

Hepatitis B Virus Screening and Management for Patients With Cancer Prior to Therapy: ASCO Provisional Clinical Opinion Update.

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01 11 2020 27 7 2020 38 31 482174 3698 3715 31 01 2025 14 02 2025 14 02 2025 19 02 2025 This file is available for text mining. It may also be used consistent with the principles of fair use under the copyright law. Purpose: This Provisional Clinical Opinion update presents a clinically pragmatic approach to hepatitis B virus (HBV) screening and management.

All patients anticipating systemic anticancer therapy should be tested for HBV by three tests--hepatitis B surface antigen (HBsAg), hepatitis B core antibody (anti-HBc) total immunoglobulin (Ig) or IgG, and anti-hepatitis B surface antibody--but anticancer therapy should not be delayed. Findings of chronic HBV (HBsAg-positive) or past HBV (HBsAg-negative and anti-HBc-positive) infection require assessment of HBV reactivation risks.

Chronic HBV patients receiving systemic anticancer therapy should receive antiviral prophylactic therapy through and for minimum 12 months following anticancer therapy. Hormonal therapy alone should not pose a substantial risk of HBV reactivation in patients with chronic HBV receiving hormonal therapy alone; these patients may follow non-cancer HBV monitoring and treatment guidance. Coordination of care with a clinician experienced in HBV management is recommended for chronic HBV patients to determine HBV monitoring and long-term antiviral therapy after

completion of anticancer therapy.

Patients with past HBV infection undergoing anticancer therapies associated with a high risk of HBV reactivation, such as anti-CD20 monoclonal antibodies or stem cell transplantation, should receive antiviral prophylaxis during and for minimum 12 months after anticancer therapy completion with individualized management thereafter. Careful monitoring may be an alternative if patients and providers can adhere to frequent, consistent follow-up so antiviral therapy may begin at the earliest sign of reactivation. Patients with past HBV undergoing other systemic anticancer therapies not clearly associated with a high risk of HBV reactivation should be monitored with HBsAg and ALT during cancer treatment; antiviral therapy should commence if HBV reactivation occurs.

Additional information is available at www.asco.org/supportive-care-guidelines.

Additional information, including a supplement with additional evidence tables, slide sets, clinical tools and resources, and links to patient information at www.cancer.net, is available at www.asco.org/supportive-care-guidelines.

In 2010, the American Society of Clinical Oncology (ASCO) published a Provisional Clinical Opinion (PCO) on chronic hepatitis B virus (HBV) infection screening in patients receiving anticancer therapy for the treatment of malignant diseases. 1 PCOs are based on a rigorous, evidence-based approach and are designed to offer timely clinical direction to ASCO membership following publication or presentation of potentially practice-changing information.

PCOs are updated periodically based on review of recently published data. ASCO published an updated PCO on this topic in 2015 that introduced a risk-adaptive clinical algorithm to help clinicians identify and treat patients with HBV infection to reduce their risk of HBV reactivation from anticancer therapy. 2 This 2020 PCO update presents a clinically pragmatic approach to HBV screening and management that calls for universal HBV serologic testing of patients at the onset of anticancer therapy.

Largely due to limited data, there has been an historical lack of agreement regarding the preferred approach to HBV serologic testing in individuals with cancer, and, as a result, HBV testing has been suboptimal. 3 – 5 A range of strategies has been previously recommended. 2, 6, 7 These include a universal screening approach in which all patients with cancer are tested, or a risk-adaptive approach that tests only those cancer patients with risk factors for HBV infection or who would be treated with anticancer therapies associated with a high risk of HBV reactivation. Table 1 offers a summary of contemporary HBV screening guidelines.

ASCO's first PCO on this topic in 2010 recommended that clinicians consider screening patients belonging to groups at heightened risk for chronic HBV infection or if highly immunosuppressive therapies, such as rituximab or hematopoietic cell transplantation, were planned. 1 In 2015, 2 ASCO's updated PCO recommended that clinicians test patients for HBV infection before starting anti-CD20 therapy or hematopoietic stem cell transplantation and that providers also test patients with risk factors for HBV infection. However, the 2015 updated PCO highlighted that current evidence at that time was insufficient to support HBV testing for patients who had neither HBV risk factors nor anticipated anticancer therapy that was not associated with a high risk of reactivation. Notably, two panel members in 2015 offered a minority viewpoint, namely, a strategy of universal HBsAg and selective anti-HBc testing.

However, recent data have called into question the utility of risk-adaptive models for HBV screening. In a multicenter, prospective cohort study of HBV status among individuals newly diagnosed with cancer (n=3051), Ramsey et al. 8 found that 21% of patients with chronic HBV had no known risk factors for HBV infection. Hwang et al. 3 conducted a large prospective observational cohort study of 2124 patients with cancer to develop various HBV screening strategies prior to the initiation of systemic anticancer therapy. In the latter study, authors reported that, regardless of the

number of questions, about 90% of patients had at least one of the significant risk variables of HBV infection and thus would have needed serologic testing, making selective screening inefficient and impractical.

The results of these 2 studies suggest that a universal screening approach, its potential harms (e.g., patient and clinician anxiety about management, financial burden associated with antiviral therapy) notwithstanding, 2, 9 is the most efficient, clinically pragmatic approach to HBV screening in persons anticipating systemic anticancer treatment. Universal HBV testing could identify all cancer patients at risk for HBV reactivation. 3 Risk-based screening approaches, by contrast, are difficult to implement—many oncologists may be unfamiliar with the risk factors for HBV infection or lack time to conduct a complete HBV risk assessment—and HBV screening rates are low. 10 These issues are discussed in more detail below in the Clinical Considerations section.

All patients with cancer anticipating systemic anticancer therapy should be tested for hepatitis B virus (HBV) by three tests—hepatitis B surface antigen (HBsAg), hepatitis B core antibody (anti-HBc) total immunoglobulin (Ig) or IgG, and antibody to hepatitis B surface antigen (anti-HBs) prior to, or at the beginning of, systemic anticancer therapy. Anticancer therapy should not be delayed for the results of these screening tests. Findings of chronic HBV (HBsAg-positive) or past HBV (HBsAg-negative and anti-HBc-positive with either negative or positive anti-HBs) infection require further action. (Type: evidence-based; benefits outweigh harms; Strength of recommendation: strong)

Patients with chronic HBV receiving any systemic anticancer therapy should receive antiviral prophylactic therapy for the duration of anticancer therapy, as well as for at least 12 months after receipt of the last anticancer therapy. Monitoring recommendations include checking alanine aminotransferase (ALT) and HBV DNA level at baseline prior to or at the beginning of their anticancer therapy, as well as every 6 months during antiviral therapy. Hepatitis flares, presenting as elevated ALT levels, can occur after the discontinuation of antiviral therapy. As such, ALT levels should be monitored frequently, at least monthly for the first 3 months after the cessation of antiviral therapy and every 3 months thereafter. Coordination of care with a clinician experienced in HBV management is highly recommended for patients with chronic HBV, especially to monitor for withdrawal flares, determine monitoring and antiviral therapy after the cessation of anticancer therapy, and evaluate for advanced liver disease such as cirrhosis or liver cancer (Type of recommendation: informal consensus, benefits outweigh harms; Strength of recommendation: strong).

Hormonal therapy without systemic anticancer therapy is unlikely to increase the risk of HBV reactivation in patients with chronic or past HBV. Antiviral therapy and management for these patients should follow national HBV guidelines, independent of cancer therapy, including management by a clinician experienced in HBV management for prevention of liver disease such as cirrhosis or liver cancer. Should their anticancer treatment regimen change beyond hormonal therapy alone, the risk of HBV reactivation based on their new anticancer therapy should be reassessed. (Type: informal consensus; benefits outweigh harms; Strength of recommendation: moderate)

Patients with past HBV receiving anticancer therapies associated with an established high risk of HBV reactivation, such as anti-CD20 monoclonal antibodies or stem-cell transplantation, should be started on antiviral prophylaxis at the beginning of anticancer therapy and continued on antiviral therapy for at least 12 months after the cessation of anticancer therapy. HBV DNA should be obtained at baseline and followed every 6 months during antiviral therapy. Patients with a negative anti-HBs may be at higher risk of HBV reactivation than patients who have a positive anti-HBs. An alternative pathway is careful monitoring with HBsAg and HBV DNA every 3 months, with immediate antiviral therapy at the earliest sign of HBV reactivation (appearance of HBsAg or HBV DNA > 1,000 IU/mL), so long as patients and providers are able to adhere to frequent and consistent follow-up during anticancer therapy and for up to 12 months after last anticancer therapy (as delayed HBV reactivation may occur years after cessation of anticancer therapy). If HBV DNA is

quantifiable but < 1,000 IU/mL, then repeat testing at monthly intervals may be indicated. Hepatitis flares, presenting as elevated ALT levels, can occur after the discontinuation of antiviral therapy. As such, ALT levels should be monitored frequently, at least monthly for the first 3 months after the cessation of antiviral therapy and every 3 months thereafter (Type of recommendation: informal consensus, benefits outweigh harms; Strength of recommendation: strong).

