National **Liver Health** Plan

2032 Challenge

Asociación Española
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Executive overview

The Spanish Association for Liver Studies (AEEH in Spanish) has developed the National Liver Health Plan: 2032 Strategy, which was conceived in response to a rise in the number of chronic hepatic pathologies, largely attributed to the obesity and *diabetes mellitus* (DM) type-2 epidemic. Metabolic dysfunction-associated steatotic liver disease (MASLD), alcohol-related liver disease and viral hepatitis are particularly relevant in this subgroup, as well as liver cancer, including hepatocarcinoma, cholangiocarcinoma, and liver transplant.

The main aim of this plan is to highlight the priority which should be attributed to prevention and early diagnosis, as they are both key aspects in modifying the natural history of these diseases, which have been previously approached through nihilistic therapeutic methods that did not actively engage with the full course of the disease. As such, an approach that may improve clinical results and the individual patient's quality of life is required.

In this sense, the importance of focusing on cirrhosis and liver disease prevention has been acknowledged, as the latter often emerges from the complication of prior chronic liver diseases and reduces the number of required liver transplants, as it is currently the primary cause of liver transplant in our medium. In this sense, precision medicine emerges as a tool destined to transform clinical investigation and patient care in itself, as it offers a broader characterization for rare liver diseases.

Considering these circumstances, fifteen strategic goals have been identified, divided among three areas of action: prevention, diagnosis, treatment, and monitoring. Prevention is chiefly concerned with the promotion of the importance of keeping a balanced diet and a healthy lifestyle, highlighting the avoidance of excessive alcohol consumption and other risk behaviors regarding the transmission of viral diseases, as well as universal vaccination for hepatitis A and B. These preventive methods could potentially reduce the burden of disease and, subsequently, the number of liver transplants.

Regarding diagnosis, early diagnosis is highlighted as fundamental in designing interventions to change the prognosis of the disease. Changes in lifestyle, including diet and exercise, can reverse the course of the disease in over 80% of metabolic liver disease patients. Similarly, cessation in alcohol consumption can counteract the effects of liver disease in most cases, while also significatively improving its prognosis. This, in turn, allows the curing of hepatitis C virus through the use of direct-acting antiviral drugs in 8-12 weeks; regarding hepatitis B, it achieves a sustained viral suppression which greatly improves the prognosis and prevents the progression of the disease.

The importance of specific testing is therefore highlighted throughout this plan, as it guarantees a more accurate assessment of each liver disease. Similarly, it seeks to raise awareness regarding the importance of early diagnosis at all levels of care, while also championing the inclusion of other social and healthcare agents in the identification of patients who are not treated in the usual medical assistance circuit. It is of utmost importance to make information and resources available, so as to achieve a more accurate performance and interpretation in diagnostic testing, chiefly through the integration of technological advances such as artificial intelligence, Big Data analysis, and virtual reality as various forms of diagnostic support.

Similarly, several strategic goals have been outlined regarding treatment and subsequent monitoring. Firstly, specialists are encouraged to explore innovative pharmacological therapies which could potentially contribute to the dechronification of liver diseases; secondly, it is suggested that patients should be activated as central elements in treatment and monitoring stages, acknowledging their active engagement and concern with their self-care in the management of their disease. Thirdly, the importance of guaranteeing an equitable access to innovative drugs is also emphasized, promoting equity and efficiency in the care and monitoring of liver patients within the National Healthcare System. Lastly, it is suggested that specific applications favoring the adherence to treatment and patient monitoring should also be applied.

1. Aims and methodology

This National Liver Health Plant seeks to define an integral strategy that will serve as a holistic approach to liver diseases and the improvement of their management at a national level, setting 2032 as a key year in its potential implementation. The term “liver disease” encompasses the following pathologies: metabolic dysfunction-associated steatotic liver disease, rare liver diseases, alcohol-related liver disease, viral hepatitis, liver cancer, and liver transplant.

Experts in each of the aforementioned diseases were recruited in order to develop this National Liver Health Plan. They were divided into six groups, with each of them including six specialists in each of the liver diseases. These specialists held several sessions in which a SWOT (Strength, Weaknesses, Opportunities and Threats) analysis was performed regarding the patient circuit (suspicion, diagnosis, treatment and monitoring) in order to identify possible areas of improvement and the specific challenges within each liver disease.

A strategic map was developed after the performance of the SWOT analysis, divided into five strategic areas (research, education, public healthcare, care models, and digitalization), each of which were also divided into three areas of action (prevention, diagnosis, treatment, and monitoring).

Fifteen strategic goals were obtained from the development of this strategic plan, which were presented to all six group coordinators to define the various courses of action for each liver disease. Subsequently, all members of each group were asked to prioritize these strategies, which gave rise to a total of 80 courses of action. Out of these, 53 were finally included in the National Liver Health Plan after being prioritized by all research groups.

A management board was also conformed, including specialists in various areas, such as primary healthcare, patient representatives, researchers, and representatives of the private sector, among others. The main goal of this management board was to ratify this National Liver Health Plan, which will be submitted to the Spanish Ministry of Health.

2. General overview of liver disease in Spain

2.1 Introduction to liver disease

Liver disease is a major cause of morbidity and mortality in Western countries [1]. It remains largely stigmatized to this day, as it tends to be associated with alcohol addiction while also affecting an increasing number of individuals due to obesity and diabetes [2]. Metabolic dysfunction-associated steatotic liver disease is the most frequent form of liver disease in Europe and Spain, associated with obesity and type-2 *diabetes mellitus*. It is estimated to affect a 30% of the general population [2].

These pathologies are also associated with social and health inequities. Vulnerable groups and unattended communities are disproportionately affected by liver disease due to various reasons, including physical, social, and economic factors. These communities tend to alleviate their psychosocial stress or confront their problems through drug and/or alcohol consumption [2]. Mortality due to alcohol-related liver disease is notably higher in vulnerable groups, particularly in younger patients, which gives rise to significant health inequality [2].

Lower socioeconomic levels have also been linked to a greater likelihood of developing risk factors of liver disease. There are substantial differences in the proportion of overweight or obese patients depending on their region, sex, and socioeconomic level. Similarly, the prevalence of obesity and diabetes was higher among adults from lower socioeconomic backgrounds, thus indicating a greater likelihood of having non-alcoholic fatty liver disease and advanced liver fibrosis [2].

Liver diseases in early stages are asymptomatic, which usually entails a late-stage diagnosis. This entails the use of costlier resources, with the National Healthcare System generally assuming such costs. In 2015, 41% of the total number of consultations performed in the participating hospital services were conformed by patients with some form of liver pathology [3].

2.2 Hospital care resources in management of liver patients

Service characterization refers to those hospitals in which liver patient management is typically carried out. This characterization was based on the 2015 project “Libro Blanco de la Hepatología en España” (“White Book of Hepatology in Spain”), in which 161 hospitals from all autonomous communities were involved. Data shown throughout this section has been extracted from this project [3].

Figure 1 shows that hepatology areas were generally located within Digestive System/Gastroenterology Services or Sections, with a representation of 41% and 31% respectively. Only Hospital Clínic (Barcelona) had an independent Hepatology Service [3]. The remaining centers included their Hepatology Services within their Internal Medicine Services and Hepatology Sections [3].

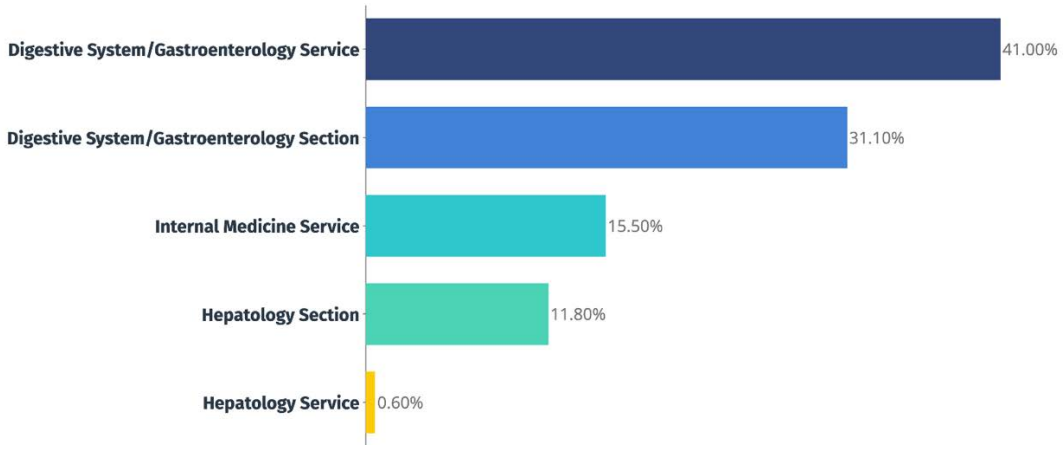

Figure 1 | Location of Hepatology areas in hospital centers [3]

2.2.1 Administratively recognized functional hepatology units

26.1% of consulted centers have an administratively recognized Functional Hepatology Unit. In total, 70.7% of them can be found in hospitals with over 500 beds, whereas 19.5% are located in hospitals with 200-500 beds; finally, 9.8% are found in hospitals with less than 200 beds [3].

2.2.2 Centers and hospitals with Hepatology units

All participating centers have a digestive system/gastroenterology service or section, internal medicine service, or a hepatology section or service. The following figure shows the number of centers that have undertaken liver disease patient care, distributed throughout the various Spanish autonomous communities [3].

Figure 2 | Number of centers with hepatology services per autonomous community [3]

3. Metabolic dysfunction-associated steatotic liver disease: a twenty-first century epidemic

3.1 Introduction to metabolic dysfunction-associated steatotic liver disease

Metabolic dysfunction-associated steatotic liver disease (MASLD) is produced by the accumulation of fat in the liver, which can lead to fibrosis or irreversible cirrhosis and ultimately into hepatocarcinoma [4].

In the absence of excessive alcohol consumption, metabolic dysfunction-associated steatotic liver disease is caused by fat accumulation in the liver once it surpasses 5% of its weight and can be reversible in its early stages [4].

Fat accumulation in the liver becomes toxic in roughly 5-20% of cases, which results in damage to the liver as it causes inflammation (hepatitis) and cellular damage; it is also the stage in which MASLD develops. In its clinical course, approximately 10-20% develop higher-grade fibrosis and 5% progress to cirrhosis [5].

3.1.1 Epidemiology and risk factors

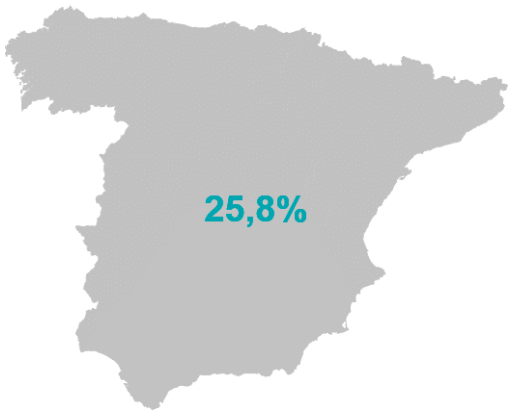

Figure 3 | MASLD prevalence in Spain

According to population-based studies, the prevalence of MASLD in Spain is of 25.8%, whereas the level of significant fibrosis estimated through the sequential combination of transitional elastography and liver biopsy is 2,8% within the general population [6].

The prevalence of MASLD rises proportionally to the prevalence of metabolic syndrome (MetS) and its components, particularly obesity and type-2 *diabetes mellitus* (DM) [6].

It has been demonstrated through various studies that the prevalence of MASLD is significantly superior in patients with MetS or in presence of certain comorbidities, particularly obesity, DM, but also arterial hypertension [6].

The prevalence of MASLD in obese patients undergoing bariatric surgery has been estimated at 91% and 37% respectively, while being found to be around 40-70% and 22% respectively in patients with DM [6].

On the other hand, Adam, S. et al. (2020) point out that the mortality rate in patients with MASLD is notably higher than in those who do not have the disease. Mortality is estimated to be around 2,556 cases per 100,000 inhabitants per year [7].

The most common cause of elevated transaminases within adults is MASLD, which is also considered as MetS, as it is the result of a complex interaction between genetic, hormonal, and nutritional factors [5] [8].

3.2 Challenges and opportunities in approaching MASLD

MASLD management currently suffers from several deficiencies which negatively impact the entirety of patient circuits, from suspicion to monitoring. As such, it also worsens their quality of life [9].

Some of the main challenges to be tackled are the low level of awareness within the general population, but also among professionals and health authorities. Difficulties in making correct diagnosis due to insensitive techniques stand out as a major challenge, as does the lack of knowledge of biochemical indicators. It should also be noted that professionals tend to lack clinical, Spain-based guidelines to correctly manage the pathology [9].

Other areas include the lack of therapeutic options, the need for multidisciplinary teams, as well as the need for broadening the community of practice [10] and the scarceness of real data regarding the disease in routine practice [9].

Figure 4 | Challenges in approaching MASLD [9]

3.2.1 Low awareness of the disease

There is currently a widespread lack of awareness regarding MASLD, both within healthcare professionals and the broader population. This entails a persistence of unhealthy lifestyle habits, such as unbalanced diets and a lack of physical activity, which contribute to the development of the disease. Furthermore, it is common for patients to be diagnosed in advanced stages of the disease due to its asymptomatic nature in its early stages. Such lack of awareness also impacts the low levels of suspicion and derivation to specialists during early stages.

As such, it is necessary to implement publicity campaigns and educational programs that promote healthy lifestyle habits and raise awareness regarding MASLD, both within the medical field and the broader population.

3.2.2 Dificultad para el diagnóstico de la enfermedad desde atención primaria y otras especialidades

MASLD diagnosis may begin through primary healthcare or other specialties through the identification of risk factors, biochemical alterations in the liver, or imaging tests detecting hepatic steatosis. If suspicions persist, it is advised for the patient to be referred to a specialist, who may conduce more specific tests, such as elastography, while also considering the performance of a liver biopsy to confirm the diagnosis.

The main challenge for primary health and other specialties lies in the lack of information regarding the pathology, as well as the access and correct performance of diagnostic tests. Similarly, while being the only definite diagnostic test for MASLD, liver biopsy suffers from several disadvantages, such as its elevated price and its invasiveness nature.

3.2.3 Lack of guidance in diagnosis standardization to differentiate the pathology from its associated comorbidities

The lack of clinical practice guidelines specific to the management of MASLD in Spain has caused a variability in its diagnosis and treatment. Similarly, the lack of unified criteria for the use of scores and imaging techniques have hindered the approach to the disease, further heightened by the absence of standardized criteria for the classification of fibrosis.

Furthermore, many patients lack an appropriate diagnosis due to the confusion between signs and symptoms with their associated comorbidities, such as diabetes and obesity, which do not include MASLD in their respective clinical practice guidelines.

3.2.4 Issues in the promotion of healthy lifestyle habits

Most MASLD patients follow poor dietary habits and a sedentary lifestyle, which negatively affects their quality of life. Sedentarism is promoted through lengthy work hours and is further aggravated by the abundance publicity campaigns in mass media promoting fast food, alcohol, sugary drinks, and tobacco consumption. It is also worth noting that most healthy foods are generally costlier than their ultra-processed counterparts.

Primary healthcare physicians and specialists are currently facing the challenge of promoting the scientifically supported adherence to Mediterranean diet, while also emphasizing the importance of a 10% weight loss for the treatment of MASLD, dyslipidemia, and associated diabetes [11].

3.2.5 Lack of pharmacological treatment

Current approaches to MALFD are focused on changes in lifestyle habits and accomplishing the established weight loss, which presents various difficulties due to its comorbidities and unhealthy lifestyle habits. Similarly, the lack of approved pharmacological options leads to the consideration of clinical trials as an alternative.

It is important to note that available therapies, such as antidiabetics, are used out of their original indication. However, the development of future therapeutic options could entail a significant change in the approach to this disease, particularly for those patients with advanced-stage fibrosis (F3-F4), who face a greater risk of progression towards irreversible stages.

3.2.6 Limited implication of the National Healthcare System

The implication of the National Healthcare System (Sistema Nacional de Salud, SNS in Spanish) is essential to an integral approach to liver diseases such as MASLD. However, experts have pointed towards a lack of implication from the SNS in raising awareness and preventing such pathologies, both among healthcare professionals and the broader population. Furthermore, the limited slots of time during consultations makes it difficult to obtain accurate information regarding the patient's lifestyle habits, which are essential for a proper education regarding liver pathologies.

As such, the main challenge for primary healthcare physicians and specialists lies in promoting the improvement of service efficiency, while also encouraging the use of primary and secondary healthcare consultations as a means for prevention.

3.2.7 Lack of multidisciplinary teams to optimize management

Coordination among specialists is essential while approaching the pathology, from suspicion to patient monitoring. The lack such collaboration entails a decrease in early-stage detection of new patients, as well as those with associated comorbidities, particularly in cases of advanced-stage fibrosis. Similarly, it negatively impacts the handling of patients, which may influence the progression of the disease towards an irreversible stage.

Furthermore, the lack of awareness in certain specialties and the scarcity of diagnostic resources result in a lack of referral of patients with fibrosis indicators.

3.2.8. Variability among hospitals in knowledge and resources for disease management

A broad difference in the degree of awareness and knowledge of the disease has been noted between hospitals specialized in MASLD and other regional hospitals with a smaller population and less resources regarding MASLD patients. This lack of awareness and knowledge has a direct impact on the patients' quality of life and causes great differences in their approach depending on the center they visit.

3.2.9 Requirement of real data regarding the pathology in routine clinical practice to conduct an analysis of its prevalence and burden

Current information regarding the pathology is based on estimations made through patient records created by different scientific societies. These records are independent and hold information deemed relevant by each society. However, the lack of unified criteria for patient selection and the limited availability of hospital databases create an information gap in routine clinical practice.

It is important to obtain more data regarding the adherence to treatment, comorbidities, and the effectiveness of new treatments under study.

4. Rare liver diseases: uncharted territory

4.1 Introduction to rare liver diseases

Rare liver diseases affect a small percentage of the population and may cause progressive liver damage, which may develop into fibrosis and, in more advanced cases, into cirrhosis [12].

The *European Reference Networks Rare – Liver* (ERN Rare – Liver) was created in 2017 to classify rare liver diseases in three main groups: autoimmune diseases, toxic-metabolic diseases, and hepatic vascular diseases. Each group was assigned several reference centers on a European level [12].

4.1.1 Types of rare liver disease

The following figure shows the three types of rare liver disease that will be addressed throughout this report:

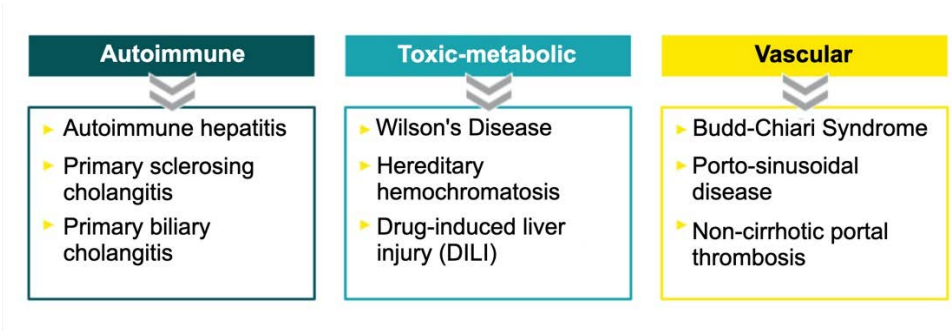

Figure 5 | Classification of rare liver diseases [13]

4.1.2 Epidemiology

According to European Union standards, a disease is considered rare when it has a prevalence lower than 50 cases per 100,000 inhabitants.

Rare liver diseases have different prevalence rates, according to several scientific publications. Autoimmune liver diseases are estimated to have a prevalence of 16-18 cases per 100,000 inhabitants, with an incidence of 0.1-0.9 per 100,000 inhabitants [14]. The prevalence of primary biliary cholangitis is estimated to be of 35-40 cases per 100,000 inhabitants and an incidence of 0.51-3.86 cases per 100,000 inhabitants respectively [15], whereas primary sclerosing cholangitis has a prevalence of 0.22 per 100,000 inhabitants and an incidence 0.016 cases per 100,000 inhabitants respectively [16].

Regarding toxic-metabolic diseases, Wilson's Disease has a prevalence of 1-3 cases per 100,000 inhabitants [17] and an incidence of 3.33 cases per 100,000 inhabitants (according to global data). Hereditary hemochromatosis has a prevalence of 200 cases per 100,000 inhabitants [18] (global data); drug-induced liver injuries (DILI) suggest a prevalence of 2.7-19 cases per 100,000 inhabitants [19] (European data) and an incidence of 13.9 per 100,000 inhabitants [20].

Lastly, vascular diseases include porto-sinusoidal disease, non-cirrhotic portal thrombosis, and Budd-Chiari Syndrome. Non-cirrhotic portal thrombosis has a prevalence of 0.7-3.7 cases per 100,000 inhabitants [21], whereas Budd-Chiari Syndrome has a prevalence of 0.24-3.31 per 100,000 inhabitants and an incidence of 0.0168-0.409 per 100,000 inhabitants (European data) [22]. No epidemiological studies regarding the prevalence and incidence of porto-sinusoidal disease or the incidence of non-cirrhotic portal thrombosis have been found.

It is worth noting that epidemiological information regarding these diseases is not completely precise, due to a lack in patient registration and a consequent scarceness in research [9]. *Figure 6* shows epidemiologic data regarding each type of rare liver disease:

	Autoimmune hepatitis	Primary sclerosing cholangitis	Primary biliar cholangitis	Wilson's Disease	Hereditary hemochromatosis	DILI	Porto-sinusoidal disease	Non-cirrhotic portal thrombosis	Budd-Chiari Syndrome
Prevalence	16 – 18 / 100,000 inhabitants	0.22 / 100,000 inhabitants	34 – 35 / 100,000 inhabitants	1 – 3 / 100,000 inhabitants	200 / 100,000 inhabitants	2.7 – 19 / 100,000 inhabitants	ND	0.7 – 3.7 / 100,000 inhabitants	0.24 – 3.31 / 100,000 inhabitants
Incidence	0.1-0.9 / 100,000 inhabitants	0.016 / 100,000 inhabitants	0.51 – 3.86 / 100,000 inhabitants	3.33 / 100,000 inhabitants	ND	13.9 / 100,000 inhabitants	ND	ND	0.0168 – 0.409 / 100,000 inhabitants

ND: No data

Figure 6 | Epidemiological data regarding rare liver disease

4.2 Challenges and opportunities in approaching rare liver disease

Several inefficiencies have been pointed out in the management of rare liver diseases from early-stage diagnosis to monitoring. The lack of awareness from specialized physicians and primary healthcare limits their ability to correctly perform genetic counseling and to make the appropriate referrals [9]. As such, specialized units and multidisciplinary teams are required; however, the lack of interest from the pharmaceutical industry complicates the research and development of new treatments for such pathologies.

There is a clear variability in resources and knowledge among hospitals, as well as a general lack of economic resources from the SNS to approach these diseases compared to other common liver diseases. As such, it is vital to raise awareness and visibility, while also developing national applications to improve patient-specialist interactions [9].

Figure 7 | Challenges in approaching rare liver disease [9]

4.2.1 Lack of awareness among specialists and primary healthcare

There is a significant lack of awareness regarding rare liver diseases in both specialists and primary healthcare physicians. Due to their specific nature and their low prevalence, suspicions and diagnosis regarding these diseases tend to be difficult. However, it is important to note that there are biomarkers, symptoms, and signs that may help in early suspicion and diagnosis.

The main challenge regarding rare liver disease management therefore lies precisely in this lack of familiarity and awareness both in primary healthcare and other specialties, which results in a lack of adequate referrals to experts.

4.2.2 Lack of protocolization in genetic counseling

Genetic rare liver diseases are a sub-group among rare liver diseases. They require the appropriate genetic counseling, despite the general lack of expertise among specialists. A consensus regarding genetic counseling would be useful in early-stage detection of such pathologies.

4.2.3 Difficulties in diagnosis and referral from primary healthcare

Diagnostic techniques used in rare liver diseases include laboratory analysis, imaging, and biomarkers. Although such techniques cannot confirm the diagnosis, they may help in early suspicion stages. However, precise diagnosis requires advanced techniques with limited availability, while also requiring a high level of medical expertise.

The lack of such level of expertise, both in primary healthcare and in specialists, makes the diagnostic process much more difficult and poses a very important challenge to their diagnosis.

4.2.4 Lack of specialized units and multidisciplinary teams

An appropriate approach to rare diseases requires the adequate coordination among different types of specialists in all stages of the process of patient care. The lack of knowledge and awareness regarding such diseases among primary healthcare and specialist physicians can negatively impact the referral process through erroneous referral or altogether failing to refer the patient to an adequate specialist.

Such circumstances may prompt delays in early detection of new cases and an inappropriate management, which may negatively impact its development and/or prognosis towards irreversible stages.

4.2.5 Low interest in conducting research on rare liver diseases

Although rare liver diseases affect a minority of the population compared to more common liver diseases, their impact on public health is still quite significant. However, their treatments often focus on alleviating symptoms or treating their associated comorbidities rather than addressing the underlying cause of the pathology. This is partly due to a low interest from the pharmaceutical industry regarding research and the possibility of finding new drugs that may specifically help in treating these diseases.

4.2.6 Scarce economic resources from the National Healthcare System

Due to their low prevalence, rare liver diseases have received an unequal assignation of economic resources from the SNS compared to more common liver diseases.

Similarly, these diseases can be very costly, as they affect a very small proportion of the population and require a high level of specialization in interpreting diagnostic tests, while also requiring lengthy amounts of time to develop an accurate diagnosis.

4.2.7 Issues regarding public visibility

There are no current visibility campaigns for rare liver diseases, which directly impacts the lack of awareness within both the general population and the scientific community.

Diagnostic processes are often prolonged due to factors such as prior incorrect diagnosis, the importance of undergoing several different tests, and the general lack of knowledge regarding these pathologies. Furthermore, the scare awareness among the general population negatively impacts the quality of the patients' psychosocial support, as most of them do not have any direct referents in their lives who might share their pathology.

4.2.8 Issues in the development of applications for the general population

There are no nationwide applications for patient-specialist interaction. A continuous flow of communication during treatment and monitoring can be improved through the implementation of such applications.

4.2.9 Variability among hospitals in knowledge and resources for disease management

Access to diagnostic techniques and professional knowledge regarding rare liver diseases varies from specialized hospitals to regional centers. The availability of complex diagnosis techniques is only available in specialized centers.

5. Alcohol-related liver disease: a socially rooted rising threat

5.1 Introduction to alcohol-related liver disease

Alcohol-related liver disease (ARLD) arises from liver damage caused by excessive alcohol intake. This pathology does present a single clinical manifestation, but rather may present several modalities depending on the amount of alcohol intake [23].

There are three major forms of alcohol-related liver disease: alcoholic hepatic steatosis, alcoholic hepatitis, and alcoholic cirrhosis [23].

Time of alcohol consumption must be considered in relation to liver damage. It is estimated that at least five years of excessive alcohol intake are necessary for the development of liver damage. However, not all indviduals who consume excessive amounts of alcohol develop liver disease, which implies that an unidentified individual susceptibility can be understood as a determining factor in the development of the pathology, which leads some patients to develop cirrhosis whereas others only show steatosis [23].

Gender should also be considered as a determining factor, as it has been observed in various scientific revisions that excessive alcohol intake tends to affect women more severely [23].

Figure 8 | Risk factors in the development of ARLD [24]

It is worth noting that there is no safe level of alcohol intake, although it is largely considered a risk factor once it surpasses 40g/day in men and 20g/day in women [24].

Alcohol-related hepatic steatosis tends to be asymptomatic and does not generally present alterations in clinical analysis. As such, patients whose alcohol intake does not decrease in early stages their disease might develop into alcoholic hepatitis and even cirrhosis [23].

Alcoholic hepatitis and cirrhosis are more severe conditions, which usually entail symptoms such as jaundice, fatigue, general weakness, right upper abdominal pain, and ascites, among others [23].

It should also be noted that addictive alcohol intake may lead to the development of mental and behavioral disorders [23].

5.1.1 Epidemiology

Alcohol is a psychoactive substance with dependence-inducing properties. Alcohol intake-related disorders causes a high burden of disease as well as having serious social, economic, and safety consequences. Furthermore, it is one of the most common causes of chronic liver disease, while also being associated with the risk of developing multiple health disorders [25].

Similarly, it is a causal factor in over 200 diseases, including mental disorders, alcohol-addictive behaviors, liver cirrhosis, and cardiovascular diseases [25].

Annual alcohol intake in individuals aged fifteen or older decreased progressively between 2010 and 2013 (from 10.2L of pure alcohol consumed *per capita* to 9.5L). In contrast, general alcohol intake *per capita* later increased to 12.7 between 2013 and 2019 [26].

In this sense, an increasement in alcohol intake necessarily entails an increasement in the incidence of alcohol-related liver disease, particularly in poorer societies. However, it is also worth noting that improvements in prevention and treatment of viral hepatitis have helped in decreasing the burden of chronic liver disease. As a result of both trends, it is estimated that half of all liver disease-related deaths worldwide are caused by alcohol-related liver disease [25].

ARLD is the most common cause of advanced liver disease and liver cirrhosis in Europe, including Spain. Its prevalence among the general population is estimated to be 2% [24].

Ethyl alcohol-related cirrhosis is the leading cause of alcohol-related mortality in Europe. It was estimated that, of all the cases of liver cirrhosis registered in Spain in 2016, 73.8% of cases in men and 56.3% of cases in women were ascribable to alcohol consumption [24].

Despite lacking precise data on the prevalence and incidence of alcohol-related liver disease, there is enough proof to assert that alcohol is one of the main causes of death due to liver cirrhosis worldwide, including Spain. This, in turn, clearly makes it a public health issue [24].

5.2 Challenges and opportunities in approaching alcohol-related liver disease

Alcohol-related liver disease management shows several issues throughout the patient circuit. Some of them include the lack of general awareness among the populating, risk factors associated with the pathology, the lack of tools for early detection, and the influence of the alcohol industry in the country [9].

On the other hand, the social stigma associated with this disease hinders its identification and the establishment of a homogeneous circuit of care and referral to medical specialists [9].

Figure 9 | Challenges in approaching alcohol-related liver disease [9]

5.2.1 Lack of social awareness on the risks of excessive alcohol consumption

Alcohol consumption is largely socially accepted, which entails a widespread unawareness of its risks regarding liver health. Furthermore, early diagnosis in alcohol-related liver disease is clearly affected by the absence of symptoms and overt signs of the pathology.

In addition, patients tend to develop addictive behaviors regarding alcohol, which hastens progression. Youths tend to normalize the presence of alcohol and its consumption in their social environment, further influenced by its easy accessibility and low costs, which make it prevalent even among minors. Addressing this issue would necessarily require a cultural shift towards a broader social awareness of the harmful effects of alcohol consumption on the liver.

