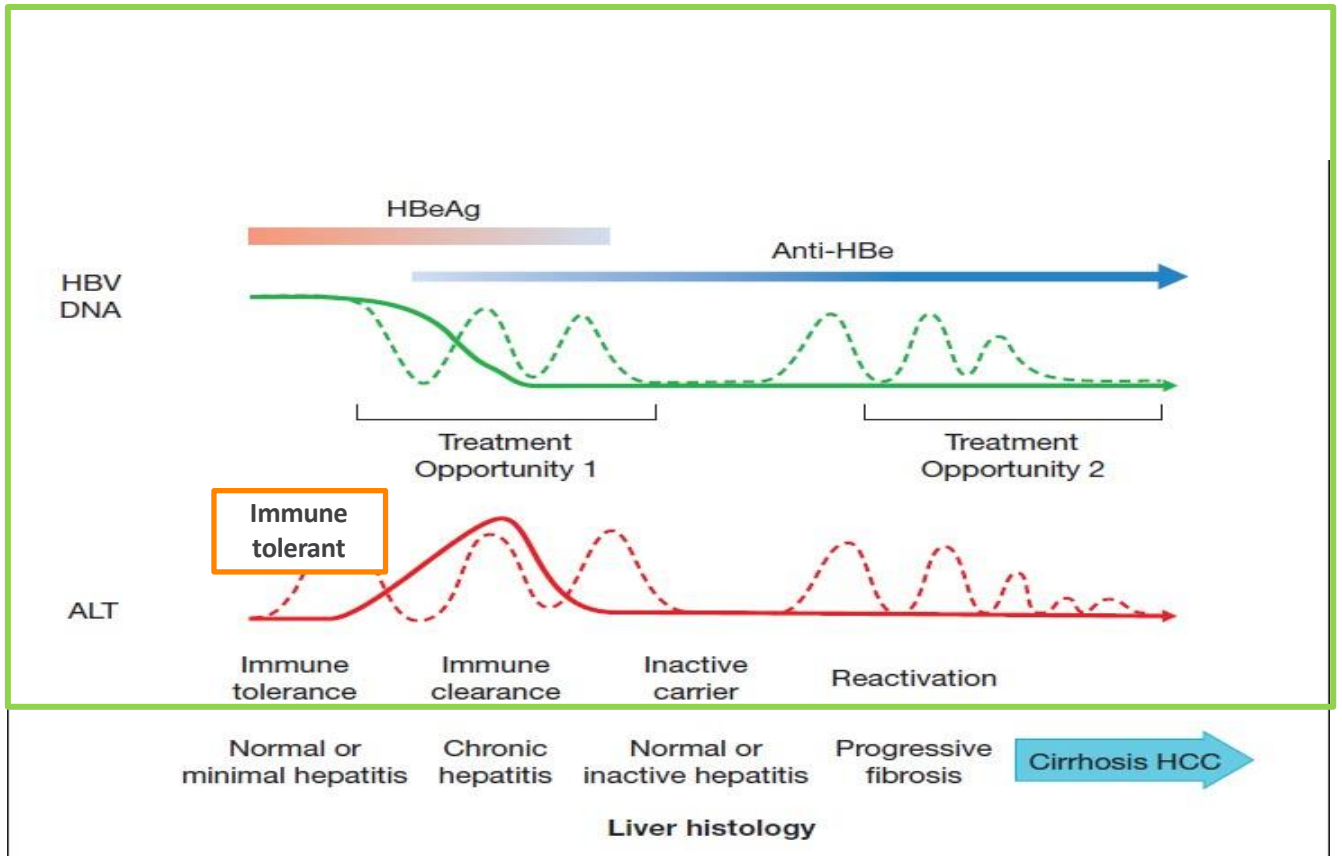
AASLD 2016

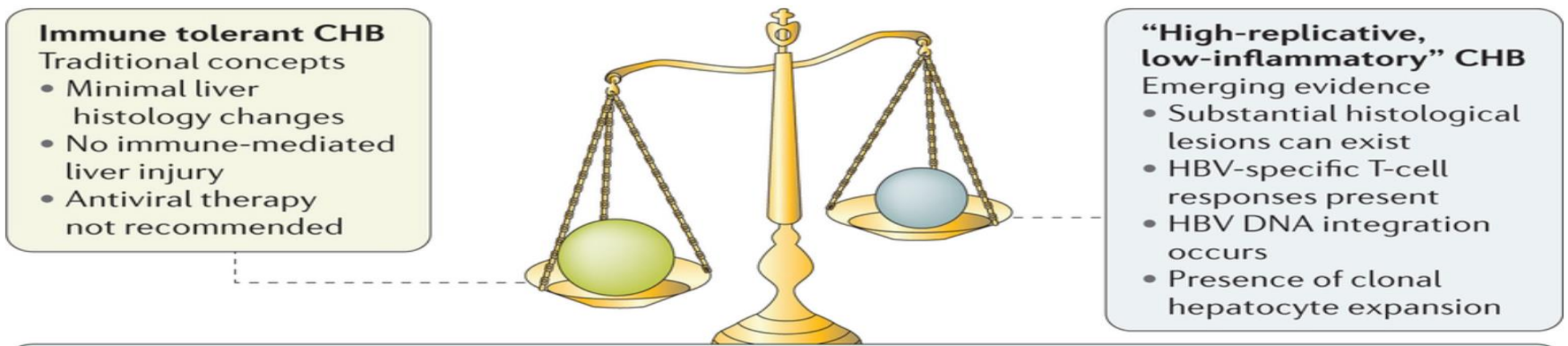
Immune tolerant phase HBV

NAFLD diagnostic

HCC



Modified from Chan HLY and Wong VWS. Hepatitis B. In Zakim and Boyers's Hepatology 2012



Nature Reviews | Gastroenterology & Hepatology

AASLD recommends against antiviral therapy for adults with immune tolerant CHB

- No studies demonstrating antiviral is beneficial in reducing rates of HCC, cirrhosis and liver-related death in patients with immune tolerant CHB

- Potential harm, including cost, antiviral drug side effects and development of resistance, outweighs benefits

