



EASL

European Association
for the Study of the Liver

HEPAMAP:

A ROADMAP FOR HEPATOLOGY RESEARCH IN EUROPE:

AN OVERVIEW FOR POLICY MAKERS

HEPAMAP: A Roadmap For Hepatology Research In Europe: An Overview For Policy Makers

Liver diseases are extremely costly in terms of human suffering, general practitioner and hospital visits, and premature loss of productivity. In 2013, 29 million people in the European Union (EU) were documented as suffering from a chronic liver condition.

The incidence and prevalence of two conditions in particular, cirrhosis (liver scarring) and primary liver cancer, are key to understanding the burden of liver disease as they represent the end-stage of liver pathology and thus are indicative of the associated mortality. According to the World Health Organization (WHO), **in 2013, liver cirrhosis accounted for around 170,000 deaths in Europe and liver cancer accounted for around 47,000 deaths in the EU.**

The statistics become more chilling once estimated projections are taken into consideration. For example, statistics from 2012 from The Organisation for Economic Co-operation and Development (OECD), estimate that 52% of the EU population is overweight or obese. Research from EASL and other liver organizations reveals that up to 44% of these people are likely to suffer from non-alcoholic fatty liver disease (NAFLD), suggesting that **116 million people in the EU suffer from NAFLD** alone. Once other liver condition projections are added – such as for cryptogenic cirrhosis, alcoholic liver disease (ALD), liver cancer and viral hepatitis – this

number increases to well over 120 million: **people whose quality of life, productivity and potential could be improved through world-class science and innovation.**

Hepamap identifies opportunities to significantly reduce liver mortality and decrease the burden of liver conditions in the EU by the end of 2020, with particular emphasis on recommending tackling alcohol- and obesity-related liver conditions with evidence-based policy measures. Furthermore, there is a great potential to eliminate hepatitis C and control hepatitis B within the EU.

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EASL urges EU policy makers to support the liver disease research as outlined in Hepamap in the context of:

- Horizon 2020 – the EU Framework Programme for Research and Innovation, under the programme section: Health, Demographic Change and Wellbeing;
- The Innovative Medicines Initiative 2 – Europe’s largest public-private initiative;
- National research funding mechanisms.

The EU supported research on liver diseases during the Framework Programme 7 (2007 – 2013) with approximately €147.8 million. This represented less than 3% of available EU funding for health research. **In the light of the evidence presented in Hepamap, EASL recommends that the EU allocate €423.3 million towards liver research over the lifetime of its Horizon 2020 framework programme for research (2014 – 2020).** This represents 5.7% of the overall Horizon 2020 health funding, proportional to the 5.7% of the EU population with a known chronic liver condition, excluding NAFLD.

During the past 30 years, liver disease research has delivered significant breakthroughs consistently. Mortality from liver cirrhosis has declined due to the reduction in alcoholic liver disease prevalence in some regions of Europe; the fall in the transmission of viral hepatitis C; and

vaccination campaigns against viral hepatitis B. However, recognizing liver disease as a growing problem despite these advances, significantly more funding is needed to achieve better liver health for all; to keep older people active and independent for longer; to develop new, safer and more effective interventions; and to achieve sustainable health and care systems.

Hepamap has been developed over two years under the auspices of the EASL Governing Board, with leading members of EASL each advising within their specialty field and conducting gap analysis in line with major liver research literature and events, such as the International Liver Congress, hosted by EASL, and The Liver Meeting, hosted by the American Association for the Study of Liver Diseases. The liver research proposed in *Hepamap* has been structured into two time periods, 2014 – 2016 and 2017 – 2020; and into two degrees of challenge, whereby the results of the “moderate challenge” are required to inform the next stage, the “major challenge”. In places, research has been categorized into “basic science” and “clinical/translational”, to reflect the difference between laboratory-based research and research relating to delivering solutions to the public. **Hepamap identifies the greatest research gaps and recommends the most optimal ways to prevent, screen, treat and manage liver conditions.** Suggestions concerning optimum care for liver disease patients are provided throughout.

