Guidelines Provide Accurate Direction for HCC Surveillance in HBV Patients

Amit G. Singal MD MS

David Bruton Professor of in Clinical Cancer Research

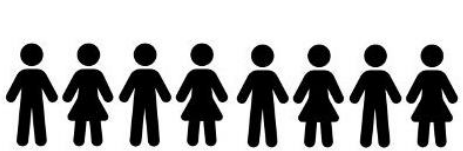
Chief of Hepatology and Medical Director Liver Tumor Program

UT Southwestern Medical Center

Disclosures

- I have served as a consultant or served on advisory boards for Genentech, Bayer, Eisai, AstraZeneca, Bristol Meyer Squibb, Exelixis, Wako Diagnostics, Glycotest, Exact Sciences, Roche, and GRAIL

Assessment of guideline recommendations must be considered in light of their scope and purpose



Population Health Model

- Focus on Population
- Access to care
- Allocation of resources
  - Between groups of patients
  - Between primary and specialty care
  - Between healthcare and other sectors of the economy
- Disease prevention

Medical Model

- Focus on Individual
- Diagnosis
- Evidence-based Treatment

As with other guidance documents, it is not intended to replace clinical judgment, but rather to provide general guidance applicable to the majority of patients. They are intended to be flexible, in contrast to formal treatment recommendations, and clinical considerations may justify a course of action that differs from this guidance.

Target Populations for HCC Surveillance

Population Group	Threshold Incidence for Efficacy of Surveillance (>0.25 LYG; % per year)	Incidence of HCC
Surveillance benefit		
Asian male hepatitis B carriers over age 40	0.2	0.4%-0.6% per year
Asian female hepatitis B carriers over age 50	0.2	0.3%-0.6% per year
Hepatitis B carrier with family history of HCC	0.2	Incidence higher than without family history
African and/or North American blacks with hepatitis B	0.2	HCC occurs at a younger age
Hepatitis B carriers with cirrhosis	0.2-1.5	3%-8% per year
Hepatitis C cirrhosis	1.5	3%-5% per year
Stage 4 PBC	1.5	3%-5% per year
Genetic hemochromatosis and cirrhosis	1.5	Unknown, but probably >1.5% per year
Alpha-1 antitrypsin deficiency and cirrhosis	1.5	Unknown, but probably >1.5% per year
Other cirrhosis	1.5	Unknown
Surveillance benefit uncertain		
Hepatitis B carriers younger than 40 (males) or 50 (females)	0.2	<0.2% per year
Hepatitis C and stage 3 fibrosis	1.5	<1.5% per year
NAFLD without cirrhosis	1.5	<1.5% per year

- Cirrhotic patients, Child-Pugh stage A and B **(evidence low; recommendation strong)**
- Cirrhotic patients, Child-Pugh stage C awaiting liver transplantation (**evidence low; recommendation strong**)
- Non-cirrhotic HBV patients at intermediate or high risk of HCC* (according to PAGE-B† classes for Caucasian subjects, respectively 10–17 and ≥18 score points) (**evidence low; recommendation weak**)
- Non-cirrhotic F3 patients, regardless of aetiology may be considered for surveillance based on an individual risk assessment (**evidence low; recommendation weak**)

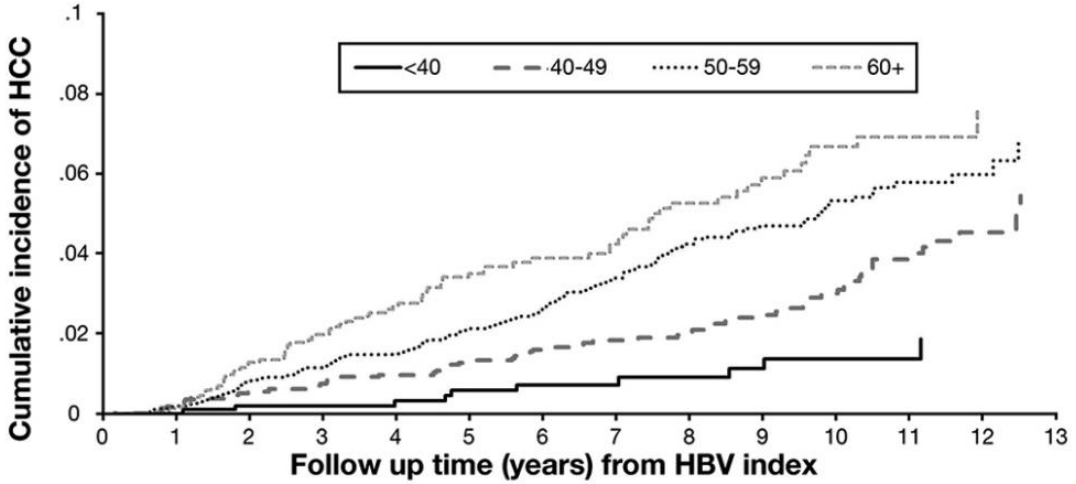
Age, race, and presence of cirrhosis can identify those at risk for HCC