Patients with past HBV undergoing anticancer therapies that are not clearly associated with a high risk of HBV reactivation (eg, regimens that do not include anti-CD20 monoclonal antibodies or stem-cell transplantation) should be followed carefully during cancer treatment, with HBsAg and ALT testing every 3 months (with subsequent HBV DNA testing if a hepatitis flare develops), with initiation of antiviral therapy only if HBsAg becomes positive or HBV DNA exceeds 1,000 IU/mL in the setting of a hepatitis flare. Follow-up testing after the cessation of anticancer therapy is likely not necessary (Type of recommendation: informal consensus, benefits outweigh harms; Strength of recommendation: strong).

ASCO PCOs are updated by an Expert Panel on the basis of periodic review and analysis of new information on the topic. The members of the Expert Panel are listed in Appendix Table A1 (online only). This guidance product was developed by a multidisciplinary Expert Panel, which included a patient representative and an ASCO guidelines staff with health research methodology expertise. The Expert Panel met via teleconference and webinar, and the group corresponded through e-mail. Based upon the consideration of the evidence, the authors were asked to contribute to the development of the PCO, to provide critical review, and to finalize the provisional opinion. The PCO was sent for an open comment period of two weeks allowing the public to review and comment on the recommendations after submitting a confidentiality agreement. These comments were taken into consideration while finalizing the opinion. Members of the Expert Panel were responsible for reviewing and approving the penultimate version of the PCO, which was then circulated for external review, and submitted to the Journal of Clinical Oncology for editorial review and consideration for publication. All ASCO guidance products are ultimately reviewed and approved by the Expert Panel and the ASCO Clinical Practice Guidelines Committee prior to publication. All funding for the administration of the project was provided by ASCO.

The Clinical Practice Guidelines and other guidance published herein are provided by the American Society of Clinical Oncology, Inc. (ASCO) to assist providers in clinical decision making. The information therein should not be relied upon as being complete or accurate, nor should it be considered as inclusive of all proper treatments or methods of care or as a statement of the standard of care. With the rapid development of scientific knowledge, new evidence may emerge between the time information is developed and when it is published or read. The information is not continually updated and may not reflect the most recent evidence. The information addresses only the topics specifically identified therein and is not applicable to other interventions, diseases, or stages of diseases. This information does not mandate any particular course of medical care. Further, the information is not intended to substitute for the independent professional judgment of the treating provider, as the information does not account for individual variation among patients. Recommendations reflect high, moderate or low confidence that the recommendation reflects the net effect of a given course of action. The use of words like “must,” “must not,” “should,” and “should not” indicate that a course of action is recommended or not recommended for either most or many patients, but there is latitude for the treating physician to select other courses of action in individual cases. In all cases, the selected course of action should be considered by the treating provider in the context of treating the individual patient. Use of the information is voluntary. ASCO provides this information on an “as is” basis, and makes no warranty, express or implied, regarding the information. ASCO specifically disclaims any warranties of merchantability or fitness for a particular use or purpose. ASCO assumes no responsibility for any injury or damage to persons or property arising out of or related to any use of this information or for any errors or omissions.

The Expert Panel was assembled in accordance with ASCO's Conflict of Interest Policy Implementation for Clinical Practice Guidelines (“Policy,” found at <http://www.asco.org/rwc>). All members of the Expert Panel completed ASCO's disclosure form, which requires disclosure of

financial and other interests, including relationships with commercial entities that are reasonably likely to experience direct regulatory or commercial impact as a result of promulgation of the guideline. Categories for disclosure include employment; leadership; stock or other ownership; honoraria, consulting or advisory role; speaker's bureau; research funding; patents, royalties, other intellectual property; expert testimony; travel, accommodations, expenses; and other relationships. In accordance with the Policy, the majority of the members of the Expert Panel did not disclose any relationships constituting a conflict under the Policy.

ASCO staff conducted a search for new evidence on HBV screening in individuals with cancer to identify relevant randomized controlled trials (RCT) that have been published since the 2015 ASCO PCO. The PubMed database was searched from January 2014 to January 2020 (see Data Supplement).

A medical librarian at The University of Texas MD Anderson Cancer Center supplemented the search for RCTs with a broad search of the literature to identify studies on screening and management of hepatitis B infection among cancer patients receiving systemic anticancer therapy, including immunotherapies or chemotherapies, and studies on prevention of HBV reactivation after anticancer therapy. Controlled vocabulary supplemented with keywords was used to search Ovid Medline, Ovid Embase, and PubMed from January 2009 through January 2020 (see Data Supplement).

Articles were selected for inclusion in the review of the evidence if they were phase III randomized controlled trials (hepatitis B virus screening question) or studies of prevalence HBV infection, predictive models of HBV infection, or HBV reactivation. Articles were excluded from the review if they were (1) meeting abstracts not subsequently published in peer-reviewed journals; (2) editorials, commentaries, news articles, case reports, narrative reviews, studies of children; and (3) published in a non-English language.

As expected, the search conducted to identify RCTs of HBV screening in patients with cancer yielded no relevant records. The search, in combination with articles identified by individual Panel members, identified several practice guidelines that had been published since the 2015 PCO. 6 , 11 – 16 The recommendations for HBV screening, use of serological tests, and antiviral prophylaxis from selected national and international guidelines are summarized in Table 1 . Articles identified by individual Panel members, combined with results from the formal searches, informed the Panel's consensus opinions.

Absent evidence from RCTs on the comparative utility of risk-based HBV screening versus universal screening strategies or on the predictors of HBV reactivation, especially the risk caused by a myriad of anticancer therapies, the Panel outlined several clinical considerations to support and amplify the recommendations offered in the PCO and associated clinical algorithm (Fig 1).

The definition of HBV reactivation has been inconsistent, which has contributed to imprecise estimates of risk and incidence of reactivation. The Expert Panel supports the American Association for the Study of Liver Diseases definition of HBV reactivation and adverse clinical liver-associated outcomes as outlined in the 2018 HBV Guidance 17 and summarized in Table 2 . In our PCO (Fig 1), we use a simplified cut-off threshold of HBV DNA > 1,000 IU/mL to assist and guide oncology providers with respect to the threshold above which further management is warranted in patients with past HBV infection. Asymptomatic rises in HBV DNA are very different from clinical hepatitis flares and thus should be interpreted with caution depending on the definitions used.

Chronic HBV infection refers to patients who are HBsAg-positive regardless of anti-HBc status, although most will be anti-HBc-positive. Past HBV infection refers to patients who have a negative HBsAg with positive anti-HBc, regardless of anti-HBs status; HBV DNA is usually undetectable. Among patients with past HBV, if the anti-HBs is positive, then this is considered resolved HBV

infection; if the anti-HBs is negative, then this is considered isolated anti-HBc–positive. See Table 3 for details of the HBV conditions based on screening test results.

Since the Panel's 2015 PCO, 2 there has been a series of informative and independent studies to clarify the optimal screening HBV screening approach. Randomized clinical trials of universal HBV screening compared to HBV risk-based or no HBV screening are considered unethical to conduct, as patients with known HBV risk factors might be not tested. However, the following large, prospective cohort studies 3 , 8 , 18 provide strong, albeit indirect, evidence that supports universal HBV screening in patients with cancer.

In 2015, Brasseur et al. 18 published a study of 388 patients with a solid tumor who completed a brief survey about potential risks for HBV infection—including birthplace in high HBV prevalence area, drug use, transfusions, among others—and who had HBV testing over a 14-month period of time during 2012–2013 in Reims, France. The investigators found that the sensitivity and specificity of the HBV risk factor questions were 46% and 56%, respectively. However, this study's resultant poor positive predictive value (9%) of this selective tool discourages use of an HBV-risk factor approach to screening patients with cancer for HBV.

