

Randomized Clinical Trial of Serum Biomarkers versus Ultrasound for Early Detection of Hepatocellular Carcinoma

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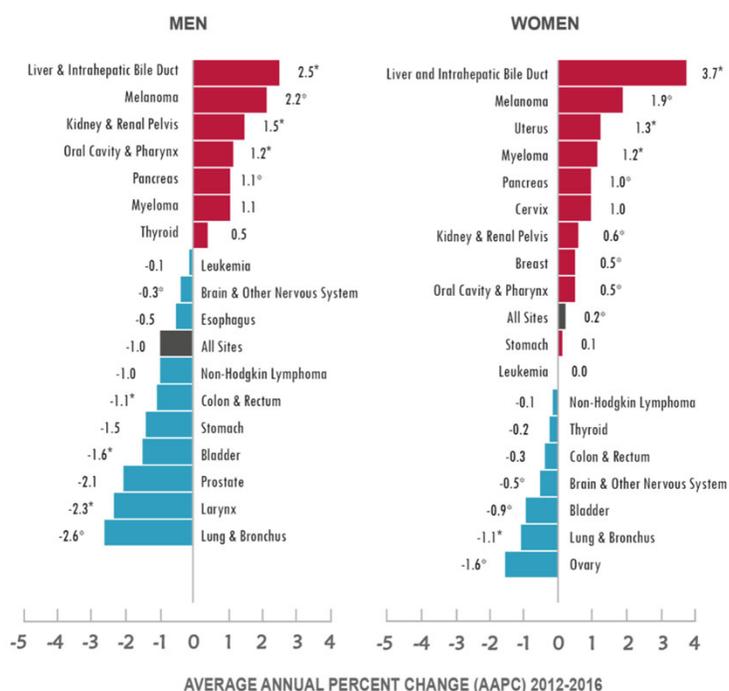
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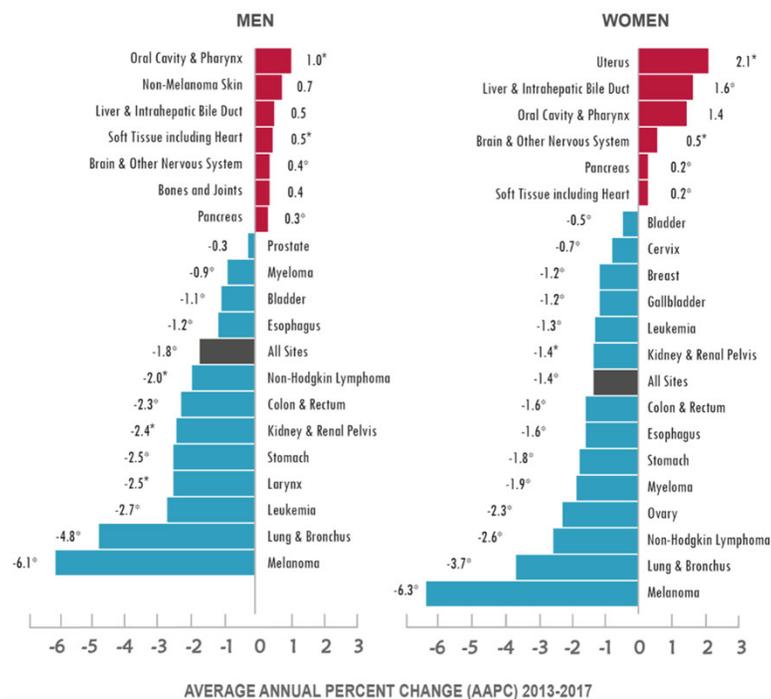
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Incidence and mortality of hepatocellular carcinoma (HCC) increasing in the United States

