Geneva, 17 February 22

EASL's response to the European Commission call for evidence on cancer screening

The European Association for the Study of the Liver (EASL) welcomes the open call for evidence to update the 2003 Council Recommendation on cancer and to extend the screening to other types of cancer.

EASL recommends extending the Recommendation to liver cancer for high-risk groups living with chronic liver diseases; these patients are identifiable, have a high risk of liver cancer, and can be offered curative treatment if their liver cancer is diagnosed early. Furthermore, liver cancer detection tools are easily available and affordable.

Liver cancer is a broad public health concern

Liver cancer and chronic liver disease go hand in hand, and 90% of patients with liver cancer have an underlying chronic liver disease[1] . **Mortality from liver cancer has increased** in most European countries since 1980 due to our failure to stop the tide of chronic liver disease resulting mainly from viral hepatitis, non-alcoholic fatty liver disease (NAFLD/NASH), and harmful alcohol consumption[2-3]. Liver cancer is now the **sixth-most common cancer** and the **third-most frequent cause of cancer-related death globally**, and it has become a **major health burden** in the European Union. In 2019, 87,000 Europeans were diagnosed with liver cancer, and 78,000 died from liver cancer[4]. That number—78,000 dead Europeans—is 70% higher than what it was in 1990[5].To make matters worse, liver cancer is more common in deprived areas and therefore contributes to **inequity in health[6]** -[7]. A do-nothing scenario will result in an increased burden of liver cancer in Europe over the next decade. By contrast, South-East Asia has demonstrated that screening and other preventive measures effectively reduce the burden of liver cancer [8-9]. In other countries, such as the United States, liver cancer screening in patients with chronic hepatitis B has also been shown to reduce mortality.

In December 2021 was published the report of **EASL - *Lancet* Liver Commission** "***Protecting the next generation of Europeans against liver disease complications and premature mortality***". The EASL -*Lancet* Liver Commission warns that Europe's fragmented health policies and health systems urgently need to become more integrated, coordinated, and effective to enable earlier detection of liver diseases and liver cancer[10]. At the report's launch, Ursula von der Leyen, President of the European Commission, reminded that each year, almost 300,000 people in Europe die prematurely due to problems of the liver. Many of them could have lived longer and healthier lives, because today, in most European countries, there is good access to secondary care.

Survival is improved by early diagnosis

Liver cancer has the poorest survival of all cancers monitored by the Joint Research Centre[11-12]. **Detection of liver cancer at an early stage could reduce mortality** to a maximum of 5 years of life lost relative to the general population, but unfortunately more than 60% of patients with liver cancer in Europe are diagnosed at the more advanced, intermediate or advanced stages[13-14]. This is in contrast to Japan, where more than 60% of these patients are now diagnosed at the early stage, and 5-year survival has improved from 5.1% in 1978–1982 to 42.7% in 2003–2005[15].These improvements are attributed to the establishment of the screening system, advances in diagnostic imaging, and therapeutic technologies. This makes a strong case for liver cancer screening in Europe. We look with envy to the South-East Asian high-income countries whose massive liver cancer screening

programmes have resulted in better survival. Europe must take this as an example and promote screening for liver cancer**.**

High-risk populations for liver cancer are well known

Liver cancer develops in people with chronic liver disease, often in those with advanced stage characterized by presence of cirrhosis. Chronic liver disease is almost universally **caused by viral hepatitis, non-alcoholic fatty liver disease, and/or harmful alcohol consumption**. Patients with one or more of these risk factors are the high-risk populations for liver cancer. Many of them are already followed in an outpatient or primary care setting for their cirrhosis, and it is straightforward and feasible to implement a recommendation of liver cancer screening in these patients. The patients who are not followed must be identified and offered screening and linkage to healthcare. **Screening for liver cancer is done with an ultrasound examination of the liver with or without a blood test foralpha-fetoprotein (AFP) every 6 months [16].** General practitioners, hepato-gastroenterologists, and patients must be informed about this key screening practice. Some patients known to be at very high risk of liver cancer due to clinical and genetic characteristics are offered more sensitive screening tests; risk stratification is a highly active research area.

The community of hepatologists, oncologists, gastroenterologists and large patient organisations fully support liver cancer screening

Offering liver cancer screening to people with risk factors for chronic liver disease serves three purposes: 1) screening for liver cirrhosis; 2) screening for liver cancer; 3) linkage to healthcare. **Liver cancer screening in high-risk populations is endorsed by all clinical stakeholders.** Currently the updated version of the European Association for the Study of the Liver (EASL) and European Organisation for Research and Treatment of Cancer (EORTC) HCC guidelines [16] endorse liver cancer surveillance as a crucial public health goal, and all other international guidelines agree[17]. The EASL Open Letter to the EU institutions includes ten asks to improve liver cancer care and prevention. One of EASL's asks is to add liver cancer to the future EU screening scheme list. **The open letter is signed by more than 1500 experts, patients and supporters and endorsed by 197 organisations.**

The number of deaths from liver cancer is increasing in Europe. Screening for liver cancer can stop this trend, and it will reduce health inequality, too. **We know *who* to screen, and we know *how* to screen: Implementation is key!** EASL urges that targeted liver cancer screening in high-risk populations be recommended by the new EU-supported Cancer Screening Scheme.

