

# Barriers to Effective Hepatocellular Carcinoma Surveillance and Potential Role of Biomarkers

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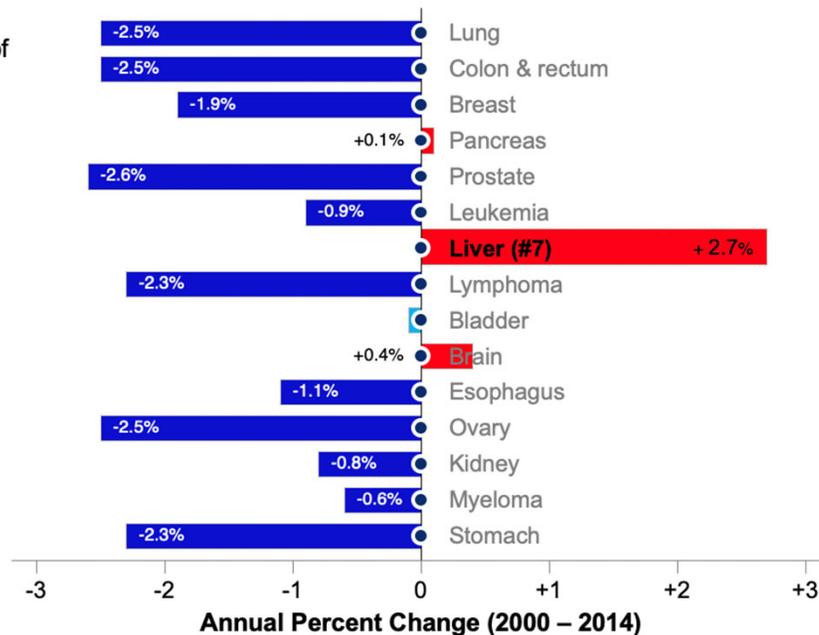
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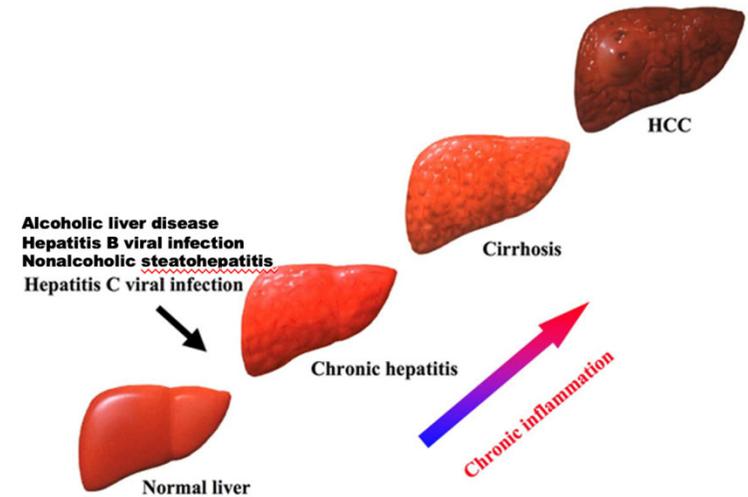
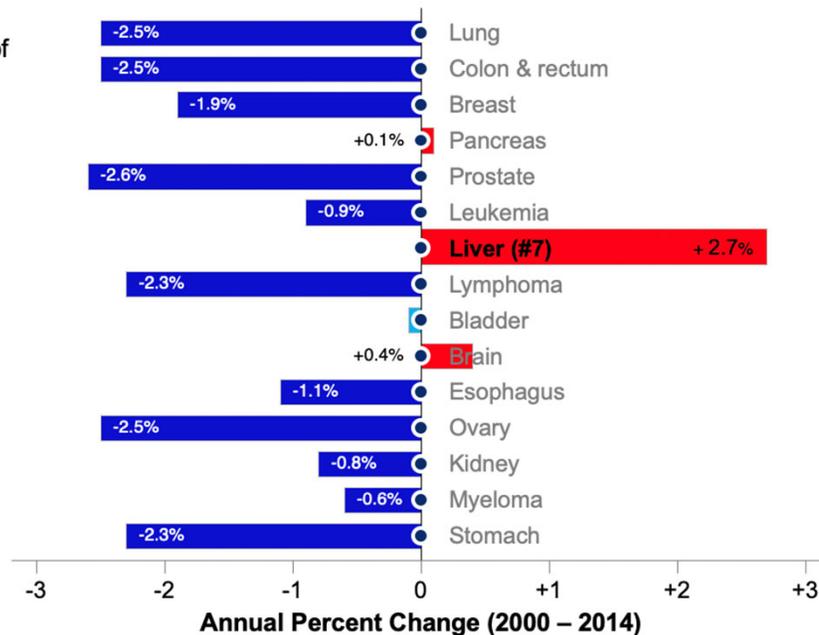
# Hepatocellular carcinoma is one of the fastest increasing causes of cancer-related death in the U.S.

Top 15 causes of cancer death United States 2010-2014



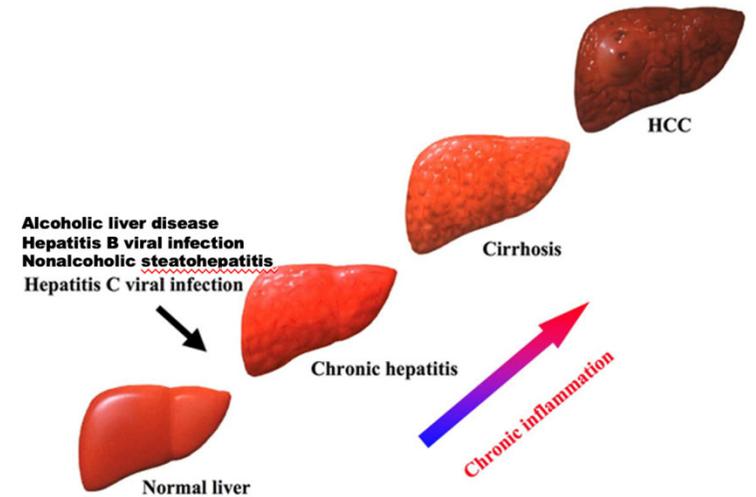
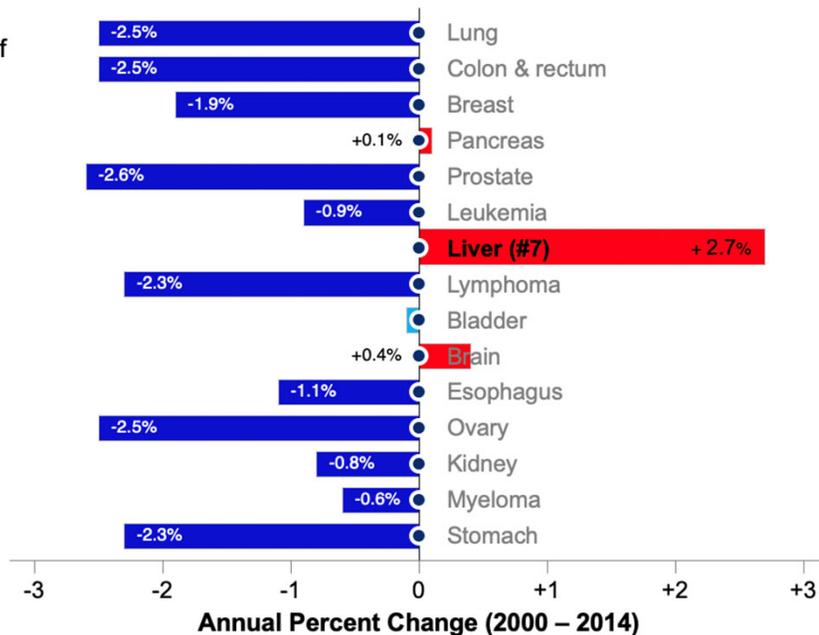
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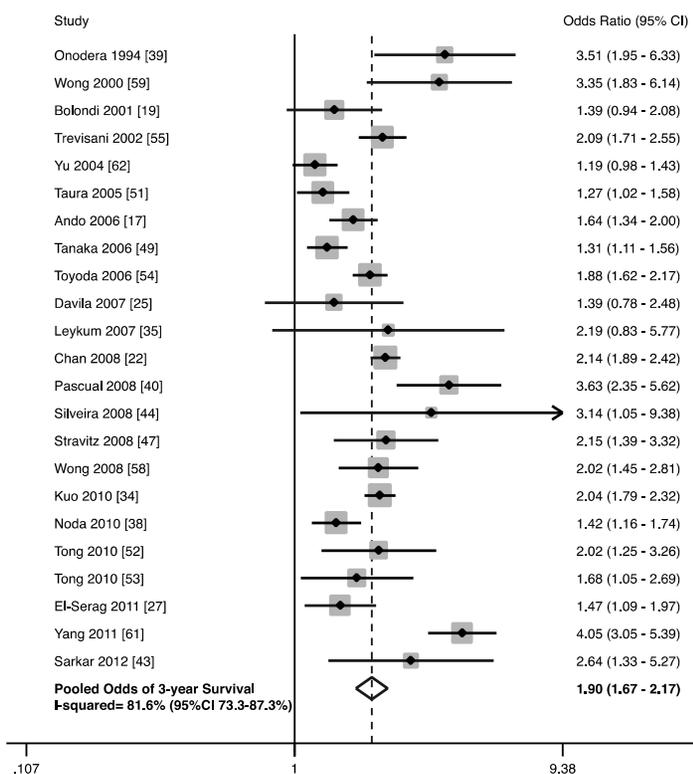


