity

Globally, one in four people are living with fatty liver disease, with obesity, alcohol consumption, and sedentary lifestyles as key contributors. The "Metabolism, alcohol and toxicity" track at Digital ILC 2020 explored the metabolic factors associated with liver disease and how they interact with genetics, inflammation, and the gut–liver axis. The development of new therapies, the use of biomarkers in non-alcoholic fatty liver disease (NAFLD), and how microbiota and genes can modulate alcohol-related liver disease (ARLD) were some of the key questions during the congress.

TURNING THE TIDE ON NAFLD AND NASH

NAFLD is estimated to affect approximately 25% of the global population and is the fastest growing liver disease worldwide, while NASH puts patients at risk for complications such as HCC and cirrhosis.

Historically, NAFLD has been diagnosed and prognosticated by performing liver biopsy, a costly and invasive procedure that carries a risk of morbidity, and there is a significant unmet need for better non-invasive methods to detect NAFLD. In addition, there are still no available pharmacological treatments for NAFLD in clinical use. As the twin global epidemics of NAFLD and obesity continue to grow, it is more important than ever to develop new and effective management strategies to tackle NAFLD and NASH.

At Digital ILC 2020, there was a focus on novel methods of non-invasive testing for NAFLD, promising results from early-phase trials on agents under investigation for the treatment of NASH, and discussion of the use of precision medicine as a treatment strategy in this key area.

NOVEL METHODS OF NON-INVASIVE TESTING FOR NAFLD

In a dedicated session, several groups presented the results of their research into the non-invasive assessment of liver health, including novel techniques and improvements in established methods.

Using data from 40,729 individuals from the population-based AMORIS cohort in Stockholm, Sweden, one study demonstrated that, by having repeated FIB-4 measurements within 5 years of follow-up, it was possible to improve the prediction of cirrhosis and complications in patients with NAFLD compared with single FIB-4 measurements. Another method was presented by a team from the United States, using a cross-sectional analysis of 311 consecutive patients from the prospective University of California, San Diego-NAFLD cohort who had biopsy-proven NAFLD and contemporaneous magnetic resonance elastography (MRE). The study showed that combining FIB-4 with MRE could be used to identify patients at risk of progressing to stage ≥2 fibrosis.

A second group, from the United States, used vibration-controlled transient elastography (VCTE) to investigate longitudinal changes in liver stiffness (LS) and factors associated with developing LS-defined cirrhosis. In a cohort of 1,010 individuals with NAFLD, 58% of whom had definite NASH and 8% had cirrhosis on biopsy, the annual risk of developing LS-defined cirrhosis was 7% in patients without LS-defined cirrhosis at first VCTE visit. Higher portal inflammation, fibrosis, and international normalized ratio (INR) were associated with increased risk of LS-defined cirrhosis. The authors hope these data will help inform the use of non-invasive endpoints in future clinical trials.

In addition to data on already established methods, several researchers reported on novel non-invasive NAFLD diagnostic methods, including machine-learning techniques and biomarkers.

Current staging systems for NASH have limited utility for quantitative analyses. One study used convolutional neural networks (CNNs) to produce continuous scores for key NASH features from almost 5,000 biopsy images and assessed the ability of these models to predict NASH-related biomarkers compared with pathologist-derived scores. CNN scores were highly correlated with those of a central pathologist, suggesting a potentially useful novel automated strategy for quantitative histological analysis of biopsy samples.

MiR-34a has been previously proposed as a biomarker for NASH. A study of serum MiR-34a levels in 1,214 patients with a liver biopsy and 100 blood donors (healthy controls) showed that MiR-34a is a reliable biomarker that can be used efficiently to rule-out NAFLD in healthy subjects and in patients with suspected NAFLD, supporting its use in screening populations with risk factors for NASH.

As the prevalence of NAFLD and NASH continues to increase worldwide, such developments in non-invasive testing will be key to identifying people at risk, improving standard of care and potentially leading to better outcomes for patients.

EXPLORING NEW TREATMENT OPTIONS FOR NAFLD AND NASH

Several abstracts presented at Digital ILC 2020 reported promising results from Phase II trials on new agents targeting a number of novel mechanisms of action.