5.2.2 Lack of strategies to identify excessive alcohol consumption

Suspicions regarding excessive alcohol intake are currently difficult to prove from a clinical perspective, as there are no reliable biomarkers. Early detection usually relies on AUDIT tests, which can be short (3 questions) or long (around 10 questions) to identify alcohol-addictive behaviors. It is also advisable to create specialized alcohol units, since addictive behavior units do not tend to focus on these types of addictions.

The lack of multidisciplinary teams in many Spanish centers also hinders the appropriate management of these patients, who require care for both liver disease and alcohol addiction.

5.2.3 Scarce economic and care resources specialized in alcohol-related liver disease

The Spanish healthcare system is currently facing a lack of resources and an overburden due to underinvestment in infrastructure and medical personnel, which was further aggravated by the COVID-19 pandemic. Resources are typically focused on emerging liver diseases, such as MASLD.

Such overburden results in long waits, which limits consultation time and further difficult the completion of AUDIT-C questionnaires in primary healthcare. As such, the main challenge for primary healthcare physicians and specialists lies in this lack of investment and resources to adequately address alcohol-related liver disease.

5.2.4 Limited government support and lack of legal support

Alcohol can be very easily accessed as its sales remain poorly unsupervised, which in turn makes it a widely consumed legal drug in Spain. Although information regarding its risks is widely available, a widespread campaign focusing on responsible consumption has never been carried out in collaboration with the authorities. Similarly, public investment in prevention and research into specific biomarkers remains insufficient.

Furthermore, the alcohol industry has further hindered its restriction and limits efforts to reduce the economic and social burden of alcohol-related liver disease. As such, a continued support from public administrations remains crucial in the challenge of implementing preventing measures and promoting a significant social change in terms of alcohol consumption.

5.2.5 Influence of producers and marketers on social perceptions of the alcohol industry as a driving force within the economy

The alcohol industry has a very strong influence on public opinion and political decisions, which further complicates the possibility of raising awareness regarding liver diseases and their indirect costs, as well as the risks associated with addictive behaviors. Similarly, publicity campaigns tend to promote alcohol consumption, further hindering efforts to educate the general population about its risks and the importance of regulating the industry.

It is therefore necessary to collaborate with the industry and policy makers not only to reduce the impact of excessive alcohol consumption, but also to find effective solutions to this issue.

5.2.6 Stigmatization of alcohol-related liver disease

ARLD suffers from a persistent stigma due to the social repercussions associated with alcohol-addictive behaviors. Many consider it a personal choice rather than a disease, which leads to judgment instead of support. In addition, patients may choose to hide their addiction or lie in medical consultations, which further complicates their detection.

Stigmatization should be efficiently approached in order to provide patients with comprehensive support, always seeking to promote multidisciplinary management and the creation of centers specializing in alcohol-related issues.

5.2.7 Heterogeneity in subclinical evoluton of the disease

The impact of alcohol on the body varies between individuals, as the intake of identical amounts has vastly different effects on each person. For instance, women may suffer from poorer metabolization processes due to genetic factors.

Subjective perceptions on the meaning of risky consumption and the general lack of awareness may lead to an inadvertent development of liver disease. Similarly, negative effects of alcohol consumption tend to lack overt symptoms; as such, detection is largely up to the affected individual and their close social surroundings.

In short, alcohol may cause disproportionate damage and healthy individuals with no apparent symptoms.

5.2.8 Challenges in early detection due to being an asymptomatic disease

ARLD is generally asymptomatic in its early stages, which complicates its detection. Furthermore, the lack of symptoms minimizes risks and creates a general sense of unawareness regarding the disease.

Early detection remains a crucial way of avoiding the development of the pathology. However, there are no reliable biomarkers to aid in early detection and/or to indicate an individual's general alcohol consumption.

5.2.9 Lack of standardization in patient circuits and referral processes

Management of alcohol-related liver disease patients requires the interdisciplinary collaboration among various types of healthcare professionals, adapting their approach to the individual needs of each patient. Early detection is crucial to prevent the progression of the disease o to treat it in its early stages, but it can be a challenging process due to inaccurate diagnosis, particularly in early stages.

The lack of clinical guides focusing on the flow of patient care leads to a lack of of homogeneity in the diagnostic process, thus generating variability between specialized hospitals and regional centers. In addition, the lack of uniformity in referral processes results in a struggle for hepatologists and psychiatrists/psychologists alike, as the former are only able to assess the patient in advanced stages and the latter find themselves unable to properly address alcohol-addictive behaviors or their development.

6. Viral hepatitis: an unresolved challenge

6.1 Introduction to viral hepatitis

Viral hepatitis is a viral infection which causes inflammation and damage to the liver. There are several types of viruses that may cause hepatitis; at the time, hepatitis A, B, C, D and E viruses are known. Hepatitis A and E viruses tend to cause acute infection, whereas hepatitis B, C and D cause both acute and chronic infections [27].

Viral hepatitis is a communicable and therefore potentially preventable disease. Hepatitis A and E are transmitted through previously contaminated water and food, typically through contact with the faeces of an infected person; furthermore, hepatitis E can also be contracted by eating undercooked pork, venison, or seafood [28].

Hepatitis B, C and D are transmitted through blood contact. Hepatitis B and D can also be transmitted through bodily fluids, such as saliva, vaginal secretions, semen and urine, among others [29].

Generally speaking, those engaging in unprotected sexual intercourse with infected individuals are considered to be in risk of developing hepatitis, as is the case with frequent drug users who share their consumption material with infected individuals. Health workers are also considered to be at risk, as well as sewage workers and those working in close contact with food. It is also worth noting that certain places have a higher endemicity, and as such their inhabitants and/or visitants are considered to have a higher risk of infection [30].

Acute infections may be directly solved by the patient's body, eventually making it disappear [27]. Such infections do not confer permanent immunity; as such, preventive measures should be taken to prevent the infected individual from developing other types of viral hepatitis [1]. Chronic

disease develops when the body is unable to eliminate the virus, which is often the case with hepatitis B, C and D viruses. Chronic hepatitis can lead to cirrhosis, liver failure, and even liver cancer [27].

1.1.1 Epidemiology

Viral hepatitis is one of the most frequent infectious diseases in humans. We offer an outline of the epidemiological data regarding each of them, as there are differences in their geographical distribution regarding their prevalence [31].

Hepatitis A virus (HAV) infections are common in low-income countries with poor sanitation and hygiene conditions. It is also one of the most prevalent types of hepatitis in Spain, despite being a country of low endemicity [32]. The incidence rate of hepatitis A in Spain was of 0.64 cases per 100,000 inhabitants in 2020 [33], and the prevalence of HVA antibodies in the general population at 50 years of age ranges between 15% and 100% in European countries. HAV-related mortality is generally low, with only 0.4% of cases classified as fulminant hepatitis [34].

Hepatitis B virus (HBV) infections are common in Eastern Asian countries, the Western Pacific and Africa [35]. HBV is not prevalent in Spain, with an incidence rate of 0.71 cases per 100,000 inhabitants in 2020 and a prevalence of 0.22% in 2018. There has been a progressive decrease in annual incidence rates since 2014. In 2019, 954 HBV-related deaths (2.07 cases per 100,000) were reported [36].

Hepatitis C virus (HCV) is most frequently found in the Eastern Mediterranean region and Europe, followed by Southeast Asia and the Western Pacific region [37]. It is estimated that 0.22% of the general population in Spain suffered from active HCV infection [38]; the incidence of acute and chronic cases was found to be of 1,382 cases in 2019. Similarly, 4,817 HCV-related deaths (5.9 cases per 100,000 inhabitants) were registered in 2019 [36].

The highest burden of hepatitis D disease is found in areas such as Mongolia, the Republic of Moldova and certain Central and West African countries [39]. A study conducted in Spain based on the monitoring of patients with chronic hepatitis B, the prevalence of hepatitis D virus (HDV) was estimated to be less than 5% among HBV patients [40]. Data regarding the incidence and mortality of hepatitis delta in Spain remains limited; however, according to the Pan-American Health Organization (PAHO), mortality rates due to hepatitis D infection in chronic HBV patients vary between 2% and 20% [41].

Hepatitis E is prevalent in low-income countries with poor sanitation and hygiene conditions [42]. The prevalence of hepatitis E virus (HEV) remains uncertain even in developed countries; it is estimated that it oscillates between 0.6% and 12% in Spain [43]. HEV-related mortality varies between 1% and 4% in the general population, although it considerably increases in pregnant women, reaching 20-30% [44].

It is important to note that viral hepatitis is a public health issue, despite advances in treatment and elimination plans, as it continues to have a high burden of disease.

6.2 Challenges and opportunities in approaching viral hepatitis

Significant progress has been made in the prevention and treatment of viral hepatitis in recent years, especially in hepatitis C [9].

However, such pathologies remain a public health issue, with ample areas of improvement such as its persistent infection rates, ineffectiveness in certain treatments, deficiencies in the healthcare system, lack of available diagnostic tests [9], and late diagnosis [45].

Figure 10 | Challenges in approaching viral hepatitis [9]

6.2.1 Lack of social awareness

Knowledge regarding transmission mechanisms and risk factors in viral hepatitis remains limited in the broader population, which hinders its prevention and control. Similarly, the shift in sexual trends and the lack of preventive measures has led to an increase in cases, particularly in hepatitis B virus infection as a consequence of unprotected sex between men. Furthermore, hepatitis B virus transmission has also increased due to an increment in drug use.

Finally, it is worth noting that the anti-vaccine movement could have an impact on prevention, despite the availability of HBV vaccines in the established childhood vaccination schedules, which also includes HAV in Catalonia.

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6.2.2 Challenges in primary healthcare and other specialties in diagnosis and treatment

The lack of knowledge regarding transmission mechanisms and risk factors in viral hepatitis also hinders diagnosis in primary healthcare and other medical specialties. Medical personnel tend to feel some degree of reluctance towards the idea of asking their patients about complex personal situations, and the lack of overt symptoms further complicates initial suspicion of these diseases. It is also worth noting that there is a tendency towards focusing on HCV detection rather than HBV. There are also limitations regarding the availability of on-site tests for early diagnosis and in the access to self-diagnostic tests for the general population.

6.2.3 Challenges in prescription, dispensation, and access to treatment

Current treatment for viral hepatitis presents several difficulties due to its exclusive prescription in specialized care, as well as its limited dispensing in hospital pharmacies.

In addition, access to new treatments can be costly and limited, with no generic options available at the time. Moreover, current approaches to HBV and HDV are not curative and require prolonged treatment.

6.2.4 Scarce investment and government support in its prevention

Viral hepatitis still poses a great challenge despite advances in prevention and therapy. The lack of effective preventive measures has been shown to contribute in the increasement of reinfection rates, particularly for HCV. As such, it is crucial to approach prevention from a more strategic angle, as was the case in the 2015 plan for chronic hepatitis C.

It is worth noting that the availability of treatment has created a false sense of safety, which in turn has led to a decrease in funding for preventive measures and awareness regarding such pathologies.

6.2.5 Limited communication and coordination between different levels of care

Treatment for viral hepatitis is negatively impacted by the lack of effective communication between medical specialists. It is crucial to approach drug-related addiction simultaneously to the patient's hepatitis treatment, in order to prevent and treat such diseases.

Similarly, special attention should be paid to patients who are frequent users of injectable drugs, as they are in far greater risk of contracting hepatitis B virus infections, similarly to patients from HBV- and human immunodeficiency virus-endemic countries. Patients from such countries also tend to pose a greater challenge, as Spanish is not usually their first language; as such, language barriers may further complicate their communication with healthcare professionals.

6.2.6 Stigma and discrimination of viral hepatitis patients

Viral hepatitis is often associated with stigmatized groups, such as injectable drug users, individuals engaging in unprotected sex, migrants, and refugees.

However, these diseases may affect any individual, regardless of their lifestyle.

6.2.7 Lack of screening programs and proactivity to reach vulnerable groups

Risk groups for hepatitis virus infection are well identified; however, their access to medical care is often limited due to cultural and legal barriers, particularly in the case of migrant individuals in irregular situations, which also affects individuals who generally have a greater difficulty in accessing medical care. As such, proactive care and screening strategies remain crucial to reduce transmission.

Furthermore, some treatments are prolonged and non-curative. As such, they pose a challenge in the management of viral hepatitis patients, particularly in migrant and culturally distant groups.

6.2.8 Late diagnosis of viral hepatitis, particularly in HBV and HCV infections

Diagnosis can be challenging, as chronic HBV and HCV infections can remain clinically silent for decades and symptoms only appear once the disease has progressed significantly.

In Spain, access to direct-acting antiviral therapy is universal; however, only half of HCV-infected patients are aware of their condition and in treatment. In this sense, screening tests to identify patients before significant liver damage have greatly helped in decreasing the incidence and prevalence of HBV and HCV; similarly, they have proved to maintain and improve quality of life [45].

7. Primary liver cancer: a current and future issue

7.1 Introduction to liver cancer

Liver cancer is a disease in which liver cells begin to proliferate in an uncontrolled manner, preventing proper liver function. It is called primary liver cancer when it originates in the liver, while secondary or metastatic liver cancer refers to those cases in which the disease has spread to the liver from its original location. Secondary liver cancer is usually more frequent than primary liver cancer [46].

Hepatocellular carcinoma (HCC) is the most frequent type of liver cancer and one of the most common causes of death in patients with liver cirrhosis. The risk of developing this neoplasm is higher in patients diagnosed with chronic liver disease [47].

In many cases, patients are diagnosed with HCC through the monitoring of prior liver disease or investigation of underlying liver disease [47].

It is worth noting that ethnicity and geographical location are relevant factors that contribute to the development of HCC. The areas with the highest incidence of HCC are Southeast Asia and sub-Saharan Africa, followed by the Mediterranean countries and the northern region of Brazil, where incidence is lower [48].

Gender also plays a determining role in the development of HCC, as it is far more common in men than in women [48]. This may be due to the effect of male hormones and the greater likelihood for men to engage more directly with risk factors [1].

7.1.1 Epidemiology

Cancer is one of the main causes of morbimortality in Spain. The number of diagnosed cancers in Spain in 2022 was of approximately 290,175 cases; it is estimated that incidence will rise to around 341,000 cases by the year 2040 [49].

Liver cancer was the eighth most frequent type of cancer diagnosed in Spanish men in 2020 and the fifteenth most frequent in women, with approximately 6,604 new cases every year. Of them, 5,100 were men and 1,504 were women [50].

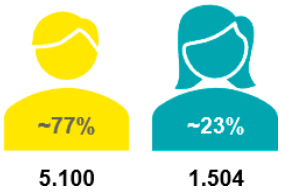

Figure 11 | Estimated incidence of liver cancer in Spain by gender [50]

According to the Spanish Network of Cancer Records (REDECAN in Spanish), it is estimated that the total prevalence of liver disease was of 11,347 cases in men and 2,982 cases in women in 2020 [50].

Regarding mortality, liver disease is the third worldwide cause of mortality, with a total of 830,180 deaths in 2020. In the same year, hepatocellular carcinoma and intrahepatic bile duct tumors accounted for 5,201 deaths, corresponding to 4.5% of cancer deaths and ranking sixth in order of frequency. Mortality was of 3,416 cases in men, sixth in order of frequency, whereas it was of 1,605 cases in women, ninth in order of frequency [50].

7.2 Challenges and opportunities in approaching liver cancer

Liver cancer is a complex disease, usually diagnosed in advanced stages due to underlying chronic liver disease. Patient circuits with such pathology present inefficiencies affecting their everyday life, such as the low level of social awareness, limited economic and care resources, lack of government support and the lack of a multidisciplinary approach through the joint efforts of hepatologists, primary healthcare, oncologists, and so on [9].

In addition, stigmatization, the lack of a shared system between autonomous communities, diagnostic challenges, and the lack of communication between patient associations and specialists can also be considered relevant challenges to the current state of liver cancer diagnosis and treatment in Spain [9].

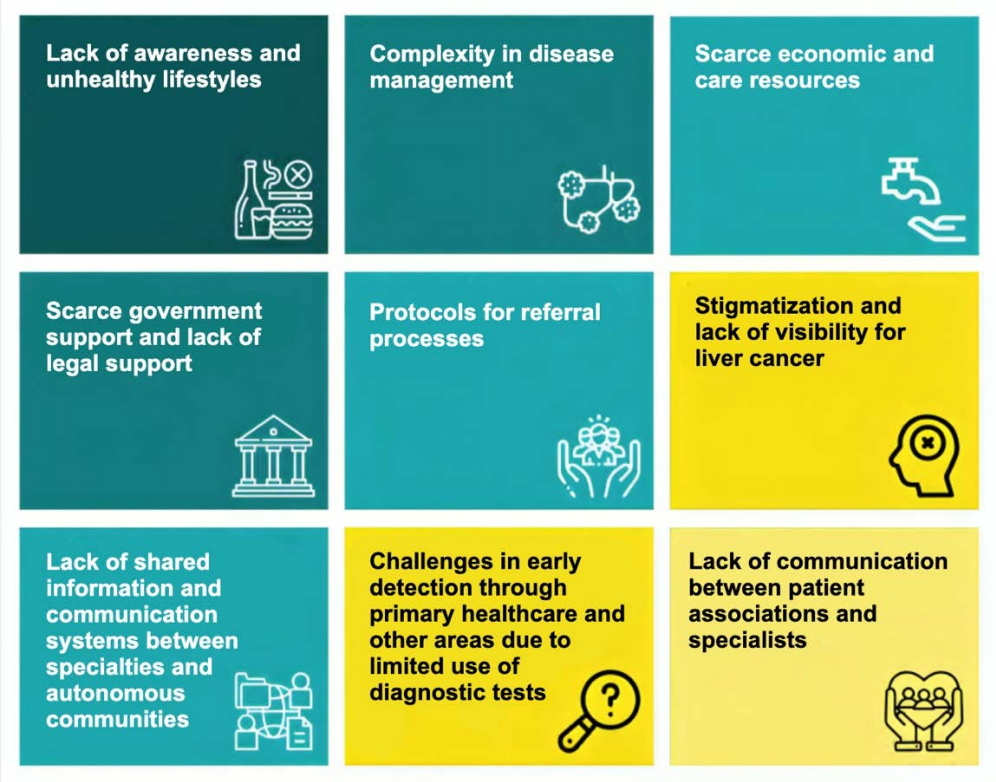

Figure 12 | Challenges in approaching liver cancer [9]

7.2.1 Lack of awareness and unhealthy lifestyle habits

Sedentary lifestyle, unhealthy diets, and excessive alcohol consumption in the general population increase the risk of liver disease and, as such, of liver cancer. Similarly, there is a widespread lack of awareness of such risk factors and prevention is scarce.

7.2.2 Complexity in disease management

Liver cancer requires a complex and multidisciplinary approach; however, many health centers lack the appropriate resources and specialists.

Coordination between primary healthcare and other specialties is therefore crucial to simultaneously address complications resulting from chronic liver disease and offering psychological support to the patient if necessary. It is also crucial to establish strategic alliances and improve the management of the side effects of pharmacological therapies.

7.2.3 Scarce economic and care resources

As it has been previously mentioned while discussing other forms of liver disease, the healthcare system is currently facing a number of challenges to provide liver disease patients with adequate care due to a lack of specialized physicians and a shortage of care and economic resources.

Similarly, the inadequate programming of diagnostic tests negatively affects screening, which is performed less frequently or removed altogether in at-risk patients.

7.2.4 Scarce government support and lack of legal support

The lack of government support for approaches to liver disease greatly affects the management of liver cancer. Investment in drugs and resources for treatment remains limited, despite scientific evidence of their efficacy.

As such, increased funding for prevention, research, and development of tests and treatment would improve the quality of care. In addition, financial endowment varies from center to center, even within the same autonomous community, limiting equitable access to quality care.

7.2.5 Protocols for referral processes

Management of liver cancer patients lacks the adequate protocols for correct referral, which results in inaccurate diagnosis and late detection of the pathology.

7.2.6 Stigmatization and lack of visibility for liver cancer

Liver disease, including liver cancer, are stigmatized due to their association with drug and alcohol consumption, which results in social discrimination. Furthermore, the lack of visibility and awareness regarding liver cancer typically entails late diagnosis and less effective treatment.

It is essential to raise awareness regarding early detection and the importance of adequate treatment to optimize the management of such pathology.

7.2.7 Lack of shared information and communication systems between specialties and autonomous communties

Health information systems are essential for coordination between healthcare professionals, centers, and autonomous communities. However, such systems suffer from several inefficiencies, such as their slowness, difficulties in their use, and a general lack of automatization.

As such, it is essential for these information systems to collect all patient information and to allow access from different centers to avoid a loss of continuity if the patient moves from one area to another. In addition, the current process could be simplified and optimized through the automatization of alarms and the scheduling of diagnostic tests.

7.2.8 Challenges in early detection through primary healthcare and other areas due to the limited use of diagnostic tests

The lack of preventive measures has contributed to an increase in liver disease and liver cancer in recent years. Lifestyle changes could prevent many liver diseases associated with toxins and metabolic syndrome. However, due to a lack of such preventive measures, the incidence of liver disease and liver cancer has increased in recent years.

Patients struggling with alcohol addiction also pose a challenge in their management due to their reluctance to attend addictive-behavior units. Similarly, early diagnosis can be difficult due to the absence of symptoms and overt signs, with patient referral often being inefficient and thus delaying their appropriate care.

7.2.9 Lack of communication between patient associations and specialists

Patient associations play a fundamental role in raising awareness regarding liver disease, as they provide patients with information, support, and a sense of community. They have consistently supported patients for approximately two years, and they require a stronger collaboration from specialists, such as oncologists and hematologists. It is worth noting that their psychology team is currently taking a specialization course on onco-psychology, as the disease requires such kind of support.

In addition, it was also noted after several interviews with liver cancer experts that there is a lack of hepatologists on the decision committees in charge of deciding on the financing of drugs at the Spanish Ministry of Health, the Health Departments in each autonomous community, and the Pharmacy Commission in each center, which remains a challenge for this pathology.

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8. Liver transplant: a source of hope in advanced liver diseases

8.1 Introduction to liver transplant

Liver transplantation (LT) is the surgical procedure to replace a diseased liver with a healthy liver from a deceased donor or a part of the liver of a living donor. LT is the only alternative that increases survival rates in patients with end-stage liver disease. HCC, which is typically associated with cirrhosis, is the fastest growing indication for transplantation in recent years [3].

Patients undergoing LT are more susceptible to new diseases, either those typical of the post-transplant period or the recurrence of their previous liver diseases [3].

8.1.1 Epidemiology

The National Transplant Organization (ONT in Spanish) is an existing organization belonging to the Spanish Ministry of Health. It is responsible of matters such as the procurement and clinical use of organs, tissues, and cells [51].

The main goal of the ONT is to promote altruistic organ donation, so that any Spanish citizen in need of a transplant may have the best chances of undergoing the procedure in optimal conditions [51].

In addition, the ONT is concerned with sharing information both nationally and internationally on transplantation. Such information encompasses patient management and epidemiological data on liver transplantation in different years, as shown in the figure below [51]:

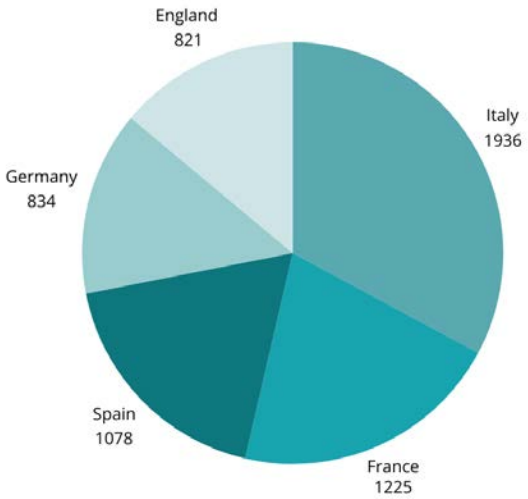

Figure 13 | Liver transplantation activity data at European level in 2021 [52]

As shown in *figure 13*, Spain currently holds the third position with 1,078 liver transplants, as opposed to the other five main healthcare systems in Europe. From a worldwide perspective, Spain ranked eighth in highest liver transplantation activity, just behind France [52].

On the other hand, recent years have shown an increase in LT in Spain. *Figure 14* shows the development of LT from 2012 to 2022. An increase of 7% can be observed in the past 10 years, surpassing values above 1,000 LT per year [53].

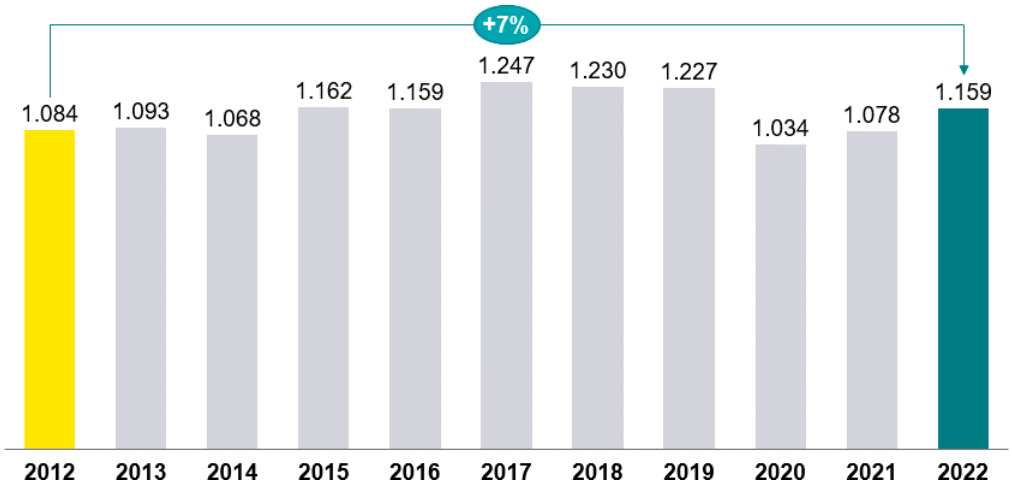

Figure 14 | Liver transplantation activity data in Spain (2012-2022) [53]

According to ONT data, the Spanish hospital in which the highest number of LT were performed was Hospital Universitario La Fe in Valencia, with a total of 117 LT in 2021. On the other hand, the Hospital Universitario Son Espases in Palma de Mallorca only performed 1 LT in 2021. *Figure 15* shows the number of LT performed per transplant center in Spain in 2021 [53].

Illustrative

Name of hospital	Number of liver transplants
Hospital Universitario La Fe	117
Hospital Universitario Cruces	71
Hospital Universitario Virgen del Rocío	66
Hospital Universitario Clínic Barcelona	54
Complejo Hospitalario Universitario A Coruña	51
Hospital Universitario Regional de Málaga	50
Hospital Universitario Reina Sofía	48
Hospital Universitario Gregorio Marañón	46
Hospital Universitario de la Arrixaca	46
Hospital Universitario 12 de Octubre	43

Figure 15 | Liver transplant procedures per transplant center in Spain (2021) [53]

8.2 Challenges and opportunities in approaching liver transplant

Liver transplant management in Spain currently faces several challenges, which directly impact the organization of the system and the quality of life of patients. Such challenges include the current variability among centers regarding access to transplants, as well as disparities in waiting lists on a national level. In addition, there is pression from the care system due to the lack of generational handover in this specialty and the phenotypic variability of recipients [9].

Similarly, the need for protocols and/or awareness regarding the referral process of patients from non-transplanting centers has been highlighted [9].

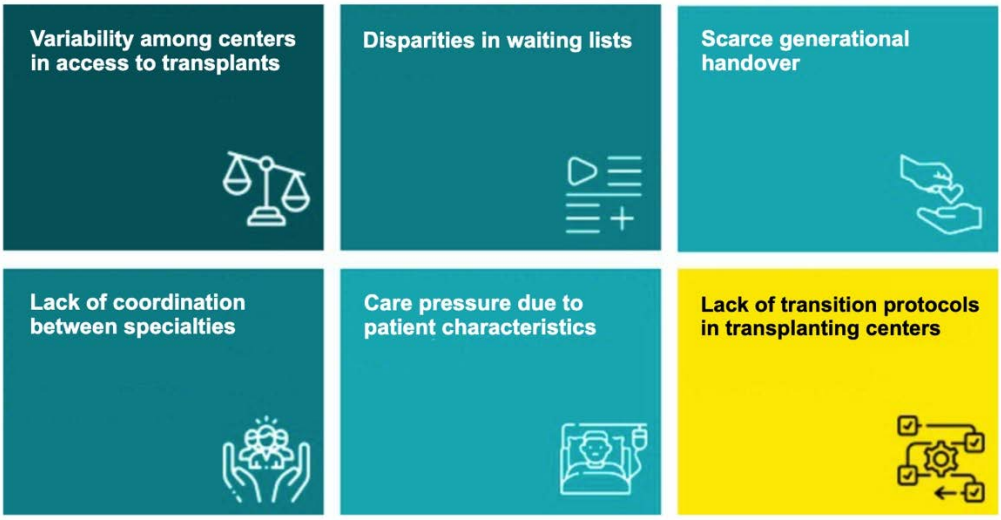

Figure 16 | Challenges in approaching liver transplant [9]

8.2.1 Variability among centers regarding Access to transplants

Availability and access to transplants vary between health centers in Spain. In some autonomous communities, such as Castille, patients struggle due to the distance from the closest transplant centers.

Similarly, there is a lack of territorial equity due to the decision-making power awarded to each region within the same autonomous community.

8.2.2 Disparities in waiting lists

Equity in waiting lists is compromised due to depending on each autonomous communities rather than being organized at a national level.

Only two autonomous communities follow the prioritization protocol established by the National Transplant Organization; as such, there is an unbalance in the number of transplants performed between men and women, as the latter tend to receive more transplants. Although there is a national waiting list for fulminating diseases, variability between autonomous communities hinders timely access to transplantation, which results in preventable deaths.

8.2.3 Scarce generational handdover

The lack of generational handover in the transplant specialty in Spain has largely been attributed to a lack of motivation, funding, and education. According to transplant experts, young people tend to prioritize their leisure time and do not wish to be permanently available to attend to transplant-related emergencies or complications. As a result, there is a shortage of health professionals in the field.

8.2.4 Lack of coordination between specialties

One of the main challenges in the approach to liver transplant is the coordination between the various types of specialists involved in pre-transplant, transplant, and post-transplant stages. Various specialists are involved in the pre-transplant stage, such as endoscopists, radiologists, infectiologists, psychiatrists, psychologists, otolaryngologists, pneumologists, nurses, and social workers. These specialists are involved in evaluation protocols which will decide whether the patient is a suitable candidate for transplantation.

On the other hand, the post-transplant stage involves other types of specialists, such as primary healthcare physicians and social services. The limited awareness from certain medical specialties, as well as interhospital variability of the nursing staff specialization process, significantly affects the quality of life of patients.

8.2.5 Care pressure due to patient characteristics

Recipients of liver transplantation currently present clinical and social characteristics different to those in previous years. Candidate patients tend to be of an advanced age, suffering from MASLD and cardiovascular diseases, and many of them are alone, which further complicates the post-transplant process. However, most transplant units offer the help of psychologists and/or social workers through patient associations.

Such variability in recipient profiles requires a broad knowledge on the part of specialists, which may prolong the required time for recovery.