# Hepatocellular carcinoma is one of the fastest increasing causes of cancer-related death in the U.S.

Top 15 causes of cancer death United States 2010-2014



# Cohort studies show HCC screening associated with early detection and improved survival in patients with cirrhosis



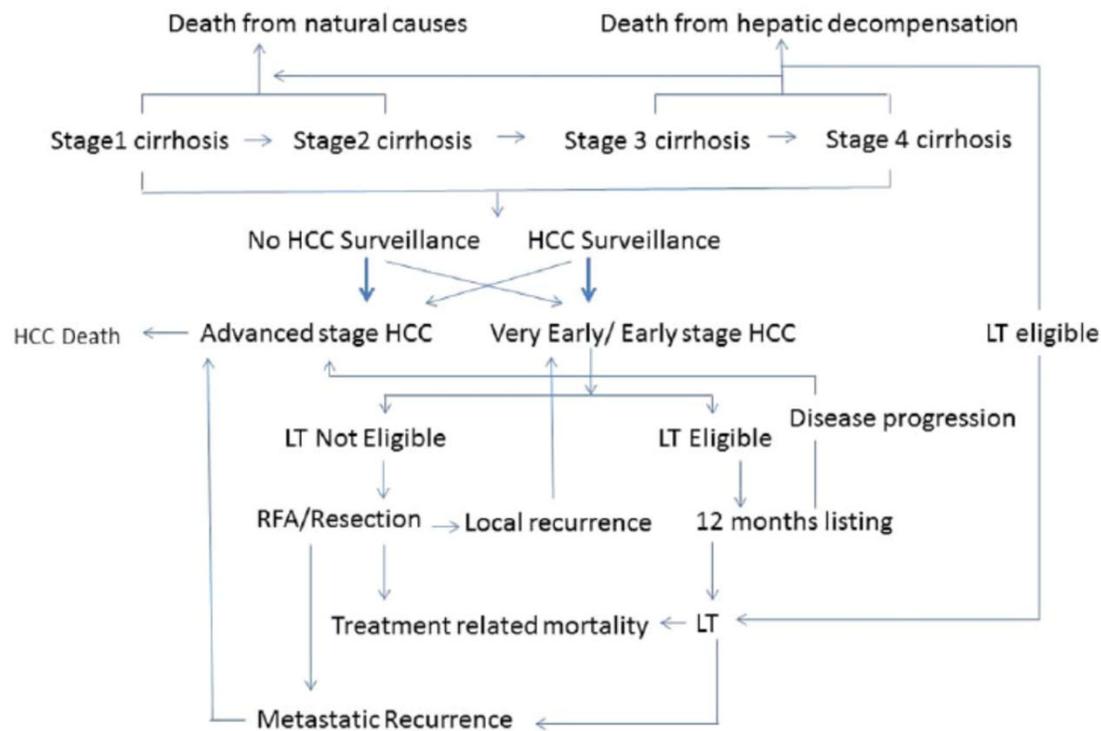
Identified 47 studies with 15,158 patients – 6284 (41.4%) detected by surveillance

Surveillance associated with:

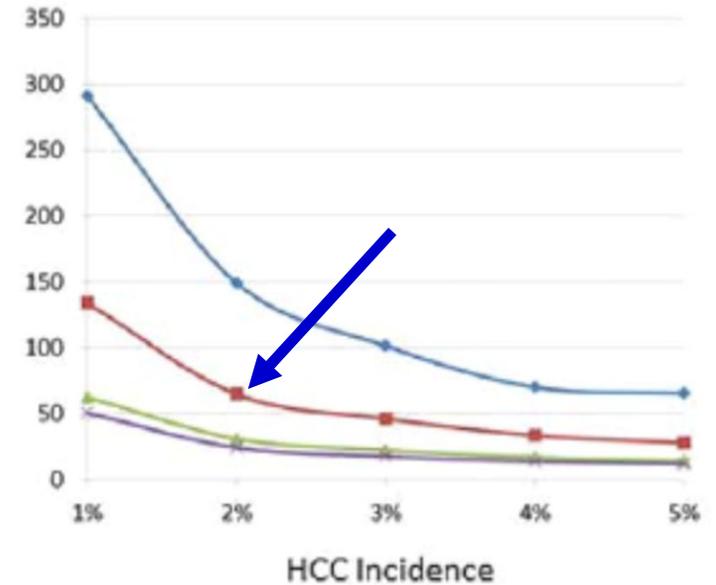
- Early detection: OR 2.08, 95%CI 1.80 – 2.37
- Curative treatment: OR 2.24, 95%CI 1.99 – 2.52
- Improved survival OR 1.90, 95%CI 1.67 – 2.17