The farnesoid X receptor (FXR), which negatively regulates hepatic gluconeogenesis, lipogenesis, and steatosis, represents a potentially important target for the treatment of NASH, and data on three FXR agonists were reported. In the Phase IIb ATLAS trial in 392 patients with advanced fibrosis, combination therapy for 48 weeks with cilofexor 30 mg (a nonsteroidal FXR agonist) and firsocostat 20 mg (an acetyl-CoA carboxylase allosteric inhibitor) was well tolerated and improved both fibrosis and NASH activity.

In the randomized placebo-controlled Phase IIa ARGON-1 study, patients with fibrotic NASH without cirrhosis treated with the novel FXR agonist EDP-305 for 12 weeks exhibited significant reductions in ALT, fat percentage, and gamma-glutamyl transferase compared with placebo. Another international randomized controlled trial in 121 patients with NASH showed significant decreases in ALT, hepatic fat fraction, and body weight compared with placebo following 12 weeks of treatment with the non-bile acid FXR partial agonist nidufexor. Results from these three trials reinforce FXR agonism as an effective therapeutic approach in NASH.

A Phase II randomized placebo-controlled trial in 78 patients evaluated the efficacy and tolerability of engineered fibroblast growth factor (FGF) 19 analogue aldafermin (NGM282) in the treatment of NASH. Over 24 weeks, patients receiving aldafermin had significant and durable improvements in liver fat content, fibrosis, and NASH histology compared with those receiving placebo.

Finally, the glucagon-like peptide-1 (GLP-1) receptor, which improves glucose control and reduces body weight by decreasing appetite, influencing hepatic lipid content and inflammation, presents another potential target. A Phase IIb study of the first-in-class GLP-1/glucagon dual-receptor agonist cotadutide in 834 patients with type 2 diabetes affected by obesity or excess weight demonstrated significant reductions in body weight and ALT over 54 weeks compared with placebo and once-daily liraglutide, as well as significant improvements in NAFLD fibrosis score and fatty liver index.

PRECISION MEDICINE FOR THE MANAGEMENT OF NAFLD

At Digital ILC 2020, an interactive session explored whether precision medicine to manage NAFLD and find new therapies for specific subtypes would be a feasible strategy to overcome the difficulties posed by the heterogeneous nature of the disease.

Evidence shows that specific metabolic traits, such as diabetes, hypertension, dyslipidaemia and obesity, and genetic mutations, can have an additive effect on the progression of fibrosis and the development of cirrhosis and HCC. Data from investigations into genetic influences on NAFLD demonstrated the potential for identifying disease subtypes. For example, *PNPLA3* and *LYPLAL1* seem to increase risk of liver disease but not metabolic disease, *TM6SF2* appears to predispose to liver disease but may be protective against dyslipidaemia and heart disease, and *GCKR* increases risk of liver disease and dyslipidaemia but protects against diabetes.

The impact of gene–environment interactions in NAFLD were also explored, with discussions around how epigenetics contributes to its phenotypic heterogeneity. Tissue-specific epigenetic modifications, such as aberrant DNA methylation, regulation of non-coding RNAs, and changes in the liver microbiome result in gradual loss of organ function and a systemic metabolic maladaptive response. However, such modifications should be at least partially reversible, and their manipulation holds much promise in the therapeutic management of NAFLD.

To end the session, a fascinating presentation demonstrated the influence of the human liver lipidome on the aetiology of NAFLD. Marked differences were revealed between NAFLD associated with metabolic syndrome and that associated with a *PNPLA3* risk allele, the former being associated with increased insulin resistance-causing ceramides and the latter with retention of polyunsaturated triglycerides in the liver. Genetic variants protective against NAFLD were also associated with increased hepatic phosphatidylcholines, suggesting a new mechanism for NAFLD that is now being investigated.

During their discussions, the panel of experts noted that some of the NAFLD-associated variants identified so far have high odds ratios that approach Mendelian levels and, when carriers of these alleles also have predisposing lifestyle/environmental factors, the effects are further amplified. This illustrates the potential for precision medicine to optimize outcomes from interventions for NAFLD by targeting them towards patients who would benefit the most.

IDENTIFYING THE CAUSES OF INTER-PATIENT STEATOHEPATITIS VARIATION IN NAFLD

With a multitude of factors contributing to NAFLD pathology, research has also been focused on biological mediators that can influence the course of the disease and specific phenotypes. With recent evidence showing pro-inflammatory activation of macrophages by saturated fatty acids independent of TLR4, the macrophage scavenger receptor 1 (MSR1) was identified in new research as a critical sensor for lipid homeostasis and as a potential therapeutic target.