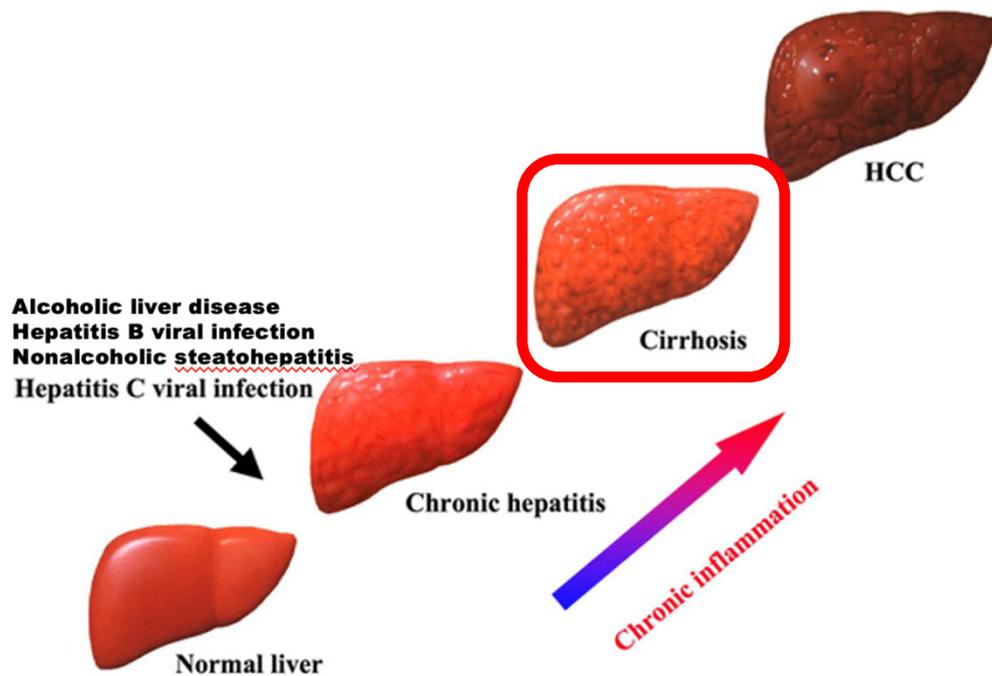
NATIONAL TRENDS IN RATES OF NEW CANCER CASES



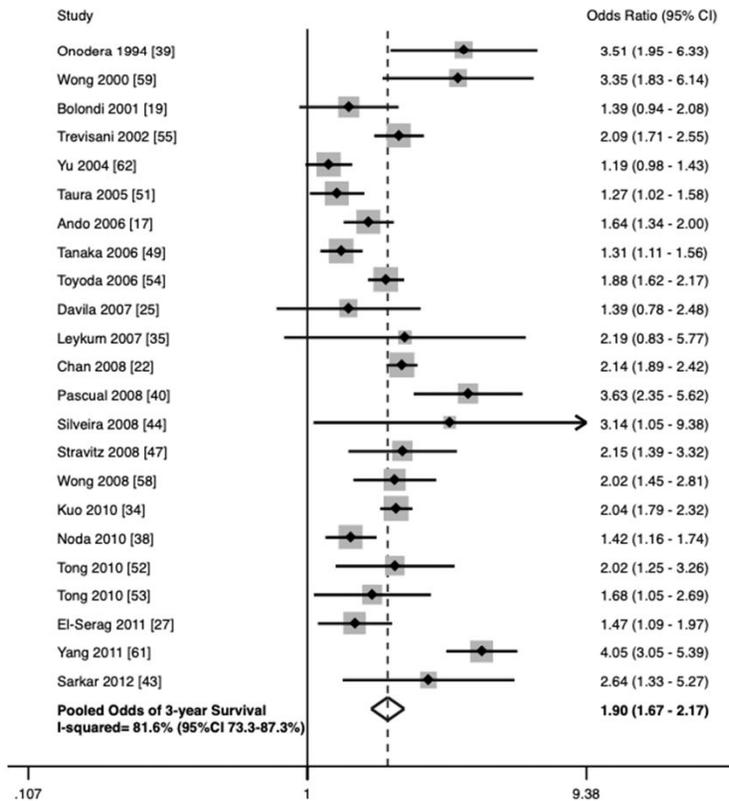
NATIONAL TRENDS IN CANCER DEATH RATES



HCC surveillance is recommended using ultrasound +/- AFP in high risk patients such as those with cirrhosis



HCC surveillance associated with early detection and improved survival in patients with cirrhosis



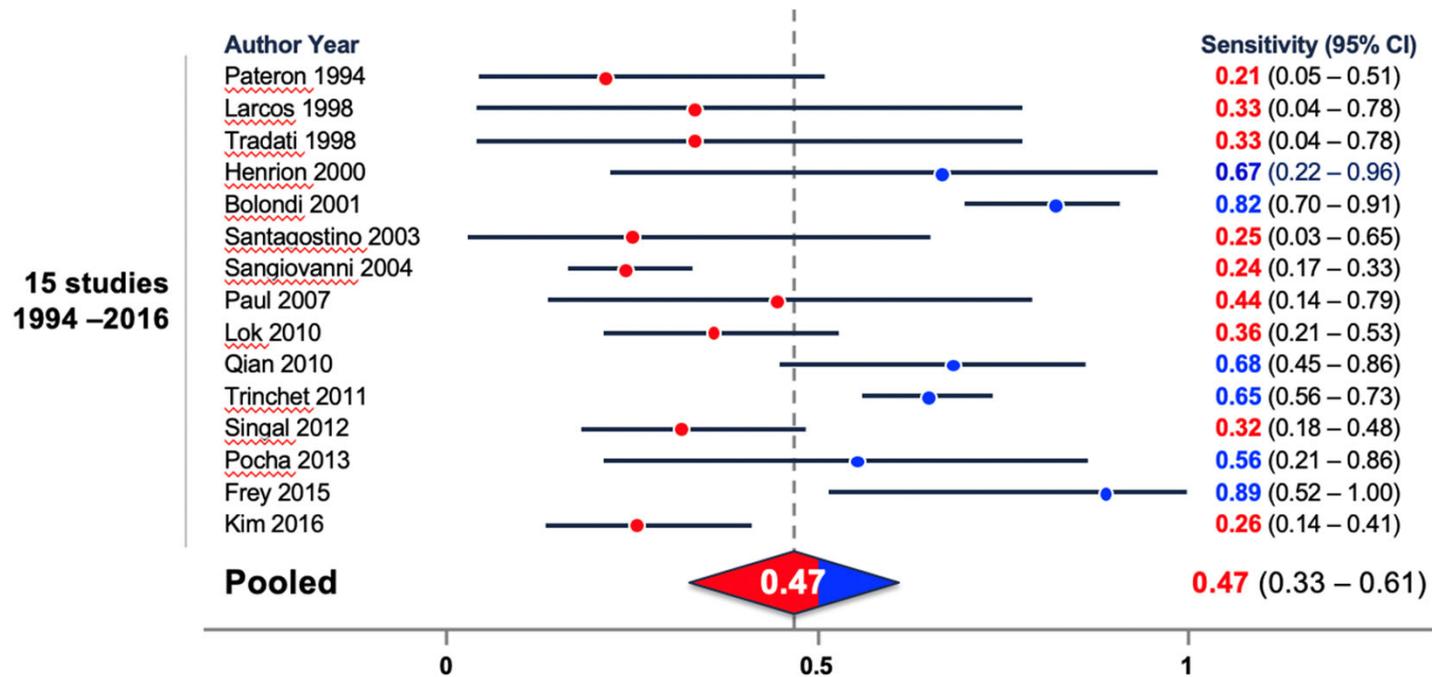
Identified 47 studies with 15,158 patients – 6284 (41.4%) detected by surveillance