8.2.6 Lack of transition protocols in transplant centers

La Referral from non-transplanting centers is heterogeneous, due to a lack of training and interest in liver diseases from certain smaller centers, where gastroenterologists tend to focus on intestinal diseases.

The COVID-19 pandemic further disorganized the Spanish health system, creating long waiting lists for diagnostic tests and hindering the adequate monitoring of patients. In addition, certain peripheric centers in some autonomous communities have shown a delay of up to a year in the performance of ultrasound scans, which causes patients to be referred to transplant centers in advanced stages of the disease.

Similarly, patient evaluation is typically delayed for several months due to delays in the results of diagnostic tests, which slows down the entire circuit.

9. National Liver Health Plan

As has been noted throughout the aims and methodology sections, we have established fifteen goals transversal to all six liver pathologies previously described. These goals have been grouped into five strategical areas: research, education, public health, care models, and digitalization. Each area has been divided into three main areas of action, which are prevention, diagnosis, and treatment and monitoring.

Identifying these fifteen strategical goals and their classification in groups and areas of action constitute a solid basis for the cross-cutting management of liver diseases, optimizing their approach at a national level.

Such strategic areas have been selected considering their relevance and contribution to the integral approach to liver disease. Each of these areas plays a specific and complementary role in improving the management of such diseases, and are defined as follows:

- Research: key element in current and future approaches to liver diseases. Research necessarily propels scientific and therapeutic advances, which will improve diagnosis, treatment, and ultimately the quality of life of patients.

- Education: the education and sensibilization of all involved agents in the management of liver disease should be promoted. Providing them with updated information and promoting training in healthcare professionals, patients and the broader community enhances the social and sanitary understanding of these diseases, favoring the development of healthy lifestyle practices.

- Public healthcare: a holistic view of liver diseases should be encouraged from a public healthcare perspective. Social and economic factors greatly impact prevention, early detection, and the treatment of these diseases; as such, policies and actions promoting liver health should be implemented.

- Care models: the current care model in liver disease should be optimized and standardized. In doing so, patients will have access to high-quality and equal medical care, which should always be based on the best practices available. This necessarily implies the establishment of protocols and guidelines which will also improve the coordination among the various types of healthcare professionals involved in the management of these liver diseases.

- Digitalization: key tool in the transformation of the liver disease patient care circuit. The implementation of digital technologies enhances the efficiency of clinical information management, simplifies patient monitoring, and improves the care and communication processes between healthcare professionals.

A detailed analysis through the corresponding descriptive to each line of action has been provided for each of the strategic goals shown in *figure 17*, considering their respective classifications in the selected groups and areas of action. This will help in the development of a thorough and structured guide for the effective implementation of the National Liver Health Plan, ensuring that each strategic goal is adequately approached and that the desired results are obtained.

The descriptive corresponding to each line of action has been structured in various sections, with the aim of giving a thorough and detailed view of each strategic goal. The first section explains the strategic goal itself and justifies its election, providing the reader with a clear context. Next, the possible actions to be carried out are presented, followed by the expected timeframe for their implementation, in order to address the line of action proposed by the expert groups and prioritized by the advisory committee in a more efficient way. Lastly, the liver diseases involved in each strategic goal are specified for a more precise understanding of the scope of the proposed actions.

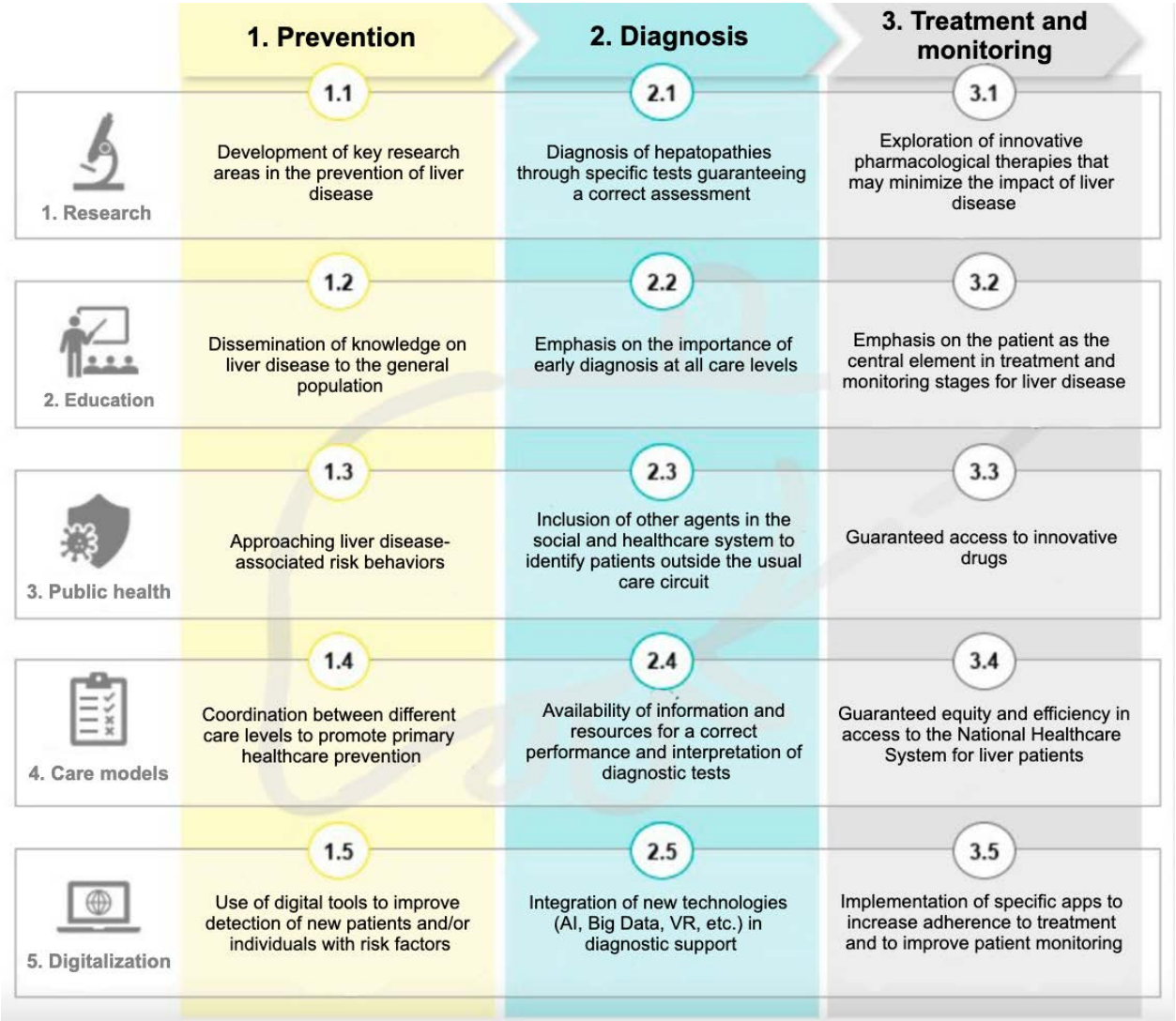

Figure 17 | Conceptualization of the National Liver Health Plan

Contents

1 Prevention *(1/2)*

Research

1.1 Deployment of key research areas for the prevention of liver disease

1.1.1 Promote **research into biomarkers** to further develop precision medicine in liver health	Click to access
1.1.2 Promote research towards the development of **vaccines for liver health**	Click to access
1.1.3 Research the efficacy of **population-level interventions** to reduce liver disease	Click to access
1.1.4 Promote **research projects** oriented towards a better knowledge of liver disease	Click to access

Education

1.2 Dissemination of knowledge of liver disease aimed at the general population

1.2.1 Integrate the promotion of liver health in broader **educational competencies** regarding healthy lifestyle habits	Click to access
1.2.2 **Organize educational campaigns for the general population** in order to raise awareness about prevention measures regarding liver disease	Click to access
1.2.3 Promote educational activities focused on **reducing the stigma surrounding liver disease**	Click to access

Public Health

1.3 Addressing risk behaviors associated with liver disease

1.3.1 Encourage and promote the **healthy food industry**	Click to access
1.3.2 Raise awareness regarding **vaccination against liver disease**	Click to access
1.3.3 Regulate **the marketing and access to herbal products** due to their potential impact on the development of liver disease	Click to access
1.3.4 **Regulate marketing campaigns, advertising, and access** to products containing alcohol	Click to access

1 Prevention *(2/2)*

Care models

1.4 Coordination between the different levels of care to enhance primary prevention

1.4.1 Emphasize the importance of prevention in **alcohol consumption, obesity and metabolic syndrome through primary healthcare** as a preventive measure for liver disease	Click to access
1.4.2 Create **patient care circuits emerging from structures outside the National Healthcare System** (drug addiction centers, etc.)	Click to access
1.4.3 Implementation of **biomarkers indicating risk of liver disease** in primary healthcare and in all other care circuits	Click to access
1.4.4 Guarantee **access to precision medicine** in the prevention of liver disease	Click to access

Digitalization

1.5 Use of digital tools to improve detection strategies in new patients and/or at-risk population

1.5.1 Implementation of **a digital system for the prevention and control of liver disease**, making epidemiologic information available and promoting its study	Click to access

2 Diagnosis *(1/2)*

Research

2.1 Diagnosis of liver diseases through specific tests that guarantee their correct assessment

2.1.1 Promote research into **simple and fast biomarkers which may simplify and facilitate** diagnosis	Click to access
2.1.2 Promote **the creation of cohorts/registers** for research into liver disease	Click to access
2.1.3 Research the use of **advanced diagnostic techniques** (liquid biopsy, medical imaging) for early diagnosis	Click to access

Education

2.2 Assertion of the importance of early diagnosis at all care levels

2.2.1 Creation of **educational campaigns focusing on at-risk population** to raise awareness regarding transmission mechanisms and diagnostic security	Click to access
2.2.2 Development of **training activities for healthcare professionals** to improve the quality and accuracy of liver disease diagnosis	Click to access

Public Health

2.3 Guarantee an accurate liver disease diagnosis at all care levels

2.3.1 **Screen the entire adult population for hepatitis C** at least once in a lifetime	Click to access
2.3.2 Promote **mechanisms for the identification of patients at risk of metabolic and/or alcohol-related liver disease** at all care levels	Click to access
2.3.3 Encourage **the implementation of screening for advanced occult liver disease** using FIB-4	Click to access
2.3.4 Guarantee **screening for liver cancer in all patients** with advanced liver disease	Click to access

2 Diagnosis (2/2)

Care models

2.4 Availability of resources to correctly diagnose liver disease

2.4.1 Development of clinical practice guidelines for the diagnosis of different liver diseases that also specify monitoring and referral criteria for other specialties	Click to access
2.4.2 Establishment of **reference centers to manage complex diagnosis and including rare liver diseases**, thus guaranteeing equitable access	Click to access
2.4.3 Facilitate **one-step, decentralized and comprehensive diagnosis in at-risk patients for viral hepatitis, HIV and/or other sexually transmitted infections**	Click to access
2.4.4 Promote the **identification, diagnosis, and referral of liver disease susceptible of liver transplant** at a nation-wide level	Click to access

Digitalization

2.5 Integration of new technologies (AI, Big Data, VR, etc.) as forms of diagnostic support

2.5.1 **Digitalize and automatize unified diagnostic processes** at a nation-wide level so as to guarantee patient traceability, positively impacting resource efficiency	Click to access
2.5.2 Use of **digitalization to link diagnosis with treatment processes**, guaranteeing treatment for all patients with liver disease	Click to access
2.5.3 Development of **an automatic alert system to guarantee care continuity**	Click to access
2.5.4 Integration of **AI tools** to improve liver disease diagnosis	Click to access

3 Treatment and monitoring *(1/2)*

Research

3.1 Exploration of innovative pharmacological therapies to minimize the impact of liver disease

3.1.1 Encourage **collaboration with national and international research networks**, promoting private-public collaboration and the exchange of knowledge between different care levels	Click to access
3.1.2 **Stimulate research and funding for effective pharmacological therapies**, while also promoting innovative treatments to improve liver disease management	Click to access
3.1.3 **Perform socio-economic studies regarding the burden of certain liver diseases** to seek the appropriate funding from public administrations	Click to access

Education

3.2 Implementation of the perception of the patient as a central element in the treatment and monitoring phases of liver disease

3.2.1 Creation of **communities of patient experts** in liver disease	Click to access
3.2.2 Promote **the recognition of rare liver diseases at a health management level** to ensure equity of access to the healthcare system	Click to access
3.2.3 Development of a comprehensive and multidisciplinary program to train and involve patients in their own **self-care and treatment**	Click to access
3.2.4 Facilitate patient identification of **potential side effects of treatments**	Click to access
3.2.5 Promote **engagement with patient associations** to promote healthy lifestyles and raise awareness of the importance of adherence to treatment through the exchange of information and resources	Click to access

Public Health

3.3 Guarantee of access to innovative treatments

3.3.1 Facilitate **access to innovative drugs** once approved	Click to access
3.3.2 **Guarantee funding for innovative treatments**, thus guaranteeing equitable access to innovation	Click to access
3.3.3 Minimize **evaluation periods at a national and autonomical level** for innovative drugs	Click to access
3.3.4 Assess **the impact on health results** of approved innovative drugs	Click to access

3 Treatment and monitoring *(2/2)*

Care models

3.4 Guarantee of equity and efficiency in access to the National Healthcare System for liver patients

3.4.1 Creation of **multidisciplinary groups for the management of comorbidities** and secondary effects of treatments	Click to access
3.4.2 Promotion of **advanced practical nursing** within hepatology for ambulatory management of patients	Click to access
3.4.3 Development of **a comprehensive, multidisciplinary care approach** for liver patients from early diagnosis to long-term monitoring to ensure efficient care	Click to access
3.4.4 Implementation of **intensified post-liver surgery recovery programs**	Click to access
3.4.5 **Establishment of priorization and donor-receptor coupling models** according to risk variables in order to achieve good organ allocation	Click to access

Digitalization

3.5 Incoporation of specific apps to improve adherence to treatment and patient monitoring

3.5.1 Use of **telemedicine to maintain a doctor-patient relationship** that reinforces adherence to treatment, particularly in the case of long-term treatment	Click to access
3.5.2 Establishment of **a unified and interconnected nation-wide data system** to optimize access to clinical histories of patients referred to other autonomous communities, thus avoiding the unnecessary repetition of tests	Click to access
3.5.3 Development of a **mobile device platform** integrating clinical information for all patients	Click to access

12 lines of action prioritized by the advisory committee

Prevention

1. **Integrate the promotion of liver health in broader educational competencies** regarding healthy lifestyle habits	Click to access Click to access
2. Promote educational activities focused on **reducing the stigma surrounding liver disease**	Click to access
3. **Regulate marketing campaigns, advertising, and access** to products containing alcohol while also promoting healthy lifestyle habits	Click to access Click to access

Diagnosis

4. **Promote research into simple and fast biomarkers** (liquid biopsy, medical imaging, etc.) **which may simplify and facilitate** diagnosis	Click to access Click to access
5. Encourage **the implementation of screening for advanced occult liver disease** using FIB-4	Click to access
6. **Screen the entire adult population for hepatitis C** at least once in a lifetime	Click to access
7. Guarantee **screening for liver cancer in all patients** with advanced liver disease	Click to access
8. Facilitate **one-step, decentralized and comprehensive diagnosis in at-risk patients for viral hepatitis, HIV and/or other sexually transmitted infections**	Click to access

Treatment and monitoring

9. **Guarantee funding for innovative treatments**, thus guaranteeing equitable access to innovation	Click to access Click to access
10. Development of **a comprehensive, multidisciplinary care approach** for liver patients from early diagnosis to long-term monitoring to ensure efficient care	Click to access Click to access
11. **Establishment of priorization and donor-receptor coupling models** according to risk variables in order to achieve good organ allocation	Click to access
12. Establishment of **a unified and interconnected nation-wide data system** to optimize access to clinical histories of patients referred to other autonomous communities, thus avoiding the unnecessary repetition of tests	Click to access

Introduction to all involved agents in the development and execution of the National Liver Health Plan: 2032 Challenge

Agent	Definition
Scientific society	▸ **Institutions specialized in research, training and medical assistance** related to liver pathology, promoting scientific dissemination and health campaigns
Private industry	▸ **Non-governmental organizations** which seek to generate economic benefit through the production and sale of goods or services
Ministry/ Department/ Government	▸ **Governmental entities** responsible for the administration and regulation of public affairs, policies and services in a nation or territory
Research centers	▸ **Centers focused on academic and scientific advancement in different areas of knowledge**, particularly in liver pathologies, through research and experimentation
Hospital care	▸ **Medical services and specialized care** provided to inpatients for diagnosis, treatment and recovery from illness or injury
Primary healthcare	▸ **Initial level of contact with the health system**, providing comprehensive, preventive and curative care
Patients/general society	▸ Patients are a set of **individuals who receive medical care**. On the other hand, general society refers to those **healthy individuals who benefit from healthcare services**

1.1 Deployment of key research areas for the prevention of liver disease

Execution: 2025 - 2032

Line of action 1.1.1

Promote research into biomarkers to further develop precision medicine in liver health

Justification

Enables early detection, the identification of at-risk groups, a thorough customization of preventive interventions and response monitoring, thus optimizing prevention and reducing the burden of liver disease

	Specific actions	Leadership[1]
1	**Establishment of research programs** focused on the identification and validation of specific biomarkers for liver disease. This includes the allocation of the necessary financial and human resources, as well as collaboration with academic and scientific institutions	SS HC RC
2	**Promote the collection of biological samples**, such as blood and liver tissue, from patients with liver disease, as well as from healthy individuals. This is necessarily done in collaboration with hospitals, clinics and biobanks to collect and store samples.	SS HC RC
3	**Performance of validation studies** to assess the efficacy and accuracy of the identified biomarkers through the analysis of collected samples and their comparison with clinical data from patients with liver disease as well as healthy individuals	SS HC RC
4	**Promote interdisciplinary collaboration** between researchers, clinicians, data scientists, and other healthcare professionals to share knowledge and resources in the field of liver biomarkers	SS HC RC
5	**Establishment of biomarker registries:** databases and registries of liver biomarkers will be created and made available for the scientific community, so as to compile and share research findings. In order to promote transparency, access to information and knowledge will be made available to the entire scientific community, which may in turn facilitate the development of precision medicine in liver health	SS HC PI RC
6	**Encourage training:** sensitize the medical community to the importance of biomarkers in the prevention of liver diseases through conferences, seminars, and educational campaigns to disseminate updated information and promote participation in research studies	SS HC RC

Diseases it applies to

- Viral hepatitis
- Liver cancer
- MASLD
- Rare liver diseases
- Alcohol-related liver disease

Impact

- **Prevention and management of complications:** biomarkers allow early detection of biological changes that indicate progression to liver complications. This facilitates timely intervention before complications become irreversible or difficult to manage

Key

1. Leadership is used here to define the agents in charge of performing each action

Private industry (PI) · Hospital care (HC) · Research centers (RC) · Scientific societies (SS)

1.1 Deployment of key research areas for the prevention of liver disease

Execution: 2025 - 2032

Line of action 1.1.2

Promote research towards the development of vaccines for liver health

Justification

Vaccines are the safest and most effective way to protect individuals and society at large from contracting preventable diseases

	Specific actions	Leadership[1]
1	**Analyze collaborations between institutions and experts:** fostering collaborations with research centers, universities, the pharmaceutical industry and experts in hepatology is key to boosting vaccine development	PI, SS, RC
2	**Establish research networks:** enhance collaboration among researchers by creating research networks to facilitate the exchange of knowledge, resources and data, while also promoting cooperation in vaccine trials	PI, SS, RC
3	**Stimulate basic and applied research:** basic research is key to understanding the mechanisms of liver diseases. On the other hand, applied research seeks to translate this knowledge into effective vaccines	PI, HC, RC
4	**Support clinical trials**, which are crucial for the development of vaccines. It is therefore necessary to support and facilitate the performance of such trials in patients diagnosed with liver disease so as to develop vaccines for the prevention of such diseases	PI, HC, RC
5	**Promote the dissemination and exchange of knowledge:** it is essential to promote the dissemination and exchange of scientific knowledge and discoveries in liver diseases. This may be achieved through conferences, symposia and scientific publications	PI, HC, PH

Disease it applies to	Impact
Viral hepatitis	▶ **Reducing drug costs**, as only pre-vaccine cases will require treatment ▶ **Exponential decrease** in the number of patients diagnosed with viral hepatitis ▶ Decrease **the long-term burden** of the disease

Key

1. Leadership is used here to define the agents in charge of performing each action

Private industry (PI) · Hospital care (HC) · Research centers (RC) · Primary healthcare (PH) · Scientific societies (SS)

1.1 Deployment of key research areas for the prevention of liver disease

Execution: 2026 - 2032

Line of action 1.1.3

Research the efficacy of population-level interventions to reduce liver disease

Justification

Researching interventions to reduce addictive disorders in liver health is critical to address a significant public health issue, while also creating benefits for society at large and improving liver health outcomes

	Specific actions	Leadership[1]
1	**Collect epidemiological data and review existing literature:** all information on addictive disorders associated with liver health should be reviewed in order to acquire a holistic view of the current situation; this, in turn, will enable medical professionals and researchers alike to improve or support other already taken lines of actions. This will also provide a solid base of prior knowledge and help in the identification of gaps within current research	PI, SS, RC
2	**Conduct cohort studies:** cohort studies follow a group of individuals over a long period of time and evaluate the efficacy of specific interventions in reducing the prevalence of addictive disorders such as binge drinking and its correlation with the development of liver disease. These studies can provide strong evidence on the long-term outcomes of interventions and facilitate the analysis of different risk and protective factors	PI, HC, RC
3	**Encourage randomized clinical trials:** randomized studies facilitate the evaluation of the efficacy of specific interventions in the target population, as well as the development of liver disease due to addictive disorders, thus allowing direct comparison between different approaches	PI, HC, RC
4	**Evaluate existing programs:** it is important to promote the dissemination and exchange of scientific knowledge and discoveries in liver diseases, which can be achieved through conferences, symposia, scientific publications, among other means	PI, SS
5	**Analyze the costs and benefits of carrying out specific interventions:** it is useful to analyze the economic impact of carrying out specific interventions and thus assess whether they are cost-effective, which may help inform public policy decisions and resource allocation	MDG
6	**Establish multidisciplinary collaborations** with experts in different disciplines to obtain a comprehensive view of addictive behaviors and liver diseases	HC, PH

Disease it applies to	Impact
Alcohol-related liver disease	▶ The implementation of specific interventions will have a direct impact on the improvement of **early diagnosis** as opposed to **diagnosis in advanced stages**, during which the patient faces a far more serious condition ▶ To **reduce the costs of this disease**, as the goal is for the at-risk individual to never enter the healthcare circuit through sufficient prevention and control of their alcohol-addictive behaviors

Key

1. Leadership is used here to define the agents in charge of performing each action

Private industry (PI) · Ministry/Department/ Government (MDG) · Primary healthcare (PH) · Hospital care (HC) · Research centers (RC) · Scientific societies (SS)

1.1 Deployment of key research areas for the prevention of liver disease

Execution: 2026 - 2032

Line of action 1.1.4

Promote research projects oriented towards a better knowledge of liver disease

Justification

Liver diseases are often unknown by the scientific society and society in general; as such, it is crucial to encourage research projects on this clinical area

	Specific actions	Leadership[1]
1	**Establish collaborations with academic and medical institutions:** fostering collaborations with academic and medical institutions, universities, hospitals, and research centers will promote collaboration among experts in the field of hepatology	PI, SS, RC
2	**Seek funding for research projects** and demand the existance of funding programs to support research in liver diseases	PH, SS, HC
3	**Propose a call for research proposals:** organize an open call for researchers and health professionals to submit proposals for projects related to liver diseases, defining and sharing eligibility criteria and priority research areas	PI, HC, SS, PH
4	**Identify areas for improvement in the field of hepatology** through an exhaustive analysis of the existing scientific literature to identify those areas that are most limited in research in relation to liver diseases. This identification will help to prioritize research in these areas of improvement	PH, SS, HC
5	**Encourage translational research:** translational research integrates laboratory findings and clinical research to better understand the mechanisms of liver disease and improve prevention, diagnosis and treatment strategies, while also stimulating collaboration between basic scientists and clinicians to jointly address this issue	PI, SS, RC
6	**Evaluate results and disseminate knowledge** by publishing scientific articles, organizing hepatology conferences and participating in scientific events to share results with the scientific community and healthcare professionals	PH, SS, HC

Diseases it applies to

- Viral hepatitis
- Liver cancer
- MASLD
- Rare liver diseases
- Alcohol-related liver disease

Impact

- Increasing the knowledge of the scientific society and health professionals about liver diseases and thus **avoiding misdiagnosis** in other diseases

Key

1. Leadership is used here to define the agents in charge of performing each action

Private industry (PI) · Hospital care (HC) · Research centers (RC) · Primary healthcare (PH) · Scientific societies (SS)

1.2 Dissemination of knowledge of liver diseases aimed at the general population

Execution: 2024 - 2032

Line of action 1.2.1

Integrate the promotion of liver health in broader educational competencies regarding healthy lifestyle habits

Justification

This action seeks to promote the integral development of primary and secondary education students, empowering them to make informed decisions regarding their health and encouraging the adoption of healthy lifestyle habits from an early age

	Specific actions	Leadership[1]
1	**Align action with current curricular standards:** examine the curricular standards and educational guidelines in force in each autonomous community with the purpose of ensuring that the subject is in line with the established educational requirements and objectives	SS, MDG
2	**Establish contact with regional education departments:** due to their regional competence, the promotion of liver health at an educational level requires an adaptation to local circumstances and institutional support to integrate a new subject into the educational program	SS, MDG
3	**Adapt to current curricula** to include key topics and concepts to be addressed throughout the school year, as well as appropriate assessment methods to measure student progress and their understanding of the importance of healthy lifestyle habits and physical activity	MDG
4	**Development of educational and interactive materials** to facilitate student learning through clear and understandable language	SS, MDG
5	**Define teaching methods** and pedagogical approaches used to teach healthy lifestyle habits, such as theoretical lessons with hands-on activities, group discussions, interactive games, etc.	MDG
6	**Provide teacher training on the subject**, providing them with tools and strategies to transmit concepts in an understandable and interactive way	MDG
7	**Encourage parental involvement** through meetings, educational sessions, and events in which parents can be actively involved and acquire knowledge alongsidetheir children in order to promote healthy lifestyle habits	SS, MDG, P/GS

Disease it applies to	Impact
MASLD	▶ **Lifestyle changes** in students and their families ▶ Decrease in **associated risk factors** ▶ **Empowerment of students** to take informed decisions regarding their health

Key

1. Leadership is used here to define the agents in charge of performing each action

Private industry (PI) | Patients/general society (P/GS) | Scientific societies (SS)

1.2 Dissemination of knowledge of liver diseases aimed at the general population

Execution: 2024 - 2032

Line of action 1.2.2

Organize educational campaigns for the general population in order to raise awareness about prevention measures regarding liver disease

Justification

To raise awareness of the importance of prevention, encourage the adoption of healthy lifestyles, and provide information and tools to reduce the risk of liver disease

	Specific actions	Leadership[1]
1	**Research and collect detailed information** about liver risks related to the use of herbal products, as well as the importance of adopting healthy lifestyle habits, using condoms, reducing alcohol consumption, etc.	SS, RC
2	**Develop educational materials** such as informational brochures and videos to effectively disseminate information about liver risks and the preventive measures mentioned above	SS, HC
3	**Disseminate information:** implement outreach strategies such as social media campaigns, collaborations with health organizations and local communities to reach and raise awareness among a wider audience	SS, PI
4	**Collaboration with healthcare professionals:** establish partnerships with physicians and other health professionals such as nutritionists and psychologists (among others) to provide informative talks and ensure accurate dissemination of information	SS, HC
5	**Conduct periodic evaluations** to measure the impact of educational campaigns and collect data on the level of knowledge, changes in population behavior and adoption of new preventive measures, ensuring the effectiveness of awareness-raising initiatives	SS, HC

Disease it applies to	Impact
Viral hepatitis	▶ **Prevention of transmission** by raising awareness of the routes of transmission and the importance of taking precautions ▶ **Stigma reduction** by educating the general population ▶ Increase in **vaccination coverage** for the general population
Alcohol-related liver disease	▶ **Prevalence decrease** by raising awareness of the risks associated with excessive alcohol consumption ▶ **Improvement of access to resources and support** by offering information on the available services for treatment and rehabilitation regarding alcohol addiction
Rare liver diseases	▶ **Promotion of research** and support for scientific research in this field ▶ **Detection of unidentified cases** due to information on symptoms and risk factors

Key

1. Leadership is used here to define the agents in charge of performing each action

Private industry (PI) · Hospital care (HC) · Research centers (RC) · Scientific societies (SS)

1.2 Dissemination of knowledge of liver diseases aimed at the general population

Execution: 2024 - 2032

Line of action 1.2.3

Promote educational activities focused on reducing the stigma surrounding liver disease

Justification

To raise social awareness, understanding and empathy, providing support to affected individuals and promoting their inclusion and full participation in society

	Specific actions	Leadership[1]
1	**Conduct comprehensive research to understand the extent of stigma** associated with liver disease, identifying underlying factors and misperceptions and collecting accurate data on the education and awareness needs of the target population through interviews and surveys	SS, HC
2	**Promote information and education:** facilitate access to accurate and up-to-date information on liver diseases, their causes, symptoms, treatments and care. Provide educational resources, such as brochures, teaching materials, and seminars for health professionals, patients and society in general	SS, HC, PH
3	**Development of awareness campaigns:** design and implement awareness and education campaigns aimed at the general population, with the objective of promoting knowledge and understanding of liver diseases, demystifying misconceptions and combating stigma	SS, HC
4	**Collaboration with relevant institutions and organizations:** such as health institutions and other key players in the field of liver diseases, working together to develop awareness campaigns to help reduce stigma and promote greater understanding of these diseases	SS, HC, PI
5	**Encourage patient and support group participation:** establish meeting and support spaces for people affected by liver diseases, where they can share experiences, receive guidance and find emotional support	SS, P/GS

Diseases it applies to

- Viral hepatitis
- MASLD
- Alcohol-related liver disease

Impact

- **Demystification and education:** educational actions can help to demystify the misconceptions and stigmatizing beliefs related to these pathologies
- **Promotion of empathy and inclusion:** raising awareness of these diseases and highlighting the importance of support and solidarity towards those affected fosters an environment of empathy and understanding, which in turn may counteract stigma and promote their inclusion in society

Key

1. Leadership is used here to define the agents in charge of performing each action

Private industry (PI) · Patients/general society (P/GS) · Hospital care (HC) · Primary healthcare (PH) · Scientific societies (SS)

1.3 Addressing risk behaviors associated with liver disease

Execution: 2024 - 2032

Line of action 1.3.1

Encourage and promote the healthy food industry

Justification

In order to increase the availability, accessibility and variety of nutritious food options, thus promoting healthy and balanced eating habits