Survival benefit persisted in studies adjusting for lead time bias

# Number needed to screen to reduce 1 HCC death in patients with cirrhosis is low



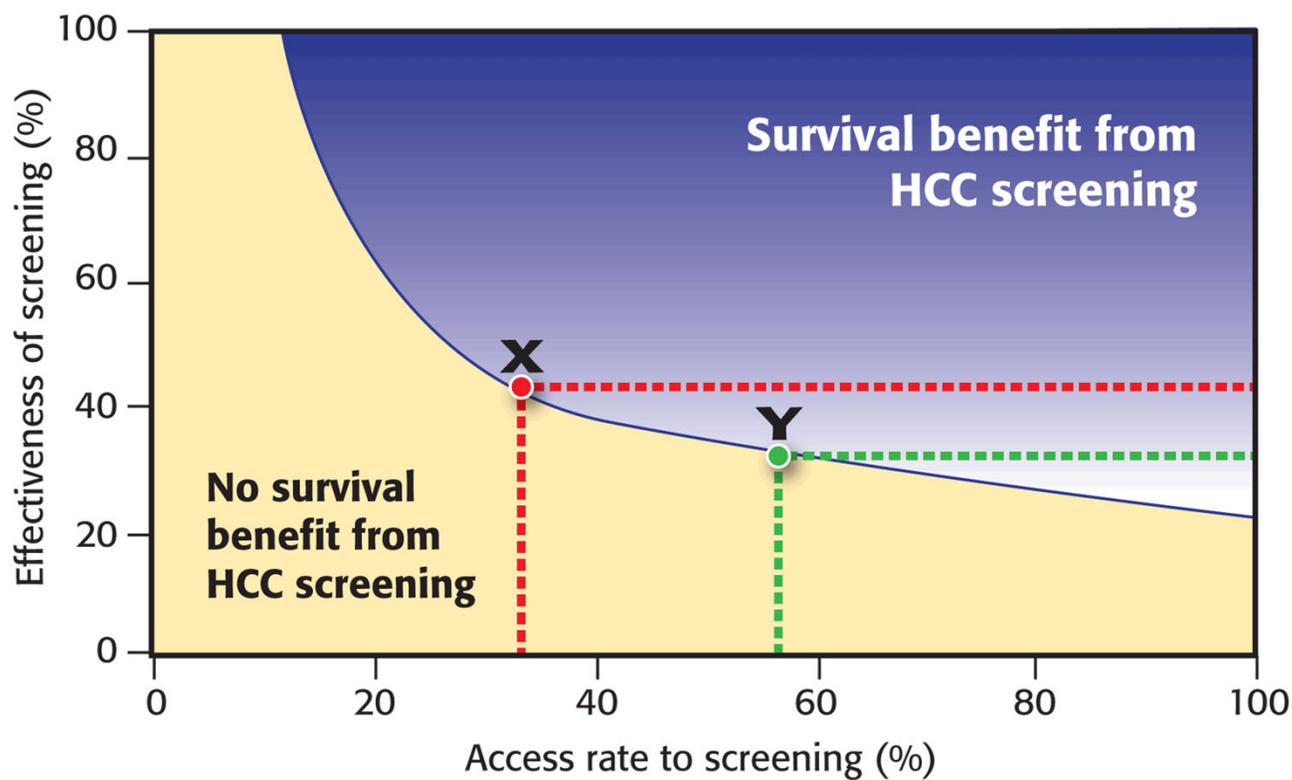
NNS to prevent one HCC-related death



## Factors that should be taken into consideration for new early HCC detection biomarker

- Test performance for early HCC detection
  - Sensitivity (early detection) *and* specificity (screening harms)
  - Variability in performance among subgroups (viral vs. non-viral)
- Screening test utilization
- Risk of overdiagnosis and stopping rules
- Differential benefit based on patient characteristics

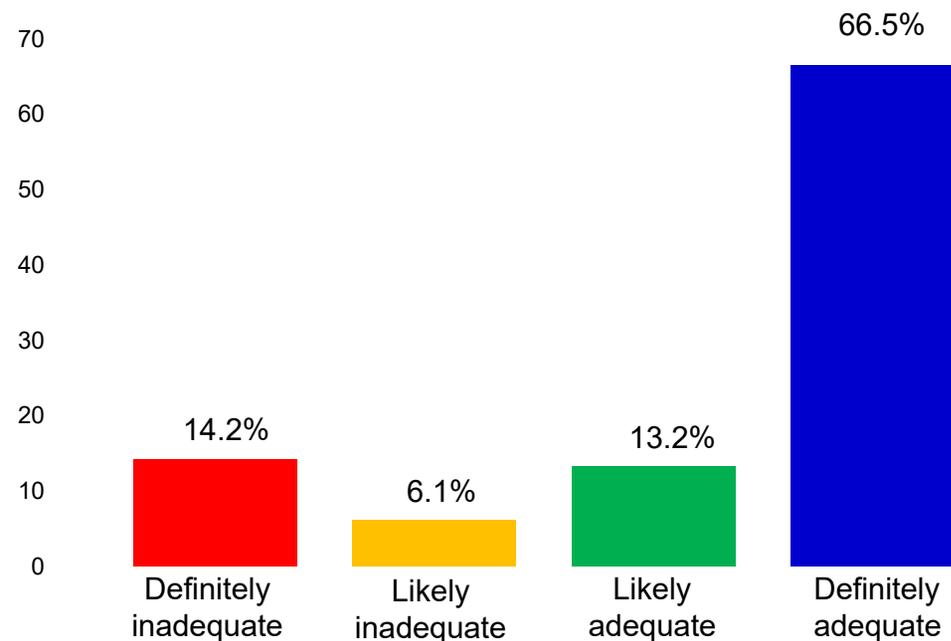
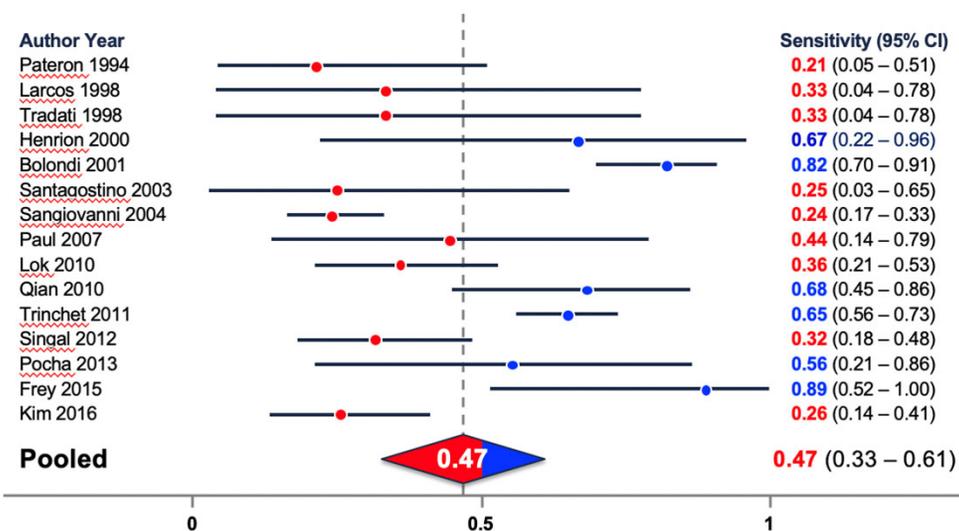
# Screening utilization and test effectiveness are two critical factors to HCC screening reducing mortality



