

# Screening for Hepatocellular Carcinoma

**Jon Gerry, MD FACS**

**The Oregon Clinic, Center for Advanced Surgery  
Hepatobiliary and Pancreas Surgery**

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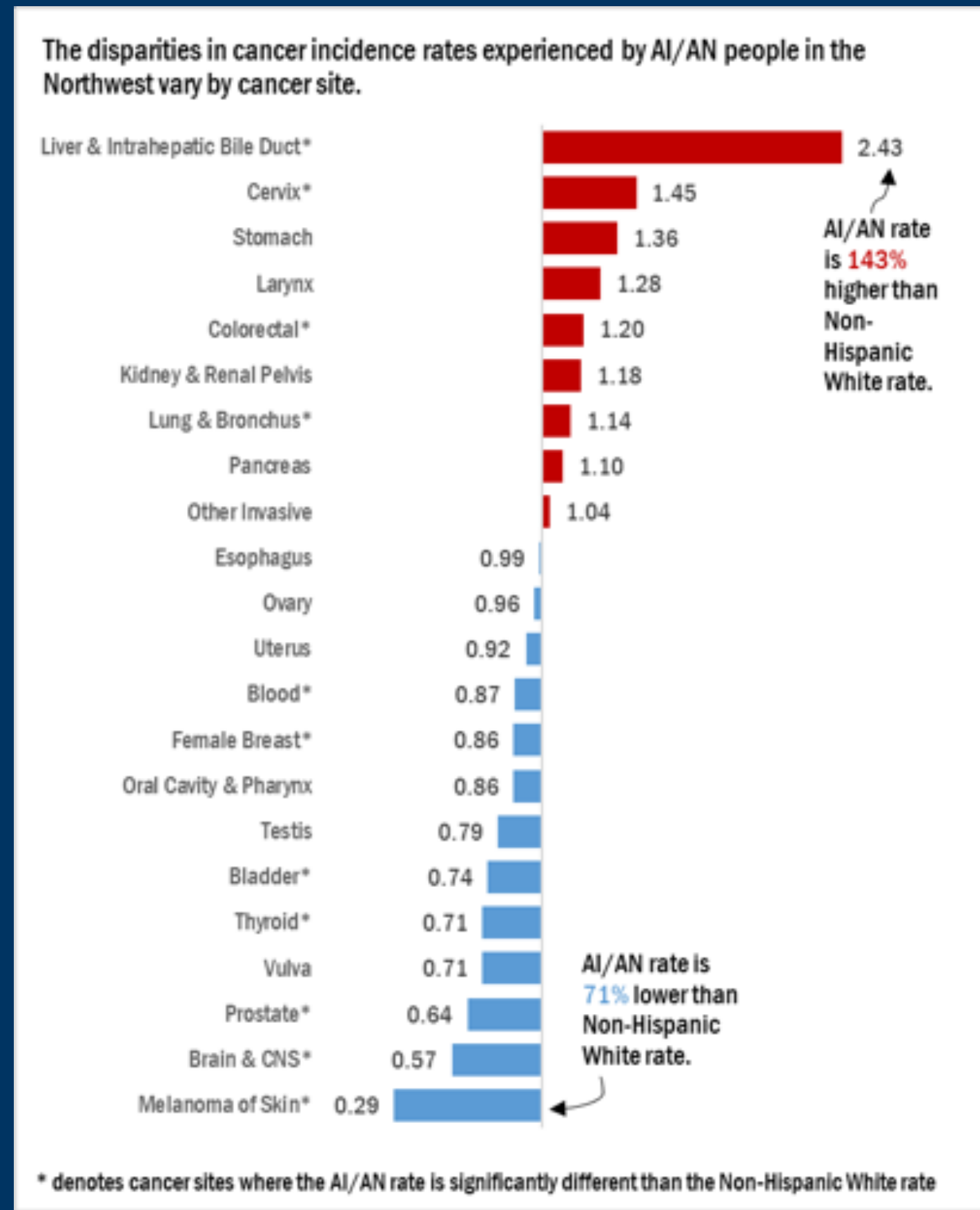
# Hepatocellular Carcinoma (HCC) is an emerging public health concern

In the US, HCC is the only cancer that has increased in incidence from 1975 to 2012, in both men in women, with increased mortality (about 6.5 per 100,000)

Estimate HCC will be 3rd leading cause of cancer-related death in US by 2035

5-year survival is still poor, around 20%, only esophageal and pancreas cancer worse