	Specific actions	Leadership[1]
1	**Analyze fiscal policies and regulations** to promote the production, marketing and consumption of healthy foods. Among these measures to be developed are the implementation of clear and understandable labeling, tax incentives to reduce taxes on basic healthy foods, restrictions on the advertisement of unhealthy foods, etc.	SS, MDG
2	**Emphasize the need for investments and subsidies:** facilitate access to financing for entrepreneurs and companies engaged in the production of healthy foods through actions such as the establishment of subsidy programs or preferential credits, the creation of specific investment funds, etc.	SS, MDG, PI
3	**Establish alliances with supermarket chains** to increase the availability of healthy foods by defining a healthy and affordable shopping basket	SS, PI
4	**Collaborate with the tourism and gastronomic sectors:** introduce healthy menu options in restaurants, hotels and touristic areas by offering incentives for those establishments offering healthy options, as well as promoting chefs and restaurants specialized in healthy eating, etc.	SS, MDG, PI
5	**Promote consumer awareness and education programs:** implement nutrition education programs in schools and workplaces to raise awareness among the general population of the importance of a healthy and balanced diet	SS, MDG

Disease it applies to	Impact
MASLD	► Increased **demand for organic and sustainable products** ► **Decrease in ultra-processed food consumption** through tax incentives on healthy products (vegetables, fish, etc.) ► **Prevention of obesity and metabolic diseases** within the general population, from children to adults

Key

1. Leadership is used here to define the agents in charge of performing each action

Private industry (PI) · Ministry/Department/ Government (MDG) · Scientific societies (SS)

1.3 Addressing risk behaviors associated with liver disease

Execution: 2026 - 2032

Line of action 1.3.2

Raise awareness regarding vaccination against viral hepatitis

Justification

Vaccination is essential in order to address the epidemiology of liver diseases, particularly hepatitis B and C, based on comprehensive strategies that include prevention measures, through education of the general population

	Specific actions	Leadership[1]
1	**Collect and analyze information on liver diseases and their management**, systematizing all collected data in order to identify existing needs and gaps	SS, RC
2	**Establish partnerships with laboratories and health services to promote viral hepatitis screening days** focused on risk groups, such as people with a history of intravenous drug use, individuals who have been exposed to blood or body fluids of an infected person, etc.	SS, PH, RC
3	**Develop awareness and education campaigns** to reduce the stigma associated with viral hepatitis and promote the importance of hepatitis B vaccination, highlighting the benefits of immunization and recommended dosing schedules	SS, HC
4	**Collaboration with health authorities and vaccination** services to promote vaccination against hepatitis B among vulnerable groups, while also carrying out actions aimed at anti-vaccination groups in order to encourage their active participation in the vaccination schedule	SS, PH, PI
5	**Promote access to appropriate care:** provide support and counseling to patients with viral hepatitis, facilitating guidance on healthy lifestyles and the importance of following strategies to prevent transmission to others	SS, HC
6	**Develop surveillance and monitoring systems** to detect and record cases of hepatitis B and C, as well as transmission trends and general characteristics of risk groups	SS, HC

Disease it applies to	Impact
Viral hepatitis	► **Promotion of early detection of viral hepatitis** and monitoring of affected individuals to ensure comprehensive and continuous care ► **Contribution to the global goal of reducing the prevalence of viral hepatitis** as a public health problem by controlling transmission and improving the quality of life of those affected ► **Reducing the stigma** associated with this pathology through campaigns to raise awareness and educate the general population

Key

1. Leadership is used here to define the agents in charge of performing each action

Private industry (PI) · Hospital care (HC) · Research centers (RC) · Primary healthcare (PH) · Scientific societies (SS)

1.3 Addressing risk behaviors associated with liver disease

Execution: 2024 - 2032

Line of action 1.3.3

Regulate the marketing of and access to herbal products due to their potential impact on the development of liver diseases

Justification

Aiming to provide consumers with the ability to make informed decisions about the use of these products and understand their potential effects on liver health, while also promoting awareness of the importance of seeking advice from health professionals before using such products, especially for those with pre-existing liver conditions

	Specific actions	Leadership[1]
1	**Research and promote the exchange of information** on the adverse effects of herbal products with the objective of supporting the implementation of actions based on scientific evidence	SS, RC
2	**Promote the establishment of rules and regulations** to control the marketing and advertising of products that negatively affect liver health	SS, MDG
3	**Encourage collaboration with health authorities, regulatory agencies, and private sector entities** to promote responsible practices in the marketing, sale and consumption of such products	SS, MDG, PI
4	**Encourage the strengthening of supervision and control mechanisms** to guarantee compliance with established regulations through periodic inspections and effective sanctions in case of non-compliance, in order to ensure the protection of general liver health	MDG
5	**Develop training and education programs aimed at health professionals** to equip them with adequate guidance on the hepatic risks associated with the consumption of herbal products, promoting prevention measures and early detection of hepatic diseases	SS, HC

Disease it applies to	Impact
Rare liver diseases	► **Improvements in quality of life** through the avoidance of products that may worsen the condition and **encouraging a responsible and safe use of herbal products**

Key

1. Leadership is used here to define the agents in charge of performing each action

Private industry (PI) · Ministry/Department/ Government (MDG) · Hospital care (HC) · Research centers (RC) · Scientific societies (SS)

1.3 Addressing risk behaviors associated with liver disease

Execution: 2025 - 2032

Line of action 1.3.4

Regulate marketing campaigns, advertising, and access to products containing alcohol

Justification

This line of action focuses on protecting particularly vulnerable social groups, such as minors, who are more susceptible to the negative effects of alcohol on their physical, mental and social development, as well as mitigating the impact on public health and the economic burden it entails

	Specific actions	Leadership[1]
1	**Conduct comprehensive** research on alcohol consumption and its consequences in society, including demographics, drinking patterns, risk factors, and health outcomes. These studies will provide a solid base of information to support the development of effective actions	SS, RC
2	**Restrict alcohol advertising:** regulate alcohol advertising to reduce its impact on promoting excessive consumption. This includes limiting advertisemeny to minors, restricting the placement of ads near schools and sensitive areas, and establishing clear guidelines on the content and format of advertising campaigns	SS, MDG, PI
3	**Raise awareness and promote public education:** implement awareness and education campaigns aimed at the general population about the risks associated with alcohol consumption and the benefits of responsible drinking. These campaigns can include information on the short- and long-term effects of alcohol, tips for reducing heavy drinking, and support resources for those who need help	SS, HC
4	**Establish intersectoral partnerships:** collaborate with different sectors, such as health, education, and industry, in order to develop comprehensive alcohol prevention and control strategies. These partnerships will strengthen the coordinated and multifaceted public health response	SS, HC, PI
5	**Enhance training for healthcare professionals:** provide specialized training to doctors, nurses and other healthcare professionals on how to address alcohol use, early detection of related problems and appropriate referral to treatment and rehabilitation services	SS, PH

Disease it applies to	Impact
Alcohol-related liver disease	▶ **Reduction of incidence:** by regulating the marketing of and access to alcohol, cases of this pathology can be prevented ▶ **Protection of vulnerable groups:** vulnerable social groups, such as young people and individuals suffering from alcohol use disorders, can be protected through this action, as restricting access and advertising can help prevent the early onset of alcohol consumption and reduce the risk of associated health problems

Key

1. Leadership is used here to define the agents in charge of performing each action

Private industry (PI) · Ministry/Department/ Government (MDG) · Primary healthcare (PH) · Hospital care (HC) · Research centers (RC) · Scientific societies (SS)

1.4 Coordination between the different levels of care to enhance primary prevention

Execution: 2025 - 2032

Line of action 1.4.1

Emphasize the importance of prevention in alcohol consumption, obesity and metabolic syndrome through primary healthcare as a preventive measure for liver disease

Justification

Given that alcoholism, obesity and metabolic syndrome, among others, are the most frequent comorbidities that lead to the development of fatty liver disease, primary care should coordinate prevention measures with other levels of care

	Specific actions	Leadership[1]
1	**Analyze the current situation of alcoholism, obesity and metabolic syndrome in Spain:** it is essential for the various agents involved to have a high level of knowledge of the current situation	SS, RC
2	**Assess risk:** an assessment of obesity risk can be carried out through primary healthcare by measuring weight, body mass index (BMI), blood pressure, waist circumference, alcohol consumption, blood glucose levels and lipid profile, thus facilitating early intervention in at-risk patients	PH
3	**Counseling and support:** consultation with primary healthcare professionals is typically the first form of contact that individuals have with the healthcare system, which means that they must provide comprehensive and personalized counseling on the importance of following healthy lifestyle habits (e.g., maintaining an adequate weight, being physically active, following a balanced diet, and reducing or stopping alcohol consumption). In addition, it is essential for primary healthcare physicians to offer emotional support to help patients make the appropriate lifestyle changes	SS, PH
4	**Refer to specialist if necessary:** in cases of excessive alcoholism, severe obesity or advanced metabolic syndrome, referral to specialists such as endocrinologists, nutritionists or psychologists specialized in eating disorders may be considered. These professionals can offer a multidisciplinary approach to the treatment and monitoring of patients	PH, HC
5	**Consolidate partnerships with local sports centers, associations and organizations** to provide accessible and affordable options for the general public to stay active and also encourage self-care and a supportive environment for patients	SS, PH

Disease it applies to	Impact
MASLD	► Prevention and control of obesity and metabolic syndrome has **a significant impact on reducing the likelihood of developing metabolic liver disease** (MASLD) while also contributing to decreasing the risk of primary liver cancer and/or liver cirrhosis
Alcohol-related liver disease	► Awareness and prevention of excessive or prolonged alcohol consumption helps in avoiding and/or reducing liver damage, which can range from hepatic steatosis to cirrhosis

Key

1. Leadership is used here to define the agents in charge of performing each action

Hospital care (HC) · Primary healthcare (PH) · Research centers (RC) · Scientific societies (SS)

1.4 Coordination between the different levels of care to enhance primary prevention

Execution: 2026 - 2032

Line of action 1.4.2

Create patient care circuits emerging from structures outside the National Healthcare System (drug addiction centers, STD centers, etc.)

Justification

There is a group of patients with liver diseases who remain unidentified by the National Healthcare System, typically because they are in drug addiction or other forms of social care centers; it is therefore necessary to unify all levels of care to provide comprehensive care to these patients.

	Specific actions	Leadership[1]
1	**Establish collaboration agreements:** identify centers outside the SNS that care for patients with drug addiction or STD problems and establish collaboration agreements with them. These agreements should define the roles and responsibilities of each party, as well as the procedures for patient referral and coordination	SS, HC
2	**Design referral protocols** from outpatient centers to the SNS. These protocols should establish the referral criteria, the steps to be followed and the documentation required to ensure a smooth transition and adequate continuity of care for patients with drug addition or STD problems, as well as establishing agreements with the previously mentioned centers	SS, HC, PH
3	**Coordination of care:** establish effective channels of communication and coordination between professionals at external facilities and the healthcare services of the national system. This may include regular consultations and meetings, exchanges of relevant information and the establishment of contact points to address queries or issues	SS, HC, PH
4	**Education and training:** provide education and training to outpatient facility professionals on SNS procedures and standards of care to ensure a common understanding of protocols and facilitate collaboration in patient care	SS, HC, PH
5	**Data integration:** implement systems or tools that enable data integration between external facilities and the SNS. This may include the use of shared electronic records or the secure exchange of relevant information to ensure a complete and up-to-date view of patient care	PI, HC, PH
6	**Establish joint monitoring and care circuits:** this involves establishing periodic or joint consultations to review patient progress, as well as evaluating the effectiveness of each treatment and making adjustments if necessary	HC, PH

Disease it applies to

Viral hepatitis

Alcohol-related liver disease

Impact

- Care circuits guarantee **the continuity of medical care** for patients suffering from STDs, addictive behaviors to substances such as alcohol and/or drugs
- In addition, they **optimize resources and offer access to specialized services** resulting in improved patient prognosis

Key

1. Leadership is used here to define the agents in charge of performing each action

Private industry (PI) · Patients/general society (P/GS) · Hospital care (HC) · Primary healthcare (PH) · Scientific societies (SS)

1.4 Coordination between the different levels of care to enhance primary prevention

Execution: 2026 - 2032

Line of action 1.4.3

Implementation of biomarkers indicating risk of liver disease in primary healthcare and in all other care circuits

Justification

An accurate diagnosis provides the opportunity to initiate earlier preventive and treatment interventions, thereby improving health outcomes and reducing the progression of liver disease

	Specific actions	Leadership[1]
1	**Raise awareness and train medical personnel:** primary care physicians and other health professionals in care circuits need to be trained on the importance of biomarkers of liver disease risk and how to use them effectively. This may include workshops, lectures and educational materials	SS, HC
2	**Development of up-to-date clinical guidelines** including recommendations on the use of specific biomarkers for the detection and monitoring of liver disease. These guidelines can help physicians make informed decisions and are essential in the standardization of care	SS, HC, PH
3	**Provide access to biomarker testing:** it is essential to ensure that biomarker tests are readily available and accessible in primary healthcare settings and other care circuits. This may require collaboration with clinical laboratories and diagnostic service providers to ensure the availability and quality of tests	RC, HC, PH
4	**Integrate health information systems:** it is advisable to integrate such data into health information systems used in care circuits. This will make patient monitoring more effective and improve coordination between the various healthcare providers involved	RC, HC, PH
5	**Promote early detection:** strategies to promote early detection of liver disease should be developed, including awareness campaigns targeting the general population and specific risk groups. This can help identify those at risk and encourage biomarker testing within the primary healthcare setting	HC, PH

Diseases it applies to

- Viral hepatitis
- Liver cancer
- MASLD
- Rare liver disease
- Alcohol-related liver disease

Impact

- The implementation of risk biomarkers facilitates early detection of liver disease in the general population and in specific at-risk groups
- In addition, prevention improves individual survival prognosis

Key

1. Leadership is used here to define the agents in charge of performing each action

Hospital care (HC) · Primary healthcare (PH) · Research centers (RC) · Scientific societies (SS)

1.4 Coordination between the different levels of care to enhance primary prevention

Execution: 2026 - 2032

Line of action 1.4.4

Guarantee access to precision medicine in the prevention of liver disease

Justification

Most liver diseases are asymptomatic, which hinders their prevention and therefore their diagnosis and treatment; as such, precision medicine is key to their early detection

	Specific actions	Leadership[1]
1	**Establish collaborations:** foster collaborations between healthcare institutions, healthcare providers, researchers, and technology companies to develop and make available precision medicine platforms specific to liver disease prevention. These collaborations can facilitate access to advanced technology and thus promote joint research and development	PI, SS, RC
2	**Raise awareness and educate** by informing the general public about the benefits and potential of these platforms to identify risk factors and prevent liver disease	SS, HC, PH
3	**Develop screening tools and algorithms:** it is essential to invest in the development of specific tools and algorithms for early detection and monitoring of liver disease. These tools may include genetic analysis, specific biomarkers and predictive models to identify individual risk of liver disease and provide personalized prevention recommendations	PI, HC, RC
4	**Guarantee equitable access:** it is essential that these precision medicine platforms are available and accessible to all groups and regardless of their geographic location. This requires further investment in technological infrastructure and specific training for health professionals to use and interpret information from these platforms	MDG, SS, HC
5	**Integrate the platform into primary healthcare** and promote its use as part of screening exams and regular medical consultations, which facilitates an early detection of risk factors and liver diseases, as well as timely intervention to prevent their progression	PH, HC, RC
6	**Support research and scientific evidence** to evaluate the efficacy and usefulness of precision medicine platforms in the prevention of liver disease, creating solid evidence on the efficacy of these tools and supporting their integration into clinical practice	PI, HC, RC

Diseases it applies to

- Viral hepatitis
- Liver cancer
- MASLD
- Rare liver diseases
- Alcohol-related liver disease

Impact

- Precision medicine has brought about **a paradigm shift and a new reality within the healthcare system**, as it offers a more effective preventive, diagnostic and therapeutic approach to each patient

Key

1. Leadership is used here to define the agents in charge of performing each action

Private industry (PI) · Ministry/Department/ Government (MDG) · Primary healthcare (PH) · Hospital care (HC) · Research centers (RC) · Scientific societies (SS)

1.5 Use of digital tools to improve the detection of new patients and/or at-risk population

Execution: 2027 - 2032

Line of action 1.5.1

Implementation of a digital system for the prevention and control of liver disease, making epidemiologic information available and promoting its study

Justification

Collecting updated and accurate epidemiological data on liver diseases will facilitate the early identification of outbreaks, trends and risk factors, disseminating relevant information on these pathologies in a quick and efficient manner

	Specific actions	Leadership[1]
1	**Assess existing needs in terms of data collection:** epidemiological data collection, outbreak monitoring, identification of risk factors, and dissemination of relevant information on liver diseases	SS, RC
2	**Development of a digital system:** design and develop a robust and secure digital system that will allow the collection, storage and analysis of epidemiological data related to liver diseases	SS, PI, RC
3	**Implement such digital system** in hospitals and healthcare centers responsible for the prevention and control of liver diseases, providing training to healthcare professionals and personnel in charge of using the system to ensure its correct use	PH, PI, HC
4	**Promote the integration of data sources** from various sources, such as laboratories, healthcare centers and other health information systems in order to have a complete and updated view of the epidemiological situation regarding liver diseases	SS, PI, RC, PH, HC
5	**Disseminate information:** establish efficient communication channels to disseminate relevant information on liver diseases to healthcare professionals, health authorities and the general population, using digital systems as a tool to share epidemiological reports, prevention guides, awareness campaigns and other educational resources	SS, PI, PH, HC

Diseases it applies to	Impact
Viral hepatitis	► **Increased knowledge and understanding**: the collection and dissemination of accurate epidemiological information will provide a clearer and more holistic view on the prevalence, risk factors, and trends of viral liver diseases, helping healthcare professionals
MASLD	► **Exponential reduction of the incidence** of patients who may develop MASLD, since early identification of obesity and metabolic syndrome is key to the development of this disease
Alcohol-related liver disease	► **Increase in awareness of the different patterns of alcohol consumption** that any individual and/or patient may have ► Significant decrease in **medical and socio-economic costs**

Key

1. Leadership is used here to define the agents in charge of performing each action

Private industry (PI) · Primary healthcare (PH) · Hospital care (HC) · Research centers (RC) · Scientific societies (SS)

2.1 Diagnosis of liver diseases through specific tests that guarantee their correct assessment

Line of action 2.1.1

Execution: 2024 - 2032

Promote research into simple and fast biomarkers which may simplify and facilitate diagnosis

Justification

Early identification of signs or indications of liver diseases allows a faster and more timely diagnosis. This will lead to reduce the progression of the pathology, improve clinical outcomes and reduce the burden on both patients and the healthcare system.

	Specific actions	Leadership[1]
1	**Establish research programs** focused on the identification and validation of simple and rapid biomarkers for liver diseases	SS, RC
2	**Foster collaborations and strategic alliances** with health agencies, academic institutions, the pharmaceutical industry, and patient associations, so as to promote joint research and clinical application of the liver biomarkers developed	SS, HC, RC, PI, P/GS
3	**Promote the creation of sample banks and databases** to collect and share information on liver biomarkers in order to advance scientific knowledge and facilitate the development of more efficient diagnosis	SS, PI, HC
4	**Promote the participation of researchers and scientists** in conferences and working groups specialized in liver disease so as to share knowledge, exchange ideas and establish collaborations in biomarker research	SS, RC
5	**Promote the dissemination and publication of results** of research in liver biomarkers, so as to share scientific advances and facilitate their evaluation by the scientific and medical community	SS, RC
6	**Support the dissemination of knowledge and technologies** from liver biomarker research to clinical practice through collaboration with health authorities and the updating of clinical guidelines, so as to ensure their integration and their effective use in the diagnosis of liver diseases	SS, PH, HC

Diseases it applies to	Impact
Viral hepatitis	► **Prevents transmission** through the identification of asymptomatic cases and providing adequate care
MASLD	► **Improvement in the understanding of its nature**, leading to early identification and diagnosis
Alcohol-related liver disease	► **Facilitates the identification of at-risk individuals,** allowing for preventive interventions and early treatment to take place
Liver cancer	► **Facilitates early detection**, which increases survival rates and patient prognosis

Key

1. Leadership is used here to define the agents in charge of performing each action

Private industry (PI) · Ministry/Department/ Government (MDG) · Primary healthcare (PH) · Hospital care (HC) · Research centers (RC) · Scientific societies (SS)

2.1 Diagnosis of liver diseases through specific tests that guarantee their correct assessment

Execution: 2025 - 2028

Line of action 2.1.2

Promote the creation of cohorts/registers for research into liver disease

Justification

It is essential to obtain accurate epidemiological data, identify risk factors, evaluate the effectiveness of interventions and advance scientific knowledge, thus improving the diagnosis of these diseases

	Specific actions	Leadership[1]
1	**Identify and establish collaborations** with medical institutions, research centers and health organizations interested in participating in the creation of cohorts/registers for liver diseases	SS HC RC
2	**Design a research protocol** including inclusion and exclusion criteria, variables to be measured, data collection methods and follow-up of participants over time	SS HC RC
3	**Obtain ethical and regulatory approvals**, which are necessary for the creation and management of cohorts/records, ensuring the privacy and confidentiality of the information collected	SS HC RC MDG
4	**Select and recruit participants** who meet the inclusion criteria, obtaining their informed consent and providing the necessary information on the purpose and benefits of the study	SS HC RC
5	**Establish an efficient data collection, storage and management system**, using appropriate tools and technologies to ensure the quality and integrity of the collected data	SS HC RC
6	**Analyze and use data collected** in cohorts/registers to conduct scientific research, generate knowledge, and identify patterns and risk factors so as to improve general understanding of liver diseases and enhance accurate diagnoses	HC RC
7	**Disseminate research findings and results** through scientific publications, conferences and other means of dissemination, contributing to the advancement of knowledge and the improvement of care and diagnosis of liver diseases	SS HC RC

Diseases it applies to

- Viral hepatitis
- Liver cancer
- MASLD
- Rare liver diseases
- Alcohol-related liver disease

Impact

- **Better understanding of each pathology:** cohorts/registers provide valuable information on the prevalence, clinical characteristics and risk factors of liver diseases, which aids in the development of early detection strategies and identification of therapeutic target

Key

1. Leadership is used here to define the agents in charge of performing each action

Ministry/Department/ Government (MDG) · Primary healthcare (PH) · Hospital care (HC) · Research centers (RC) · Scientific societies (SS)

2.1 Diagnosis of liver diseases through specific tests that guarantee their correct assessment

Execution: 2024 - 2032

Line of action 2.1.3

Research the use of advanced diagnostic techniques (liquid biopsy, medical imaging) for early diagnosis

Justification

Advanced diagnosis techniques facilitate early-stage detection of the disease, improving the chances of effective treatment, reducing the invasiveness of interventions and increasing therapeutic options to improve the quality of life and survival rates

	Specific actions	Leadership[1]
1	**Promote interdisciplinary collaboration among researchers** in areas such as oncology, genetics, molecular biology and medical imaging so as to foster the integration of knowledge and technologies in the research of advanced diagnostic techniques	SS, RC, HC
2	**Promote funding for liver cancer research** through state funding, grants and collaborations with medical research organizations and entities	SS, PI
3	**Conduct clinical studies and trials** evaluating the efficacy and accuracy of advanced diagnostic techniques in the early detection of liver cancer	RC, HC
4	**Establish education and training programs** for healthcare professionals in the use and interpretation of advanced diagnostic techniques, ensuring their correct implementation and application in clinical practice	SS, PH, HC
5	**Promote the dissemination and diffusion of research results** through scientific publications and conferences so that the medical and scientific community can benefit from the advances and knowledge obtained	SS, RC, HC

Disease it applies to	Impact
Liver cancer	▶ **Earlier and more accurate diagnosis:** research and financial support for the development of advanced diagnostic techniques in the field of liver cancer have a significant impact on the early detection of the disease. This translates into improved clinical outcomes, as early diagnosis allows for the implementation of more effective therapeutic strategies and the optimization of patient prognoses ▶ **Enhancement of non-invasive techniques:** such diagnostic techniques reduce the need for more invasive procedures and provide a more accurate assessment of disease status, contributing to more informed and personalized therapeutic decision-making

Key

1. Leadership is used here to define the agents in charge of performing each action

Hospital care (HC) · Primary healthcare (PH) · Research centers (RC) · Scientific societies (SS)

2.2 Assertion of the importance of early diagnosis at all care levels

Execution: 2026 - 2028

Line of action 2.2.1

Creation of educational campaigns focusing on at-risk population to raise awareness regarding transmission mechanisms and diagnostic security

Justification

In order to raise awareness, prevent the onset of liver disease, promote early diagnosis and reduce the associated stigma, thereby improving liver health and the quality of life of patients

	Specific actions	Leadership[1]
1	**Conduct awareness and education campaigns** at schools, universities and workplaces to inform about the risks of liver diseases and promote the importance of early diagnosis	SS, PI, HC
2	**Organize workshops and training sessions** for healthcare professionals and educators, providing up-to-date information on methods of diagnosing liver disease and the importance of early detection	SS, PH, HC
3	**Establish partnerships** with health institutions and clinical laboratories to facilitate access to accurate diagnostic tests, especially in communities with a higher prevalence of liver disease	SS, RC, HC
4	**Develop educational materials** and easy-to-understand visual resources such as brochures, infographics and videos that explain the steps and processes of liver disease diagnosis, thus helping to increase social awareness and understanding	SS, HC
5	**Develop mass screening campaigns** for at-risk communities, providing testing and counseling, as well as offering referrals to specialized healthcare services when necessary	SS, HC

Diseases it applies to	Impact
MASLD	► **Increased awareness of risk factors**, such as obesity and diabetes. Through awareness campaigns, the general population is provided with a better understanding of how these conditions can impact their liver health; this, in turn, encourages the pursuit of appropriate and early screening and diagnostic tests
Viral hepatitis	► **Increase in the detection of cases:** informing the general population about transmisión mechanisms and the diagnostic safety of this pathology promotes the performance of screening tests in at-risk individuals, facilitating the diagnosis of a greater number of cases
Alcohol-related liver disease	► **Reduction in late diagnosis** by raising public awareness of the risks of excessive alcohol consumption and the importance of seeking medical attention and early diagnostic testing

Key

1. Leadership is used here to define the agents in charge of performing each action

Private industry (PI) · Primary healthcare (PH) · Hospital care (HC) · Research centers (RC) · Scientific societies (SS)

2.2 Assertion of the importance of early diagnosis at all care levels

Execution: 2026 - 2028

Line of action 2.2.2

Development of training activities for healthcare professionals to improve the quality and accuracy of liver disease diagnosis

Justification

This line of action aims to improve early detection and liver disease management. This ensures greater accuracy in clinical evaluation, test interpretation and the use of specific protocols, resulting in a reduction of diagnostic errors and more effective care

	Specific actions	Leadership[1]
1	**Conduct a needs assessment:** identify areas of knowledge and skills in liver disease diagnosis that require strengthening by healthcare professionals through surveys or interviews	SS, HC, PH
2	**Design a training plan:** based on the results of the needs assessment, a detailed plan that includes the topics to be addressed, teaching methods, evaluation strategies and necessary resources should be developed. This plan should be aligned with the guidelines and recommendations established by health authorities and scientific societies	SS, MDG, HC
3	**Establish collaborations**: identify and establish collaborations with experts in hepatology, research institutions, medical associations, and other related entities to share information and resources in the development and implementation of training actions	SS, HC, RC, PI
4	**Organize specific education and training programs on liver diseases**, addressing topics such as pathophysiology, diagnostic methods, test interpretation and clinical evaluation tools	SS, HC, PI
5	**Develop educational materials and teaching resources:** such as reference guides, diagnostic manuals and audiovisual materials to support the continuing education of healthcare professionals in the field of liver disease	SS, HC

Diseases it applies to

- Viral hepatitis
- Liver cancer
- MASLD
- Rare liver diseases
- Alcohol-related liver disease

Impact

- **Improvements in early detection:** training healthcare professionals in liver disease diagnosis facilitates an early identification of cases, facilitating timely interventions and offering more effective treatment options
- **Greater diagnostic precision:** qualified healthcare professionals have a broader knowledge and skills to perform an accurate diagnosis of liver disease, preventing misdiagnosis
- **Reduced disease burden:** early and accurate diagnosis of liver disease can help prevent disease progression, reduce associated complications and improve clinical outcomes for patients

Key

1. Leadership is used here to define the agents in charge of performing each action

Ministry/Department/ Government (MDG) · Primary healthcare (PH) · Hospital care (HC) · Research centers (RC) · Scientific societies (SS)

2.3 Guarantee an accurate liver disease diagnosis at all care levels

Execution: 2026 - 2032

Line of action 2.3.1

Screen the entire adult population for hepatitis C at least once in a lifetime

Justification

It is essential to identify the pathology early and provide timely treatment. This reduces the burden of the disease, improves the quality of life of patients, prevents transmission and optimizes health resources by avoiding more costly treatments in advanced stages of the disease

	Specific actions	Leadership[1]
1	**Assess the prevalence of hepatitis C** in the general population through epidemiological studies and health data analysis	SS, RC, HC
2	**Design outreach and mass communication strategies** to inform the population about the importance of being screened for hepatitis C and the benefits of early diagnosis	SS, HC, PH
3	**Collaborate with primary care centers and other healthcare providers** to offer hepatitis C screening at regular health examinations for adults, especially those at high risk or with risk practices	SS, HC, PH
4	**Train healthcare professionals** in the performance of hepatitis C screening tests, ensuring the quality and accuracy of results	SS, HC, PH
5	**Establish efficient systems** for the processing and analysis of screening tests, ensuring fast and reliable results	SS, HC, PH
6	**Regularly evaluate the coverage and impact of the hepatitis C screening program**, monitoring the number of tests performed, detection of new cases, and long-term health outcomes	SS, HC, PH

Disease it applies to	Impact
Viral hepatitis	▶ **Early detection:** by screening for hepatitis C in regular health examinations, the possibility of identifying cases of this pathology in early stages of the disease is increased, allowing treatment to be initiated in a timely manner ▶ **Reducing transmission:** by screening the entire adult population, individuals who are carriers of the hepatitis C virus but who may be unaware of their status will be identified. By providing them with appropriate treatment, the risk of transmission to others is reduced ▶ **Reduced economic burden:** early detection and timely treatment of hepatitis C can result in lower long-term healthcare costs. By preventing the progression of the disease and its complications, expenses associated with hospitalizations, surgeries and more intensive treatments are reduced

Key

1. Leadership is used here to define the agents in charge of performing each action

Hospital care (HC) · Primary healthcare (PH) · Research centers (RC) · Scientific societies (SS)

2.3 Guarantee an accurate liver disease diagnosis at all care levels

Execution: 2025 - 2027

Line of action 2.3.2

Promote mechanisms for the identification of patients at risk of metabolic and/or alcohol-related liver disease at all care levels

Justification

Promoting early detection and timely management of liver diseases reduces complications, improves clinical outcomes and optimizes the allocation of health resources