Cohort of 8329 patients from VA with HBV infection (at least two positive HBV tests >6 months apart)

During mean follow-up 7.1 years, 303 incident HCC (annual incidence 0.5%)

Annual HCC incidence higher in Asian Pacific Islanders (HR 2.0, 95%CI 1.3 – 3.2) and increased with age (40-49 years: HR 2.0, 95%CI 1.0 – 3.9); 50-59 years: HR 3.0, 9%CI 1.6 – 5.8; 60+ years: HR 4.0, 95%CI 2.0 – 7.9).

Among those without cirrhosis, annual HCC risk > 0.2% in those >40 years but not younger patients



Subgroups	Patients, N	Annual incidence (/100 PY)	Adjusted hazard ratio (95% CI)
Age < 40 *y*			
White	279	0.14	1.0
African American	382	0.03	0.46 (0.04–4.89)
Asian Pacific Islander	233	0.14	8.81 (0.82–93.74)
Age ≥ 40 *y*			
White	3219	0.61	1.0
African American	2866	0.45	0.88 (0.67–1.15)
Asian Pacific Islander	429	0.90	2.06 (1.14–3.17)
With prevalent cirrhosis			
White	1302	1.17	1.0
African American	870	0.94	0.85 (0.60–1.20)
Asian Pacific Islander	91	3.40	2.74 (1.62–4.66)
Without prevalent cirrhosis			
White	2196	0.28	1.0
African American	2378	0.23	0.88 (0.58–1.35)
Asian Pacific Islander	568	0.29	1.70 (0.86–3.34)
Age ≥ 40 without cirrhosis			
White	1961	0.32	1.0
African American	2032	0.27	0.83 (0.55–1.27)
Asian Pacific Islander	343	0.42	1.47 (0.73–2.95)
Age ≥ 40 without cirrhosis but high ALT level			
White	1258	0.40	1.0
African American	1193	0.31	0.72 (0.44–1.17)
Asian Pacific Islander	211	0.54	1.45 (0.66–3.17)
Age ≥ 40 without cirrhosis and normal ALT level			
White	657	0.18	1.0
African American	802	0.17	1.05 (0.43–2.56)
Asian Pacific Islander	126	0.12	0.67 (0.08–5.45)
HBV mono-infection			
White	2625	0.52	1.0
African American	2394	0.45	1.14 (0.84–1.54)
Asian Pacific Islander	624	0.63	2.03 (1.30–3.17)

Mittal et al. *Clin Gastro Hep* 2018

Patients with low PAGE-B scores have low HCC risk

Cohort of 1951 chronic HBV patients (526 with cirrhosis) from Europe treated with ETV/TDF for >12 months

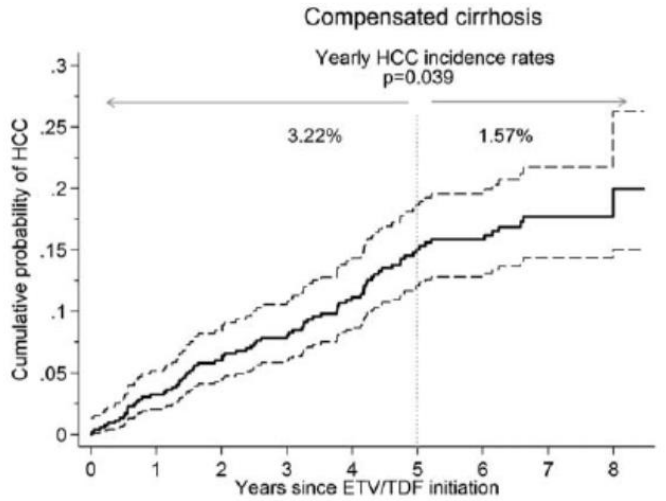
- 1205 patients followed >5 years (325 with cirrhosis)

