Cost-Effectiveness Analysis of Hepatitis B Virus Screening and Management in Patients With Hematologic or Solid Malignancies Anticipating Immunosuppressive Cancer Therapy

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abstract

PURPOSE National hepatitis B virus (HBV) screening recommendations for patients with cancer anticipating systemic anticancer therapy range from universal screening to screening based on risk of HBV infection, cancer therapy-specific risk of HBV reactivation, or both. We conducted cost-effectiveness analyses to identify optimal HBV screening strategies.

PATIENTS AND METHODS We constructed decision-analytic models to analyze three strategies (no screening, universal screening, and selective screening based on use of an HBV infection risk tool) for hypothetical cohorts of patients anticipating anticancer therapy at high or lower risk for HBV reactivation. Model parameters were drawn from previously published studies, the SEER-Medicare database, and other online resources. Outcomes included lifetime expected cost, quality-adjusted life expectancy, and incremental cost-effectiveness ratio, measured in US dollars required to gain an additional quality-adjusted life-year (QALY).

RESULTS For patients at high reactivation risk, universal screening dominated (ie, was cheaper and more effective than) the other two strategies. Universal screening was associated with a gain in life expectancy of 0.01 QALY compared with no screening and cost \$76.06 less than no screening and \$4.34 less than selective screening. For those at lower reactivation risk, universal screening still dominated selective screening; however, the incremental cost-effectiveness ratio of the universal screening strategy compared with no screening was \$186,917 per QALY gained.

CONCLUSION Universal HBV screening is cost effective and cheaper for patients receiving anticancer therapy associated with a high reactivation risk. For patients receiving anticancer therapy associated with a lower reactivation risk, universal screening is not cost effective.

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INTRODUCTION

Although patients with chronic hepatitis B virus (HBV) infection are at higher risk for HBV reactivation than those with past HBV infection, both groups are at risk and require personalized care during and after anticancer therapy, including consideration of anti-HBV prophylaxis, as well as regular HBV monitoring (HBV DNA in both groups, hepatitis B surface antigen [HBsAg] in past HBV group) and liver function testing. Some national groups recommend HBV screening for any person with risk factors to prevent liver cancer,¹ whereas others recommend universal HBV screening for patients with cancer before anticancer therapy to prevent HBV reactivation and associated adverse liver outcomes,²⁻⁴ such as hepatitis flare, liver failure, and even death. In part because of concerns that universal screening may not be cost effective, other national

groups recommend selective HBV screening based on risk factors for HBV infection and/or type of anticancer therapy.⁵⁻⁷ In the United States, the prevalence of chronic HBV infection (indicated by presence of HBsAg and hepatitis B core antibody [anti-HBc]) has been reported to be > 1%, and the prevalence of past HBV infection (absence of HBsAg, presence of anti-HBc) is approximately 5%⁸; similar HBV prevalences have been reported among patients with cancer.^{9,10}

One approach is to screen only patients who have a risk factor for HBV infection, such as birthplace in a high-prevalence region of the world, household contact with a person with HBV infection, or history of high-risk behavior, such as injection drug use or high-risk sexual behaviors. A second approach is to test only patients with hematologic malignancies. A third approach is to screen only patients anticipated to receive

ASSOCIATED CONTENT

Appendix

Author affiliations and support information (if applicable) appear at the end of this article.

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CONTEXT

Key Objective

What is the most cost-effective hepatitis B virus (HBV) screening strategy for patients with cancer anticipating immunosuppressive therapy: no screening, universal screening, or screening based on risk factors for HBV infection?

Knowledge Generated

Our analysis, conducted from a health care provider's perspective and based on current data, showed that screening provided more benefits than no screening, and benefits in terms of quality-adjusted life expectancy were similar for universal screening and selective screening. For patients at high reactivation risk, universal screening was cheaper and more effective than the other strategies; for those at lower reactivation risk, a small improvement in quality-adjusted life expectancy with the universal screening strategy was not cost effective.