Our goal is to reduce the number of people who die from liver cancer. Our road to success is early case finding in high-risk populations.

In view of this evidence, EASL recommend that in the updated Council Recommendation:

1. Liver cancer be included in the list of cancers which are specifically mentioned, alongside breast, colorectal, and cervical cancers.
2. People with chronic liver disease be included in the list of criteria when taking account of the specific needs for persons who might be at a higher cancer risk (currently Recital 11).

More information on the main risk factors for liver cancer:

- **Liver cirrhosis**, the stepping-stone towards liver cancer, has a very poor prognosis, even without liver cancer. Cirrhosis has a long, asymptomatic compensated phase followed by a short, decompensated phase characterized by high morbidity and mortality. We must identify liver cancer while the patient is still in the compensated phase of cirrhosis. Consequently, we must involve the primary healthcare setting in early identification of not only liver cancer, but also liver cirrhosis. Screening for liver cancer in populations with risk factors for chronic liver disease serves three purposes: 1) screening for liver cirrhosis; 2) screening for liver cancer; 3) linkage to healthcare**.** Patients known to have liver cirrhosis must be included in liver cancer screening programs, and they will benefit from the second and third purposes.

- **Hepatitis B virus (HBV) infection and Hepatitis C virus C (HCV) infection** are responsible for over 70% of liver cancer cases and are defined as cancer preventable risk factors by WHO and recognized as such in Europe's Beating Cancer Plan[18]. HBV is preventable with a specific vaccine and, when there is a chronic hepatitis, the disease can be controlled with oral therapies, which have also been proven to reduce the risk of developing cancer. Vaccination is key to prevent hepatitis type B**.** All children must be vaccinated against hepatitis B. Hepatitis C does not have a specific vaccine but has a very effective oral short duration (8-12 weeks) therapy that can cure chronic hepatitis C infection in more than 95% of cases and reduce the associated morbidity and mortality. This therapy can also be used as prevention of the infection in absence of vaccine. However, between 20% and 90% of people infected in Europe are unaware of their infection status (9-10 million)[19], especially vulnerable groups who are disproportionally affected by HCV such as people who use drugs or men who have sex with men. Without being linked to care, their liver health gradually deteriorates, ending in liver cirrhosis with a yearly risk of developing liver cancer. Health economic models suggest that the elimination of viral hepatitis C alone would reduce the burden of liver cancer through morbidity and death by more than 65%[20].

- **Non-alcoholic fatty liver disease (NAFLD)** is a major health burden, affecting as much as 25% of the global population[21], and is the only liver disease with growing prevalence globally, synchronous with the increasing rates of obesity and type-2 diabetes[22]. NAFLD can cause liver cirrhosis and liver cancer, and it is the fastest growing cause of liver cancer. General practitioners must use the non-invasive evaluation tools based on existing biological parameters to detect those who have cirrhosis and are at risk for liver cancer. The challenge is that this patient identification tool must be promoted to primary care providers.

- **Alcohol-related Liver Disease (ARLD)** is the major cause of liver disease in Europe, and since it depends mostly on harmful alcohol consumption, it is a preventable disease. According to the Global Burden of Disease, 1,256,900 deaths occurred worldwide due to liver disease in 2016, of which 334,900 (27%) were attributable to alcohol.[23] Additionally, 245,000 liver cancer deaths were associated with alcohol intake (30% of all liver cancers deaths). In Europe, from the countries included in the HEPAHEALTH report there were 38,378 deaths in the last year available (2012-2015) that were coded as alcohol related liver disease[24]. Liver disease accounts for significant health and economic losses, as two-thirds of potential years of life lost are working years [1], which contrasts with other chronic diseases where onset and death generally occur at a later age. Furthermore, of these 35 European countries 32 have experienced increasing prevalence in the levels of cirrhosis since 1990.

Primary liver cancer: a cancer that starts in the liver is called primary liver cancer. There is more than one kind of primary liver cancer. Hepatocellular carcinoma (HCC) is the most common form of liver cancer in adults. The content in this document is about hepatocellular cancers (HCC).

The mission of the European Association for the Study of the Liver is to be the Home of Hepatology so that everyone involved in treating patients with liver disease can realise their full potential to cure and prevent it.

We promote communication among all professionals, in Europe and beyond, interested in the liver and its disorders, particularly by:

- *promoting liver research and facilitating scientific exchange*
- *fostering research interactions across Europe and beyond*
- *supporting the next generation of researchers, including Young Investigators, as they develop through involvement in EASL activities*
- *promoting education of physicians, scientists, allied health professionals, other medical professionals, and patients*
- *promoting public awareness of liver diseases and their management acting as an advisor to European and national health authorities concerning liver diseases, the provision of clinical services, and the need for research funding*
- *working with patient groups to ensure their perspectives and views are represented in our work*

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