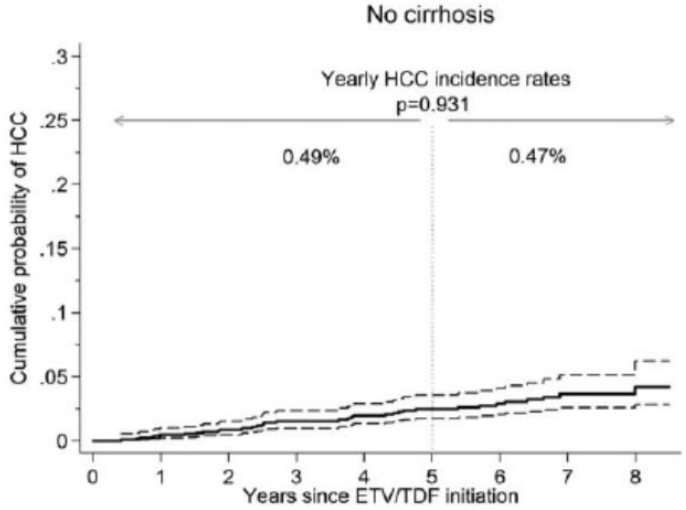
HCC diagnosed in 101 patients, with 17 HCC after 5 years

- Incidence 1.22% within 5 years and 0.73% after 5 years

Intermediate and high PAGE-B both had annual incidence >0.2% whereas no HCC cases in patients with low PAGE-B score

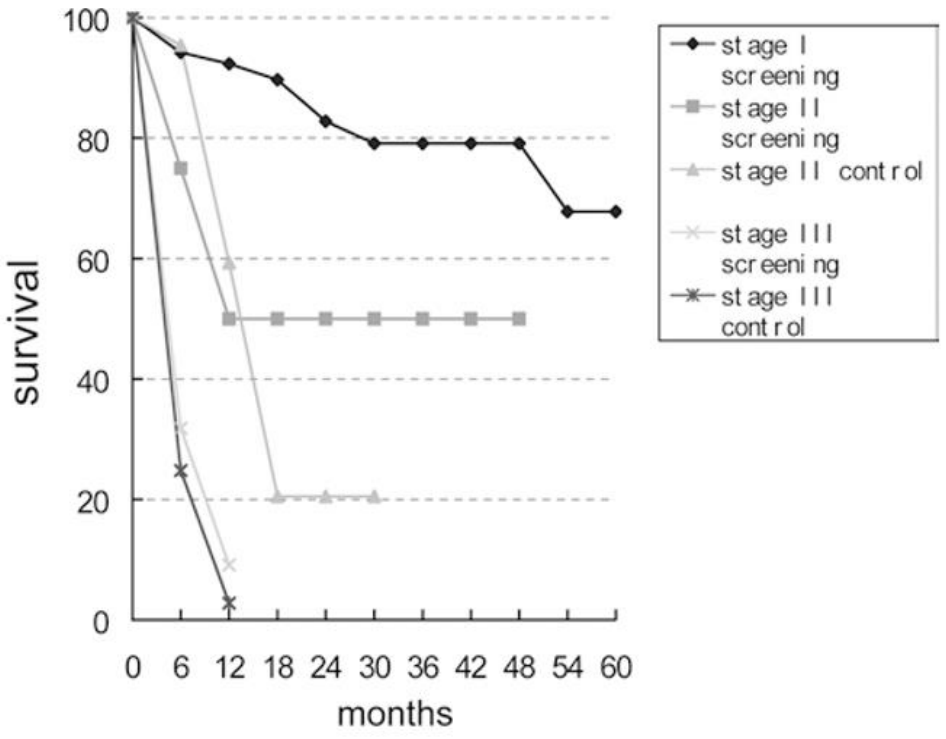
	Univariable Analysis		Multivariable Analysis			
	All Factors		Baseline Factors		Factors at Year 5	
	HR (95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)	*P*
Age at baseline or year 5 (per year increase)	1.07 (1.02-1.12)	0.003	1.06 (1.01-1.11)	0.032	1.06 (1.00-1.13)	0.047
Gender (male versus female)	1.32 (0.43-4.05)	0.626				
HBeAg status at baseline (neg. versus pos.)	3.86 (0.51-29.11)	0.190				
HBeAg status at year 5 (neg. versus pos.)	24.13 (0.01-62,054)	0.427				
Body mass index at baseline (per kg/m^2)	1.04 (0.99-1.09)	0.133				
ALT at baseline (per IU/L)	1.00 (0.99-1.00)	0.569				
ALT at baseline (normal versus elevated)	0.72 (0.28-1.89)	0.505				
ALT at year 1 (normal versus elevated)	0.90 (0.20-4.03)	0.892				
ALT at year 5 (normal versus elevated)	0.99 (0.94-1.03)	0.601				
Platelets at baseline (per 10^3/mm^3)	0.99 (0.98-1.00)	0.004	0.99 (0.98-1.00)	0.021		
Platelets at year 5 (per 10^3/mm^3)	0.98 (0.97-0.99)	0.001			0.98 (0.97-0.99)	0.004
HBV DNA at baseline (per $\log_{10}$ IU/ml)	0.76 (0.60-0.96)	0.024	0.79 (0.60-1.03)	0.078		
(Peg-)IFNa in the past (yes versus no)	0.81 (0.26-2.48)	0.711				
NA(s) before ETV/TDF (yes versus no)	2.21 (0.81-6.02)	0.121				
Cirrhosis at baseline (yes versus no)	3.10 (1.19-8.07)	0.021	1.38 (0.46-4.13)	0.324		
Liver stiffness at year 5 (≥12 versus <12 kPa)	6.89 (2.12-22.42)	0.001			4.10 (1.10-15.33)	0.036
Liver stiffness at year 5 (<12 versus ≥12 kPa) (among those with cirrhosis at baseline)	0.24 (0.06-0.98)	0.047			0.30* (0.07-1.25)	0.099*
Initial antiviral regimen (ETV versus TDF)	1.33 (0.51-3.48)	0.563				