Relevance

Our findings can help physicians, hospitals, and health care systems make difficult choices about which patients with cancer to screen for HBV infection. Specifically, we believe that our findings weigh in favor of universal screening for patients who are at high risk of HBV reactivation because of the type of anticancer therapy they are expected to receive and weigh against universal screening for patients who are at low risk of HBV reactivation. We acknowledge, however, that decisions about HBV screening remain difficult because current evidence is not strong enough to identify one strategy as definitively superior to others for all patients with cancer.

anticancer therapies associated with a high risk of HBV reactivation, such as stem-cell transplantation or anti-CD20 monoclonal antibody therapy.

Given the low prevalence of HBV infection in the United States and the costly consequences of HBV reactivation, we hypothesized that a selective screening strategy based on risk factors for HBV infection and risk factors for HBV reactivation would be cost effective in patients with cancer. To test this hypothesis, we used real-world data and scenarios to evaluate the cost effectiveness of risk-based HBV screening before anticancer therapy as compared with universal HBV screening or no HBV screening.

PATIENTS AND METHODS

Overview

We created a decision-analytic model (Fig 1) incorporating the costs and effectiveness of three strategies for HBV screening before anticancer therapy: no HBV screening, universal HBV screening, and selective screening based on use of an HBV infection risk tool. The three strategies were applied to hypothetical cohorts of patients with cancer anticipating a 12-month course of systemic anticancer therapy considered to be associated with high or lower risk of HBV reactivation.

Strategies

In the no-screening strategy, patients are not screened for HBV infection regardless of HBV reactivation risk. In this strategy, patients who have either chronic or past HBV infection are at risk for HBV reactivation. We defined HBV reactivation as an elevation in ALT level to at least three times the baseline level before anticancer therapy accompanied by an increase in serum HBV DNA level $> 1 \log_{10}$ IU/mL from baseline.^{11,12} Possible outcomes of HBV reactivation included liver failure and death. Patients who

develop HBV reactivation would be started on anti-HBV treatment with entecavir.^{6,7} Once started, entecavir therapy would be continued until 6 months after the last dose of anticancer therapy associated with a lower risk of HBV reactivation and 12 months after the last dose of anticancer therapy associated with a high risk of HBV reactivation. Risk of liver failure and death would be decreased but not eliminated by antiviral therapy.

In the universal screening strategy, all patients are screened for HBV infection using HBsAg and anti-HBc tests before initiation of anticancer therapy. Patients with chronic HBV infection (positive anti-HBc and HBsAg test results) would be started on entecavir prophylaxis before initiation of anticancer therapy, and entecavir would be continued until 6 or 12 months after the last dose of anticancer therapy, depending on reactivation risk, as outlined in the preceding paragraph. We assumed that anti-HBV prophylaxis started before initiation of anticancer therapy would be 100% effective (ie, no cases of reactivation would occur in patients who receive prophylaxis). All patients with chronic HBV infection receiving anti-HBV prophylaxis would be monitored with tests for HBV DNA, ALT level, total bilirubin level, and prothrombin time/international normalized ratio at baseline and every 3 months during anti-HBV prophylaxis and anticancer therapy. Patients with past HBV infection (negative HBsAg test result, positive anti-HBc test result) would be monitored every 3 months with tests similar to those used to monitor patients with chronic HBV infection plus one additional test, for HBsAg, which can be detected if HBV reactivation occurs in this group. Patients with past HBV infection would not receive antiviral therapy (unless they were to receive treatment associated with a high risk of HBV reactivation)

FIG 1. Decision-analytic model for hepatitis B virus (HBV) screening in patients with cancer anticipating anticancer therapy associated with high or lower risk of HBV reactivation. Anti-HBc, hepatitis B core antibody; HBsAg, hepatitis B surface antigen; QALY, quality-adjusted life-year.

unless HBV reactivation is detected, when they would be started on entecavir treatment. Patients with negative HBsAg and anti-HBc test results would not receive prophylaxis and would not have additional monitoring beyond standard of care for patients receiving anticancer therapy.