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

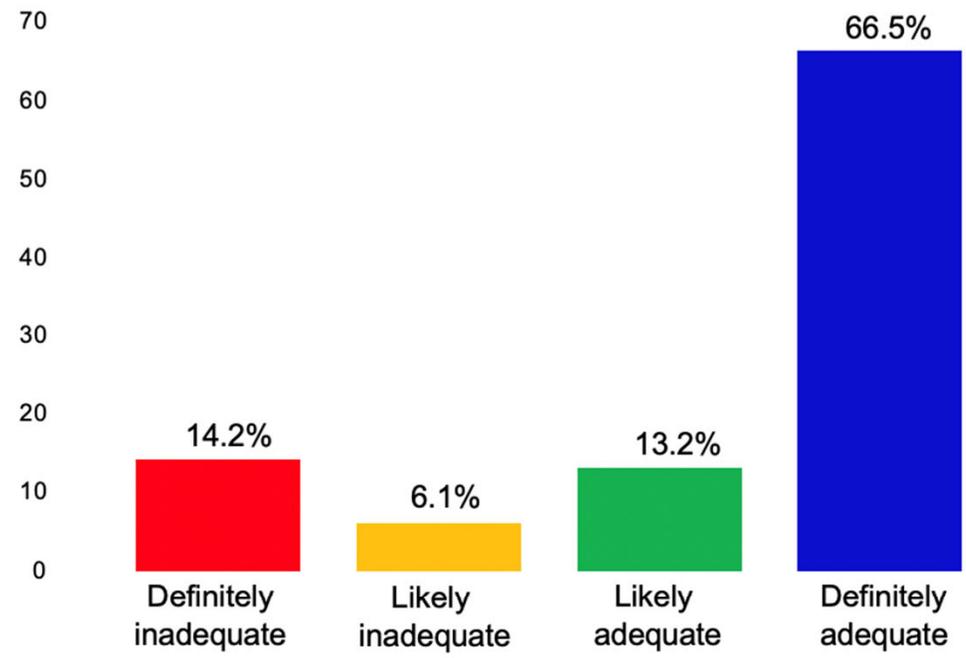
Survival benefit persisted in studies adjusting for lead time bias

Sensitivity of ultrasound +/- AFP for early HCC detection is suboptimal



Sensitivity of ultrasound and AFP significantly higher but only 63% for early stage HCC

Nearly 1 in 5 ultrasounds suboptimal visualization for HCC surveillance




Child Pugh B/C
 OR 1.65 (1.06 – 2.57)


Obesity
 OR 2.60 (1.36 – 4.97)

Morbid Obesity
 OR 8.86 (4.02 – 19.5)

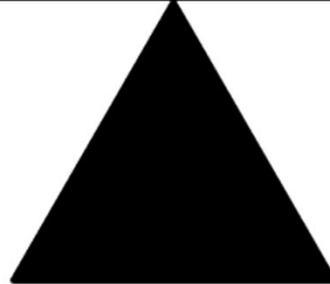

Alcohol-related cirrhosis
 OR 1.84 (1.09 – 3.09)


NASH cirrhosis
 OR 2.48 (1.30 – 4.75)