Terrault N, et al. Hepatology 2016;63:261-83

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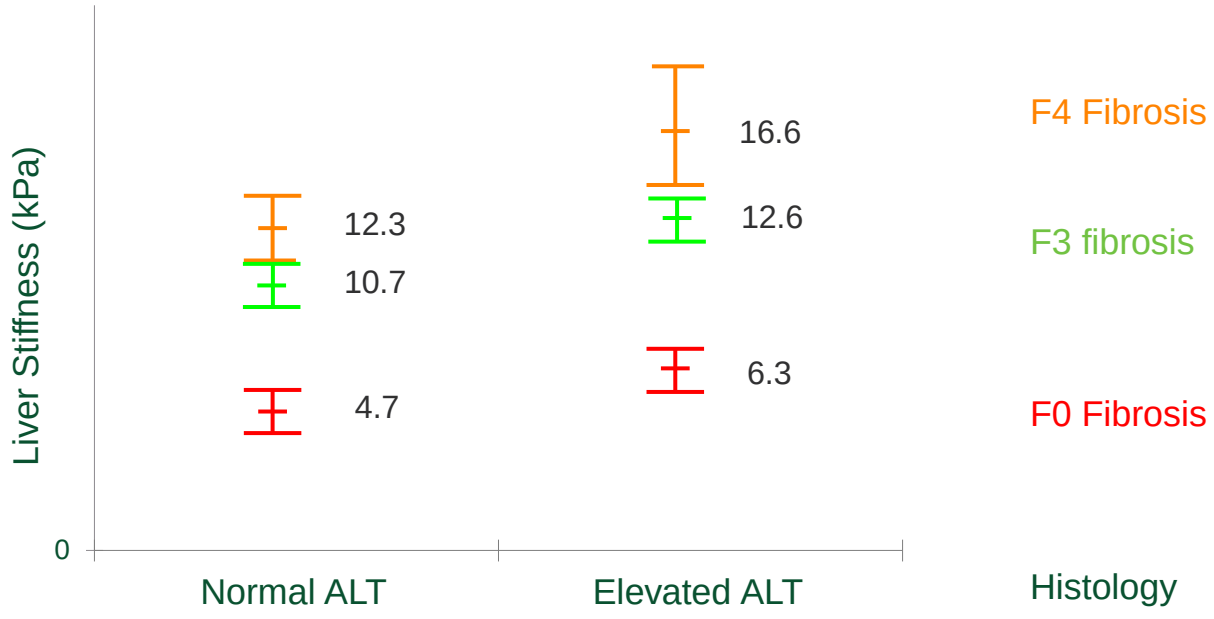
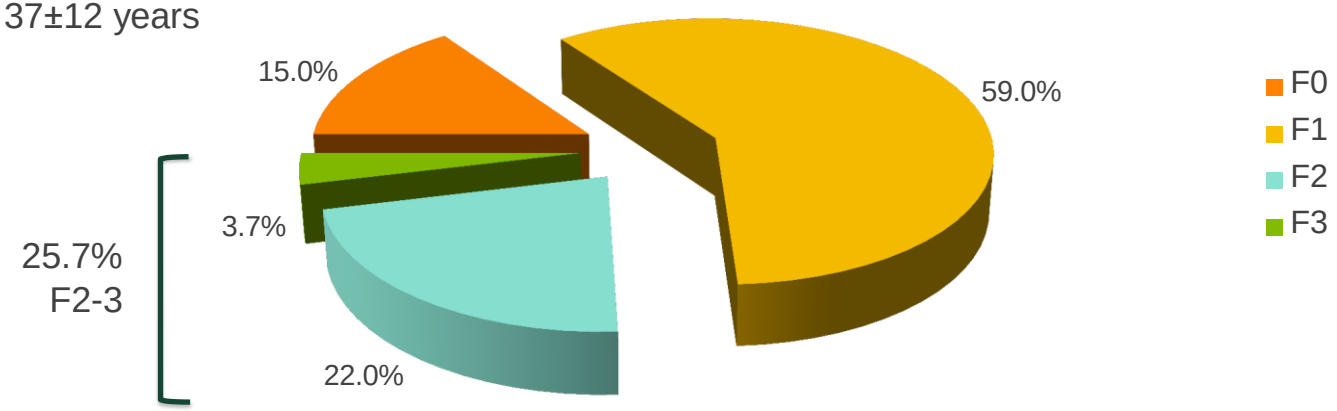
Liver stiffness is least affected if serum ALT is normal on elastography



Chan HLY, et al. J Viral Hepat 2009;16:36-44

Histology series in Asian-Americans with positive HBeAg, normal ALT (AASLD criteria) and high HBV DNA (mean 7.7 logs copies/ml)

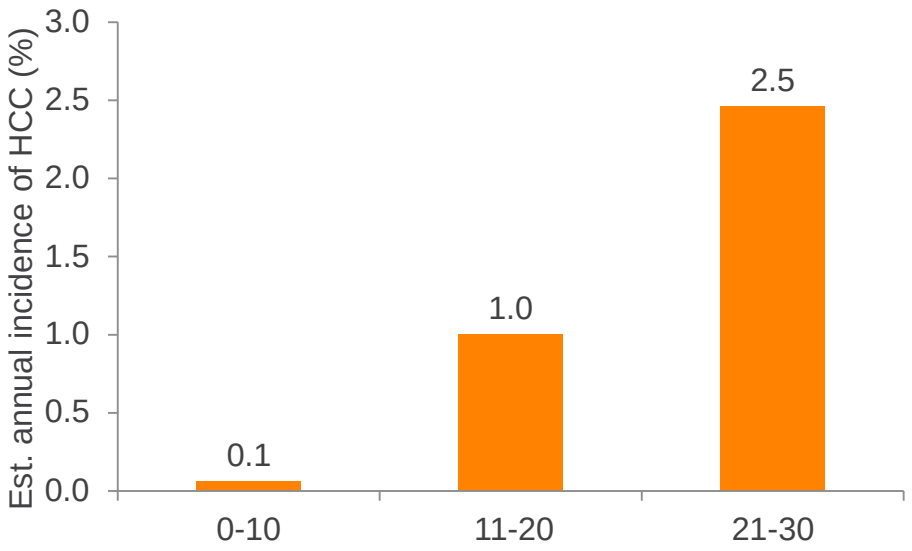
27 patients
Age 37±12 years



Nguyen MH, et al. Am J Gastroenterol 2009;104:2206-13

Factors	Score
Age	
> 50 years	+10
≤ 50 years	0
Albumin	
≤ 35g/l	+1
> 35g/l	0
HBV DNA	
> 200,000 IU/ml	+5
≤ 200,000 IU/ml	0
Liver stiffness	
≤ 8.0 kPa	0
8.1-12.0 kPa	+8
> 12.0 kPa	+14