The selective screening strategy is based on use of an HBV risk tool that was validated in patients with cancer.¹⁰ The risk tool, based on the Centers for Disease Control and

Prevention viral survey,¹³ asks patients seven questions, about their sex, race/ethnicity, birthplace, parents' birthplace, household contacts, sexual behavior, and injection drug use. In the selective screening strategy, all patients complete the risk tool, and those with at least one risk factor for HBV infection would be screened for HBV infection using HBsAg and anti-HBc tests. Actions after positive or negative HBV screening results would be the same as

described in the universal screening strategy. Patients with negative responses to all questions on the HBV risk tool would not be screened for HBV or monitored for HBV reactivation.

Given that different anticancer therapies are associated with different risks of HBV reactivation, we specified two cohorts entering the decision-analytic model. The first cohort consisted of patients awaiting anticancer therapies known to be associated with a high risk of HBV reactivation (eg, stem-cell transplantation or anti-CD20 monoclonal antibody therapy),^{7,11,14,15} regardless of a patient's risk for HBV infection (high reactivation risk cohort). The second cohort consisted of patients awaiting all other systemic anticancer therapies (lower reactivation risk cohort).

Perspective

The decision-analytic models used a health care provider's perspective, with key parameters coming from patients treated in a clinical environment. A health care provider's perspective means we included the direct costs of HBV screening and treatment, rather than the charges issued to patients. Because our goal was to determine whether it is cost effective for health care providers to screen patients, we did not include patient time or lost productivity costs in our models. Similarly, because the focus of the model was HBV screening strategies, we excluded anticancer therapy, because costs of anticancer therapy are likely to be the same across all three strategies, therefore not leading to differences in an incremental analysis.

Timeframe

In the base case scenario, we considered patients with cancer entering the model at age 65 years. Our decision tree has an initial time horizon of 2 years, which covers the period of anticancer therapy administration, anti-HBV prophylaxis or treatment, and occurrence of HBV reactivation and subsequent liver failure. The following Markov model calculations and the economic analysis after initial treatment adopt a lifetime horizon to capture patients' long-term survival. This meets the guidelines for cost-effectiveness analysis proposed by the Panel for Cost-Effectiveness in Health and Medicine.¹⁶ In our base case scenario, we made the simplifying assumptions that a patient with cancer would have a 5-year survival probability of 67%¹⁷ and, if still alive after those 5 years, would be considered cured of the cancer and revert to a survival probability similar to that of someone of the same age in the general population (base case or cured cohort). In an alternative sensitivity analysis, we constructed a scenario that assumed patients had a 5-year survival probability of 67% and, after those 5 years, continued to have the same 67% survival probability (alternative case).

Model Parameters

Model parameters were derived from the results of a previous retrospective observational study¹⁸ and other

published studies (Table 1). If no studies were available, expert opinion was used. The sensitivity and specificity of the HBV risk tool were taken from a prospective observational study.¹⁰ Mortality rates by age for all cancers were calculated using SEER data.¹⁹ The life table for the general population was obtained from the Centers for Disease Control and Prevention for all-cause mortality rates, which provided mortality rates and life expectancies of patients at the beginning of chemotherapy.²⁰

Costs and Utilities

Because the analysis was conducted from a health care provider's perspective, we determined the direct costs of HBV screening and treatment, including the costs of clinical visits and hourly wages of relevant medical personnel (Table 2). Costs of cancer care in the initial, continuing, and terminal stages were assigned accordingly throughout the model.³⁶ Critical variables in the model include the mean costs of managing liver failure and survival time after liver failure, which could not be readily found in the literature. There is no International Classification of Diseases, Ninth Revision, code for liver failure. Therefore, we used codes such as necrosis of the liver, hepatic encephalopathy, toxic liver disease, or ascites as surrogates of liver failure (Appendix). We then estimated the mean costs of liver failure and survival time after liver failure using SEER-Medicare linked data³⁷ in a high reactivation risk group of patients who were receiving rituximab therapy. All costs in the model were adjusted for inflation using the medical care component of the consumer price index.³⁸