Surveillance benefits must be considered in light of potential harms

Benefits

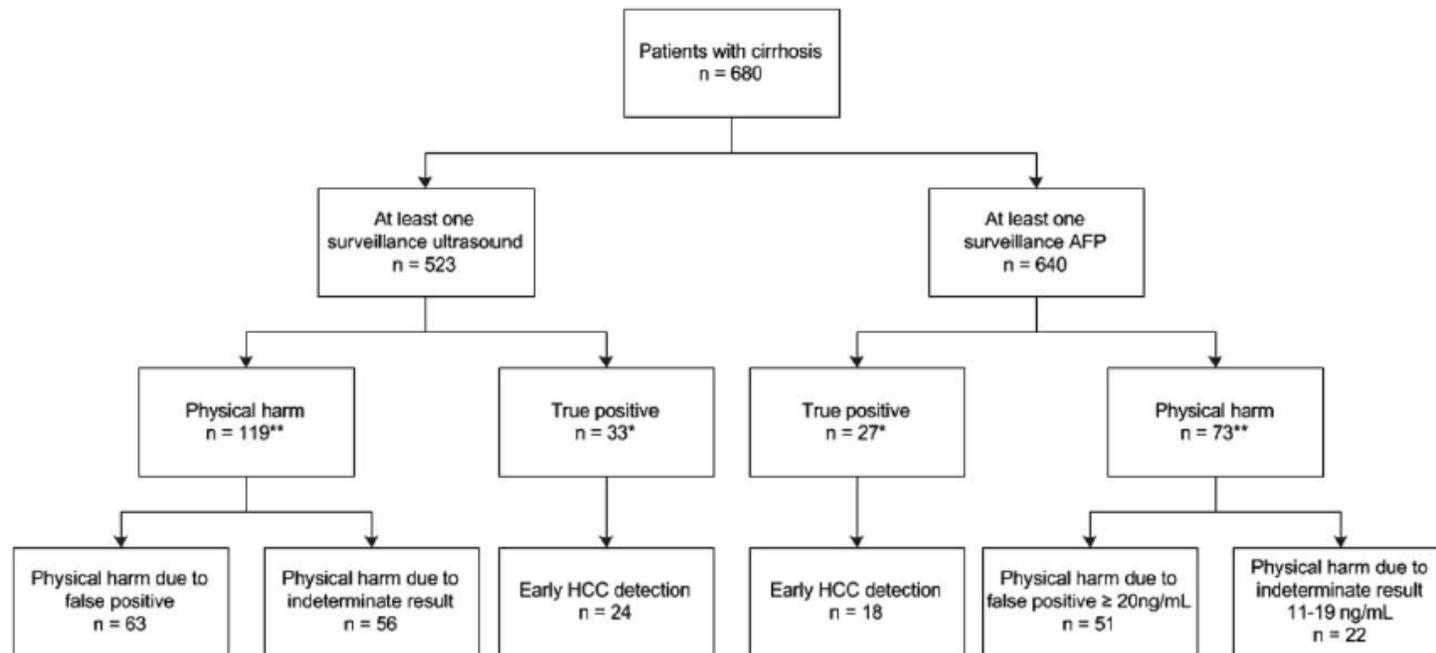
Early stage detection
Improve mortality



Harms

Repeat CT/MRI
Inadequate US
Indirect Costs
Low utilization

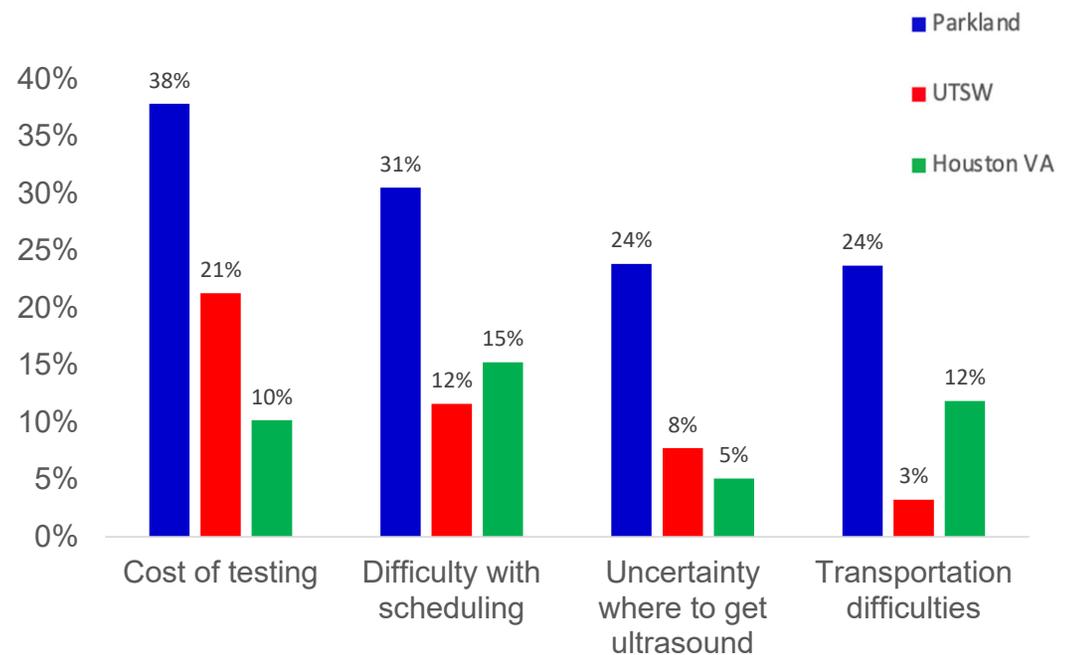
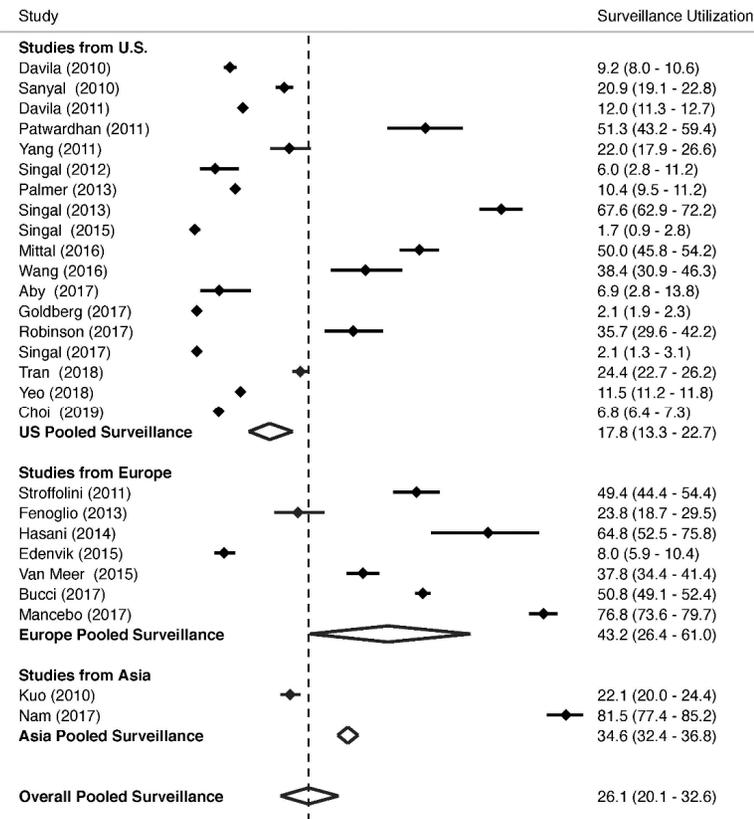
HCC surveillance associated with potential screening-related harms



* 12 HCC detected by both ultrasound and AFP

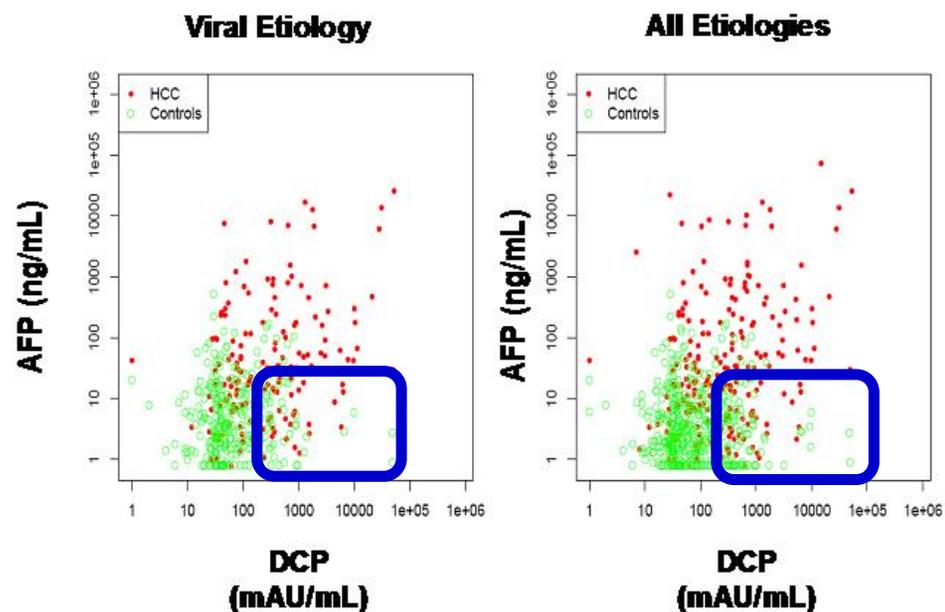
** 7 patients with physical harm due to false positive ultrasound and AFP