1555 CHB patients (25% HBeAg positive, 66% normal ALT; 38% received antiviral therapy) FU 69±9 months
38 patients developed HCC



Modified from Wong GL, et al. J Hepatol 2014;60:339-45

Start Treatment for HBeAg positive patients

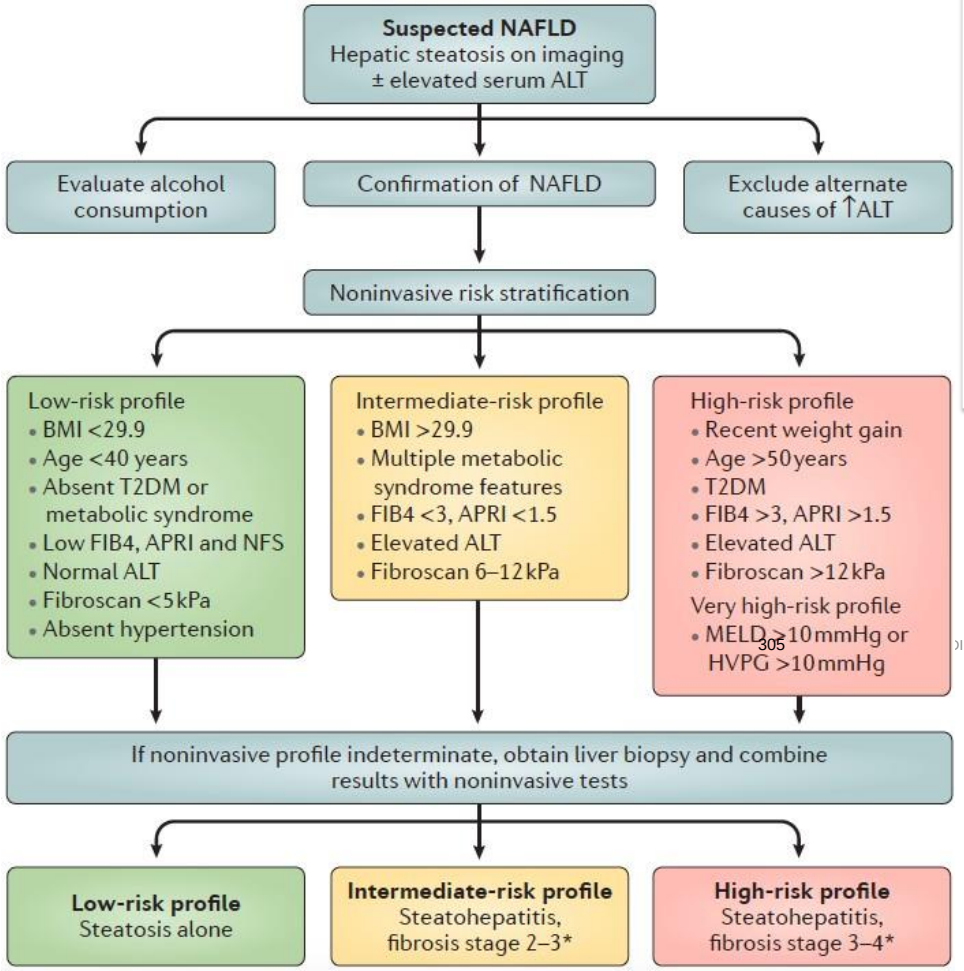
- ALT > 2x ULN and HBV DNA >20000 IU/ml
- ALT >1-2x ULN, HBV DNA >2000 IU/ml with moderate/severe inflammation or significant liver fibrosis
- Compensated liver cirrhosis with detectable HBV DNA (HBV DNA >2000 IU/ml or elevated ALT with detectable HBV DNA in APASL guideline)
- Decompensated liver cirrhosis with detectable HBV DNA

Terrault N, et alHepatology 2016;63:261-83;
EASL. J Hepatol 2012;57:167-85;
Sarin S, et al. Hepatol Int 2016;10:1-98.

