APPENDIX INFORMATION

Goossens N, Singal AG, King LY, et al. Cost-effectiveness of risk score-stratified hepatocellular carcinoma screening in patients with cirrhosis.

Appendix Methods

Model and patient population

A previously reported Markov cohort model simulating HCC screening, diagnosis and therapy in a cohort of adult patients with compensated cirrhosis was refined and updated using TreeAge Pro software (TreeAge Software, Williamstown, MA) [1]. We adopted a health system perspective and followed the recommendations of the Panel on Cost-Effectiveness in Health and Medicine [2].

The baseline population was a cohort of 50-year old subjects with compensated cirrhosis followed up for a period of up to 30 years. Patients entered the model and cycled between principal health states every 6 months to reflect the natural history of cirrhosis with or without HCC (**Figure 1**). Transition probabilities were derived from published literature (**Table 1**). Per-cycle transition probabilities were derived from cumulative probabilities using the declining exponential approximation of life expectancy (DEALE) method [3].

To estimate the effectiveness of different screening strategies, the model distinguishes between screening-detected and undetected HCC. Depending on the performance of screening modalities, HCC could be detected at an early stage or remain undetected until an advanced stage. Patients with compensated cirrhosis, in whom HCC was detected at an early stage, i.e., within the Milan criteria, were eligible for liver transplantation, resection, or local ablative therapies; whereas patients with decompensated cirrhosis and early-stage HCC were eligible for liver transplantation or local ablative therapies. Patients with advanced tumors received palliative treatments, including chemoembolization, systemic therapy, or best supportive care as recommended by the AASLD guideline [4].

The following assumptions were made in our model: (1) positive screening tests (i.e., lesions ≥1 cm in diameter) were evaluated with diagnostic contrast-enhanced MRI; (2) patients with characteristic findings of HCC on the diagnostic MRI did not undergo further diagnostic evaluation prior to treatment; (3) patients with a positive screening test but negative diagnostic MRI underwent biopsy to evaluate the suspicious nodule; (4) patients with false positive screening tests returned to prior screening strategy if biopsy confirmed that no HCC was present; (5) risk of HCC was stable over time during the observation period.

HCC screening strategies

As the reference strategy, biannual abdominal ultrasound with 100% utilization rate (US2×-100%), was used as the current standard of care per practice guidelines, and compared to two non-risk-stratified screening strategies: (1) biannual dynamic contrast-enhanced triple-phase MRI (full MRI) with 100% utilization rate (MRI2×-100%); (2) biannual abbreviated contrast-enhanced MRI (AMRI) [5] with 100% utilization rate (AMRI2×-100%), and 14 risk-stratified strategies with various combinations of screening modalities assigned for each risk subgroup (**Table 2**). In each of the risk-stratified strategies, patients were first stratified into high-, intermediate-, and low-risk groups by applying either of two published integrative molecular and clinical HCC risk scores elaborated in the next section [6-9]. Subsequently, each risk group was subjected to different screening protocols according to the HCC risk level. The 16 experimental strategies were also compared to another alternative reference strategy, biannual ultrasound with 15% utilization rate (US2×-15%), representing the current real-world usage of HCC screening in the U.S. [10].

Baseline estimates of clinical parameters

Table 1 summarizes model parameters, base case values, and plausible ranges based on our previously published model [1], updated literature review [10], and expert input for sensitivity analyses. When several estimates were available, we prioritized estimates from meta-analyses and/or larger studies when available.

Natural history of cirrhosis: The adjusted annual excess mortality of compensated cirrhosis was estimated as 4%, and 5% of compensated cirrhosis progress to decompensated cirrhosis each year based on a systematic review of 118 studies [11]. As in the prior model, mortality rates were adjusted to avoid double counting HCC-related mortality [1].

