

# NAFLD and cancer prediction: mechanistic and clinical implication

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**Mount  
Sinai**

# Disclosure

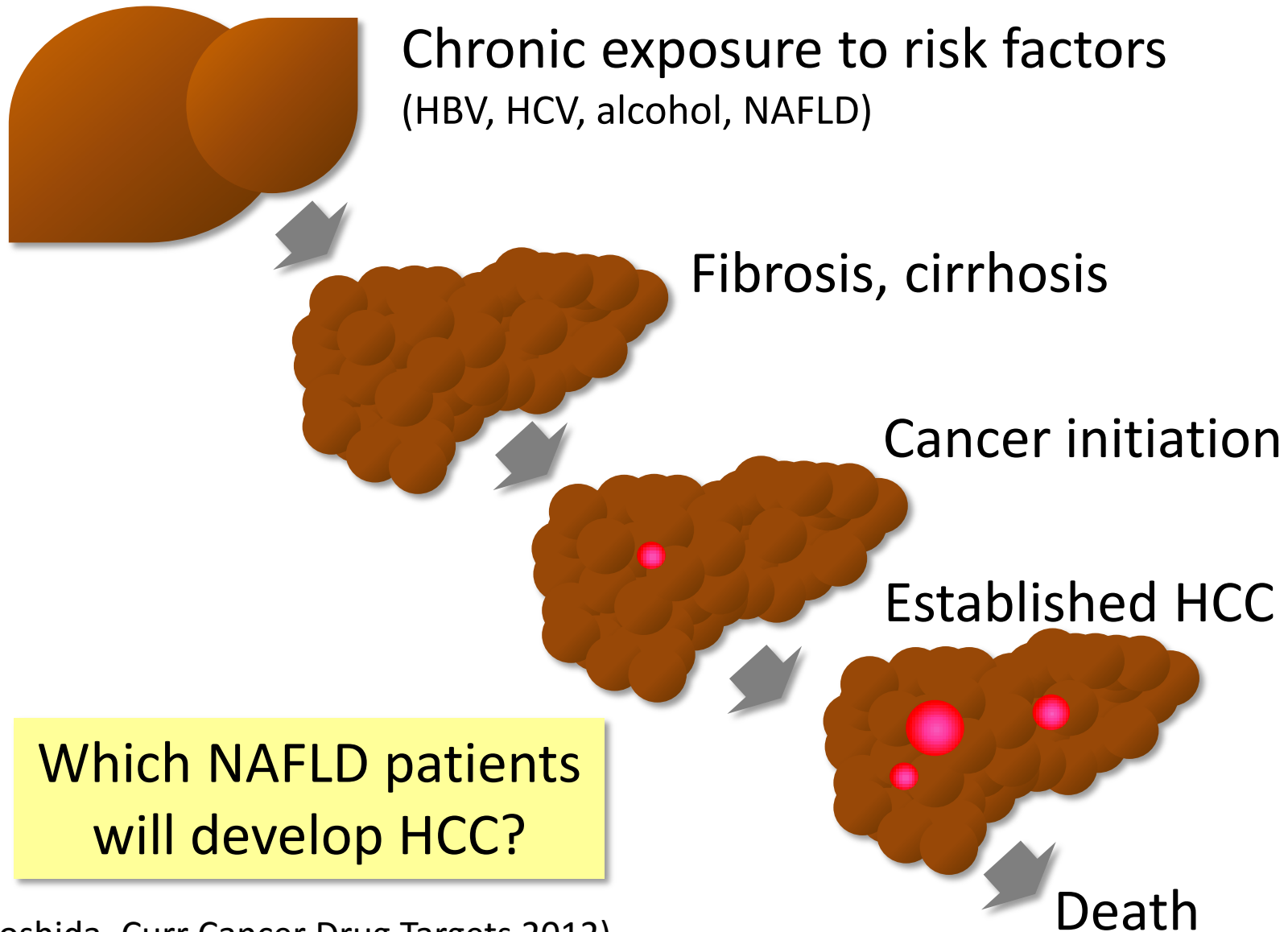
## Lectures

- Merck
- Celgene
- H3 Biomedicine
- Epizyme
- BMS

## Research grants

- H3 Biomedicine
- AbbVie
- Tobira Therapeutics
- Kyowa Kirin
- Roche

# Hepatocellular carcinoma (HCC) development

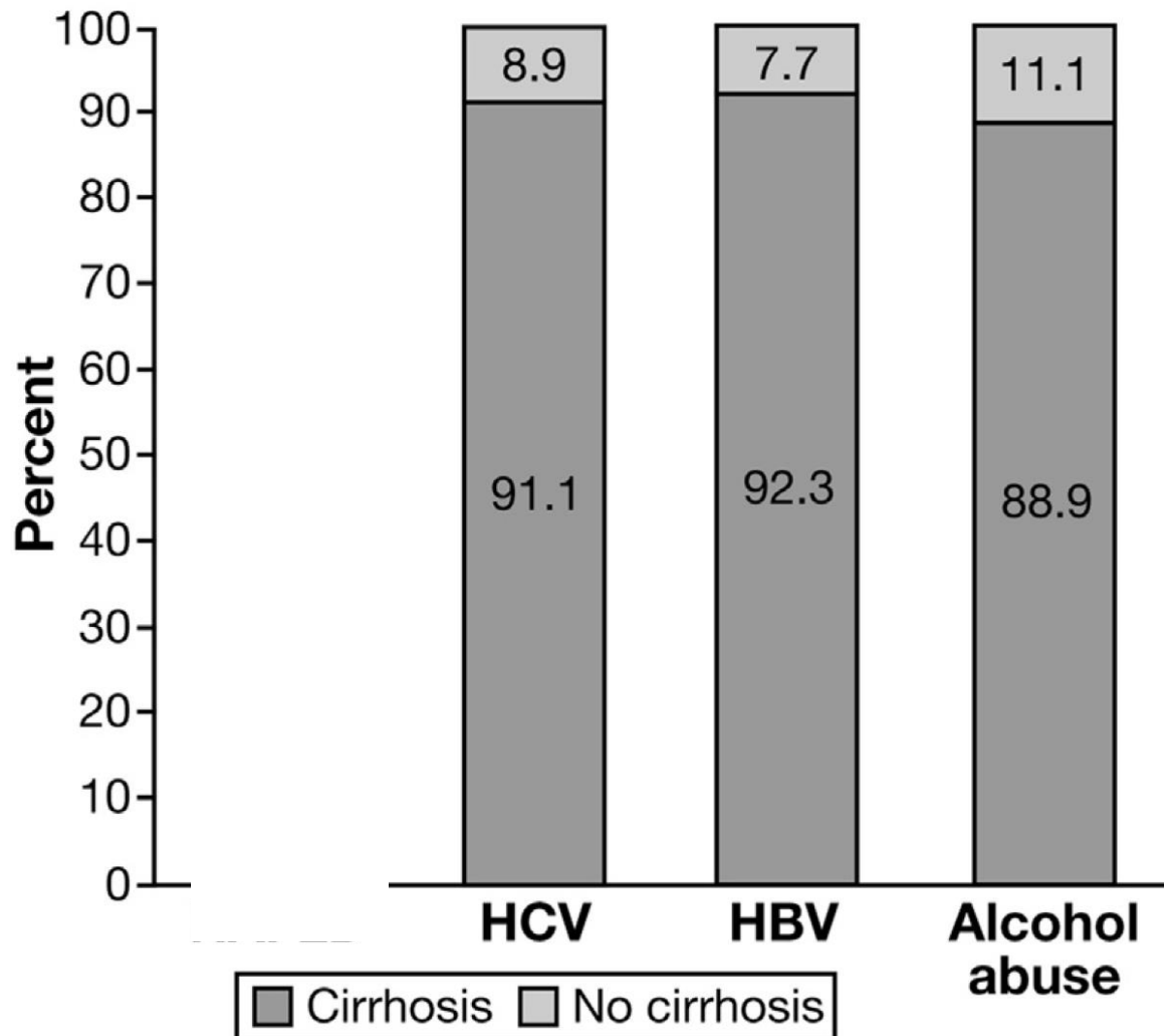


(Hoshida, Curr Cancer Drug Targets 2012)

# What is unique to NAFLD-related HCC?

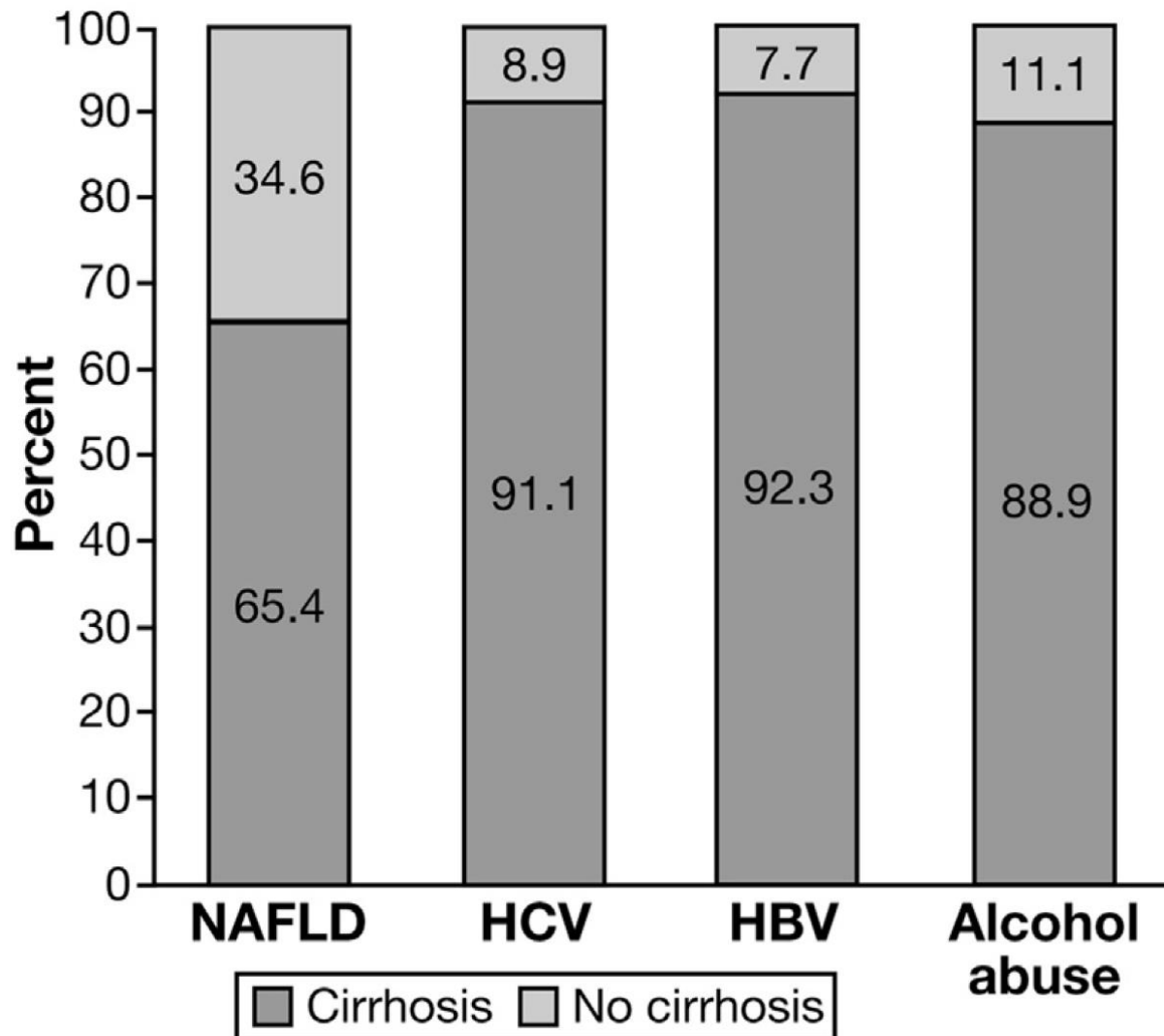
- Molecular drivers supporting HCC initiation?
- Hallmark of initiating HCC clone?
- Biological characteristics of established HCC tumor?
- Tumor progression/prognosis?
- Characteristics shared with other etiologies?

# Cirrhosis as clinical HCC risk factor



(Mittal, Clin Gastro Hep 2016)

# Cirrhosis as clinical HCC risk factor



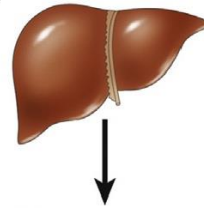
(Mittal, Clin Gastro Hep 2016)

# Distinct from alcohol-related HCC?

## ALD

Obesity, T2D [2-5] Cirrhosis Hepatic iron deposition [10]	SNP: <i>PNPLA3</i> [11-12], <i>TM6SF2?</i> , <i>MPO</i> , <i>SOD2</i> , <i>RANTES</i> [13-16]
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Predisposing factors  
(in fibrosis/cirrhosis)



## NAFLD

Obesity, T2D [2-6] Cirrhosis HCC in non-cirrhotic liver (35%-50%) [6, 7] Higher GGT? [9]	SNP: <i>PNPLA3</i> [11-12]
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Clinical