	Specific actions	Leadership[1]
1	**Assessment of capacities and resources:** evaluate available resources within the healthcare system to implement actions to identify patients at risk, detecting possible gaps and needs to be addressed	SS, HC
2	**Develop protocols and guidelines:** establish clear, evidence-based guidelines for the identification of patients at risk of developing metabolic and/or alcohol-related liver disease. These protocols should include appropriate evaluation criteria, screening tests, and assessment tools	SS, HC
3	**Train healthcare professionals:** provide specialized training to healthcare professionals on the detection and evaluation of liver disease. This includes education on risk factors and the use of screening questionnaires, as well as on the interpretation of liver function tests	SS, HC, PH
4	**Implement screening programs:** establish systematic screening programs in primary healthcare centers and other healthcare settings to identify patients at risk. These programs may include liver function tests, screening questionnaires, and lifestyle assessments	SS, HC, PH
5	**Interdisciplinary collaboration:** encourage collaboration between different medical specialties, such as hepatology, gastroenterology, family medicine, and primary care so as to ensure comprehensive detection and appropriate care for patients identified as being at risk	SS, HC, PH

Disease it applies to	Impact
MASLD	► **Early diagnosis and adequate management: e**arly identification of patients at risk of developing the disease makes it possible for initiating medical interventions and lifestyle changes in a timely manner, which can prevent progression
Alcohol-related liver disease	► **Early intervention and reduction of alcohol consumption:** identifying patients at risk of alcohol abuse facilitates early intervention and the provision of detoxification programs, rehabilitation therapy and psychosocial support. Reducing alcohol consumption can prevent further liver damage and improve liver function

Key

1. Leadership is used here to define the agents in charge of performing each action

Hospital care (HC) · Primary healthcare (PH) · Scientific societies (SS)

2.3 Guarantee an accurate liver disease diagnosis at all care levels

Execution: 2024 - 2032

Line of action 2.3.3

Encourage the implementation of screening for advanced occult liver disease using FIB-4

Justification

This line of action is based on the need to address an important public health problem. Many cases of advanced liver disease have no obvious symptoms, leading to late diagnosis and poorer clinical outcomes

	Specific actions	Leadership[1]
1	**Training of healthcare professionals** on the characteristics, detection methods and clinical relevance of occult liver disease	SS, HC
2	**Raise awareness and educate:** develop education programs aimed at health professionals and the community in general, with the goal of increasing awareness on the importance of early detection of liver disease and promoting the use of the non-invasive index FIB-4	SS, HC, PH
3	**Integrate into care protocols:** include FIB-4 test in care protocols and clinical guidelines related to liver disease, in order to establish clear guidelines for its implementation and to promote its systematic use in the assessment of patients at risk of liver disease	SS, HC
4	**Incorporate the FIB-4 index as a screening tool in social and healthcare centers** with the aim of reaching vulnerable groups, thus improving the early identification of hidden liver diseases, facilitating their clinical approach and reducing health disparities in these populations	SS, HC, PH
5	**Research and development** to promote ongoing research in the field of liver disease detection, including the FIB-4 index as a form of improving the accuracy and efficacy of diagnostic tests	SS, RC

Diseases it applies to

- MASLD
- Viral hepatitis
- Alcohol-related liver disease

Impact

- **Increased use of the FIB-4 index**, which allows a non-invasive and accurate assessment of the degree of liver fibrosis, especially in certain age groups (35 - 65 years), which in turn facilitates clinical decision making. It also helps in the identification of patients who require more aggressive interventions, antiviral treatment or consideration for liver transplant. It also allows close monitoring to detect complications and adjust therapeutic management accordingly

Key

1. Leadership is used here to define the agents in charge of performing each action

Hospital care (HC) · Primary healthcare (PH) · Research centers (RC) · Scientific societies (SS)

2.3 Guarantee an accurate liver disease diagnosis at all care levels

Execution: 2024 - 2032

Line of action 2.3.4

Guarantee screening for liver cancer in all patients with advanced liver disease

Justification

It is essential to ensure early detection and timely management of liver cancer, reducing the burden of disease, improving clinical outcomes and increasing survival rates. Furthermore, screening will facilitate the implementation of appropriate preventive and therapeutic interventions, as well as regular monitoring for early detection of possible clinical recurrences

	Specific actions	Leadership[1]
1	**Implement training and refresher programs** for healthcare professionals on screening criteria and recommendations for liver cancer screening in patients with advanced liver disease	SS, HC
2	**Establish protocols and guidelines** including routine liver cancer screening for all patients with advanced liver disease	SS, HC
3	**Promote reminder andmonitoring strategies** to ensure that patients with advanced liver disease are regularly screened for liver cancer	SS, HC
4	**Conduct awareness campaigns** targeting patients on the importance of regular screening for liver cancer in the presence of advanced liver disease and the advantages of early detection	SS, HC, PH
5	**Promote collaboration between different medical specialties**, such as hepatology, oncology, and radiology to ensure comprehensive and coordinated care in the diagnosis and treatment of liver cancer	SS, HC
6	**Establish systems for recording and monitoring the results of screening**, facilitating a continuous evaluation of the effectiveness and impact of the actions implemented	SS, HC, PH

Disease it applies to	Impact
Liver cancer	► **Regular screening of patients with advanced liver disease** helps to improve the detection and early diagnosis of precancerous or malignant liver lesions, enabling more effective therapeutic interventions and reducing the need for invasive or higher-risk treatments. Consequently, it promotes a significant impact on the quality of life of patients and on the efficiency of health services

Key

1. Leadership is used here to define the agents in charge of performing each action

Hospital care (HC) · Primary healthcare (PH) · Scientific societies (SS)

2.4 Availability of resources to correctly diagnose liver disease

Execution: 2026 - 2028

Line of action 2.4.1

Development of clinical practice guidelines for the diagnosis of different liver diseases that also specify monitoring and referral criteria for other specialties

Justification

This line of action will help in the standardization of care protocols, the optimization of available resources, the promotion of coordination between specialties and in ensuring quality care for patients, thus improving diagnostic results in the health care setting

Specific actions	Leadership[1]
1 **Form a multidisciplinary teams including** hepatologists, gastroenterologists, radiologists, and other relevant specialists to develop clinical practice guidelines	SS, HC
2 **Conduct a comprehensive review of the scientific literature and evidence** to support the recommendations in the guidelines	SS, HC, RC
3 **Promote reminder and monitoring strategies** to ensure that patients with advanced liver disease are regularly screened for liver cancer	SS, HC
4 **Define diagnostic criteria for each liver disease**, taking into account technological advances and the best clinical practices	SS, HC
5 **Develop monitoring algorithms** to regularly evaluate disease progression in each patient and make modifications to treatment based on the obtained results	SS, HC
6 **Validate the guidelines** through the participation of experts and healthcare professionals in the field of liver disease	SS, HC
7 **Promote the dissemination of the guidelines** at a national level, in order to ensure their adoption and application at all healthcare centers and hospitals	SS, HC

Diseases it applies to

- Viral hepatitis
- Liver cancer
- MASLD
- Rare liver diseases
- Alcohol-related liver disease

Impact

- **Provide comprehensive and quality care** through the standardization and improvement of the quality of diagnosis, monitoring and referral of patients. As a result, earlier detection, more timely and appropriate treatment, and improved clinical outcomes and quality of life for patients are enhanced

Key

1. Leadership is used here to define the agents in charge of performing each action

Hospital care (HC) · Primary healthcare (PH) · Research centers (RC) · Scientific societies (SS)

2.4 Availability of resources to correctly diagnose liver disease

Execution: 2026 - 2028

Line of action 2.4.2

Establishment of reference centers to manage complex diagnosis and including rare liver diseases, thus guaranteeing equitable access

Justification

This line of action ensures the availability of adequate technical and human resources, as well as the necessary expertise to make accurate and timely diagnoses. It is especially important for rare liver diseases, which require specialized knowledge and specific tests for their detection

	Specific actions	Leadership[1]
1	**Promote the identification and evaluation of health centers and hospitals** that meet the necessary criteria to become reference centers for the diagnosis of liver diseases, including a review of their infrastructure, equipment and trained personnel	SS, HC
2	**Establish specific criteria and requirements** for the designation of a center as a reference center for liver diseases, including adequate infrastructure, trained personnel and the necessary technical resources	SS, HC
3	**Facilitate the training and continuous updating of medical and laboratory personnel** in the diagnosis of liver diseases, including minority liver diseases	SS, HC, RC
4	**Implement referral and coordination mechanisms** between the different levels of care to ensure timely and equitable access of patients to referral centers	SS, HC
5	**Create clear workflows** for the management of complex cases, ensuring a comprehensive and multidisciplinary assessment of each patient	SS, HC
6	**Regularly evaluate the quality and efficiency of the reference centers** through indicators and periodic audits to guarantee excellence in the diagnosis of liver diseases	SS, HC

Disease it applies to	Impact
Rare liver diseases	► **Improved diagnostic accuracy and speed of diagnosis**, allowing early initiation of appropriate treatment ► **Equitable access to high-quality diagnostic services** for patients with rare liver diseases, regardless of their geographic location ► **Increased knowledge and specialized expertise in the management of rare liver diseases**, leading to more personalized and effective care

Key

1. Leadership is used here to define the agents in charge of performing each action

Hospital care (HC) · Research centers (RC) · Scientific societies (SS)

2.4 Availability of resources to correctly diagnose liver disease

Execution: 2026 - 2032

Line of action 2.4.3

Facilitate one-step, decentralized and comprehensive diagnosis in at-risk patients for viral hepatitis, HIV and/or other sexually transmitted infections

Justification

Decentralizing and simplifying the diagnostic process speeds up the identification of these diseases, allowing early initiation of preventive and treatment interventions. This contributes to improving health outcomes, reducing the transmission of infections, and optimizing healthcare resources

	Specific actions	Leadership[1]
1	**Conduct epidemiological studies** to identify the prevalence and distribution of viral liver diseases, HIV and other sexually transmitted infections in at-risk population	SS, HC, RC
2	**Implement comprehensive care centers** with trained personnel and adequate equipment for testing for viral hepatitis, HIV and other sexually transmitted infections	SS, HC
3	**Develop standardized diagnostic protocols and guidelines** including specific single-step detection tests, ensuring diagnostic efficiency and accuracy	SS, HC
4	**Establish coordination systems** between different levels of care to ensure the decentralization of diagnostic tests, making them available in different healthcare centers and hospitals even in remote areas	SS, HC
5	**Promote education and awareness** in healthcare professionals and the general population about the importance of early detection of these diseases and the benefits of one-step diagnosis	SS, HC, PH
6	**Implement adequate monitoring and referral systems** to ensure that diagnosed patients receive the necessary treatment and monitoring in a timely manner	SS, HC

Disease it applies to	Impact
Viral hepatitis	► **Improved diagnostic access:** by decentralizing and facilitating diagnosis in a single step, the need for multiple visits or trips to different care centers is eliminated. As a result, faster and more convenient access to screening tests is ensured ► **Timely detection:** performing a comprehensive diagnosis that covers different aspects of the disease facilitates early detection

Key

1. Leadership is used here to define the agents in charge of performing each action

Hospital care (HC) · Primary healthcare (PH) · Research centers (RC) · Scientific societies (SS)

2.4 Availability of resources to correctly diagnose liver disease

Execution: 2025 - 2027

Line of action 2.4.4

Promote the identification, diagnosis, and referral of liver disease susceptible of liver transplant at a nation-wide level

Justification

This line of action facilitates coordination between different health services, reducing waiting times and optimizing resource allocation. It also ensures comprehensive and timely care, improving clinical outcomes and patient experience

	Specific actions	Leadership[1]
1	**Establish clear and updated protocols and clinical guidelines** for the identification and diagnosis of liver diseases which may opt for liver transplant	SS, HC
2	**Implement screening and early detection systems** at different levels of care to identify patients at risk of advanced liver disease	SS, HC
3	**Improve training of health professionals** in the recognition and diagnosis of liver diseases, including laboratory tests, imaging and clinical evaluation	SS, HC, PH
4	**Establish coordination systems between different levels of care** to ensure decentralization of diagnostic tests, making them available in different health centers and hospitals, even in remote areas	SS, HC
5	**Promote collaboration and coordination among agents in the healthcare system**, including specialists in hepatology, liver surgery, and transplant centers in order to streamline referral processes and ensure comprehensive and timely care for patients	SS, HC
6	**Implement systems for registration and monitoring of referred patients** to evaluate waiting time, access to specialized services, and treatment outcomes	SS, HC

Diseases it applies to

- Viral hepatitis
- Liver cancer
- MASLD
- Rare liver diseases
- Alcohol-related liver disease

Impact

- **Early detection and accurate diagnosis:** digitization will enable fast and centralized access to medical information, which will facilitate early identification of liver disease, which in turn will improve diagnostic accuracy and enable early initiation of treatment

Key

1. Leadership is used here to define the agents in charge of performing each action

Hospital care (HC) · Primary healthcare (PH) · Scientific societies (SS)

2.5 Integration of new technologies (AI, Big Data, VR, etc.) as forms of diagnostic support

Execution: 2028 - 2032

Line of action 2.5.1

Digitalize and automatize unified diagnostic processes at a nation-wide level so as to guarantee patient traceability, positively impacting resource efficiency

Justification

The implementation of digital technologies will facilitate the integration of clinical data, improve coordination among healthcare professionals and promote more efficient and personalized care

	Specific actions	Leadership[1]
1	**Conduct an exhaustive analysis of the technological infrastructure and available resources** in healthcare centers and hospitals to determine the specific needs and requirements for a total digitalization and automation of the diagnostic process	SS, HC, PI
2	**Establish alliances and collaborations** with medical technology providers and companies specialized in digital solutions for the implementation of electronic record systems and data interconnection platforms	SS, HC, PI
3	**Implement electronic registration systems** for patients and diagnostic test results in all healthcare centers and hospitals at a nation-wide scale	SS, HC, PI
4	**Develop interconnection or data exchange platforms** between institutions and healthcare professionals to facilitate access and consultation of diagnostic information	SS, HC, PI
5	**Establish protocols and standards for the digitalization and automation** of the diagnostic process, ensuring data integrity, confidentiality and security	SS, HC, PI
6	**Train healthcare personnel** in the use of digital tools and their use in the interpretation and management of electronic diagnostic data	SS, HC, PH

Diseases it applies to

- Viral hepatitis
- Liver cancer
- MASLD
- Rare liver diseases
- Alcohol-related liver disease

Impact

- **Faster and more accurate diagnosis:** digitizing the diagnostic process enables the implementation of advanced data analysis tools and artificial intelligence algorithms that can help identify specific patterns and characteristics of liver diseases, resulting in an enhanced diagnosis
- **Resource efficiency:** automating the diagnostic process can help optimize the allocation of medical resources. By reducing the administrative burden and streamlining diagnostic procedures, additional resources can be freed up and used more effectively in medical care

Key

1. Leadership is used here to define the agents in charge of performing each action

Private industry (PI) · Primary healthcare (PH) · Hospital care (HC) · Research centers (RC) · Scientific societies (SS)

2.5 Integration of new technologies (AI, Big Data, VR, etc.) as forms of diagnostic support

Execution: 2028 - 2032

Line of action 2.5.2

Use of digitalization to link diagnosis with treatment processes, guaranteeing treatment for all patients with liver disease

Justification

Linking diagnosis to treatment through the use of digital tools is key to providing fast and efficient access to medical records for patients with liver disease, while also improving coordination within the medical team

	Specific actions	Leadership[1]
1	**Implement electronic health record (EHR) systems:** introduce EHR systems into the medical environment to ensure that all patient data is available electronically	SS, HC, PI
2	**Integrate liver patient data:** ensure that EHR systems are interconnected with laboratories, medical imaging services and other data sources. This ensures fast and complete access to patient information	SS, HC, PI
3	**Integrate the digital medical record** for each patient, including relevant data on their liver disease, previous diagnoses and test results	SS, HC, PI
4	**Develop alert and reminder systems** in EHRs to inform physicians of the most current treatment guidelines for liver disease. This helps ensure that best treatment practices are followed	SS, HC, PI
5	**Institute standardized treatment protocols** based on the latest medical recommendations. These should be available in the EHR and easily accessible to physicians	SS, HC, PI
6	**Patient empowerment:** providing patients with access to relevant information about their liver disease and treatment through an online patient portal	SS, HC, PH

Diseases it applies to

- Viral hepatitis
- Liver cancer
- MASLD
- Rare liver diseases
- Alcohol-related liver disease

Impact

- **More accurate diagnosis:** digitization enables quick access to past medical records, test results and relevant patient data, thus facilitating a more informed way of clinical decision-making. This leads to more accurate diagnoses and a more holistic understanding of each patient and their specific liver disease
- **Optimization of clinical data management:** digitization enables the analysis of large clinical data sets to identify patterns and trends in the treatment of liver diseases. This can lead to continuous improvements in treatment protocols and more personalized care

Key

1. Leadership is used here to define the agents in charge of performing each action

Private industry (PI) · Primary healthcare (PH) · Hospital care (HC) · Scientific societies (SS)

2.5 Integration of new technologies (AI, Big Data, VR, etc.) as forms of diagnostic support

Execution: 2028 - 2032

Line of action 2.5.3

Development of an automatic alert system to guarantee care continuity

Justification

This line of action seeks to achieve efficient communication between different healthcare providers, enabling effective coordination and rapid exchange of relevant information. Automated alerts are also a fundamental tool to prevent errors and omissions in the care of patients with liver disease

	Specific actions	Leadership[1]
1	**Conduct an analysis of the specific needs and requirements of the alert system** in the context of liver disease diagnosis, analyzing the existing challenges and obstacles, as well as identifying areas where automated alerts can have the greatest impact	SS, HC
2	**Identify key situations to generate alerts** in the process of diagnosing liver disease that require a rapid and timely response. These may include abnormal test results, significant changes in symptoms or need for specialized monitoring	SS, HC
3	**Integrate the alert system within medical records and diagnostic systems:** ensure that the automatic alert system is integrated within the medical records and diagnostic systems used in the diagnosis of liver disease	SS, HC, PI
4	**Establish efficient communication channels:** implement efficient communication channels for the delivery of alerts to healthcare professionals involved in the diagnosis. Such channels may include notifications in electronic health systems, text messages, etc.	SS, HC, PI
5	**Train health professionals in the use of the alert system:** on how to use and respond appropriately to alerts generated by the automatic system	SS, HC, PH

Diseases it applies to

- Viral hepatitis
- Liver cancer
- MASLD
- Rare liver diseases
- Alcohol-related liver disease

Impact

- **Improved continuity of care:** the implementation of an automatic alert system will ensure smooth communication and effective coordination among healthcare personnel. As a result, it will improve continuity of care by ensuring that healthcare professionals are informed of relevant situations and allowed to take timely action, avoiding delays in monitoring and guaranteeing continued quality care

Key

1. Leadership is used here to define the agents in charge of performing each action

Private industry (PI) · Primary healthcare (PH) · Hospital care (HC) · Scientific societies (SS)

2.5 Integration of new technologies (AI, Big Data, VR, etc.) as forms of diagnostic support

Execution: 2028 - 2032

Line of action 2.5.4

Integration of AI tools to improve liver disease diagnosis

Justification

This line of action aims to significantly improve diagnostic accuracy and precision, optimizing the efficiency of the diagnostic process and providing valuable clinical decision support. As a result, it promotes more effective medical care and improved health outcomes for patients with liver disease

	Specific actions	Leadership[1]
1	**Assess the feasibility and applicability of AI in the diagnosis of liver disease** through a revision of the existing scientific literature, consulting with experts in the field, and considering factors such as the availability of adequate data, technical capacity, and the resources needed to implement and maintain AI tools	SS, HC
2	**Collect and prepare a wide variety of clinical and radiological data** related to liver disease, such as medical history information, laboratory test results, medical imaging, genetic data and risk factors	SS, HC, PI
3	**Implement a data management system** to efficiently store, organize and access data needed for liver disease diagnosis. This may involve the use of secure databases and cloud storage systems	SS, HC, PI
4	**Develop AI models** specific for the diagnosis of liver diseases. This involves the implementation of machine learning algorithms and image processing techniques that can analyze clinical and radiological data to identify relevant patterns, features, and abnormalities	SS, HC, PI
5	**Integrate AI tools** into existing systems and diagnostic workflows	SS, HC, PI
6	**Provide education to healthcare professionals** on the proper use of AI tools in the diagnosis of liver disease	SS, HC, PH

Diseases it applies to

- Viral hepatitis
- Liver cancer
- MASLD
- Rare liver diseases
- Alcohol-related liver disease

Impact

- **Improved early detection and accurate diagnosis:** the integration of AI tools can make early detection of liver diseases more effective. By analyzing large volumes of clinical and radiological data, AI can identify specific patterns and features that might go unnoticed by healthcare professionals

Key

1. Leadership is used here to define the agents in charge of performing each action

Private industry (PI) · Primary healthcare (PH) · Hospital care (HC) · Scientific societies (SS)

3.1 Exploration of innovative pharmacological therapies to minimize the impact of liver disease

Execution: 2027 - 2032

Line of action 3.1.1

Encourage collaboration with national and international research networks, promoting private-public collaboration and the exchange of knowledge between different care levels

Justification

Public-private funding for research into treatments for liver disease is essential for the dissemination of knowledge and information

	Specific actions	Leadership[1]
1	**Establish alliances and research networks** between private companies, governmental organizations, research centers, and academic institutions, which will facilitate the exchange of information and knowledge about liver diseases while also addressing global health problems	PI, MDG, SS, RC
2	**Promote joint funding of research projects:** government entities and private companies can join forces to fund projects on new treatments for liver diseases with a common goal; public-private collaboration in research funding can, in this sense, enhance the development of new treatments	PI, MDG, SS, RC
3	**Facilitate the exchange of knowledge and data:** it is essential to create platforms or databases at a national level in order to share knowledge and information. On the other hand, symposiums and/or conferences are also a valuable way of sharing research results	PI, PH, HC, RC
4	**Promote collaboration in clinical trials**, which are essential to prove the efficacy and safety of medical treatments	PI, HC, RC
5	**Stimulate technology transfer:** public-private collaboration can promote technology transfer between academia and the private sector, facilitating the practical application of research results in hepatology-focused medical treatments	PI, HC, RC

Diseases it applies to

- Viral hepatitis
- Liver cancer
- MASLD
- Rare liver diseases
- Alcohol-related liver disease
- Liver transplant

Impact

- Collaboration with national and international networks in treatment research has a **positive impact on scientific advancement** and the development of more effective therapies for liver diseases
- In addition, public-private collaboration and knowledge sharing **maximize resources**, enrich research and accelerate the development of innovative treatments

Key

1. Leadership is used here to define the agents in charge of performing each action

Private industry (PI) · Ministry/Department/ Government (MDG) · Primary healthcare (PH) · Hospital care (HC) · Research centers (RC) · Scientific societies (SS)

3.1 Exploration of innovative pharmacological therapies to minimize the impact of liver disease

Execution: 2027 - 2029

Line of action 3.1.2

Stimulate research and funding for effective pharmacological therapies, while also promoting innovative treatments to improve liver disease management

Justification

Currently, most liver diseases have neither effective nor curative treatments, which is a major barrier for patients suffering from these diseases

	Specific actions	Leadership[1]
1	**Encourage collaboration between researchers and academic institutions:** promote collaboration between researchers, universities and research centers to share knowledge and resources in order to accelerate the process of developing drug therapies for liver diseases	PI, SS, RC
2	**Establish fiscal and financial incentives:** governmental organizations can offer fiscal and financial incentives to the private industry in order to boost research in the innovation of therapies in the field of hepatology	PI, MDG, RC
3	**Improve access to data and biological samples:** it is essential to have good quality biological samples for liver disease research, which is why data banks and biobanks are essential in collecting and sharing information	PI, HC, RC
4	**Promote collaboration in clinical trials:** these are essential to prove the efficacy and safety of medical treatments	PI, HC, RC
5	**Establish training programs:** it is essential to train new researchers in the field of liver disease and establish specific research programs to help drive innovation	PI, HC, RC

Diseases it applies to	Impact
MASLD	► Finding a **curative treatment for this pathology** will have a direct impact on patient quality of life and on not having to treat only the associated comorbidities
Viral hepatitis	► Obtaining **curative treatments for viral hepatitis B and D** will lead to a decrease in the incidence of patients and also to substantial savings in drugs and resources
Alcohol-related liver disease	► The absence of **effective pharmacological therapies** hinders the cessation of addictive behaviors; obtaining such therapies would represent a change in the paradigm of addictive behavior
Liver cancer	► There are **no current promising drug therapies** for this liver disease, so the development of potential new treatments will entail a big change for patients and their quality of life
Liver transplant	► Obtaining **innovative immunosuppressive treatments** for this disease will mean achieving an operational tolerance that will have a direct impact on patient quality of life and prognosis

Key

1. Leadership is used here to define the agents in charge of performing each action

Private industry (PI) · Ministry/Department/ Government (MDG) · Hospital care (HC) · Research centers (RC) · Scientific societies (SS)

3.1 Exploration of innovative pharmacological therapies to minimize the impact of liver disease

Execution: 2027 - 2029

Line of action 3.1.3

Perform socio-economic studies regarding the burden of certain liver diseases to seek the appropriate funding from public administrations

Justification

Socio-economic studies make known the different diseases, in this case hepatopathies, which tend to be little known and therefore tend to allocate fewer resources, both economic and in personnel numbers

	Specific actions	Leadership[1]
1	**Collect epidemiological data:** it is essential to collect accurate and up-to-date data on the incidence, prevalence, and burden of specific liver diseases in the population. This may require collaboration with health institutions, disease registries and population studies	SS, HC, RC
2	**Analyze the economic impact** to assess the impact of liver disease on the healthcare system and the economy in general. These analyses may include the cost of medical care, the impact on labor productivity, disability-related expenses, and other direct and indirect costs associated with liver disease	SS, MDG
3	**Evaluate the efficacy and cost-effectiveness of innovative treatments** for liver diseases, which includes analyzing the scientific evidence, clinical outcomes, potential benefits and costs associated with these treatments	MDG
4	**Identify vulnerable groups** who are more susceptible to developing liver disease. This may include socioeconomically disadvantaged groups, people with underlying chronic diseases, patients with limited access to health care services, etc.	SS, HC, PH
5	**Advocate and promote health policies:** the results of socioeconomic and impact studies should be used to advocate for health policies that allocate adequate resources to the access to innovative treatments. This involves collaborating with patient organizations, advocacy groups and health professionals to influence decision-making and promote positive changes in resource allocation	SS, MDG
6	**Participate in decision-making processes:** look out for opportunities to participate in governmental and administrative decision-making processes, such as health technology assessment committees and regulatory agencies. Solid data and evidence to support the need for adequate resource allocation to liver diseases and innovative treatments should be provided	SS, MDG

Diseases it applies to

- Liver cancer
- MASLD
- Rare liver diseases
- Alcohol-related liver disease
- Liver transplant
- Viral hepatitis

Impact

- Socioeconomic studies of liver diseases can provide essential data to support **appropriate resource allocation** and **informed decision making** from regional and national administrations
- These studies can influence **access to innovative treatments**, the development of effective health policies, and awareness of the importance of addressing liver diseases in a comprehensive manner

Key

1. Leadership is used here to define the agents in charge of performing each action

Atención primaria (AP) · Ministry/Department/Government (MDG) · Hospital care (HC) · Research centers (RC) · Scientific societies (SS)

3.2 Implementation of the perception of the patient as a central element in the treatment and monitoring phases of liver disease

Execution: 2025 - 2028

Line of action 3.2.1

Creation of communities of patient experts in liver disease

Justification

It is a fact that most patients diagnosed with liver disease have limited knowledge about these diseases and this is due to the lack of information or communication they receive

	Specific actions	Leadership[1]
1	**Establish support groups:** organize face-to-face or remote support groups where patients with liver disease can meet and share their experiences in order to feel part of a community	PI, SS, RC
2	**Create online platforms:** such as discussion forums or social networks specific to liver diseases where patients can express themselves, ask questions and obtain updated information	PI, MDG, RC
3	**Organize educational events:** hold educational events, such as seminars, conferences or webinars, aimed at patients with liver disease and their families. These events can address relevant topics, such as disease management, treatment options, and the importance of following a healthy lifestyle	PI, HC
4	**Promote participation in clinical trials:** inform and motivate patients with liver disease to participate in clinical trials and research projects. This gives them the opportunity to actively contribute to scientific progress and the development of new treatments and in some cases early access to innovative therapies	PI, HC, RC
5	**Establish partnerships with patient organizations and medical associations:** collaborate with patient organizations and medical associations specialized in liver diseases to promote the creation of expert patient communities	PI, HC, RC
6	**Promote the training of patient leaders:** identify and train patients with experience of liver disease to become community leaders and advocates. These leaders can play a crucial role by sharing information, advocating for patients rights, and facilitating connection and support among community members	P/GS

Diseases it applies to

- Liver cancer
- MASLD
- Rare liver diseases
- Alcohol-related liver disease
- Liver transplant
- Viral hepatitis

Impact

- The creation of specific patient communities for each of the hepatopathies will help patients immediately **in increasing their knowledge about the pathology**, while also offering comfort in feeling part of a community, as they are often diseases unknown to the general population; it will also provide them with the option to be experts in their own disease and give them a more holistic view of it

Key

1. Leadership is used here to define the agents in charge of performing each action

Private industry (PI) · Ministry/Department/ Government (MDG) · Primary healthcare (PH) · Hospital care (HC) · Research centers (RC) · Scientific societies (SS)

3.2 Implementation of the perception of the patient as a central element in the treatment and monitoring phases of liver disease

Execution: 2028 - 2029

Line of action 3.2.2

Promote the recognition of rare liver diseases at a health management level to ensure equity of access to the healthcare system

Justification

Rare liver diseases, as their name suggests, are diseases that do not affect a large number of the population, which leads to misdiagnosis due to a lack of knowledge within the healthcare system

Specific actions	Leadership[1]
1 **Encourage collaboration between institutions:** alliances between different organizations specialized in rare liver diseases are essential to improve their understanding, diagnosis, and the nature of each one of them, and thus make a correct approach	PI, SS, RC
2 **Raise awareness and educate:** it is essential to sensitize healthcare system managers to the existence and seriousness of rare liver diseases, mainly due to their lack of understanding among healthcare professionals and the general population	PI, HC, RC
3 **Develop guidelines and protocols:** healthcare system managers can collaborate with experts in rare liver diseases to develop specific guidelines and protocols for the diagnosis and treatment of these diseases. These guidelines should be based on up-to-date scientific evidence and ensure equity of access to health services for all patients	SS, HC
4 **Establish patient registries:** rare liver diseases are often under-diagnosed, which makes it difficult to accurately assess their prevalence; it is therefore essential to establish patient registries at the state level to keep track of patients and thus make managers aware of the problem and support research in this area	SS, HC
5 **Promoting access to treatments and medicines:** this requires health system managers to work together with regulatory authorities and pharmaceutical industries to facilitate access to innovative therapies and ensure the financial sustainability of treatments	PI, MDG
6 **Include patient participation:** it is imperative to involve patients and their families in decision-making related to these liver diseases. Healthcare system managers can facilitate patient participation through policy-making committees, working groups, and other decision-making bodies, which will ensure that their perspectives and needs are taken into account	SS, HC, P/GS