Using a histological and transcriptomics approach to human liver and adipose tissue samples, MSR1 expression in the liver was associated with greater disease activity and occurrence of hepatic lipid-laden foamy macrophages. Four single nucleotide polymorphisms at the MSR1 locus reaching statistical significance for histologically proven NAFLD were also identified in a genome-wide association study.

Furthermore, transgenic mouse models found that MSR1-null mice were protected against diet-induced metabolic disorder, with less hepatic inflammation and fibrosis, reduced circulating fatty acids, lower hepatic triglyceride levels, and more lipid storage in adipocytes versus wild-type. MSR1 was also found to trigger inflammatory activation of liver macrophages in vitro and in vivo in the presence of lipids and c-Jun N-terminal kinase (JNK).

IS EARLY TRANSPLANTATION THE ANSWER IN SEVERE ALCOHOLIC HEPATITIS NOT RESPONSIVE TO MEDICAL TREATMENT?

ARLD remains the major cause of liver injury in Western countries. One emerging therapy for severe alcoholic hepatitis (SAH) is early liver transplantation (eLT). However, robust data from prospective controlled studies are needed to demonstrate the effectiveness of such strategies in patients who are not responsive to medical treatment. The French-Belgian QuickTrans trial, the first prospective controlled study in this field, showed high survival rates (~89%) following eLT among patients with SAH who had not responded to medical treatment. These patients were, however, more likely to relapse than patients receiving transplantation for alcohol-related cirrhosis following 6 months of abstinence: the rate of relapse was 34% versus 25%, respectively.

TARGETING GUT MICROBIOTA IN THE MANAGEMENT OF ARLD

There is potential therapeutic value in the manipulation of the gut microbiome in the treatment of many different aspects of liver disease.

Bacterial virulence factors are proteins or peptides encoded by bacterial genes that help micro-organisms colonize the intestine or mediate disease. A multicentre, observational study conducted in Europe, the United States, and Mexico evaluated the presence of virulence factors of the commensal gut microbiota in patients with ARLD and attempted to correlate virulence factors with outcome in alcoholic hepatitis patients.

The investigators found significantly higher virulence factors in the intestinal bacterial metagenomes from 81 patients with alcoholic hepatitis compared with 41 patients with alcohol use disorder, or nine controls without. In addition, patients with virulence factors had a five-fold increased risk of mortality compared with those without virulence factors (18% vs 82%, respectively, were alive 180 days after enrolment).

The authors concluded that assessing specific virulence factors in the commensal gut microbiota could be used to determine mortality in patients with alcoholic hepatitis and might lead to new diagnostic biomarkers and treatments.

Viral hepatitis

The World Health Organization (WHO) has called for elimination of viral hepatitis as a global public health threat by the year 2030. Digital ILC 2020 provided a platform for leading experts to discuss the remaining obstacles to HCV elimination and review the upcoming treatments and new insights for other forms of viral hepatitis.

HEPATITIS C: THE JOURNEY TOWARDS ELIMINATION

It is important for us to evaluate our response to the HCV epidemic at both a national and international level now that we are only a decade away from the WHO's 2030 goal to eliminate viral hepatitis. At Digital ILC 2020, clinicians, scientists, and programme managers from around the world convened to share research and best practice to help achieve this goal.

Researchers from Tayside, Scotland, proposed a new approach to displaying HCV cascades of care that give yearly snapshots of the epidemic and show cumulative progress towards elimination targets. This novel methodology could provide a way to improve national and international reporting and facilitate local service planning and knowledge exchange.

An update from the country of Georgia showed how their national strategy has made substantial progress toward eliminating hepatitis C, with more than half of infected people identified and registered for treatment and very high cure rates (98% SVR12) among those in whom treatment response has been evaluated to date. Despite this, challenges remain in identifying individuals living with HCV and, in particular, linking them to care.

In perhaps one of the most striking success stories, the provision of universal access to testing and treatment for HCV in Spanish prisons has led to a significant decrease in the prevalence of HCV infection in this high-risk population, with high screening and treatment rates that are close to those considered by the WHO to be required to achieve elimination.

In other settings, studies from the UK and Canada have demonstrated substantial progress in the uptake of testing and treatment for hepatitis C and reduction in the incidence of HCV infection among men who have sex with men, while a study from Myanmar reported data showing that community-based point-of-care testing and treatment initiated by general practitioners together form a feasible and effective strategy in low- and middle-income settings, with SVR12 rates of 93%.