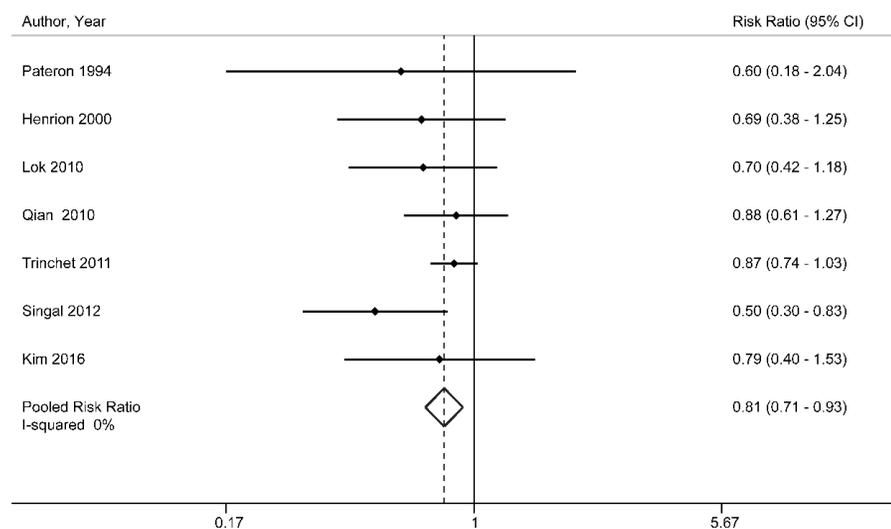
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# Ultrasound alone has poor sensitivity for early HCC detection, particularly in those with non-viral liver disease

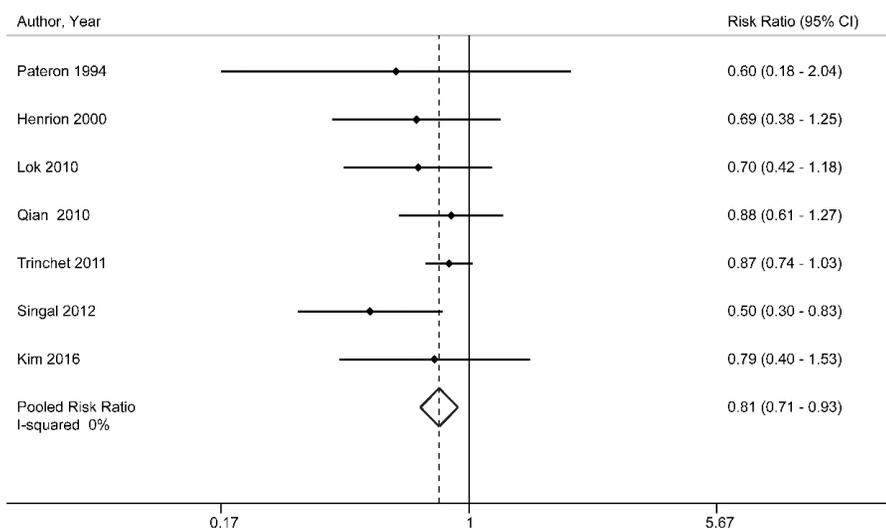


# Ultrasound alone has poor sensitivity for early HCC detection but adding biomarkers appears beneficial



Sensitivity of US with vs without AFP for early-stage HCC:  
63% vs. 45% ( $p=.002$ )

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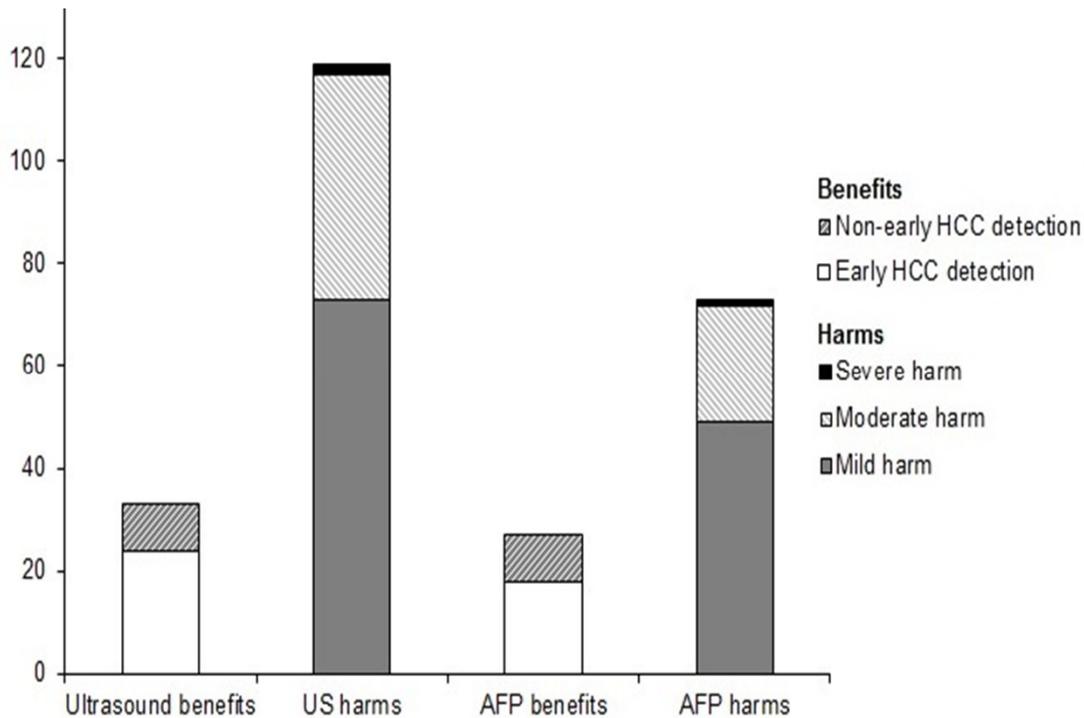
Sensitivity of US alone vs. US + AFP for early-stage HCC:  
45% vs. 63% ( $p=.002$ )

Performance of GALAD Panel for HCC detection		
Cohort	Sensitivity Early HCC	Specificity
UK cohort	80.2%	89.7%
Japan cohort	60.6%	95.8%
Germany cohort	67.4%	88.6%

Any differential performance of biomarkers is historically converse to that of ultrasound, i.e. higher accuracy in non-viral subgroups than those with viral-mediated cirrhosis

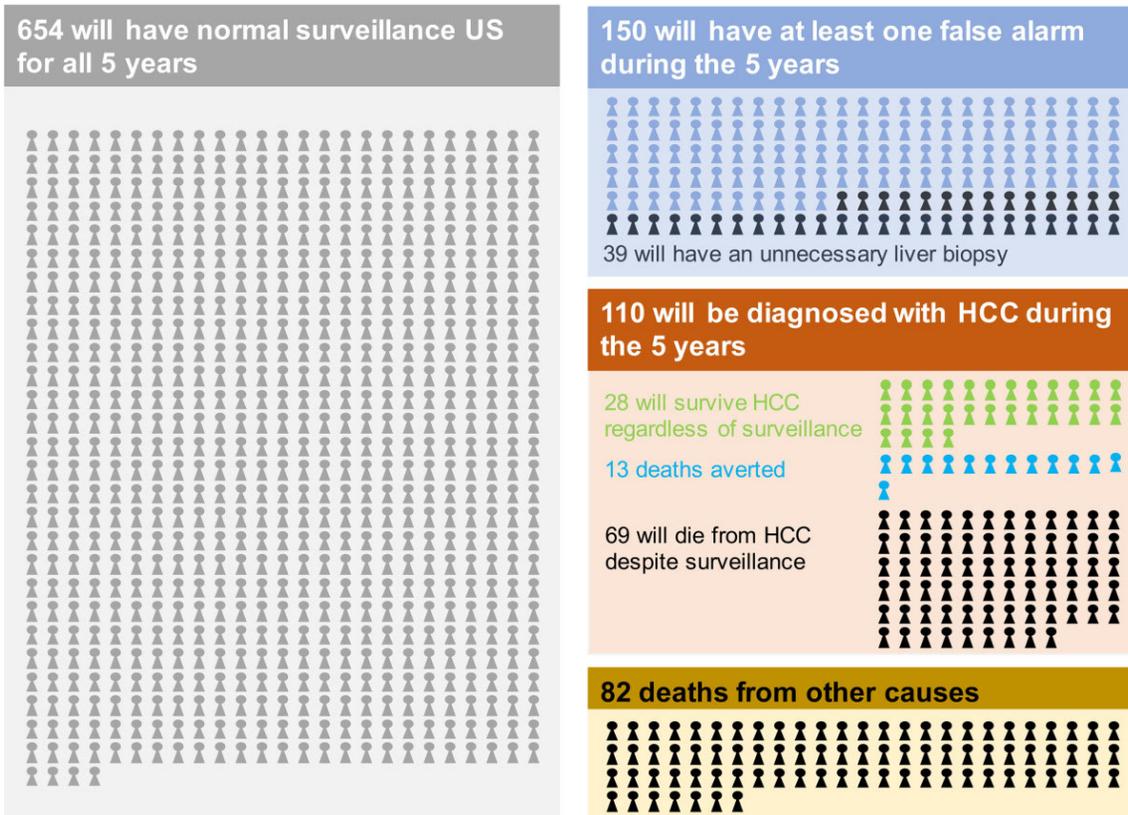
Performance can also be improved by longitudinal assessment of biomarker levels