Imaging-based surveillance plagued by low utilization in practice



EDRN phase II study has facilitated biomarker validation

Early HCC (n=208)	Sensitivity (%)	Specificity (%)
DCP 222 mAU/mL	56 (47 – 87)	77 (46 – 86)
AFP-L3% 1.7%	37 (31 – 45)	94 (91 – 96))
AFP 10.9 ng/mL	66 (56 – 77)	82 (71 – 90)
AFP and DCP	70 (62 – 82)	80 (69 -88)



Biomarkers Tested in Phase 2 Reference Set

- **GALAD**
- **Glycotest**
- Fucosylated kinninogen
- Golgi protein 73
- AFP + PIVKA II (Architect platform)

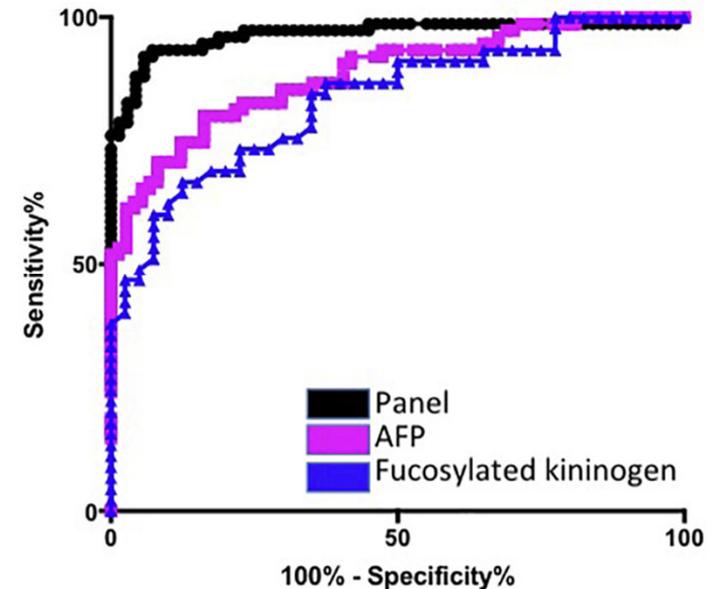
Novel biomarkers have demonstrated promising phase II data

GALAD: **G**ender, **A**ge, **A**FP-L3, **A**FP, and **D**CP

Multi-national nested case control with 6834 patients (2430 HCC, 4404 CLD)

Variable	Sensitivity	Specificity	Correctly classified
UK cohort (all)	91.6%	89.7%	90.6%
UK cohort (Milan)	80.2%	89.7%	87.9%
Japan cohort (all)	70.5%	95.8%	87.2%
Japan cohort (Milan)	60.6%	95.8%	87.7%
Germany cohort (all)	87.6%	88.6%	88.3%
Germany cohort (<u>unifocal < 5cm</u>)	67.4%	88.6%	87.5%

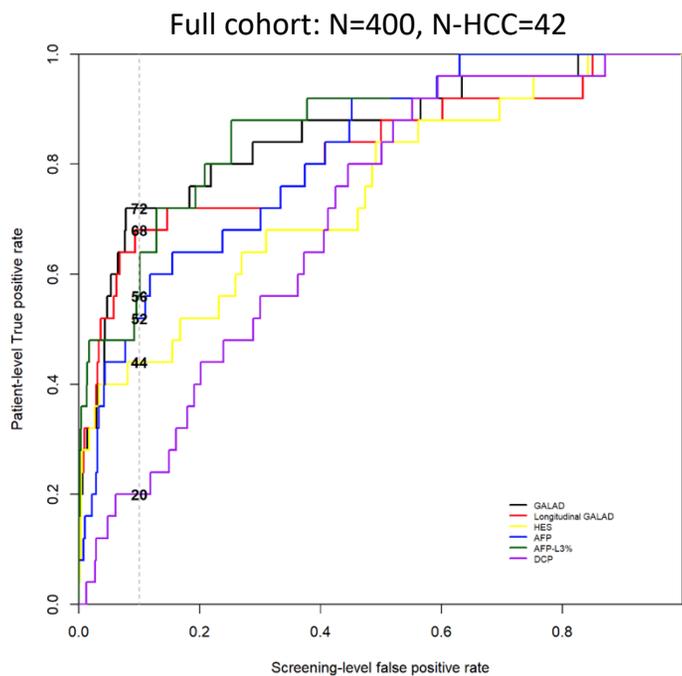
No difference in GALAD performance by cirrhosis etiology, SVR, or HBV treatment