Risk-stratification strategies and HCC incidence: A 186-gene signature-based HCC risk score, comprised of the liver gene signature, bilirubin, and platelet count, was used as the example of biomarker-based risk stratification in our base model [8 12]. With the score, proportions of high-, intermediate-, and low-risk groups were 36%, 37%, and 27%, respectively. The baseline annual HCC incidence for the entire cohort, HCC high-, intermediate-, and low-risk groups were 2.9%, 4.9%, 3.3%, and 0.8%, respectively, based on a prospective-retrospective cohort study of HCV-infected compensated cirrhosis patients followed up for up to 23 years [8]. As an additional example, another HCC risk score based on epidermal growth factor (EGF) SNP, which can be measured using buccal swab, was also tested [6]. The score comprises the EGF SNP, age, sex, smoking status, alkaline phosphatase level, and platelet count. With the use of the EGF-based score, proportions of HCC high-, intermediate-, and low-risk groups were 14%, 29%, 57%, respectively. The annual HCC incidence for the entire cohort, HCC high-, intermediate-, and low-risk groups were 1.4%, 5.0%, 1.8%, and 0.4%, respectively, based on a secondary analysis of the HALT-C Trial cohort [6]. Range of annual HCC incidences tested was 0.5% to 7.0%, covering HCC incidence in global populations with a variety of liver disease etiologies [13-20].

Progression of HCC: Rate of annual progression from small to advanced HCC was 40% and annual mortality of advanced HCC was 75% [21 22]. Tumor growth was assumed to be linear, with a doubling time between 117 and 195 days, resulting in approximately 40% of tumors progressing from early to advanced stage each year if not treated [10].

HCC screening test performance: Sensitivity and specificity of screening ultrasound to detect HCC at an early stage were estimated as 63% and 91%, respectively, based on a meta-analysis of ultrasound performance characteristics [23-26]. Sensitivity and specificity of screening full MRI were estimated as 96 and 94%, respectively, based a cohort study of 638 consecutive patients [27]. Sensitivity and specificity of AMRI were estimated as 83 and 93%, respectively, based on a cohort study of 298 consecutive patients [5]. Patients who did not undergo screening were assumed to have a 30% likelihood of being detected at an early stage incidentally using data from a systematic review of HCC screening studies [10]. Diagnostic MRI had sensitivity and specificity of 88% and 94%, respectively, based on previous cohort and case-control studies [25 26 28-31]. Biopsy was assumed to have sensitivity of 62% based on prior cohort studies and specificity of 100% based on expert opinion [32].

HCC treatment and prognosis: Based on data from a meta-analysis of HCC treatment utilization, we estimated the probabilities of any treatment in compensated and decompensated

cirrhosis patients were 69% and 30%, respectively [33 34]. The proportions of treatment-eligible patients with compensated cirrhosis and early HCC undergoing resection, transplantation, and local ablation were 40%, 20%, and 40%, respectively, based on population studies [34 35]. Treatment-eligible patients with decompensated cirrhosis and early HCC were treated with liver transplantation in 40% of cases [1]. Five-year survival rates after surgical resection, liver transplantation, and local ablation were 44%, 70%, and 46%, and perioperative mortality of resection, transplantation, and local ablation were 3.9%, 4.3%, and 0.3%, respectively, based on several large cohort studies [36-48]. These estimates were widely varied in sensitivity analyses to evaluate robustness of the model outputs (**Table 1**).

Costs and utility: Costs of screening tests were calculated based on 2015 Medicare Current Procedural Terminology (CPT) reimbursement global costs. The cost of AMRI was conservatively estimated by halving the technical cost of full MRI [49] (**Appendix Table 1**). Cost of the HCC risk biomarker test was calculated as median of multi-gene gapfill CPT codes in Clinical Laboratory Fee Schedule (CLFS) (**Appendix Table 2**). Other direct medical costs were derived from Medicare CPT reimbursement, Nationwide Inpatient Sample, and published literature [50-52] and adjusted for inflation to 2014 costs using the Consumer Price Index inflation calculator from the U.S. Bureau of Labor Statistics (Labor UDo, CPI Inflation Calculator, www.bls.gov/data/inflation_calculator.htm, accessed May, 2016). Literature-based estimates were used for the quality-of-life weights [1].

