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Advances in Early Detection and Risk Stratification of HCC: Integrating Biomarkers, Imaging, and Artificial Intelligence

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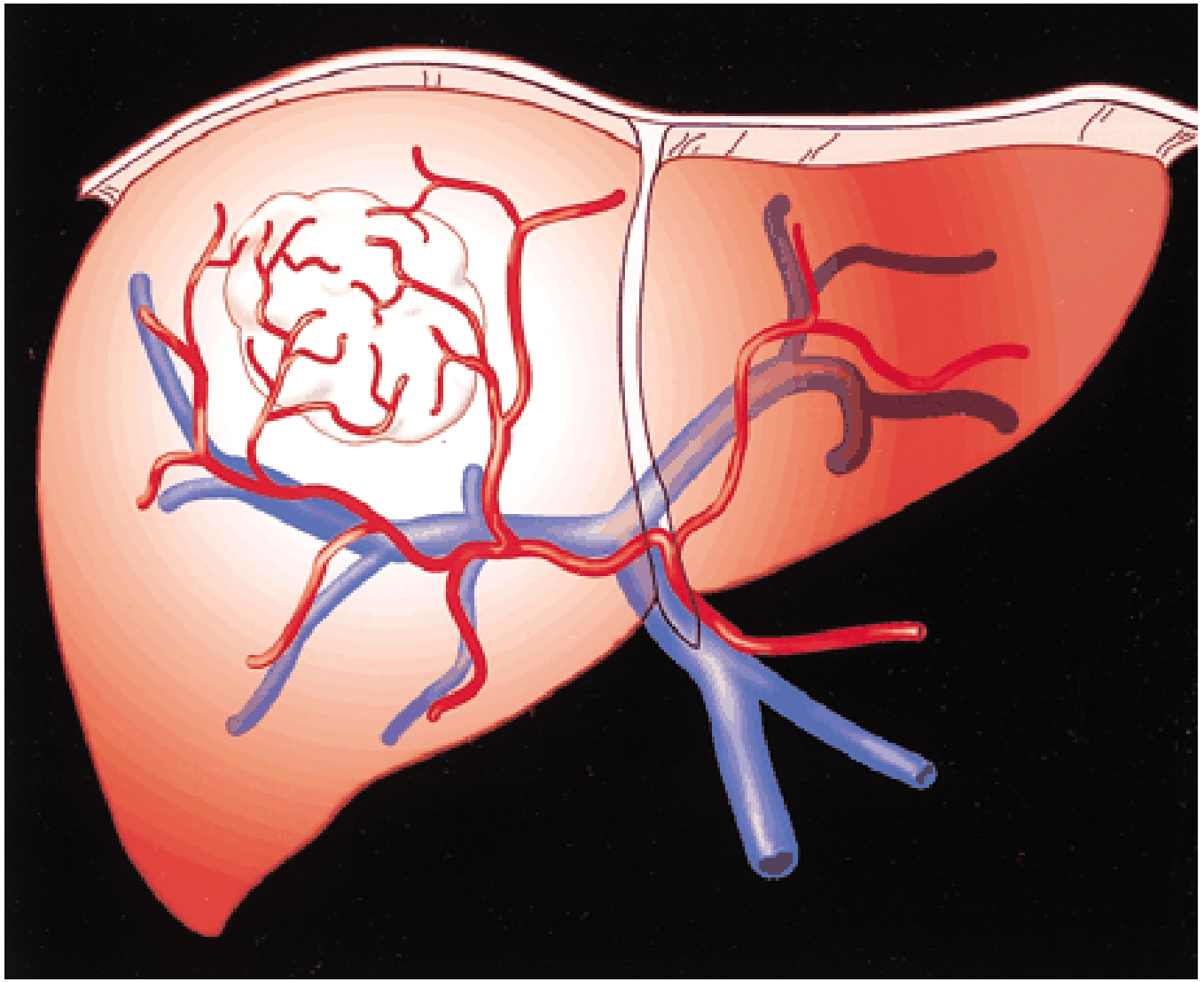
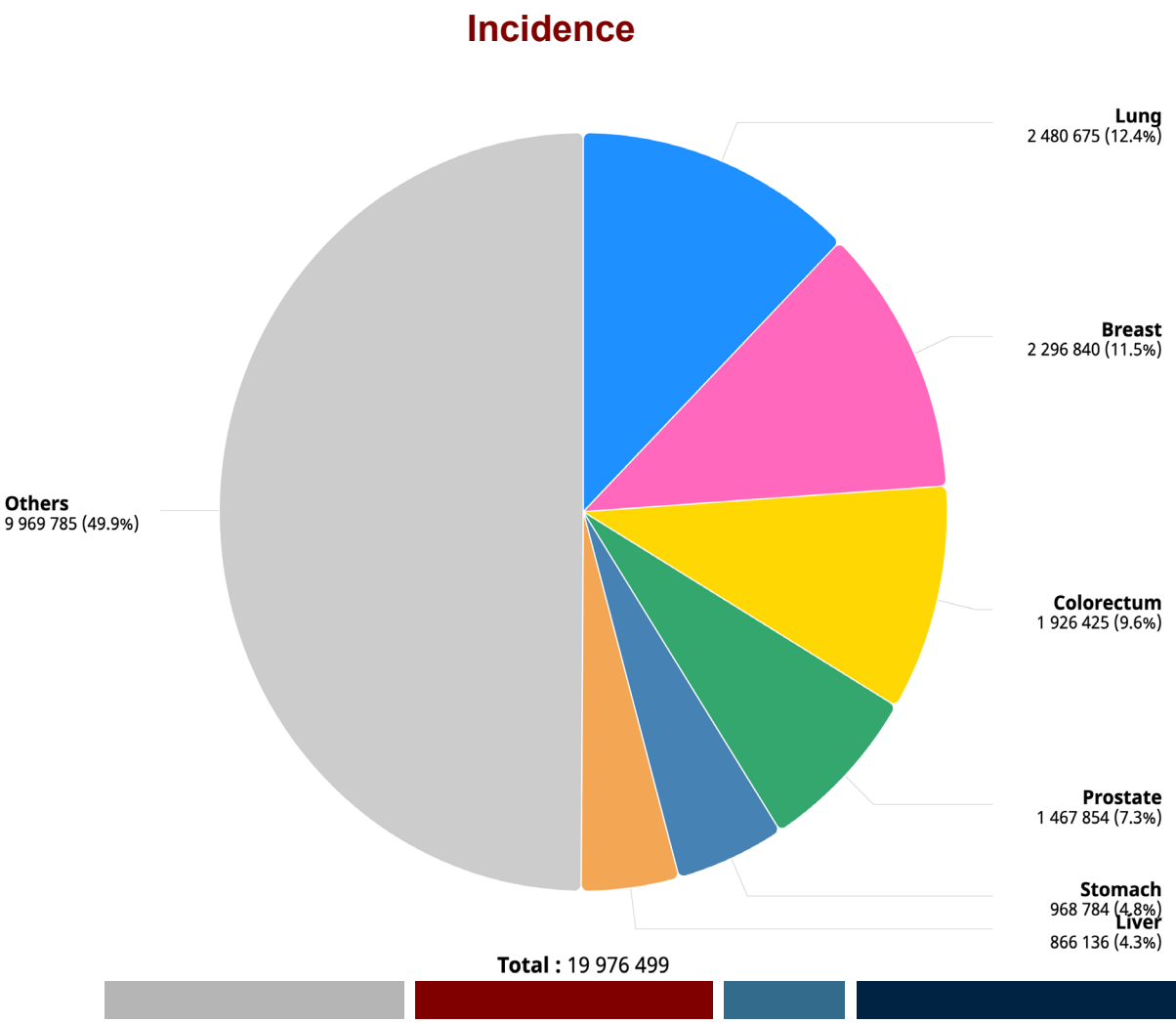
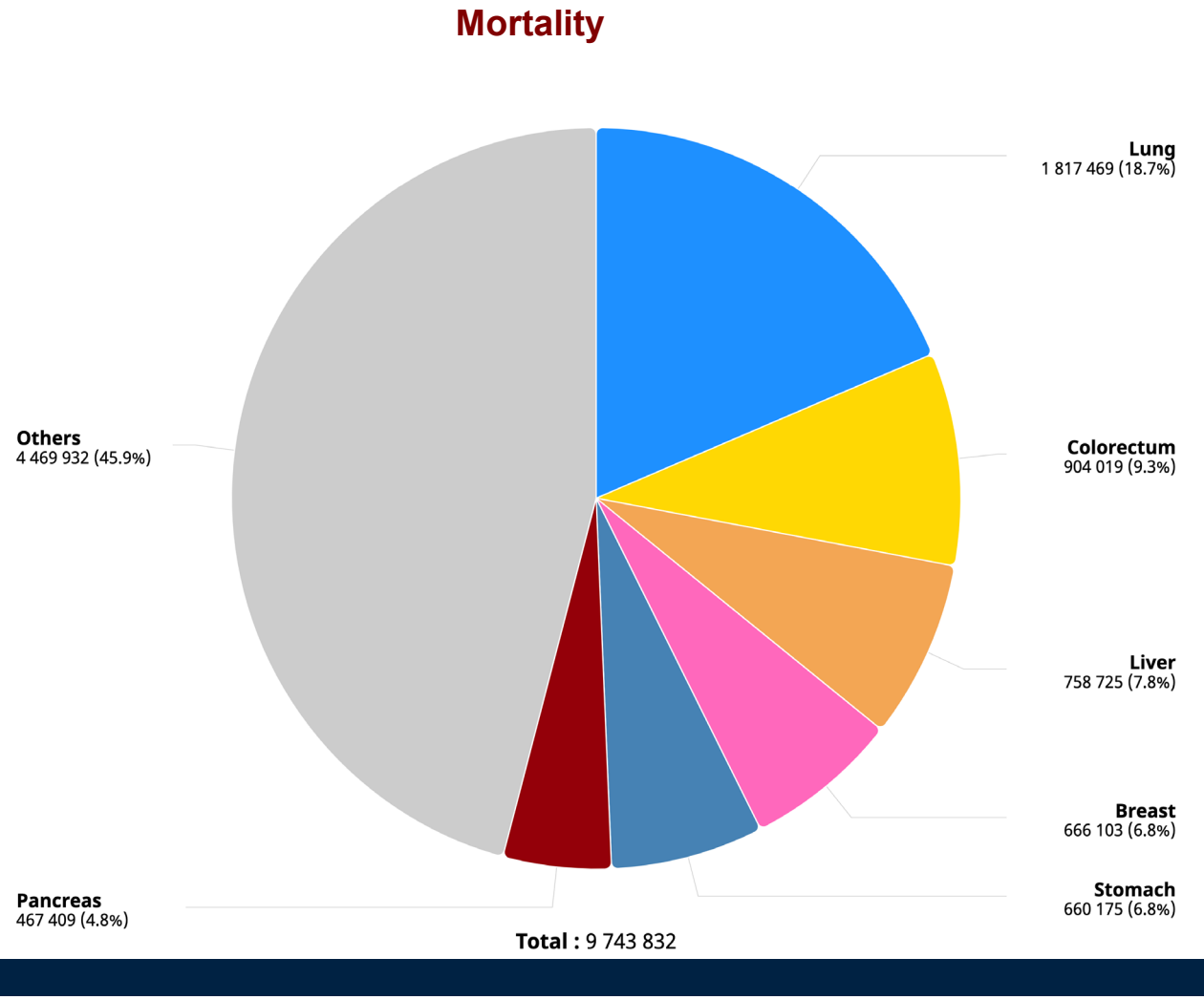
Topics

- Epidemiology
- Early Detection
- Risk-Stratification
- Summary



HCC Worldwide Epidemiology





GLOBOCAN 2022

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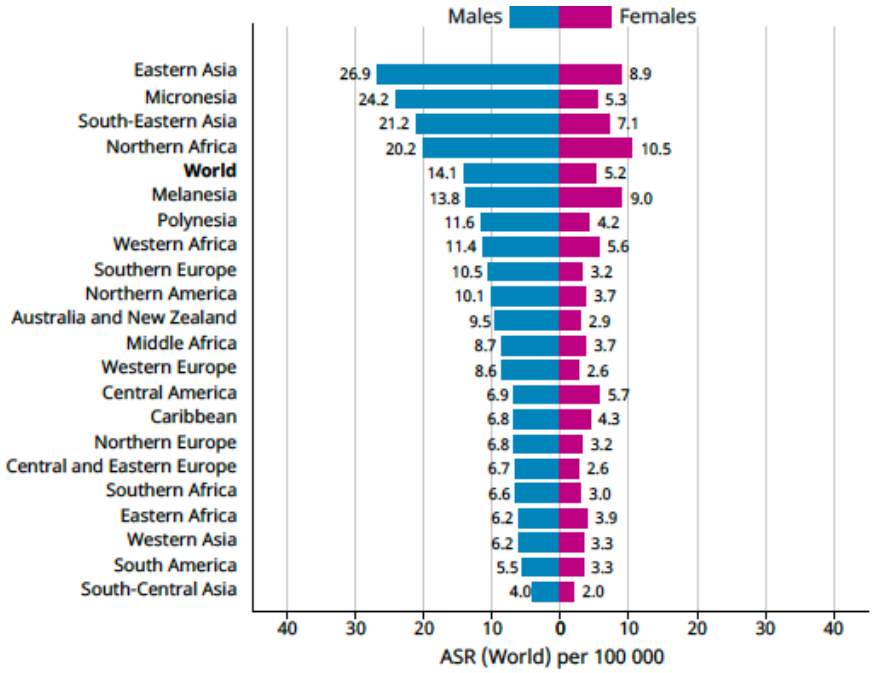
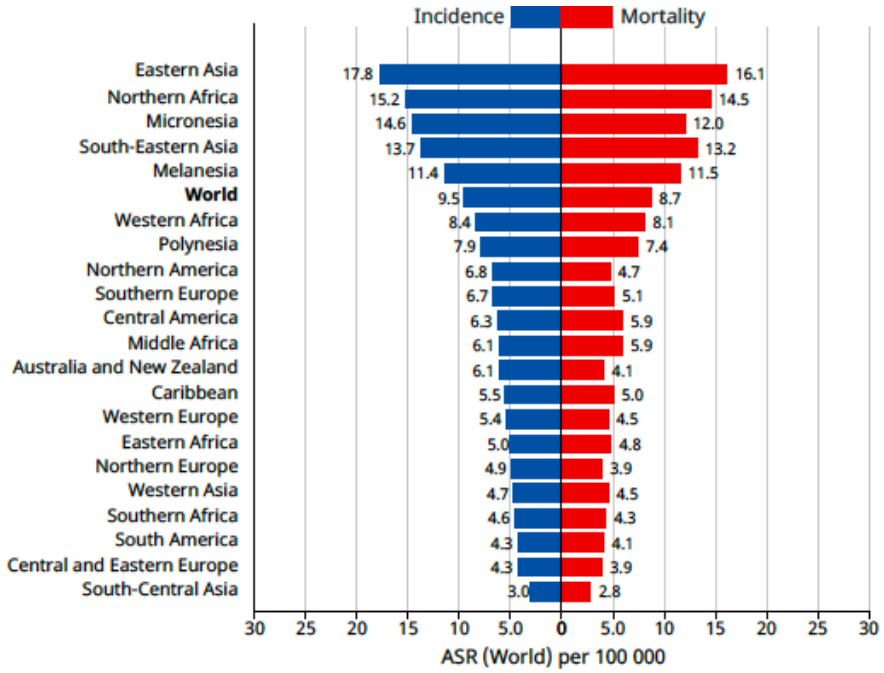
HCC Worldwide Incidence and Mortality

- **Men:woman ratio > 2:1**
- **Asia leads incidence**



- **Deadly tumor**
- **Incidence approximates mortality rates**



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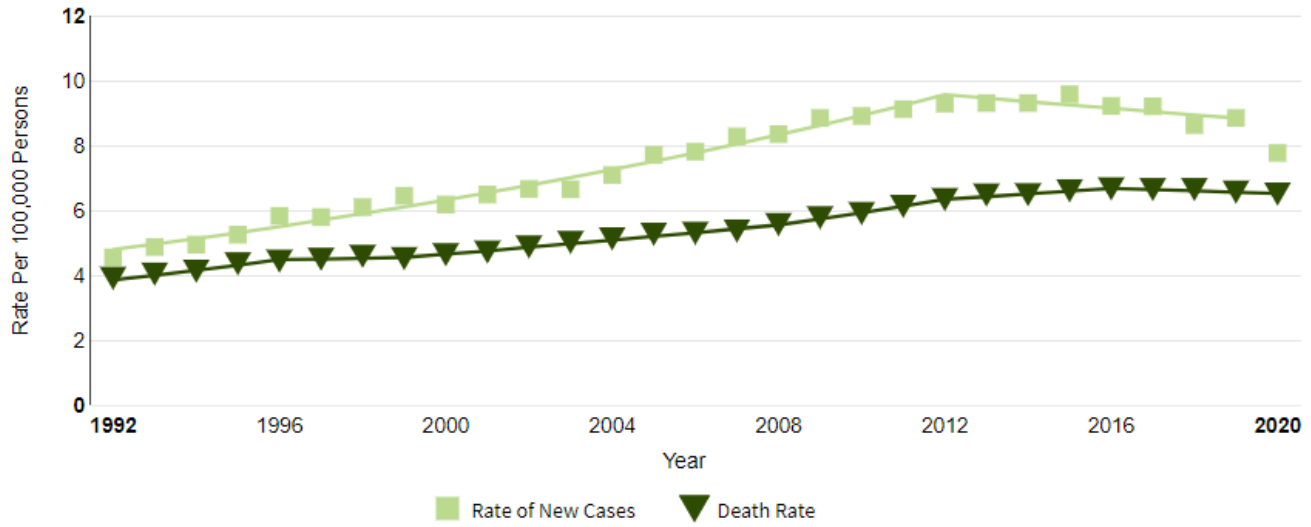
Incidence and Mortality of HCC in USA