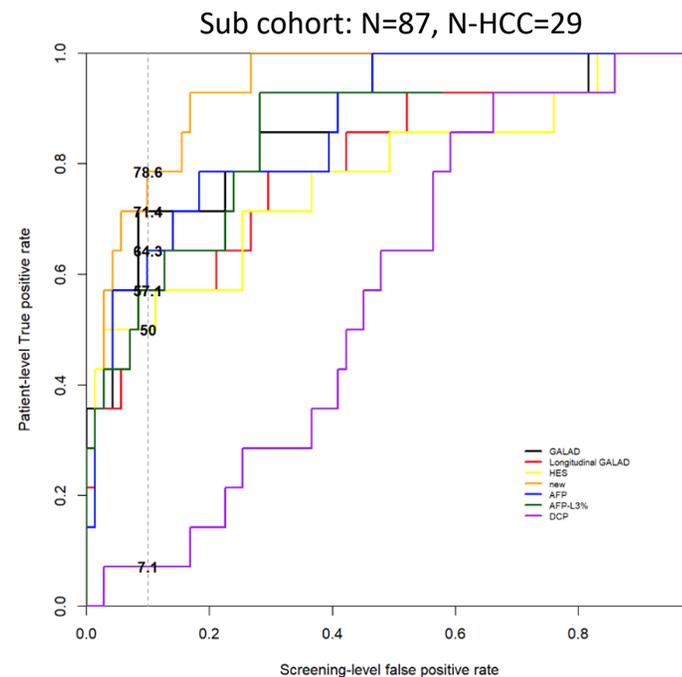
Michigan cohort: GALAD and Glycotest appear promising

Results based on specimens collected within six months prior to HCC diagnosis

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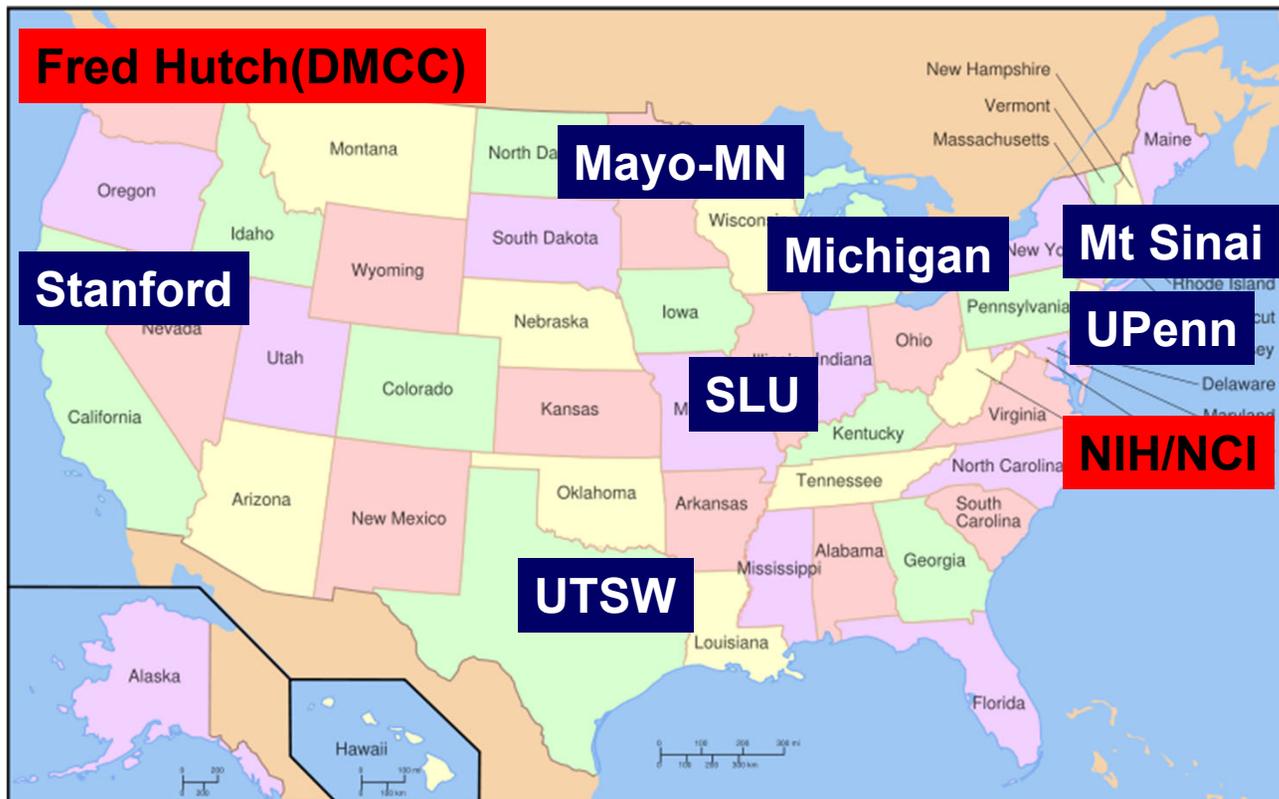


With 10% FPR, TPR for GALAD 72% vs. AFP 52%



TPR for Glycotest 78.6% and GALAD 71.4% vs. AFP 64.3%

EDRN-funded Hepatocellular carcinoma Early Detection Strategy (HEDS) study phase III infrastructure



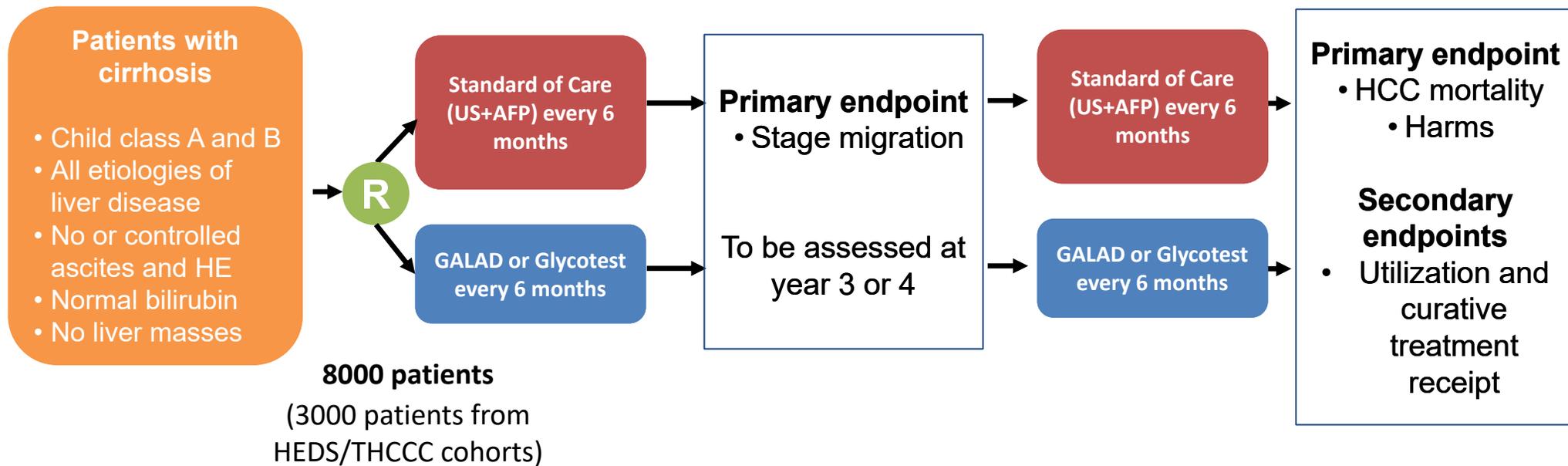
- 1,559 patients enrolled with median follow up of 3.4 years
- Men 53%; 79% NHW; median BMI 30.1
- HCV 42%; NAFLD 21.6% ; Alcohol 20.8%
- 87 incidence HCC; incidence rate 2.6% per 1,000 person-years