Study outcomes

Model outcomes included lifetime costs, quality-adjusted life expectancy (QALE), and incremental cost-effectiveness ratios (ICER), defined as incremental cost in U.S.$ per quality-adjusted life year (QALY) gained. An ICER of less than $50,000 was regarded as cost-effective. One-way sensitivity analyses were performed on all transition probabilities, costs, and utilities to identify influential variables on cost-effectiveness. Two-way sensitivity analyses were performed for annual HCC incidence and variables found to affect cost-effectiveness in one-way sensitivity analyses. Subgroup analyses were performed for a subset of subjects who were diagnosed for HCC as well as for each HCC risk group. A hypothetical cohort of 10,000 patients was simulated by Monte-Carlo simulation. Validity of the model was assessed by comparing overall survival rates in the entire cohort and HCC-developing patients derived from the model with those in published systematic reviews. All other statistical analyses were performed using the R statistical package (www.r-project.org).

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Appendix Table 1
Cost of abbreviated full MRI and abbreviated MRI (AMRI).

	Full MRI (CPT 74182)	AMRI
Technical Component	$429.73	214.87*
Professional component	$98.11	$98.11
Total cost	$527.84	$312.98

Based on Medicare 2015 reimbursement costs.
*Halved technical cost for standard MRI.
MRI, magnetic resonance imaging; AMRI: abbreviated MRI.

Appendix Table 2
Estimated cost of HCC risk biomarker test.

Multi-gene molecular test	National limit for clinical laboratory fee schedule gapfill
#1	$795.95
#2	$795.95
#3	$597.31
#4	$647.75
#5	$3,416.00
#6	$3,416.00
Median	$795.95

From 2015 national limits for Clinical Laboratory Fee Schedule gapfill pricing.
HCC: hepatocellular carcinoma.

Appendix Table 3
Subgroup analysis of cost-effectiveness of risk-stratified screening strategies within high-, intermediate- and low-risk groups.

Risk group	Risk-stratified screening strategy	QALE	Cost	ICER (vs US2×-100%)	ICER (vs US2×-15%)
Low	US2×-100%	7.01	$48,258	-	-
Low	US2×-15%	6.95	$39,888	-	-
Low	US4×-US4×-none	7.02	$38,812	Dominant	Dominant
Low	US4×-none-none	7.02	$38,812	Dominant	Dominant
Low	US4×-US2×-none	7.02	$38,812	Dominant	Dominant
Low	US4×-US2×-US2×	7.01	$49,661	Dominated	$162,886
Low	AMRI-AMRI-none	7.02	$38,812	Dominant	Dominant
Low	AMRI-none-none	7.02	$38,812	Dominant	Dominant
Low	AMRI-US2×-none	7.02	$38,812	Dominant	Dominant
Low	AMRI-US2×-US2×	7.01	$49,661	Dominated	$162,886
Low	MRI-MRI-none	7.02	$38,812	Dominant	Dominant
Low	MRI-none-none	7.02	$38,812	Dominant	Dominant
Low	MRI-US2×-none	7.02	$38,812	Dominant	Dominant
Low	MRI-US2×-US2×	7.01	$49,661	Dominated	$162,886
Low	US2×-none-none	7.02	$38,812	Dominant	Dominant
Low	US2×-US2×-none	7.02	$38,812	Dominant	Dominant
Intermediate	US2×-100%	6.48	$49,824	-	-
Intermediate	US2×-15%	6.38	$44,589	-	-
Intermediate	US4×-US4×-none	6.48	$59,696	Dominated	$151,070
Intermediate	US4×-none-none	6.2	$45,324	Less effective	Less effective
Intermediate	US4×-US2×-none	6.48	$50,620	Dominated	$60,309
Intermediate	US4×-US2×-US2×	6.48	$50,620	Dominated	$60,309
Intermediate	AMRI-AMRI-none	6.51	$52,647	$94,107	$61,986
Intermediate	AMRI-none-none	6.2	$45,324	Less effective	Less effective
Intermediate	AMRI-US2×-none	6.48	$50,620	Dominated	$60,309
Intermediate	AMRI-US2×-US2×	6.48	$50,620	Dominated	$60,309
Intermediate	MRI-MRI-none	6.48	$56,364	Dominated	$117,754
Intermediate	MRI-none-none	6.2	$45,324	Less effective	Less effective
Intermediate	MRI-US2×-none	6.48	$50,620	Dominated	$60,309
Intermediate	MRI-US2×-US2×	6.48	$50,620	Dominated	$60,309
Intermediate	US2×-none-none	6.2	$45,324	Less effective	Less effective
Intermediate	US2×-US2×-none	6.48	$50,620	Dominated	$60,309
High	US2×-100%	6.27	$54,942	-	-
High	US2×-15%	6.04	$46,041	-	-
High	US4×-US4×-none	6.27	$60,760	Dominated	$63,998
High	US4×-none-none	6.27	$60,760	Dominated	$63,998
High	US4×-US2×-none	6.27	$60,760	Dominated	$63,998
High	US4×-US2×-US2×	6.27	$60,760	Dominated	$63,998
High	AMRI-AMRI-none	6.28	$56,177	$123,509	$42,234
High	AMRI-none-none	6.28	$56,177	$123,509	$42,234
High	AMRI-US2×-none	6.28	$56,177	$123,509	$42,234
High	AMRI-US2×-US2×	6.28	$56,177	$123,509	$42,234
High	MRI-MRI-none	6.32	$58,920	$79,576	$45,999