Hepamap includes the following subject areas:

- 1) Viral hepatitis: basic science
- 2) Viral hepatitis: clinical / translational
- 3) Alcoholic Liver Disease and Non-Alcoholic Liver Disease
- 4) Genetic and autoimmune diseases
- 5) Hepatocellular carcinoma: basic science
- 6) Hepatocellular carcinoma: clinical / translational
- 7) Cirrhosis and portal hypertension
- 8) Cholestatic and drug-induced liver disease
- 9) Liver transplantation
- 10) Acute liver failure and hepatic regeneration
- 11) Public health

The past years have seen significant EU funding into tackling various chronic diseases – cancers, cardiovascular disease and diabetes – and yet, given the links between these diseases and liver diseases, and given their common risk factors – obesity, alcohol consumption and sedentary life styles – **by extending greater funding also into liver disease research, it may become possible to address several high-concern chronic diseases more effectively.**

EASL has taken steps to accompany Hepamap with a number of collaborative approaches:

- With view to enhancing cooperation between educational and EU programmes and the EASL Governing Board, EASL has established a Concerted Action Group focusing on public health;
- In order to inform decision making and to encourage communication, EASL created the “Friends of the Liver” Members of Parliament (MEP) group, together with members of the European Parliament with shared interests;
- To further understanding about liver disease, EASL issued a white paper entitled The Burden of Liver Disease in Europe – a review of available epidemiological data, this being a first milestone in EASL’s public health efforts;
- Going forward, EASL’s Fellowship Program is available to actively promote scientific exchange among research units in hepatology, and thereby enhance the mobility and training of young researchers within European institutions;
- EASL has provided seed funding to three EU centers to develop pan-European data registries, to improve EU’s epidemiological data concerning liver disease, as more efforts are needed to fully understand the extent of the burden of liver disease in Europe.
- To ensure future research under Hepamap is distributed successfully, EASL will make available some of its events, including the annual International Liver Congress, to serve as a forum.

EASL is the leading liver association in Europe, which includes in its membership the foremost European hepatology experts. Throughout its almost 50-year existence, it has established an impressive track record in promoting quality liver disease research; supporting wider education about liver health; and promoting

changes in European liver policies. EASL’s annual five-day event, the International Liver Congress, attracts over 11,000 delegates and its much-acclaimed publication, the Journal of Hepatology, has a readership of over 40,000 and an impact factor of 10.4, making it the fastest growing journal in the field over the last eight years.

Please find in the following pages short summaries of EASL's proposed research subjects under Hepamap for 2014 – 2020.

1) VIRAL HEPATITIS: BASIC SCIENCE

Hepatitis B virus (HBV)

Infected adults often remain undiagnosed and therefore untreated until it is too late. Cirrhosis occurs in 20 - 30% of infected patients, with the risk of developing hepatocellular carcinoma at about 25%, and thus HBV is responsible for 10 - 15% of primary liver cancers. There are 300 million chronic carriers of HBV worldwide despite an available vaccine.

Recommended research focus for HBV includes:

- Fully understanding the virus' entry process;
- The cellular factors involved in the formation of HBV cccDNA;
- The host-factors promoting or restricting viral replication;
- The function of the HBx protein;
- 3D structures of all the HBV proteins;
- Virus-host interactions to identify novel antiviral targets;
- HBV interaction with the immune system;
- Host genetic determinants of HBV infection.

Hepatitis C virus (HCV)

In Europe, a significant number of people acquired HCV in the 1970s - 1980s before the virus was identified. Since then, transmission of infection has been greatly reduced and the overall prevalence in Europe now varies between 0.12 - 3.23%. About 90% of HCV infection is asymptomatic and the disease has a prolonged time-course with individuals developing cirrhosis within 20 years, and so the disease burden of HCV in Europe is at its peak only now. Studies show that up to 85% of infected patients develop a chronic infection, with 10 - 20% progressing to cirrhosis. HCV is an important risk factor for hepatocellular carcinoma, which will have its peak in Europe only around 2030. There is no vaccine for HCV but a promise of a cure exists for most patients.

Recommended research focus for HCV includes:

- HCV life cycle and pathogenesis;
- Viral entry;
- Genome translation;
- Replication, packaging and 3D structure of all proteins;
- Viral entry and egress mechanisms via the use of functional primary human hepatocytes;
- Defining how HCV evades the host immune system;
- Pre-existing immune parameters that may lead to spontaneous clearance versus chronicity;
- The impact of HCV on liver metabolism;
- The intra-hepatic immune responses.