Disease it applies to	Impact
Rare liver diseases	▶ The **recognition of these pathologies** by health system managers will have a positive impact, leading to a greater understanding and thus to **an improvement in their diagnosis and treatment**

Key

1. Leadership is used here to define the agents in charge of performing each action

Private industry (PI) · Ministry/Department/ Government (MDG) · Primary healthcare (PH) · Hospital care (HC) · Research centers (RC) · Scientific societies (SS)

3.2 Implementation of the perception of the patient as a central element in the treatment and monitoring phases of liver disease

Execution: 2025 - 2026

Line of action 3.2.3

Development of a comprehensive and multidisciplinary program to train and involve patients in their own self-care and treatment

Justification

Patients diagnosed with liver disease have often undergone an infinite number of diagnostic tests, which leads to demotivation. Involving them in their treatment promotes emotional well-being

	Specific actions	Leadership[1]
1	**Establish multidisciplinary teams:** it is necessary to form teams made up of different specialties, as liver diseases often require it, chiefly through the inclusion of psychiatrists/psychologists, dieticians, specialized nurses, etc. to provide comprehensive care	SS, HC
2	**Conduct an initial assessment** to understand individual patient needs, skills, and self-care goals. This comprehensive assessment may include medical, psychological, self-care skills and social assessments	HC
3	**Establish a personalized plan:** patients suffering from any liver disease differ from each other so a personalized self-care; as such, individual treatment plans taking into account the medical situation, preferences, abilities, and available resources are required	HC
4	**Educate and empower the patient:** provide the patient with clear and accurate information about their liver disease, recommended treatment and self-care strategies. It is key to use visual educational resources and mobile applications to facilitate learning	SS, HC, P/GS
5	**Promote active patient participation:** active patient participation in making decisions related to their own self-care and treatment is key to improving their prognosis. Furthermore, patients should be encouraged to ask questions, express their concerns, and share their personal goals	HC, P/GS
6	**Provide continuous support:** providing support to the patient, whether by healthcare professionals or their own family, promotes adherence to treatment and better self-care. For this reason, continuous monitoring of patient condition by the various healthcare professionals involved in their care is essential to the development of their disease	HC, PH

Diseases it applies to

- Liver cancer
- MASLD
- Rare liver diseases
- Alcohol-related liver disease
- Liver transplant
- Viral hepatitis

Impact

- Encouraging **active patient participation** in their own self-care and treatment can have a significant impact on **patient health and well-being**, as well as on the efficiency of the healthcare system as a whole
- In addition, it provides emotional well-being by providing education and increased compliance with treatment because the **patient becomes an active partner**

Key

1. Leadership is used here to define the agents in charge of performing each action

Private industry (PI) · Primary healthcare (PH) · Hospital care (HC) · Research centers (RC) · Scientific societies (SS)

3.2 Implementation of the perception of the patient as a central element in the treatment and monitoring phases of liver disease

Execution: 2025 - 2026

Line of action 3.2.4

Facilitate patient identification of potential side effects of treatments

Justification

Patients diagnosed with liver cancer are at risk of suffering adverse effects from cancer treatments; however, these require specialized management that the patients themselves are unable to obtain

	Specific actions	Leadership[1]
1	**Define and validate brochures and educational materials:** prepare brochures, fact sheets or other educational materials that describe the common side effects of oncologic treatments for liver cancer. In addition, they should include how to detect the side effects of such treatments, what are the symptoms, how to act, and where to go if necessary	SS, HC
2	**Promote education and communication:** provide the patient with clear and understandable information about the possible side effects of cancer treatments and verify that the patient has correctly understood all the information given by the healthcare professional	SS, HC
3	**Provide individualized counseling:** it is essential to conduct individualized counseling sessions with the patient to discuss the specific side effects of their treatment	HC
4	**Track symptoms** through a tool to record the symptoms being experiencing and linking them back to the medical team for any change or worsening of symptoms, while also offering a more accurate form of communication	HC
5	**Set up group information sessions:** organize informative sessions where cancer patients can learn and share experiences about the side effects of treatments. This can provide emotional support and encourage the sharing of strategies for coping with side effects	HC, P/GS

Disease it applies to	Impact
Liver cancer	► Empowering oncology patients with information on the detection of side effects of the treatments themselves leads to the patient having **a greater sense of self-confidence** and having more control over their disease

Key

1. Leadership is used here to define the agents in charge of performing each action

Patients/general society (P/GS) · Hospital care (HC) · Scientific societies (SS)

3.2 Implementation of the perception of the patient as a central element in the treatment and monitoring phases of liver disease

Execution: 2025 - 2026

Line of action 3.2.5

Promote engagement with patient associations to promote healthy lifestyles and raise awareness of the importance of adherence to treatment through the exchange of information and resources

Justification

Adherence to treatment is usually better when the patient knows that by following unhealthy lifestyle habits they are damaging their liver and consequently developing liver disease, which makes patient associations essential in raising awareness

	Specific actions	Leadership[1]
1	**Establish alliances:** identify patient associations specific for each liver disease in order to establish partnerships with them and thus promote healthy lifestyles and the importance of adherence to treatment	PI, SS, HC
2	**Share information and resources** through educational materials, infographics, brochures or links to websites in order to disseminate knowledge about each liver disease and the importance for diagnosed patients to be treated appropriately	PI, SS, HC
3	**Organize joint events:** healthcare professionals with expertise in hepatology should work together with patient associations to continue promoting awareness campaigns on the importance of adherence to treatment and the benefits of a healthy lifestyle, since most liver diseases emerge due to a lack of healthy lifestyle habits	PI, SS, HC
4	**Schedule regular meetings:** establish regular meetings with patient associations to exchange information, discuss strategies and plan joint activities to foster ongoing collaboration to address specific patient needs	PI, HC, P/GS
5	**Encourage sharing of experiences:** sessions where patients can share their experiences in adopting healthy lifestyles and adherence to treatment can inspire other patients and strengthen the sense of community and mutual support	PI, HC, P/GS

Diseases it applies to

- Liver cancer
- MASLD
- Rare liver diseases
- Alcohol-related liver disease
- Liver transplant
- Viral hepatitis

Impact

- Patient associations play a very important role for both patients and the scientific community, so their involvement in promoting healthy lifestyles will result in **fewer hospitalizations and complications**
- In addition, it will result in a **higher level of patient awareness** and understanding

Key

1. Leadership is used here to define the agents in charge of performing each action

Private industry (PI) · Patients/general society (P/GS) · Hospital care (HC) · Scientific societies (SS)

3.3 Guarantee of access to innovative treatments

Execution: 2025 - 2026

Line of action 3.3.1

Facilitate access to innovative drugs once approved

Justification

Once approved by the EMA, drug therapies are not immediately accessible to patients, but after approval, each member of the EEA (European Economic Area) decides whether to approve them in their country. In this case, the process is lengthy and it takes time for patients to have access to innovative treatments

	Specific actions	Leadership[1]
1	**Streamline regulatory processes:** work in collaboration with regulatory authorities to speed up the approval and evaluation processes for innovative drugs, particularly drugs for liver diseases. This involves establishing mechanisms to enable faster and more efficient review of drugs by the EMA	SS, MDG
2	**Apply to early access programs** to treat liver disease and improve prognosis	PI
3	**Negotiate early pricing and reimbursement arrangements:** establish early negotiations with the pharmaceutical industry producing the innovative drug to treat liver diseases to agree on pricing and reimbursement modalities once approved by the EMA. This may include negotiating prices based on the therapeutic value of the drug and implementing risk-sharing agreements	PI, SS, MDG
4	**Improve coordination among stakeholders:** promote collaboration between regulators, healthcare providers, payers, and the pharmaceutical industry to streamline the processes for accessing innovative drugs. This involves establishing communication channels and sharing relevant information efficiently	PI, SS, MDG
5	**Establish flexible financing programs:** implement flexible financing programs that allow access to innovative drugs even in situations of uncertainty about their long-term efficacy and safety. These programs can be based on real-time data analysis and monitoring to continuously assess the efficacy and safety of drugs	PI, HC, MDG

Diseases it applies to

- Liver cancer
- MASLD
- Rare liver diseases
- Alcohol-related liver disease
- Liver transplant
- Viral hepatitis

Impact

- Early access to innovative drugs **allows patients to benefit from more effective and targeted treatments** for liver disease, and can also lead to improved survival rates and reduced patient complications
- On the other hand, it **reduces the burden of liver disease**, as innovative drugs tend to be more effective

Key

1. Leadership is used here to define the agents in charge of performing each action

Private industry (PI) · Ministry/Department/Government (MDG) · Hospital care (HC) · Scientific societies (SS)

3.3 Guarantee of access to innovative treatments

Execution: 2024 - 2032

Line of action 3.3.2

Guarantee funding for innovative treatments, thus guaranteeing equitable access to innovation

Justification

Currently, patients diagnosed with liver disease are not treated equally at a national level, as their treatment periods and management depend on their autonomous community. It is therefore essential for all patients to be treated equally regardless of their origin

	Specific actions	Leadership[1]
1	**Collaboration between health authorities and manufacturers:** encourage collaboration between health authorities and manufacturers of innovative liver treatments to establish pricing and reimbursement agreements that are fair and sustainable. This may include early negotiations, as well as pricing arrangements based on therapeutic value	PI, SS, MDG
2	**Evaluate and revise reimbursement policies:** review and update reimbursement and financing policies for liver treatments to ensure that they are inclusive and consider the incorporation of innovative treatments. It is important to evaluate the scientific evidence, therapeutic value, and clinical impact of new treatments for liver disease in order to make outcome-based decisions and promote equity of access	SS, MDG
3	**Create specific funds** with the objective of financing innovative liver treatments, ensuring that resources are available and equitably allocated. These funds can be used to guarantee access to treatments and cover the associated costs, especially for those patients who do not have adequate health coverage or who face financial barriers	PI, SS, MDG
4	**Promote equity in access** to innovative liver treatments through policies and programs that address inequities in care. This involves considering factors such as geography, age, gender, and socioeconomic status of patients, and taking steps to remove barriers to equitable access	SS, MDG
5	**Establish active patient and advocacy groups participation:** involve patients and advocacy groups in the decision-making process regarding the funding of innovative liver treatments. Their perspectives and experiences can help shape more inclusive policies and ensure equitable access to innovation	P/GS, SS, MDG

Diseases it applies to

- Liver cancer
- MASLD
- Rare liver diseases
- Alcohol-related liver disease
- Liver transplant
- Viral hepatitis

Impact

- The availability and funding of innovative treatments to treat liver disease provides long-term cost savings and **the opportunity to treat patients equitably without depending on their geographical location**

Key

1. Leadership is used here to define the agents in charge of performing each action

Private industry (PI) · Ministry/Department/ Government (MDG) · Hospital care (HC) · Scientific societies (SS)

3.3 Guarantee of access to innovative treatments

Execution: 2026 - 2027

Line of action 3.3.3

Minimize evaluation periods at a national and autonomical level for innovative drugs

Justification

The evaluation process for innovative drugs is often inefficient in its agility, which slows down the access of these drugs to treat patients with liver diseases, which is why minimizing time provides the opportunity to improve the quality of life of patients

Specific actions	Leadership[1]
1 **Coordinate collaborations between national authorities** responsible for the evaluation of innovative drugs for liver diseases	SS, MDG
2 **Analyze current processes** in order to try to cut time for each stage of the evaluation process with clear objectives and deadlines to ensure steady progress and avoid unnecessary delays	SS, MDG
3 **Use prior evidence** if the drug in question has been previously evaluated and approved in other countries, as this may speed up the evaluation process	PI, SS
4 **Conduct a parallel assessment:** conduct the national and regional assessments in parallel rather than sequentially, making the different levels of assessment work together and share information to reduce the total time needed to complete the process	MDG
5 **Collaborate with the pharmaceutical industry:** work closely with the pharmaceutical industry to expedite the submission of documentation and data required for the assessment. Establish efficient and clear communication channels to facilitate interaction between regulatory authorities and manufacturers	PI, MDG

Diseases it applies to

- Liver cancer
- MASLD
- Rare liver diseases
- Alcohol-related liver disease
- Liver transplant
- Viral hepatitis

Impact

- Shortening the evaluation time for innovative drugs **at national and regional levels** means that patients can be treated earlier and slow down the progression of liver disease
- In addition, it also **reduces costs in the long run** due to a reduction in hospitalizations and/or complications

Key

1. Leadership is used here to define the agents in charge of performing each action

Private industry (PI) · Ministry/Department/ Government (MDG) · Scientific societies (SS)

3.3 Guarantee of access to innovative treatments

Execution: 2025 - 2027

Line of action 3.3.4

Assess the impact on health results of approved innovative drugs

Justification

It is crucial to analyze the health outcomes of drugs as they are evaluated in real clinical practice, which provides different data from the results of clinical trials. In addition, this facilitates the identification of the patient groups benefitting the most from these drugs

	Specific actions	Leadership[1]
1	**Coordinate and conduct clinical research studies** to assess the impact of innovative drugs on health outcomes. These studies may include controlled clinical trials and observational studies to collect data on the efficacy, safety and clinical outcomes of drugs	PI, SS, RC
2	**Analyze real-life data:** use databases and health registries to perform analyses of real-life data. These analyses can provide information on how innovative drugs are used in clinical practice, their effectiveness in the real world, and their impact on health outcomes	PI, HC, RC
3	**Conduct economic and cost-effectiveness evaluations** to analyze the economic impact and cost-benefit ratio of innovative drugs. These analyses can help determine the therapeutic value of drugs and their impact on health outcomes in relation to the associated costs	PI, HC
4	**Long-term follow-up** of patients receiving innovative drug treatments to assess their impact on long-term health outcomes. This can help identify long-term effects, such as long-term survival, quality of life and incidence of adverse events	PI, HC
5	**Collaborate with patient associations:** work in partnership with patient organizations to collect data on the health outcomes of patients receiving innovative drugs. This may involve surveys, interviews or collecting data from patient reports to get a more complete picture of the outcomes experienced by patients in the real world	PI, SS, HC

Diseases it applies to

- Liver cancer
- MASLD
- Rare liver diseases
- Alcohol-related liver disease
- Liver transplant
- Viral hepatitis

Impact

- Improves **medical care** by identifying those treatments that provide the greatest clinical benefits and contributes to improved health outcomes for liver patients

Key

1. Leadership is used here to define the agents in charge of performing each action

Private industry (PI) · Ministry/Department/ Government (MDG) · Hospital care (HC) · Research centers (RC) · Scientific societies (SS)

3.4 Guarantee of equity and efficiency in access to the National Healthcare System for liver patients

Execution: 2025 - 2027

Line of action 3.4.1

Creation of multidisciplinary groups for the management of comorbidities and secondary effects of treatments

Justification

Liver diseases are complex in nature, since they require different specialties to provide correct treatment and monitoring

	Specific actions	Leadership[1]
1	**Identify and bring together professionals from different disciplines** relevant to the management of comorbidities and side effects of liver treatments. This may include hepatologists, gastroenterologists, infectious disease specialists, nurse practitioners, pharmacists, nutritionists, psychiatrists/psychologists, and social workers	PI, SS, HC
2	**Establish a leadership and coordination structure:** designate a leader or coordinating team that is responsible for facilitating and managing the activities of the multidisciplinary group. This person or team should have the ability to organize meetings, set agendas, assign tasks and ensure effective communication among group members	SS, HC
3	**Define roles and responsibilities for each member of the multidisciplinary team:** each professional should specialize in a different area and contribute with their expertise to address comorbidities and side effects of liver treatments in a comprehensive manner	SS, HC
4	**Develop protocols and management guidelines:** it is essential to define standardized protocols and management guidelines to address comorbidities and specific side effects of liver treatments. These protocols should be evidence-based and updated based on the latest clinical guidelines and recommendations for each liver disease	SS, HC
5	**Take a patient-centered approach** in all actions and decisions of the multidisciplinary group. This involves considering each patient's individual needs and preferences, as well as their social and emotional context, to provide comprehensive and personalized management of comorbidities and side effects	HC
6	**Evaluate and continuously improve performance:** establish evaluation and feedback mechanisms to track the multidisciplinary team so that improvements can be made if necessary. This may involve review of clinical outcomes, patient feedback, and the identification of areas for improvement in the care and management of comorbidities and side effects	P/GS, SS, HC

Diseases it applies to

- Liver cancer
- MASLD
- Rare liver diseases
- Alcohol-related liver disease
- Liver transplant
- Viral hepatitis

Impact

- The creation of multidisciplinary teams enables **comprehensive and holistic care** for patients with comorbidities and side effects of liver treatments
- In addition, it **improves patient quality of life** because the care they receive is more complete and personalized

Key

1. Leadership is used here to define the agents in charge of performing each action

Private industry (PI) · Ministry/Department/ Government (MDG) · Hospital care (HC) · Scientific societies (SS)

3.4 Guarantee of equity and efficiency in access to the National Healthcare System for liver patients

Execution: 2024 - 2032

Line of action 3.4.2

Promotion of advanced practical nursing within hepatology for ambulatory management of patients

Justification

Advanced practice nurses in the field of hepatology are essential in order to provide patients with comprehensive medical care, in addition to assisting specialists

	Specific actions	Leadership[1]
1	**Collaborate with educational institutions** to promote training programs specialized in hepatology for nurses interested in becoming advanced practice nurses in such specialty	SS, HC, PH
2	**Raise awareness and educate:** conduct awareness and education activities aimed at healthcare professionals, healthcare administrators, and patients about the role and competencies of the advanced practice nurse in hepatology. This may include seminars, workshops, and awareness campaigns to promote a clear understanding of their role in the outpatient management of liver patients	SS, HC, PH
3	**Develop advanced practice programs** in order for nurses to acquire the necessary knowledge, clinical experience and skills. These programs may include clinical rotations	HC, PH
4	**Develop management protocols and guidelines:** collaborate in the creation and updating of evidence-based practice guidelines and protocols to ensure the best management of liver patients. Advanced practice nurses can play a key role in the development and implementation of these guidelines, ensuring standardized, high-quality care	SS, HC, PH
5	**Participate in multidisciplinary teams:** include advanced practice hepatology nurses in multidisciplinary ambulatory care teams. This will allow effective collaboration with other healthcare professionals, such as hepatologists, gastroenterologists, dieticians and pharmacists, to provide comprehensive and coordinated care to patients	HC, PH
6	**Promote interprofessional collaboration:** foster collaboration and teamwork between advanced practice hepatology nurses and other healthcare professionals. This can be accomplished through regular meetings, clinical case discussions, and joint professional development activities	HC, PH

Diseases it applies to

- Liver cancer
- MASLD
- Rare liver diseases
- Alcohol-related liver disease
- Liver transplant
- Viral hepatitis

Impact

- **Advanced practice hepatology nurses** are essential, as they reduce the burden on medical specialists while also having the ability to provide comprehensive and coordinated care to patients

Key

1. Leadership is used here to define the agents in charge of performing each action

Primary healthcare (PH) · Hospital care (HC) · Scientific societies (SS)

3.4 Guarantee of equity and efficiency in access to the National Healthcare System for liver patients

Execution: 2024 - 2032

Line of action 3.4.3

Development of a comprehensive, multidisciplinary care approach for liver patients from early diagnosis to long-term monitoring to ensure efficient care

Justification

Early diagnosis is crucial for liver patients, but not always possible. However, continuous patient monitoring through comprehensive care and multidisciplinary teams offers optimal care

	Specific actions	Leadership[1]
1	**Establish multidisciplinary care teams** which include hepatologists, gastroenterologists, surgeons, nurses, dietitians, pharmacists, and other healthcare professionals involved in liver care. These teams will work together to provide comprehensive and coordinated care to patients	SS, HC, PH
2	**Implement standardized care protocols:** develop and use standardized care protocols that cover all aspects of liver patient management, from diagnosis to long-term follow-up. These protocols should be based on best practices and the latest available clinical guidelines	SS, HC, PH
3	**Promote early diagnosis:** establish screening and early diagnosis programs for liver diseases, especially for those that may be asymptomatic in the early stages. This may include awareness campaigns, screening tests, and the incorporation of liver tests in routine examinations	SS, HC, PH
4	**Coordinate referral and monitoring:** establish effective coordination mechanisms between the different healthcare professionals involved in the management of liver patients. This involves ensuring appropriate referral of patients, sharing relevant information and guaranteeing continuous and timely monitoring	HC, PH
5	**Develop personalized treatment plans:** create customized treatment plans for each liver patient, taking into account their specific condition, comorbidities, preferences, and individual needs. This involves a thorough assessment and consideration of the different aspects of care, such as pharmacological therapy, nutrition, physical activity, and psychosocial support	HC, PH
6	**Encourage collaboration with other care facilities:** establish collaborations and care networks with other specialized liver disease centers to facilitate referral and sharing of expertise and resources. This ensures that patients can access the most specialized care when needed	SS, HC, PH

Diseases it applies to

- Liver cancer
- MASLD
- Rare liver diseases
- Alcohol-related liver disease
- Liver transplant
- Viral hepatitis

Impact

- A comprehensive, multi-disciplinary approach facilitates a **better management of liver disease** and ultimately improves patient health outcomes

Key

1. Leadership is used here to define the agents in charge of performing each action

Primary healthcare (PH) · Hospital care (HC) · Scientific societies (SS)

3.4 Guarantee of equity and efficiency in access to the National Healthcare System for liver patients

Execution: 2028 - 2029

Line of action 3.4.4

Implementation of intensified post-liver surgery recovery programs

Justification

Intensified recovery programs are key to optimizing the postoperative period in liver surgery and thus reduce postoperative complications

	Specific actions	Leadership[1]
1	**Educate and train:** provide education and training to healthcare professionals involved in liver surgery on the principles and practices of ERAS programs. This includes hepatologists, surgeons, anesthesiologists, nurses, physical therapists, and other members of the surgical team. The training should address key aspects of the program, perioperative care protocols and pain management strategies	SS, HC, PH
2	**Establish a multidisciplinary team** made up of different healthcare professionals involved in patient care before, during, and after liver surgery with the aim of collaborating in the design and implementation of ERAS programs. This includes hepatologists, surgeons, anesthesiologists, nurses, physiotherapists, nutritionists, and pharmacists	SS, HC, PH
3	**Develop clinical protocols and guidelines:** define evidence-based clinical practice protocols and guidelines for the perioperative management of patients undergoing liver surgery. These protocols should include clear guidelines on preoperative preparation, optimization of nutritional status, pain management, early mobilization, and other key aspects of ERAS programs	SS, HC, PH
4	**Improve patient pain management:** implement multimodal pain management strategies that minimize opioid dependence and promote patient comfort and well-being. In addition, clear guidelines for postoperative pain management should be established	HC, PH
5	**Establish monitoring and evaluation measures:** put in place a monitoring and evaluation system to measure compliance with ERAS protocols and patient outcomes. This allows areas in need of improvement to be identified and for program adjustments to be made as needed. In addition, key performance indicators can be used to monitor the success of the program	HC, PH

Disease it applies to	Impact
Liver transplant	► The implementation of ERAS programs has a positive impact on the reduction of hospital stay, **the reduction of complications**, and the reduction of the number of patients who are admitted to the hospital

Key

1. Leadership is used here to define the agents in charge of performing each action

Primary healthcare (PH) · Hospital care (HC) · Scientific societies (SS)

3.4 Guarantee of equity and efficiency in access to the National Healthcare System for liver patients

Execution: 2024 - 2032

Line of action 3.4.5

Establishment of priorization and donor-receptor coupling models according to risk variables in order to achieve good organ allocation

Justification

A change is currently taking place in the clinical and social characteristics of transplant recipients that complicates donor-recipient matching

	Specific actions	Leadership[1]
1	**Define eligibility and exclusion criteria:** establish clear eligibility and exclusion criteria for organ allocation based on risk variables. These criteria should be developed in consultation with medical and ethical experts, and consider factors such as severity of disease, prognosis, immunological compatibility, and likelihood of transplant success	SS, HC
2	**Assess and weigh risk variables:** identify and assess risk variables that have a significant impact on transplant outcomes, such as recipient and donor age, blood compatibility, presence of antibodies, liver and renal function, and relevant comorbidities, later weighing these variables according to their relative importance in organ allocation	SS, HC, PH
3	**Develop scoring and ranking models:** use the assessed risk variables to develop scoring and ranking models to prioritize patients on the transplant waiting list. These models can be based on existing scoring systems for liver transplantation or can be specific to the disease or organ in question	SS, HC, PH
4	**Establish emergency and urgency criteria:** consider specific criteria for prioritizing organ allocation to patients in emergency or highly urgent situations, such as those with severe acute liver disease or in critical condition. These criteria should be fair and transparent, and should be applied consistently and equitably	HC, PH
5	**Maintain a robust data registry:** establish a transplant registry that collects and analyzes relevant data, such as transplant outcomes, waiting times, and allocation criteria used. This will allow the effectiveness and fairness of prioritization models to be evaluated and adjustments to be made where necessary	HC, PH

Disease it applies to	Impact
Liver transplant	► The implementation of prioritization models favors the **reduction of the waiting list** and the **increase in the survival rates** of recipients

Key

1. Leadership is used here to define the agents in charge of performing each action

Primary healthcare (PH) · Hospital care (HC) · Scientific societies (SS)

3.5 Incoporation of specific apps to improve adherence to treatment and patient monitoring

Execution: 2024 - 2032

Line of action 3.5.1

Use of telemedicine to maintain a doctor-patient relationship that reinforces adherence to treatment, particularly in the case of long-term treatment

Justification

Patients diagnosed with liver disease are often prescribed long-term treatments, which makes adherence difficult; as such, continuous interaction through telemedicine is essential

	Specific actions	Leadership[1]
1	**Develop validated applications:** work in collaboration with hepatology experts and software developers to create mobile applications or online platforms that are safe, reliable, and validated by these experts	SS, HC
2	**Educate and empower the patient:** provide online educational resources, such as videos or interactive brochures, to help patients understand their medical condition, recommended treatment, and the benefits of telemedicine. This will help to empower patients and encourage greater adherence to treatment	SS, HC, PH
3	**Conduct regular virtual consultations:** establish a regular schedule of virtual consultations between the physician and patient to follow up on treatment and address any concerns or questions. These consultations can be done via videoconference or secure messaging through the validated application	HC, PH
4	**Use remote monitoring devices:** in cases of long-term treatment, the use of remote monitoring devices, such as sensors or wearable devices, may be considered, as they can securely transmit relevant health data to the physician. This will allow the physician to continuously track the progress of treatment and make adjustments if needed	HC, PH
5	**Add reminders and notifications:** implement automatic reminders in the validated application so that patients receive notifications about medication intake, medical appointments, and other important aspects of treatment. These reminders can help improve adherence to treatment and prevent forgetfulness	HC, PH
6	**Track adherence to treatment:** use telemedicine to track adherence to treatment by allowing patients to record medication intake, keep a symptom diary, and receive feedback from their physician on their progress	HC, PH

Diseases it applies to

- Liver cancer
- MASLD
- Rare liver diseases
- Alcohol-related liver disease
- Liver transplant
- Viral hepatitis

Impact

- Telemedicine allows patients with liver disease to **access medical care without geographical restrictions**, promoting territorial equity
- In addition, it offers a **direct and secure communication channel** between hepatologists and patients

Key

1. Leadership is used here to define the agents in charge of performing each action

Primary healthcare (PH) · Hospital care (HC) · Scientific societies (SS)

3.5 Incoporation of specific apps to improve adherence to treatment and patient monitoring

Execution: 2024 - 2032

Line of action 3.5.2

Establishment of a unified and interconnected nation-wide data system to optimize access to clinical histories of patients referred to other autonomous communities, thus avoiding the unnecessary repetition of tests

Justification

There is no statewide shared space where all patient documentation is stored, which makes it difficult when patients move locations and medical information is lost and tests are repeated

	Specific actions	Leadership[1]
1	**Establish standards and protocols:** it is necessary to develop standards and protocols for the management of clinical data between different health systems so that electronic medical records can be shared and accessed, regardless of the autonomous community	SS, HC, MDG
2	**Implement a centralized data storage system:** create a centralized platform or database that securely stores the medical information of patients with liver disease. It should be noted that the platform must comply with data privacy and security requirements and be accessible to authorized healthcare professionals in all autonomous communities	SS, HC, PH
3	**Establish data exchange agreements:** it is necessary to establish data exchange agreements and policies between the different autonomous communities and responsible health entities. These agreements should define how clinical data will be shared and accessed, ensuring the protection of privacy and confidentiality of the information	SS, HC, MDG
4	**Establish unique patient identifiers** at a national level to allow the medical information of each patient to be unequivocally linked, regardless of the autonomous community in which they are located. This will facilitate the identification and monitoring of each patient's clinical history, avoiding the duplication of tests	HC
5	**Develop data interconnection systems** between the different regional healthcare systems, using compatible standards and technologies. This will allow the secure and fluid exchange of clinical data, including test reports, diagnoses, treatments and follow-up of liver disease	HC, MDG
6	**Train and raise awareness:** provide information to healthcare professionals on the proper use of the unified data system and the importance of avoiding unnecessary repetitions of tests. In addition, it is important to make patients aware of the importance of reporting their medical history and sharing relevant information when changing autonomous communities	SS, HC

Diseases it applies to

- Liver cancer
- MASLD
- Rare liver diseases
- Alcohol-related liver disease
- Liver transplant
- Viral hepatitis

Impact

- A unified system has **a positive impact on the continuity of care**, avoiding unnecesary test repetitions, while also allowing a better coordination between healthcare professionals, efficiency of care, and patient safety
- These benefits lead to **improved quality of care and health outcomes** for patients with liver disease

Key

1. Leadership is used here to define the agents in charge of performing each action

Ministry/Department/Government (MDG) · Primary healthcare (PH) · Hospital care (HC) · Scientific societies (SS)

3.5 Incoporation of specific apps to improve adherence to treatment and patient monitoring

Execution: 2028 - 2032

Line of action 3.5.3

Development of a mobile device platform integrating clinical information for all patients

Justification

The availability of digital platforms which unify all information on patients diagnosed with liver diseases optimizes resources and simplifies information

	Specific actions	Leadership[1]
1	**Identify key requirements and functionalities:** conduct a thorough analysis of the requirements and functionalities needed for the platform. This involves defining what clinical information should be integrated, how it should be presented, what security and privacy features are required, and what additional functionality may be beneficial, such as medication reminders or appointment scheduling	SS, HC, MDG
2	**Establish interoperability standards:** define interoperability standards to ensure that the platform can communicate efficiently with different electronic medical record systems and clinical data sources. This will ensure proper integration of patient clinical information regardless of source or format	SS, HC, PH
3	**Design an intuitive user interface:** create a user interface that is easy to use and adapts to mobile devices. The platform should be intuitive and user-friendly, allowing users to easily navigate clinical information, search for specific records and access additional functionalities, as a user-centered design is essential to ensure a positive experience	SS, HC, MDG
4	**Implement robust security and privacy measures:** protection of clinical information is of paramount importance. Ensure the implementation of robust security and privacy measures, such as data encryption, user authentication, access control, and log auditing. Comply with healthcare industry data security regulations and standards	HC
5	**Integrate with electronic health record systems:** work in collaboration with electronic health record (EHR) system vendors to enable the integration of clinical information. This involves establishing secure connections and communication protocols to extract and synchronize relevant data	HC, MDG
6	**Implementar capacidad de sincronización en tiempo real:** la plataforma móvil debe tener la capacidad de sincronizarse en tiempo real con los sistemas de registros médicos electrónicos y otras fuentes de datos clínicos. Esto garantiza que la información clínica se mantenga actualizada y precisa en todo momento	SS, HC

Diseases it applies to

- Liver cancer
- MASLD
- Rare liver diseases
- Alcohol-related liver disease
- Liver transplant
- Viral hepatitis

Impact

- The creation of a digital platform that stores all the information of patients diagnosed with liver disease **helps healthcare professionals to identify the medical history of each patient** and thus optimize time and resources

Key

1. Leadership is used here to define the agents in charge of performing each action

Ministry/Department/Government (MDG) · Primary healthcare (PH) · Hospital care (HC) · Scientific societies (SS)

Appendixes: patient circuits

A1. Metabolic dysfunction-associated liver disease

The patient circuit is divided into 4 phases (suspicion, diagnosis, treatment, and monitoring). The circuit starts through suspicion during routine analysis, which tends to show various altered biomarkers. After these results, the patient is diagnosed as low or moderate/high risk through non-invasive tests such as FibroScan®. Lastly, liver biopsy is considered in order to complete evaluation.