Estimated New Cases in 2023	41,210
% of All New Cancer Cases	2.1%

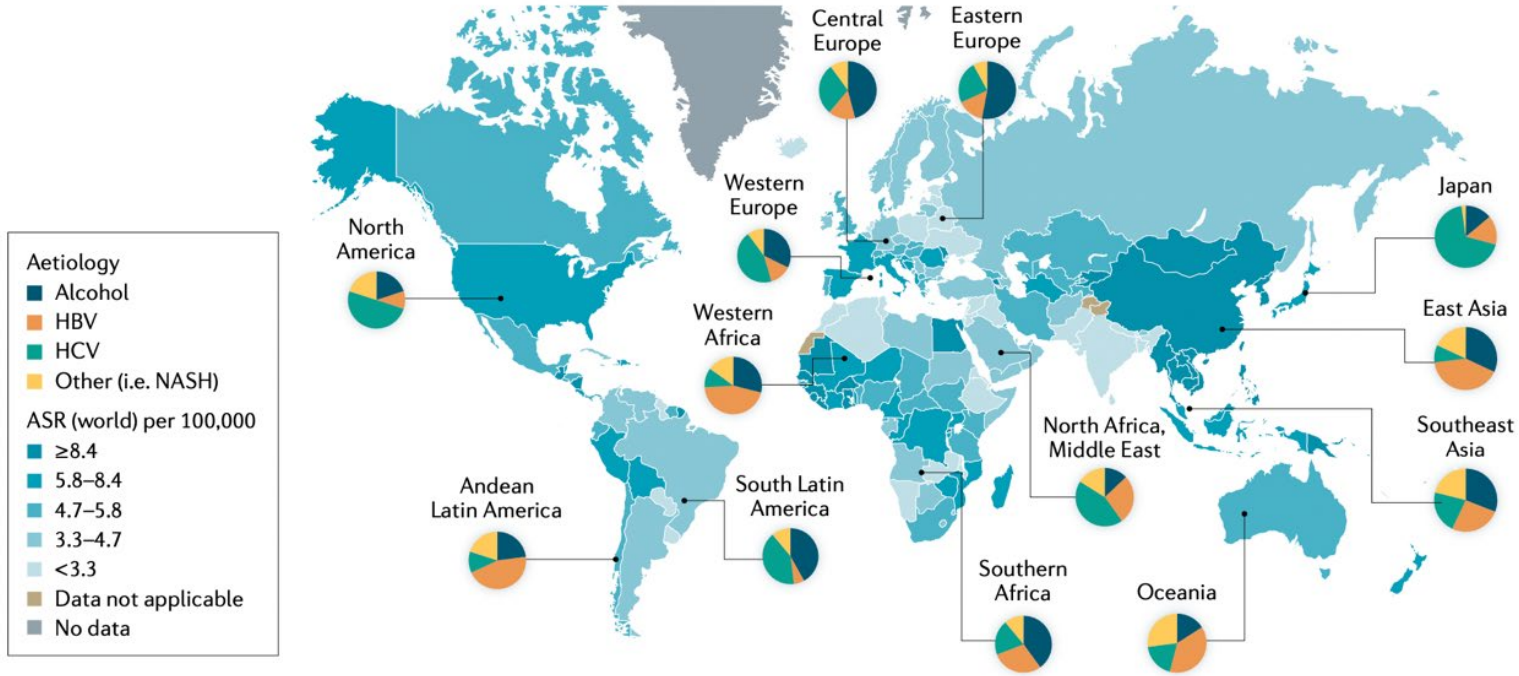
Estimated Deaths in 2023	29,380
% of All Cancer Deaths	4.8%

5-Year Relative Survival
21.6%
2013–2019

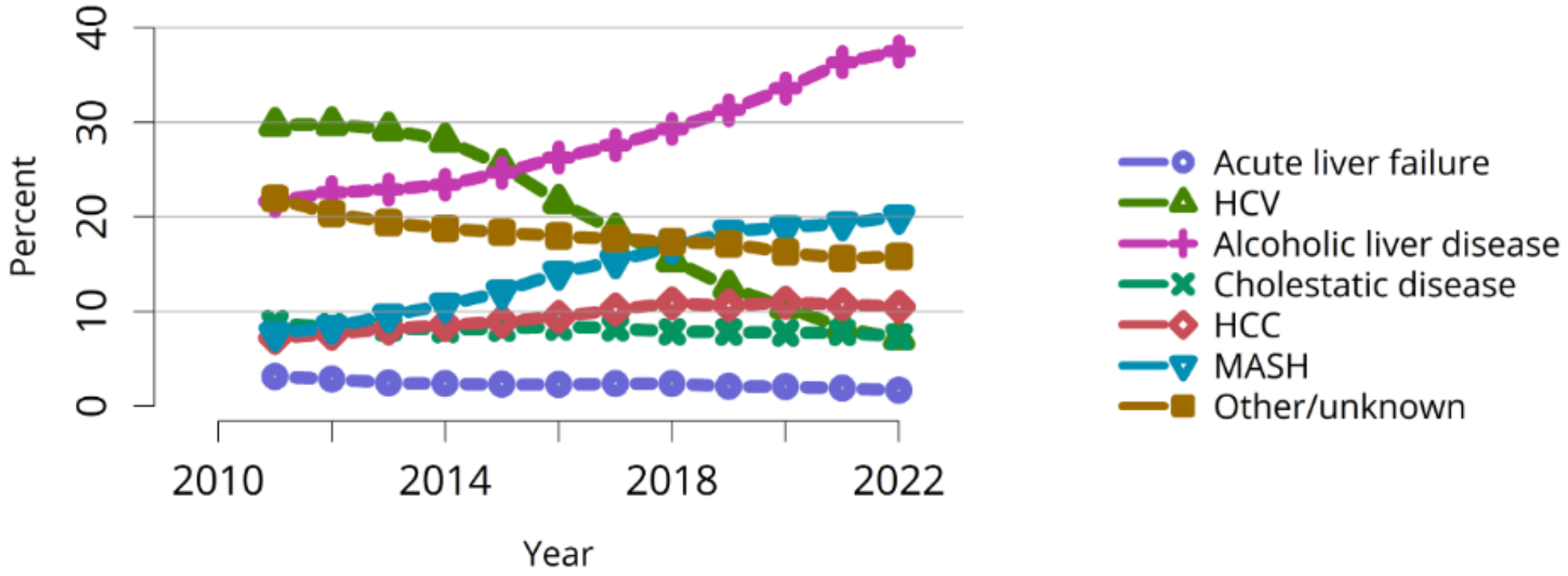


https://seer.cancer.gov/statfacts/html/livibd.html

Etiological Causes of HCC



Etiology of Liver Disease at Listing for Liver Transplantation



Kwong AJ, et al. Am J Transplant 2024

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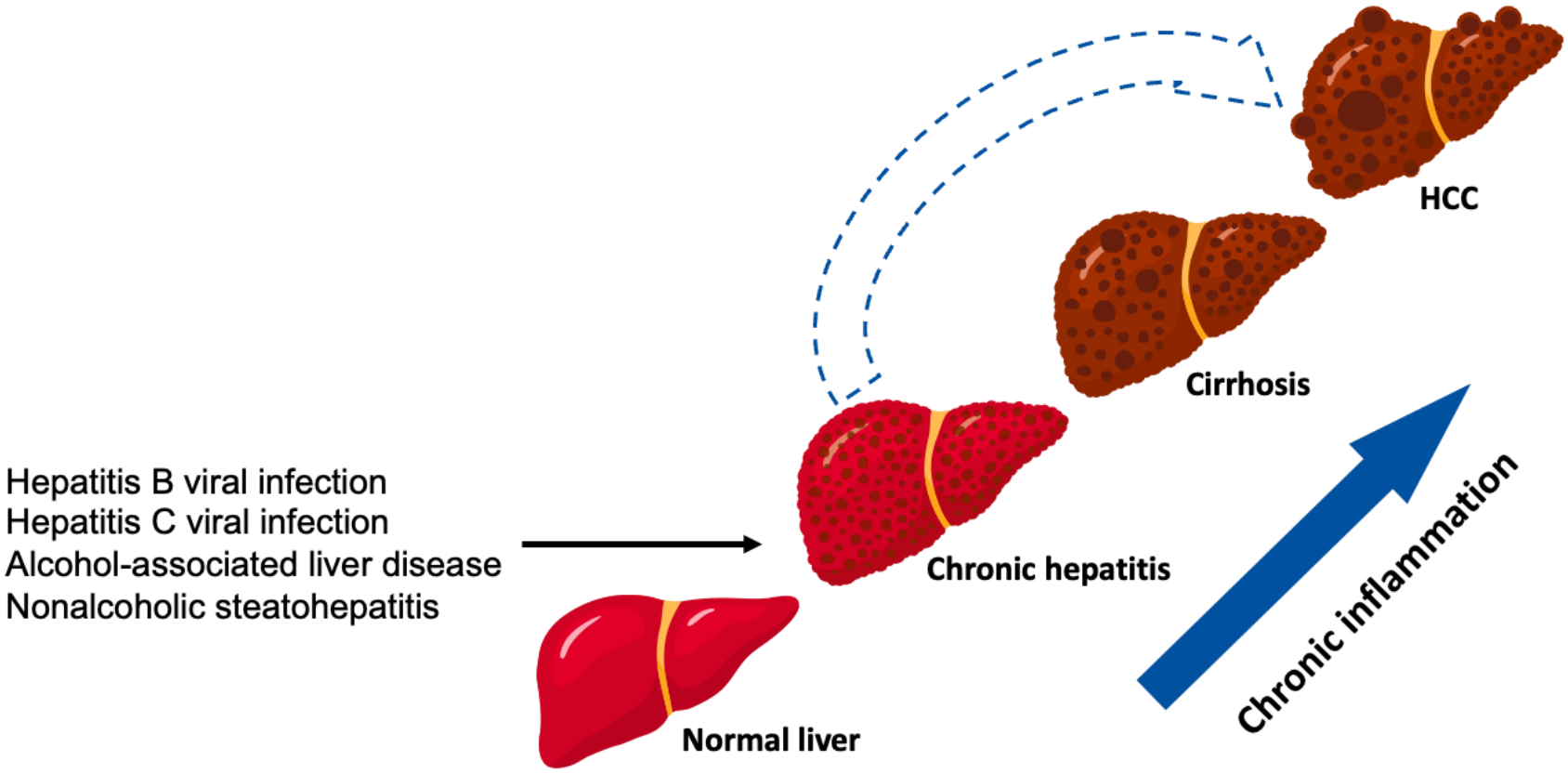
Who is the target population for HCC Surveillance?



Courtesy of Dr. Amit Singal

At-risk Population for HCC Surveillance

Population group	Incidence of HCC
Sufficient risk to warrant surveillance	
Child-Pugh A–B cirrhosis, any etiology Hepatitis B Hepatitis C (viremic or post-SVR) Alcohol associated cirrhosis Nonalcoholic steatohepatitis Other etiologies	≥ 1.0% per year
Child-Pugh C cirrhosis, transplant candidate	
Non-cirrhotic chronic hepatitis B Man from endemic country[a] age > 40 y Woman from endemic country[a] age > 50 y Person from Africa at earlier age[b] Family history of HCC PAGE-B score ≥ 10[c]	≥ 0.2% per year
Insufficient risk and in need of risk stratification models/biomarkers	
Hepatitis C and stage 3 fibrosis	< 0.2% per year
Noncirrhotic NAFLD	

Singal AG, et al. Hepatol 2023

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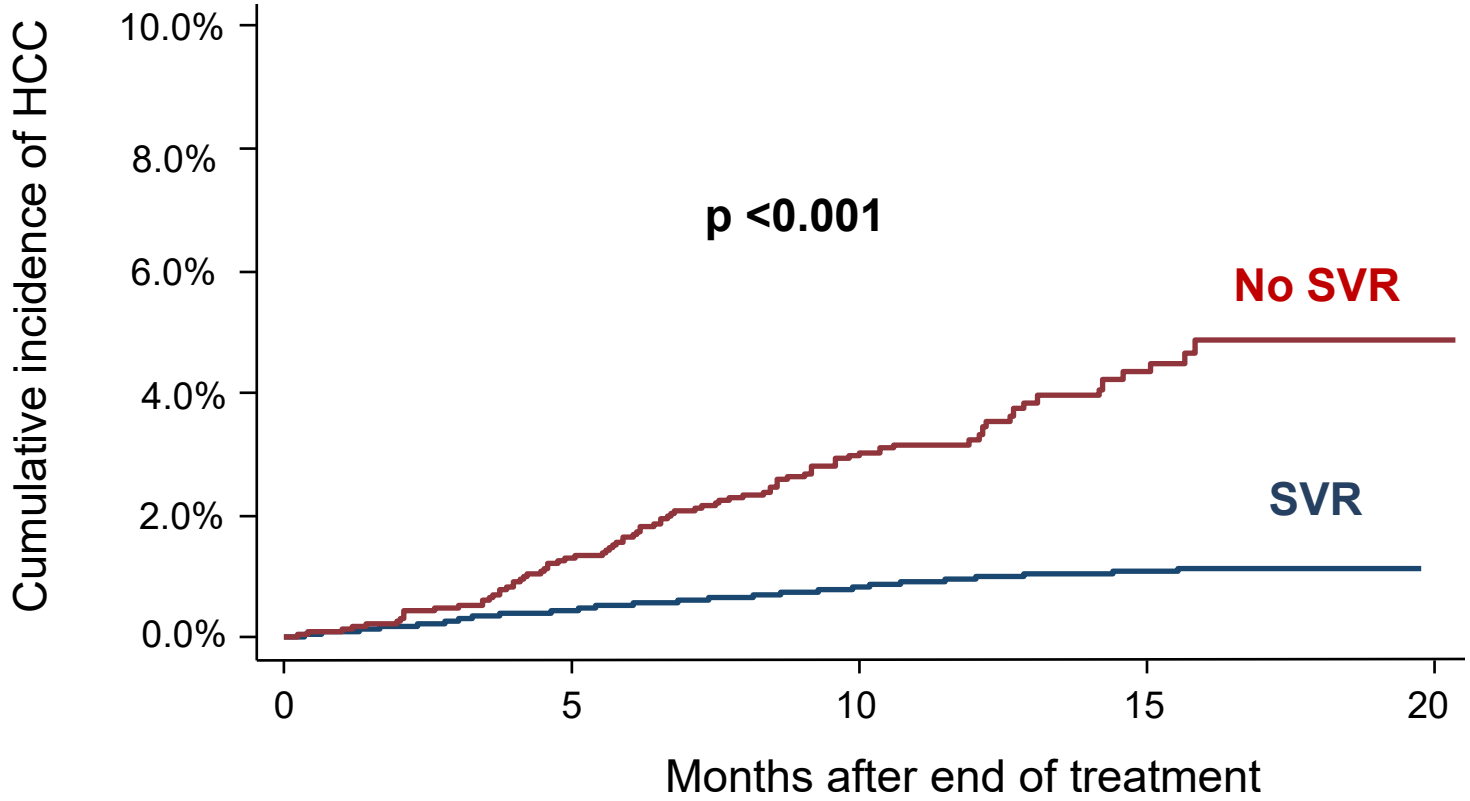
DAA-based Sustained Viral Response Reduces HCC Incidence in hepatitis C Cirrhosis



Kanwal et al. Gastro 2017

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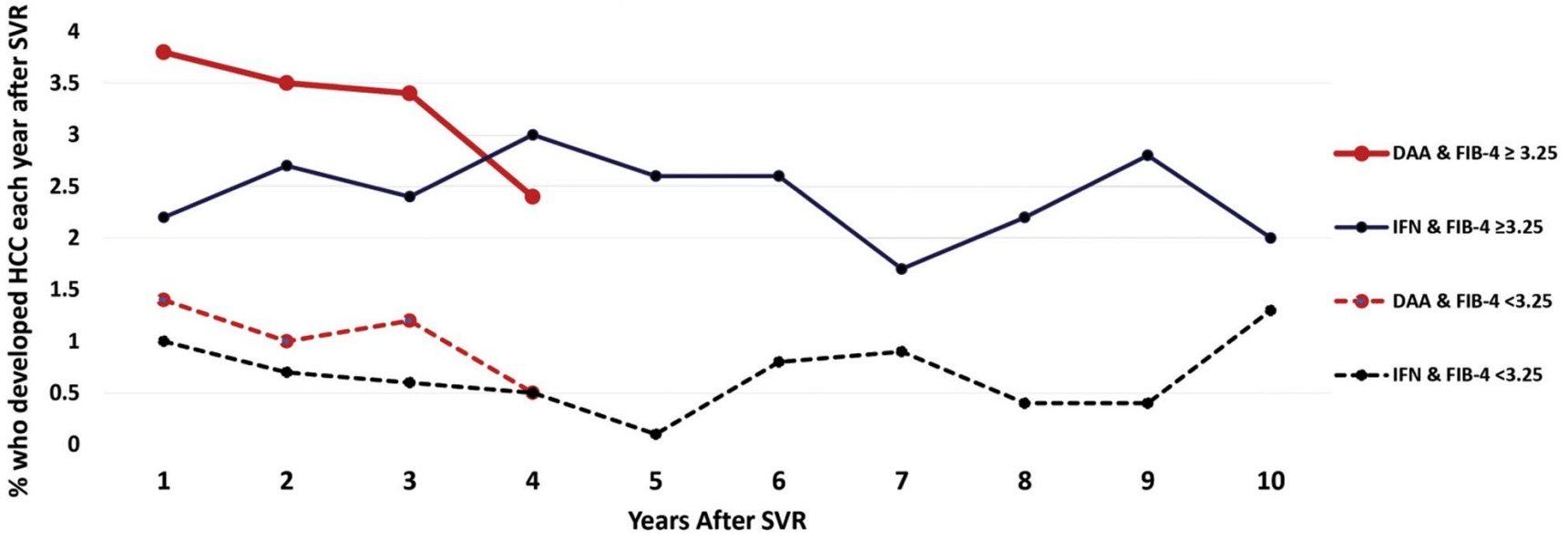
Increased Risk of HCC After HCV Eradication