# Hepatocellular Carcinoma (HCC) is a significant cancer for AI/AN people

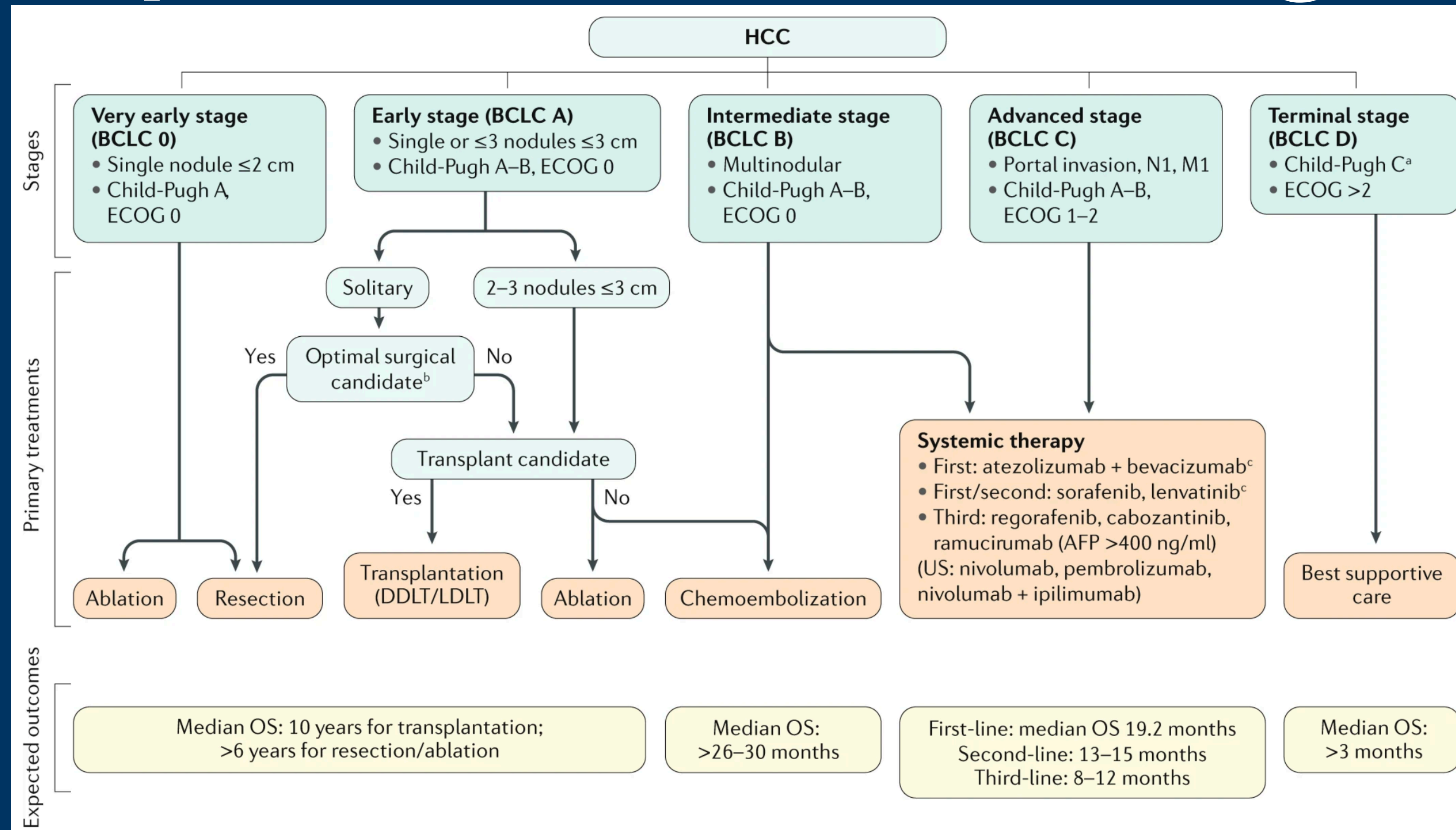


## Cancer incidence for AI/AN People by sex, Northwest region, 2013-2017

Rank	Males	%	Females	%
1	PROSTATE	15.4%	BREAST	28.3%
2	LUNG & BRONCHUS	13.7%	LUNG & BRONCHUS	13.2%
3	BLOOD	10.9%	COLORECTAL	8.8%
4	COLORECTAL	10.8%	BLOOD	7.4%
5	LIVER & INTRAHEPATIC BILE DUCT	8.1%	UTERUS	6.9%
6	KIDNEY & RENAL PELVIS	6.1%	THYROID	4.6%
7	BLADDER	5.3%	KIDNEY & RENAL PELVIS	3.5%
8	ORAL CAVITY & PHARYNX	4.3%	PANCREAS	2.9%

Courtesy of Sujata Joshi

# Hepatocellular Carcinoma (HCC) is treatable if caught early



# Current Screening for HCC, who?

**Screening if benefit > 0.25 LYG**

**Cirrhosis of any etiology**

**Childs-Pugh A or B cirrhosis or Childs-Pugh C cirrhosis on the transplant waitlist**

**Hepatitis B carriers (without cirrhosis)**

**Asian males over 40, Asian females over 50**

**African or North American Blacks**

**Family history of HCC**

# Current Screening for HCC, who?

**Below calculated threshold for screening**

**Non-alcoholic Fatty Liver Disease (NAFLD) without cirrhosis**

**Hepatitis C without cirrhosis**

**Young hepatitis B carriers**

# Current Screening for HCC, how?

Ultrasound with or without a serum Alpha-fetoprotein (AFP) level

## Ultrasound

**Negative** - no solid lesions are seen

**Indeterminate** - solid lesion seen < 10 mm

**Positive** - solid lesion  $\geq$  10 mm seen

## AFP

**Negative**  $\leq$  20 ng/mL

**Positive** > 20 ng/mL (sensitivity of 60%, specificity of 90%)

# Current Screening for HCC, how?

Screening US every 4-8 months, really every 6 months in practice

CT - no significant change in detection as compared to US

MR – this is more sensitive and specific than US, but costly and time-consuming



# Current Screening for HCC, when?

Screening US every 4-8 months, really every 6 months in practice

510 patients screened at 6 months vs. 139 patients screened at 12 months showed a median survival difference of 40 vs. 30 months when corrected for lead time bias.