The following figure shows the complete patient circuit, specifying which healthcare professionals are involved and their roles in each of the 4 stages:

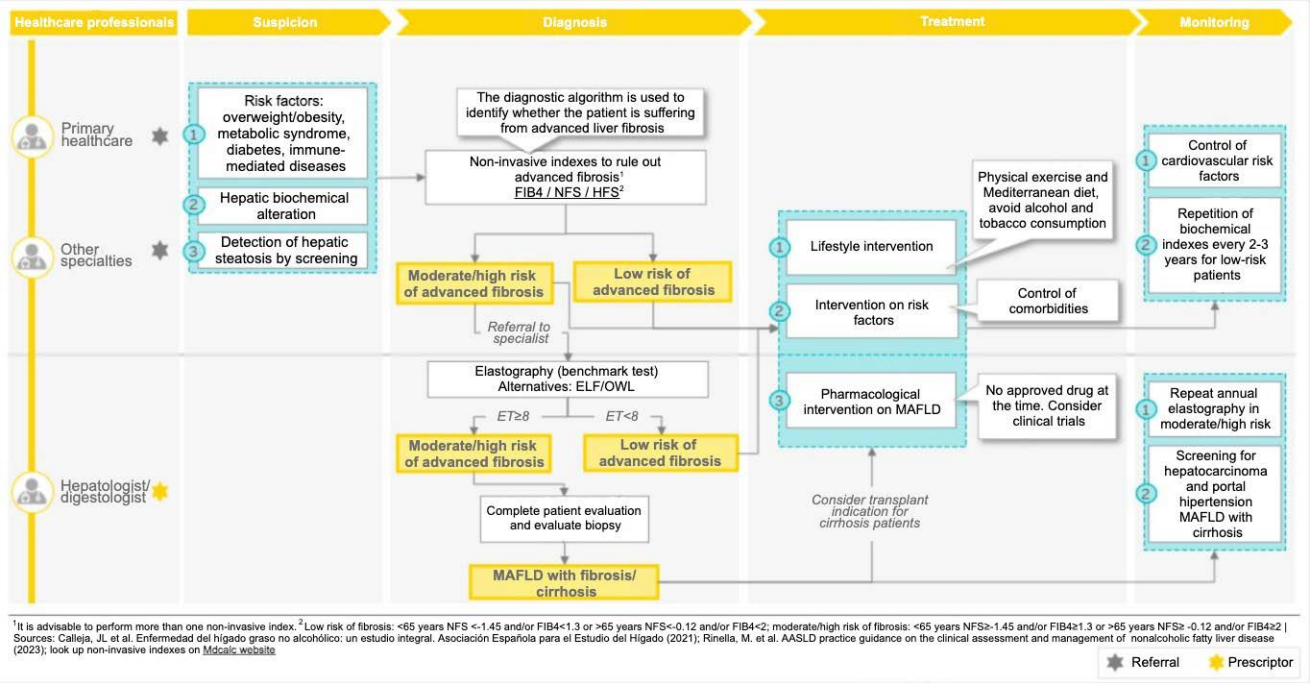

Figure A1 | Outline of patient circuit [9]

Suspicion

Suspicion is the first stage in the patient circuit, in which primary healthcare and other specialties are the main agents. There are 3 indicators used to prioritize the performance of a routine analysis on the patient: overt signs of risk factors, such as overweight or obesity, SM, DM and immuno-mediated diseases; hepatic biochemical alteration; and, lastly, the detection of hepatic steatosis by screening (elastography) [9].

Diagnosis

El Diagnosis is the second stage in the patient circuit. Its main aim is to identify whether the patient suffers from advanced liver fibrosis. Such identification is made through indexes based on non-invasive tests (FIB-4, NFS and HFS) according to the patient's age: if they are under 65 and show NFS<-1.45 and/or FIB-4<1.3, they are classified as low risk of advanced fibrosis. If the

tne patient is over 65 and shows NFS<-0.12 and/or FIB-4<2 they are also classified as low risk of advanced fibrosis. On the other hand, patients under 65 who show NFS≥-1.45 and or FIB-4≥1.3 or over 65 with NFS≥-1.45 and/or FIB-4≥1.3 or over 65 with NFS≥-0.12 and/or FIB-4≥2 are classified as moderate/high risk of advanced fibrosis [9].

Patients classified as low risk of advanced fibrosis will not be referred to specialists, and their management will be carried out through primary healthcare. On the other hand, patients classified as moderate/high risk of advanced fibrosis will be referred to a hepatologist or gastroenterologist to perform an elastography. If the elastography results are higher or equal to 8 kPa, the patient is classified as moderate/high risk of advanced fibrosis and further assessed through liver biopsy. However, if the result is lower than 8 kPa, the patient is classified as low risk of advanced fibrosis [9].

Treatment

Treatment is the third phase of the patient circuit, carried out by either primary healthcare physicians or hepatologists/gastroenterologists depending on the situation [9].

Patients classified as low risk of advanced fibrosis, who do not require to undergo elastography, should be advised to follow healthy lifestyles, promoting physical exercise and healthy diets (such as Mediterranean diet) as well as the avoidance of alcohol and tobacco consumption, thus raising awareness about the main risk factors [9].

Patients referred to specialists in the diagnosis stage are treated by hepatologists / gastroenterologists, who may consider their inclusion in clinical trials, as there is no approved drug for MASLD to this day. Liver transplant should be considered in the case of cirrhotic patients [9].

Monitoring

Monitoring is the last phase in the patient circuit and, as is the case in the treatment phase, low-risk patients are supervised through primary healthcare and other specialties. Monitoring typically consists on controlling cardiovascular risk factors and repeating the analysis of their biochemical indexes every 2-3 years [9].

Patients with moderate/high risk of advanced fibrosis are supervised by hepatologists or gastroenterologists and are annually tested through elastography. In addition, screenings for hepatocarcinoma and portal hypertension will also be carried out in cirrhotic patients [9].

A2. Rare liver diseases

The patient circuit is divided into 4 phases (suspicion, diagnosis, treatment, and monitoring). As such, a detailed guideline for each of the mentioned rare liver diseases will be provided below [9].

A2.1 Autoimmune hepatitis, primary sclerosing cholangitis and primary biliary cholangitis

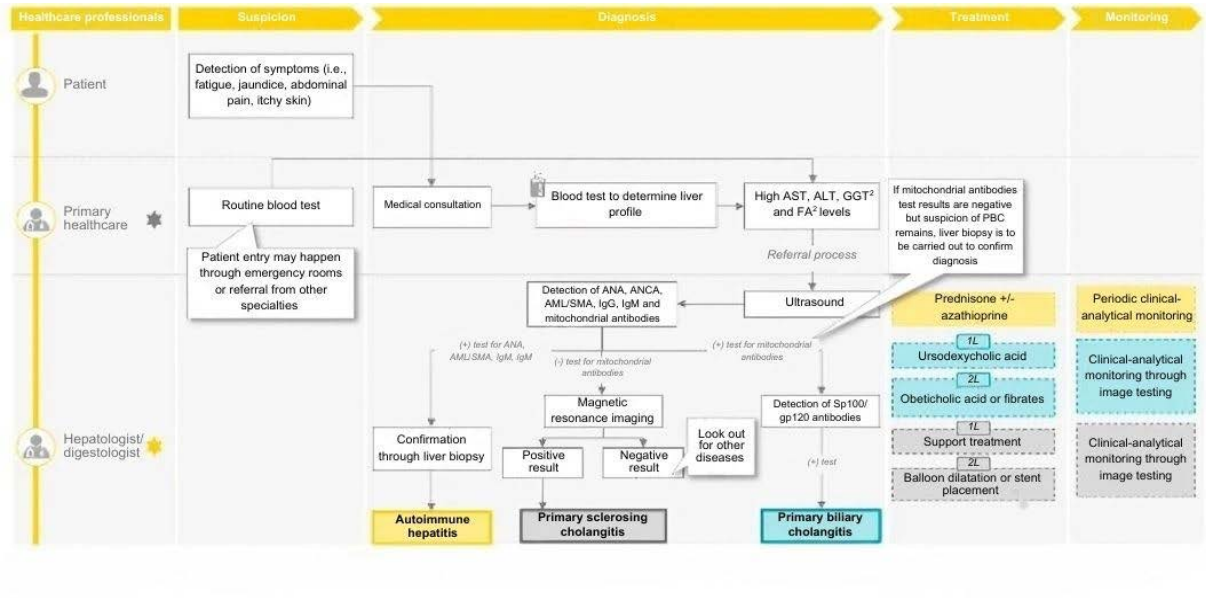

Figure A2 | Outline of patient circuit in rare autoimmune disease [9]

Suspicion

Suspicion may arise in various ways: firstly, through the detection of symptoms such as fatigue, jaundice, or abdominal pain; secondly, through the detection of an anomaly through routine blood tests or an unrelated visit to the emergency room. Primary healthcare physicians are the professionals at play in this stage, except in the case of those cases detected through a visit to the emergency room, in which specialists become involved in the process of suspicion [9].

Diagnosis

Diagnosis consists in the identification of anomalies through blood analysis or a further study of any possible symptoms. If blood test results show elevated values of aspartate transaminases (AST), alanine aminotransferase (ALT), gamma-glutamyl transferase (GGT), and alkaline phosphatase (ALP), the patient will be referred to a specialist, just like the patient referred through routine medical consultation after showing the aforementioned elevated parameters [9].

Once the patient is referred, the specialist is tasked with performing a series of tests. Firstly, an ultrasound and a serological test are performed for the detection of antinuclear antibodies (ANA), anti-neutrophil cytoplasmic antibodies (ANCA), anti-smooth muscle antibodies (SMA), mitochondrial antibodies, immunoglobulin G (IgG) and immunoglobulin M (IgM). The specialist must consider the performance of liver biopsy to confirm diagnosis if the results are positive for

ANA, SMA and the patient shows low levels of IgG and IgM. If so, the patient is then diagnosed with autoimmune hepatitis [9].

On the other hand, if the test is positive for mitochondrial antibodies, Sp100 and Gp120 antibodies are determined; if these are positive, the patient is then diagnosed with primary biliary cholangitis [9]. If no mitochondrial antibodies are found and the specialist still suspects primary biliary cholangitis, a liver biopsy should be performed to confirm the diagnosis.

Lastly, if no mitochondrial antibodies are detected, magnetic resonance imaging (MRI) will be performed for the diagnosis of primary sclerosing cholangitis; however, if the MRI is not suggestive, the specialist should look for other diseases [9].

Treatment

The specialist is the sole agent involved in the treatment phase [9].

Patients diagnosed with autoimmune hepatitis are prescribed prednisone with or without azathioprine [9].

Patients diagnosed with primary sclerosing cholangitis are prescribed first-line supportive treatment consisting in controlling complications and monitoring liver damage. As a second line of treatment, balloon dilatation or stent placement are performed on non-responsive patients [9].

Patients diagnosed with primary biliary cholangitis are prescribed ursodexycholic acid as the first line of treatment. If they are non-responsive, they will be prescribed obeticholic acid or fibrates [9].

Severe complications in patients with any of the 3 previously described diseases should lead to consideration of liver transplantation [9].

Monitoring

As is the case with the treatment phase, the specialist is the sole agent involved in the monitoring phase [9].

Patients diagnosed with autoimmune hepatitis undergo periodic clinical and analytical monitoring, depending on the severity of the disease [9].

Patients diagnosed with primary sclerosing cholangitis and primary biliary cholangitis undergo clinical and analytical monitoring through screening tests [9].

A2.2 Wilson's disease and hemochromatosis

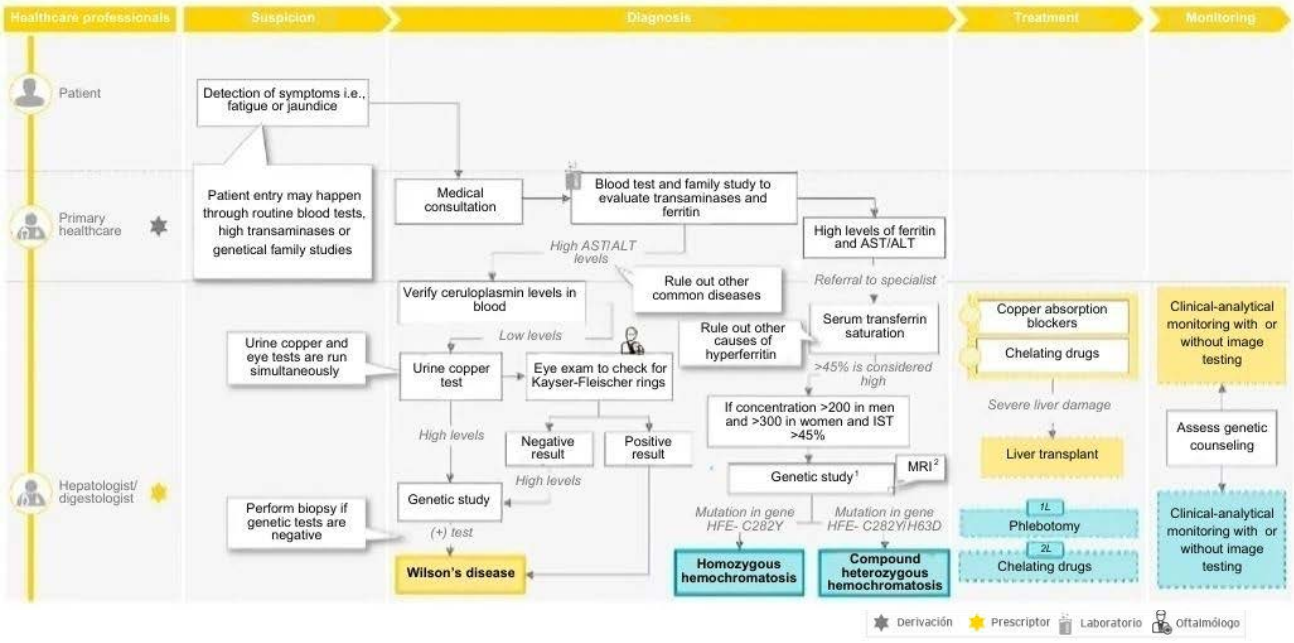

Figure A3 | Outline of patient circuit in rare metabolic-genetic disease [9]

Suspicion

Suspicion may arise through symptoms such as fatigue and jaundice, routine blood analysis showing high transaminase levels, or through a genetic family study. Only primary healthcare physicians are involved at this stage [9].

Diagnosis

El Blood tests should be carried out by primary healthcare physicians to evaluate transaminases, ferritin, and the prior family study. If the results show high levels of AST and ALT, the patient is referred to a specialist, who will verify the blood level of ceruloplasmin. If the results show low levels a urine copper test and an eye test to detect Kayser-Fleischer rings should be carried out simultaneously. If the levels of urine copper are high and the result of the Kayser-Fleischer rings test is negative, a genetic study will then be carried out; if the result is positive, the patient is diagnosed with Wilson's disease. On the other hand, a liver biopsy will be performed if the genetic study is negative in order to confirm the result. Eye exams seldom show the presence of Kayser-Fleischer rings; if such is the case, the diagnosis of Wilson's disease becomes irrefutable [9].

If the blood test results show high levels of transaminases and ferritin, patients are referred from primary healthcare to a specialist, whose first task is to rule out other causes of hyperferritinemia using a serum transferrin saturation test. If the result shows an index above 45%, which is considered to be high, serum ferritin concentration will be measured. Results should be analyzed keeping in mind that different levels are to be kept in mind depending on the patient's gender: if the patient is a woman, the level of concentration must be above 300 ng/mL to be considered high, whereas a result above 200 ng/mL would be considered high in men [9].

If results show ferritin concentration levels higher than those described earlier coupled with a saturation index higher than 45%, a genetic study will be performed. If a mutation is observed in gene HFE-C282Y, the patient is diagnosed with homozygous hemochromatosis; on the other hand, if a mutation is observed in gene HFE-C282Y/H63D, the patient is diagnosed with compound heterozygous hemochromatosis [9].
It is worth noting that there is a form of hemochromatosis which is not associated with the HFE gene, which further complicates its diagnosis [9].

In any case, specialists should perform an MRI on patients diagnosed with hemochromatosis to measure iron overload.

Treatment

Treatment is the third phase in the circuit patient and is prescribed solely by specialists in both pathologies [9].

Patients diagnosed with Wilson's disease can be treated with either copper absorption blockers or chelating drugs, so as to bind copper and release it into the bloodstream. Pharmacological options depend on individual patient profiles. Liver transplant can be considered in cases of severe liver damage [9].

Patients diagnosed with hereditary hemochromatosis are treated through the performance of a phlebotomy (blood collection) as first-line treatment, aiming to decrease iron levels. The amount of blood collected and the frequency of collection depends on age and the severity of iron excess in each patient [9].

Patients with anemia and cardiac complications cannot undergo phlebotomy and should be treated with iron chelators [9].

Monitoring

Specialists will oversee the monitoring phase in both Wilson's disease and hemochromatosis.

Patient monitoring in Wilson's disease and hereditary hemochromatosis does not differ, as they both share the aim of periodically assessing clinical-analytical profiles, which may or may not be done through image testing.

Given that both are rare genetic diseases, genetic counseling is required for both Wilson's disease and hemochromatosis.

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A2.3 Budd-Chiari syndrome

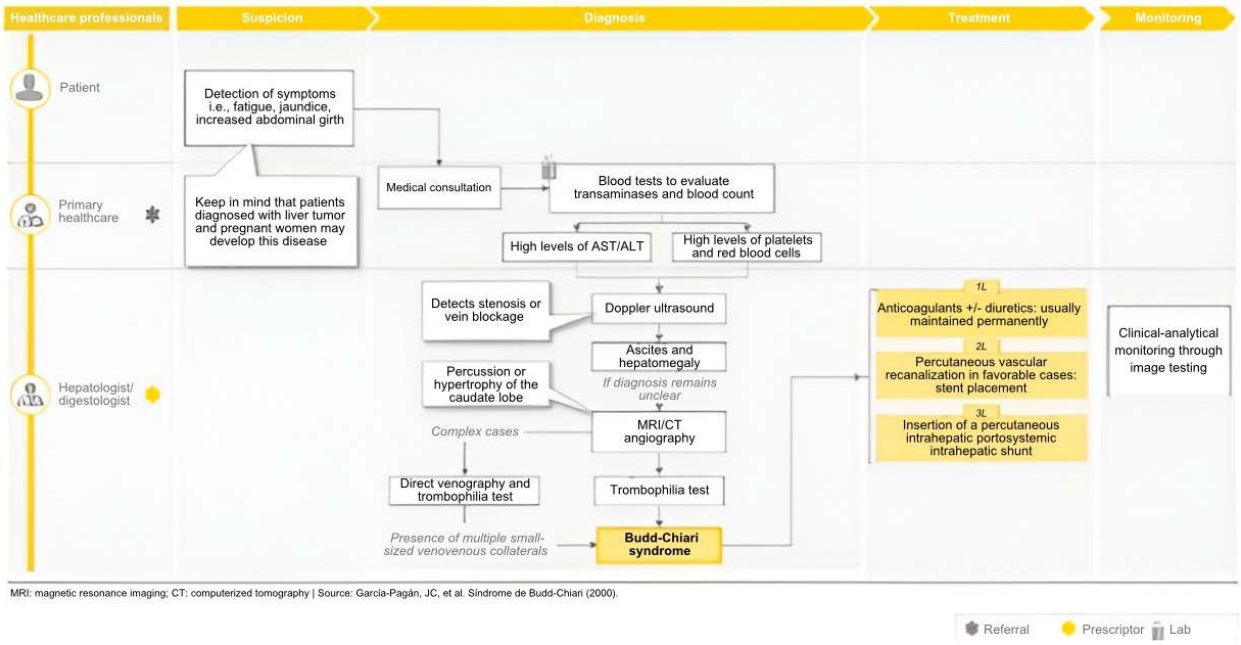

Figure A4 | Outline of patient circuit in rare vascular disease [9]

Suspicion

Suspicion may arise from overt symptoms, such as fatigue, jaundice, and abdominal pain; however, patients diagnosed with liver cancer and pregnant women should also be kept in mind. During this phase, specialist and primary healthcare physicians are equally involved [9].

Diagnosis

Patients typically request medical consultation due to the appearance of symptoms, during which their primary healthcare physician should perform a blood test to determine their level of transaminases. If the result is high, the patient is referred to a specialist, who will perform a Doppler ultrasound. If diagnosis remains unclear, an MRI angiography or computed tomography (CT) is performed to determine whether the patient suffers from thrombophilia. After this diagnostic test, the patient is diagnosed with Budd-Chiari syndrome. A direct venography and thrombophilia study may be used in complex cases, particularly if the presence of small venovenous collaterals is observed, after which the patient is diagnosed with Budd-Chiari syndrome [9].

Treatment

Treatment is the third phase of the patient circuit and it is exclusively carried out by specialists [9].

Patients diagnosed with Budd-Chiari syndrome are treated with anticoagulants, which may be coupled with diuretics as first-line treatment. These drugs are usually maintained permanently. Second-line treatment consists of percutaneous vascular recanalization in favorable cases, contemplating a stent placement. In patients who remain unresponsive to the

first two lines of treatment outlined above will be treated by the insertion of a percutaneous intrahepatic portosystemic shunt [9].

Monitoring

Monitoring is the last phase in the circuit and is also exclusively carried out by specialists. The main aim in this phase is to analyze clinical-analytical profiles through image testing [9].

A2.4 Porto-sinusoidal vascular disease

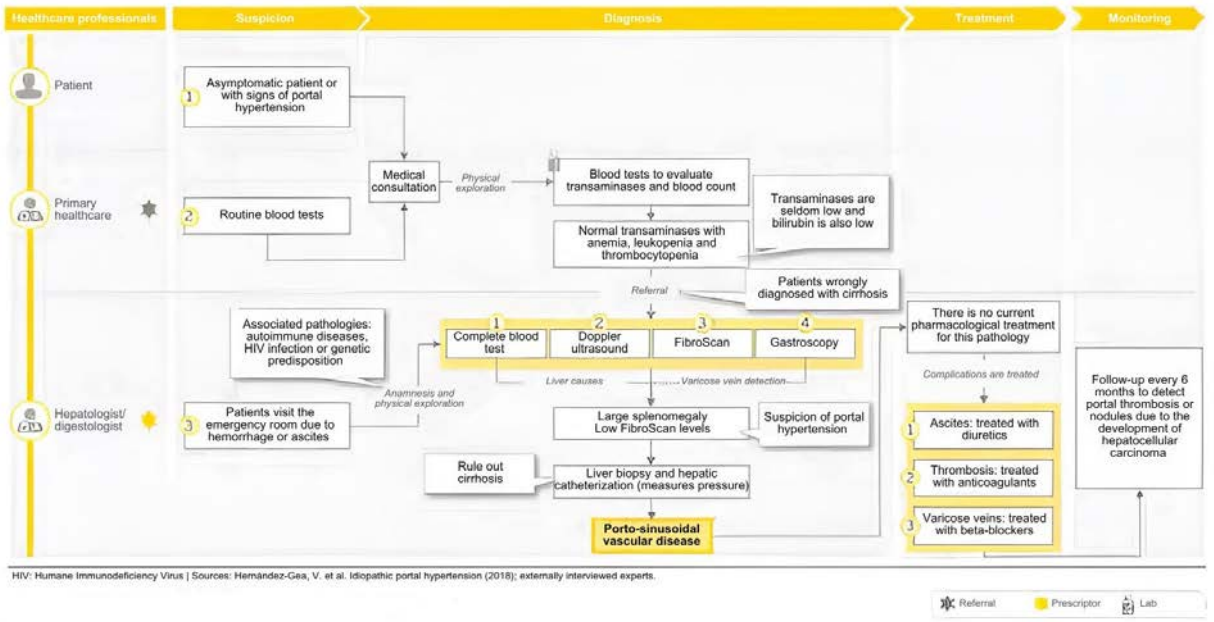

Figure A5 | Outline of patient circuit in rare vascular disease [9]

Suspicion

There are several ways in which patients may enter the circuit. Firstly, the patient may be asymptomatic or show signs of portal hypertension. Secondly, routine tests may hint at the possibility. Both situations generally happen through primary healthcare. On the other hand, the patient may be referred to a specialist if they visit the emergency room due to hemorrhage or ascites [9].

Diagnosis

Patients initially undergo a physical examination conducted by primary healthcare physicians, as well as blood tests to evaluate their transaminases and develop a full blood count. If transaminase levels are normal but the blood count indicates anemia, leukopenia and thrombocytopenia, the patient will be referred to a specialist. In this case, transaminases and bilirubin are seldom altered [9].

It is worth noting that at this stage of the patient circuit patients tend to be referred with an erroneous diagnosis of cirrhosis [9].

On the other hand, patients typically undergo anamnesis and a physical exploration once they visit the emergency room, while also being questioned about other associated pathologies, such as autoimmune diseases, human immunodeficiency virus (HIV) infection, or genetic predisposition [9].

The patient undergoes a parallel battery of tests once they are referred to a specialist, including a complete blood test to rule out hepatic causes, a Doppler ultrasound, FibroScan® and a gastroscopy to detect esophageal varices. If the results show splenomegaly and low FibroScan® levels, the specialist may suspect portal hypertension. At this point, a liver biopsy is performed to rule out cirrhosis, while also performing a catheterization to measure pressure, after which the patient is diagnosed with porto-sinusoidal vascular disease [9].

Treatment

The specialist is the only agent involved in the treatment stage.

There are no current therapeutic options for this disease besides the treatment of its complications. Ascites is treated with diuretics, thrombosis is treated with anticoagulants, and varices are treated with beta-blockers [9].

Monitoring

Monitoring is the fourth stage in the patient circuit, also supervised by the specialist [9].

Los pacientes diagnosticados de enfermedad porto sinusoidal deben hacer un seguimiento cada 6 meses para detectar la aparición de trombosis portal o nódulos ya que el desarrollo de carcinoma hepatocelular es plausible [9].

A2.5 Non-cirrhotic portal thrombosis

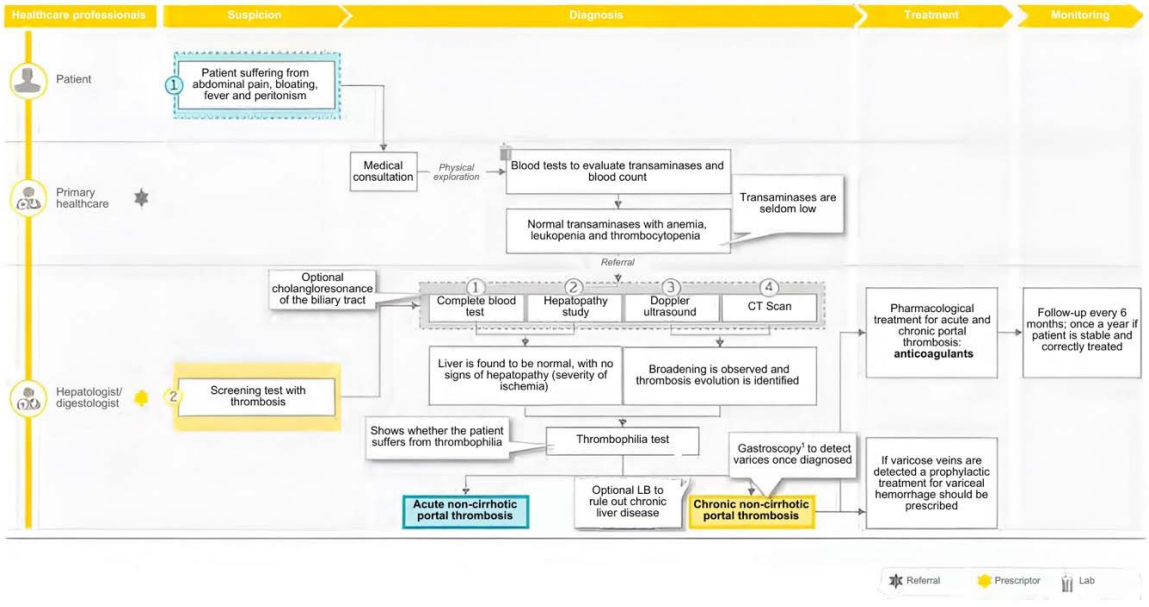

Figure A6 | Outline of patient circuit in rare vascular disease [9]

Suspicion

Suspicion can vary from patients suffering acute disease, who typically suffer from abdominal pain, bloating, fever, and peritonism, and patients suffering chronic disease, who undergo screen testing to identify thrombosis [9].

Diagnosis

Primary healthcare physicians and specialists are involved in the diagnosis stage [9].

Patients suffering from acute disease typically request medical consultation, where they undergo a physical exploration and blood tests to evaluate their transaminase levels and a full blood count. If the results show normal transaminase levels but the blood count reveals anemia, leukopenia and thrombocytopenia, the patient is referred to a specialist. It is worth noting that this pathology seldom shows high transaminase levels [9].

Chronic patients are referred to a specialist, who performs a number of tests: a complete blood test, a liver disease study, a Doppler ultrasound, a computerized tomography (CT) and an optional cholangloresonance of the biliary tract. Liver disease studies and complete blood tests will show whether the liver is normal and/or shows signs of liver disease, while CT scans and Doppler ultrasounds help in assessing the severity of ischemia as well as its extension, identifying the evolutive movement of thrombosis. Once results are analyzed, the patient undergoes a thrombophilia study, which will show whether the patient suffers from thrombophilia and help in diagnosing them with acute or chronic non-cirrhotic portal thrombosis [9].

Once the patient is diagnosed, a gastroscopy must be performed in order to detect any possible esophageal varices [9].

Treatment

Treatment is the third stage in the patient circuit and it is exclusively carried out by specialists [9].