Recommended research focus for both HBV and HCV includes:

- Viral replication;
- The pathways of the innate immune response and how the T cell responses can be restored or induced;
- Novel treatments;
- The development of a reliable and immune-competent small animal model;
- The development of biomarkers to predict the progression of HBV/HCV liver disease towards liver cancers.

2) VIRAL HEPATITIS: CLINICAL / TRANSLATIONAL

Recommended research focus includes:

- The barriers to therapy to improve the proportion of treated cases and to reduce the negative outcomes of chronic HBV and HCV;
- The target groups and cost-effectiveness of screening;
- The critical factors and the identification of strong predictors of patient outcomes;
- Immune responses;
- Preventive and therapeutic vaccines;

- Identifying host genetic and viral markers to reliably predict the course of liver disease;
- Early treatment;
- Preventing the progression to chronicity;
- Management of chronic viral hepatitis;
- Treatment indications in specific subgroups of patients with chronic HBV including those with co-infections;
- Non-invasive markers;
- Predictors of fulminant liver failure;
- Evaluating the efficacy, safety and cost-effectiveness of new regimens in all patient subgroups;
- Management and preventing HCV recurrence post-liver transplant.

3) ALCOHOLIC LIVER DISEASE AND NON-ALCOHOLIC LIVER DISEASE

Alcoholic Liver Disease

Europe has the highest per capita consumption of alcohol and alcohol-associated loss of life worldwide. Alcohol consumption is the main cause of liver disease and causes substantial health, social and economic burdens. Cirrhosis is associated with significant morbidity and mortality across Europe and in 70 - 80% of cases it is caused by alcohol at least as a cofactor. The WHO report, Priority Medicines for Europe and the World, issued in 2013, mentions alcoholic liver disease among the seven high-burden conditions in Europe, for which currently available treatment is inadequate in reversing or halting the progression of disease, and which therefore require continued support for basic research.

Recommended research focus for Alcoholic Liver Disease (ALD) includes:

- Identification of genetic determinants in ALD and development of a biomarker for alcohol abuse;
- New treatments aimed at severe alcoholic hepatitis;
- Characterization of gut microbiome patterns or metabolic profiles predisposing to ALD;

- Trials of combined anti-craving medication and psychosocial therapies for alcohol use disorders;
- Trials of price, marketing or access control to reduce alcohol consumption.

Non-Alcoholic Liver Disease

Non-Alcoholic Liver Disease (NAFLD) is characterized by the development of fat accumulation in hepatocytes in the absence of alcohol abuse. NAFLD is strongly related to obesity and features of the metabolic syndrome: hypertension, hyperlipidaemia, type 2 diabetes and increased waist circumference. More than 50% of adults in the EU 27 countries are considered to be overweight or obese, and it is believed that NAFLD may affect up to 44% of the European population. NAFLD is a spectrum of disease with simple steatosis at one end of the scale and non-alcoholic steatohepatitis (NASH) with progressive fibrosis of the liver at the other. NASH may progress to cirrhosis and portal hypertension as well as hepatocellular carcinoma (HCC).

Recommended research focus for Non-Alcoholic Liver Disease includes:

- Large, community-based studies to accurately determine NAFLD and NASH prevalence and rate of disease progression.
- Identify determinants of liver morbidity/mortality in NAFLD patients.
- Identify gut microbiome patterns or metabolic profiles predisposing to NASH.
- Establish non-invasive methods to distinguish NASH and alcoholic steatohepatitis (ASH) from steatosis.
- Develop effective lifestyle interventions to reduce disease progression in NASH.
- Biomarker discovery and clinical score development to assist in discrimination of steatosis from NASH and/or predict risk of fibrosis progression.
- Novel therapeutic strategies to ameliorate NASH related liver damage and slow fibrosis.

4) GENETIC AND AUTOIMMUNE DISEASES

In the absence of thorough epidemiological data, by way of a sample, the prevalence of genetic and autoimmune diseases is estimated to range from 5 - 20 per 100,000 among the Caucasian population in Western Europe. It is estimated to account for up to about 20% of cases of chronic liver disease among the Caucasian population of North America and Western Europe. Most of the genes and their variants responsible for genetic liver diseases have been cloned and characterized, but work is needed to explain the clinical heterogeneity of genetic liver diseases.