There is no difference in outcome with screening done at 3 months vs. 6 months.

# Current Screening for HCC, does it work?

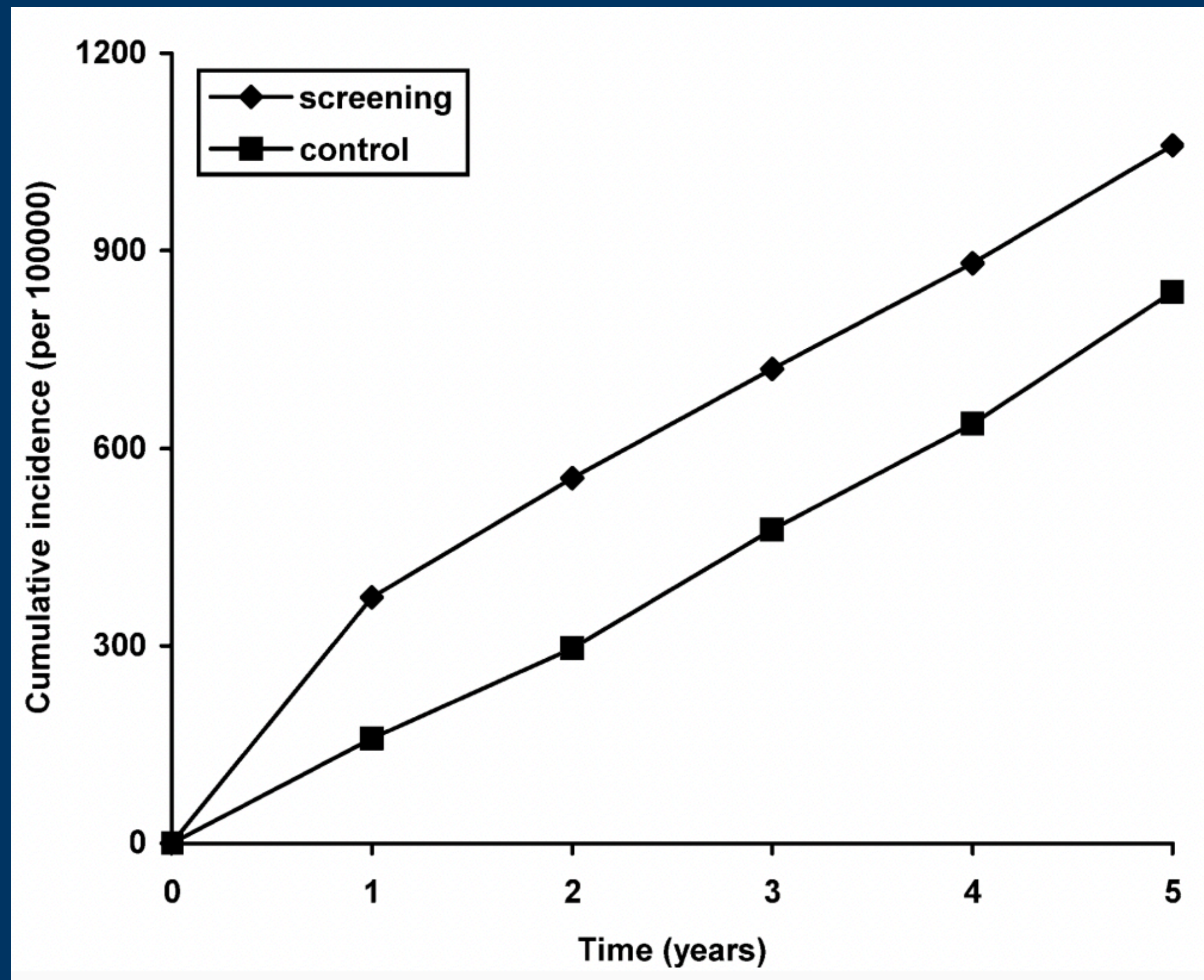
A single RCT demonstrated decreased HCC-related mortality  
China, 2004

19200 HBV infected people 35-59 years old, 9373 randomized to  
screening, 9443 **NOT TOLD** and used as controls for no screening.

Enrolled Jan 1993 to Dec 1995. Mortality measured at Dec 1998.