Papatheiodoridis et al. *Hepatology* 2017

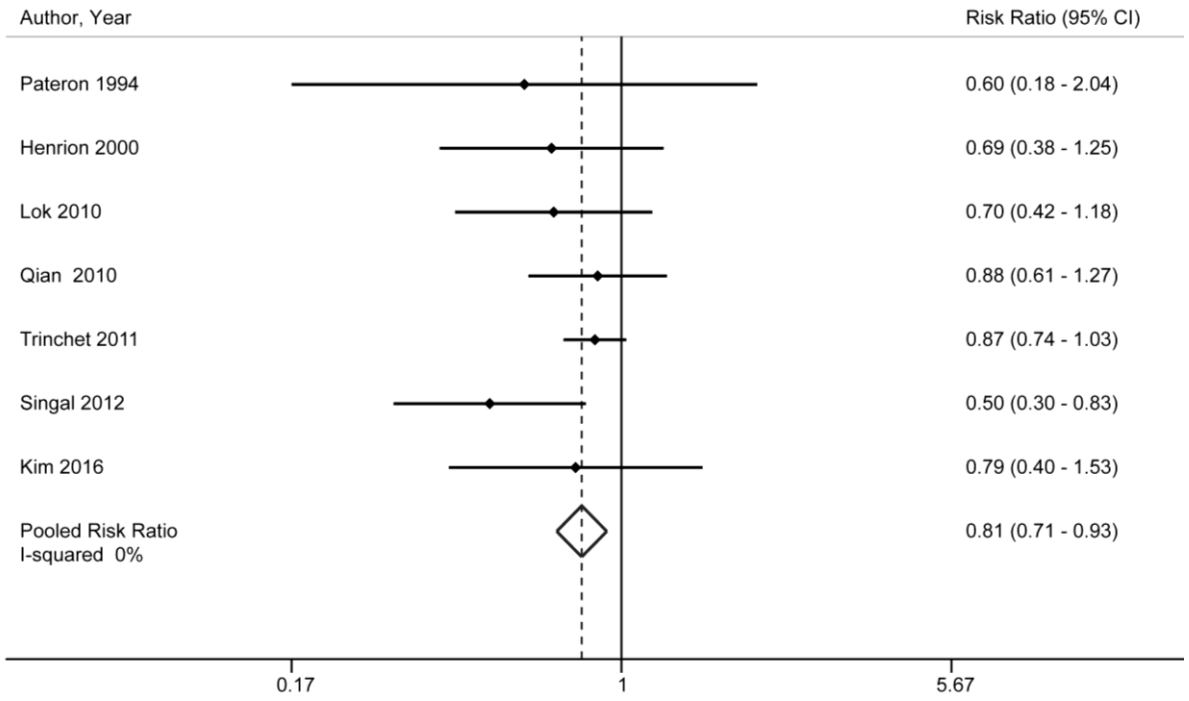
Level I evidence supporting surveillance using ultrasound and AFP