In 2019, Ramsey et al. 8 published a study of HBV, hepatitis C virus (HCV), and HIV screening among 3051 patients with a hematologic malignancy or a solid tumor awaiting any anticancer therapy over a nearly 42-month period of time during 2013–2017 among 18 institutions within the SWOG Cancer Research Network, a member of the National Clinical Trials Network. Participants completed a survey about viral risk factors drawn from the National Health Interview Survey and the Centers for Disease Control and Prevention (CDC) and had serologic testing for HBV, hepatitis C virus, and HIV. Among the patients with chronic HBV (prevalence 0.6%, 19/3050), 21% (n=4) had no known HBV risk factors. Among patients with past HBV (prevalence 6.5%; 197/3050), 27% (n=54) had no known HBV risk factors. HBV risk factors for this study did not include age or race/ethnicity, which could explain the difference in prevalence of HBV risk factors in this study compared to the study below. 3 In summary, this study by Ramsey et al. does not support HBV risk-based screening given that a large portion of patients with chronic or past HBV did not have known HBV risk factors, contributing to the evidence that indirectly supports universal HBV testing in patients with cancer prior to anticancer therapy.

In another prospective study, Hwang et al. 3 explored a broader set of HBV risk factors in a study of 2124 patients with a hematologic malignancy or a solid tumor awaiting systemic anticancer therapy over a 17-month period during 2013–2014 in Houston, Texas. Study participants were tested for HBV and completed a 19-item HBV risk survey based on the CDC hepatitis risk assessment that was modified to include ethnicity/race variables. Using bootstrapping methods, the investigators developed various models to determine the most efficient number and type of HBV risk questions to minimize the false negative rate so that patients with HBV would not be missed, as this would be potentially devastating after anticancer therapy. Brief risk tools of 5–7 items were developed which yielded high sensitivities of 99–100%. However, the specificities of the brief tools were low (<15%), likely due to the high prevalence of having at least one of the significant risk variables in the models—for instance, 76% of the participants were greater than 50 years of age. As such, nearly 90% of the patients who completed a survey would need serologic testing for HBV infection, making selective HBV screening impracticable among patients with cancer. 3

In view of these recent studies, the Panel recommends HBsAg and anti-HBc testing in all patients with cancer prior to systemic anticancer therapy to determine HBV status (see Table 3) and appropriate HBV management in order to prevent HBV reactivation (see HBV Management section below).

An alternative approach to screening using both HBsAg and anti-HBc tests would be to advise HBsAg testing in all cancer patients, regardless of treatment regimen, and to limit anti-HBc testing to those receiving cancer therapy for which there is an appreciable risk of reactivation thus requiring surveillance and/or antiviral therapy. However, the major challenge with such an approach is the

rapid evolution of cancer therapy and the unknown reactivation risk for many regimens. It is clear that for anti-HBc-positive patients receiving high-risk anticancer therapies like anti-CD20 monoclonal antibodies or stem cell transplantation, the risk of reactivation is substantial and either close monitoring or pre-emptive antiviral therapy is recommended. In contrast, for lower-risk anticancer therapies--likely most standard solid tumor regimens--the reactivation risk may be very low and surveillance or antiviral therapy may not be required. However, operationalizing such an alternative, universal HBV screening strategy may be difficult.

The Panel further recommends anti-HBs be performed as part of the screening panel. It is not only the standard of care for HBV screening aligned with public health guidelines, ¹² but a positive anti-HBs likely attenuates the risk of HBV reactivation in patients with past HBV infection. ¹⁷ In a meta-analysis of 20 studies involving 1672 patients with hematologic malignancies, the reactivation risk was 14% in 388 patients who were anti-HBc-positive and anti-HBs-negative while 5% in 1284 patients who were anti-HBc-positive and anti-HBs-positive. ¹⁹ Other studies have shown that the timing and presence of anti-HBs at baseline before anticancer therapy, ²⁰ as well as a high titer of anti-HBs, ²¹ is protective against HBV reactivation among patients with hematologic malignancies. A positive anti-HBs alone (with negative HBsAg and anti-HBc) indicates vaccine-induced protective immunity and would not require further testing or management.

The interpretation of HBV test results may be complicated in patients who have received intravenous immunoglobulin (IVIG) known to produce passive transfer of anti-HBc, leading to false-positive anti-HBc test results. To further complicate matters, patients with cancer who receive IVIG usually have a hematologic malignancy and could also be receiving anticancer therapies that pose a high risk of HBV reactivation, such as B-cell depleting strategies or stem cell transplantation. In one retrospective study conducted in a single institution during 2004–2011, ²² the rate of passive transfer of anti-HBc after IVIG was 15% and the probability of positive anti-HBc decreased with time after IVIG administration. As such, anti-HBc testing after IVIG should be interpreted with caution. Universal HBV screening before the initiation of IVIG administration in patients with cancer would, however, mostly obviate this diagnostic challenge.

Most published efforts use electronic health records (EHR). In primary care–based HBV screening, an EHR alert in Epic Systems was shown to significantly increase HBsAg testing in a high-risk patient population in a group of providers using alerts compared with a control group (odds ratio, 2.64; 95% CI, 1.88 to 3.73; $P < .001$). ²³ In another study, a simple alert system was used to promote the referral of HBsAg patients to hepatologists through EHR, increasing referrals from 28% (5/18) to 73% (11/15; $P = .009$). ²⁴

In one study, a multidisciplinary team of clinicians, pharmacists, and public health professionals prospectively studied HBV screening and antiviral use among patients in the Veterans Health Administration receiving anti-CD20 therapy. ²⁵ Using a comprehensive set of multimodal interventions which included pharmacy staff checking for HBV screening and treatment prior to anti-CD20 therapy and an electronic medication order review to assess appropriate HBV testing and antiviral treatment before anti-CD20 therapy, investigators found that HBV screening prior to anti-CD20 therapy increased national rates of HBV testing to >90% and antiviral prophylaxis to >80%.

In another study of 965 patients with cancer at a single hospital in Taiwan from 2011 to 2012 who received systemic anticancer therapy and were not previously screened for HBV, a computer assisted system was used to send reminders to oncology providers to order HBsAg prior to ordering anticancer therapy, and, if the test was positive, to start antiviral therapy and refer to hepatology. ²⁶ HBV screening increased from a baseline of 8% to an overall rate of 86% (825/965), without significant differences according to cancer type. However, the overall antiviral prophylactic rate was only 46% (61/134). The rates of antiviral prophylaxis were lower for doctors treating lung, breast, and colorectal cancers than for those treating hematological malignancies (all $p < 0.05$). The rate of HBV reactivation was lower in patients who received antiviral prophylaxis than in those who did not (1.6% vs. 15.1%; $p < 0.01$).

Chronic HBV infection, as part of its natural course, may lead to cirrhosis, liver failure, and/or hepatocellular carcinoma (HCC). The risks vary according to patient factors (eg, immune competence, sex, age, family history), viral factors (eg, viral load, genotype), as well as environmental factors (eg, concurrent viral infections, alcohol use, metabolic syndrome). 11 Patients with hematologic malignancies and chronic HBV are at high risk of HBV reactivation (approximately 50%) and associated adverse liver outcomes, and, as such, they should receive antiviral prophylaxis to prevent HBV reactivation. 17 , 27 , 28 Similarly, patients with HCC due to underlying chronic HBV should be continued or treated with antiviral therapy due to the high risk of reactivation—up to 30% after various systemic anticancer therapies including combined chemoradiation. 29 , 30 Antiviral therapy also reduces the risk of HCC recurrence after potentially curative HCC therapy. Patients with chronic HBV with solid tumors other than HCC are also at heightened risk for HBV reactivation and thus would need antiviral therapy. However, in this latter group, the optimal timing for the antiviral initiation is not yet clear, as strong data about the risk of HBV reactivation due to various anticancer therapies are not available. Until such data are available, our Panel recommends that HBsAg-positive patients with solid tumors should be initiated on antiviral prophylaxis before and continue through systemic anticancer therapy. In summary, patients with chronic HBV receiving any systemic anticancer therapy should be started on antiviral prophylaxis for the duration of anticancer therapy, as well as for at least 12 months after receipt of the last anticancer therapy, and they should have a baseline HBV DNA prior to or at the beginning of their anticancer therapy, as well as every 6 months during antiviral therapy.

One exception may be the HBsAg-positive patient receiving hormonal therapy alone. Based on unpublished analyses of data from the National Cancer Database (L. Nogueira, personal communication, January 2020), an estimated 12% of newly diagnosed cancer patients in 2016 received single-agent hormonal therapy as first-line treatment. This group included about 43% of patients diagnosed with breast cancer and 23% of patients diagnosed with prostate cancer. However, hormonal therapy with steroids such as used with abiraterone plus low-dose prednisone 31 could confer a higher risk of HBV reactivation than hormonal therapy alone, and these patients may need a personalized management plan including antiviral prophylaxis or close monitoring.