Screening with Ultrasound and AFP every 6 months

# Current Screening for HCC, does it work?



	Screening group (86)	Control group (67)
<b>Stage<sup>a</sup></b>		
Stage I	52(60.5%)	0(0%)
Stage II	12(13.9%)	25(37.3%)
Stage III	22(25.6%)	42(62.7%)
Small HCC	39(45.3%)	0
<b>Treatment</b>		
Resection	40(46.5%)	5(7.5%)
TACE/PEI	28(32.6%)	28(41.8%)
Conservative treatment	18(20.9%)	34(50.7%)
<b>Survival (%)<sup>b</sup></b>		
1-year	65.9	31.2
2-year	59.9	7.2
3-year	52.6	7.2
4-year	52.6	0
5-year	46.4	0

<sup>a</sup>  $\chi^2 = 61.41, p < 0.01$   
<sup>b</sup> Log-rank  $\chi^2 = 35.50, p < 0.01$

# Current Screening for HCC, does it work?

A meta-analysis of 62 studies from Jan 2014 to July 2020, 15 studies from North America

Pooled association between HCC screening and curative treatment OR (95% CI) 1.83 (1.69-1.97)

Pooled association between HCC and overall mortality OR (95% CI) 0.67 (0.61-0.72)

# Current Screening for HCC, Pitfalls?

## Screening underuse

Retrospective review of patients with cirrhosis who had a diagnosis of HCC from 2011 to 2019

377 total patients

93 (25%) regular screening

161 (43%) inconsistent screening

**123 (33%) no screening**

91% provider failure to recognize liver disease or order screening

8% patient failure to adhere to screening ultrasound appointment

# Current Screening for HCC, Pitfalls?

Poor recognition of viral hepatitis

11488 participants in the National Health Nutrition and Examination Survey 2013-2016.

Chronic hepatitis B infection (34% were aware)

Past hepatitis B infection (12%)

Hepatitis C infection (56%)

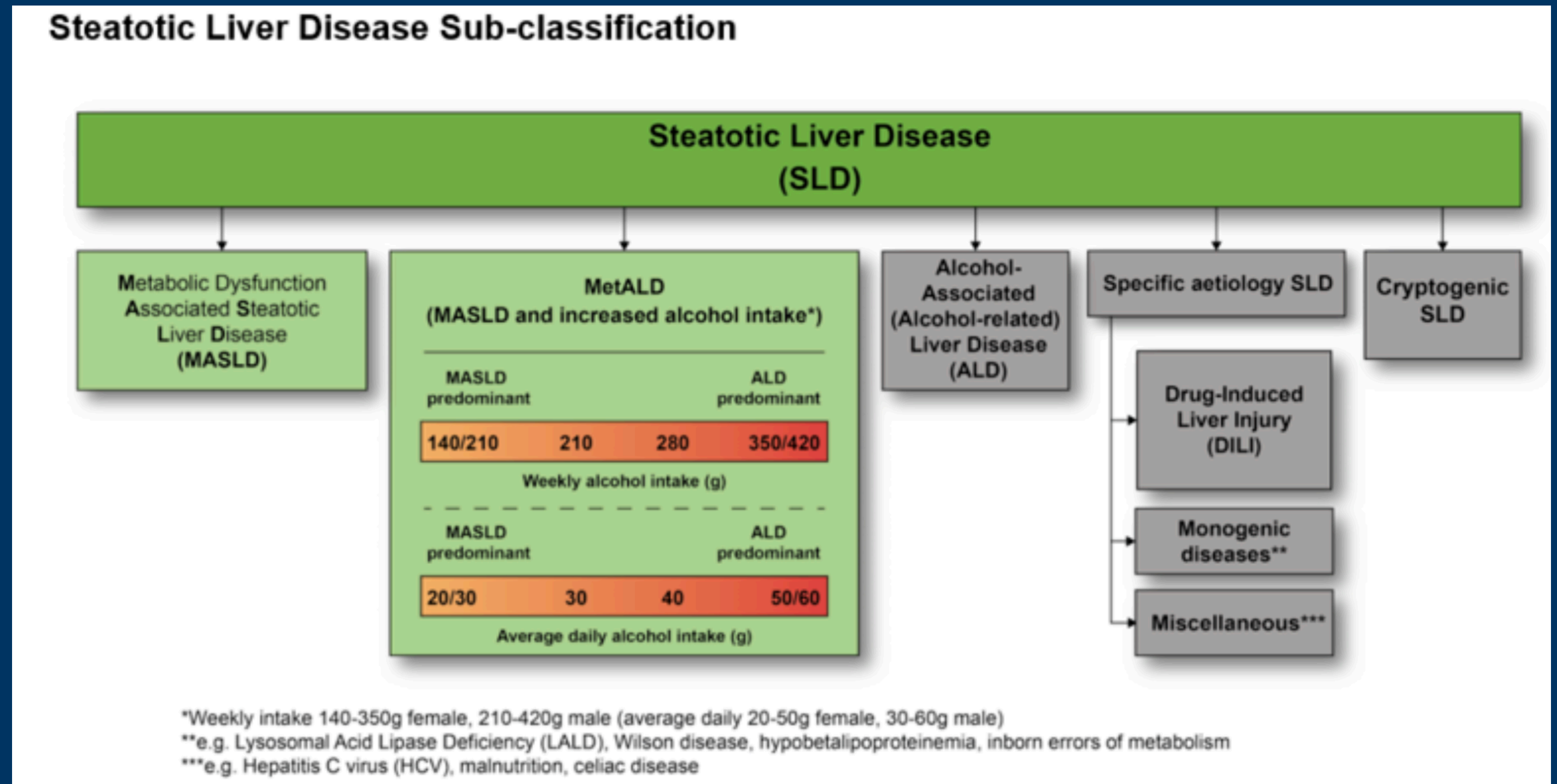
USPSTF recommends universal one-time HCV screen

CDC recommends universal one-time HBV triple test screen

# Current Screening for HCC, Pitfalls?

## NAFLD

30% of the US has NAFLD  
20% of those have NASH



# Current Screening for HCC, Pitfalls?

## Recognition of fibrosis/cirrhosis

1. Liver biopsy is the GOLD standard
2. Non-invasive methods

A - Transient elastography - Measures velocity of a low-frequency wave through the liver. It can be done in less than 5 minutes in clinic with short learning curve.