Summary

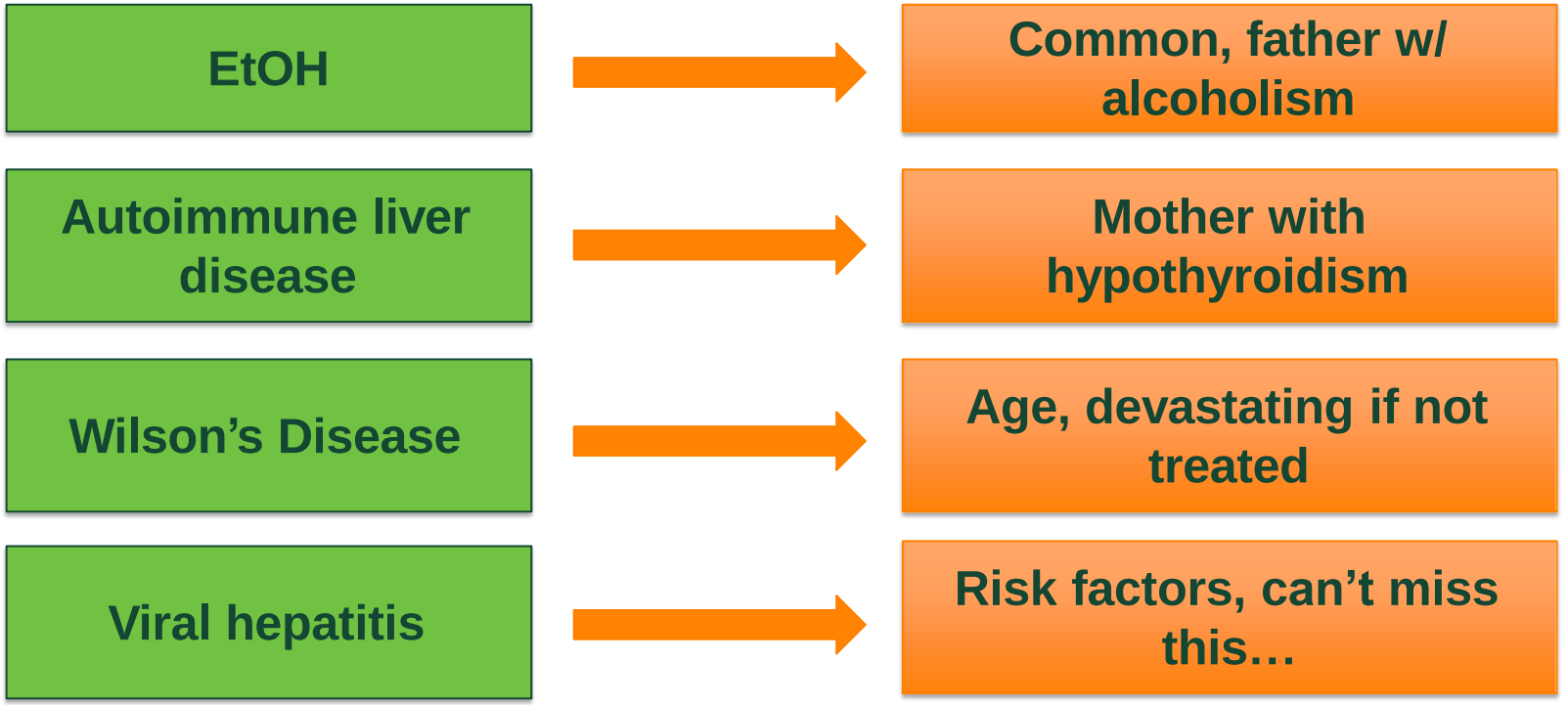
- For HBeAg positive patients with normal ALT and high viral load, liver fibrosis assessment is needed if the patient is older or has family history of HCC

- For immune tolerant patients (with no significant fibrosis), the risk of disease progression is small. Complete viral suppression by NA is difficult and off- treatment relapse is frequent. Evidence for long-term benefit of treatment is lacking. Regular monitoring is therefore recommended.



Rinella and Sanyal, Nature Reviews Gastroenterology and Hepatology 2016

What diseases need to be excluded in this patient?



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Wilson's disease

- Coombs – ve hemolytic anemia
- Hypouricemia
- Low alkaline phosphatase
- High bilirubin Alk phos ratio

Diagnosis of Wilson Disease

	Normal	Wilson's
○ Serum Copper (micgm/dl)	80-140	<80
○ Urine Copper (mcg/24 hr)	<40	>100
○ Serum ceruloplasmin (mg/dl)	20-40	<20
○ Hepatic copper (micg/gm dw)	15-50	250-3000

- Serum Free-Copper Concentration
  = Total Cu - Ceruloplasmin X 3.15
  - Free Cu usually < 100 μg/L
  - Wilson's Disease: Free Cu >200 μg/L

LAB TRACKER - COPPER CALCULATOR

Serum Copper (mcg/dl)	Ceruloplasmin (mg/dl)	Non-Ceruloplasmin Copper	
			Calculate

Serum Copper (micromoles/liter)	Ceruloplasmin (mg/L)	Non-Ceruloplasmin Copper	
			Calculate

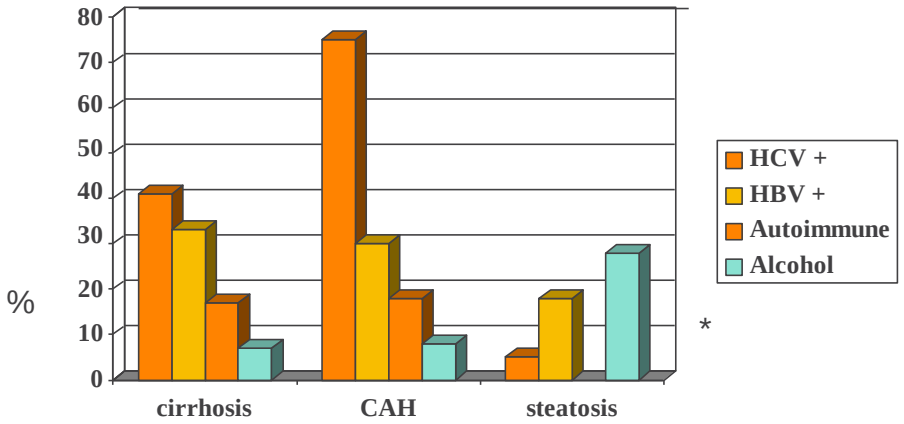
Copper Concentration (micromoles/liter)	Volume (liters)	Copper per 24 hours (micrograms)	
			Calculate

Copper concentration (mcg/dl)	Volume (liters)	Copper per 24 hours (micrograms)	
			Calculate

Copper concentration (mcg/liter)	Volume (liters)	Copper per 24 hours (micrograms)	
			Calculate

Zinc concentration (mcg/liter)	Volume (liter)	Zinc per 24 hours (micrograms)	
			Calculate