WHAT'S IN THE PIPELINE FOR HEPATITIS B AND D TREATMENT?

Although there are highly effective drugs for the treatment of infection with HBV, currently none of the available therapies offer the reliable prospect of a cure. Additionally, there are few available options for HDV. Emerging therapies that exploit novel mechanisms of action to target HBV and HBV/HDV coinfection may have the potential to bring us closer to a cure, and several were presented at Digital ILC 2020.

Results were reported from Phase II clinical trials in patients with chronic HBV infection treated with four different agents that act by targeting the production of viral proteins, including RNA interference therapies VIR-2218 and JNJ-3989 and the antisense oligonucleotides ISIS 505358/GSK3228836 and RO7062931. All four therapies were reported to be well tolerated and to lead to significant reductions in HBV surface antigen levels. Data on longer-term studies in larger numbers of patients are eagerly awaited.

Further Phase II clinical trials evaluated the HBV core inhibitor ABI-H0731 and the oral TLR8 agonist selgantolimod in patients with chronic HBV who had achieved viral suppression on standard therapy. Both treatments demonstrated promising efficacy and favourable safety profiles. ABI-H0731 works by directly targeting viral proteins, while selgantolimod is an immunomodulator. Together, these data demonstrate the potential viability of multiple routes towards a cure for chronic hepatitis B.

There are very few treatment options for patients with chronic HBV/HDV coinfection. A Phase II trial in 30 HBV/HDV coinfected patients reported that high doses of the first-in-class entry inhibitor bulevirtide, administered in combination with pegylated interferon alfa-2a (PEG-IFNα) or tenofovir, were well tolerated and led to a continuous decline in HDV RNA that was maintained over 48 weeks of treatment. These data highlight a potential new treatment option for an infection that represents the most severe form of viral hepatitis and a significant unmet need in the field.

IS DURABLE IMMUNE CONTROL AND FUNCTIONAL CURE POSSIBLE IN CHRONIC HEPATITIS B?

The Stop-NUC trial – the first large-scale prospective, multicentre randomized study of its kind – evaluated the potential of discontinuation of long-term nucleos(t)ide analogues (NUCs) in HBV e-antigen (HBeAg)-negative patients without cirrhosis who had successfully achieved HBV DNA suppression for ≥4 years during NUC therapy.

Patients who continued treatment with NUCs had more stable disease control than patients who discontinued therapy. However, although patients who discontinued NUCs were more likely to experience HBV DNA flare (viral load >20 IU/mL), at 96 weeks one-third of patients had HBV DNA levels ≤20 IU/mL, ALT flare occurred only in one-third, and ALT levels were within normal ranges in 88% of patients. No patient experienced a serious adverse event as a result of discontinuing NUCs. In addition, NUCs were only restarted in 14% of patients, while 68% had no indication for treatment according to current EASL recommendations.

These findings demonstrate the potential for induction of durable immune control and functional cure in patients with chronic HBeAg-negative chronic hepatitis B.

HEV: FROM VIROLOGY TO TREATMENT

Infection with hepatitis E virus (HEV) is one of the most common causes of acute hepatitis and jaundice worldwide, and there are significant challenges when it comes to managing the disease. Significant knowledge gaps exist in the molecular virology, pathogenesis, epidemiology, and transmission of HEV, and researchers still seek standardized diagnostics, improved treatments, and a better understanding of the viral and host determinants of clinical outcomes. Leading experts in the field provided a comprehensive overview of the current knowledge of HEV and prospects for future treatments.

While many people with HEV are asymptomatic or have only mild hepatitis, data from multiple countries underscored the potential seriousness of HEV infection, showing that small but significant numbers of patients experience severe or life-threatening manifestations. Approximately 6% of patients experience acute-on-chronic liver failure (ACLF), 5% experience neurological complications, and data from a French cohort reported a HEV-related mortality rate of 7%.

The pathogenesis of HEV was also discussed, with four key mechanisms underlying many of its diverse manifestations: an inappropriate immune response in acute liver failure, ACLF or neurological injury; extrahepatic replication in neurological injury, acute kidney injury, and pregnancy complications; chronic immune stimulation in cryoglobulinaemia, acute liver injury, and lymphoma; and immunodeficiency in chronic HEV infection and subsequent cirrhosis and liver cancer.