Regardless of whether patients with past HBV infection have resolved HBV infection or isolated anti-HBc positivity (see Table 3), it is important to note that covalently closed circular DNA remains and is capable of replicating in the liver of individuals with this serologic profile. It is believed that such replication is inhibited by a host's strong immune control and thus HBV reactivation occurs only with potent immunosuppression. Patients with past HBV with hematologic malignancies anticipating anti-CD20 or stem cell transplantation have a high risk of HBV reactivation. These patients should start antiviral prophylaxis prior to anticancer therapy and continue it at least 12 months after the end of anticancer therapy, and even longer as their cumulative risk of reactivation increases until nearly two years after the cessation of anticancer therapy. The risk of HBV reactivation is higher in patients with negative anti-HBs than in those who are anti-HBs-positive, supporting anti-HBs testing in these patients. In one study of 63 HBsAg-negative and anti-HBc-positive patients with lymphoma, undetectable anti-HBs at baseline prior to rituximab-containing anticancer therapy was a significant predictor of HBV reactivation (hazard ratio 3.51; 95% CI 1.37–8.98, $p=0.009$). 20

An alternative approach to antiviral prophylaxis among patients with a hematologic malignancy was evaluated by Seto et al. 32 but requires commitment to careful clinical and laboratory monitoring. In this study, 83 HBsAg-negative and anti-HBc-positive patients with a hematologic malignancy receiving anti-CD20 therapy were followed with frequent labs every four weeks without antiviral therapy. The rate of reactivation, defined as appearance of HBV DNA at any level, was 25% and, once reactivation developed, the follow-up frequency increased to every two weeks. All patients who developed HBV reactivation and had evidence of active HBV disease (defined in this study as HBsAg seroreversion from HBsAg-negative to HBsAg-positive or who had an increase in ALT > twice upper limit of normal) received antiviral therapy and all had normalization of ALT with return of HBV DNA to undetectable levels. There were no cases of clinical hepatitis, liver failure, or death.

Currently, there are seven anti-hepatitis B antiviral therapies and, among these, three are preferred medications--entecavir, tenofovir disoproxil fumarate, and tenofovir alafenamide--due to their higher potency and high viral resistance barrier. 17 These three antiviral therapies are recommended to be used in the prophylaxis or treatment of HBV reactivation and are recommended to be given concomitantly with anticancer therapy, although only the efficacy of entecavir has been established in a randomized clinical trial with the less potent antiviral lamivudine. 33 All of these antiviral therapies suppress HBV replication but do not eliminate the viral genome from the liver and thus require long-term therapy. It is important to test for HIV prior to starting entecavir, tenofovir disoproxil fumarate, or tenofovir alafenamide in patients with HBV since these medications have anti-HIV properties, and HIV monotherapy is not recommended for patients with HIV. Newer anti-HBV antiviral therapies are in development that may allow a functional cure or sustained HBsAg clearance and undetectable viral levels. 34

We have described the patient population at risk for HBV reactivation in the 2015 PCO. 2 In brief, HBV reactivation has been well-characterized among HBV patients with a hematologic malignancy where the risk of reactivation ranges from 48% among patients with chronic HBV to 18% among those with past HBV. 35 , 36 HBV reactivation has been studied less frequently among HBV patients with a solid tumor 37 where the risk of reactivation has been estimated to be approximately 25% among those with chronic HBV and 3% among those with past HBV.

Currently, there is a lack of data to accurately ascertain the risk of HBV reactivation by anticancer class or specific drug, apart from the established high risk after anti-CD 20 monoclonal antibodies or stem cell transplantation. Multi-agent regimens, varied duration of therapy, and effects of prior lines of therapy preclude precise estimates of HBV reactivation as the risk by drug or class would be unclear. We highlight several anticancer therapies where data is evolving, and treatment options are expanding.

Of concern is the recent signal of potential complications from HBV after checkpoint blockade immunotherapy. Previous immunotherapy clinical trials excluded HBV patients; however, a few case reports of HBV reactivation have been published. 38 , 39 Recently, a prospective study followed 129 HBsAg-positive patients after PD-1 blockade. 40 Among those who had undetectable HBV DNA and had not been on antiviral therapy at baseline, the rate of HBV reactivation was 21% (5/24). Specific challenges with checkpoint blockade include the known risks of immune-related hepatitis and further immune suppression and risk of HBV reactivation if patients receive high-dose steroids for immune-related adverse events. HBV DNA contains a transcriptional regulatory element that has been shown to be activated by glucocorticoids. 41

The risk of reactivation among HBsAg-positive HCC patients has been reported to be 6% after radiation therapy and 20% after radiation therapy and transarterial chemoembolization in one large retrospective study of 133 patients. 42 In another study that included 109 HBsAg-negative/anti-HBc-positive HCC patients, 43 the risk of reactivation was 14% after radiation therapy and transarterial chemoembolization among HCC patients with past HBV.

The reactivation risk identified from rituximab has been extended to other anti-CD20 therapies including obinutuzumab and ofatumumab. We anticipate other agents such as blinatumomab and inotuzumab producing B-cell aplasia to have high HBV reactivation risks; however, studies of these agents have excluded patients with HBV. Similarly, CD19 chimeric antigen receptor T-cells (CAR-T) represent a unique high-risk group based on biology that aims to cause B-cell aplasia. Most of these patients have received highly immunosuppressive lymphodepleting regimens and prior anti-CD20 exposure. Case reports of HBV reactivation have been reported after CAR-T therapy in patients with known HBV infection. 44 , 45 Taken together, regimens producing profound B-cell aplasia may warrant careful monitoring and may require HBV prophylaxis. For B-cell modulating agents such as Bruton tyrosine kinase inhibitors (e.g., ibrutinib), cases of HBV reactivation have been reported but the degree of risk has not yet been clearly established. 46 , 47

The decision for oncologists to screen aging patients with cancer who are debilitated or frail and whose life expectancy is limited warrants consideration of risks and benefits of screening and antiviral therapy. This could be explored using geriatric assessments to improve patient-centered communication about cancer care and management of comorbid conditions, as well as aging concerns. 48

The risk of HBV reactivation among patients with solid tumors—who make up the majority of patients with cancer—is very likely lower than for patients with hematologic malignancies. However, because these patients have not been well studied, large randomized studies are needed to determine optimal management strategies. In addition, patients with past HBV, especially those who are not receiving anti-CD20 therapy or stem cell transplantation, have a lower risk of HBV reactivation than those with chronic HBV; studies should be conducted to elucidate optimal clinical care paths for these patients.

Future studies will be needed to make universal HBV screening and linkage to care efficient and systematic, likely based in EHR systems. Ongoing studies of HBV tests such as ultrasensitive HBsAg, 49 HBV RNA, hepatitis B core antigen 50 are being studied and may be useful in predicting risk of HBV reactivation.

Identifying the mechanism and risks of reactivation due to specific types of anticancer drugs has been problematic. While prospective studies are needed, they would likely be impractical; thus, large, multicenter retrospective studies with long-term follow up may be a preferred option. Specifically, patients with cancer and past HBV infection, who represent a significant proportion of the cancer patient population (about 7%), 3, 8 could be at risk for adverse liver outcomes from newer anticancer therapies such as immunotherapy and should be systematically monitored. Our Panel specifically identified a research gap of HBV reactivation risks for the growing list of agents that deplete or modulate B-cells.

Anti-HBs testing allows for assessing immunity. Individuals who are negative for HBsAg and anti-HBc, as well as anti-HBs, have never been exposed to HBV, are not immune, and thus are susceptible to HBV infection. Vaccination can be recommended, taking into consideration a patient's clinical situation and timing. Insufficient data exist to recommend vaccination specifically for immunocompromised individuals, but cancer survivors who are not immunocompromised may fall into one of the other groups for whom vaccination is recommended. 51 Some recommendations suggest waiting 3–6 months after cessation of anticancer treatment. 52 Because anticancer therapy can dampen immunogenicity of HBV vaccination, higher doses or more intensive vaccination regimens may be needed to achieve protective levels of anti-HBs. If immunocompromised patients receive vaccination, post-vaccination serology testing has been suggested. 51 Future work is needed to determine optimal timing and best practices.