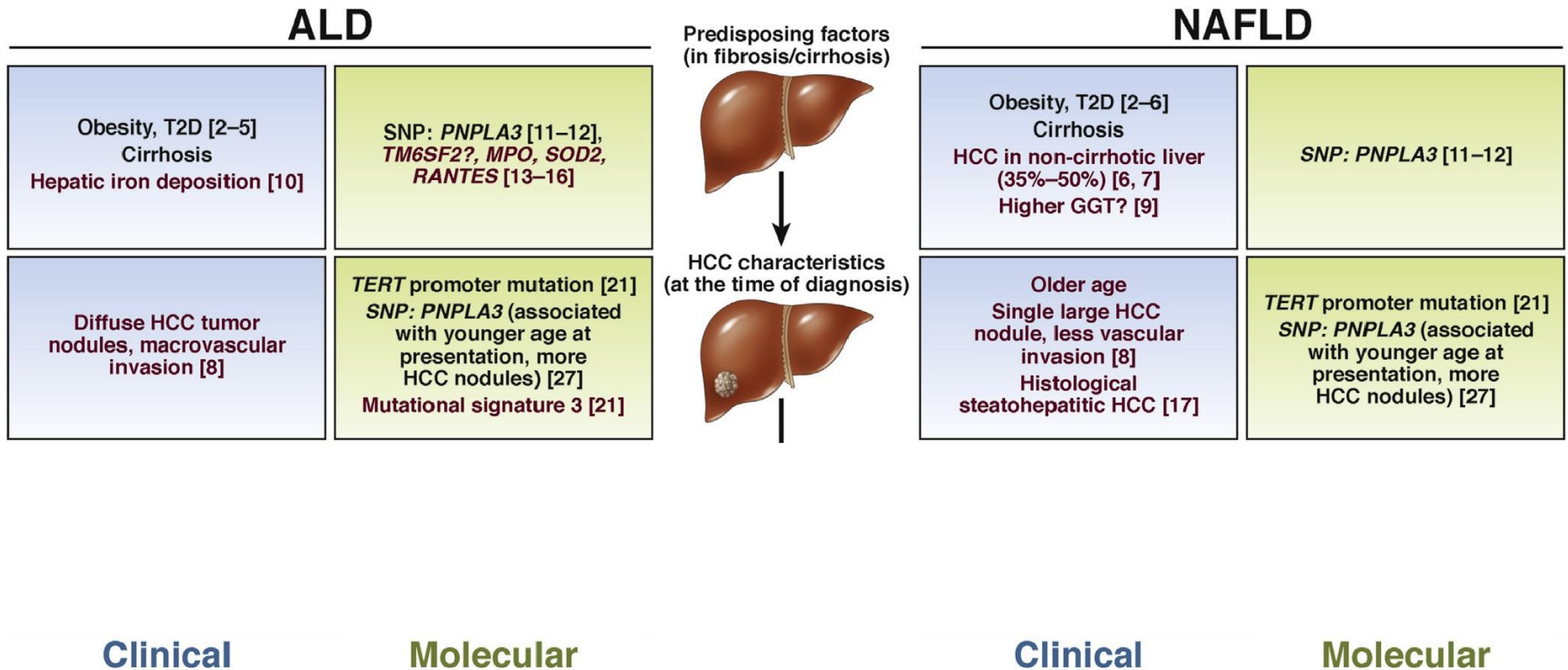
Molecular

Clinical

Molecular

(Goossens, Gastro 2016)

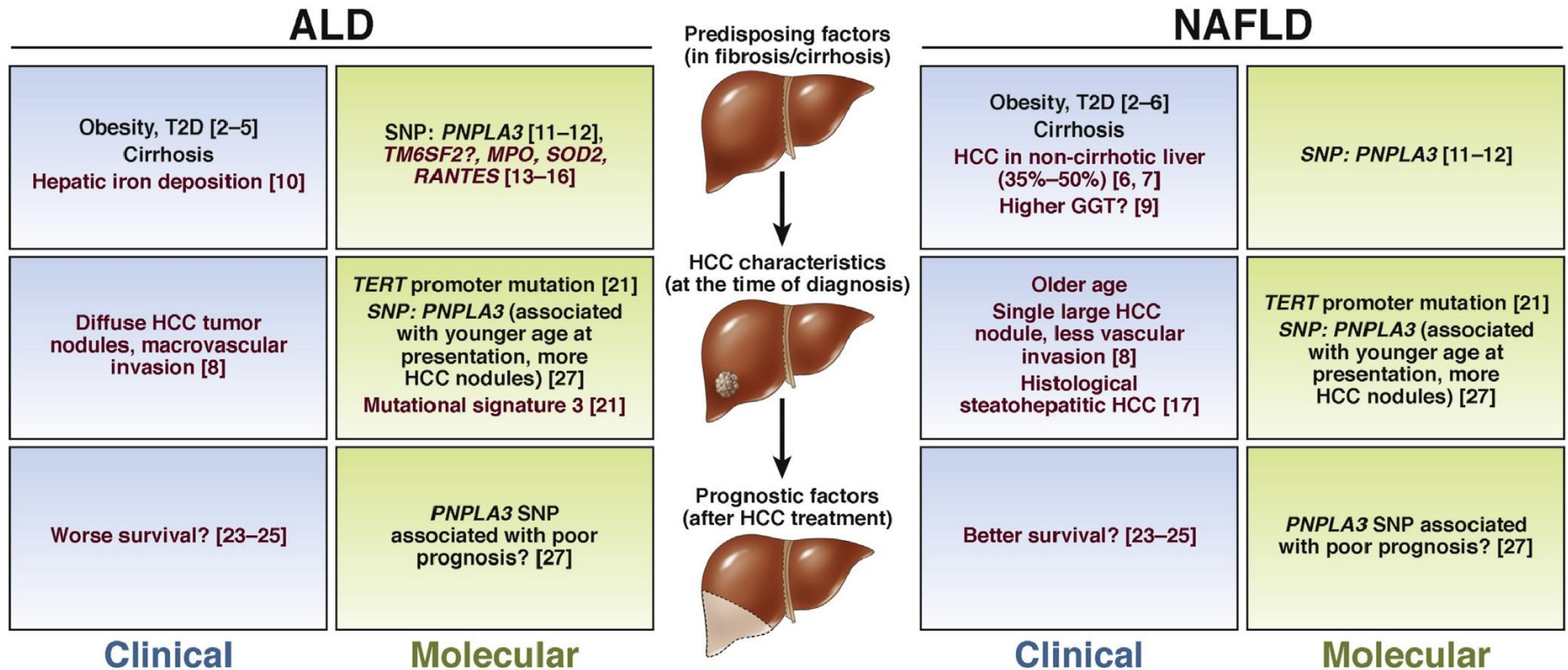
# Distinct from alcohol-related HCC?



(Goossens, Gastro 2016)