Primary prevention of HEV infection remains a challenge, notably because the virus is resistant to alcohol and many disinfectants. New host and viral therapeutic targets were described that could form the basis for potential treatment strategies. Although, to date, only PEG-IFNα and ribavirin are recommended by EASL, testing and validation of combination and sequential treatment approaches with ribavirin, sofosbuvir, and silvestrol may expand treatment options.

Liver tumours

The landscape of liver cancer is changing. With recent progress in the treatment and elimination of HCV, liver tumours caused by viral hepatitis are becoming less common. Yet a worsening obesity epidemic is shifting liver cancer towards a greater prevalence of metabolic disease-related tumours. Improving our understanding of the mechanisms of liver cancer and developing new therapies remains crucial. The "Liver tumours" track at Digital ILC 2020 showcased the latest advances and helped equip clinicians for the coming challenges in the field of liver cancer.

NOVEL IMMUNOTHERAPIES DEMONSTRATE POTENTIAL IN ADVANCED HCC

Patients with advanced or unresectable HCC have limited treatment options. While the anti-angiogenic therapy sorafenib currently forms the backbone of treatment, prognosis remains poor, and 1- and 3-year survival is low. However, several late-breaking presentations delivered at Digital ILC 2020 highlighted the potential for new immunotherapies in the treatment of patients with unresectable HCC.

Results from the open-label Phase III IMbrave 150 study demonstrated that atezolizumab plus the anti-vascular endothelial growth factor antibody bevacizumab has a safety profile that is comparable with sorafenib as first-line therapy for patients with unresectable HCC. Similarly, a Phase Ib study of first-line therapy with the multikinase inhibitor lenvatinib in combination with the anti-programmed death-1 monoclonal antibody pembrolizumab also reported an acceptable safety profile, alongside promising anti-tumour activity, triggering initiation of a Phase III trial of this treatment combination in patients with HCC.

Additional studies of immunotherapies for patients with HCC were reported. A subgroup analysis from the Phase I/II CheckMate 040 study demonstrated clinically meaningful benefits and a manageable safety profile with a combination of nivolumab and ipilimumab in patients with advanced HCC previously treated with sorafenib.

Genetically engineered ADP-A2AFP specific peptide enhanced affinity receptor (SPEAR) Tcells that target α-fetoprotein-positive tumours in the context of HLA-A*02 are currently being investigated in a Phase I study of patients with HCC. There were no clear reports of T-cell related on-target or off-target toxicity from this first-in-human study in patients with HCC, and no protocol-defined dose-limiting toxicities.

With positive efficacy results and acceptable safety and tolerability profiles being reported for both antibody- and T-cell-based immunotherapies across these studies, improved outcomes for patients with advanced or unresectable HCC may be a step closer.

TARGETING GUT MICROBIOTA IN THE MANAGEMENT OF LIVER CANCER

Associations between an imbalance in the gut microbiome and chronic liver disease are being reported more frequently. However, the molecular mechanisms by which intestinal microbiota affect the development of HCC are less well established. Using an experimental mouse model of steatohepatitis, one research group investigated how NLRP6-mediated intestinal dysbiosis and modulation of dynamic microbiota controlled hepatocarcinogenesis. They demonstrated that intestinal dysbiosis was associated with more pronounced steatohepatitis and that the gut microbiota drives steatohepatitis progression towards HCC by promoting TLR4-dependent expansion of monocytic myeloid-derived suppressor cells, thereby shaping the hepatic inflammatory micro-environment. Modulating or reconstituting the microbiota may offer new therapeutic avenues for future cancer prevention and therapy.

EXTERNAL PROTON BEAM RADIOTHERAPY AS AN ALTERNATIVE TO RADIOFREQUENCY ABLATION

External proton beam radiotherapy (PBT) is under investigation in patients with HCC not suitable for surgery, and previous Phase II data have shown promising local control of tumour growth and tolerability. Data were reported at Digital ILC 2020 from the Phase III APROH trial in patients with recurrent or residual HCC showing that PBT was non-inferior to radiofrequency ablation for local progression-free survival and had tolerability consistent with its known safety profile.

Cirrhosis and complications

As our knowledge of liver physiology expands, so too does our understanding of the critical role played by the vascular system in both the development and progression of liver disease. While liver sinusoidal changes are known to affect disease progression, they also have a knock-on effect, disrupting circulation in the rest of the body. The "Cirrhosis and complications" track at Digital ILC 2020 explored the complex relationship between vascular changes and liver cirrhosis and highlighted the management of portal hypertension.