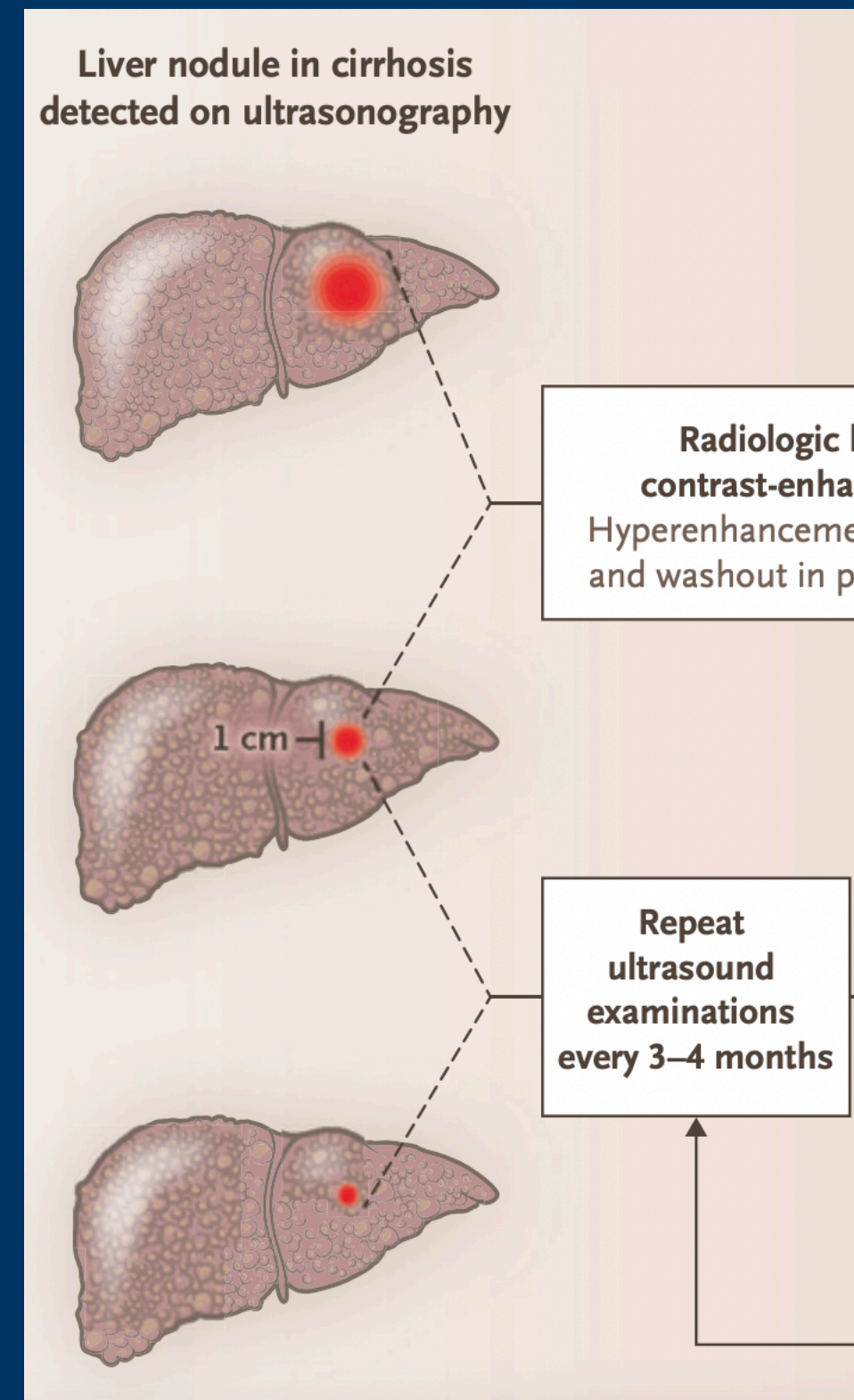
B - Serum biomarkers - Fibrotest, Enhanced Liver Fibrosis score, FibroMeter NAFLD, FIB-4, AST to platelet ratio index