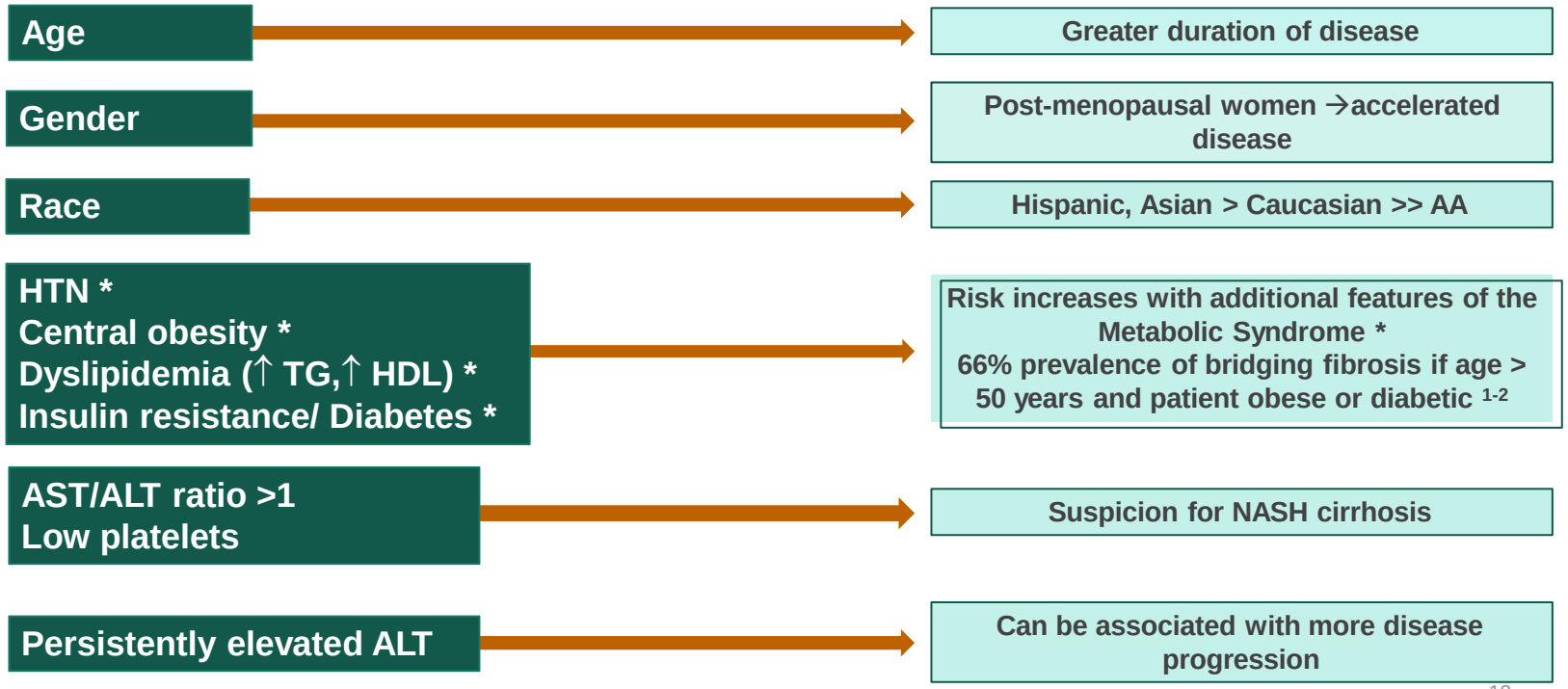
Co-existent liver disease in A_1AT



* Prior exposure PiZZ or PiZ

Propst T et al: Ann Intern Med 1992;117:641-5

Clinical predictors of NASH



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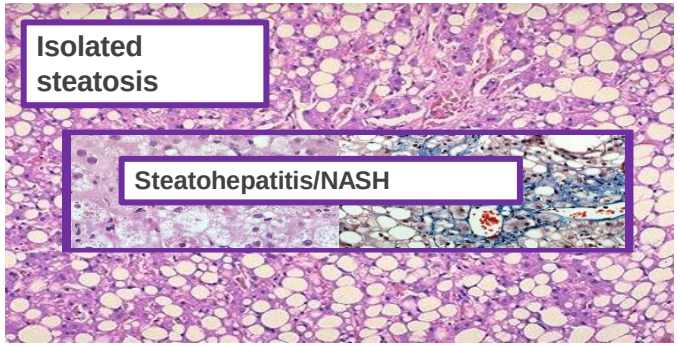
*** Based on ATP III criteria**

[1] Angulo, *Hepatology* 1999; [2] Ratziu, *Gastroenterology* 2000

The role of liver biopsy



- **Making diagnosis of NASH** (surrogates insufficient)
  - **Initiate drug therapy**
  - Assess prognosis:
    Liver, cardiovascular etc.
- **Stage fibrosis**
  - If MRE, Fibroscan® or serum markers indeterminate
- **Rule out concomitant liver disease**
  - Autoimmune, Wilsons, DILI
  - Iron overload

Association between NAFLD/NASH and DM is bidirectional

Diabetics have…

- Increased risk of dying from cirrhosis
- 3x risk of chronic liver disease, mostly NAFLD
- Increased risk of advanced liver disease
- Increased risk of NASH with family history of DM

Those with NAFLD/NASH have…

- Approximately 4-fold increased risk of DM
- More than additive risk when added to other risks:
  - **Obesity, NAFLD, IR each:** 2x risk of DM
  - **All 3:** 14x

de Marco R, et al. The Verona Diabetes Study. *Diabetes Care* 1999; Campbell PT et al. *Diabetes Care* 2012; Zoppini et al. *AJG* 2014; Balkau et al *BMC Gastro* 2010; Angulo, *Hepatology* 1999; Ratziu, *Gastroenterology* 2000; Loomba et al. *Hepatology* 2012

Endocrinol Metab 2013; Ekstedt et al *Hepatology* 2006

Kasturiratne et al. JGK 2013; Shibata et al. *Diabetes Care* 2007; Sung KC,et al. *J Clin*

NAFLD - imaging

- Ultrasound
- TE Transient Elastography
- MRI PDFF - proton density fat fraction
- MRE - elastography