High	MRI-none-none	6.32	$58,920	$79,576	$45,999
High	MRI-US2×-none	6.32	$58,920	$79,576	$45,999
High	MRI-US2×-US2×	6.32	$58,920	$79,576	$45,999
High	US2×-none-none	6.27	$55,738	Dominated	$42,161
High	US2×-US2×-none	6.27	$55,738	Dominated	$42,161

2×, screening two times a year; 4×, screening four times a year; MRI and AMRI are biannual. Dominant or ICER less than $50,000 per QALY are highlighted in green.
US, ultrasound; MRI, magnetic resonance imaging; AMRI, abbreviated MRI;
QALE, quality adjusted life expectancy; ICER, incremental cost-effectiveness ratio.

Appendix Table 4
Cost-effectiveness of HCC screening strategies tested using the EGF-based risk score.

Risk group	QALE	Cost	ICER (vs. US2×-100%)	ICER (vs. US2×-15%)
No screening	6.87	$40,285		
Reference strategies				
Regular US screening (100% adherence; US2×-100%)	6.85	$48,568	Reference	
Regular US screening (15% adherence; US2×-15%)	6.855	$41,496		Reference
Non-stratified experimental strategies				
MRI for all (MRI-100%)	6.91	$54,043	$91,236	$228,126
AMRI for all (AMRI-100%)	6.86	$50,832	$226,389	$1,867,328
Risk-stratified strategies (for high-intermediate-low risk groups)				
US4×-US2×-US2×	6.85	$50,444	Dominated	Dominated
MRI-US2×-US2×	6.87	$50,384	$90,790	$592,570
AMRI-US2×-US2×	6.89	$49,995	$35,662	$242,835
US2×-US2×-none	6.91	$44,910	Dominant	$ 62,075
US4×-US4×-none	6.89	$47,419	Dominant	$169,228
MRI-MRI-none	6.93	$47,053	Dominant	$ 74,092
AMRI-AMRI-none	6.93	$45,751	Dominant	$ 56,732
US4×-US2×-none	6.91	$45,639	Dominant	$ 75,330
MRI-US2×-none	6.92	$45,579	Dominant	$ 62,817
AMRI-US2×-none	6.91	$45,189	Dominant	$ 67,159
US2×-none-none	6.9	$42,377	Dominant	$ 19,592
US4×-none-none	6.9	$43,106	Dominant	$ 35,792
MRI-none-none	6.91	$43,046	Dominant	$ 28,192
AMRI-none-none	6.91	$42,657	Dominant	$ 21,114