Other cost data in the model were identified from the following sources: drug information from the RedBook,³⁹ Medicare Clinical Laboratory Fee Schedule,⁴⁰ and Medicare Physician Fee Schedule,⁴¹ as summarized in Table 2. The costs of generic entecavir were calculated monthly and aggregated over the entire period of prophylaxis (started before anticancer therapy) or treatment (after HBV reactivation). We assumed that prophylactic entecavir would be continued until 12 months after the last dose of anticancer therapy in patients with high reactivation risk and 6 months after the last dose of anticancer therapy in patients with lower reactivation risk. The HBV risk tool is self-administered, but we assumed that a licensed practical nurse or licensed vocational nurse would require 5 minutes to enter the results into an electronic medical record or to inform the medical provider of the results.

The costs associated with screening strategies included the costs of the screening tests, monitoring tests, and follow-up visits and anti-HBV prophylaxis, where applicable. Costs associated with HBV reactivation included the overall costs of anti-HBV treatment and treatment of liver failure, if this condition developed.

Health states were given utility values (Table 1), obtained from a previous economic evaluation, that describe the quality of life in that state.³³ The utilities of having cancer

TABLE 1. Parameters for the Base Case Model

Parameter	Value	Range	Source
Prevalence of HBV infection			
Chronic	0.0110	0.008-0.014	Hwang ¹⁸
Past	0.0710	0.064-0.079	Hwang ¹⁸
Performance of HBV screening tests			
Sensitivity of anti-HBc	0.9949	NA	Abbott ²¹
Specificity of anti-HBc	0.9988	NA	Abbott ²¹
Sensitivity of HBsAg	1.0000	NA	Abbott ²²
Specificity of HBsAg	0.9927	NA	Abbott ²²
Sensitivity of risk tool	1.0000	NA	Hwang ¹⁰
Specificity of risk tool	0.1080	NA	Hwang ¹⁰
Reactivation rate with treatments associated with high risk of reactivation			
Chronic HBV	0.48	0.25-0.75	Lok ²³
Chronic HBV (prophylaxis)	0.06	0-0.12	Loomba, ²⁴ Hsu, ²⁵ Lau ²⁶
Past HBV	0.18	0.075-0.335	Huang ²⁷
Past HBV (prophylaxis)	0.02	0.001-0.129	Huang ²⁷
Reactivation rate with treatments associated with lower risk of reactivation			
Chronic HBV	0.25	0.04-0.68	Paul ²⁸
Chronic HBV (prophylaxis)	0.06	0.023-0.05	Loomba, ²⁴ Hsu, ²⁵ Lau ²⁶
Past HBV	0.03	0.003-0.09	Paul ²⁸
Past HBV (prophylaxis)	0.01	0.007-0.014	Expert opinion
Liver failure rate with high-risk treatment			
Chronic HBV	0.25	0.03-0.65	Hwang, ¹⁸ Wong, ²⁹ Fattovich, ³⁰ D'Amico, ³¹ Kanwal ³²
Chronic HBV (prophylaxis)	0.03	0-0.05	Expert opinion
Past HBV	0.05	0-0.1	Expert opinion
Past HBV (prophylaxis)	0.01	0-0.05	Expert opinion
Liver failure rate with lower-risk treatment			
Chronic HBV	0.02	0.01-0.2	Paul ²⁸
Chronic HBV (prophylaxis)	0.01	0-0.01	Expert opinion
Past HBV	0.02	0-0.05	Expert opinion
Past HBV (prophylaxis)	0.01	0-0.05	Expert opinion
Utility weights			
Utility of liver failure	0.80	—	Lazar, ³³ Schultz ³⁴
Utility of cancer	0.80	—	Pickard ³⁵
Survival probability			
Cancer related	0.67	—	American Cancer Society ¹⁷
General health	Life table	—	Centers for Disease Control and Prevention ²⁰

Abbreviations: anti-HBc, hepatitis B core antibody; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus.

and having liver failure were assumed to be multiplicative and calculated by multiplying the utility of having cancer by the utility of having liver failure. These utilities were used to adjust the total life expectancy depending on the patient's health state.