# Current Screening for HCC, Pitfalls?

About 1/2 of small HCC are **MISSED** by screening US

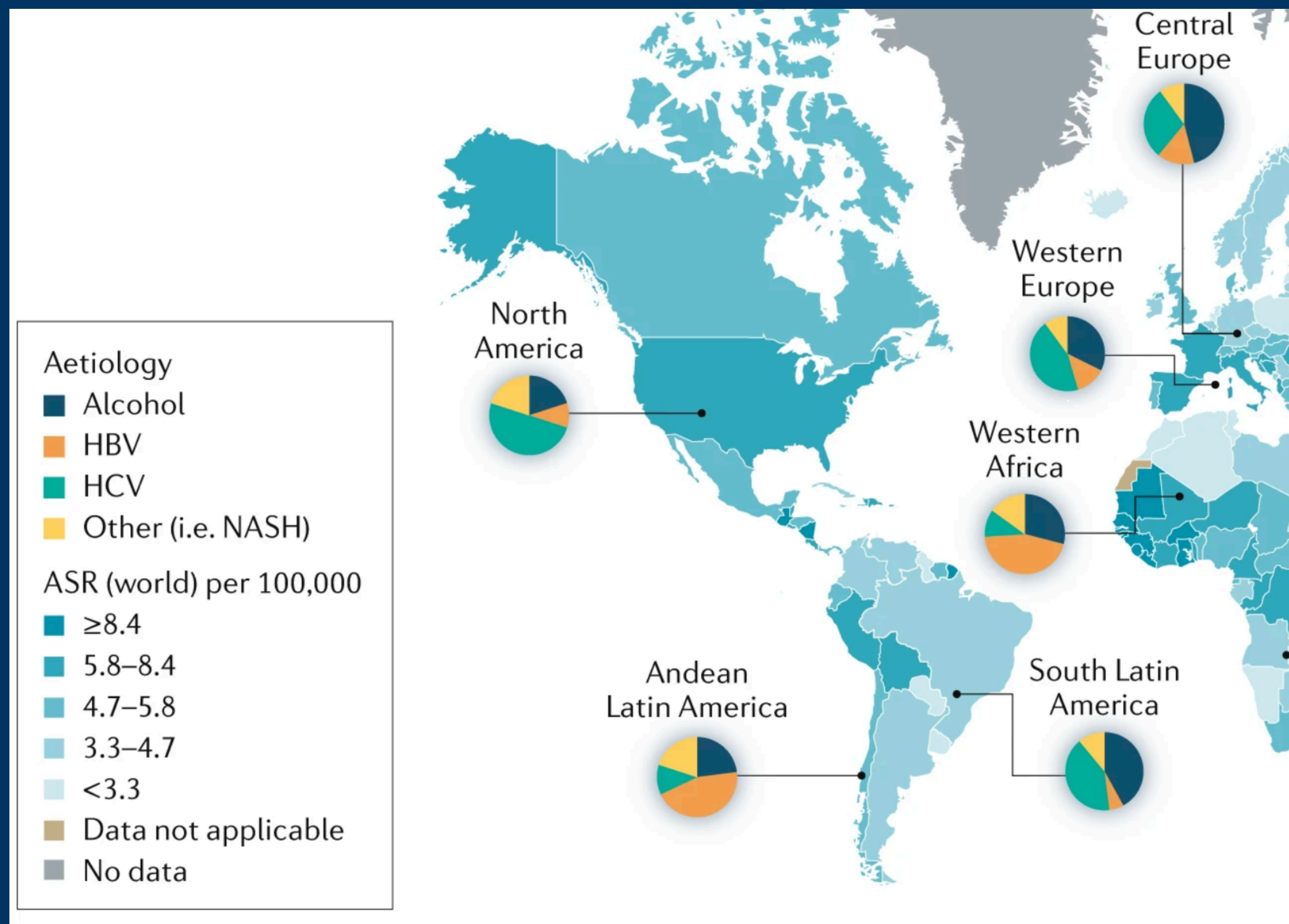
- Nodules all over, what is an early tumor?
- NASH obscures deep views
- obesity similarly obscures views
- operator dependent



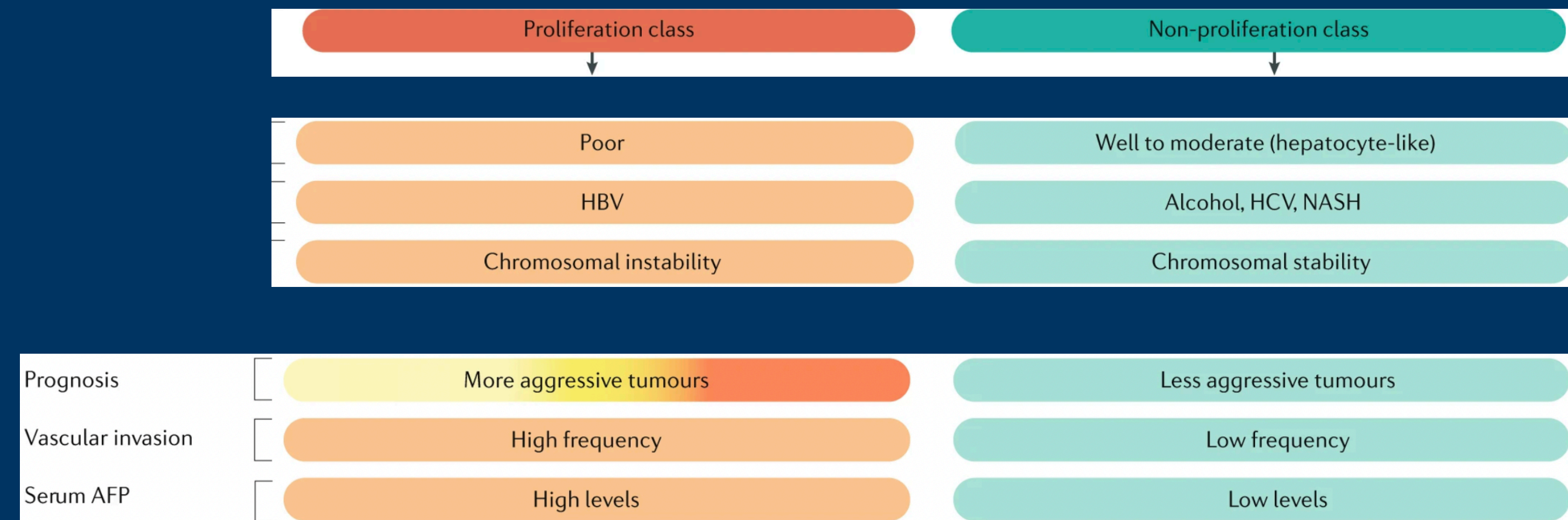
Appearance	Ishak stage: categorical description	Ishak	Metavir
	No fibrosis (normal)	0	F0
	Fibrosis expansion of some portal areas ± short fibrous septa	1	F1
	Fibrosis expansion of portal areas ± short fibrous septa	2	F2
	Fibrosis expansion of most portal areas with occasional portal to portal (P-P) bridging	3	
	Fibrosis expansion of portal areas with marked portal to portal (P-P) bridging as well as portal to central (P-C)	4	F3
	Marked bridging (P-P and / or P-C) with occasional nodules (incomplete cirrhosis)	5	
	Cirrhosis, probable or definite	6	F4