2×, screening two times a year; 4×, screening four times a year; MRI and AMRI are biannual.
Dominant and cost-effective strategies (ICER <$50,000) are in green.
US, ultrasound; MRI, magnetic resonance imaging; AMRI, abbreviated MRI;
QALE, quality adjusted life expectancy; ICER, incremental cost-effectiveness ratio.

Appendix Table 5
Range and references for HCC incidence according to HCC etiology (Figure 2D main text).

Etiology	Range of HCC incidence	References
HBV cirrhosis	3.0% - 8.0%	(1)
HCV cirrhosis	3.0% - 5.0%	(1)
HCV post SVR	0.3% - 1.4%	(2, 3)
ALD cirrhosis	0.2% - 2.6%	(4-6)
NAFLD cirrhosis	0.3% - 2.3%	(7-11)

ALD, alcoholic liver disease; HBV, hepatitic B virus; HCV, hepatitis C virus; NAFLD, nonalcoholic fatty liver disease; SVR, sustained virological response.

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Appendix Table 6
Model variables with references (Table 1 main text)

Variable	Baseline [range tested]	References
Disease progression		
Age (years)	50 [40-60]	
Cycle time	6 months	
Compensated cirrhosis prognosis		
Adjusted annual excess mortality of compensated cirrhosis	4% [1.8%-8%]	(1)
10-year survival of compensated cirrhosis	64% [43%-80%]	(1)
Annual probability of transition from compensated to decompensated cirrhosis	5% [3%-8%]	(1)
Decompensated cirrhosis prognosis		
Annual mortality of decompensated cirrhosis	28% [18%-30%]	(1-3)
2-year survival of decompensated cirrhosis	52% [49%-67%]	(1-3)
HCC prognosis		
Annual mortality of advanced HCC	75% [30%-95%]	(4, 5)
HCC natural history		
Annual HCC probability	2.9% [0.5%-7.0%]	(6)
Annual probability of progression from small to advanced HCC	40% [20%-70%]	(7)
Probability of therapy		
Probability of HCC in compensated cirrhosis to be treated with surgical resection	40% [20%-60%]	(8, 9)
Probability of liver transplantation for early HCC in compensated cirrhosis	20% [0-50%]	(8, 9)
Probability of local ablation for HCC in decompensated cirrhosis	40% [20-100%]	(8, 9)
Probability of treatment of early HCC after identification in compensated cirrhosis	69% [50-100%]	(6, 10)
Probability of treatment of early HCC after identification in decompensated cirrhosis	30% [0-50%]	(11)

Probability of liver transplantation for early HCC in treatment-eligible decompensated cirrhosis	40% [0-80%]	(11)
Probability of local ablation for early HCC in treatment-eligible decompensated cirrhosis	60% [20-100%]	(11)
Prognosis after therapy		
5-year survival after hepatic resection for HCC	44% [38%-51%]	(12-15)
Perioperative mortality of hepatic resection	3.9% [3.7%-4.5%]	(12, 16)
5-year survival after liver transplantation for HCC	70% [65%-80%]	(12, 17-19)
Perioperative mortality of liver transplantation	4.3% [2.3%-6.3%]	(18)
5-year survival after local ablation for HCC in compensated cirrhosis	46% [32%-77%]	(20, 21, 22)
5-year survival after local ablation for HCC in decompensated cirrhosis	31% [27%-40%]	(20, 23)
Perioperative mortality of local ablation	0.3% [0-1.8%]	(24)
HCC risk score		
186-gene-based risk score, proportion of each risk group	High: 36% [0-50%] Intermediate: 37% Low: 27% [10-50%]	(25)
186-gene-based risk score, annual HCC incidence in each risk group	High: 4.9% [0.8%-12%] Intermediate: 3.3% [0.6%-8.0%] Low: 0.8% [0.1%-1.9%]	(25)
EGF genotype-based risk score, proportion of each risk group	High: 14% [0-40%] Intermediate: 29% Low: 57% [0-60%]	(26)
EGF genotype-based risk score, annual HCC incidence in each risk group	High: 5% [2.5%-10%] Intermediate: 1.8% [0.9%-3.6%] Low: 0.4% [0.2%-0.8%]	(26)
Screening and diagnosis test characteristics		
Probability of being screened for HCC	100% [15%-100%]	
Reported probability of being screened for HCC	15% [5%-60%]	(27-29)
Probability of incidental early HCC in non-screened group	30% [0%-50%]	(30)
Ultrasound sensitivity for early-stage HCC screening	63% [35%-78%]	(31, 32)