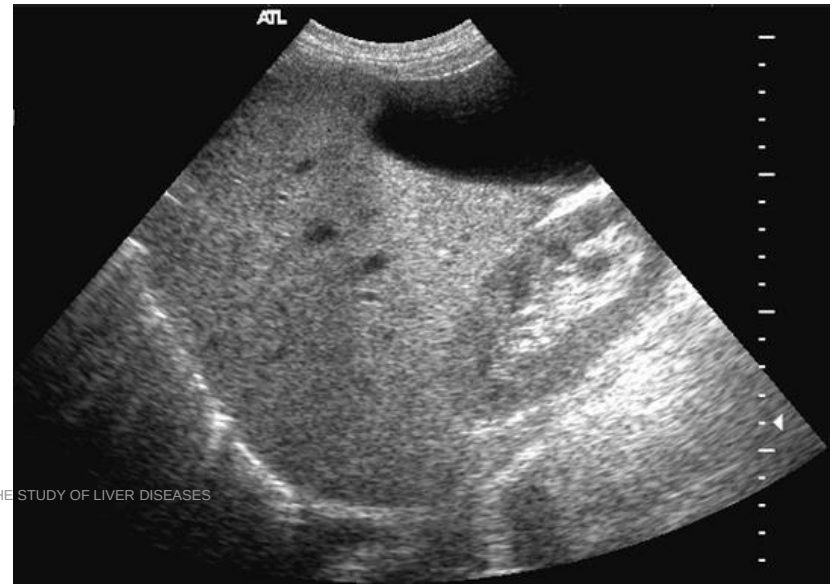
How reliable is ultrasound in diagnosis of NAFLD?

Findings:

- Bright liver
- Echotexture increased compared to kidney
- Vascular blurring

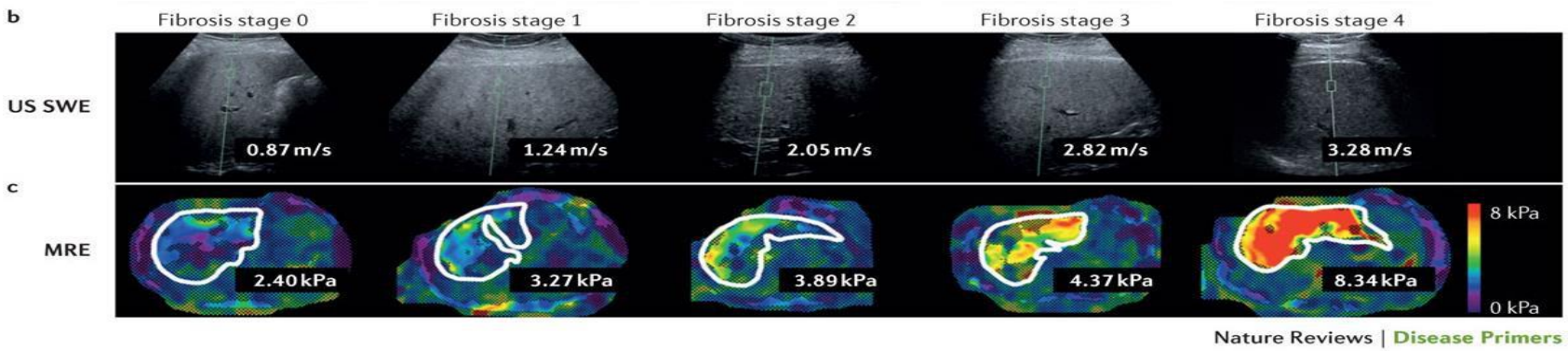
Considerations:

- Changes consistent with NAFLD may not be detected if <30% of liver has fat
- * US findings for fatty liver cannot be distinguished from those of early cirrhosis



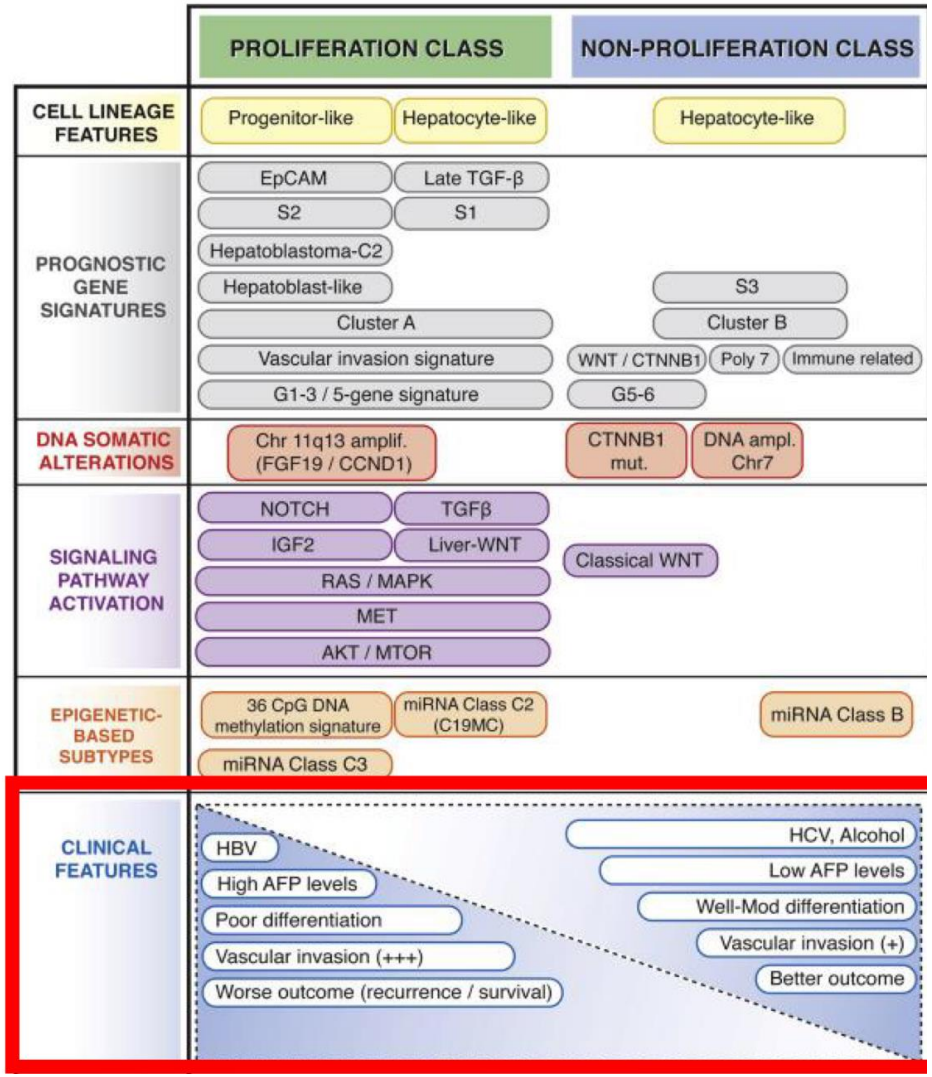
How reliable is non-invasive assessment of liver fibrosis in NAFLD?