National Liver Cancer Surveillance Trial: Study Overview

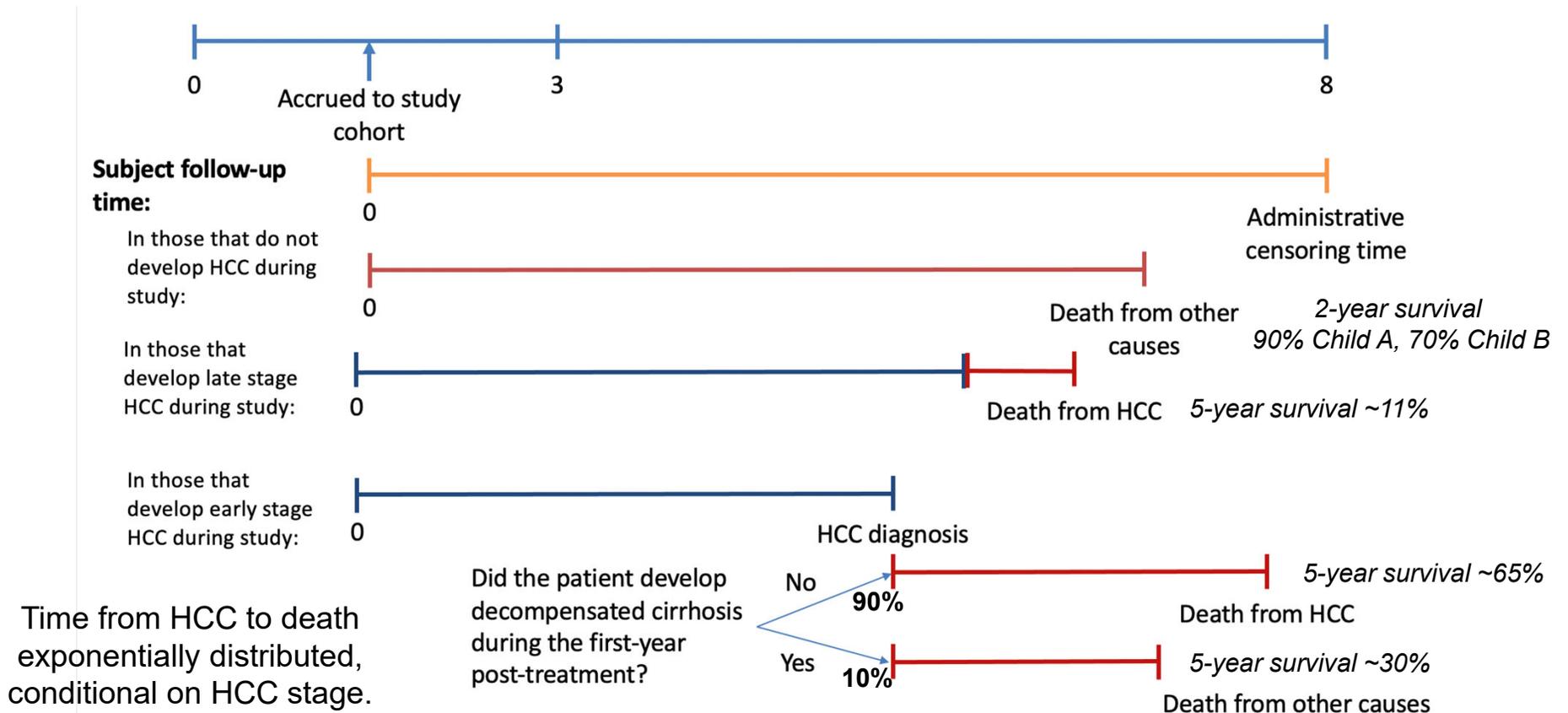
- Adaptive design with two phases
 - Randomized phase IV trial, with primary endpoint of stage migration
 - Transition to phase V trial if meets primary endpoint
- Randomized to ultrasound + AFP vs. GALAD or Glycotest
 - Stratified by site given operator dependency and site-level variation in ultrasound performance
 - Consider stratification by high- vs. low-risk if validated risk model exists