# HCC screening can also be associated with potential harms



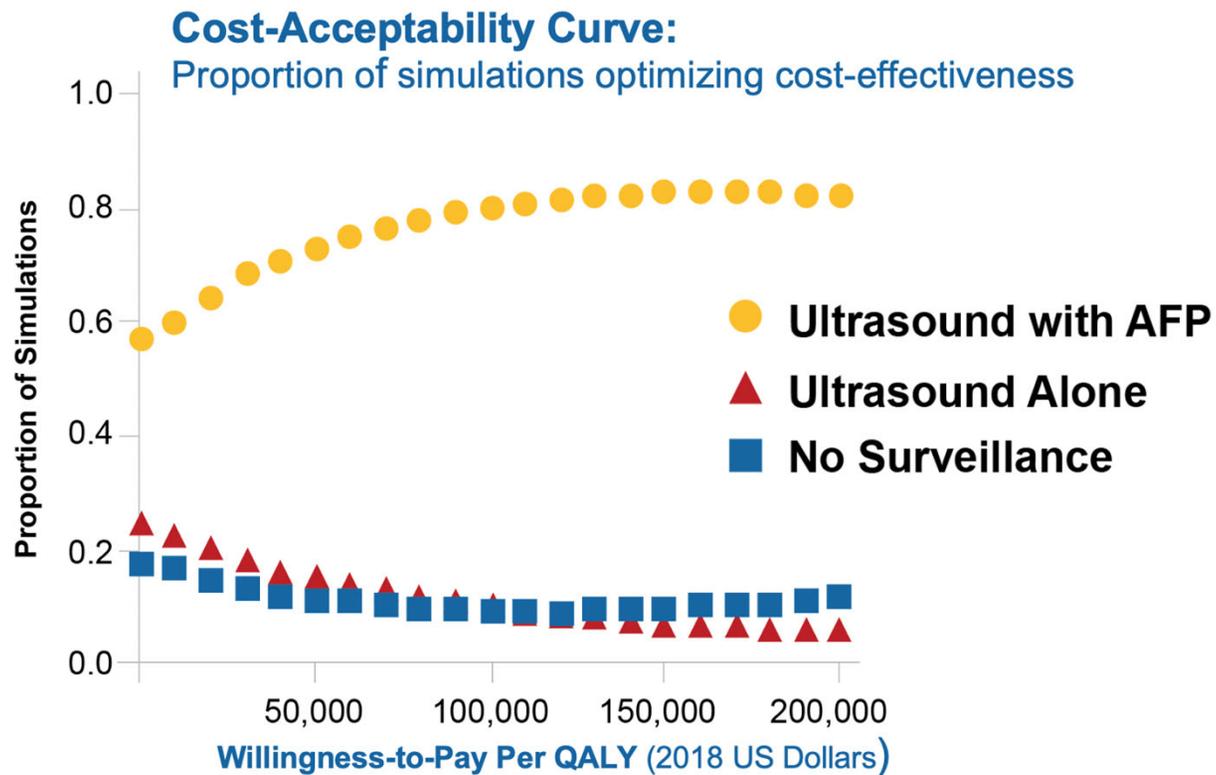
- Over 3 years, surveillance detected 48 HCC (34 (70%) early)
- Physical harms seen in 187 (28%) pts
  - Moderate-severe: 59 (10%) pts
- Despite AFP having more false positive results, a higher proportion of harms were related to US than AFP 22.8% vs. 11.4% ( $p < 0.001$ )

# Modeling benefits and harms of HCC surveillance



- Markov model for 50-year old with compensated cirrhosis
- **Benefits:** 13 fewer deaths over 5 years = NNS of 77
- **Harms:** 150 patients over 5 years = NNS of 7
- Benefits sensitive to HCC incidence and treatment benefit
- Harms sensitive to diagnostic testing for false positive or indeterminate results
  - This is uncertain for novel biomarkers

# Ultrasound and AFP is currently the cost-effective strategy



This was one of the first studies to incorporate screening-related harms

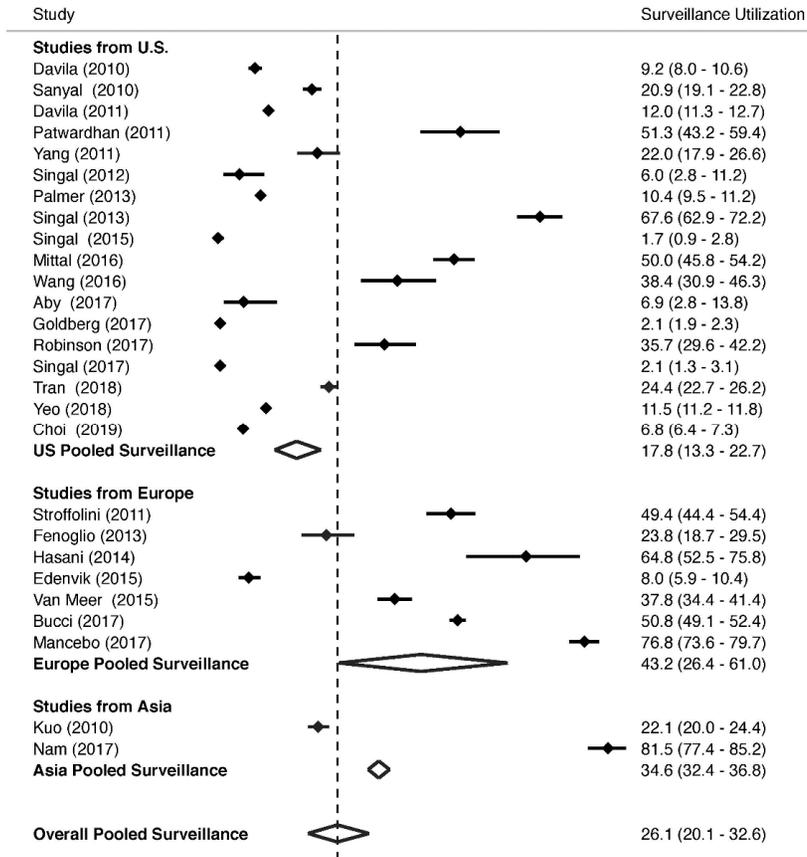
Adherence >20% was necessary to become cost-effective compared to no surveillance. Dominant strategy if adherence >59%