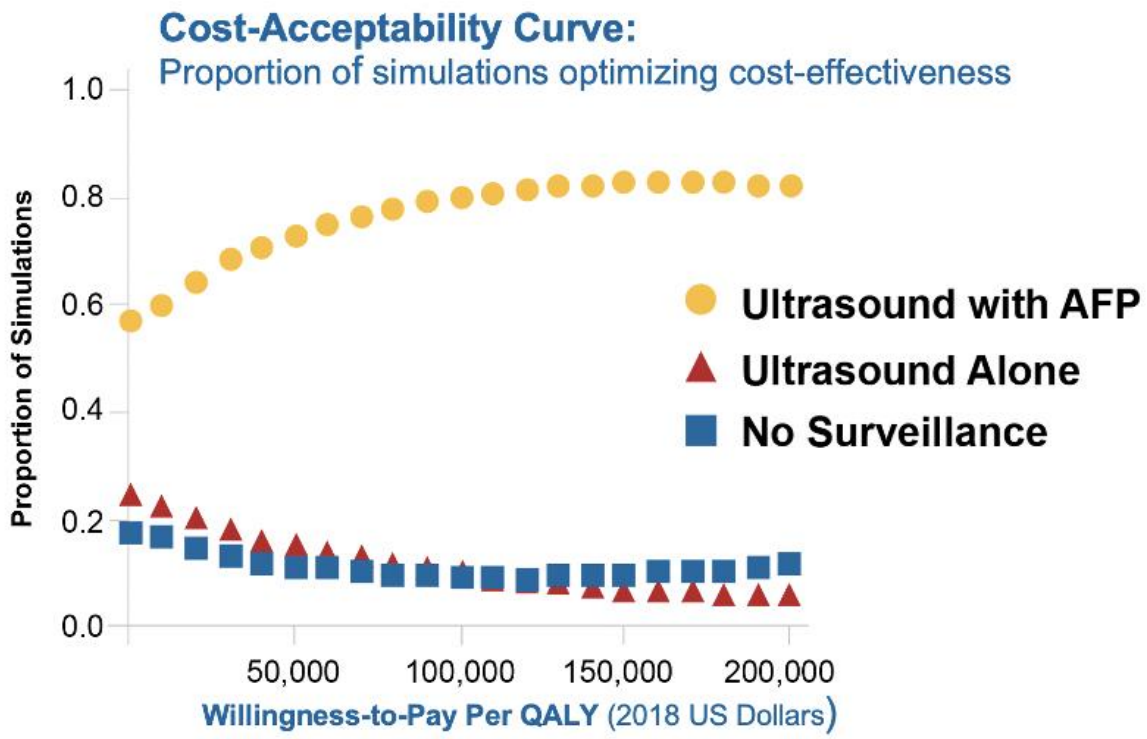


Variable	Screen Group (n=9373)	Control Group (n=9443)
HCC cases	86	67
% Stage I	60.5%	0%
% Curative treatment	46.5%	7.5%
# HCC death	32	54
Mortality (per 100,000)	83.2	131.5
Rate Ratio	0.63 (0.4-0.9)	

Zhang et al. *J Cancer Research Onc* 2004

Ultrasound + AFP has high sensitivity for early HCC and is cost-effective





Sensitivity of ultrasound and AFP 63% for early stage HCC

Tzartzeva et al. *Gastroenterology* 2018
Parikh et al. *Am J Gastro* 2021

There are promising imaging and biomarker surveillance strategies…

JAMA Oncology | Original Investigation

MRI With Liver-Specific Contrast for Surveillance of Patients With Cirrhosis at High Risk of Hepatocellular Carcinoma