# Current Screening for HCC, Pitfalls?

In the US a low percentage of HCC express high levels of AFP



## Two classes of HCC



# Current Screening for HCC, Pitfalls?

## Unanticipated harms of screening

680 patients with cirrhosis with screening over a 3-yr period, ~10% had harms related to repeated CT/MR (9.7%) or biopsy (0.4%)

999 patients followed for median 2.2 years, 69 (27%) had HCC, 187 (73%) had an indeterminate nodule, 32 (17%) experience harms by four or more cross sectional imaging studies or biopsy

# Current Screening for HCC, Pitfalls?

## Unanticipated harms of screening

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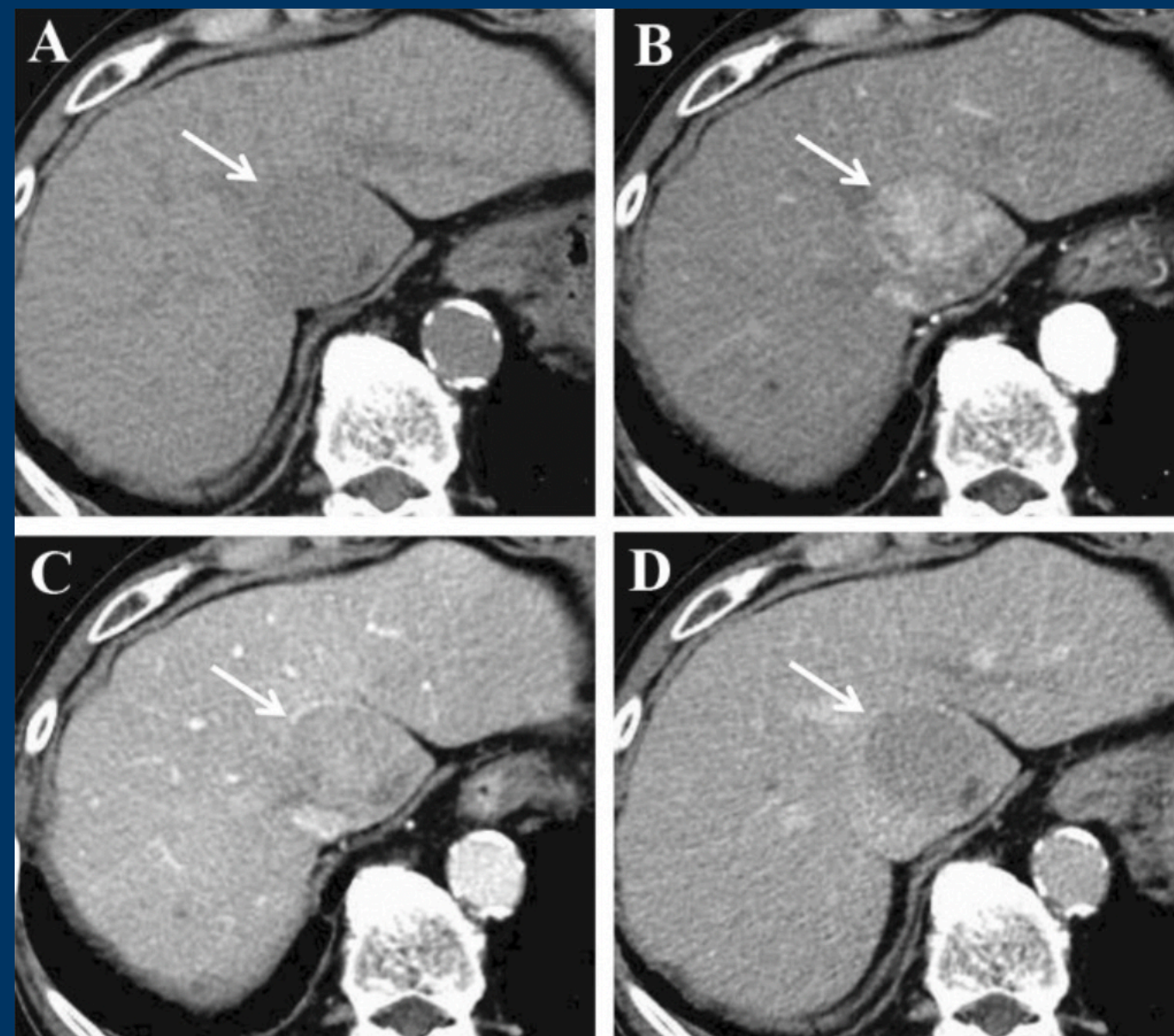
# Current Screening for HCC, Pitfalls?