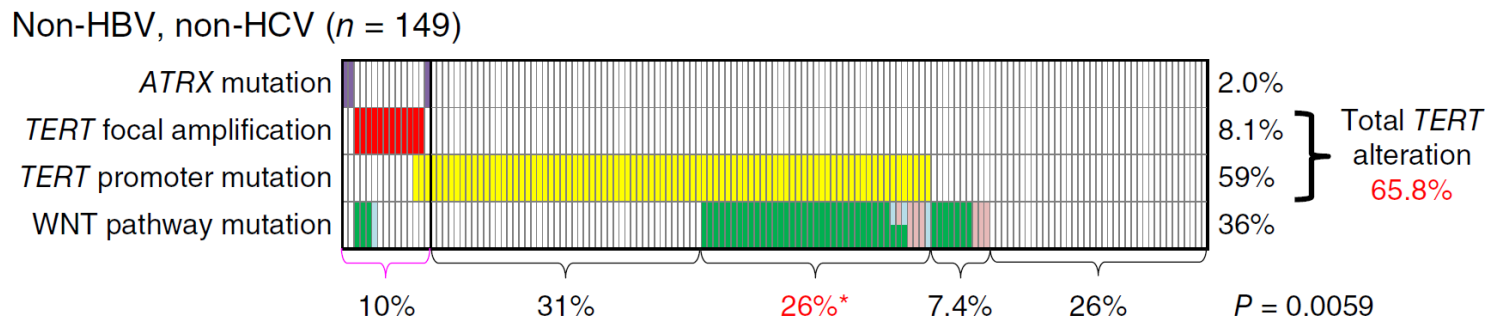
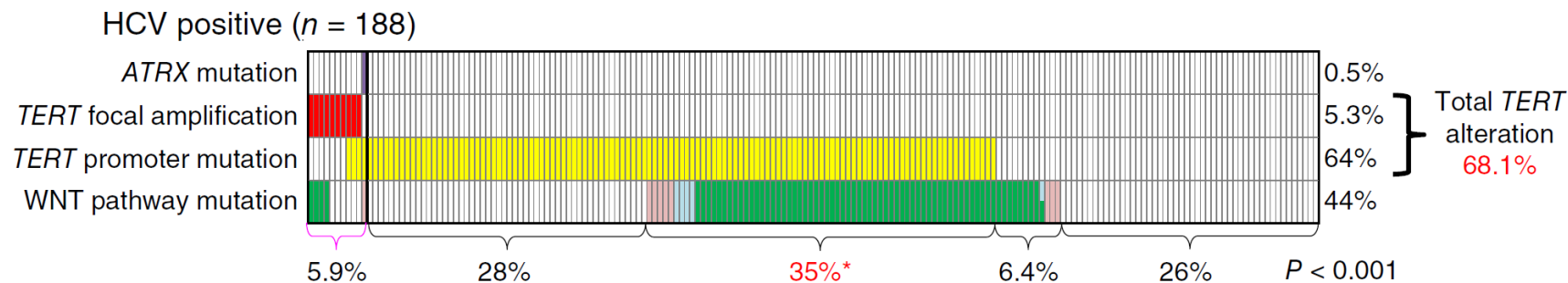
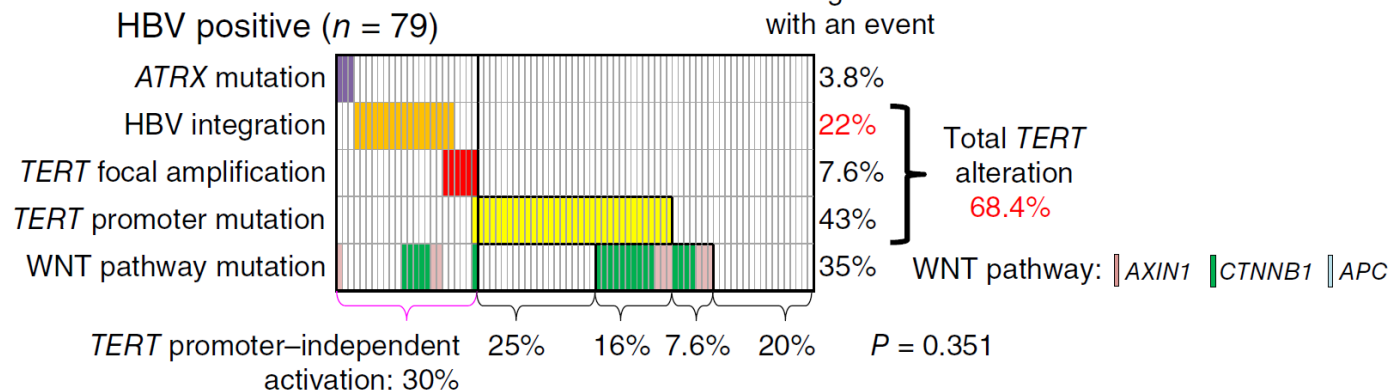
# Distinct from alcohol-related HCC?



(Goossens, Gastro 2016)

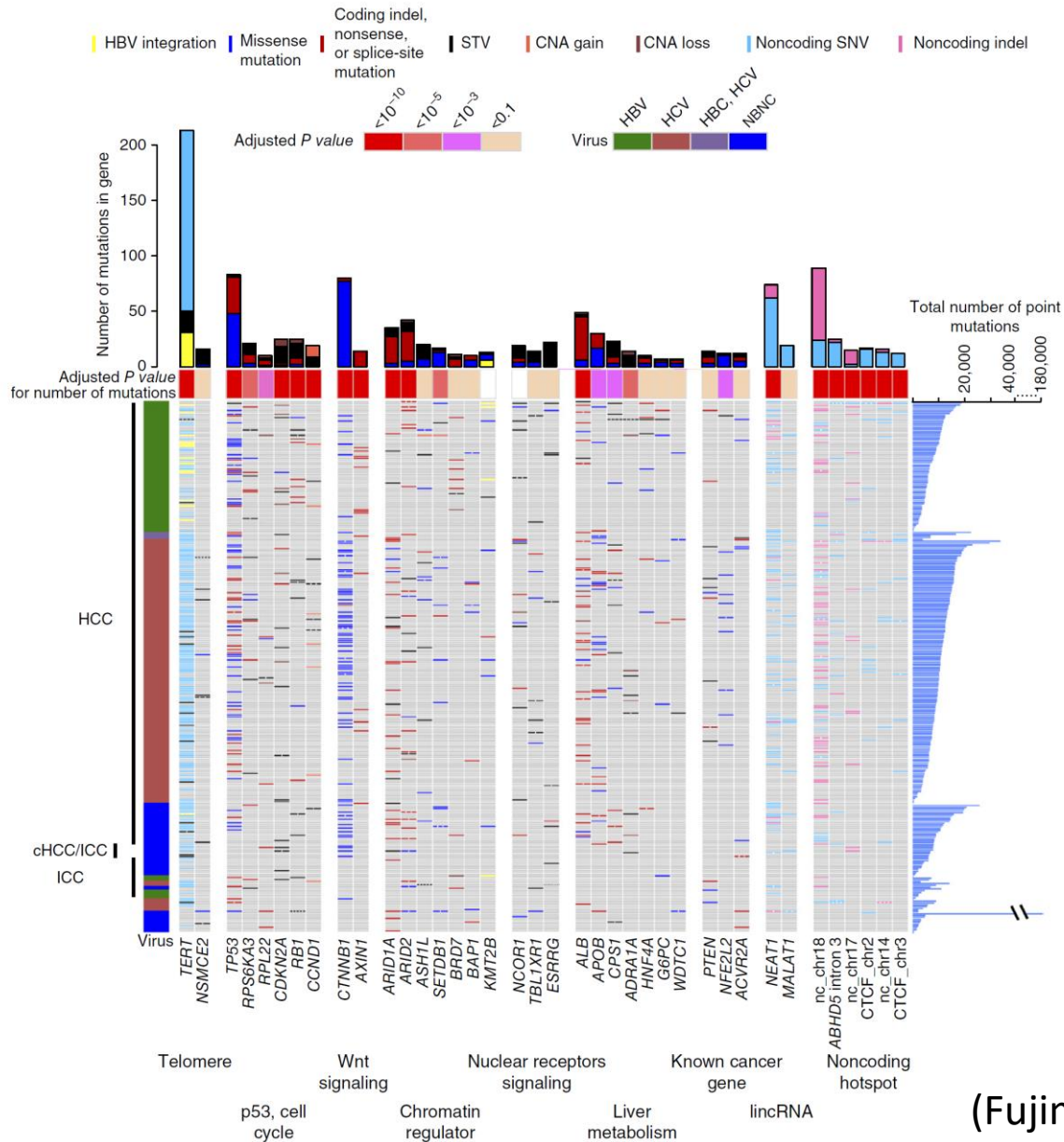
# Molecular feature of early HCC: Telomerase reactivation