ANTIBIOTIC PROPHYLAXIS AND TREATMENT IN PATIENTS WITH CIRRHOSIS

During a series of two sessions at Digital ILC 2020, including a debate for and against antibiotic prophylaxis in patients with advanced cirrhosis, experts discussed the complex role of antibiotic treatment. Central to the argument in favour of antibiotic prophylaxis was the observation that bacterial infections in this population are a major complication associated with high mortality and often deny patients the chance of a liver transplant. Although long-term prophylaxis with norfloxacin has no impact on mortality overall in patients with advanced cirrhosis, it does seem to confer a survival benefit in those with low ascitic fluid protein as well as reducing the occurrence of bacterial infection.

The lack of impact on overall survival with norfloxacin was a key point in the counter argument that there should not be a "one size fits all" approach to antibiotic prophylaxis in this patient group. It was stressed that other approaches, including judicious use of targeted empiric antibiotics informed by local epidemiology and robust identification of multidrug resistance (MDR) colonization, should also be considered and a more individualized approach taken incorporating non-antibiotic methods of infection control. The debate concluded with an audience vote overwhelmingly in favour of antibiotic prophylaxis only in patients fitting specific criteria.

The second discussion focused on the use of broad-spectrum antimicrobial therapy and the role of early cessation within treatment strategies. Broad-spectrum antibiotics are the most important measure to improve survival in patients with cirrhosis and bacterial infections, independent of the presence of ACLF. Data supporting their mandatory use in nosocomial infections in areas with high rates of MDR, as well as in sepsis and septic shock, were presented. Given that patients with advanced cirrhosis represent only 0.1% of antibiotic use, there is little evidence to suggest any impact on the global development of MDR. However, antibiotic stewardship remains a critical issue, and administration should be optimized, including rapid de-escalation to increase efficacy and reduce risk of resistance.

CLINICAL ADVANCES IN THE MANAGEMENT OF CIRRHOSIS

An international collaboration provided new evidence in support of the early use of TIPS to treat patients with high-risk liver cirrhosis who are experiencing AVB. TIPS is an important therapeutic procedure for patients with portal hypertension and one of its most life-threatening complications, variceal bleeding. Despite this, less than 10% of patients eligible for early TIPS undergo the procedure. A key reason for this is thought to be the fear of developing hepatic encephalopathy (HE) as a major potential complication following TIPS.

A multicentre, observational study of over 2,000 patients found that HE at time of hospital admission was significantly more frequent in high- versus low-risk cirrhotic patients with AVB. Furthermore, in patients with HE at admission, TIPS placement was associated with significantly better survival and less frequent recurrent HE events than endoscopic and drug treatment. These data suggest a potential way forward in closing an important clinical practice gap in liver disease.

In studies on pharmaceutical interventions in patients with cirrhosis, results from a randomized controlled trial from Korea demonstrated that 24 weeks of L-carnitine administered to patients with liver cirrhosis and covert HE resulted in improved quality of life and cognitive function, while data from the UK ATTIRE study did not support targeted weight-based infusions of 20% human albumin solution over standard care for the management of hospitalized decompensated cirrhosis.

Immune-mediated and cholestatic diseases

Significant unmet needs remain for patients with immune-mediated and cholestatic liver diseases, compounded by a broad disease manifestation spanning several body systems and a multifaceted aetiology that complicates the search for new drug targets. The dedicated track at Digital ILC 2020 brought the clinical and scientific communities together in a showcase of the latest knowledge and experience from leading experts, highlighting advances in therapeutics and regenerative medicine.

SURVIVAL ADVANTAGE WITH BEZAFIBRATE AND UDCA IN PRIMARY BILIARY CHOLANGITIS

In Europe, UDCA is the recommended first-line pharmacological treatment for primary biliary cholangitis (PBC). However, around 20% of patients show an inadequate response and are at greater risk of hepatic complications and liver transplant than treatment responders.

The clinical benefits of bezafibrate in patients with PBC and an incomplete response to UDCA are well documented but its effects on long-term survival remain to be determined. At Digital ILC 2020, data were reported from a large Japanese cohort study, initiated in 1980 and updated every 3 years, that included >8,000 patients with PBC. The study reported that, while UDCA monotherapy significantly lowered risk of all-cause death over no treatment, the addition of bezafibrate to UDCA conferred a further, significant risk reduction over UDCA monotherapy.