## Screening fatigue

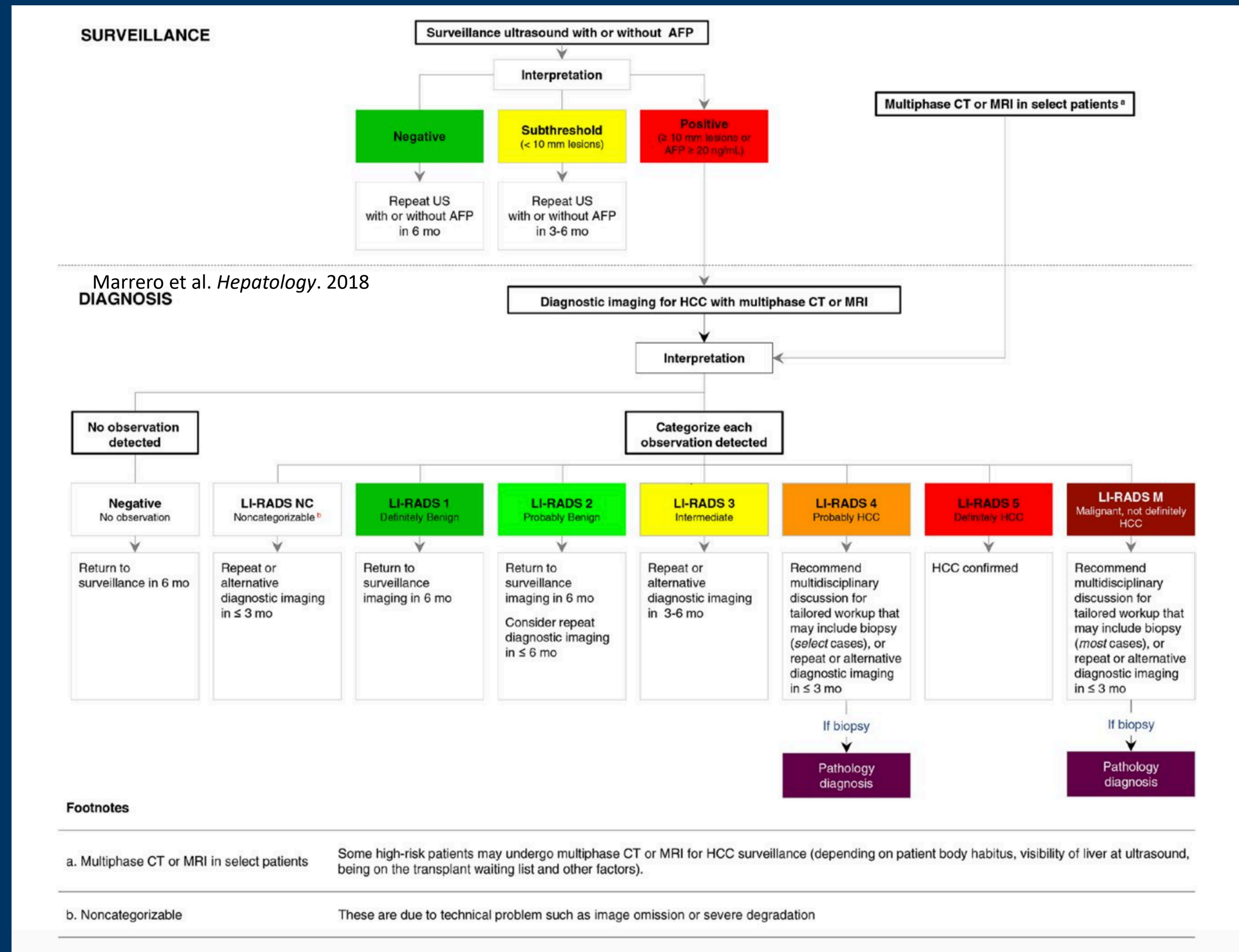
Phenomenon of stopping or interrupting screening due to barriers such as socioeconomic factors or healthcare literacy

# Current Screening for HCC, Positive finding?

Positive screen leads to diagnostic imaging with  
CT or MRI



# Current Screening for HCC, Positive finding?



Marrero et al. *Hepatology*. 2018

**Thanks**