MASAC Document #281
(Replaces Document #270)

# MASAC RECOMMENDATIONS ON SCREENING FOR DEVELOPMENT OF HEPATOCELLULAR CANCER IN PERSONS WITH HEPATITIS B AND C

*The following recommendation was approved by the Medical and Scientific Advisory Council (MASAC) on September 22, 2023, and endorsed by the NHF Board of Directors on October 27, 2023.*

## Statement of Problem

Patients with viral hepatitis due to hepatitis B (HBV) and C (HCV) infection have been shown to have a significantly increased risk of end-stage liver disease, hepatocellular cancer (HCC), and death due to these two complications of infection. The incidence of hepatocellular cancer (HCC) is rising in many countries, including the United States. Cirrhosis due to HBV and HCV infection is a major driving force behind the increased incidence in the US. Non-alcoholic fatty liver disease (NAFLD) and its more severe form (non-alcoholic steatohepatitis, NASH) are also rising in incidence with NASH-induced cirrhosis becoming the most common cause of cirrhosis in the United States. All causes of cirrhosis lead to an increased risk of developing hepatocellular cancer (HCC).

Surveillance for HCC involves determining who is at risk for the development of HCC and deciding how to screen, how frequently to screen, and what the process should be to follow up on abnormal results.

## Definition of the At-Risk Population

The incidence of HCC in a particular population of patients is used to determine if screening is appropriate for that population. Current guidelines published by the American Association for the Study of Liver Disease (AASLD) and the American Gastroenterology Association (AGA) (Loomba et al, Ref. 3) are based on a decades-old tenet of cost effectiveness being achieved if an intervention can be done at a cost of about $50,000 per year of life gained. There are published decision analysis/cost effectiveness models for HCC surveillance in chronic HBV/HCV infection and NASH. The risk of HCC is highest in patients who have cirrhosis, with an incidence of between 2-8% per year. Patients who are infected with HBV/HCV who do not have cirrhosis, or patients with NASH who do not have cirrhosis also have a higher risk of developing HCC so that screening may be indicated.

## Patients who have Been Successfully Treated for their Chronic Hepatitis C Infection

Patients with cirrhosis from HCV infection who are successfully treated and clear the HCV virus are likely to have a reduced risk of developing HCC; however, data quantifying this reduced risk are not clear. It is likely that continued surveillance will become cost-ineffective with time as the liver fibrosis improves and the risk of HCC diminishes. The current guidelines of the AASLD suggest that treated patients with advanced fibrosis or cirrhosis should continue to undergo surveillance for HCC every 4-8 months until there is evidence that their cirrhosis

and advanced fibrosis has resolved. The timeline for this improvement in fibrosis is unknown. Patients with risk factors for NAFLD continue to be at risk for HCC even after they have achieved eradication of their HCV infection. (see reference 7 for a list of risk factors that increase risk of HCC after HCV eradication.)

**Patients who are Co-infected with HCV and HIV**

Patients with HCV and Human Immunodeficiency Virus (HIV) (HCV-HIV) co-infection are likely to have advanced liver disease. When these patients develop cirrhosis, they are at increased risk of HCC and at higher risk for more aggressive HCC. Therefore, these co-infected patients should undergo HCC surveillance. The criteria for screening are the same as for mono-infected patients.

**Who to Screen for HCC:**

Based on guidelines from AASLD and the AGA (references below) these patients should be screened for HCC:

1. All patients with cirrhosis, regardless of the cause of their liver disease
2. Patients with NASH and stage 3 fibrosis (Metavir scale)
3. Patients with hepatitis B who meet certain age, gender and ethnicity characteristics:

**AASLD Guidelines 2018**

**Surveillance Benefit**

Asian (North, Southeast, East Asia [all countries], Australia and South Pacific [all countries except Australia and New Zealand]) male hepatitis B carriers over age 40
Asian female hepatitis B carriers over age 50
Hepatitis B carrier with family history of HCC
African and/or African American/Blacks with hepatitis B
Hepatitis B carriers with cirrhosis
Hepatitis C cirrhosis
Stage 4 primary biliary cholangitis
Genetic hemochromatosis and cirrhosis
Alpha-1-antitypsin deficiency and cirrhosis
Other cirrhosis

**Surveillance Benefit Uncertain**

Hepatitis B carrier younger than 40 (males) or 50 (females)
Hepatitis C and stage 3 fibrosis
NAFLD without cirrhosis

Marrero JA, Hepatology 2018; 68 (2): 723-750.