The authors of the study suggested that, ideally, the long-term effectiveness of UDCA and bezafibrate should be assessed in prospective, randomized, placebo-controlled studies.

POTENTIAL NEW ROLE FOR MONOACYLGLYCEROL LIPASE ENZYME IN LIVER REGENERATION

Lack of donor livers continues to restrict the treatment for end-stage liver disease or acute liver failure. Scientists study the mechanisms of liver regeneration in the hope that it may offer potential treatment modalities. Data reported at Digital ILC 2020 suggested that we may have taken a step forward in understanding the mechanisms of liver regeneration.

The enzyme monoacylglycerol lipase (MAGL) is a proinflammatory enzyme that reprogrammes lipid metabolism by converting monoacylglycerols into free fatty acids. Reprogramming lipid metabolism in different liver cell types has become an increasing area of focus in targeting fibrosis progression/regression. Previously, both genetic and pharmacological invalidation of MAGL have been shown to reduce inflammation and slow fibrosis progression in mice.

Here, the same research group reported data from experiments using knockout mice and hepatic cell culture to show that MAGL activity promotes liver regeneration, and how hepatocytes and specific immune cells are involved in this process.

MARALIXIBAT ENHANCES LONG-TERM NATIVE LIVER SURVIVAL IN PAEDIATRIC PROGRESSIVE FAMILIAL INTRAHEPATIC CHOLESTASIS

Children with progressive familial intrahepatic cholestasis due to bile salt export pump (BSEP) deficiency typically face debilitating symptoms including pruritus, short stature, and progressive liver disease, with around 50% of patients requiring transplant by age 10 years. However, reducing serum bile acid levels to <100 µmol/L after partial external biliary diversion can improve outcomes. Having demonstrated improvements in symptoms in the open-label INDIGO study, patients treated with maralixibat were followed up long term to investigate liver survival and liver parameters.

Of 19 patients with nontruncated BSEP mutations, seven maintained serum bile acid control (≤100 µmol/L) and remained on-study at >4.5 years, with corresponding reductions in liver enzymes. None of these patients were candidates for liver transplant. Growth and pruritus significantly improved, while maralixibat was determined to be safe and well tolerated.

The disease-modifying potential of maralixibat has several important implications for patient outcomes, including improved symptom control and the reduced need for surgery. The reported improvement in liver survival also has potential implications for reducing demand for liver donors.

Nurses and allied health professionals forum

2020 – CELEBRATING THE YEAR OF THE NURSE

In honour of the 200th anniversary of the birth of nursing pioneer Florence Nightingale, the WHO designated 2020 as the "Year of the Nurse and Midwife".

In that spirit, the Nurse and Allied Health Professional (AHP) Forum at Digital ILC 2020 shared a packed programme of state-of-the-art lectures, Meet the Expert and Case Study sessions, and oral abstract and poster presentations, all dedicated to nurses and AHPs.

The roles and responsibilities of nurses and AHPs vary dramatically according to country and region, and there was a focus on discussing these differences in order that practitioners from around the world could learn and benefit from one another.

Delegates had ample opportunity to meet and talk with the Task Force, enabling them to exchange ideas and experiences, and providing a platform to share expectations and needs.

ENHANCING KNOWLEDGE

Every year, the Nurse and AHP Forum shows its commitment to the scientific community and offers delegates the opportunity to update what they know about the ever-expanding role of nurses and AHPs in the treatment and management of liver disease. At Digital ILC 2020, the Forum looked to the future of nursing in liver disease with a heavy focus on enhancing knowledge of scientific and clinical research, encouraging individual and collective effort, and expanding diversity and interaction among healthcare communities.

IMPROVING PATIENT EDUCATION AND CARE

Patient education is one of the main tasks of nurses and AHPs, and modification of patient behaviour is a major challenge faced in daily practice. The Forum provided useful information and practical advice on how to effect meaningful and lasting behavioural change among patients. Approaches to help patients adopt healthier diets and lifestyles that have a positive impact on obesity-related liver disease were explored, as well as guidance on facilitating patients' adoption of substance- and sexual risk-reduction strategies.