Patients diagnosed with acute or chronic non-cirrhotic portal thrombosis are treated with anticoagulants. In patients with varicose veins, an additional prophylactic treatment for variceal hemorrhage is prescribed [9].

Monitoring

Monitoring is the fourth phase in the patient circuit and it is exclusively carried out by specialists [9].

Stable patients who are being correctly treated may only undergo medical consultation once a year. However, the rest are expected to undergo bi-annual medical consultations [9].

A2.6 Drug-induced hepatotoxicity

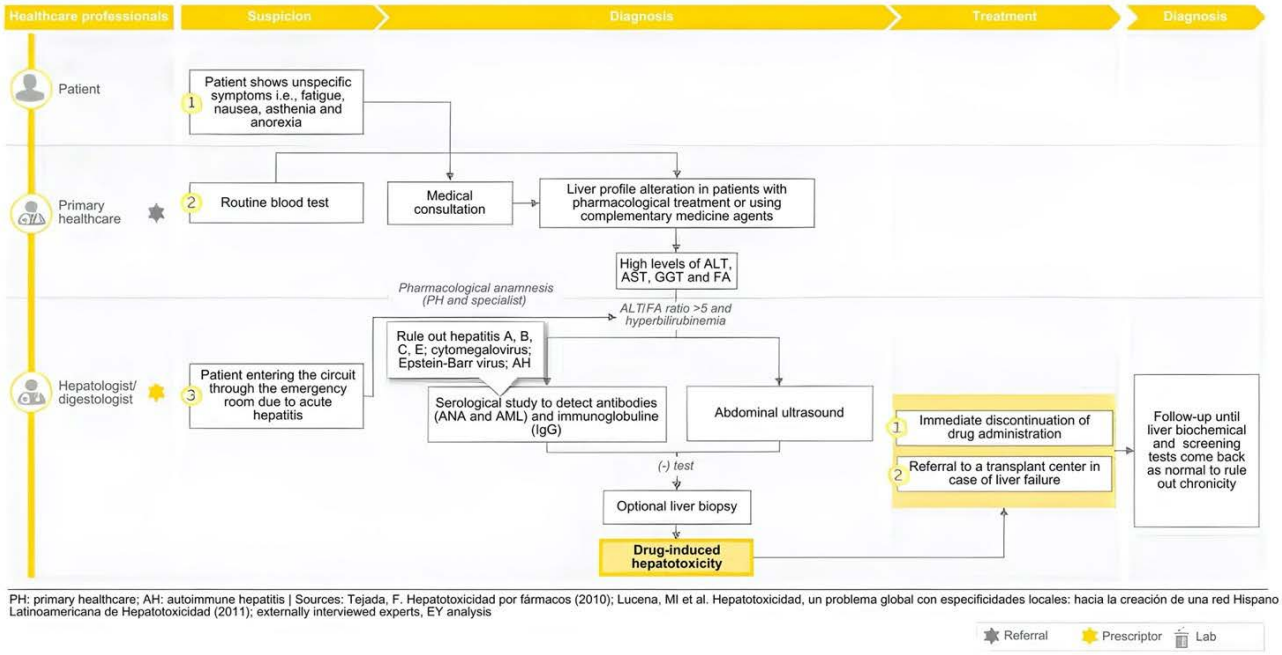

Figure A7 | Outline of patient circuit in rare toxic-metabolic disease [9].

Suspicion

Suspicion is the first stage in patient circuits and it may happen through three different possible scenarios: firstly, suspicion may arise from non-specific symptoms such as general discomfort, nausea, asthenia, and anorexia. Secondly, it may arise from routine blood testing results; thirdly, it may arise if the patient visits the emergency room due to acute hepatitis [9].

Diagnosis

Patients typically request medical consultation due to an onset of symptoms or through routine blood test. Primary healthcare physicians should then perform a blood test to observe potential alterations in liver patients with pharmacological treatment or using complementary medicine agents. If results show high levels of ALT, AST, GGT and FA with an ALT/FA ratio above 5 as well as hyperbilirubinemia, the patient is consequently referred to a specialist [9].

On the other hand, patients may enter the circuit through a visit to the emergency room due to acute hepatitis. In this case, patients are left in the care of specialists and do not engage with primary healthcare, focusing primarily on their elevated liver function values [9].

As such, patients undergo a serological study and abdominal screening once they are under a specialist's care. Serological studies are performed in order to detect ANA, SMA and IgG antibodies. At this stage, the specialist may rule out HVA, HVB, HVC, VHE, cytomegalovirus, and Epstein-Barr virus infection, as well as autoimmune hepatitis. If the results of such serological tests are negative, the possibility of performing a liver biopsy may be considered in order to confirm the diagnosis of drug-induced hepatotoxicity [9]. It should also be noted that a correct

pharmacological anamnesis should be carried out between primary healthcare physicians and specialists [9].

Treatment

The treatment stage is exclusively overseen by specialists [9].

Patients diagnosed with drug-induced hepatotoxicity should immediately discontinue drug administration to stop such toxicity. In case of liver failure, the patient should be referred to a transplantation center [9].

Monitoring

Monitoring is the fourth phase in the patient circuit and it is exclusively carried out by specialists [9].

Drug-induced hepatotoxicity patients consists must be monitored until the complete normalization of their liver biochemical and screening tests, so as to rule out chronicity [9].

A3. Alcohol-related liver disease

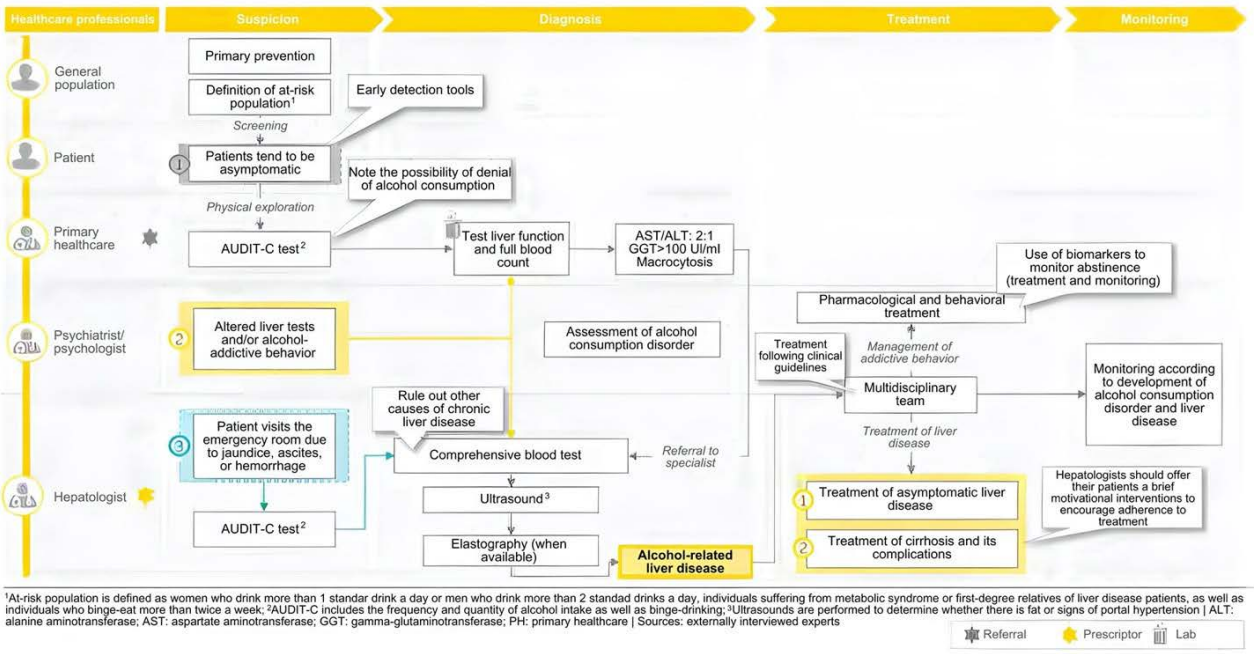

Figure A8 | Outline of patient circuit in alcohol-related liver disease [9].

Patient circuits in alcohol-related liver disease vary greatly from other circuits.

This circuit includes the general population as an agent prior to the patient, as the importance of primary prevention should be noted in order to avoid a further increasement in disease rates. Similarly, it is essential to describe the at-risk population accurately. According to expert hepatologists, at-risk population for this disease includes women who drink more than 1 standard alcoholic drink (10 g of alcohol per drink) per day or men who drink more than 2 standard alcoholic drinks per day, individuals with metabolic syndrome or first-degree relatives of alcohol-

related liver disease patients, as well as people who binge-eat more than twice a week [9].

Suspicion

Suspicion may arise from: screening of the at-risk population, as patients are typically asymptomatic; patients who visit the emergency room due to jaundice, ascites, or hemorrhage; and patients with altered liver tests or alcohol-addictive behaviors. Primary healthcare physicians, specialists, and psychiatrists/psychologists are all involved in this stage.

Primary healthcare physicians should perform AUDIT-C on asymptomatic screening patients. AUDIT-C is a questionnaire consisting in three questions about alcohol-addictive behaviors [9].

It is worth noting that AUDIT-C results may underreport the patient's real degree of alcohol consumption [9].

On the other hand, it is far more usual for the patient to visit the emergency room due to jaundice, ascites, or hemorrhage. Specialists should then perform AUDIT-C to identify alcohol-related liver disease [9].

Finally, patients may be referred to a specialist from a psychiatry unit due to alcohol-addictive behavior or altered liver tests [9].

Diagnosis

Patients who have entered the circuit through primary healthcare will undergo liver function tests and a full blood count to confirm suspicion after AUDIT-C. If liver profile results show an AST/ALT ratio above 2 and high levels of GGT, as well as macrocytosis in blood count results, patients will be referred to a specialist [9].

Once patients are referred to a hepatologist or specialist, whether it be through the emergency room, primary healthcare, or psychiatry/psychology units, a comprehensive blood test is performed, followed by an ultrasound that may reveal the presence of fat or signs of portal hypertension. Lastly, an elastography will be performed when possible, as it may shed light on the stage of fibrosis that the liver is in. The patient is then diagnosed with alcohol-related liver disease [9].

It is important to note that psychiatrists/psychologists will assess the presence of alcohol use disorder in parallel to the hepatologist's diagnosis [9].

Treatment

The main aim in the treatment phase is to treat liver disease. In this sense, asymptomatic liver disease will be treated differently from cirrhosis and its complications. At this point, experts noted that brief motivational interventions should be offered to patients in order to avoid low adherence to treatment.

On the other hand, multidisciplinary teams are a key factor in treating alcohol-related liver disease, as they will both prescribe treatment according to clinical guidelines.

Lastly, psychiatrists/psychologists should focus on correctly managing addictive behaviors through pharmacological and behavioral treatment [9].

Monitoring

Monitoring of patients with alcohol-related liver disease is carried out through alcohol use disorder and the developmental stage of liver disease [9].

Hepatologists and psychiatrists/psychologists are involved in this phase, and biomarkers will be used to monitor abstinence throughout this phase [9].

A4. Viral hepatitis

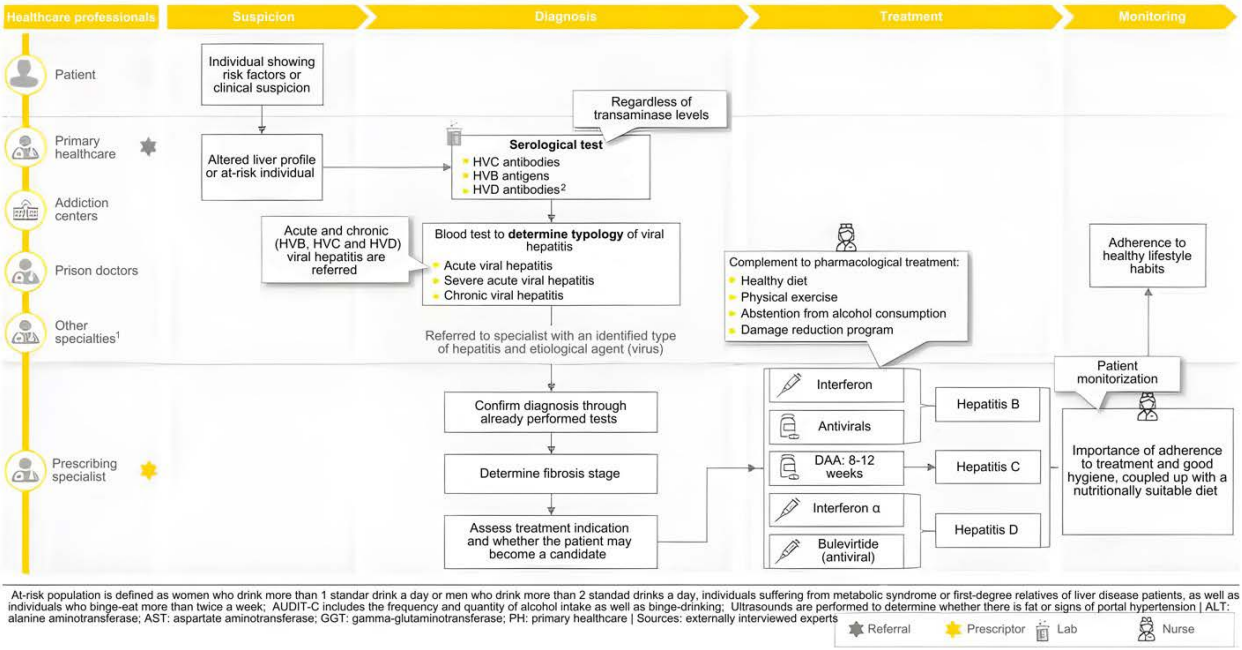

Figure A9 | Outline of patient circuit in viral hepatitis [9]

Patient circuit in viral hepatitis may begin through different specialties and levels of care; however, the process tends to become unified once diagnosis is established, with hepatologists overseeing treatment and monitoring of patients with advanced viral hepatitis [9].

Suspicion

Suspicion may arise from alterations in liver profile after blood tests or the identification of viral hepatitis risk factors, such as the use of injectable drugs, nasally-consumed drugs, and/or unprotected sexual intercourse [9].

Primary healthcare physicians, healthcare professionals working in addiction centers, prison doctors, and other specialists are all involved in this stage.

Diagnosis

Once the healthcare professional suspects a possible hepatitis virus infection, they perform a serological test to detect HVC antibodies and HVB antigens. In case HVB antigens are found, another serological test is performed in order to detect HVD antibodies. After the serological test a blood test is also performed to determine the type of hepatitis that the patient suffers from, as well as whether it is acute, severely acute, or chronic [9].

Specialists confirm the diagnosis of viral hepatitis by revising previously performed diagnostic tests and by using FibroScan®, which sheds light on the degree of liver fibrosis.

Finally, the specialist will assess treatment indications and decide whether the patient may be a candidate [9].

Treatment

Patients diagnosed with hepatitis B are treated with interferon or antiviral drugs.

Patients diagnosed with hepatitis --C are treated with direct-action antivirals (DAA) for a period of 8-12 weeks.

Patients diagnosed with hepatitis D are treated with interferon alpha or Bulevirtide, which is an antiviral drug.

On the other hand, there is no pharmacological treatment for hepatitis A and E; as such, patients will have to follow a rest regime and abstain from alcohol consumption. Generally speaking, the patient will recover on their own, as the course of the disease is acute.

Lastly, pharmacological treatment should always be coupled with a healthy diet, such as Mediterranean diet, physical exercise, abstaining from alcohol consumption, and a harm reduction program if necessary. These non-pharmacological treatments will be overseen by nurses [9].

Monitoring

Nurses and specialists are both involved in this stage. It focuses primarily on the adherence to treatment, which tend to be long and patients may eventually stop taking their medication. Their lifestyle habits are also controlled.

It is worth noting that patients with drug- or alcohol-addictive behaviors must undergo frequent medical consultation to avoid relapse [9].

A5. Primary liver cancer

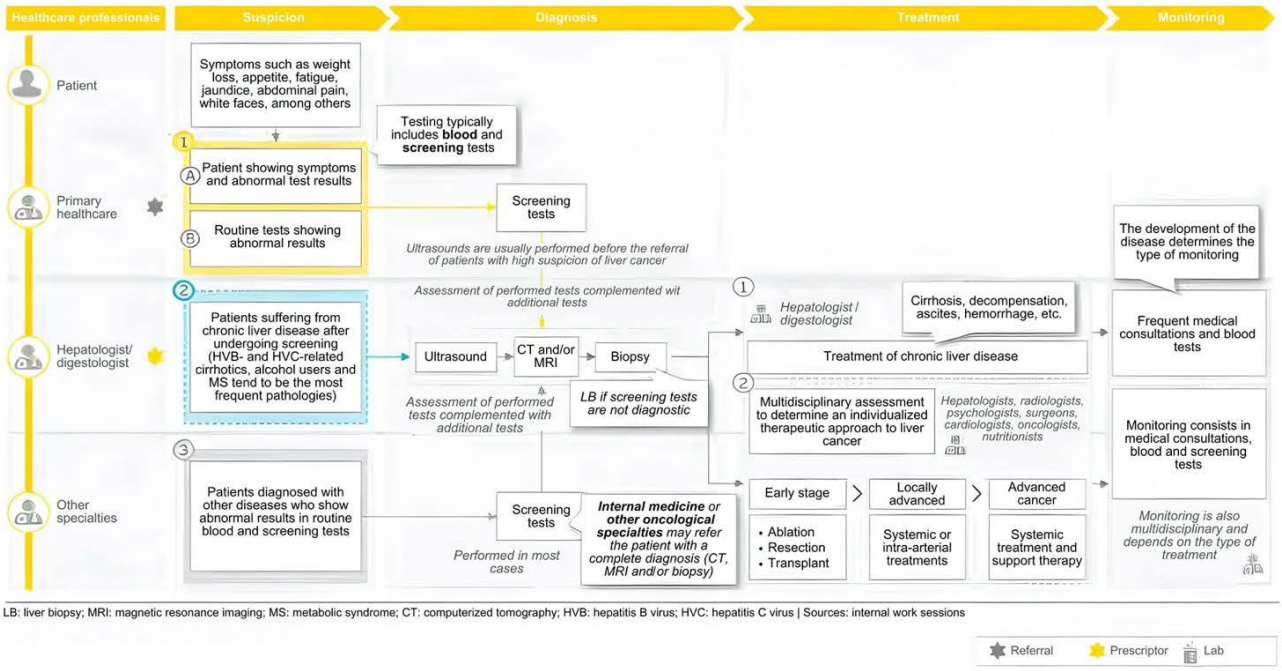

Figure A10 | Patient circuit in liver cancer [9]

The following patient circuit has been developed for two types of primary liver cancer: hepatocarcinoma and cholangiocarcinoma [9].

Managing liver cancer patients is a complex task and should always be done in the most individualized way possible. The following patient circuit offers a general overview of which might be the standard procedure for patients with HCC or cholangiocarcinoma. Similarly, treatment and monitoring must be individualized and may suffer changes and/or follow more than one treatment at once; as such, a more general overview of the most frequent treatments and their monitoring is also offered [9].

Suspicion

Suspicion may arise from: weight loss, increased appetite, fatigue, jaundice, abdominal pain and white feces, chronic liver disease or after blood tests showing an altered liver profile [9].

At this stage, primary healthcare physicians and specialists are all involved [9].

Patients showing symptoms may request primary healthcare consultation, during which a blood and/or screening test (ultrasound) should be performed, as they will indicate whether there is an alteration in liver function. It is also possible for asymptomatic patients to request medical consultation for routine tests, which may come back altered and showing signs of liver cancer [9].

The second way in which patients may be suspected of suffering from liver cancer is through direct contact with a hepatology area. Hepatologists perform screenings with patients suffering from chronic liver disease, as it is a risk factor for the development of liver cancer. These patients are typically diagnosed with HVB-, HVC-, alcohol-, or SM-related cirrhosis [9].

The third way in which patients may enter the circuit is through other medical areas, in which the patient is examined due to other reasons besides liver cancer, with their blood or imaging tests showing signs of impaired liver function [9].

Diagnosis

Patients initially managed through primary healthcare undergo an abdominal ultrasound. If the results suggest a potential liver cancer diagnosis, the patient is referred to a specialist. Other services may perform screening tests after referring the patient, in which case the specialist must revise their results and may perform complementary tests to confirm diagnosis [9].

It is important to note that internal medicine and oncology specialists typically refer the patient after having run all necessary tests and, as such, with a firm diagnosis [9].

The diagnostic process followed by hepatologists begins with an abdominal ultrasound, followed by a screening test, which may be performed through computerized tomography (CT) and/or magnetic resonance imaging (MRI). Lastly, if screening tests are not conclusive, a percutaneous liver biopsy (PLB) may be performed, although it is worth noting that it is an invasive test which entails certain risks [9].

Treatment

Patients diagnosed with liver cancer undergo a multidisciplinary assessment, performed by hepatologists, radiologists, psychologists, surgeons, cardiologists, oncologists and nutritionists among others, so as to determine the most efficient treatment for each patient. As mentioned above, cancer patients typically follow individualized treatment [9].

Figure A11 shows the different types of treatment that are typically followed depending on the evolutionary stage that the cancer patient is in [9].

Figure A11 | Treatment according to liver cancer stage [9]

Besides pharmacological treatment for liver cancer, specialists must also oversee the treatment of chronic liver disease, which typically develops complications such as cirrhosis, liver decompensation, ascites, and hemorrhage [9].

Monitoring

The monitoring stage in liver cancer is based on the pharmacological treatment prescribed by the specialist. However, it also entails continued medical consultations, blood and screening tests, and a close follow-up of the level of adherence to treatment in prolonged cases [9].

Chronic disease is monitored by the specialist, along with its treatment. Such monitoring is based on medical consultations and blood tests with a determined periodicity, in order to assess the evolution of liver disease [9].

A6. Transplants

Patient circuits for patients with LT are somewhat different from those previously described in this report. The circuit is split into two sections: pre-transplant and transplant, and post-transplant [9].

Circuits typically begin through the diagnosis of a decompensated liver disease, introduced immediately to the pre-transplantation and transplant procedure. Once the patient is transplanted, they move on to the post-transplant stage, which will be coordinated through an inter-consultation system. The following figure illustrates the patient circuit, which specifies which medical professionals are involved in each stage of the process, as well as their roles in each of the two stages [9].

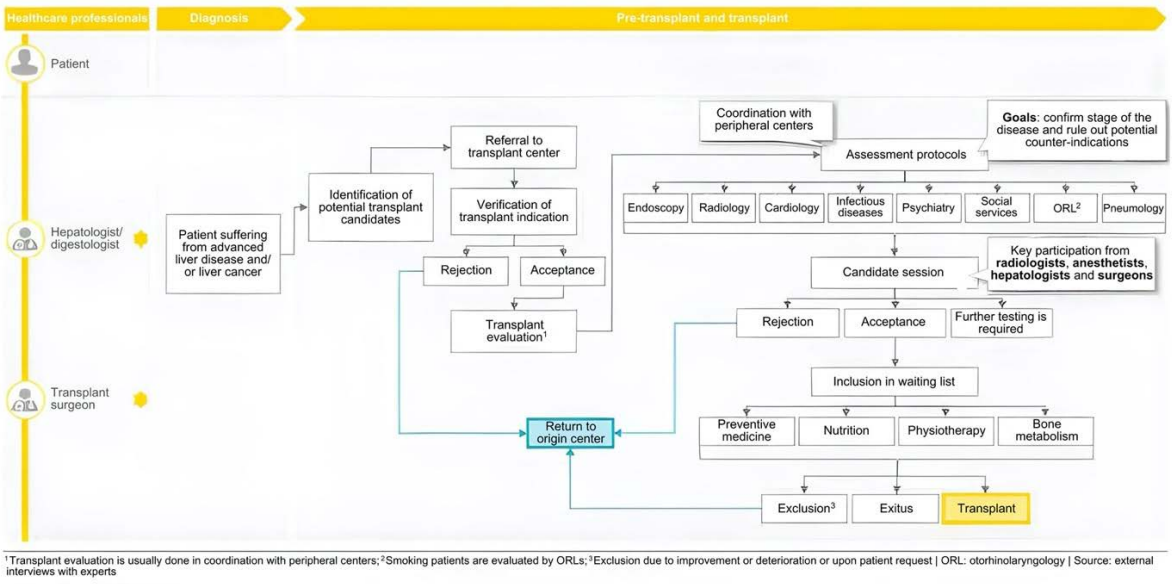

Figure A12 | Outline of patient circuit in liver transplant [9]

Figure A12 shows the first stage of patient circuits: pre-transplant and transplant.

Throughout this first stage, specialists and liver surgeons are involved in patient care [9].

Unlike other patient circuits, the suspicion stage has not been included, as the patient is already diagnosed with advanced liver disease and/or liver cancer [9].

An initial identification is performed in order to determine which patients are suitable candidates for transplantation, for which a verification of their transplant indication is performed at a transplant center. Such verification may be rejected, i.e., the patient returns to their center of origin; if accepted, the patient undergoes transplant evaluation [9].

Transplant evaluation takes place following evaluation protocols, which aim to confirm the stage of the individual patient's disease and to rule out potential counter-indications. Evaluation protocols are generally conformed by healthcare professionals from different specialties, such as endoscopy, cardiology, radiology, psychiatry, social work, otorhinolaryngology, pneumology, and infectious diseases [9].

Once transplant evaluation takes place, a candidate session is held, in which radiologists, anesthetists, hepatologists, and surgeons are all essential. Patients may be rejected, accepted, or required to undergo further testing during this session. If rejected, the patient is transferred back to their center of origin; if further testing is required, the patient must undergo evaluation once again. If accepted, the patient will be included in a waiting list. During their time on the waiting list, preventive medicine specialists, nutritionists, physiotherapists, and bone metabolism specialist will perform a series of test to assess patient conditions. During their time on the waiting list, patients may die, become excluded due to a worsening or improvement of their clinical situation, or be transplanted [9].

If transplanted, the patient moves on to the next stage: post-transplant. This stage is detailed in the following figure:

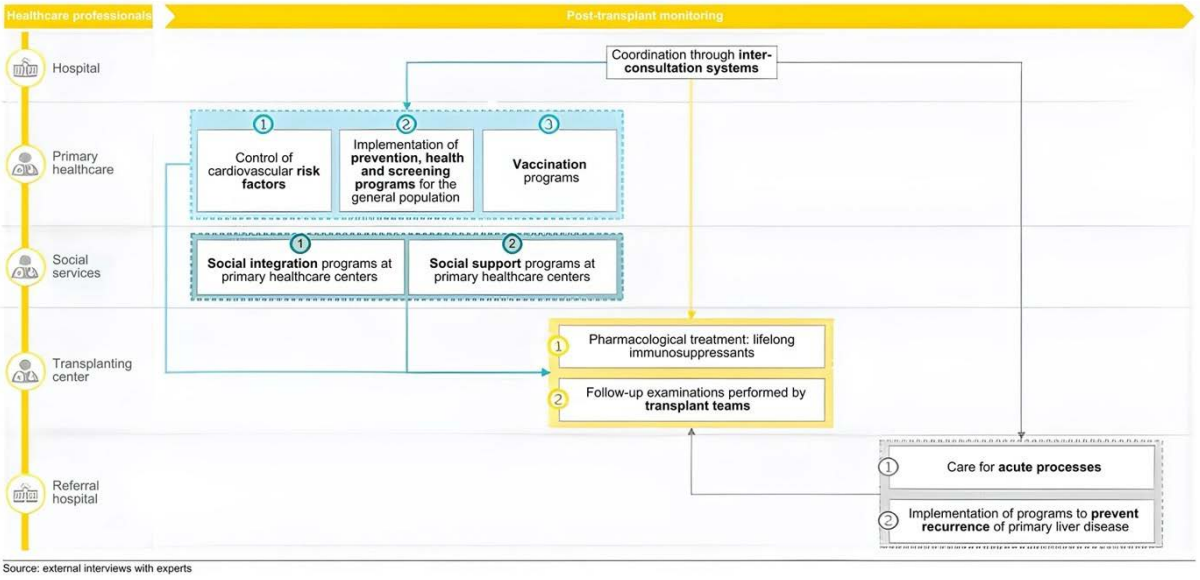

Figure A13 | Outline of patient circuit in liver transplant [9]

Once the patient is transplanted, they go on to the post-transplant monitoring stage, which is coordinated through an inter-consultation system [9].

Firstly, primary healthcare physicians are expected to control cardiovascular risk factors, to oversee patient vaccinations to avoid other types of infections, and to implement prevention programs and screenings for the general population. On the other hand, social services are involved in the implementation of integration and social support programs in primary healthcare centers [9].

Secondly, transplant centers are in charge of prescribing and overseeing pharmacological treatment for each patient. Patients are prescribed with lifelong immunosuppressants. Monitoring of transplant patients is typically carried out by transplant teams, which are formed by different specialties [9].

Thirdly, referral hospitals are responsible for caring for acute processes derived from transplantation, as well as implementing programs to prevent recurrence of primary liver disease [9].

It is important to note that transplant centers are central to the monitoring of transplanted patients. In this sense, patients who remain hospitalized at their referral hospital due to acute processes or primary relapsed disease will end up at a transplant center; as such, coordination between primary healthcare centers, transplant centers, and referral hospitals becomes essential in an effective management of liver transplant [9].

Figure index

Glossary

AEEH – Asociación española para el estudio del hígado
ALT – Alanine aminotransferase
ANA – Antinuclear antibodies
AP – Alkaline phosphatase
ANCA – Neutrophyl anti-cytoplasm
ARLD – Alcohol-related liver disease
AST - Aspartate transaminase
BCLC – Barcelona clinic liver cancer
CAT – Computerized axial tomography
CT – Computerized tomography
DAA – Direct-action antivirals
DILI – Drug-induced liver injury
DM - Diabetes mellitus
FIB - 4 - Fibrosis - 4 scoring
GGT- Gamma-glutamil transferase
HAV – Hepatitis A virus
HBV – Hepatitis B virus
HCC – Hepatocellular carcinoma
HCV – Hepatitis C virus
HDV – Hepatitis D virus
HEV – Hepatits E virus
HFS - Hepatic fibrosis score
HIV – Human immunodeficiency virus
IgG - Inmunoglobuline G
IgM - Inmunoglobuline M
Kpa – Kilopascal
LT – Liver transplant
MASLD – Metabolic dysfunction-associated steatotic liver disease
MR – Magnetic resonance
MS – Metabolic syndrome
NAFL – Non-alcoholic fatty liver
NAFLD – Nonalcoholic fatty liver disease
NASH – Nonalcoholic steatohepatitis
NFS – NAFLD fibrosis score
ONT – Organización Nacional de Trasplantes
OPS – Organización Panamericana de la Salud
PH – Portal hypertension
PH – Primary healthcare
PLB – Percutaneous liver biopsy
SMA – Smooth anti-muscle antibodies
SNS - Sistema Nacional de Salud
SWOT – Strengths, Weaknesses, Opportunties and Threats

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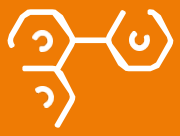

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