Percentage of tumors with an event



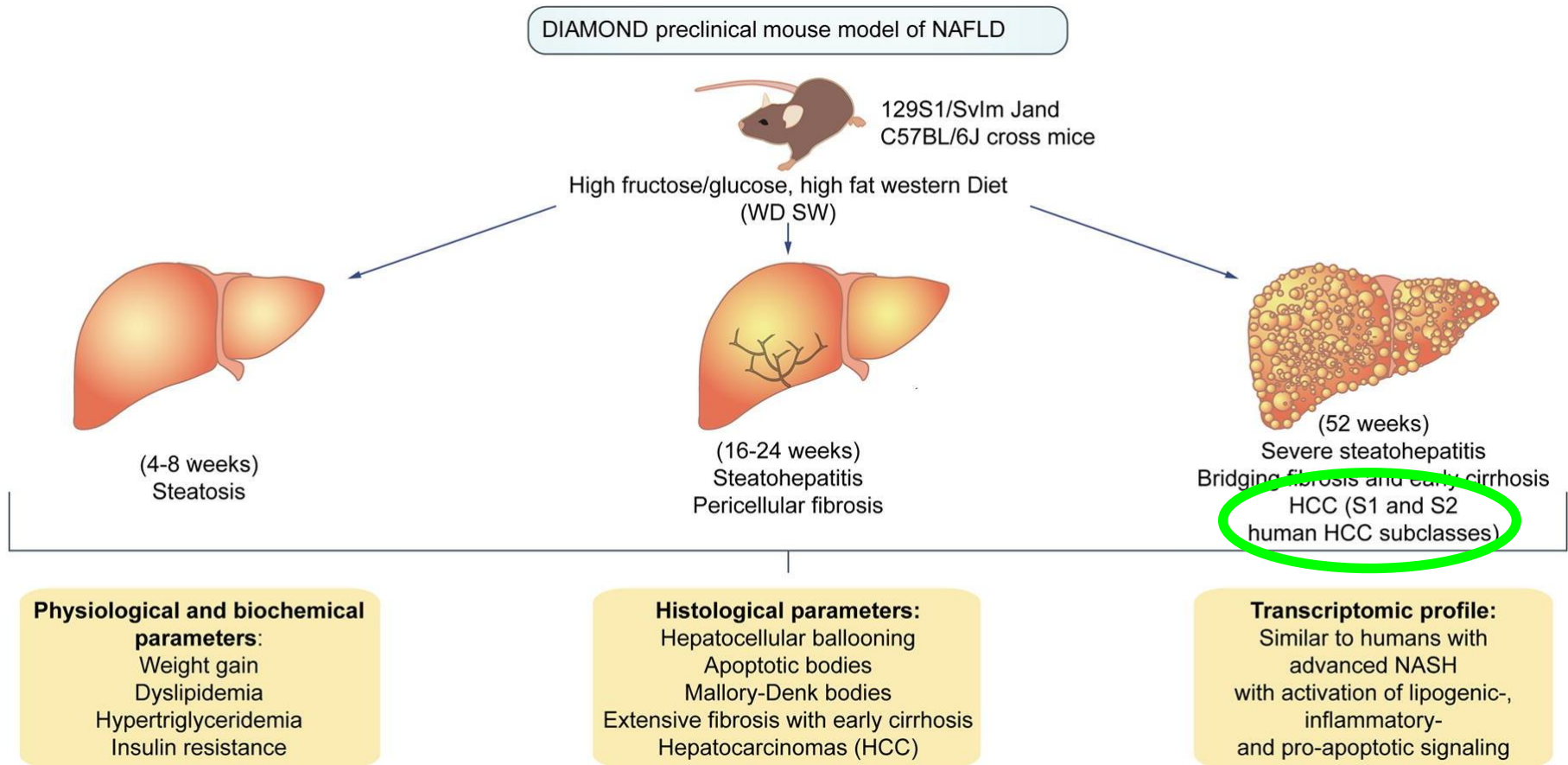
(Totoki, Nat Genet 2014)

# Established HCC tumor: somatic DNA mutations



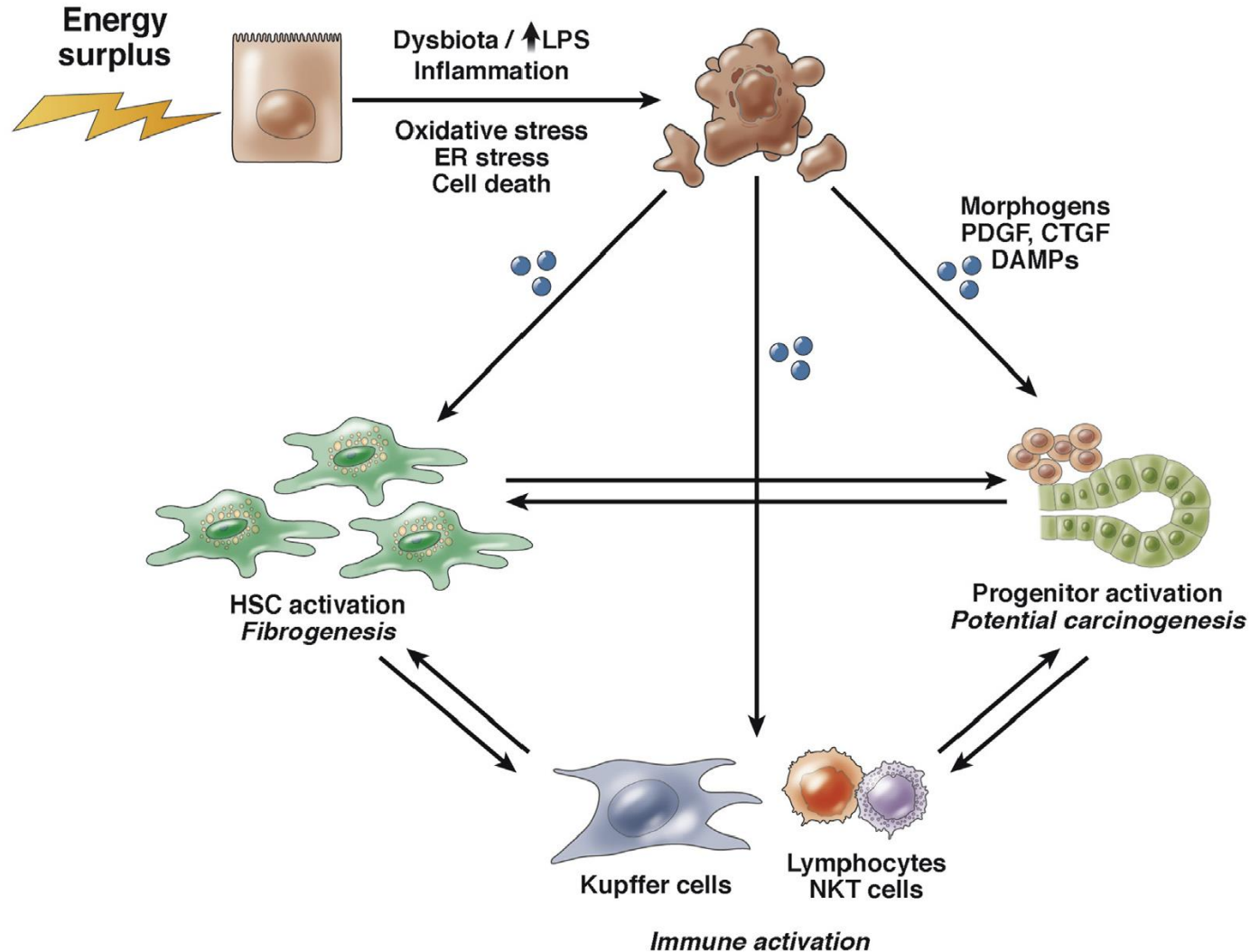
(Fujimoto, Nat Genet 2016)