Ioannou GN, et al. Gastroenterology 2019;157:1264

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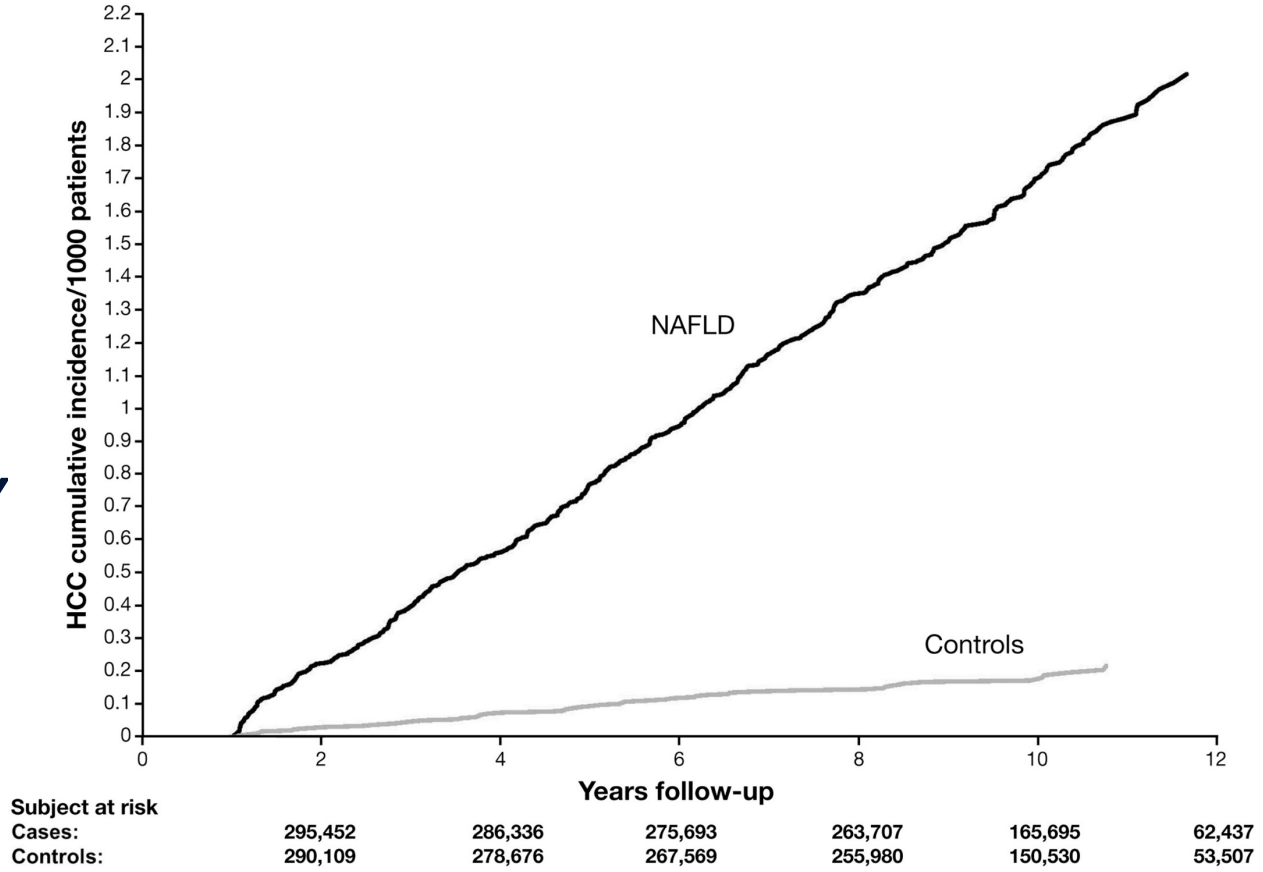
NAFLD Cirrhosis is Risk Factor for HCC

- 296,707 NAFLD patients with 296,707 matched controls.
- During 2,382,289 person-years [PY] of follow-up, 490 NAFLD patients developed HCC.

- Non-cirrhosis incidence = **0.08 per 1,000 PY**

- **Cirrhosis incidence = 10.6 per 1,000 PY**



Kanwal F, et al. Gastroenterology 2018

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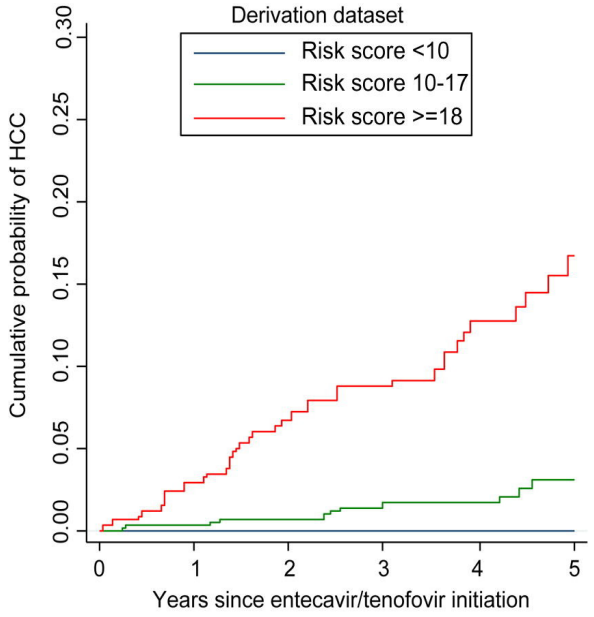
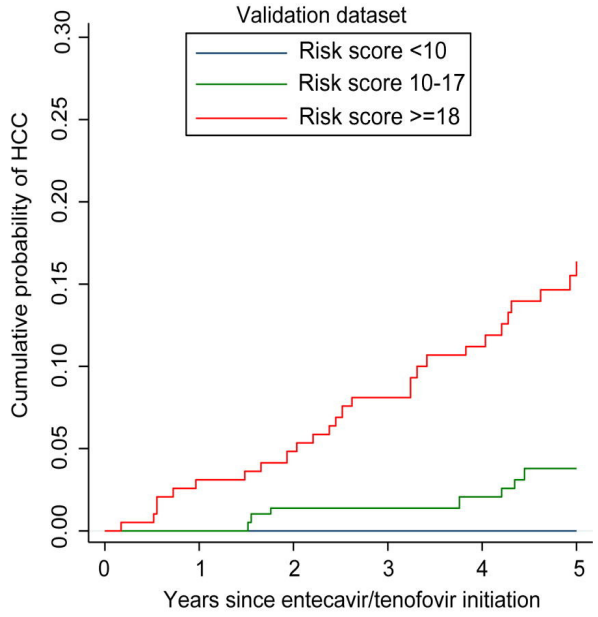
PAGE-B Score to Determine Risk of HCC in Chronic HBV Infection

Age	Gender	Platelets (/mm^3)
16-29: 0 30-39: 2 40-49: 4 50-59: 6 60-69: 8 70-75: 10	Female: 0 Male: 6	> 200,000: 0 100,000-199,999: 6 < 100,00: 9





Papatheodoris G, et al. J Hepatology 2016;64:800

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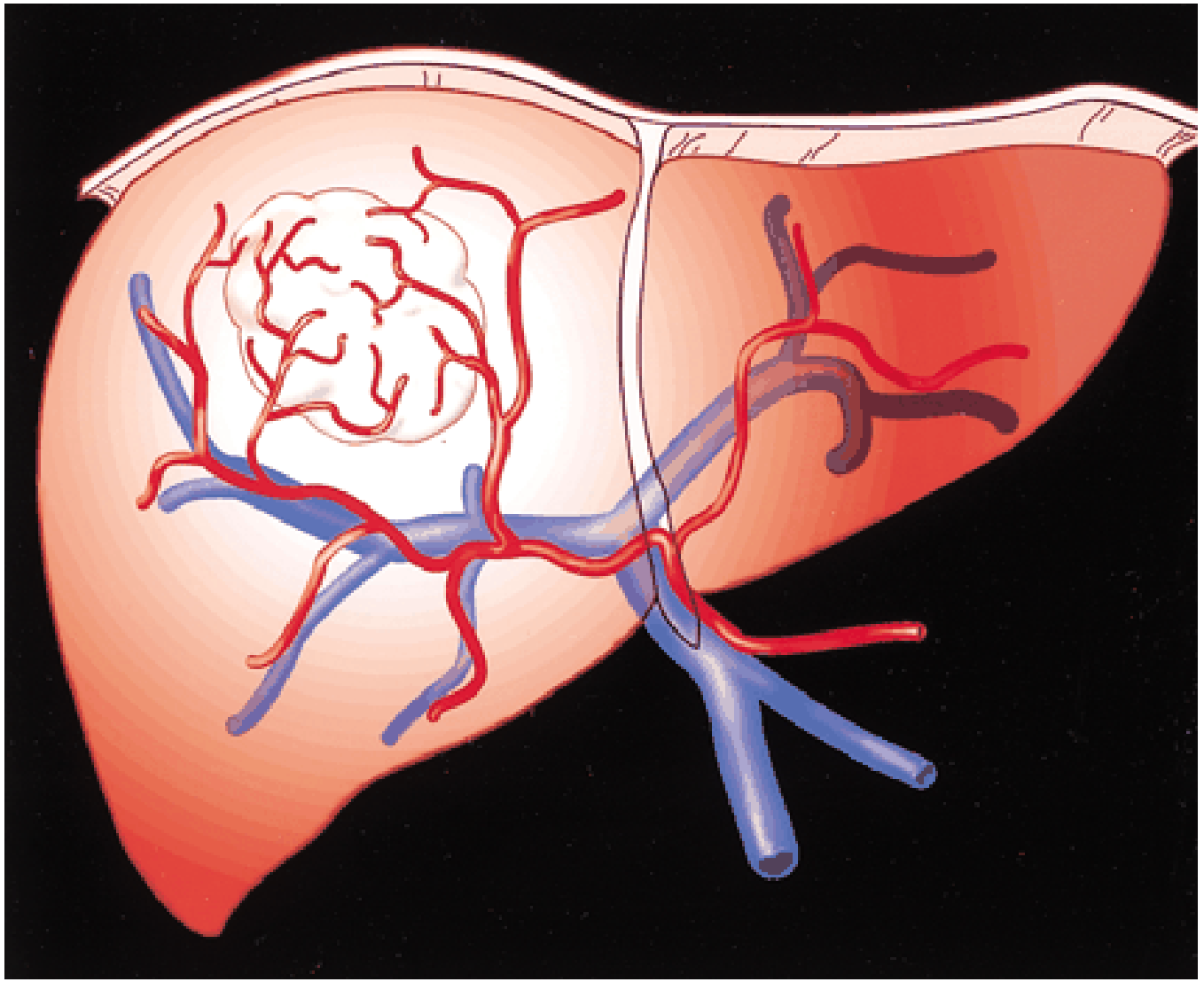

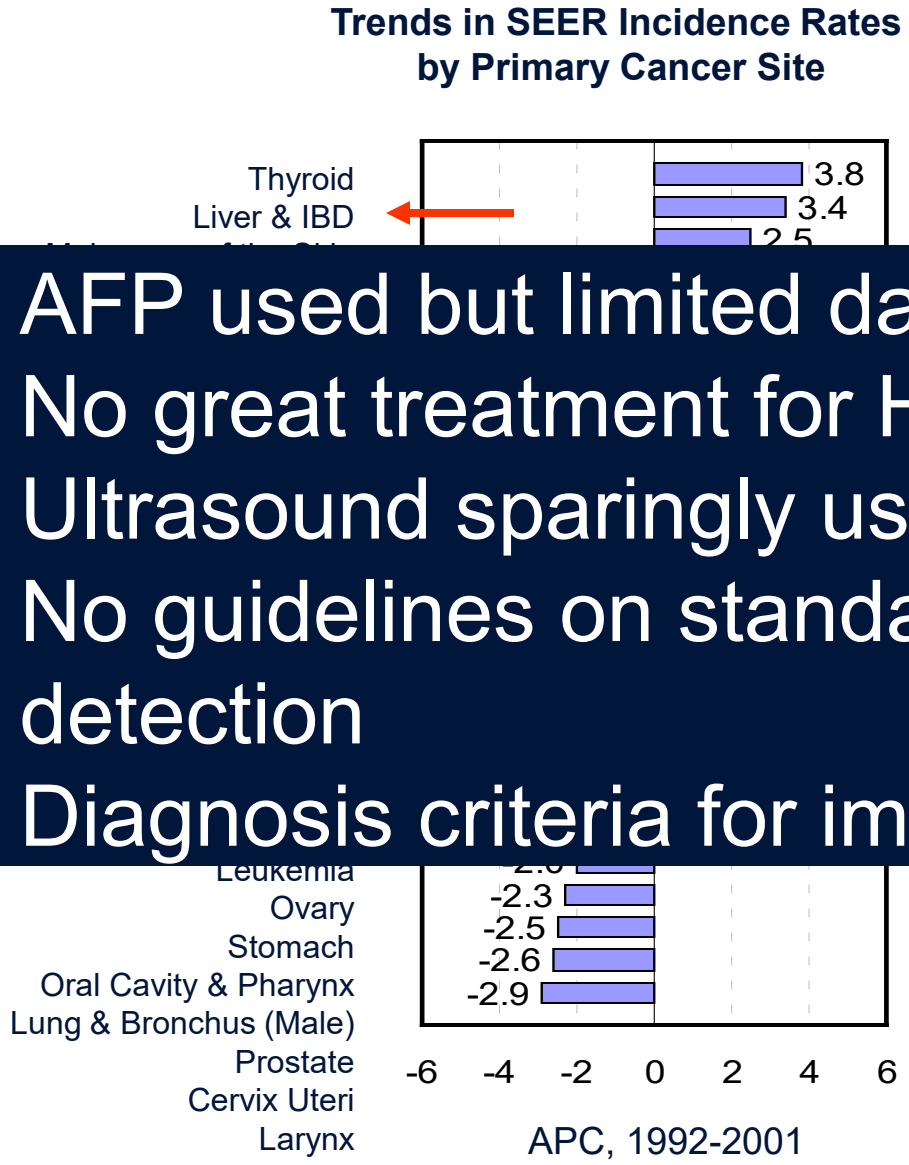

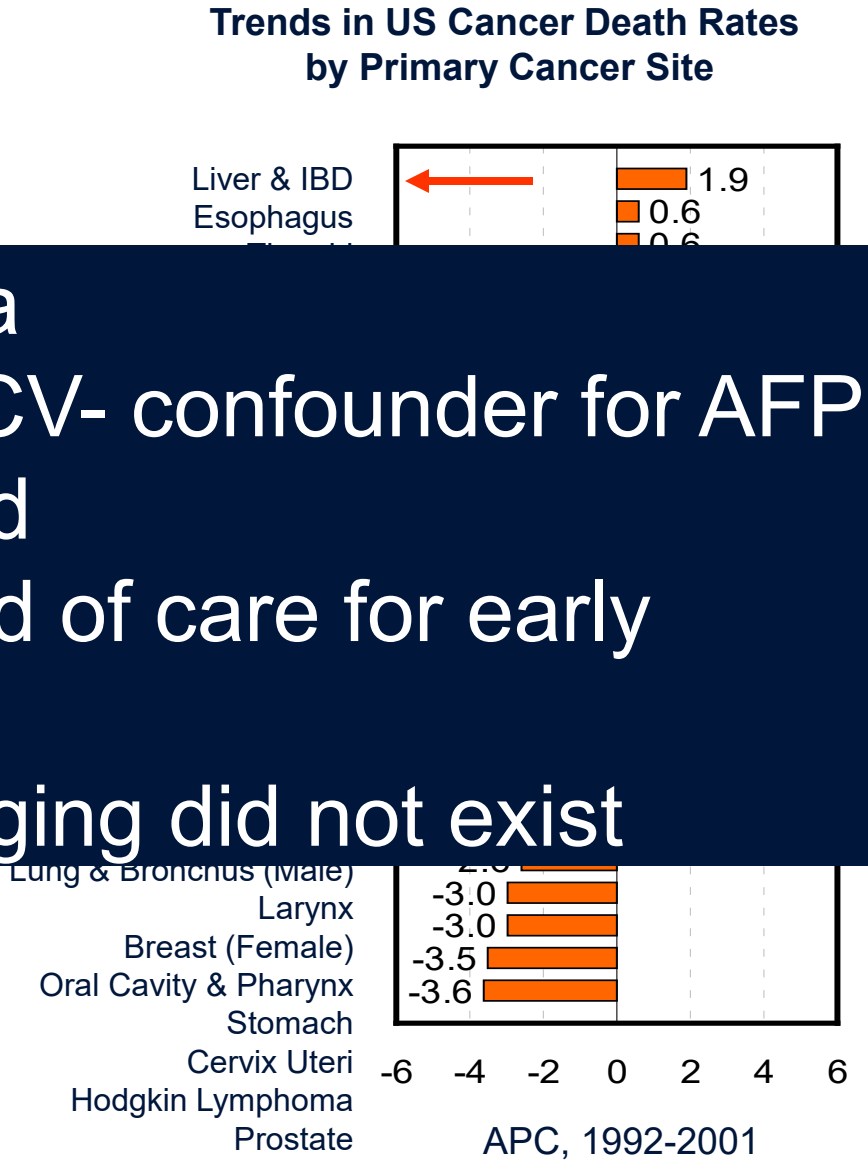

- AFP used but limited data
- No great treatment for HCV- confounder for AFP
- Ultrasound sparingly used
- No guidelines on standard of care for early detection
- Diagnosis criteria for imaging did not exist