- Laboratory tests
  - Calculated from clinical and lab parameters
  - Serum tests reflecting activation of the fibrogenic process
- Imaging techniques



Summary: Molecular Classification HCC

Zucman-Rossi *et al.*, GE 2015; 149: 1226



EASL
The Home of Hepatology

BEST OF EASL
Addis Abeba

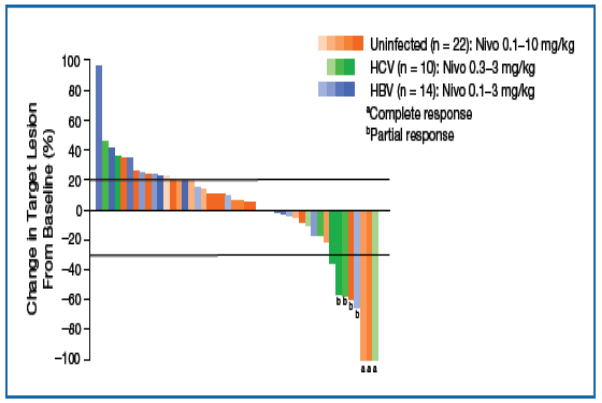
Nivolumab PI/II, CA209-040: Response

El-Khoueiry et al., ASCO 2015. Abstract LBA101, ASCO 2016, P4012

- PD-1 and PD-L1 overexpression associated with poor HCC prognosis
- HBV & HCV infections associated with PD-1 upregulation and immune exhaustion
- Nivolumab: fully human IgG4 antibody selectively inhibiting interaction PD-1 – PD-1L

Best Response in Evaluable Pts, %	Uninfected (n = 21)	HCV Infected (n = 11)	HBV Infected (n = 10)	Total (N = 42)
ORR	14	36	10	**19**
▪CR	10	0	0	5
▪PR	5	36	10	14
▪SD	48	45	50	48
▪PD	38	18	40	33

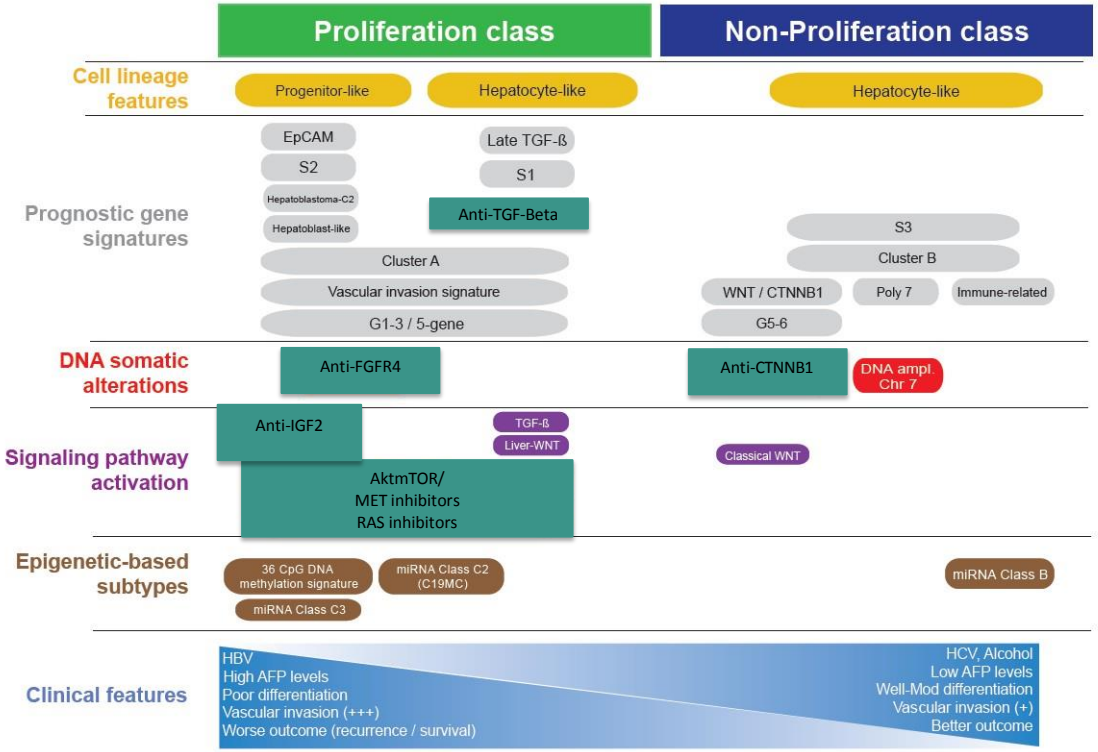
Figure 2. Maximal change in target lesions from baseline



- DoR in 8 pts with objective response: ~ 3-18+ mos
- Duration of SD in 20 evaluable pts: 1.1-17.3 mos
- Preliminary 12-mo OS: 62%

- 12-mo OS in phase III regorafenib trial after sorafenib failure: ~ 45%

Molecular classification of HCC



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Zucman J et al, Gastroenterology 2015