# Established HCC tumor: transcriptomic subtype



(Asgharpour, J Hepatol 2016)

# Path to NAFLD-HCC initiation

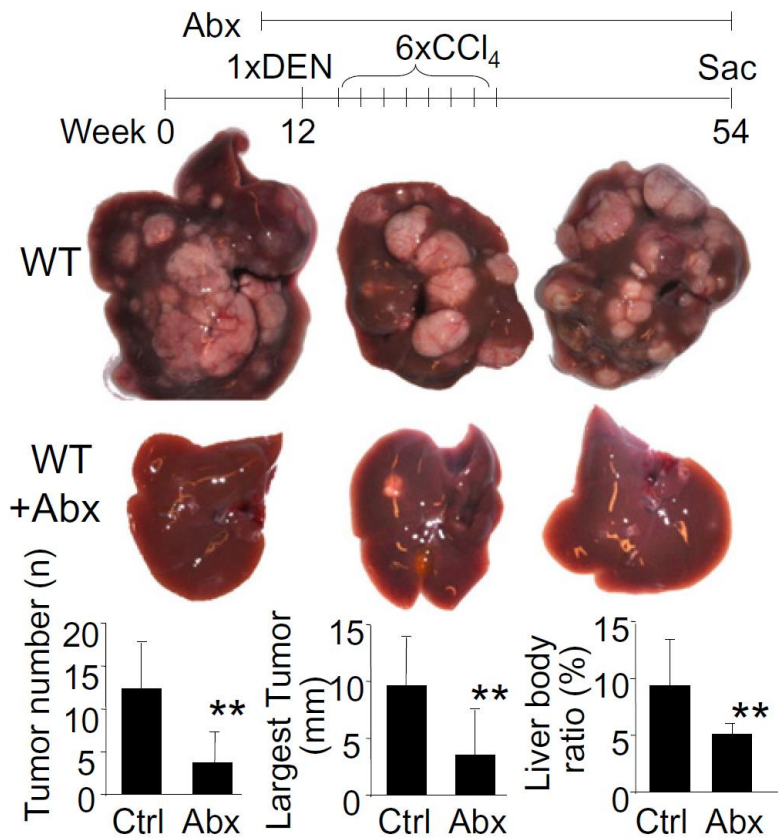


(Machado, Gastro '16, Wolf, Cancer Cell '14, Nakagawa, Cancer Cell '14, Ma, Nature '16)

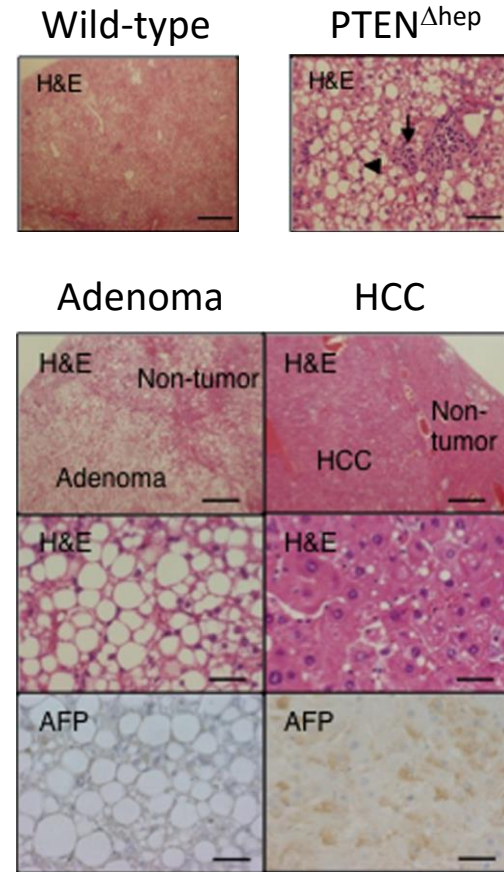


# Gut microbiota promotes NAFLD-HCC via TLR4

## Chemical-induced liver injury

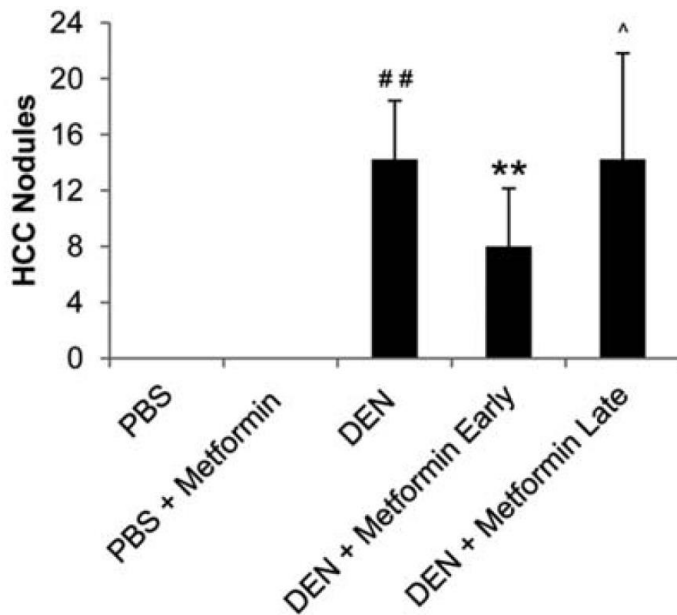


## PTEN-knockout



(Dapito, Cancer Cell 2012, Miura, JBC 2016)