Recommended research focus includes:

- Compiling clinical and omics data in population-based resources;
- Developing clinical practice guidelines for genetic and autoimmune liver diseases (haemochromatosis, Wilson disease, and cholestatic liver diseases have been completed);
- Population-based screening and targeted family-based screening strategies;
- Trials of new drugs;
- Early detection of hepatocellular carcinoma and cholangiocarcinoma and their study;
- Pathobiological aspects of genetic liver diseases and autoimmune hepatitis;
- Studies to understand the polygenic basis and the environmental triggers that are important in these diseases.

5) HEPATOCELLULAR CARCINOMA: BASIC SCIENCE

Hepatocellular carcinoma (HCC) accounts for 70 - 90% of primary liver cancers, and over half a million new cases are diagnosed annually worldwide. The cause of HCC is known in about 80% of cases, creating a unique perspective for prevention. The prevalence of HCC is closely related to liver cirrhosis, often times due to chronic viral hepatitis, but increasingly, alcohol, obesity and type 2 diabetes mellitus are also recognized as contributors. The prognosis for the majority of those affected with HCC remains poor, although life-prolonging or even curative therapy can be offered to

a carefully selected minority. The management of HCC is complicated by cirrhosis in over 80% of cases, with cirrhosis often hindering treatment and registered as the direct cause of death.

Recommended research focus includes:

- The pathogenesis and the consequences of HCC;
- Preventive strategies;
- Early detection and risk stratification;
- Novel or better-targeted medical therapies;
- Liver regeneration;
- Cancer growth;
- Preserving liver function;
- Prognostic biomarkers to identify the best responders and those who will better tolerate treatment with fewer severe side effects;
- Tumor characteristics and candidates to help to guide treatment and predict response or resistance.

6) HEPATOCELLULAR CARCINOMA: CLINICAL / TRANSLATIONAL

Recommended research focus includes:

- Screening and surveillance of known risk groups;
- Affordable imaging techniques;
- Preserving liver function and enhancing liver regeneration;
- Prioritizing patients to ensure optimal graft usage without discriminating against some patient groups;
- Cellular mechanisms associated with good outcome for options such as embolization, ablation, surgery and liver transplant;
- Reducing the recurrence rates of HCC after curative treatments;
- Alternative treatment approaches other than the inhibition of angiogenesis;
- The identification and validation of informative biomarkers;
- The utility of preventative treatments;
- The prevention of HCC risk factors in the European population at large, specifically alcohol, drug abuse, smoking, environmental pollutants and obesity.

7) CIRRHOSIS AND PORTAL HYPERTENSION

Cirrhosis represents the end stage of chronic liver disease, affects approximately 0.1% of the European population, and causes around 170,000 deaths annually, representing 1.8% of all deaths in the EU, and yet little attention is paid to the disease. Cirrhosis is the most frequent indication to liver transplant in Europe. Portal hypertension refers to a blood pressure increase in the liver's portal vein.

Recommended research focus includes:

- Cirrhosis pathophysiology;
- The liver circulatory system;
- The mechanisms of fibrosis;
- The irreversibility of cirrhosis;
- Multi-organ dysfunction;
- The relationships between the liver, the gut and the gut microbiota;
- Genome-wide comprehensive approaches in conjunction with non-invasive biomarkers of disease progression in biological fluids;
- The prognostic efficacy of disease progression biomarkers and their utility in different aetiologies and situations;
- Imaging techniques;
- Metabolic syndrome;
- Nutritional components;
- Sepsis and immunological and inflammatory response to bacterial infections;
- Novel treatments.

8) CHOLESTATIC AND DRUG-INDUCED LIVER DISEASE

Liver diseases that affect bile secretion are termed 'cholestatic' and they can be caused by autoimmune damage of the bile ducts, drugs, genetic defects and developmental disorders. Cholestatic liver diseases are relatively rare, but they are associated with a significant societal and economic burden. The cholestatic diseases, primary biliary cirrhosis (alternatively primary biliary cholangitis) and primary sclerosing cholangitis,

together account for approximately 10% of the liver transplants performed in Europe during the last 20 years. Retrospective studies suggest that drugs may have caused around 10 - 20% of fulminant and subfulminant (sudden) hepatitis.