SEER, 2001

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AASLD PRACTICE GUIDELINE

HEPATOLOGY, Vol. 42, No. 5, 2005

Management of Hepatocellular Carcinoma

Jordi Bruix[1] and Morris Sherman[2]

HCC Surveillance Recommendations

Recommendations

3. Surveillance for HCC should be performed using ultrasonography (level II).

4. AFP alone should not be used for sceening unless ultrasound is not available (level II).

5. Patients should be screened at 6 to12 month intervals (level II).

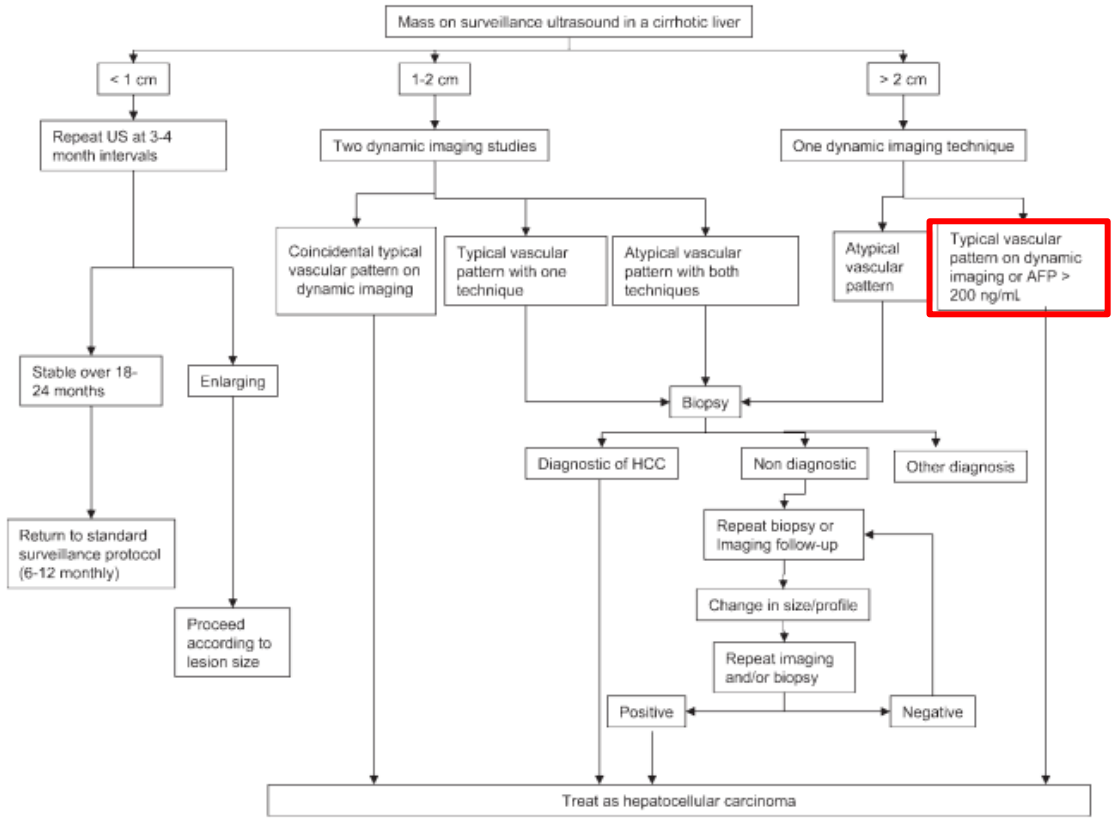
6. The surveillance interval does not need to be shortened for patients at higher risk of HCC (level III).

AASLD PRACTICE GUIDELINE

HEPATOLOGY, Vol. 42, No. 5, 2005

Management of Hepatocellular Carcinoma

Jordi Bruix[1] and Morris Sherman[2]



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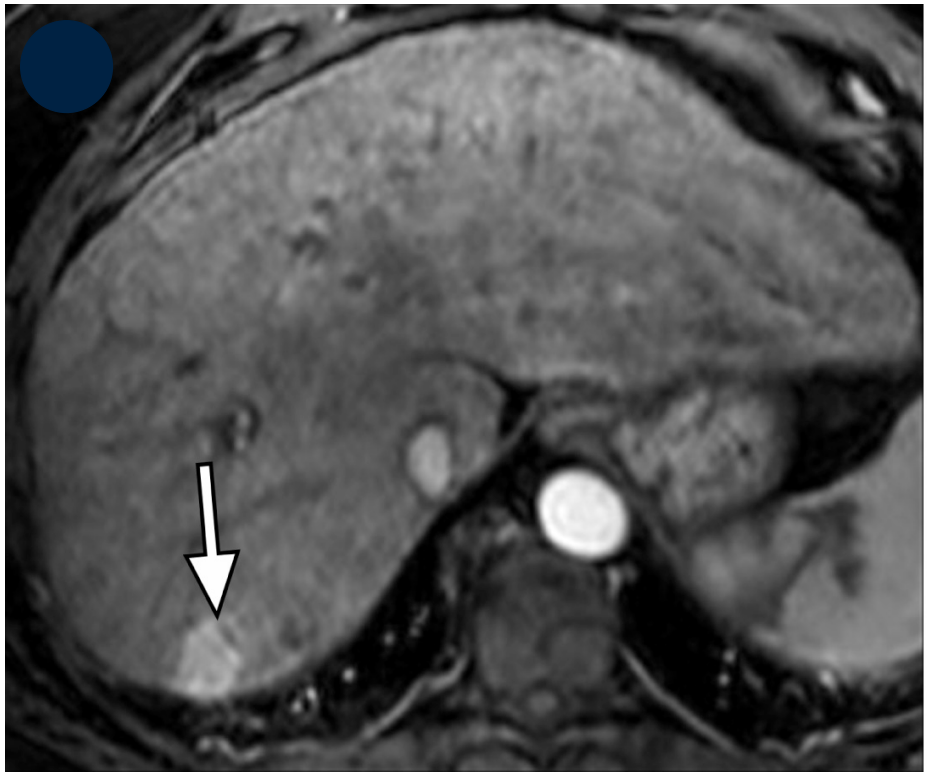
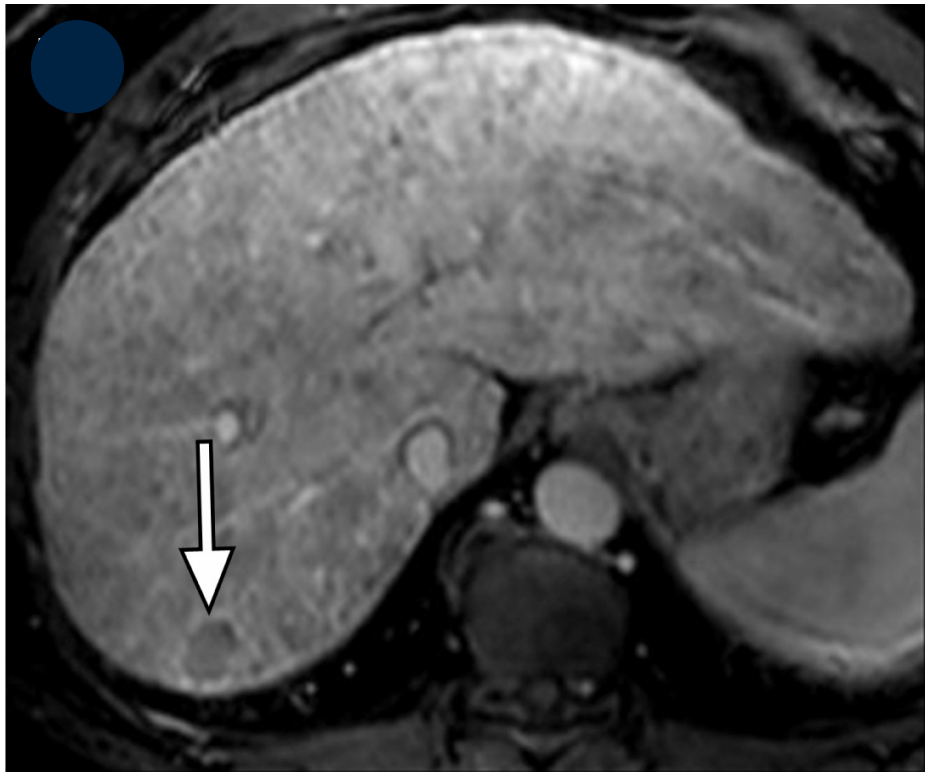
Radiologic Diagnosis of HCC



Arterial Phase



Delayed Venous Phase

Marrero JA, et al. Hepatology 2003

LI-RADS Diagnosis of HCC

Arterial phase hyperenhancement (APHE)		No APHE		Nonrim APHE		
Observation size (mm)		< 20	≥ 20	< 10	10-19	≥ 20
Count additional major features: • Enhancing "capsule" • Nonperipheral "washout" • Threshold growth	None	LR-3	LR-3	LR-3	LR-3	LR-4
	One	LR-3	LR-4	LR-4	LR-4 / LR-5	LR-5
	≥ Two	LR-4	LR-4	LR-4	LR-5	LR-5

LR-4 / LR-5

Observations in this cell are categorized based on one additional major feature:
- LR-4 – if enhancing "capsule"
- LR-5 – if nonperipheral "washout" **OR** threshold growth

Singal AG, et al. Hepatol 2023

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Surveillance for HCC Improves Mortality:
A Randomized Controlled Trial

	Screened Group	Control Group
Person-years F/U	38,444	41,077
HCC Occurrence		
HCC cases	86	67
Incidence	223.7	163.1
Rate Ratio	1.37 (0.99-1.89)	
Deaths from HCC		
Number	**32**	54
Mortality Rate	**83.2**	131.5
Rate Ratio	**0.63 (0.41-0.90)**	

Zhang BH, et al. J Cancer Res Clin Oncol 2004;130:417

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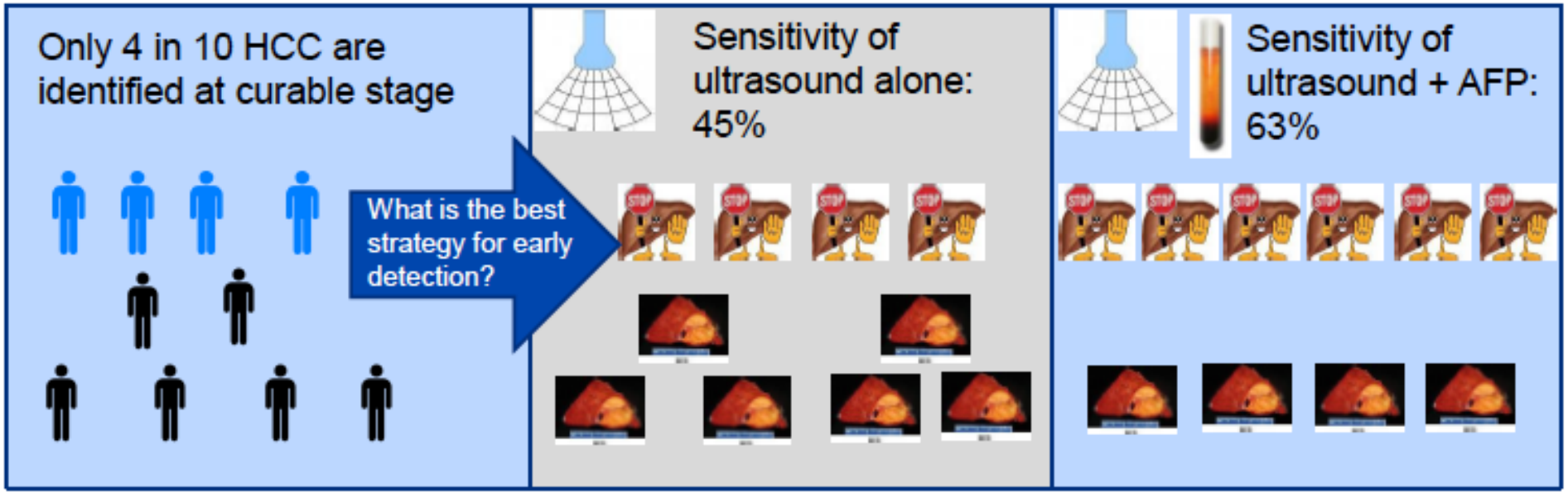
Performance of AFP and US in RCT

Test	Sensitivity	Sensitivity Early Stage	False positive rate
Ultrasound alone	43/51 (84)	**36/61 (59)**	604/20243 (3.0)
AFP alone	35/51 (69)	**29/61 (49)**	1019/20243 (5.0)
Ultrasound and AFP	47/51 (92)	**43/61 (71)**	**1519/20243 (7.5)**

Zhang BH, et al. J Med Screen 1999

Ultrasound and AFP Surveillance in Early HCC: Systematic Review



Tzarzeva K, et al. Gastroenterology 2018

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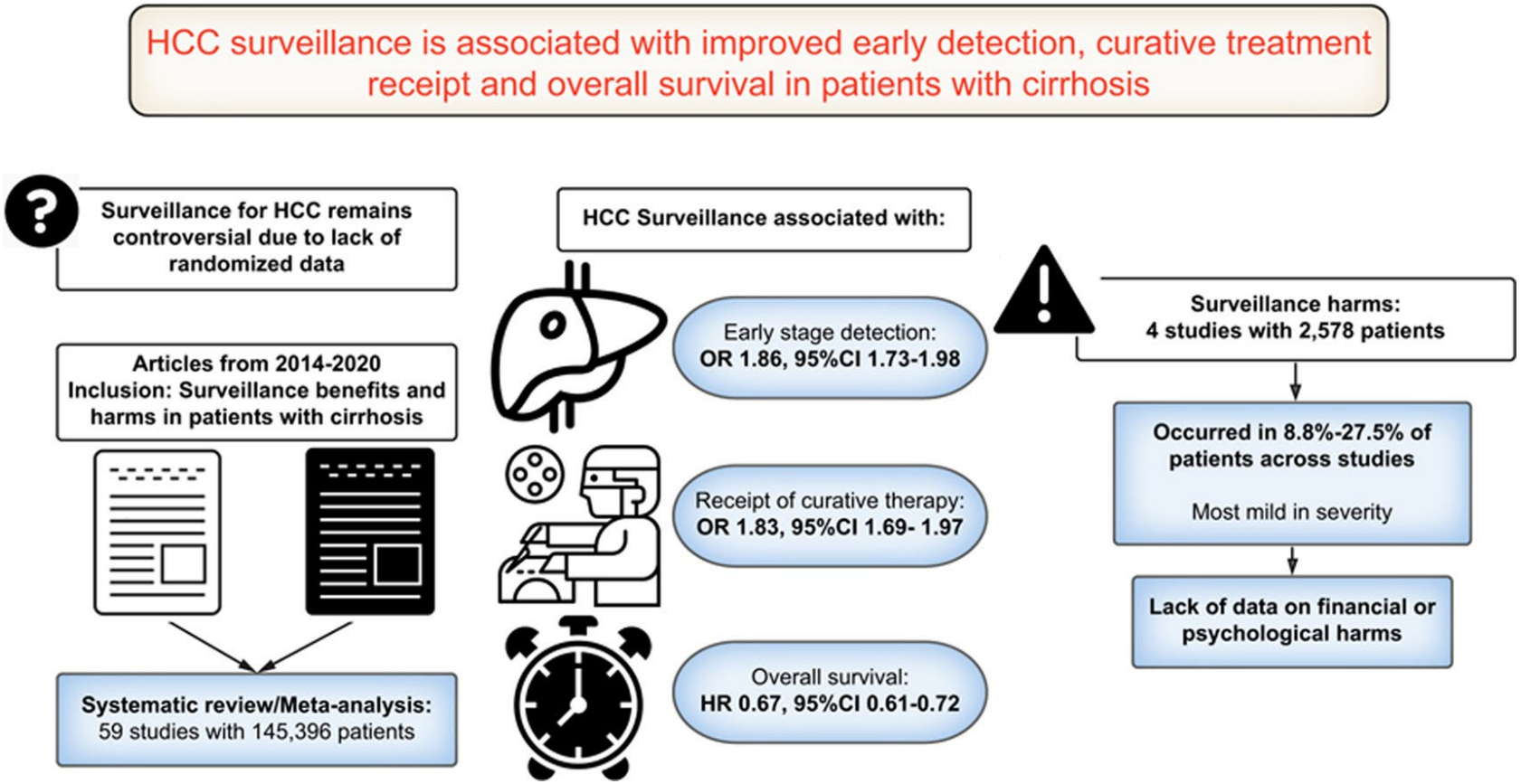
HCC Surveillance in Cirrhosis Improves Survival



Singal AS, et al. J Hepatology 2022;77:128.