# Anti-metabolic disorder drugs to prevent NAFLD-HCC



## Progenitor markers

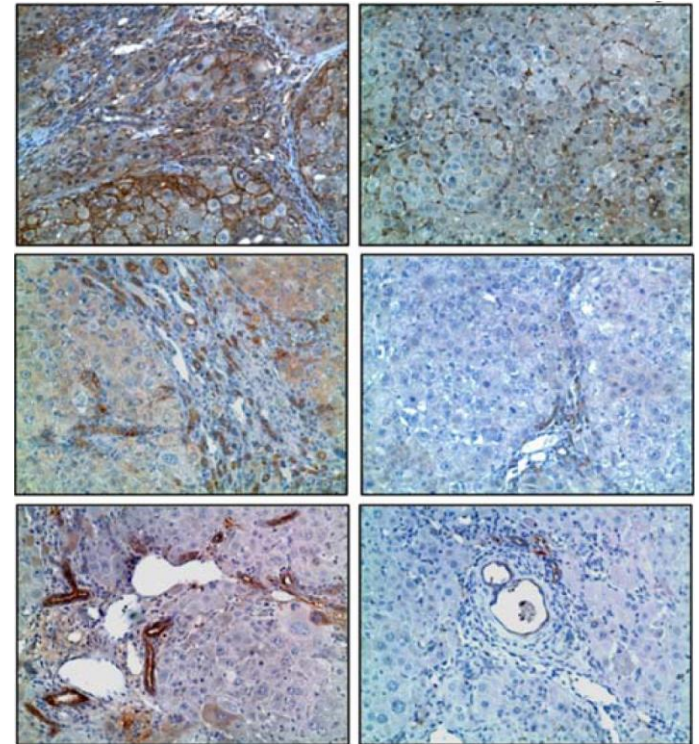
RAGE  
(soluble mediator)

DLK-1  
(prototypical marker)

OV6  
(progenitor marker)

DEN

DEN +  
Metformin, Early

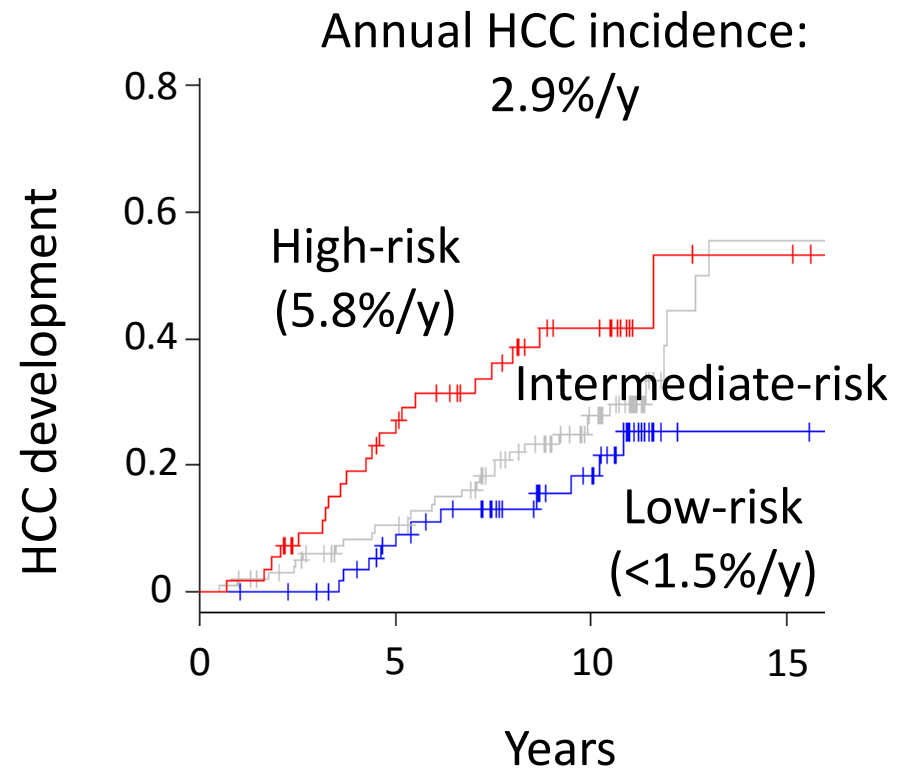
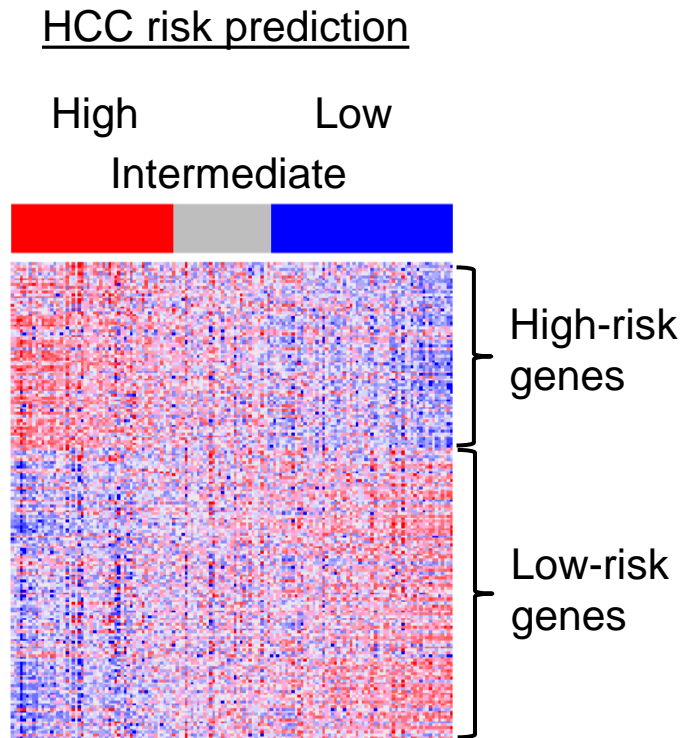


# Molecular HCC predisposing factors?

Molecular biomarker	Outcome
<b>186-gene signature</b> (Hoshida 2013, King 2014)	Overall death, Progression to adv cirrhosis, HCC
<b>HIR gene signature</b> <b>65-gene signature</b> (Kim 2014)	Early and late HCC recurrence
<b>Activated HSC signature</b> (Ji 2015)	HCC recurrence and survival
<b>SNP in <i>EGF</i> combined with clinical variables</b> (Abu Dayyeh 2011)	HCC risk
<b>Cirrhosis risk score</b> (Do 2012)	Fibrosis progression after liver transplantation
<b>SNP in <i>PNPLA3</i></b> (Guyot 2013)	HCC risk
<b>SNP in <i>MPO</i></b> (Nahon 2012)	HCC risk
<b>SNP in <i>CAT</i></b> (Nahon 2012)	HCC risk
<b>SNP in <i>HFE</i></b> (Nahon 2008)	HCC risk



# HCC risk liver transcriptome signature: *Hallmark of HCC initiation-supporting liver milieu?*



(Hoshida, NEJM 2008, Hoshida, Gastro 2013, King, Gut 2015, Finkin, Nat Immunol 2015)

# HCC risk prediction for HCC surveillance?

**Table 3. Recommendations for HCC surveillance: categories of adult patients in whom surveillance is recommended.**

1. Cirrhotic patients, Child-Pugh stage A and B\*
2. Cirrhotic patients, Child-Pugh stage C awaiting liver transplantation\*\*
3. Non-cirrhotic HBV carriers with active hepatitis or family history of HCC\*\*\*
4. Non-cirrhotic patients with chronic hepatitis C and advanced liver fibrosis F3\*\*\*\*

EASL

Surveillance

Recommendations

Surveillance for HCC in high-risk populations is recommended (2a, B).