Analysis

We performed a cost-effectiveness analysis to estimate the incremental cost-effectiveness ratio (ICER). Because quality of life was incorporated, the ICERs were measured in US dollars per quality-adjusted life-year (QALY). The

TABLE 2. Cost Sources

Cost Name	Unit	2016 Cost (US\$)*	Source
Entecavir (generic)	Month	607.50	RedBook ³⁹
HBsAg	Single test	14.07	Medicare ⁴⁰
Anti-HBc	Single test	16.41	Medicare ⁴⁰
HBV DNA	Single test	58.35	Medicare ⁴⁰
ALT	Single test	7.22	Medicare ⁴⁰
Total bilirubin	Single test	6.83	Medicare ⁴⁰
Prothrombin time/INR	Single test	5.36	Medicare ⁴⁰
Physician visit	Single visit, nonfacility price	73.40	Medicare ⁴¹
Licensed vocational nurses	Hour	21.20	Bureau of Labor and Statistics ⁴²
Initial cancer care	Year	41,810.68	Mariotto ³⁶
Continuing cancer care	Year	4,800.76	Mariotto ³⁶
Terminal cancer care	Year	111,808.16	Mariotto ³⁶
Terminal care	Year	12,427.62	Mariotto ³⁶
Liver failure	Episode per patient	72,831	Appendix

Abbreviations: anti-HBc, hepatitis B core antibody; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; INR, international normalized ratio.

*All cost items were converted to 2016 US dollars using the medical care component of the consumer price indices.³⁸

analysis was performed using TreeAge Pro 2017 (TreeAge Software, Williamstown, MA; software available at <http://www.treeage.com>). In the analysis, both costs and effectiveness were discounted at a rate of 3%.⁴³ We interpreted the cost effectiveness of screening strategies using two commonly cited willingness-to-pay thresholds: \$50,000 and \$100,000 per QALY.^{44,45} A screening strategy that was both more effective and less expensive than another strategy was considered to dominate the other strategy. A screening strategy that was both less effective and more expensive than another strategy was considered to be dominated by the other strategy.⁴⁶

We also conducted one-way sensitivity and scenario analyses on variables in the model to see how sensitive the results were to those parameters. The plausible ranges of variables were obtained from systematic reviews and primary studies (Table 1.) For probability variables without a published plausible range, we estimated and used the 95% CI, assuming binomial distribution. We received approval from the institutional review board at MD Anderson Cancer Center to conduct this cost-effectiveness study.

RESULTS

The ICERs for the cohorts with high and lower HBV reactivation risk by screening strategy for the base case (cured cohort) are listed in Table 3. For patients at high reactivation risk, universal screening was associated with a gain in effectiveness of 0.0121 QALY compared with no screening and cost \$76.06 less than no screening. Selective screening and universal screening were equally effective (ie, associated with identical quality-adjusted life expectancy); however, selective screening cost \$4.34 more than universal screening. These results suggest that

universal screening is cheaper and more effective for patients with high reactivation risk.

For patients at lower reactivation risk, selective screening was again dominated by universal screening because of the higher cost and equivalent effectiveness of selective screening. Compared with no screening, universal screening provided a marginal increase in quality-adjusted life expectancy (0.0005 QALY) at an additional cost of \$88.81. The ICER for universal screening in this group was \$186,917 per QALY compared with no screening, suggesting that universal screening is not cost effective for patients with lower reactivation risk.

Results for the alternative case scenario, in which survival was held constant after 5 years from cancer diagnosis, are also listed in Table 3. For those at high reactivation risk, universal screening and selective screening were associated with identical quality-adjusted life expectancy, which was higher than the quality-adjusted life expectancy with no screening, and both universal screening and selective screening cost less than no screening. Selective screening was again dominated by universal screening because of the higher cost and same quality-adjusted life expectancy of selective screening. For those at lower reactivation risk, the ICER for universal screening compared with no screening was \$271,660 per QALY. Selective screening was more expensive than universal screening and equivalent to it in terms of quality-adjusted life expectancy and thus was again dominated by universal screening for patients at lower reactivation risk.