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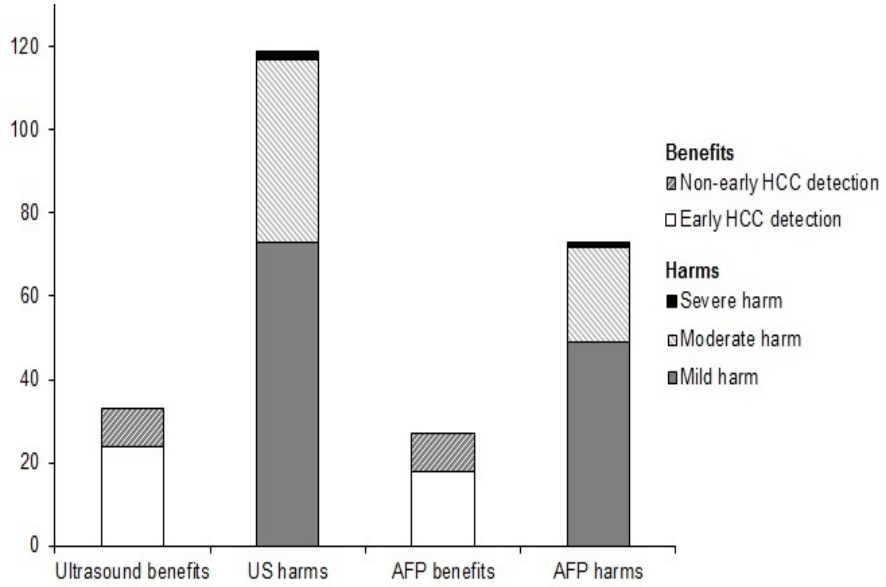
Potential Physical Harms of HCC Surveillance

- Retrospective cohort of 680 cirrhosis patients over 3 years
- **Surveillance detected 48 HCC (70% (n=34) early)**
- **Physical harms observed in 187 (28%)**
- **Moderate-severe harm in 59 (10%) patients**
- Despite similar benefits, higher proportion of harms related to US than AFP 22.8% vs. 11.4% (p<0.001)



Atiq et al Hepatology 2017

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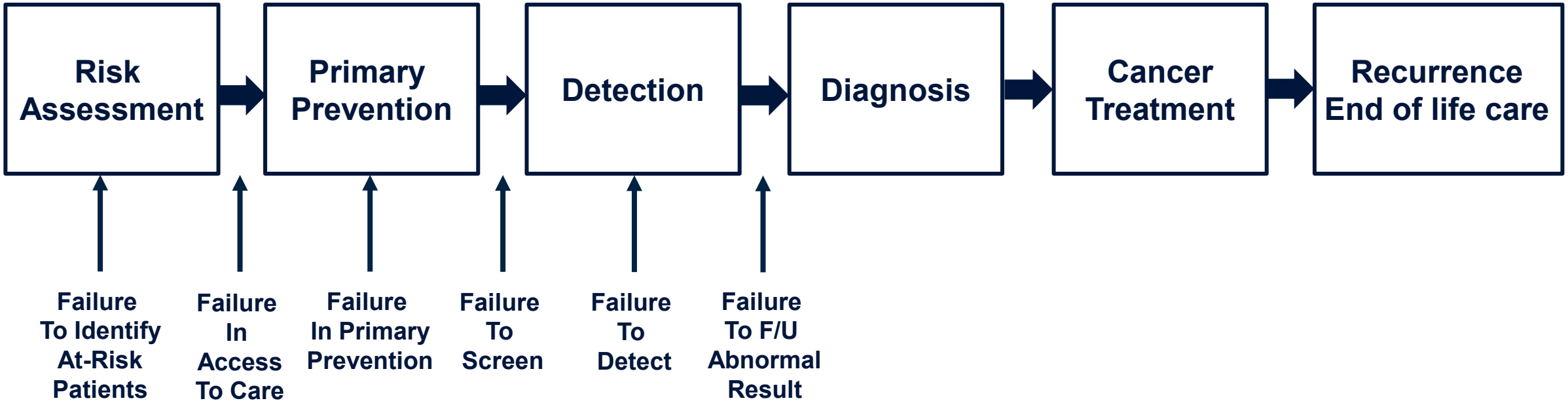
Quality in Cancer Care Continuum



Singal et al. Clin Gastro Hep 2013

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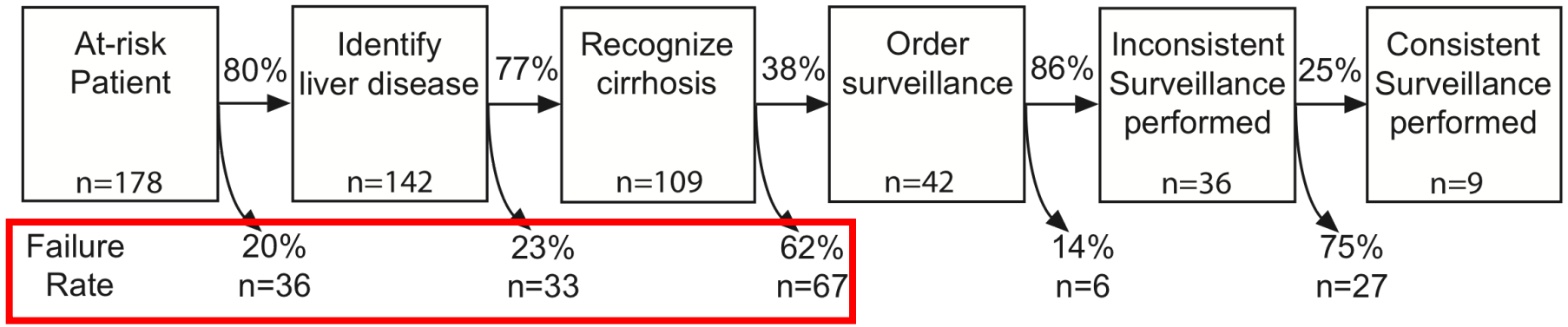
Many At-risk Patients are not Identified Prior to HCC Development



Singal et al, Cancer Prevent Research 2012

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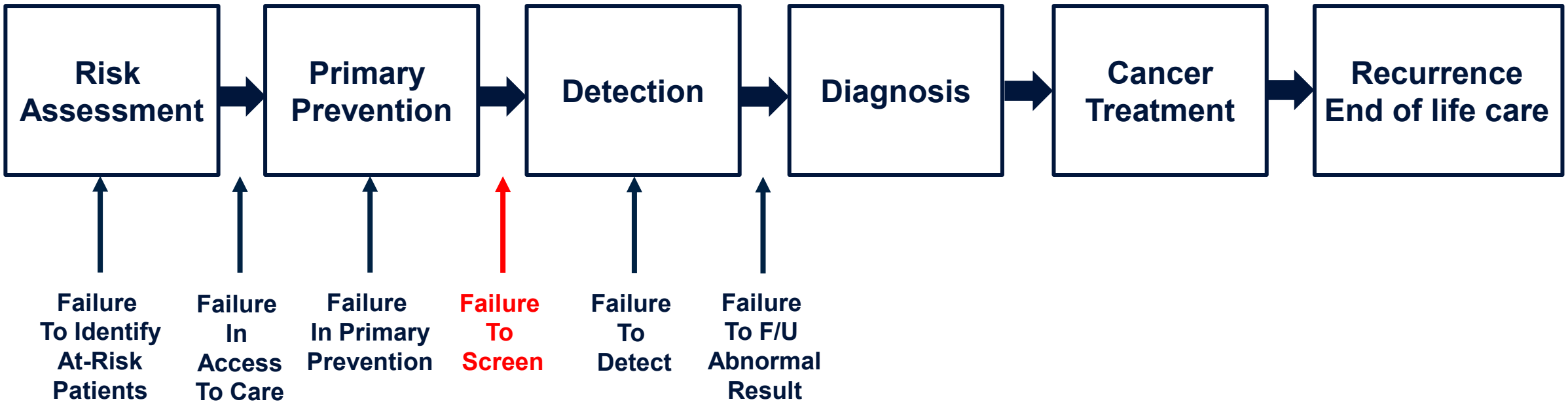
Quality in Cancer Care Continuum



Singal et al. Clin Gastro Hep 2013

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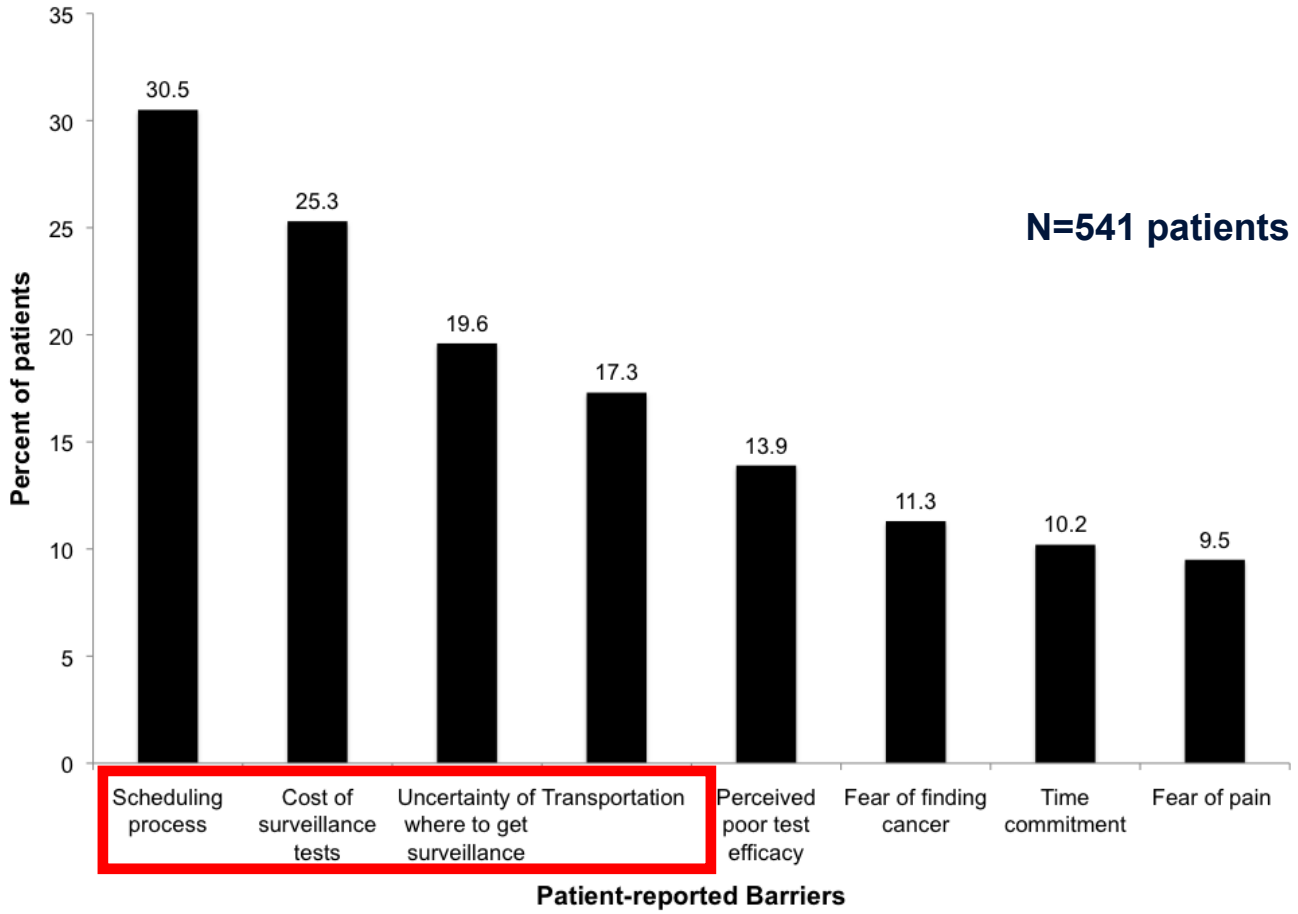
Providers report potential barriers to HCC surveillance

Provider-reported barriers	Safety-net health system (n=77)	Tertiary care system (n=100)
Lack of knowledge about guidelines	68.2%	79.1%
Competing interests in clinic	51.6%	37.4%
Lack of time in clinic	40.5%	52.8%
Difficulty recognizing at-risk patients	35.4%	30.0%
Ultrasound capacity	23.0%	10.1%
Responsibility of subspecialists > PCP	5.3%	29.4%

Dalton Fitzgerald et al. Clin Gastro Hep 2015
Simmons et al Clin Gastro Hep 2018

Patients report barriers to HCC surveillance



Receipt of HCC surveillance was significantly lower in patients reporting barriers to surveillance (54% vs. 71%; OR 0.42, 95%CI 0.25 – 0.70)

Farvardin et al. Hepatology 2017

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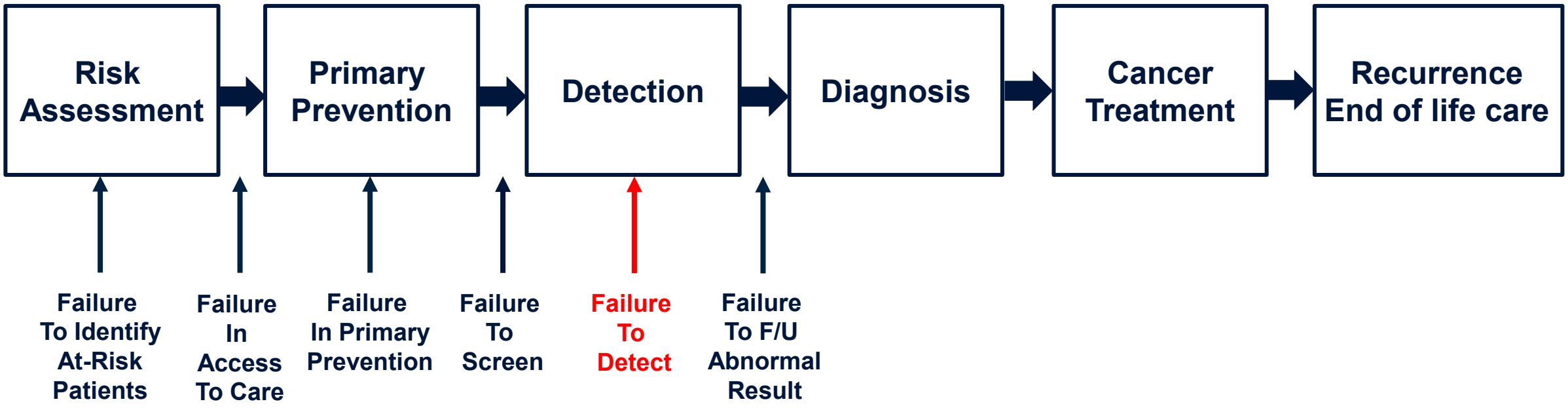
Quality in Cancer Care Continuum



Singal et al. Clin Gastro Hep 2013

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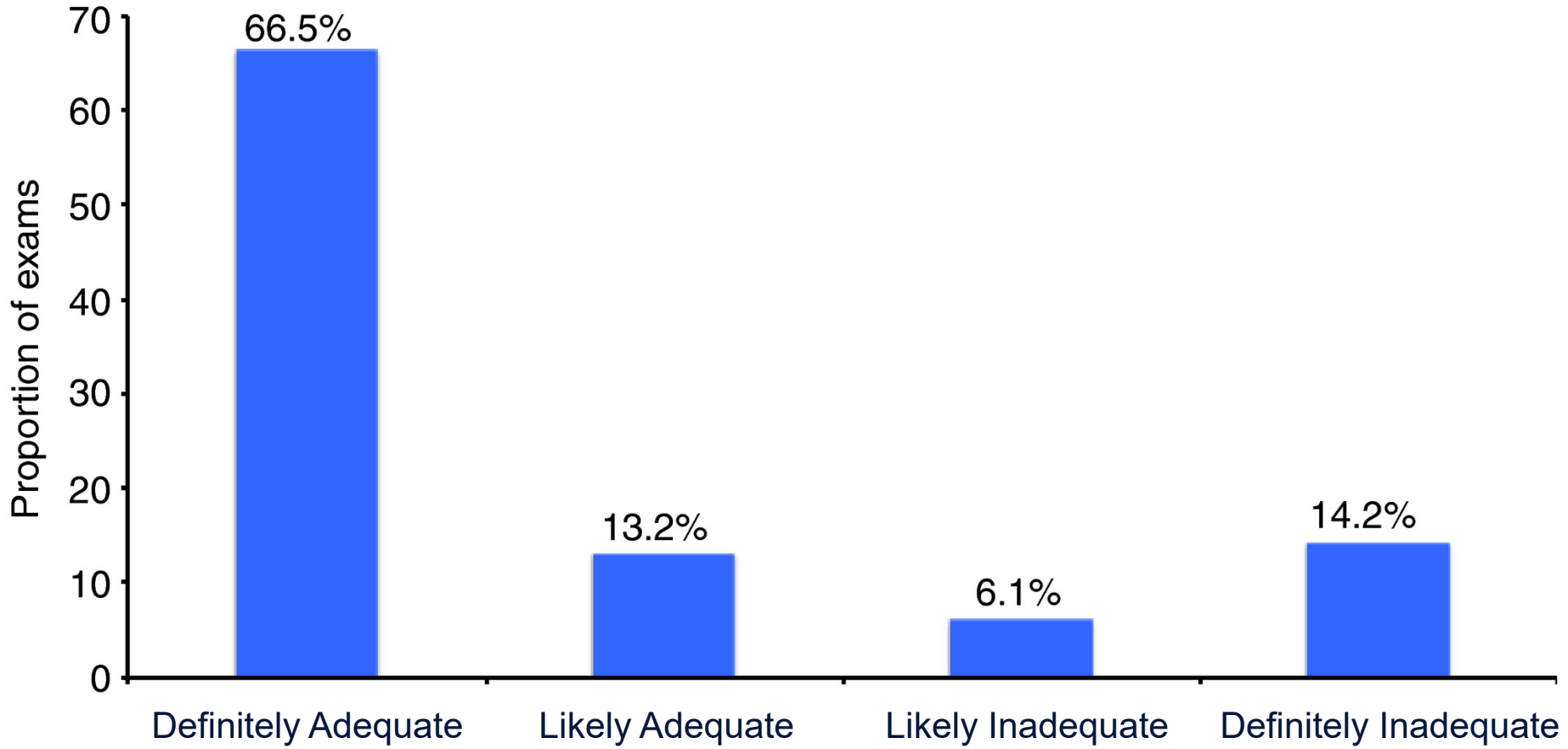
US Quality in Surveillance of HCC



Simmons O, et al. Aliment Pharmacol Ther 2017 Jan;45(1):169

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Utilization of Surveillance for HCC is Low