Ultrasound specificity for early-stage HCC screening	91% [70%-95%]	(31, 33, 34)
Screening full MRI sensitivity for early-stage HCC screening	96% [80%-100%]	(35)
Screening full MRI specificity for early-stage HCC screening	94% [85%-98%]	(35)
Abbreviated MRI sensitivity for early-stage HCC screening	83% [70%-95%]	(36)
Abbreviated MRI specificity for early-stage HCC screening	93% [86%-96%]	(36)
Diagnostic MRI sensitivity for early-stage HCC	88% [78%-92%]	(32, 33, 37-40)
Diagnostic MRI specificity for early-stage HCC	94% [85%-98%]	(32, 33, 37-39)
HCC biopsy sensitivity	62% [50%-100%]	(41)
HCC biopsy specificity	100% [80%-100%]	(11)
Costs ($)	Medicare, National Impatient Sample	(10, 42, 43)
Annual cost of compensated cirrhosis	1,220 [610-2,440]	
Annual cost of decompensated cirrhosis	15,000 [7,500-30,000]	
Annual cost after liver transplantation	14,600 [7,300-29,200]	
Annual cost of advanced HCC	41,320 [20,660-82,640]	
Cost of hepatic resection	42,540 [21,270-85,080]	
Cost of liver transplantation	177,000 [88,500-354,000]	
Cost of local ablation	3,650 [1,825-7,300]	
Cost of imaging-guided HCC biopsy	750 [375-1,500]	
Cost of ultrasound	143 [71-285]	Medicare (CPT 76700)
Cost of screening full MRI	528 [264-1,056]	Medicare (standard MRI, CPT 74182)
Cost of screening abbreviated MRI	313 [156-626]	Medicare (standard MRI, CPT 74182, technical cost halved)
Cost of diagnostic MRI	528 [264-528]	Medicare (standard MRI, CPT 74182)
Cost of risk score	796 [500-4,000]	Median of multi-gene gapfill CPT codes Medicare 2015

Rate of discounting costs	3%	
Quality-of-life weights		(10, 43, 44)
Utility of compensated cirrhosis	0.8 [0.6-1.0]	
Utility of decompensated cirrhosis	0.65 [0.5-0.8]	
Utility after HCC diagnosis	0.3 [0.1-0.4]	
Utility after liver transplantation	0.73 [0.5-0.8]	

AMRI, abbreviated MRI; CPT, current procedural terminology; EGF, epidermal growth factor; HCC, hepatocellular carcinoma; MRI, magnetic resonance imaging.