Among patients who have isolated anti-HBc-positive with negative HBsAg and anti-HBs, studies have shown that protective levels of anti-HBs can decrease risk of HBV reactivation, 19 – 21 Thus, future research should assess the efficacy of HBV vaccination to achieve protective anti-HBs levels, 53 which could decrease risk of HBV reactivation. 19 – 21

In the United States, the rise in the acute HBV infection due to the opioid crisis 54 may be shifting national HBV screening and vaccination practices to expand. A universal HBV screening strategy would be aligned with national universal screening guidelines for HCV 55 and for HIV. 56 Further, universal HBV screening before anticancer therapy may ultimately be pre-empted by universal population-based HBV screening and management.

The draft statements were released to the public for open comment from February 10, 2020, through February 24, 2020. Response categories of “Agree as written,” “Agree with suggested modifications,” and “Disagree. See comments” were captured for every proposed statement, and 25 written comments were received. A total of seven of the 10 respondents either agreed or agreed

with slight modifications with the recommendations, and three of the respondents disagreed with at least one of the recommendations. Panel members reviewed comments from all sources and determined whether to maintain original draft statements, revise with minor language changes, or consider major recommendation revisions. All changes were incorporated prior to Clinical Practice Guidelines Committee review and approval.

For recommendations and strategies to optimize patient-clinician communication, see Patient-Clinician Communication: American Society of Clinical Oncology Consensus Guideline. 57 Communication topics of particular relevance to HBV screening and management are briefly discussed below.

Patients should be informed of their HBV testing results.

Patients who are found to have chronic HBV infection should be informed of their status. These patients should be referred to and managed in collaboration with a clinician experienced in HBV management, which could include a hepatologist, an infectious disease clinician, a gastroenterologist, or a primary care provider with HBV experience. Even if HBV treatment is not indicated during their cancer treatment, it is important for them to receive ongoing care for their HBV, including assessment for long-term antiviral therapy based on standard HBV guidelines and evaluation for HCC screening. Patients with a positive HBsAg test should be counseled that they are potentially infectious to others through bloodborne, perinatal, and sexual transmission as well as through close household contact. 7, 10 Screening and vaccination of partners and household contacts is recommended.

Patients who have isolated anti-HBc may need further workup because the HBV management for these patients depends on the type of anticancer therapy administered. These patients are not at risk for transmission through sexually or close personal contact. 17

Patients with a detectable anti-HBs but are negative for HBsAg and anti-HBc can be counseled that they have protective levels of antibody from previous vaccination.

Patients who are positive for anti-HBc and anti-HBs have resolved hepatitis B infection and should be counseled that they are at risk, albeit lower than if they had a negative anti-HBs, of HBV reactivation.

Patients who are negative for all HBV screening tests (negative HBsAg, anti-HBc, and anti-HBs) are considered not to be immune to HBV, have never exposed to HBV, and may benefit from HBV vaccination 14 taking into consideration a patient's clinical situation and timing of anticancer therapy.

Although ASCO clinical practice guidelines represent expert recommendations on the best practices in disease management to provide the highest level of cancer care, it is important to note that many patients have limited access to medical care. Racial and ethnic disparities in health care contribute significantly to this problem in the United States. Patients with cancer who are members of racial/ethnic minorities suffer disproportionately from comorbidities such as HBV infection and could experience more substantial obstacles to receiving care. They face barriers due to language and culture are more likely to be uninsured, and they are at greater risk of receiving care of poor quality than other Americans. Many other patients lack access to care because of their geographic location and distance from appropriate treatment facilities. Awareness of these disparities in access to care should be considered in the context of this clinical practice guideline, and health care providers should strive to deliver the highest level of cancer care to these vulnerable populations.

Creating evidence-based recommendations to inform treatment of patients with additional chronic conditions, a situation in which the patient may have two or more such conditions—referred to as multiple chronic conditions (MCC)—is challenging. Patients with MCC are a complex and

heterogeneous population, making it difficult to account for all of the possible permutations to develop specific recommendations for care. In addition, the best available evidence for treating index conditions, such as cancer, is often from clinical trials whose study selection criteria may exclude these patients in order to avoid potential interaction effects or confounding of results associated with MCC. As a result, the reliability of outcome data from these studies may be limited, thereby creating constraints for expert groups to make recommendations for care in this heterogeneous patient population.

We lack evidence in patients with MCC. Important factors to consider are if concurrent medical conditions further amplify HBV reactivation risks (e.g., immunosuppression for other conditions), drug interactions with antiviral therapy, and patient goals. Accounting for these factors will promote shared decision making.

Increasingly, individuals with cancer are required to pay a larger proportion of their treatment costs through deductibles and co-insurance. 58 , 59 Higher patient out-of-pocket costs have been shown to be a barrier to initiating and adhering to recommended cancer treatments. 60 , 61 Discussion of cost can be an important part of shared decision-making. 62

The targeted literature search conducted for this cost section yielded 59 abstracts, of which six were considered relevant to the topic of HBV screening and management in patients with cancer anticipating systemic anticancer therapy. 63 – 68 Excluded from consideration by ASCO are cost-effectiveness analyses that lack contemporary cost data; agents that are not currently available in either the United States; and/or are industry-sponsored.

Table 4 summarizes the methods and results of the six cost-effectiveness analyses identified by the targeted literature search. The consistency of the results from studies estimating the cost-effectiveness of different screening or prophylaxis approaches vary depending on the population studied. Universal HBV screening 63 and antiviral prophylaxis approaches 64 , 68 were found to be cost-effective in studies of patients with hematological malignancies at high risk of HBV reactivation. Studies of solid tumor patients, by contrast, at lower risk of HBV reactivation due to the treatments received, have been less consistent. Universal HBV screening before the start of anticancer therapy for patients with solid tumors was found to be cost-effective in analyses conducted by Konijeti et al. 65 and by Wong et al., 67 but not cost-effective in analyses conducted by Hwang et al. 63 and Tan et al. 66 Additional research is needed on HBV screening to address cost-effectiveness more definitively, particularly in patients with solid tumors for whom adequate data on the reactivation risk of commonly used anticancer treatments are lacking.

The Expert Panel wishes to thank [Insert all external reviewers and CPGC reviewers] and the Clinical Practice Guidelines Committee for their thoughtful reviews and insightful comments on this PCO. The Panel also thanks Laurissa Gann, MSLS, AHIP, Manager, Education & Access Services, at MD Anderson Cancer Center for her assistance with the review of the literature; and Leticia Nogueira, PhD, MPH, Senior Principal Scientist, Health Services Research at the American Cancer Society, Inc. for conducting analyses to inform this PCO. Finally, the Panel is grateful to Brittany Harvey for her assistance with the manuscript preparation.

More information, including a supplement with additional evidence tables, slide sets, and clinical tools and resources, is available at www.asco.org/supportive-care-guidelines . Patient information is available at www.cancer.net .

Related ASCO Guidelines Integration of Palliative Care Into Standard Oncology Care: American Society of Clinical Oncology Clinical Practice Guideline Update (<http://ascopubs.org/doi/10.1200/JCO.2016.70.1474>)

Patient-Clinician Communication: American Society of Clinical Oncology Consensus Guideline (<http://ascopubs.org/doi/10.1200/JCO.2017.75.2311>)

Authors' disclosures of potential conflicts of interest and author contributions are found at the end of this article.