The dedicated Nurses and AHP Meet the Expert session on liver cancer offered key information and insights on improved patient management, and a Case Studies session took a multidisciplinary approach to look at cirrhosis and the struggles faced by patients while they wait for LT.

INDUSTRY AND SATELLITE SYMPOSIUM PROGRAMME

A full programme of industry symposia ensured that, even in a digital format, delegates could still be updated on exciting new therapies and products in the hepatology field. Digital exhibition booths were also available for delegates to explore through the congress platform while networking with colleagues and industry professionals.

Industry and satellite symposium programme

novo nordisk®	**NASH – the metabolic disease of the liver** **Chair:** Elisabetta Bugianesi (Italy) **Speakers:** Arun Sanyal (United States), Quentin Anstee (United Kingdom), Manal Abdelmalek (United States)
Intercept	**Emerging trends in the care pathway for patients with NASH** **Speakers:** Rohit Loomba (United States), Mazen Noureddin (United States), Jerome Boursier (France), Vlad Ratziu (France)
Intercept	**FXR agonism in clinical practice: new perspectives from the real-world experience in PBC** **Speakers:** David Jones (United Kingdom), Antonio Moschetta (Italy), Conrado Manuel Fernandez Rodriguez (Spain), Umberto Vespasiani Gentilucci (Italy), Palak Trivedi (United Kingdom)
GRIFOLS	**Albumin: a disease-modifying agent in decompensated cirrhosis** **Speakers:** Alexander Gerbes (Germany), Paolo Caraceni (Italy), Javier Fernándes (Spain)
GILEAD Creating Possible	**A new virus in the mix: re-imagining liver disease care in the COVID-19 era** **Speakers:** Tram Tran (United States), Graham Foster (United Kingdom), Marc Bourlière (France), Ivan Gardini (Italy), Juan Turnes (Spain)
Albireo	**Challenges in the management of patients with cholestatic liver diseases** **Speakers:** Ulrich Baumann (Germany), Patrick McKiernan (United States), Verena Keitel (Germany)
INTERNATIONAL MEDICAL PRESS	**Obesity management in NAFLD/NASH: can we do more?** **Chair:** Rachel Batterham (United Kingdom) **Speakers:** Lawrence Serfaty (France), Philippe Mathurin (France)
Bristol Myers Squibb™	**Evolving treatment landscape of HCC** **Chair:** Bruno Sangro (Spain) **Speakers:** Thomas Decaens (France), David J. Pinato (United Kingdom)
sobi rare strength	**Avatrombopag for severe thrombocytopenia: paving the way for procedures in adult patients with CLD who are scheduled to undergo an invasive procedure** **Chair:** Markus Peck-Radosavljevic (Austria) **Speakers:** Kosh Agarwal (United Kingdom), Douglas Dieterich (United States)
abbvie	**How can we accelerate HCV elimination in the current landscape?** **Chair:** Jean-Michel Pawlotsky (France) **Speaker:** Robert Brown (United States)
Pfizer	**Addressing the metabolic drivers of NASH** **Speakers:** Quentin Anstee (United Kingdom), Samuel Klein (United States)

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EASL | Coming up in 2021

2021

5–6 February
EASL Meetings
Digital Liver Cancer Summit - *Digital*

May
EASL/AASLD Meetings
Digital HBV Endpoints - *Digital*

7–8 May
EASL Meetings
Biliary Fibrosis: Pathophysiology and translational opportunities - *Florence*

11–12 June
EASL Courses, Schools & Masterclasses
Progress, pitfalls and challenges in the management of portal hypertension - *Barcelona*

18–19 June
EASL Courses, Schools & Masterclasses
Rare liver diseases: Improving diagnosis and care - *Hamburg*

23–26 June
Annual Congress
The International Liver Congress 2021 - *Digital*

1–2 July
EASL Courses, Schools & Masterclasses
School of pathology - *Amsterdam*

2–3 July
EASL Courses, Schools & Masterclasses
Management of acute-on-chronic liver failure - *Frankfurt*

16–18 September
EASL Meetings
NAFLD Summit 2021 - *Dublin*

7–9 October
EASL Meetings
Bleeding, thrombosis and vascular liver diseases - *Geneva*

3–4 October
EASL/AASLD Meetings
EASL-AASLD Endpoints - *Amsterdam*

December
EASL Courses, Schools & Masterclasses
AASLD/EASL Masterclass 2021 - *Digital*

Due to the current circumstances, event dates may change. Please check our website for the latest information

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