Study	Study period	Location	Study setting	Study population	Utilization of surveillance
Clinical cohorts with data verified by chart review					
Mohammed et al.[190]	2007–2009	USA	Tertiary centre	369 patients with cirrhosis (alcohol 32%, NAFLD 23%, HCV 21%)	14% underwent surveillance scans every 6 months
Signorelli et al.[191]	2012–2014	Brazil	A tertiary centre and a private centre	253 patients with cirrhosis (alcohol 37.9%, HBV 13.8%)	6.3% received an ultrasound every 6 months
Tran et al.[34]	2001–2015	USA	Tertiary centre	2,366 patients with HCV cirrhosis	24.4% adhered to imaging every 6 months and 44% to imaging at least every 12 months
Administrative data base studies					
Palmer et al.[192]	2006–2007	USA	Data from an insurance claims data base	5,061 patients with cirrhosis (alcohol 59%, HCV 30%, HBV 4%)	26% underwent at least one imaging test over 15 months
Goldberg et al.[33]	2008–2010	USA	Data from the Veterans Health Administration	26,577 patients with cirrhosis (HCV, alcohol or a combination in >80% of included patients)	Up-to-date with ultrasound for HCC surveillance 17.8% of the time (mean for all patients)
Davila et al.[32]	1998–2005	USA	Data from the Veterans Health Administration	13,002 patients with HCV cirrhosis	12% received routine surveillance (ultrasound and AFP levels during at least 2 consecutive years in the 4 years after cirrhosis diagnosis)
Yeo et al.[36]	2007–2016	USA	Nationwide administrative claims data base	82,427 patients with cirrhosis (viral hepatitis 2.1%; NAFLD 6.9%; alcohol 2.8%; others 88.2%)	8.8% received surveillance every 6–12 months
Singal et al.[193]	2010–2012	USA	Integrated health-care delivery system in Washington State	1,137 patients with cirrhosis (HCV 28.9%, NASH 28.7%)	2% received surveillance every 6 months, 33% received ≥1 ultrasound during the 2-year follow-up period
Nguyen et al.[35]	2013–2019	USA	Nationwide administrative claims data	15,543 patients with cirrhosis (NASH 38.2%, HCV 29.1%, alcohol 27.3%)	Patients were up-to-date with recommended surveillance for only 31% (days covered/days of follow-up) of a median 1.3-year follow-up (any abdominal imaging was considered to provide 6 months of days covered)
Chang et al.[194]	2000–2015	Taiwan	National health insurance data base	4,641 patients with HCV cirrhosis	14% adhered to annual HCC surveillance (abdominal ultrasound and AFP test) during the follow-up period

Huang DQ, et al. Nat Rev Gastroenterol Hepatol 2023

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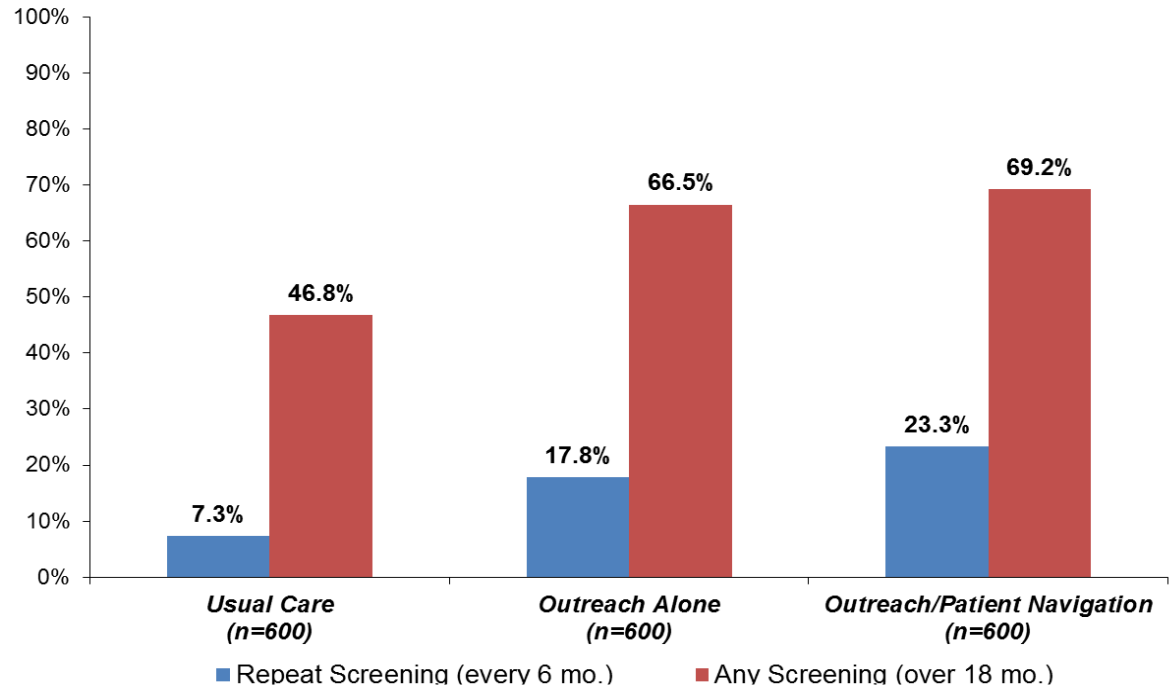
Population-based Interventions Significantly Increase Surveillance Rates



Singal AG, et al Gastroenterology 2017
Singal AG, et al. Hepatology 2018

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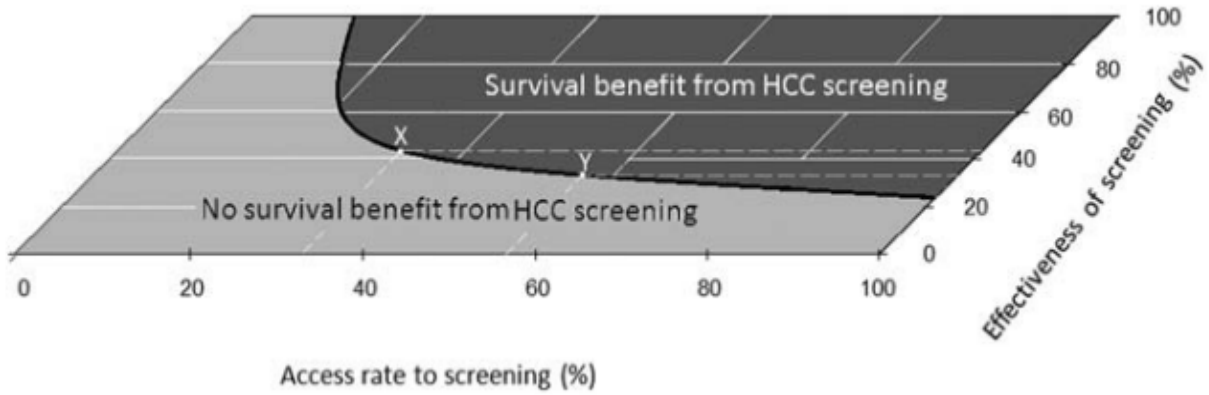
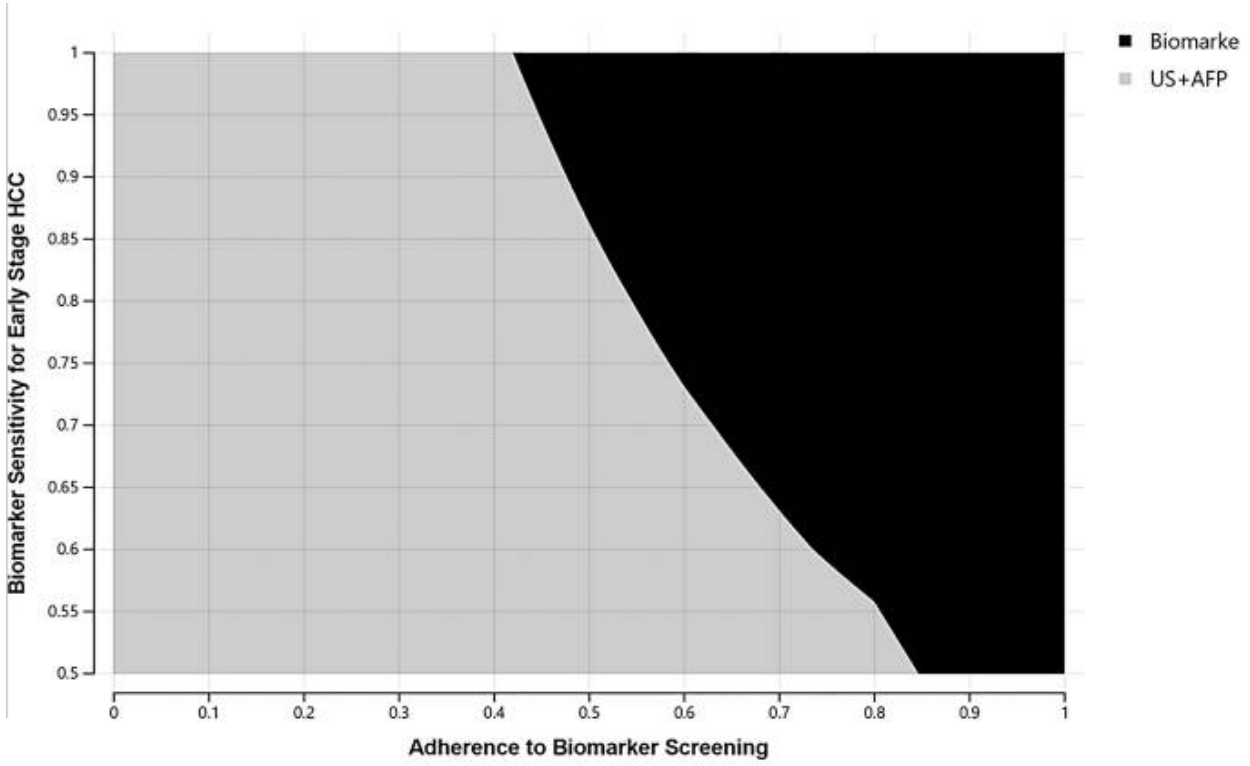
Surveillance Testing and Utilization are linked





Mourad A, et al. Hepatology 2014
Singal AG, et al. Liver Cancer 2024

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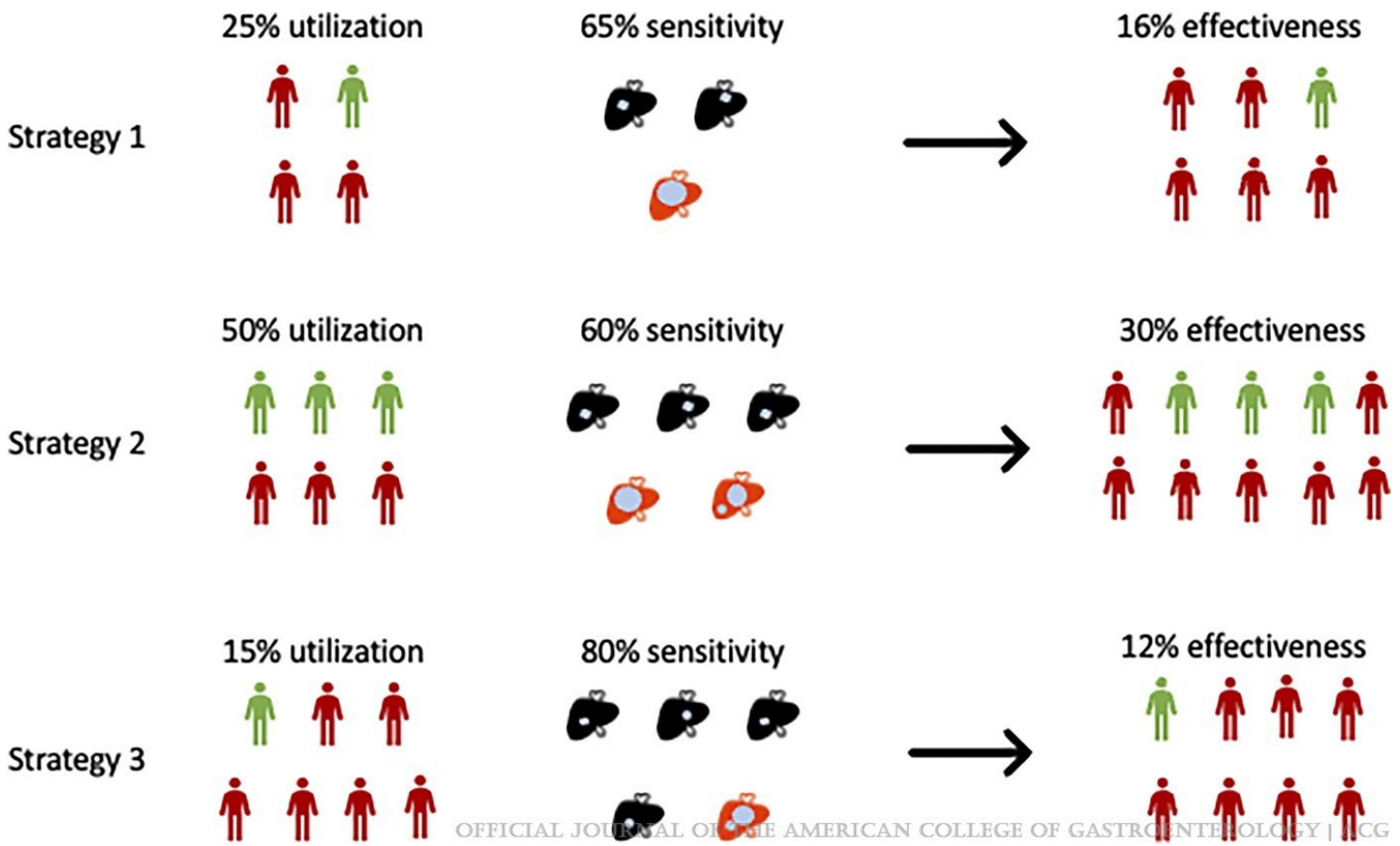
Adherence Improves the Effectiveness of Screening



Singal AG, et al. Am J Gastroenterol 2022;117:1948

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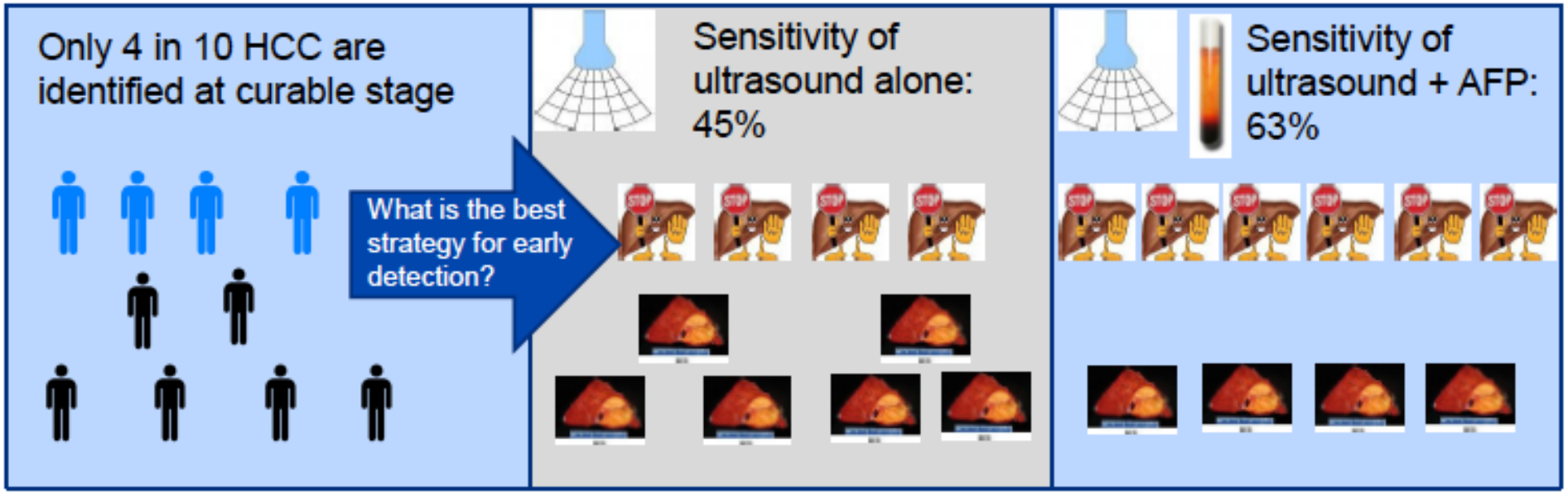