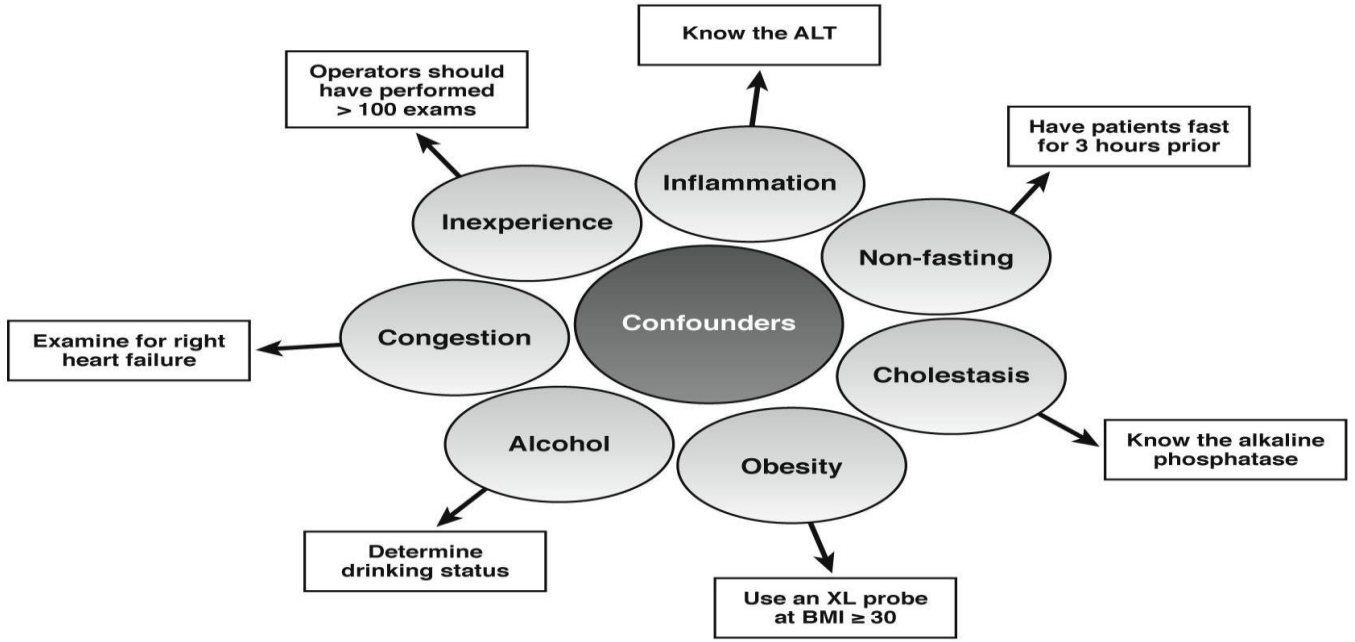
Fibrosis progression is uncommon in immune tolerant CHB

- 48 immune tolerant patients with paired liver biopsy at 5 years
- 3 (6.8%) patients had fibrosis progression
- 4 patients with F1 fibrosis at baseline had fibrosis regression to F0

Fibrosis stage	Initial liver biopsy	FU liver biopsy	P value
F0	15	16	0.58
F1	33	31	
F2	0	1	

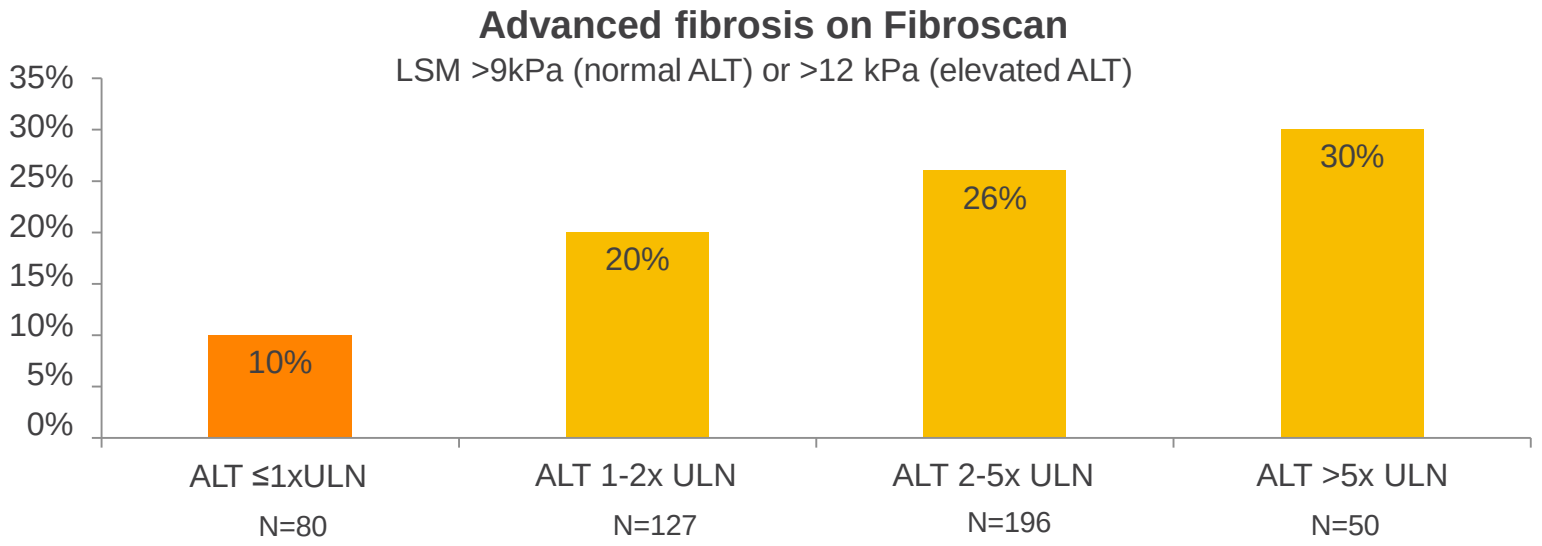
Hui CK, et al. Hepatology 2007;46:395-401

Non-invasive assessment of liver fibrosis: Confounders



Tapper et al. CGH 2015

10% of HBeAg positive patients with normal ALT (AASLD criteria) have advanced fibrosis



Wong GL, et al. Clin Gastroenterol Hepatol 2009;7:227-233

- **REVEAL-HBV cohort**

  - 3653 Taiwanese patients followed for 11.4 years
  - Increased risk of HCC with HBV DNA level >2000 IU/ml
  - Age <30 = 0%, 30-39 = 33%
  - HBeAg positive = 15%
  - ALT normal (<45 U/L) = 94%
  - Liver cirrhosis = 2%

- Most patients were older HBeAg-negative inactive CHB but NOT immune tolerant patients

Chen CJ et al. *JAMA.* 2006;295:65-73