Platform for novel biomarker evaluation but uncertain inputs including provider action for biomarker results, particularly when repeated over time

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- Differential benefit based on patient characteristics

# HCC surveillance is underused in clinical practice



Identified 29 studies between Jan 2010 – Aug 2018

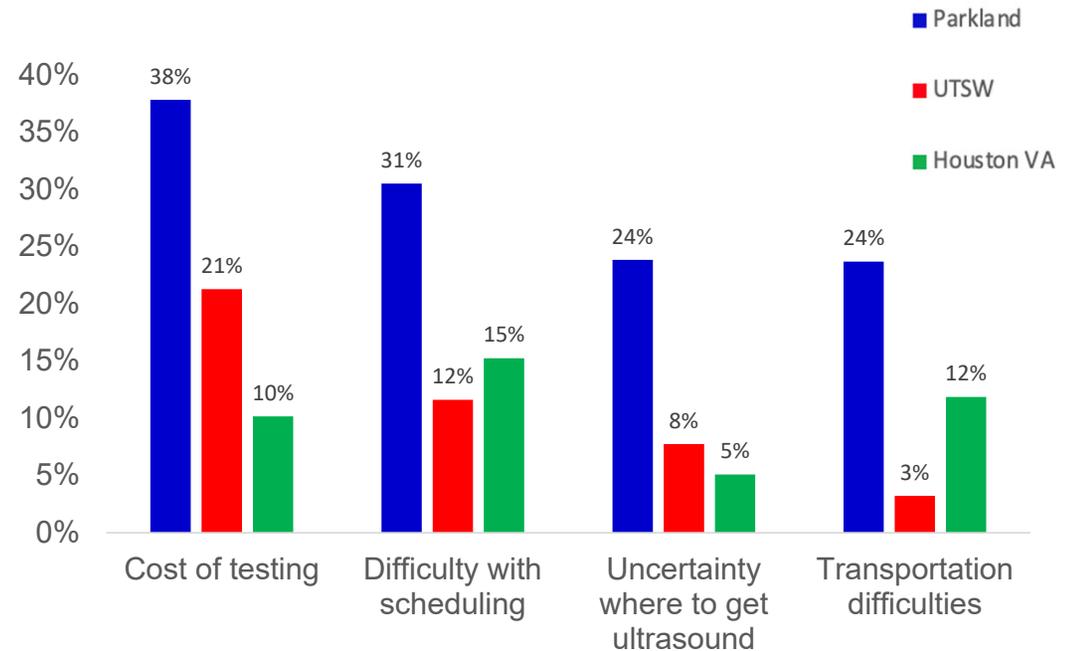
Pooled surveillance estimate was only 26.1%

- Lower surveillance in US studies vs. Europe and Asia (17.8% vs. 43.2% and 34.6%)
- Higher surveillance in GI/Hepatology clinics vs. academic primary care clinics and population-based cohorts (73.7% vs. 29.5% and 8.8%)

Consistent correlates included higher surveillance with GI/Hepatology subspecialty care and increased number of clinic visits and lower surveillance in patients with NASH or alcohol-related cirrhosis.

# Providers and patients both report barriers to HCC surveillance

Provider-reported barriers	Primary care Providers (n=177)
Lack of knowledge about guidelines	74.6%
Competing interests in clinic	43.5%
Lack of time in clinic	47.5%
Difficulty recognizing at-risk pts	32.2%
Ultrasound capacity	15.8%
Responsibility of subspecialists	18.6%



# Interventions can significantly increase HCC surveillance

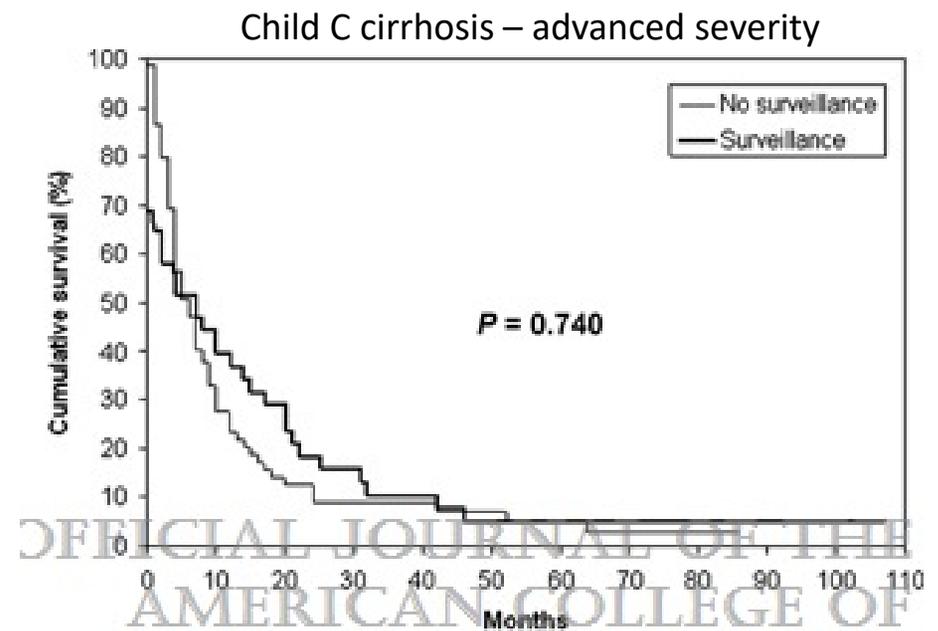
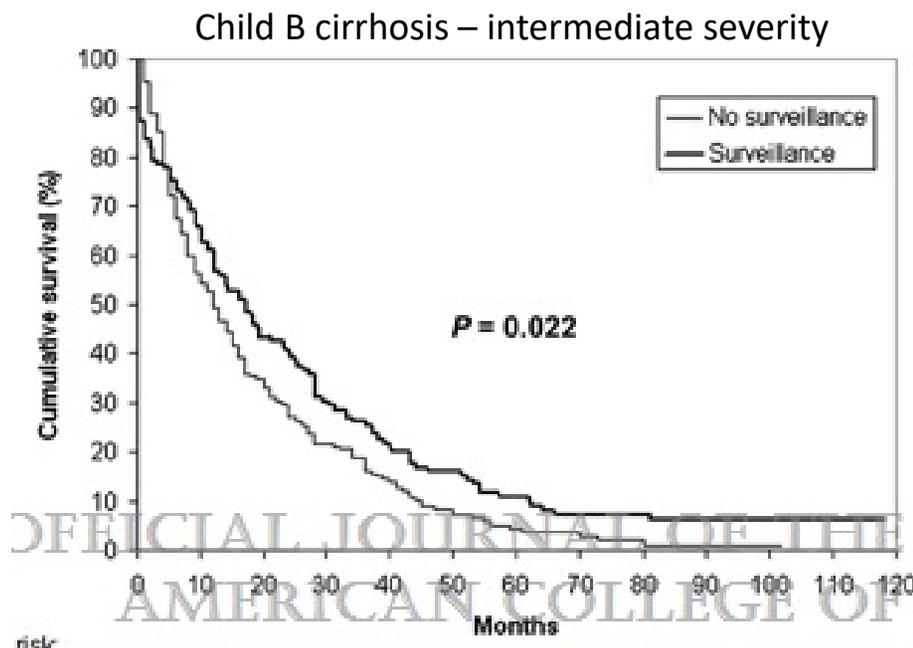
Author, year	Study Setting	Study Period	Intervention	Outcome	Pre-Intervention [n (%)]	Post-Intervention [n (%)]	Absolute Difference	Relative Difference
Aberra, 2013	U. Michigan, USA	2008-2011	Nurse base protocol	One-time abdominal imaging	119/160 <sup>b</sup> (74.4)	331/355 (93.2)	18.8%	25.3%
Kennedy, 2013	Flinders Medical Center, Australia	2007-2009	PCP and patient education, system redesign	Semi-annual US and AFP for two years	0/22 (0)	14/22 (63.6)	63.6%	-
Beste, 2015	Northwest Veterans Affairs, USA	2011-2012	EMR Reminder	≥2 abdominal imaging within 18 months	103/564 (18.2)	218/790 (27.6)	9.4%	51.6%
Del Poggio, 2015	120 PCPs, Italy	1994-2013	PCP Education	HCC diagnosed by surveillance	85/244 (34.8)	105/190 (55.3)	20.5%	58.9%
Nazareth 2016	Royal Perth Hospital, Australia	2010-2015	Nurse-led clinic	Semi-annual ultrasound	-	40/76 (52.6)	-	-
Farrell 2017	Royal Liverpool Hospital, UK	2009-2013	Radiology led recall	Semi-annual US	-	368/804 (45.8)	-	-
Bui 2017	KP Northern California, USA	Not reported	EMR identification and physician extender	3 abdominal imaging in 2 years	51/224 (22.8)	183/224 (81.7)	58.9%	258.3%
Singal, 2019	Parkland, Dallas, TX	2014-2016	Mailed outreach	Semi-annual US over 18 months	44/600 (7.3)	247/1200 (20.6)	13.3%	182.2%