Tzarzeva K, et al. Gastroenterology 2018

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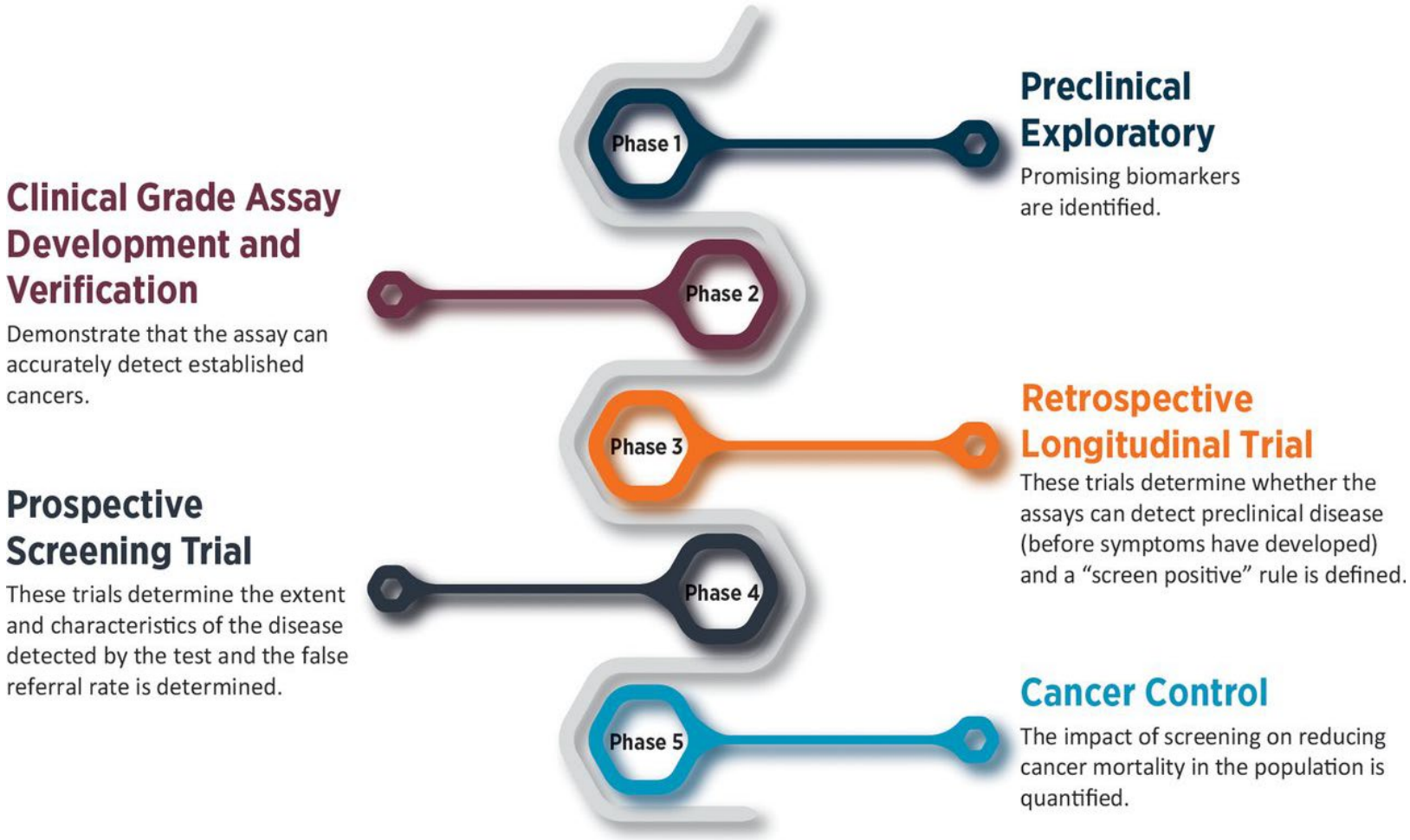
Phases of Biomarker Development for Early Detection of Cancer



Parikh N, et al. J Hep 2023
Pepe MS, et al. J NCI 2001;93:1054

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Performance of AFP, AFP-L3 and DCP in Early Stage HCC

	Cutpoint (95%CI)	Sensitivity (%)	Specificity (%)
DCP mAU/mL	202 (61-331)	56	77
AFP-L3 %	0.6 (0.6-1.9)	37	93
Total AFP ng/mL	10.9 (5.7-18.4)	66	82

Marrero JA, et al. Gastroenterology 2009

GALAD for the detection of Early Stage HCC in Cirrhosis

$$Z = -10.08 + 0.09 \times \text{age} + 1.67 \times \text{sex} + 2.34 \times \log(\text{AFP}) + 0.04 \times \text{AFP-L3} + 1.33 \times \log(\text{DCP})$$

Set		True HCC	True non-HCC	False HCC	False non-HCC	Sensitivity	Specificity	Correctly classified	Cutoff
All data: BRM and NCL	Max. sens. (spec. = 0.80)	367	347	87	15	96	80	88	−1.36
Model 5	Max. spec. (sens. = 0.80)	306	420	14	76	80	97	89	0.88
	Max. sens.+ spec.	356	385	49	26	93	89	91	−0.63

Johnson PJ, et al. Cancer Epidemiol Biomarkers Prev 2013;23:144

Validation of GALAD for the Early Detection of HCC in Cirrhosis

		Any stage HCC		Early-stage HCC	
		Any time prior to HCC	0–6 months prior to HCC	Any time prior to HCC	0–6 months prior to HCC
GALAD (−0.63)	Patient-level sensitivity	57.1 (41.9–72.4)	72.0 (53.8–89.3)	53.8 (33.3–73.3)	73.7 (52.6–93.3)
	Screening-level specificity	86.5 (83.0–89.9)			
HES algorithm (10.17)	Patient-level sensitivity	45.2 (30.4–60.0)	44.0 (23.8–62.5)	34.6 (15.4–54.2)	42.1 (19.0–66.7)
	Screening-level specificity	90.5(87.7–93.1)			
AFP 20 ng/mL	Patient-level sensitivity	35.7 (21.7–51.4)	48.0 (28.0–68.8)	46.2 (26.1–65.4)	57.9 (33.3–80.0)
	Screening-level specificity	91.7 (88.9–94.3)			
AFP-L3% 10%	Patient-level sensitivity	66.7 (52.0–81.3)	72.0 (52.4–88.9)	73.1 (54.2–88.9)	73.7 (52.4–93.3)
	Screening-level specificity	82.7 (78.5–86.5)			
DCP 7.5 ng/mL	Patient-level sensitivity	23.8 (11.6–37.5)	20.0 (5.0–37.5)	30.8 (13.6–50.0)	26.3 (6.7–48.5)
	Screening-level specificity	92.3 (89.8–94.6)			

Singal AG, et al. Hepatology 2022;75:541

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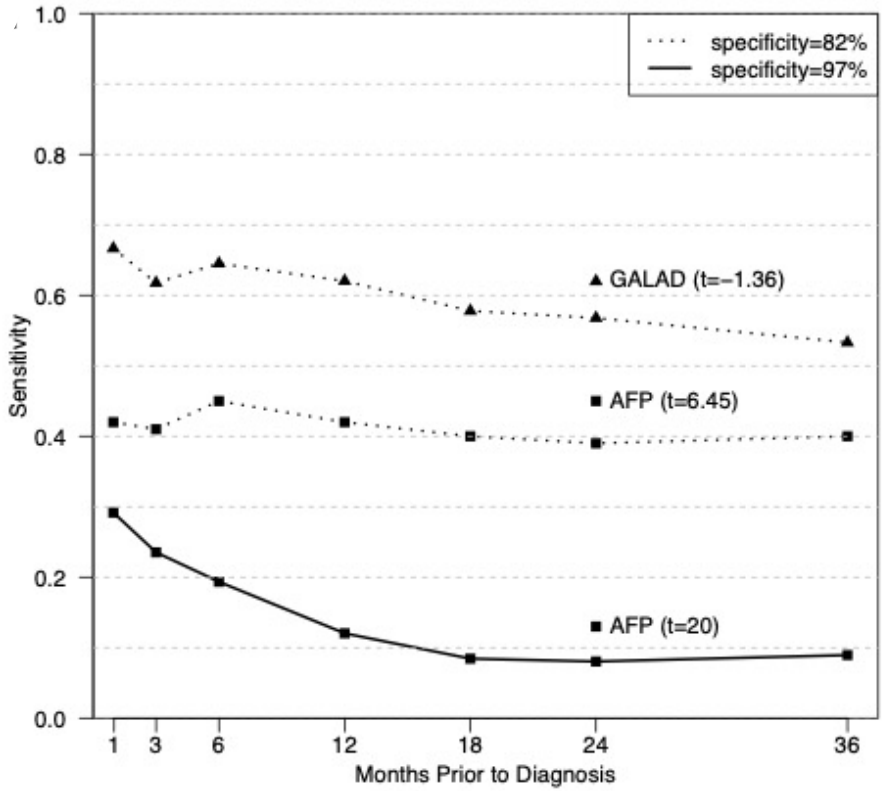
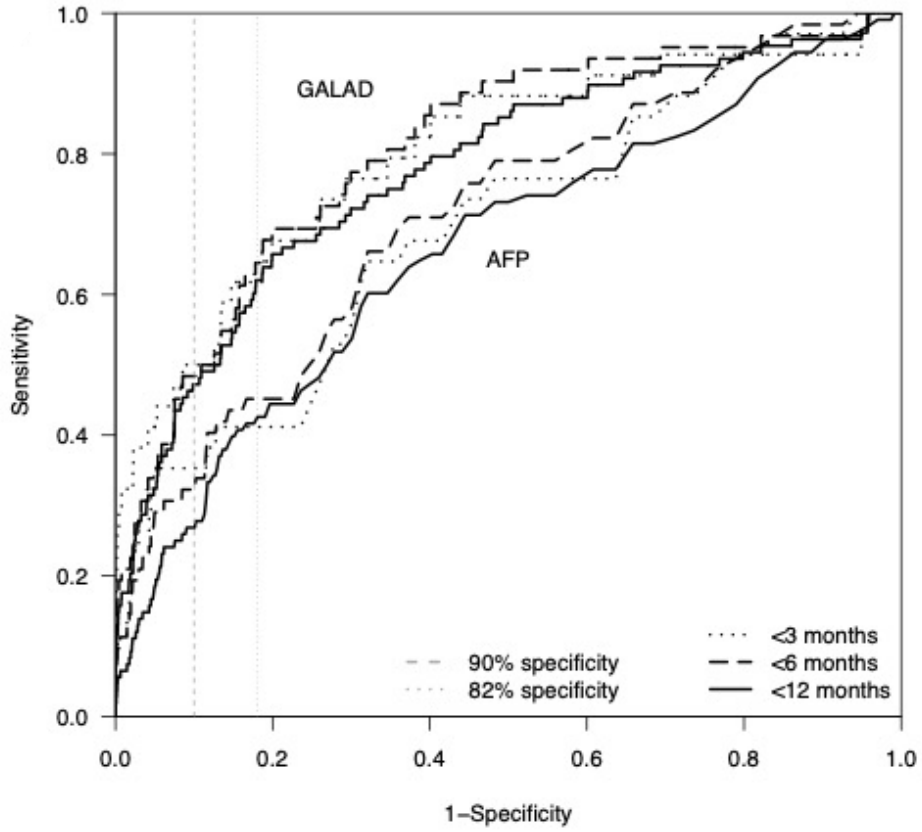
Phase 3 validation of GALAD in HCC: HEDS Study





Marsh T, et al. Gastroenterology 202 PMID: 39293548

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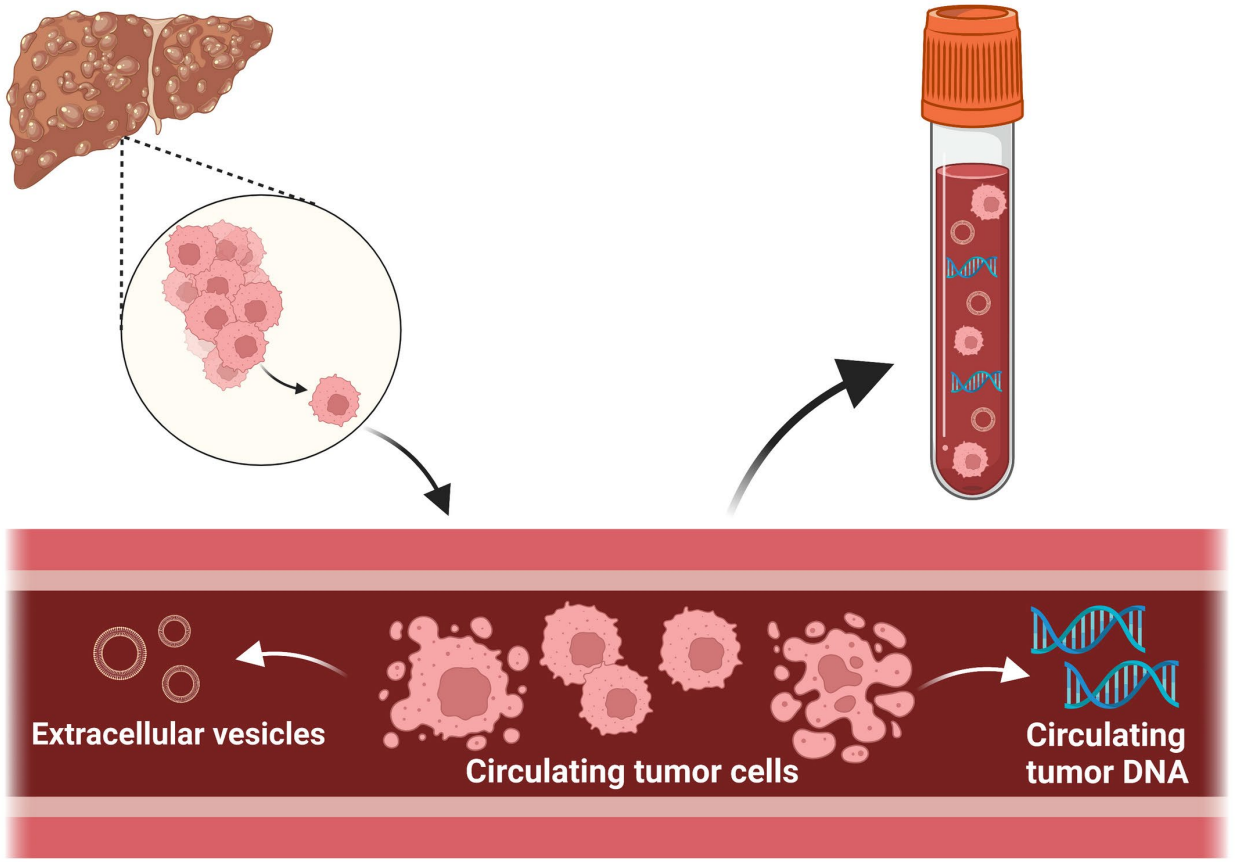
HCC Surveillance Tests Undergoing Validation

Test	Level of Evidence
GALAD	Phase 4/5 validation
PEB Longitudinal GALAD and AFP	Phase 3
Methylation DNA algorithm*	Phase 2 validation
Fucosylated Kinninogen**	Phase 2 validation
Cell-free DNA***	Phase 2 validation
mSEPT9	Phase 2 validation
Multicenter platform	Phase 2 validation
Multiphase MRI	Phase 1/2
Abbreviated MRI	Phase 2

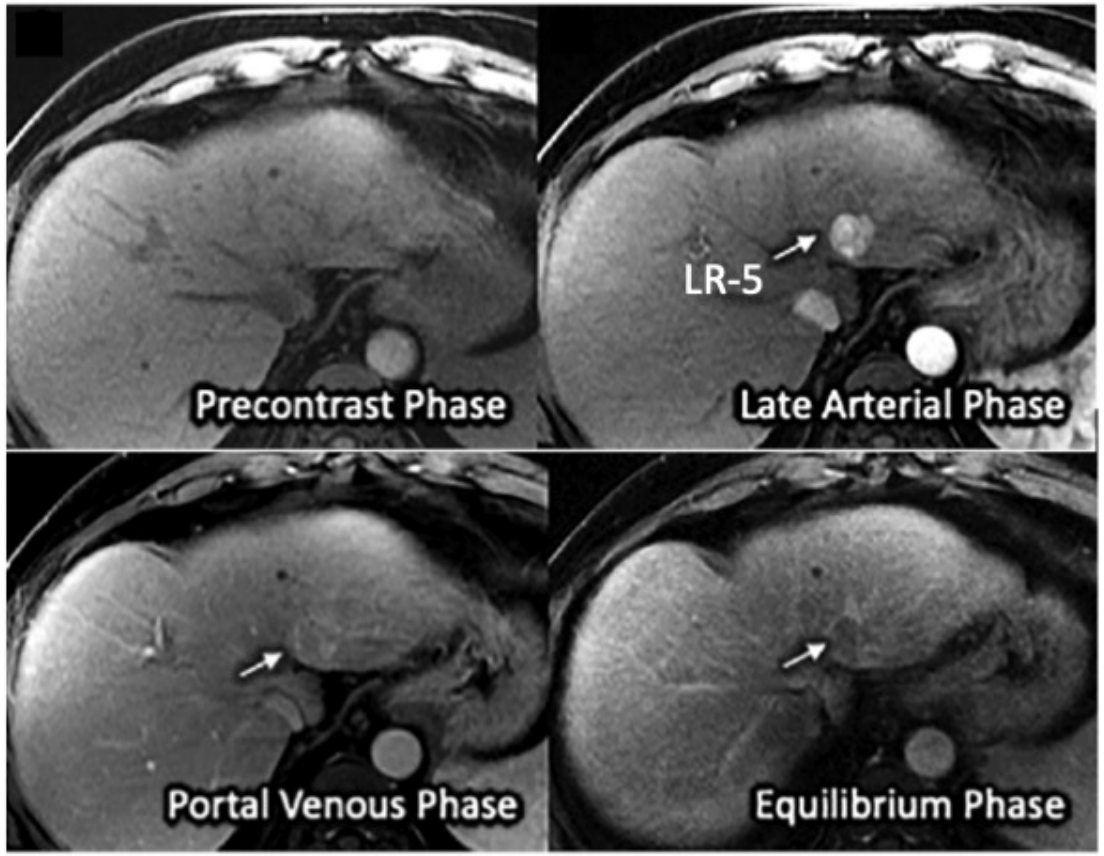
*Oncoguard **Glycotest ***HelioLiver

Emerging Techniques for Liquid Biopsy



Arvind A, et al. Clinical Liver Disease 2022;20:18

Multicenter Validation of Abbreviated MRI for Early Stage HCC



- Retrospective study in 161 patients with cirrhosis who underwent MRI followed by resection or transplant for early stage HCC. 138 controls without HCC
- Dynamic abbreviated MRI had a sensitivity of 88% and specificity of 89% for early stage HCC
- 54 (33%) had HCC between 1-1.9 cm
- Patient-level sensitivity was lower in Child-Pugh B or C cirrhosis than class A
- **Issues with cost, capacity, patient preference**