Hepatitis B Virus Screening Expert Panel Membership

20516452 10.1200/JCO.2010.30.0673 2. Hwang JP , Somerfield MR , Alston-Johnson DE , : Hepatitis B Virus Screening for Patients With Cancer Before Therapy: American Society of Clinical Oncology Provisional Clinical Opinion Update . J Clin Oncol 33 : 2212 – 20 , 2015 25964247 10.1200/JCO.2015.61.3745 PMC4477791 3. Hwang JP , Lok AS , Fisch MJ , : Models to Predict Hepatitis B Virus Infection Among Patients With Cancer Undergoing Systemic Anticancer Therapy: A Prospective Cohort Study . J Clin Oncol : JCO2017756387 , 2018 10.1200/JCO.2017.75.6387 PMC7351320 29447061 4. Hwang JP , Fisch MJ , Zhang H , : Low rates of hepatitis B virus screening at the onset of chemotherapy . J Oncol Pract 8 : e32 – 9 , 2012 23180996 10.1200/JOP.2011.000450 PMC3396827 5. Day FL , Link E , Thursky K , : Current hepatitis B screening practices and clinical experience of reactivation in patients undergoing chemotherapy for solid tumors: a nationwide survey of medical oncologists . J Oncol Pract 7 : 141 – 7 , 2011 21886492 10.1200/JOP.2010.000133 PMC3092651 6. Reddy KR , Beavers KL , Hammond SP , : American Gastroenterological Association Institute guideline on the prevention and treatment of hepatitis B virus reactivation during immunosuppressive drug therapy . Gastroenterology 148 : 215 – 9 ; quiz e16–7 , 2015 25447850 10.1053/j.gastro.2014.10.039 7. Weinbaum CM , Williams I , Mast EE , : Recommendations for identification and public health management of persons with chronic hepatitis B virus infection . MMWR Recomm Rep 57 : 1 – 20 , 2008 18802412 8. Ramsey SD , Unger JM , Baker LH , : Prevalence of Hepatitis B Virus, Hepatitis C Virus, and HIV Infection Among Patients With Newly Diagnosed Cancer From Academic and Community Oncology Practices . JAMA Oncol 5 : 497 – 505 , 2019 30653226 10.1001/jamaoncol.2018.6437 PMC6459217 9. Artz AS , Paul S : Screening for Hepatitis B Virus Infection: Are We Asking the Right Questions? J Clin Oncol 36 : 935 – 936 , 2018 29470142 10.1200/JCO.2018.77.7128 10. Wi CI , Loo NM , Larson JJ , : Low level of hepatitis B virus screening among patients receiving chemotherapy . Clin Gastroenterol Hepatol 13 : 970 – 5 ; quiz e51 , 2015 25460017 10.1016/j.cgh.2014.10.032 PMC4547834 11. Terrault NA , Bzowej NH , Chang KM , : AASLD guidelines for treatment of chronic hepatitis B . Hepatology 63 : 261 – 83 , 2016 26566064 10.1002/hep.28156 PMC5987259 12. LeFevre ML , Force USPST: Screening for hepatitis B virus infection in nonpregnant adolescents and adults: U.S. Preventive Services Task Force recommendation statement . Ann Intern Med 161 : 58 – 66 , 2014 24863637 10.7326/M14-1018 13. Doyle J , Raggatt M , Slavin M , : Hepatitis B management during immunosuppression for haematological and solid organ malignancies: an Australian consensus statement . Med J Aust 210 : 462 – 468 , 2019 31104328 10.5694/mja2.50160 14. Abara WE , Qaseem A , Schillie S , : Hepatitis B Vaccination, Screening, and Linkage to Care: Best Practice Advice From the American College of Physicians and the Centers for Disease Control and Prevention . Ann Intern Med 167 : 794 – 804 , 2017 29159414 10.7326/M17-1106 15. Dreyling M , Ghielmini M , Rule S , : Newly diagnosed and relapsed follicular lymphoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up . Ann Oncol 27 : v83 – v90 , 2016 27664263 10.1093/annonc/mdw400 16. Arora A , Anand AC , Kumar A , : INASL Guidelines on Management of Hepatitis B Virus Infection in Patients receiving Chemotherapy, Biologicals, Immunosuppressants, or Corticosteroids . J Clin Exp Hepatol 8 : 403 – 431 , 2018 30568345 10.1016/j.jceh.2018.06.010 PMC6286881 17. Terrault NA , Lok ASF , McMahon BJ , : Update on prevention, diagnosis, and treatment of chronic hepatitis B: AASLD 2018 hepatitis B guidance . Hepatology 67 : 1560 – 1599 , 2018 29405329 10.1002/hep.29800 PMC5975958 18. Brasseur M , Heurgue-Berlot A , Barbe C , : Prevalence of hepatitis B and C and sensibility of a selective screening questionnaire in patients receiving chemotherapy for solid tumors . BMC Cancer 15 : 999 , 2015 26694960 10.1186/s12885-015-2033-z PMC4688993 19. Paul S , Dickstein A , Saxena A , : Role of surface antibody in hepatitis B reactivation in patients with resolved infection and hematologic malignancy: A meta-analysis . Hepatology 66 : 379 – 388 , 2017 28128861 10.1002/hep.29082 PMC6485929 20. Seto WK , Chan TS , Hwang YY , : Hepatitis B reactivation in patients with previous hepatitis B virus exposure undergoing rituximab-containing chemotherapy for lymphoma: a prospective study . J Clin Oncol 32 : 3736 – 43 , 2014 25287829 10.1200/JCO.2014.56.7081 21. Yang HC , Tsou HH ,

Pei SN , : Quantification of HBV core antibodies may help predict HBV reactivation in patients with lymphoma and resolved HBV infection . *J Hepatol* 69 : 286 – 292 , 2018 29551710 10.1016/j.jhep.2018.02.033 22. Lu H , Lok AS , Warneke CL , : Passive transfer of anti-HBc after intravenous immunoglobulin administration in patients with cancer: a retrospective chart review . *Lancet Haematol* 5 : e474 – e478 , 2018 30290904 10.1016/S2352-3026(18)30152-2 PMC6247917 23. Chak E , Taefi A , Li CS , : Electronic Medical Alerts Increase Screening for Chronic Hepatitis B: A Randomized, Double-Blind, Controlled Trial . *Cancer Epidemiol Biomarkers Prev* 27 : 1352 – 1357 , 2018 30089680 10.1158/1055-9965.EPI-18-0448 PMC6214733 24. Fujii H , Yamaguchi S , Kurai O , : Putting “sticky notes” on the electronic medical record to promote intra-hospital referral of hepatitis B and C virus-positive patients to hepatology specialists: an exploratory study . *BMC Infect Dis* 16 : 410 , 2016 27519695 10.1186/s12879-016-1765-y PMC4983008 25. Jasmine Bullard A , Cunningham FE , Volpp BD , : Preventing Hepatitis B Reactivation During Anti-CD20 Antibody Treatment in the Veterans Health Administration . *Hepatol Commun* 2 : 1136 – 1146 , 2018 30202826 10.1002/hep4.1238 PMC6128236 26. Sun WC , Hsu PI , Yu HC , : The compliance of doctors with viral hepatitis B screening and antiviral prophylaxis in cancer patients receiving cytotoxic chemotherapy using a hospital-based screening reminder system . *PLoS One* 10 : e0116978 , 2015 25658926 10.1371/journal.pone.0116978 PMC4319781 27. Lau GK , Yiu HH , Fong DY , : Early is superior to deferred preemptive lamivudine therapy for hepatitis B patients undergoing chemotherapy . *Gastroenterology* 125 : 1742 – 9 , 2003 14724827 10.1053/j.gastro.2003.09.026 28. Hsu C , Hsiung CA , Su IJ , : A revisit of prophylactic lamivudine for chemotherapy-associated hepatitis B reactivation in non-Hodgkin's lymphoma: a randomized trial . *Hepatology* 47 : 844 – 53 , 2008 18302293 10.1002/hep.22106 29. Jang JW , Bae SH , Choi JY , : Early virological response predicts outcome during extended lamivudine retreatment in patients with chronic hepatitis B who relapsed after initial HBeAg responses . *J Gastroenterol Hepatol* 21 : 384 – 91 , 2006 16509863 10.1111/j.1440-1746.2005.04035.x 30. Jang JH , Kim JW , Jeong SH , : Clevudine for chronic hepatitis B: antiviral response, predictors of response, and development of myopathy . *J Viral Hepat* 18 : 84 – 90 , 2011 20196804 10.1111/j.1365-2893.2010.01281.x 31. Fizazi K , Tran N , Fein L , : Abiraterone plus Prednisone in Metastatic, Castration-Sensitive Prostate Cancer . *N Engl J Med* 377 : 352 – 360 , 2017 28578607 10.1056/NEJMoa1704174 32. Seto WK , Chan TS , Hwang YY , : Monitoring and Treatment of Patients Undergoing Immunotherapy With Anti-CD20 Who are Exposed to HBV . *Clin Gastroenterol Hepatol* 17 : 1410 – 1412 , 2019 30243760 10.1016/j.cgh.2018.09.020 33. Huang H , Li X , Zhu J , : Entecavir vs lamivudine for prevention of hepatitis B virus reactivation among patients with untreated diffuse large B-cell lymphoma receiving R-CHOP chemotherapy: a randomized clinical trial . *JAMA* 312 : 2521 – 30 , 2014 25514302 10.1001/jama.2014.15704 34. Soriano V , Barreiro P , Benitez L , : New antivirals for the treatment of chronic hepatitis B . *Expert Opin Investig Drugs* 26 : 843 – 851 , 2017 10.1080/13543784.2017.1333105 28521532 35. Loomba R , Rowley A , Wesley R , : Systematic review: the effect of preventive lamivudine on hepatitis B reactivation during chemotherapy . *Ann Intern Med* 148 : 519 – 28 , 2008 18378948 10.7326/0003-4819-148-7-200804010-00008 PMC2729097 36. Huang YH , Hsiao LT , Hong YC , : Randomized controlled trial of entecavir prophylaxis for rituximab-associated hepatitis B virus reactivation in patients with lymphoma and resolved hepatitis B . *J Clin Oncol* 31 : 2765 – 72 , 2013 23775967 10.1200/JCO.2012.48.5938 37. Paul S , Saxena A , Terrin N , : Hepatitis B Virus Reactivation and Prophylaxis During Solid Tumor Chemotherapy: A Systematic Review and Meta-analysis . *Ann Intern Med* 164 : 30 – 40 , 2016 26595058 10.7326/M15-1121 PMC6410701 38. Lake AC : Hepatitis B reactivation in a long-term nonprogressor due to nivolumab therapy . *AIDS* 31 : 2115 – 2118 , 2017 28906278 10.1097/QAD.0000000000001599 39. Pandey A , Ezemenari S , Liaukovich M , : A Rare Case of Pembrolizumab-Induced Reactivation of Hepatitis B . *Case Rep Oncol Med* 2018 : 5985131 , 2018 30416833 10.1155/2018/5985131 PMC6207901 40. Zhang X , Zhou Y , Chen C , : Hepatitis B virus reactivation in cancer patients with positive Hepatitis B surface antigen undergoing PD-1 inhibition . *J Immunother Cancer* 7 : 322 , 2019 31753012 10.1186/s40425-019-0808-5 PMC6873745 41. Tur-Kaspa R , Burk RD , Shaul Y , : Hepatitis B virus DNA contains a glucocorticoid-responsive element . *Proc Natl Acad Sci U S A* 83 : 1627 – 31 , 1986 3006059 10.1073/pnas.83.6.1627 PMC323136 42. Jun BG , Kim YD , Kim SG , : Hepatitis B virus reactivation after radiotherapy for hepatocellular carcinoma and efficacy of antiviral treatment: A multicenter study . *PLoS One* 13 : e0201316 , 2018 30059513 10.1371/journal.pone.0201316 PMC6066246 43. Jang JW , Kim YW , Lee SW , : Reactivation of hepatitis B virus in