Surveillance for HCC should be performed by ultrasonography (US) and  $\alpha$ -fetoprotein (AFP) every 6 months (2a, B).

APASL

**Annual HCC incidence >1.5%**

Surveillance recommended

Population group

Asian male hepatitis B carriers over age 40	0.2
Asian female hepatitis B carriers over age 50	0.2
Hepatitis B carrier with family history of HCC	0.2
African/North American Blacks with hepatitis B	0.2
Cirrhotic hepatitis B carriers	0.2-1.5
Hepatitis C cirrhosis	1.5
Stage 4 primary biliary cirrhosis	1.5
Genetic hemochromatosis and cirrhosis	1.5
Alpha 1-antitrypsin deficiency and cirrhosis	1.5
Other cirrhosis	1.5

Threshold incidence for efficacy of surveillance (> .25 IYG)(%/year)

Asian male hepatitis B carriers over age 40	0.2
Asian female hepatitis B carriers over age 50	0.2
Hepatitis B carrier with family history of HCC	0.2
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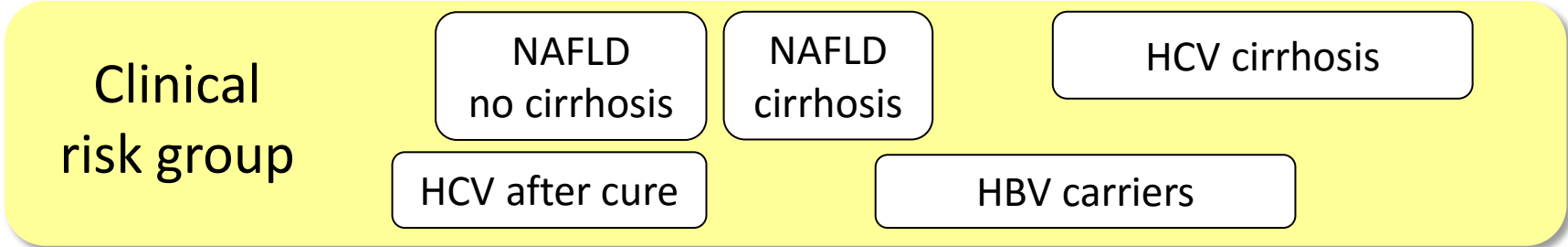
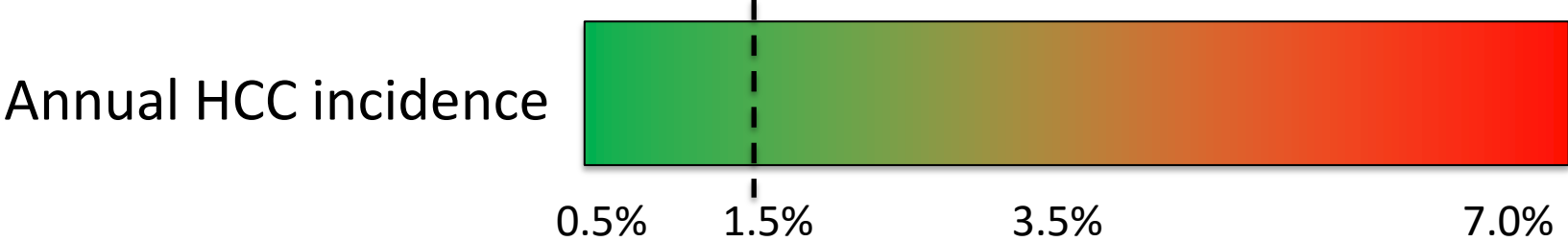
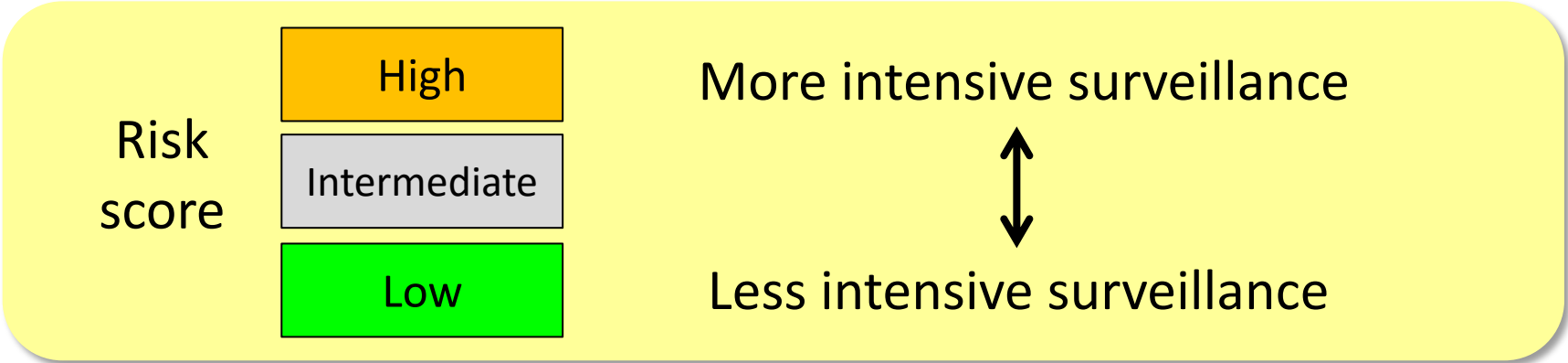
Incidence of HCC

Asian male hepatitis B carriers over age 40	0.4-0.6%/year
Asian female hepatitis B carriers over age 50	0.3-0.6%/year
Hepatitis B carrier with family history of HCC	Incidence higher than without family history
African/North American Blacks with hepatitis B	HCC occurs at a younger age
Cirrhotic hepatitis B carriers	3-8%/yr
Hepatitis C cirrhosis	3-5%/yr
Stage 4 primary biliary cirrhosis	3-5%/yr
Genetic hemochromatosis and cirrhosis	Unknown, but probably > 1.5%/year
Alpha 1-antitrypsin deficiency and cirrhosis	Unknown, but probably > 1.5%/year
Other cirrhosis	Unknown

AASLD

“One size fits all”: biannual US recommended in at-risk population defined by disease etiology/severity

# Risk-based personalized HCC surveillance



# Summary

- NAFLD HCC risk prediction is urgently needed.
- Many molecular features in NAFLD HCC are shared with other etiologies.
- Several pathways, e.g., gut microbiota-TLR4 axis, may play major role in NAFLD HCC development and/or progression.
- Hepatic progenitor cell activation by NAFLD-specific milieu may serve as target of NAFLD HCC prevention.
- HCC risk biomarker/score may enable cost-effective personalized HCC surveillance.