Yokoo T, et al. Radiology 2023;307:e220917

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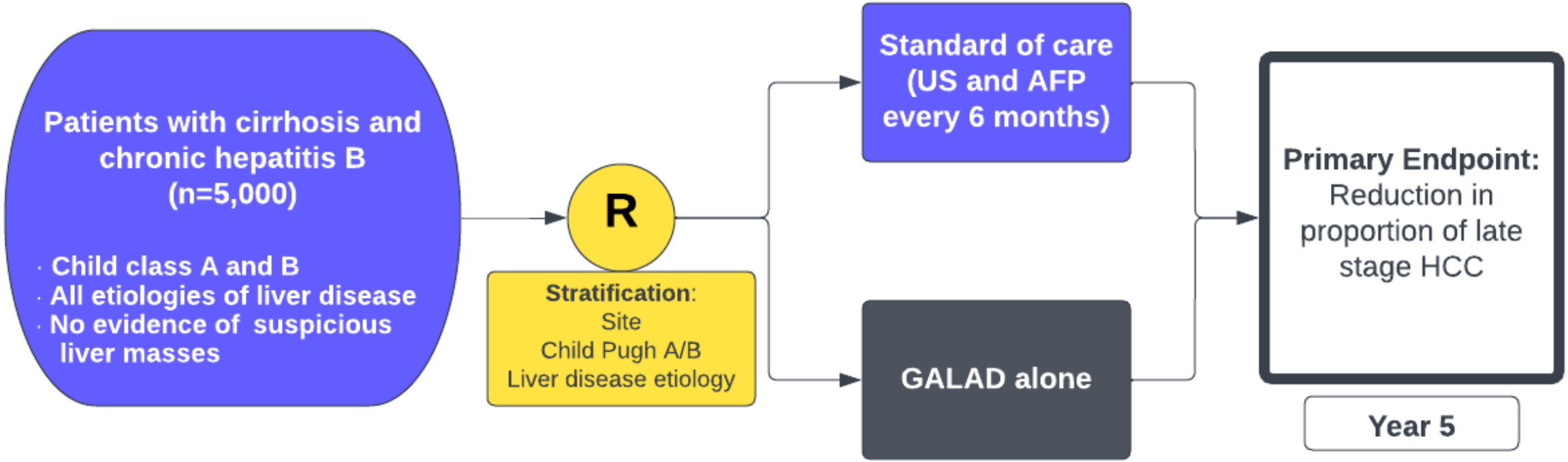
National Liver Cancer Screening Trial



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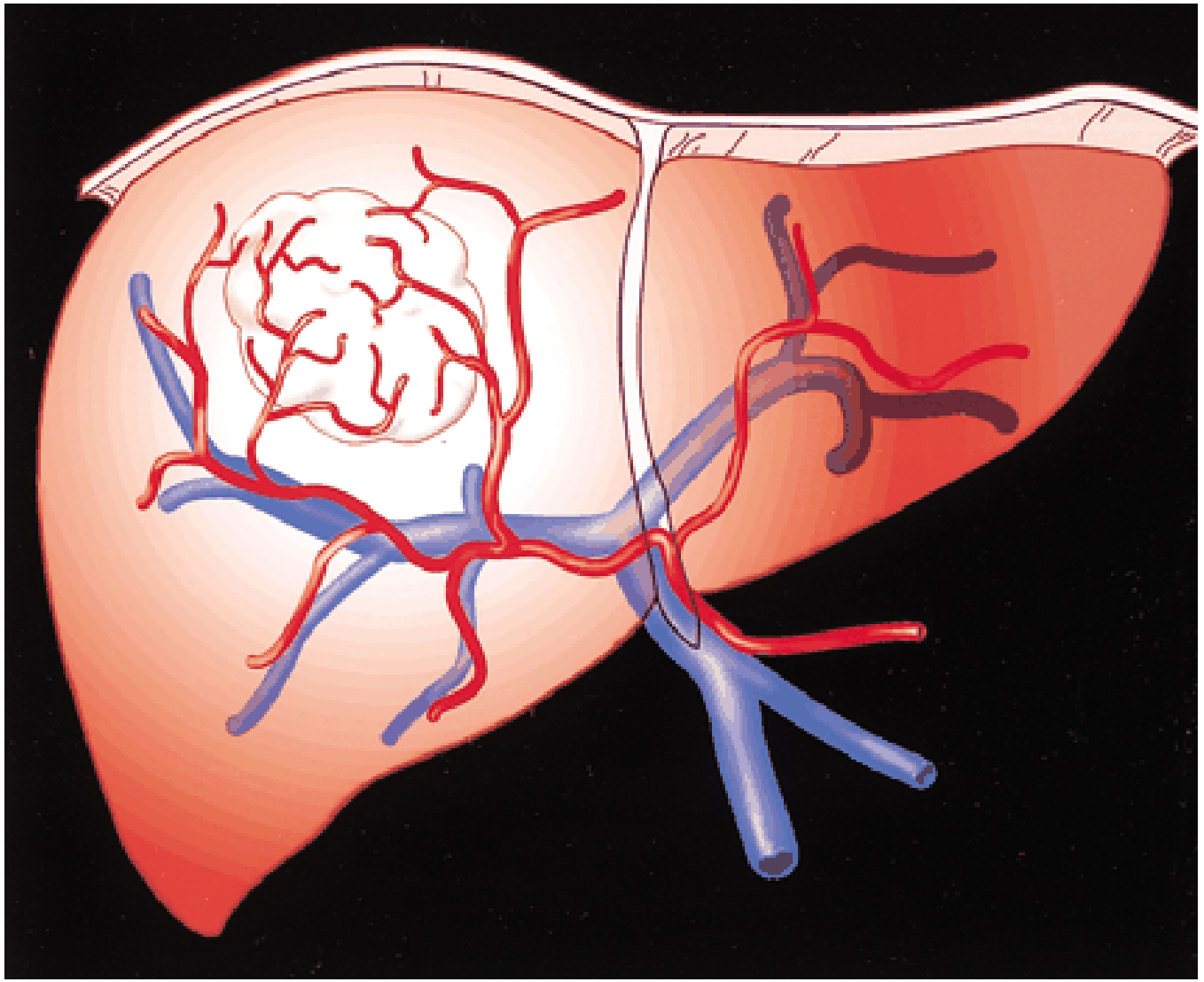
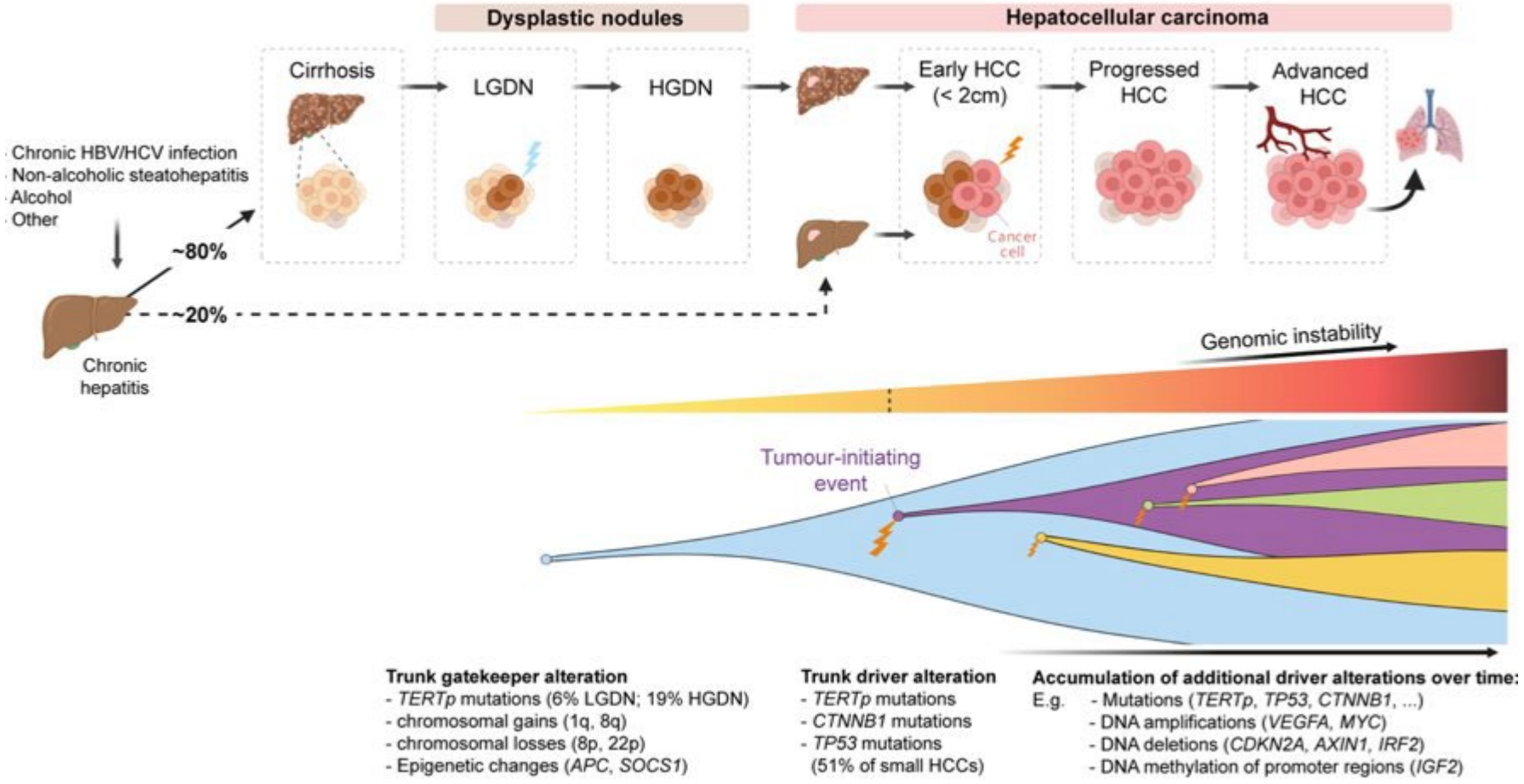
Topics

- Epidemiology
- Early Detection
- Risk-Stratification
- Summary



Cirrhosis is the Main Risk factor for HCC



Llovet JM, et al. Nat Cancer 2022;3:386

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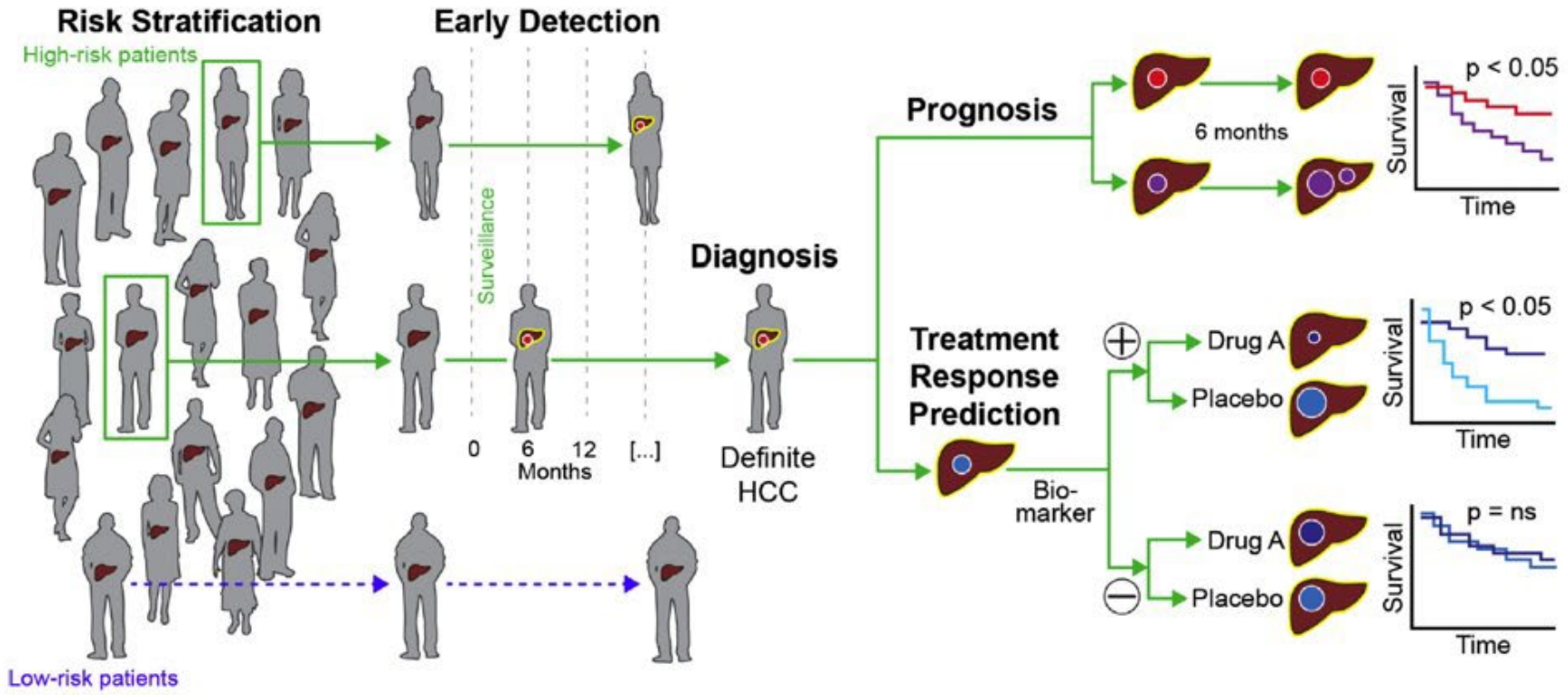
Opportunities in Risk-Stratification for Development of HCC



Singal A, et al. Gastroenterology 2021;160:2572

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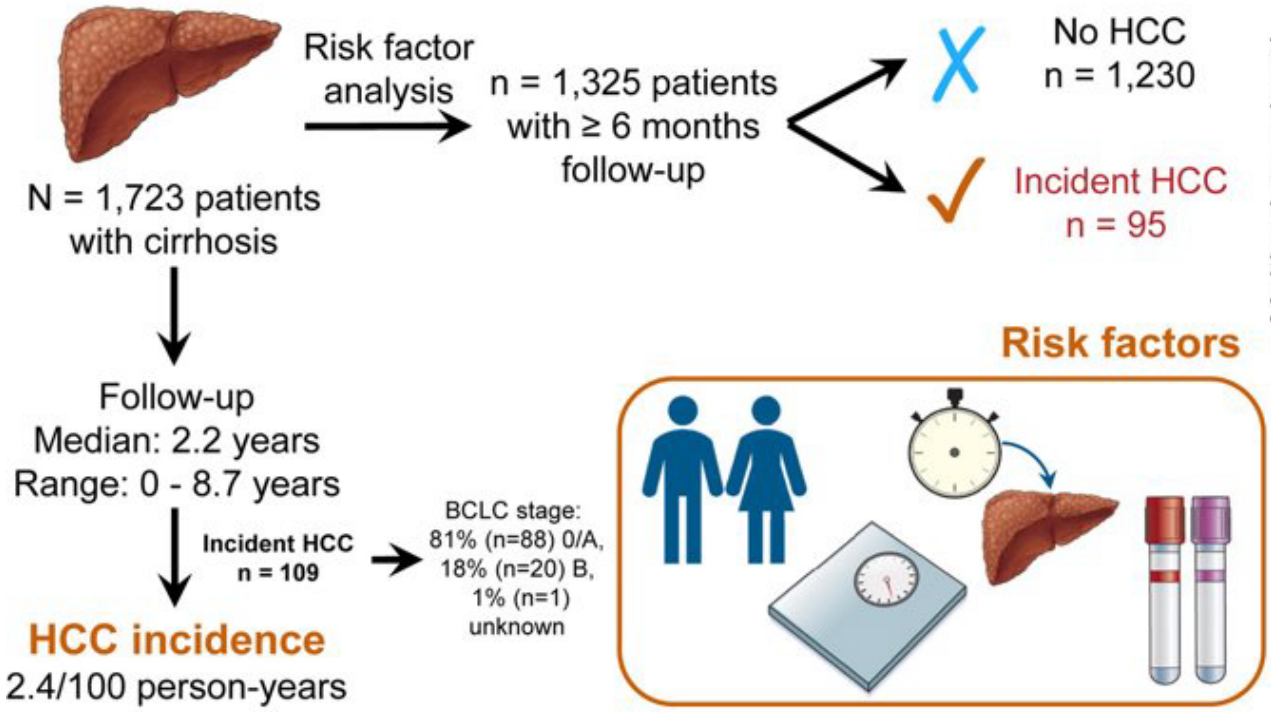
Independent Risk Factors for HCC in Cirrhosis: HEDS Study



Multivariate subset*	*p-value, OR, 95% CI*
Gender	<0.001, 2.47, 1.54 - 4.07
Years with cirrhosis	0.004, 1.06, 1.02 - 1.1
Family h/o liver cancer	0.02, 2.69, 1.11 - 5.86
Age	0.02, 1.17, 1.03 - 1.33
Obesity	0.02, 1.7, 1.08 - 2.73
AST	0.06, 1.54, 0.97 - 2.42
AFP	0.07, 1.32, 0.97 - 1.77
Albumin	0.10, 0.7, 0.46 - 1.07

*Fourteen risk factors for HCC were significant (p<0.05) in univariate analyses, and the multivariate subset was selected by stepwise logistic regression. Only patients with complete datasets for all 8 variables were included: HCC n=88, no HCC n=1,172.

Gastroenterology

Reddy R, et al. Gastroenterology 2023;165:1053

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Summary II

- The phases of biomarker validation are critical to provide the best evidence for validating for detection of cancer
- The aims of new biomarkers should be to improve sensitivity and also increase utilization
- We showed in a large phase 3 that GALAD is more sensitive than AFP
- National Liver Cancer Screening Trial will answer whether GALAD will lead to better effectiveness of HCC screening
- There are other potential biomarkers for HCC surveillance that need further validation