HBsAg-negative patients with hepatocellular carcinoma . PLoS One 10 : e0122041 , 2015 25894607 10.1371/journal.pone.0122041 PMC4403914 44. Wei J , Zhu X , Mao X , : Severe early hepatitis B reactivation in a patient receiving anti-CD19 and anti-CD22 CAR T cells for the treatment of diffuse large B-cell lymphoma . J Immunother Cancer 7 : 315 , 2019 31753002 10.1186/s40425-019-0790-y PMC6868854 45. Strati P , Nastoupil LJ , Fayad LE , : Safety of CAR T-cell therapy in patients with B-cell lymphoma and chronic hepatitis B or C virus infection . Blood 133 : 2800 – 2802 , 2019 31101626 10.1182/blood.2019000888 PMC7265784 46. Hammond SP , Chen K , Pandit A , : Risk of hepatitis B virus reactivation in patients treated with ibrutinib . Blood 131 : 1987 – 1989 , 2018 29490923 10.1182/blood-2018-01-826495 47. Malek AE , Nieto Y , Szvalb AD , : Hepatitis B Virus-associated Liver Failure in a Patient With B-cell Non-Hodgkin Lymphoma After Anti-cancer Therapy Including Ibrutinib . Clin Lymphoma Myeloma Leuk 20 : e124 – e127 , 2020 31932250 10.1016/j.clml.2019.12.006 PMC8262650 48. Mohile SG , Epstein RM , Hurria A , : Communication With Older Patients With Cancer Using Geriatric Assessment: A Cluster-Randomized Clinical Trial From the National Cancer Institute Community Oncology Research Program . JAMA Oncol : 1 – 9 , 2019 10.1001/jamaoncol.2019.4728 PMC6865234 31697365 49. Shinkai N , Kusumoto S , Murakami S , : Novel monitoring of hepatitis B reactivation based on ultra-high sensitive hepatitis B surface antigen assay . Liver Int 37 : 1138 – 1147 , 2017 27992664 10.1111/liv.13349 50. Seto WK , Wong DK , Chan TS , : Association of Hepatitis B Core-Related Antigen With Hepatitis B Virus Reactivation in Occult Viral Carriers Undergoing High-Risk Immunosuppressive Therapy . Am J Gastroenterol 111 : 1788 – 1795 , 2016 27644733 10.1038/ajg.2016.436 51. Schillie S , Vellozzi C , Reingold A , : Prevention of Hepatitis B Virus Infection in the United States: Recommendations of the Advisory Committee on Immunization Practices . MMWR Recomm Rep 67 : 1 – 31 , 2018 10.15585/mmwr.rr6701a1 PMC5837403 29939980 52. Rubin LG , Levin MJ , Ljungman P , : 2013 IDSA clinical practice guideline for vaccination of the immunocompromised host . Clin Infect Dis 58 : e44 – 100 , 2014 24311479 10.1093/cid/cit684 53. Ozkurt ZN , Suyani E , Haznedar R , : A Randomized Study Comparing the Efficacy of Three Hepatitis B Vaccine Induction Regimens in Adult Patients with Hematological Malignancies . Turk J Haematol 33 : 231 – 5 , 2016 27094506 10.4274/tjh.2015.0079 PMC5111469 54. Harris AM , Iqbal K , Schillie S , : Increases in Acute Hepatitis B Virus Infections - Kentucky, Tennessee, and West Virginia, 2006–2013 . MMWR Morb Mortal Wkly Rep 65 : 47 – 50 , 2016 26821369 10.15585/mmwr.mm6503a2 55. Force USPST , Owens DK , Davidson KW , : Screening for Hepatitis C Virus Infection in Adolescents and Adults: US Preventive Services Task Force Recommendation Statement . JAMA , 2020 10.1001/jama.2020.1123 32119076 56. Branson BM , Handsfield HH , Lampe MA , : Revised recommendations for HIV testing of adults, adolescents, and pregnant women in health-care settings . MMWR Recomm Rep 55 : 1 – 17 ; quiz CE1–4 , 2006 16988643 57. Gilligan T , Coyle N , Frankel RM , : Patient-Clinician Communication: American Society of Clinical Oncology Consensus Guideline . J Clin Oncol 35 : 3618 – 3632 , 2017 28892432 10.1200/JCO.2017.75.2311 58. Schnipper LE , Davidson NE , Wollins DS , : American Society of Clinical Oncology Statement: A Conceptual Framework to Assess the Value of Cancer Treatment Options . J Clin Oncol 33 : 2563 – 77 , 2015 26101248 10.1200/JCO.2015.61.6706 PMC5015427 59. Schnipper LE , Davidson NE , Wollins DS , : Updating the American Society of Clinical Oncology Value Framework: Revisions and Reflections in Response to Comments Received . J Clin Oncol 34 : 2925 – 34 , 2016 27247218 10.1200/JCO.2016.68.2518 60. Streeter SB , Schwartzberg L , Husain N , : Patient and plan characteristics affecting abandonment of oral oncolytic prescriptions . J Oncol Pract 7 : 46s – 51s , 2011 21886519 10.1200/JOP.2011.000316 PMC3092458 61. Dusetzina SB , Winn AN , Abel GA , : Cost sharing and adherence to tyrosine kinase inhibitors for patients with chronic myeloid leukemia . J Clin Oncol 32 : 306 – 11 , 2014 24366936 10.1200/JCO.2013.52.9123 62. Meropol NJ , Schrag D , Smith TJ , : American Society of Clinical Oncology guidance statement: the cost of cancer care . J Clin Oncol 27 : 3868 – 74 , 2009 19581533 10.1200/JCO.2009.23.1183 63. Hwang JP , Huang D , Vierling JM , : Cost-Effectiveness Analysis of Hepatitis B Virus Screening and Management in Patients With Hematologic or Solid Malignancies Anticipating Immunosuppressive Cancer Therapy . JCO Clin Cancer Inform 3 : 1 – 12 , 2019 10.1200/CCI.18.00097 PMC6874018 30892921 64. Crespo J , Esteban R , Torres C , : Cost-effectiveness of a hepatitis B virus screening strategy to prevent reactivation in patients with hematologic neoplasms . Rev Esp Enferm Dig 109 : 619 – 626 , 2017 28648087 10.17235/reed.2017.4693/2016 65. Konijeti GG , Grandhe S , Konerman M , : Cost-Effectiveness Analysis of Screening for Hepatitis B Virus Infection in Patients with Solid Tumors before Initiating