***All listed interventions are likely more effective when considering same-day blood-based biomarker than imaging-based screening***

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- Risk of overdiagnosis and stopping rules
  - Is this a concern for HCC?
- Differential benefit based on patient characteristics

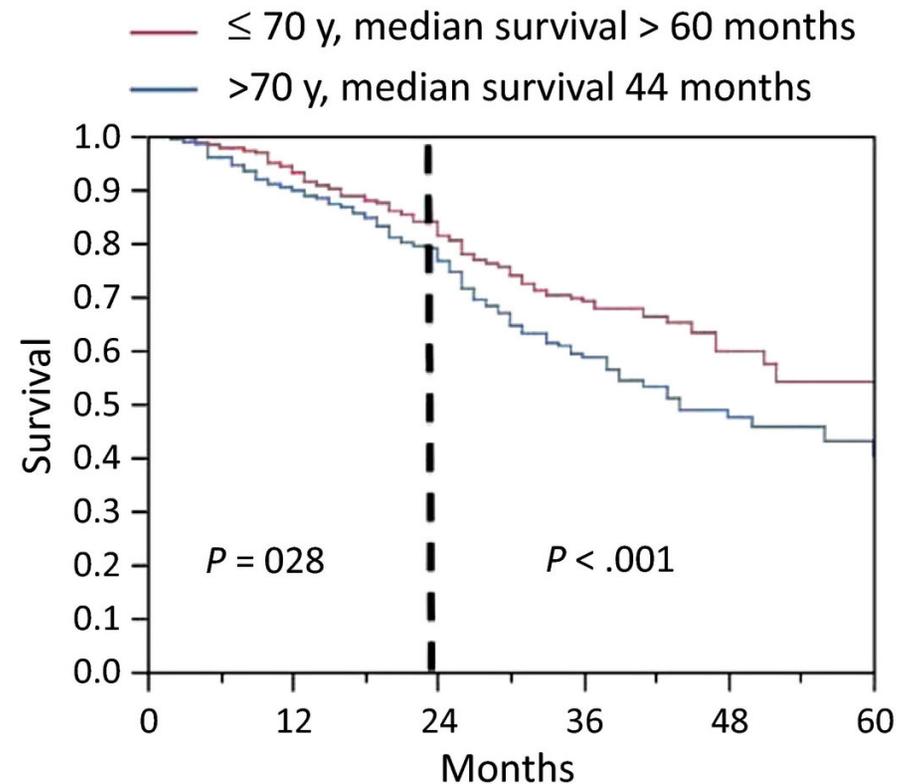
# Competing risk of liver-related mortality precludes benefit of HCC screening in those with advanced cirrhosis



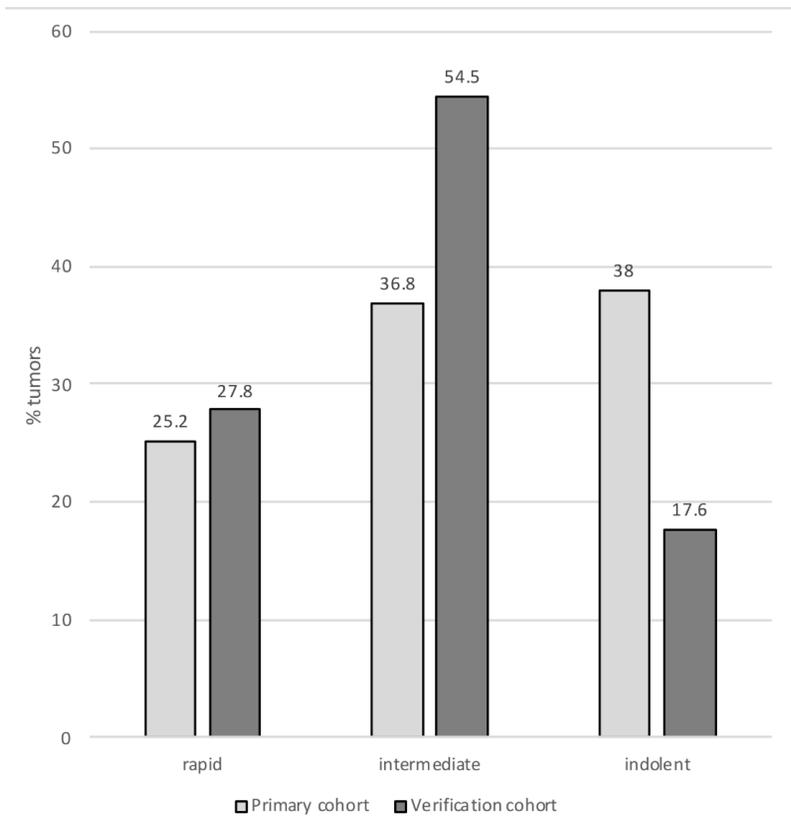
Guidelines recommend against screening if patient has Child C (advanced) cirrhosis unless listed for transplant

## Unclear if age alone should be used for stopping rules

- Multi-site Italian study of 1069 patients with HCC (529 early stage HCC)
- Similar early tumor stage detection (50.7% vs. 48.5%) but older patients less likely to undergo curative treatment (37.1% vs. 45.1%)
- Age >70 years associated with mortality (HR 1.18, 95%CI 1.04 – 1.34).
  - Greatest difference among subgroup with early stage disease (median >60 vs. 44 months)