National Liver Cancer Surveillance Trial

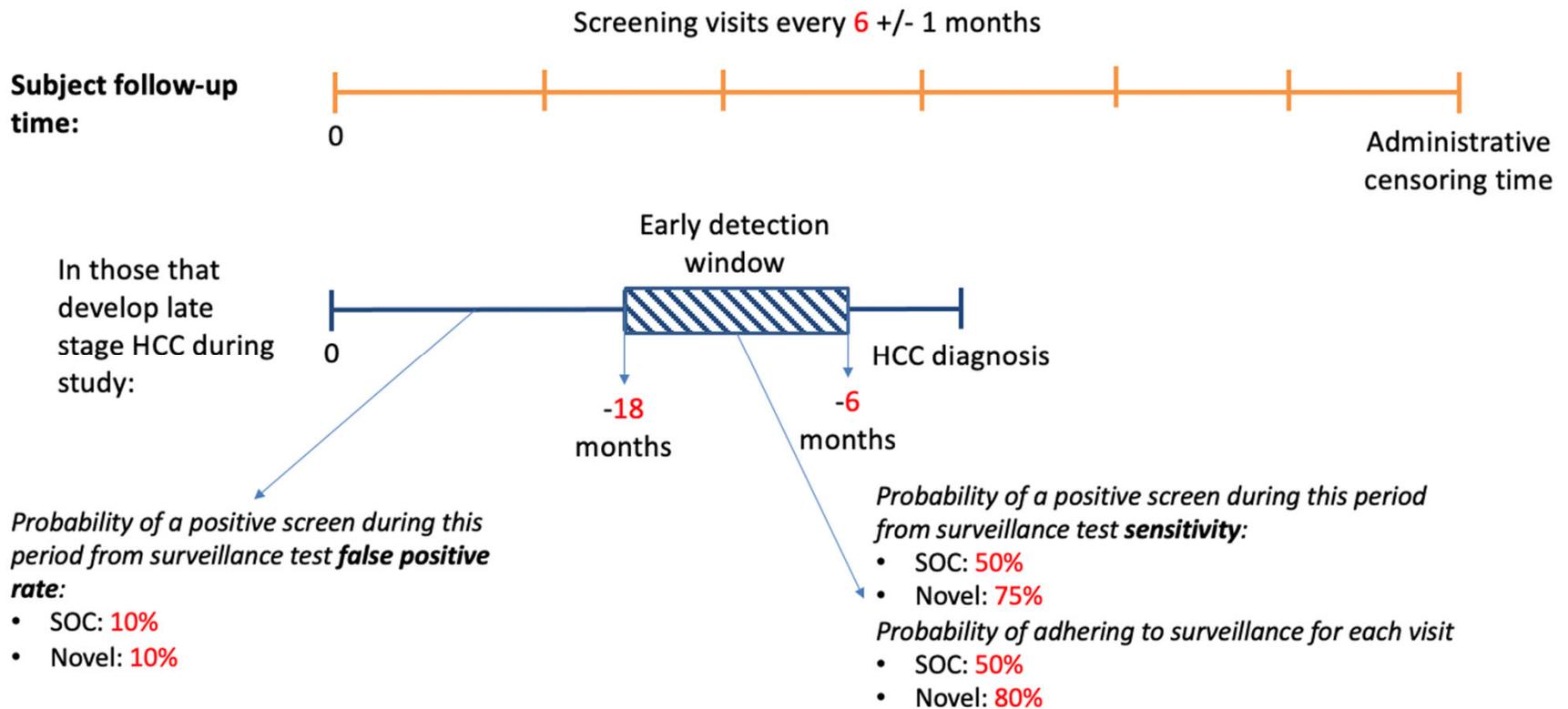
- National, adaptive design that includes Phase 4 and 5 biomarker studies
 - Transition to Phase 5 if meets endpoint



National Liver Cancer Surveillance Trial: Patient course



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National Liver Cancer Surveillance Trial: Phase IV endpoints

- Positive predictive value vs. stage migration
 - **Positive predictive value** = $TP / (TP + FP)$
 - True positives assessed at last screening visit prior to HCC diagnoses whereas false positives assessed at earlier visits among HCC patients and anytime among non-HCC patients
 - **Stage migration** – proportion of early stage diagnosis
- Study will assess Phase V endpoints if we reject the null hypothesis of no difference between the two arms at the interim analysis.

National Liver Cancer Surveillance Trial: Phase V endpoints

- Time from HCC diagnosis to death
 - Increased risk of lead time bias, particularly if may be indolent
- Time from randomization to all-cause death in all patients
 - Concerns about required sample size
- Time from randomization to HCC-related death in all patients
 - Competing risk analysis for death from other causes
- Harms (physical, financial, psychological)
- Power calculations assume interim analysis for phase IV at year 4

National Liver Cancer Surveillance Trial: Phase IV Trial: endpoints

	Null (no difference) (n=8000)	Alternative (difference) (n=8000)	Anticipated situation (n=8000)
Ultrasound and AFP			
Sens/ spec/ adherence	50% / 90% / 50%	50% / 90% / 50%	50% / 90% / 50%
GALAD			
Sens/ spec/ adherence	50% / 90% / 50%	85% / 90% / 90%	70% / 90% / 80%
Positive predictive value	Type I error interim analysis 45% and final analysis 12.5%		
Probability terminate phase IV	58.7%	18.4%	29.8%
Power for time for HCC-related and all death in all patients	5.0% and 4.7%	66.4% and 29.1%	49.5% and 20.5%
Proportion early stage	Type I error interim analysis 25% and final analysis 17.5%		
Probability terminate phase IV	76.8%	0%	0%
Power for time for HCC-related and all death in all patients	5.0% and 5.2%	87.7% and 42.5%	80.5% and 38.1%

National Liver Cancer Surveillance Trial: Recommended endpoints

- Phase IV trial primary endpoint: Stage migration
- Phase V Trial primary endpoint: Reduction of HCC-related mortality in all patients
- Co-primary endpoint: Screening-related harms (physical, financial, psychological)
 - Secondary endpoints: Utilization, stage migration, curative treatment receipt

Summary

- HCC mortality is increasing in the US, largely related to late stage diagnoses
- Despite having an identifiable at-risk population, current HCC surveillance strategies are suboptimal with low sensitivity for early detection
- EDRN has identified several promising biomarkers, which are undergoing phase III evaluation
- A clinical utility trial using an adaptive phase IV-V design is feasible and would be a significant contribution to HCC management