Chemotherapy . Clin Gastroenterol Hepatol , 2019 10.1016/j.cgh.2019.10.039 31678602 66. Tan G , Zhou K , Tan CH , : Cost Effectiveness of Universal Hepatitis B Virus Screening in Patients Beginning Chemotherapy for Sarcomas or GI Stromal Tumors . J Glob Oncol 2 : 186 – 199 , 2016 28717701 10.1200/JGO.2015.001669 PMC5497623 67. Wong WW , Hicks LK , Tu HA , : Hepatitis B virus screening before adjuvant chemotherapy in patients with early-stage breast cancer: a cost-effectiveness analysis . Breast Cancer Res Treat 151 : 639 – 52 , 2015 25962692 10.1007/s10549-015-3382-7 68. Tsou HH , Yang HC , Hsiao CF , : Cost-effectiveness of preventing hepatitis B virus reactivation in patients with lymphoma and resolved HBV infection . J Formos Med Assoc 119 : 335 – 344 , 2020 31235201 10.1016/j.jfma.2019.05.027 Fig 1. (*) Evidence of hepatitis B virus (HBV) infection refers to hepatitis B surface antigen (HBsAg)–positive or hepatitis B core antibody (HBc)–positive (either total immunoglobulin [Ig] or IgG; do not order IgM unless acute HBV infection is suspected). If evidence of HBV infection, do not delay anticancer therapy while obtaining further testing or referrals. See Table 3 for details for serologic interpretation of HBV screening tests. (†) Past HBV: HBsAg-negative, anti-HBc–positive, regardless of anti-HBs status. A positive anti-HBs test likely attenuates the risk of reactivation in patients with past HBV infection (see text for details). (‡) All other systemic anticancer therapy besides anti-CD20 therapy or stem-cell transplantation. Due to the lack of strong data, the risk of HBV reactivation is unclear for specific anticancer drugs besides anti-CD20 therapy or stem-cell transplantation. It is possible that these anticancer therapies have a low risk of reactivation for patients with past HBV infection and may not require routine monitoring. (§) An alternative pathway is careful monitoring with HBsAg and HBV DNA every 3 months with immediate antiviral therapy at the earliest sign of HBV reactivation so long as patients and providers are able to adhere to frequent and consistent follow-up during and for up to 12 months after last anticancer therapy (see text for details). (¶) Hepatitis flare: alanine aminotransferase (ALT) > 100 U/mL and 3 times baseline. 17 (¶¶) Long-term antiviral therapy management for patients with cancer after the cessation of anticancer therapy should follow national hepatology recommendations for all patients with chronic HBV. 11 , 17 An HBV specialist is a clinician experienced in HBV management.

Selected Guidance Documents with Recommendations for Hepatitis B Screening and Management

Pre-emptive antiviral therapy with ETV, TDF or TAF should be started immediately on detection of HBsAg or HBV DNA positivity.

Pre-emptive antiviral therapy in patients with isolated anti-HBc-positive (with HBsAg and HBV DNA negative) can be initiated in high-risk groups such as patients with lymphoma under a rituximab-containing regimen or those undergoing HSCT.

Abbreviations: ALT, alanine aminotransferase; anti-HBc, hepatitis B core antibody; anti-HBs, antibody to hepatitis B surface antigen; ETV, entecavir; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; HSCT, hematopoietic stem cell transplantation; mos, months; PCR, polymerase chain reaction; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate

Definitions of HBV Reactivation and Related Outcomes 17

≥2 log (100-fold) increase in HBV DNA compared to baseline, or

HBV DNA ≥3 log (1,000) IU/mL if previously undetectable HBV DNA, or

HBsAg seroreversion (HBsAg-negative to HBsAg-positive)

Impaired synthetic function (total bilirubin >3 mg/dL or INR >1.5), or

Anti-HBc total immunoglobulin (Ig) or IgG test (not IgM which if positive would indicate acute HBV infection). Although the sensitivity and specificity of the anti-HBc test exceeds 99%, positive anti-HBc test results may, in rare cases, indicate a false positive result (e.g., after administration of

intravenous Ig). As such, clinical assessment and evaluation may be warranted.

Summary of Recent (2015–2020) Cost-Effectiveness Analyses of Screening for Hepatitis B Virus Infection in Cancer Patients

Newly diagnosed patients receiving anticancer therapy.

Medical oncologists, hematologists, oncology nurses, oncology pharmacists, and other health care professionals who care for patients with cancer, and patients with cancer.

A search for new evidence on HBV screening in individuals with cancer was conducted to identify relevant studies published since the 2015 ASCO PCO.

All patients with cancer anticipating systemic anticancer therapy should be tested for hepatitis B virus (HBV) by three tests--hepatitis B surface antigen (HBsAg), hepatitis B core antibody (anti-HBc) total immunoglobulin (Ig) or IgG, and antibody to hepatitis B surface antigen (anti-HBs) prior to, or at the beginning of, systemic anticancer therapy. Anticancer therapy should not be delayed for the results of these screening tests. Findings of chronic HBV (HBsAg-positive) or past HBV (HBsAg-negative and anti-HBc-positive with either negative or positive anti-HBs) infection require further action. (Type: evidence-based; benefits outweigh harms; Strength of recommendation: strong)

Patients with chronic HBV receiving any systemic anticancer therapy should receive antiviral prophylactic therapy for the duration of anticancer therapy, as well as for at least 12 months after receipt of the last anticancer therapy. Monitoring recommendations include checking alanine aminotransferase (ALT) and HBV DNA level at baseline prior to or at the beginning of their anticancer therapy, as well as every 6 months during antiviral therapy. Hepatitis flares, presenting as elevated ALT levels, can occur after the discontinuation of antiviral therapy. As such, ALT levels should be monitored frequently, at least monthly for the first 3 months after the cessation of antiviral therapy and every 3 months thereafter. Coordination of care with a clinician experienced in HBV management is highly recommended for patients with chronic HBV, especially to monitor for withdrawal flares, determine monitoring and antiviral therapy after the cessation of anticancer therapy, and evaluate for advanced liver disease such as cirrhosis or liver cancer (Type: informal consensus, benefits outweigh harms; Strength of recommendation: strong).

Hormonal therapy without systemic anticancer therapy is unlikely to increase the risk of HBV reactivation in patients with chronic or past HBV. Antiviral therapy and management for these patients should follow national HBV guidelines, independent of cancer therapy, including management by a clinician experienced in HBV management for prevention of liver disease such as cirrhosis or liver cancer. Should their anticancer treatment regimen change beyond hormonal therapy alone, the risk of HBV reactivation based on their new anticancer therapy should be reassessed. (Type: informal consensus; benefits outweigh harms; Strength of recommendation: moderate)

Patients with past HBV receiving anticancer therapies associated with an established high risk of HBV reactivation, such as anti-CD20 monoclonal antibodies or stem cell transplantation, should be started on antiviral prophylaxis at the beginning of anticancer therapy and continued on antiviral therapy for at least 12 months after the cessation of anticancer therapy. HBV DNA should be obtained at baseline and followed every 6 months during antiviral therapy. Patients with a negative anti-HBs may be at higher risk of HBV reactivation than patients who have a positive anti-HBs. An alternative pathway is careful monitoring with HBsAg and HBV DNA every 3 months with immediate antiviral therapy at the earliest sign of HBV reactivation (appearance of HBsAg or HBV DNA ≥ 1000 IU/mL) so long as patients and providers are able to adhere to frequent and consistent follow up during anticancer therapy and for up to 12 months after last anticancer therapy (as delayed HBV reactivation may occur years after cessation of anticancer therapy). If HBV DNA that is quantifiable

but < 1000 IU/mL, then repeat testing at monthly intervals may be indicated. Hepatitis flares, presenting as elevated ALT levels, can occur after the discontinuation of antiviral therapy. As such, ALT levels should be monitored frequently, at least monthly for the first 3 months after the cessation of antiviral therapy and every 3 months thereafter. (Type: informal consensus; benefits outweigh harms; Strength of recommendation: strong)

More information, including a supplement with additional evidence tables, slide sets, and clinical tools and resources, is available at www.asco.org/supportive-care-guidelines . The Methodology Manual (available at www.asco.org/guideline-methodology) provides additional information about the methods used to develop this guideline. Patient information is available at www.cancer.net .

ASCO believes that cancer clinical trials are vital to inform medical decisions and improve cancer care, and that all patients should have the opportunity to participate.