## HCC may have heterogeneous tumor growth patterns

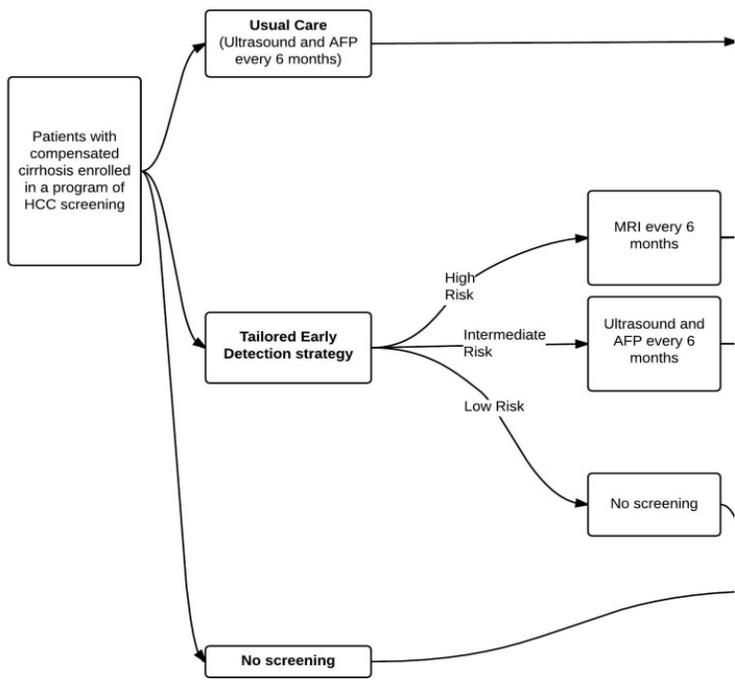
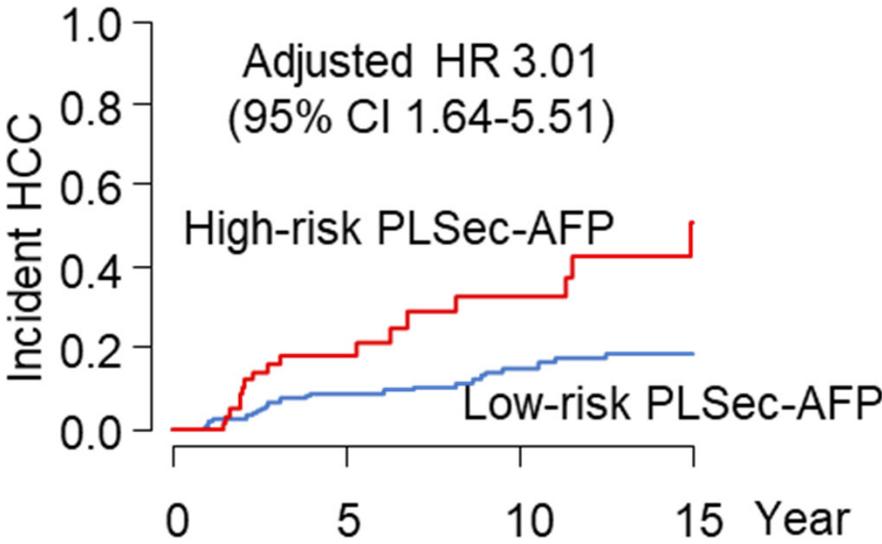


- TDT has implications for surveillance (e.g. lead time bias, risk of overdiagnosis)
- Multi-site study of HCC patients with repeat imaging without interval treatment
- Median TDT 7.5 months, with notable heterogeneity in growth patterns
- Indolent growth associated with larger tumors and AFP <20 ng/mL
  - Potential association with non-viral etiology in univariable but not multivariable analysis

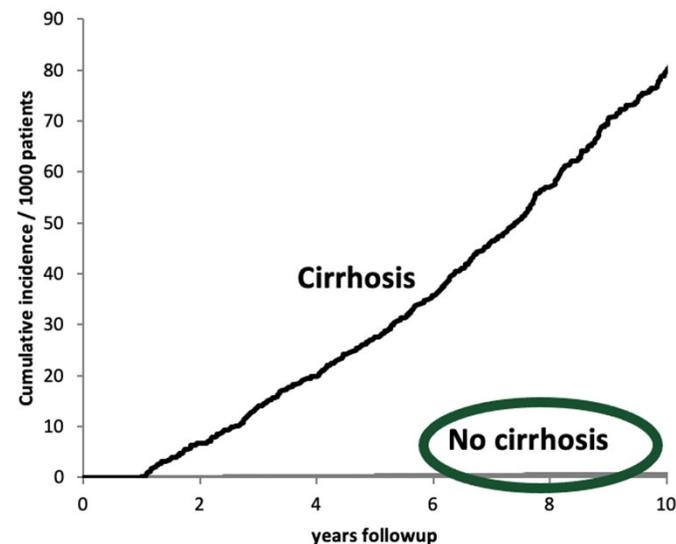
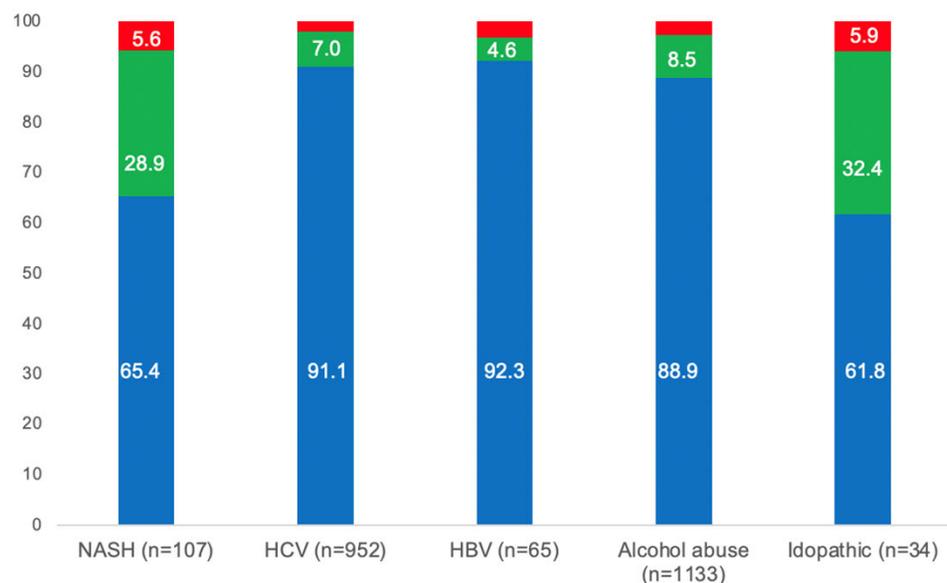
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# Risk stratification and hope for precision screening



# Role for precision screening to identify patients who otherwise would have been excluded from surveillance programs



0.008 per 100 patient-years

**Very high probability non-cirrhotic:** Histology and no features on imaging  
**High probability non-cirrhotic :** APRI <1; no features on imaging; NL albumin, plt, INR

## Considerations for simulation modeling and HCC biomarkers

- Test performance (sensitivity and specificity)
  - Surveillance value needs to consider benefits and harms
- Screening test utilization
  - Biomarker reduces barriers and can increase utilization
- Risk of overdiagnosis and stopping rules
  - In addition to age, must consider cirrhosis as competing mortality risk
- Differential benefit per patient characteristics
  - Biomarkers likely more accurate in non-viral liver disease
  - Risk stratification biomarkers may also be incorporated into decisions

# Thank you

- How should one model physician behavior for biomarker interpretation, in absence of robust data, particularly when repeated over time?
- Should HCC surveillance models account for adherence and how this impacts outcomes?