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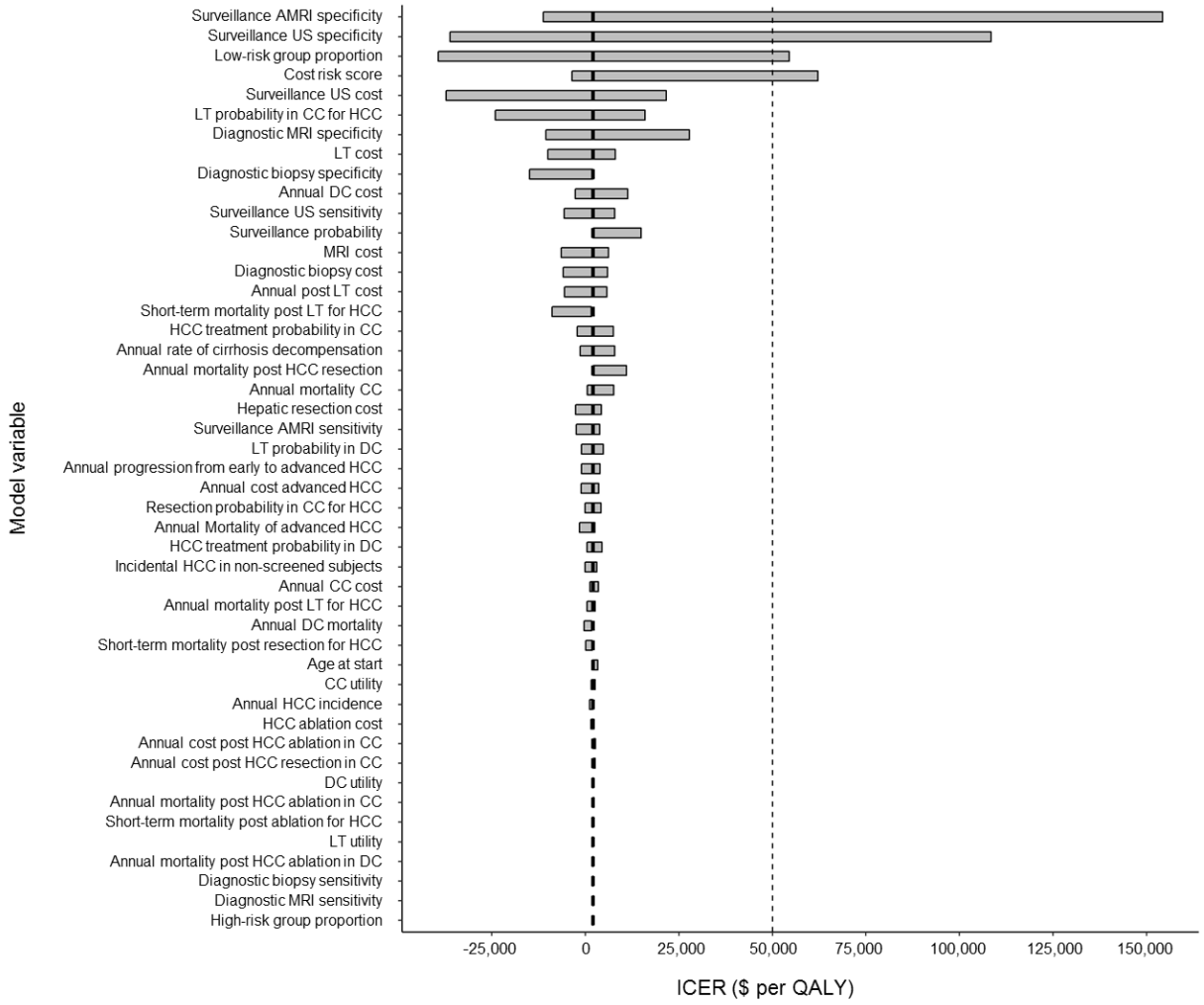
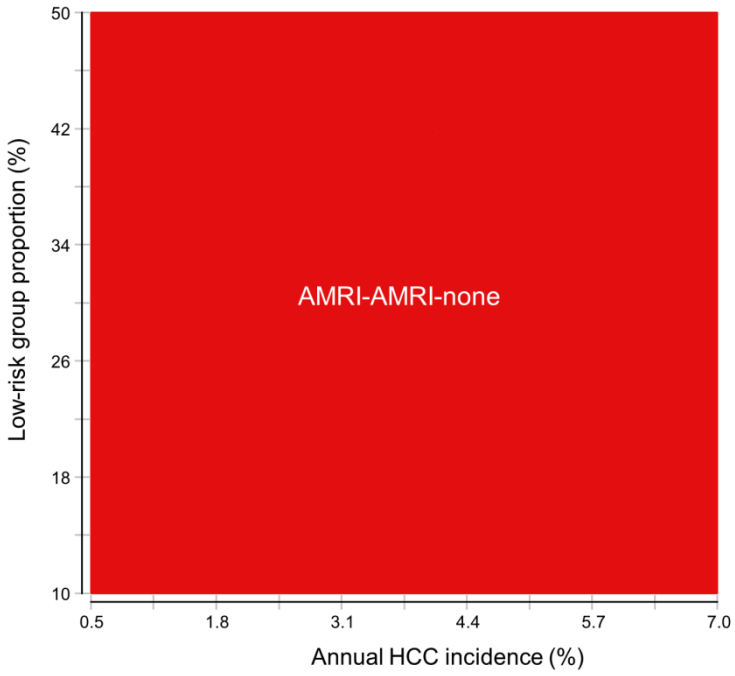