Overall, screening provided more benefits than no screening, and benefits in quality-adjusted life expectancy were similar for universal screening and selective

TABLE 3. Results of ICER

Reactivation Risk and Screening Strategy	Cost (US\$)	Incremental Cost (US\$)	QALY	Incremental QALY	ICER
Base case					
High reactivation risk					
Universal screening	20,177.50	—	9.6934	—	—
Selective screening	20,181.84	4.34	9.6934	0.0000	Dominated
No screening	20,253.56	76.06	9.6813	−0.0121	Dominated
Lower reactivation risk					
No screening	16,803.90	—	9.6985	—	—
Universal screening	16,892.71	88.81	9.6990	0.0005	186,917.33
Selective screening	16,894.66	1.95	9.6990	0.0000	Dominated
Alternative case*					
High reactivation risk					
Universal screening	50,839.75	—	6.9250	—	—
Selective screening	50,844.09	4.34	6.9250	0.0000	Dominated
No screening	50,875.78	36.02	6.9165	−0.0084	Dominated
Lower reactivation risk					
No screening	47,483.12	—	6.9286	—	—
Universal screening	47,573.51	90.39	6.9289	0.0003	271,660.42
Selective screening	47,575.46	1.95	6.9289	0.0000	Dominated

Abbreviations: ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life-year.

*Alternative case: survival was held constant after 5 years from cancer diagnosis. A strategy that was both less effective and more expensive than another strategy was considered to be dominated by the other strategy.

screening. For patients at high reactivation risk, universal screening was cheaper. For those at lower reactivation risk, a small improvement in QALYs rendered the universal screening strategy not cost effective in this group.

Sensitivity Analysis

The results were consistent under varying parameter values and assumptions. One-way sensitivity analyses showed that in the high reactivation risk group, increases in reactivation risk, liver failure risk, chronic HBV prevalence, and 5-year survival probability made screening strategies

more effective and less costly. In the lower reactivation risk group, increases in reactivation risk and liver failure risk changed the cost effectiveness of universal HBV screening. For example, as shown in [Figure 2](#), among patients with lower reactivation risk and chronic HBV infection in our base case (cured cohort), when the probability of HBV reactivation was > 40%, the ICER for universal screening dropped to the willingness-to-pay threshold of \$100,000 per QALY. Another example is illustrated in [Figure 3](#), which shows that among patients with lower reactivation risk and chronic

FIG 2. Sensitivity analysis of the probability of hepatitis B virus (HBV) reactivation among patients at lower reactivation risk with chronic HBV infection in the base case (universal screening v no screening). ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life-year.

HBV infection in our base case (cured cohort), universal screening became cost effective when the probability of liver failure reached 4%, assuming a willingness-to-pay threshold of \$100,000 per QALY, or 7%, assuming a willingness-to-pay threshold of \$50,000 per QALY.

A one-way sensitivity analysis was conducted in which the initial 5-year survival probability range of 10% to 90% was used. Changes in 5-year survival probability did not significantly change the cost effectiveness of the universal screening strategy in patients at lower reactivation risk. Assuming lifetime cancer mortality in the alternative case scenario, universal screening remained cheaper in the high reactivation risk cohort for 5-year survival probability up to 80% (base case, 67%) and was cost effective ($< \$4,500$ per QALY gained) for 5-year survival probability up to 90%. For both base case and alternative case scenarios, we observed that HBV screening became more effective as 5-year survival probability increased.

DISCUSSION

Our findings did not support our hypothesis that a selective screening strategy based on risk factors for HBV infection and risk factors for HBV reactivation would be cost effective in patients with cancer. Instead, we found that selective screening was dominated by universal screening, which we found to be cost effective in patients at high risk for HBV reactivation but not among those at lower reactivation risk.