So Yeon Kim, MD, PhD; Jihyun An, MD; Young-Suk Lim, MD, PhD; Seungbong Han, PhD; Ji-Young Lee, BN; Jae Ho Byun, MD, PhD; Hyung Jin Won, MD, PhD; So Jung Lee, MD, PhD; Han Chu Lee, MD, PhD; Yung Sang Lee, MD, PhD

Hepatocellular Carcinoma Detection by Plasma Methylated DNA: Discovery, Phase I Pilot, and Phase II Clinical Validation

DR. John B. Kisiel, MD[1], Brian A. Dukek, MS[1], Reddappa V. S. R. Kanipakam, MBBS[1], Hassan M. Ghoz, MBBCh[1], Tracy C. Yab, MBA[1], Calise K. Berger, BS[1], William R. Taylor, MS[1], Patrick H. Foote, BS[1], Nasra H. Giama, BS[1], Kristeen Onyirioha, BS[1], Mohamed A. Abdallah, MBBS[1], Kelli N. Burger, BS[1], Seth W. Slettedahl, MS[1], Douglas W. Mahoney, MS[1], Thomas C. Smyrk, MD[1], Jason T. Lewis, MD[1], Maria Giakoumopoulos, PhD[2], Hatim T. Allawi, PhD[2], Graham Lidgard, PhD[2], DR. Lewis R. Roberts, MB ChB, PhD[1], and **David A. Ahlquist, MD[1]**

Role of the GALAD and BALAD-2 Serologic Models in Diagnosis of Hepatocellular Carcinoma and Prediction of Survival in Patients

Sarah Berhane,[*] Hidenori Toyoda,[‡] Toshifumi Tada,[‡] Takashi Kumada,[‡] Chiaki Kagebayashi,[§] Shinji Satomura,[§] Nora Schweitzer,[‖] Arndt Vogel,[‖] Michael P. Manns,[‖] Julia Benckert,[¶] Thomas Berg,[¶] Maria Ebker,[#] Jan Best,[**] Alexander Dechêne,[**] Guido Gerken,[**] Joerg F. Schlaak,[‡‡] Arndt Weinmann,[§§,‖‖] Marcus A. Wörns,[§§,‖‖] Peter Galle,[§§] Winnie Yeo,[¶¶] Frankie Mo,[¶¶] Stephen L. Chan,[¶¶] Helen Reeves,[##,***] Trevor Cox,[‡‡‡] and Philip Johnson[*,§§§]

… but it's too early to celebrate and declare them ready for prime time

lance of Patient
r Carcinoma

Jae Ho Byun, MD, PhD;

d DNA:
Discovery, Phase I Pilot, and Phase II Clinical Validation

DR. John B. Kisiel, MD[1], Brian A. Dukek, MS[1], Reddappa V. S. R. Kanipakam, MBBS[1],
Hassan M.
MS[1], Patric
Abdallah, M
Thomas C.
Allawi, PhD
Ahlquist, M

Role
of H
Pati
odels in Diagnosis
of Survival in

Sarah Berhane,* Hidenori Toyoda,‡ Toshifumi Tada,‡ Takashi Kumada,‡ Chiaki Kagebayashi,§ Shinji Satomura,§ Nora Schweitzer,‖ Arndt Vogel,‖ Michael P. Manns,‖ Julia Benckert,¶ Thomas Berg,¶ Maria Ebker,# Jan Best,** Alexander Dechêne,** Guido Gerken,**

Winnie Yeo,¶¶
Johnson*,§§§

International Liver Cancer Association (ILCA) White Paper on Biomarker Development for Hepatocellular Carcinoma

Authors: Amit G. Singal[1] *, Yujin Hoshida[1], David J. Pinato[2], Jorge Marrero[1], Jean-Charles Nault[3-5], Valerie Paradis[6], Nabihah Tayob[7], Morris Sherman[8], Young Suk Lim[9], Ziding Feng[10], Anna S. Lok[11], Jo Ann Rinaudo[12], Sudhir Srivastava[12], Josep Llovet[13-15], Augusto Villanueva[13]

Summary

- Guidelines provide a framework of recommended management for cohorts, considering many factors including cost-effectiveness across large populations

- HCC surveillance is recommended in high risk patients with chronic HBV infection, whether defined by demographics or clinical risk scores such as PAGE-B

- Ultrasound and AFP have the best data as HCC surveillance tools
  - There are promising imaging and blood-based surveillance tests; however, none have sufficient evidence to be used routinely in clinical practice or incorporated into guidelines