**How to Screen for HCC**

The most widely used radiological test for surveillance for HCC is an ultrasound. Ultrasound has been reported to have a sensitivity of greater than 90% when used as a screening test. Screening should be done using a high-quality ultrasound, specifically an ultrasound that is technically adequate based on overall radiologist impression of quality based on anatomic coverage (at least 2/3 of the liver visualized), visual clarity of the liver parenchyma (including heterogeneity and nodularity), depth of penetration, and other exam limitations such as obstruction from ribs, lungs,

or bowel gas (Simmons et al, Ref. 4). In multivariable analysis in the latter study, inadequate ultrasound quality was directly associated with male gender, increasing BMI, in-patient status, alcohol-related cirrhosis, and NASH-related cirrhosis.

The use of a CT scan as a screening tool for HCC has been studied; however, its performance characteristics are not known. The theoretical disadvantage of contrast use and high levels of radiation involved in a 4-phase CT scan have limited its use as a screening test for HCC. Strategies for alternating testing modalities (e.g. ultrasound alternating with CT scan or MRI) have no basis.

**How to Follow-up Abnormal Screening Results**

Patients with a high risk for HCC who enter a surveillance system need to be notified of an abnormal result. An abnormal result is a nodule not seen on a prior study but now noted to be present, regardless of the size of the nodule. An enlarging mass or nodule is always considered abnormal and should lead to further characterization. Most liver centers use an MRI or 4-phase CT to follow-up on an abnormal ultrasound. Individual centers may prefer one modality over the other. Patients with abnormal screening results should be referred for coordinated care with a hepatologist.

**Recommendations**

1. All patients with known HCV or HBV infection should have an indirect test for liver fibrosis.
2. Patients with hemophilia and hepatitis C who have documented cirrhosis should be screened for the development of hepatocellular cancer (HCC).
3. Patients with hemophilia who have hepatitis B infection and are not cirrhotic should be screened for the development of hepatocellular cancer (HCC) in specific cases based on age, gender, and ethnicity. https://www.aasld.org/practice-guidelines/chronic-hepatitis-b
4. Patients with hemophilia who have NASH and/or advanced fibrosis (F3 on the Metavir fibrosis scale) but are not cirrhotic should be screened for the development of hepatocellular cancer (HCC).
5. Screening for HCC should be done at 4 to 8-month intervals. There is no need to change the frequency of the screening examinations for patients with a higher risk of HCC.
6. Patients with cirrhosis who have been treated and have cleared the hepatitis C virus should also continue to be screened to determine the amount of fibrosis with elastography and/or specialized blood tests annually until their liver fibrosis has improved to the point that they are no longer cirrhotic. This improvement in fibrosis is anticipated but does not always happen. Improvement in fibrosis may take years to reach the point where the risk of HCC is minimal and HCC screening is no longer warranted. https://www.aasld.org/practice-guidelines/hepatitis-c

**References**


1. Bruix J, Sherman M, American Association for the Study of Liver Diseases. Management of hepatocellular carcinoma: an update. Hepatology. 2011;53(3):1020-1022.
2. Lok AS, Seeff LB, Morgan TR, di Bisceglie AM, Sterling RK, Curto TM, Everson GT, Lindsay KL, Lee WM, Bonkovsky HL, Dienstag JL, Ghany MG, Morishima C, Goodman

ZD; HALT-C Trial Group. Incidence of hepatocellular carcinoma and associated risk factorsin hepatitis C-related advanced liver disease. Gastroenterology. 2009;136(1):138-148.
3. Loomba R, Lim J, Patton H, El-Serag H. AGA clinical practice update on screening and surveillance for hepatocellular carcinoma in patients with nonalcoholic fatty liver disease: expert review. Gastroenterology. 2020;158(6):1822-1830.
4. Simmons O, Fetzer DT, Yokoo T, Marrero JA, Uopp A, Kono Y, Parikh ND, Browning T, Singal AG. Predictors of adequate ultrasound quality for hepatocellular carcinoma surveillance in patients with cirrhosis. Aliment Pharmacol Ther 2017;45(1):169-177.
5. Marrero JA, Kulik LM, Sirlin CB, Zhu AX, Finn RS, Abecassis MM, Roberts LR, Heimbach JK. Diagnosis, staging, and management of hepatocellular carcinoma: 2018 Practice Guidance by the American Association for the Study of Liver Diseases. Hepatology. 2018 Mar; 68(2): 723-750.
6. Ioannou GN, Beste LA, Green PK, Singal AG, Tapper EB, Waljee AK, Sterling RK, Feld Kaplan DE, Taddei TH, Berry K. Increased risk for hepatocellular carcinoma persists up to 10 years after HCV eradication in patients with baseline cirrhosis or high FIB-4 scores. Gastroenterology. 2019;157(5):1264-1278.
7. Benhammou JN, Moon AM, Pisegna JR, Su F, Vutien P, Moylan CA, Ioannou GN. Nonalcoholic fatty liver disease risk factors affect liver-related outcomes after direct-acting treatment for hepatitis C. Dig Dis Sci. 2021;66(7):2394-2406.