Whereas some previously published cost-effectiveness analyses of HBV screening did not take into account all the factors associated with the risk of HBV infection, our brief HBV risk tool is based on a comprehensive set of risk factors known to be associated with HBV infection and was validated in patients with cancer. Previous reports of selective HBV screening used a limited set of risk factors for HBV infection, such as birthplace in an intermediate- to high-prevalence country among patients with hematologic malignancies.⁴⁷ Other reports of the utility of a selective

HBV screening strategy focused on patients with hematologic malignancies and did not include patients with solid tumors.^{48,49} In addition to including patients with both hematologic malignancies and solid tumors, our study included costs associated with liver failure caused by HBV reactivation derived from claims data of patients with cancer. Thus, our analysis simulated real-life clinical scenarios more accurately than some previous analyses. We also emphasized that all patients be considered for HBV screening before anticancer therapy, even if they may have been tested in the past, because transmission of virus can happen through exchange of bodily fluids and along the spectrum of age.

The results of our study take into account the economic aspects of HBV screening, which were not explored in our prospective study that identified HBV risk factors among patients with cancer and concluded that universal HBV screening was clinically effective.¹⁰ In the current study, where both clinical and economic aspects were taken into consideration, we found that universal HBV screening is clinically effective and cost effective for patients at high risk of HBV reactivation.

Our findings can help physicians, hospitals, and health care systems make at times difficult choices about which patients with cancer to screen for HBV infection. Specifically, we believe that our findings weigh in favor of universal screening for patients who are at high risk of HBV reactivation because of the type of anticancer therapy they are expected to receive and weigh against universal screening for patients who are at low risk of HBV reactivation. We acknowledge, however, that decisions about HBV screening remain difficult, because current evidence is not strong enough to identify one strategy as definitively superior to others for all patients with cancer.

Our study and previous studies share a common limitation: the assumption that we can accurately classify anticancer

FIG 3. Sensitivity analysis of the probability of liver failure among patients at lower reactivation risk with chronic HBV infection in the base case (universal screening v no screening). ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life-year.

therapies as either having a high versus lower risk for HBV reactivation and that patients would continue to receive the same anticancer therapy. Future research is needed to elucidate type-specific differences in the mechanisms of reactivation. Another limitation is the paucity of data regarding the risk of HBV reactivation among patients considered to be at lower risk and, to a lesser degree, the effectiveness of anti-HBV therapy in these patients.

We recognize that we made simplifying assumptions, such as no additional monitoring after cessation of antiviral therapy (which could miss late-onset HBV reactivation), 100% effectiveness of antiviral prophylaxis, and all anti-cancer therapies besides stem-cell transplantation and anti-CD20 therapy being lower risk. Future studies should

discern the risk of HBV reactivation based on various types of anticancer therapies. It is unclear how other new anti-cancer therapies, such as immunotherapy, might affect the risk for HBV reactivation, because evidence is currently lacking.

We conclude that universal HBV screening is cost effective and cheaper in patients at high risk of HBV reactivation by virtue of their anticipated anticancer therapy. However, among patients anticipating anticancer therapy associated with a lower risk of HBV reactivation, universal HBV screening is not cost effective. Oncology clinics should consider the risk profile of their population and their available resources and thresholds for cost effectiveness in choosing an appropriate approach to HBV screening.

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Stock and Other Ownership Interests: Anthem

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APPENDIX

Additional Methods

We derived a unique cohort of 112 patients age 66 to 90 years, diagnosed with lymphoma between 2005 and 2011, without pre-existing HBV or related conditions. Liver failure was determined by one of the following International Classification of Diseases, Ninth Revision, codes: acute and subacute necrosis of the liver (570), hepatic

encephalopathy (not viral; 572.2), other sequelae of chronic liver disease (572.8), toxic liver disease with hepatitis necrosis without coma (573.3), or ascites (789.5). In 2012 US dollars, we found that the average treatment cost of liver failure per patient, excluding costs associated with anticancer therapies, was \$64,951 (SE, \$10,543; 95% CI, \$44,286 to \$85,616). Using the medical care component of the consumer price indices,²⁵ this cost expressed in 2016 dollars would be \$72,831.