Appendix Figure 1

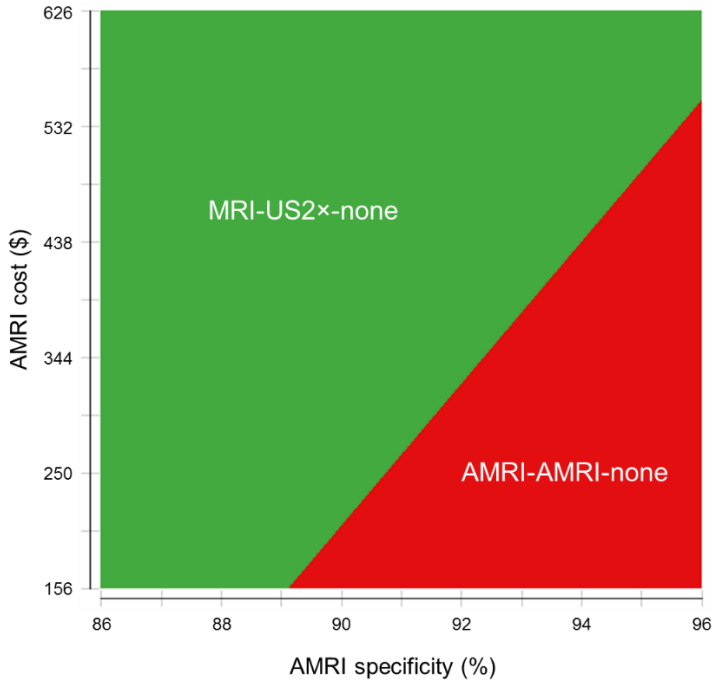
Tornado plot for AMRI-AMRI-none compared to US2×-100%.

The effect of varying all model parameters on the ICER of AMRI-AMRI-none compared to US2×-100% was assessed. The dashed line indicates an ICER of $50,000 per QALY as the threshold of cost-effectiveness.

AMRI, abbreviated MRI; CC, compensated cirrhosis; DC, decompensated cirrhosis; LT, liver transplantation; MRI, magnetic resonance imaging; US, ultrasound.



Appendix Figure 2
Two-way sensitivity analysis of annual HCC incidence vs. HCC low-risk group proportion.
Overall HCC incidence was varied along with HCC low-risk group proportion to identify the best risk-stratified HCC screening strategy over the ranges of variables.
HCC, hepatocellular carcinoma; AMRI, abbreviated magnetic resonance imaging.



Appendix Figure 3
Two-way sensitivity analysis of AMRI specificity vs. AMRI cost.
AMRI cost and specificity were varied to identify the best risk-stratified HCC screening strategy over the ranges of variables.
AMRI, abbreviated magnetic resonance imaging; US, ultrasound.