Recommended research focus includes:

- Early diagnosis of cholestatic disease using imaging technology and serum biomarkers;
- New and effective treatments, including gene therapy and stem-cell therapy;
- Training non-hepatologists to promptly recognizing drug-induced liver injury;
- Trials of interventions, which would have to run for many years to demonstrate their effectiveness.

9) LIVER TRANSPLANTATION

In Europe, 90,000 liver transplants (LTs) have been performed since the first one in 1968, and during that time, five-year patient survival rates have increased from 21% in the mid-1980s to 73% in 2014. Improvements have mainly occurred in operative techniques, organ preservation, immunosuppression and earlier treatment of complications. Currently, more than 5,500 LTs are performed in Europe per year, mainly where chronic liver disease leads to life-threatening complications with a survival prognosis of one year or less. Recommendations exist for hospital donation protocols, for addressing the increasing problem of organs shortage and rescue allocation policies, to prevent suitable donor organs being wasted.

Recommended research focus includes:

- Evaluating tolerability and efficacy of new direct-acting antiviral agents in LT waiting-list patients and post-LT patients for the treatment of HCV recurrence;
- Determining optimal immunological markers of rejection and tolerance;
- Developing stem cell research in systems of both acute and chronic liver injury;
- Evaluating the role of liver biopsy in the assessment and monitoring of patients requiring anti-viral therapy for HCV, e.g. baseline biopsies, impact of new direct anti-viral agents;

- Determining the role of protocol biopsies in monitoring graft function pre- and post- withdrawal of immunosuppression, with the aim of achieving graft tolerance;
- Validating improved allocation systems and performance of well-designed prospective studies and simulation models;
- Long-term evaluation of new immunosuppressants;
- Establishing the optimal route, indications for, and particular aspects of stem cells and derived micro-particles in the treatment of acute and chronic liver injury.

10) ACUTE LIVER FAILURE AND HEPATIC REGENERATION

Acute liver failure (ALF) is the rapid deterioration of liver function in a previously healthy individual. Hepatitis A and B viruses are a major cause of ALF; however, drug-induced liver damage, particularly due to Paracetamol, is increasingly important as a cause of ALF. ALF is rare, but it often affects young people and mortality rates are very high in the absence of adequate treatment, which is limited. Therefore, ALF represents a significant medical and economic burden in Europe.

Recommended research focus includes:

- Identifying novel clinical scores and biomarkers to predict a patient's fate with or without liver transplant;
- Understanding the molecular mechanisms driving Acute liver failure;
- Understanding liver injury and regeneration;
- Developing novel treatments, which may one day obviate the need for liver transplant;
- Innovative approaches to facilitate the preclinical testing of new drugs for their potential to cause drug-induced liver injury.

11) PUBLIC HEALTH

The four leading causes of cirrhosis and primary liver cancer in Europe are harmful alcohol consumption, viral hepatitis B and C, and metabolic syndromes related to obesity and being overweight. These major causes of liver disease are amenable to prevention and treatment, reducing the burden of liver disease in Europe and ultimately saving lives.

Recommended research focus for Alcoholic liver disease (ALD) includes:

- Determining the prevalence of ALD in Europe;
- Studying the mismatch between liver mortality and population level alcohol consumption;
- Determining co-factors that impact on alcohol-related harm;
- Assessing alcohol consumption within the European population;
- Assessing the socio-economic lessons that can be learnt from decreased alcohol consumption in France and Italy.

Recommended research focus for viral hepatitis includes:

- Providing better epidemiological data for viral hepatitis D;
- Providing better epidemiological data for HBV and HCV in selected patients groups;
- Determining the HCV re-infection rate following effective anti-viral therapy in intravenous drug users;
- Designing country-based screening policies for HBV and HCV chronic infection;
- Defining ideal access to anti-HBV and anti-HCV treatments at the national level;
- Determining the public health impact of HBV vaccination, anti-HBV and anti-HCV therapy in these groups of patients.

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HEPAMAP: Prospects for Liver Disease Research in the EU

Acknowledgements

A ROADMAP FOR HEPATOLOGY RESEARCH IN EUROPE: AN OVERVIEW FOR POLICY MAKERS

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