EASL
INTERNATIONAL
LIVER
FOUNDATION

International Conference on the Management of Liver Diseases

HCC today and the future?

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Financial Disclosures

Advisory committees: Merck, Roche, Novartis, Bayer, BMS, Gilead Sciences, Tibotec, Vertex, Janssen Cilag, Achillion, Lundbeck, GSK, GenSpera, AbbVie, Alfa Wasserman, Intercept

Speaking and teaching: Tibotec, Roche, Novartis, Bayer, BMS, Gilead Sciences, Vertex, Merck, Janssen, AbbVie

Incidence Changes of Liver Cancer 1990-2016 Global Burden of Disease

- Liver cancer is the 16th leading cause of death globally. Incident cases increased 114% from 471,000 in 1990 to 1,007,800 in 2016,causing 810,000 related deaths.

- 47% of increase is explained by changing population age structures, 35% by population growth and 8% to changing age-specific incidence rates.

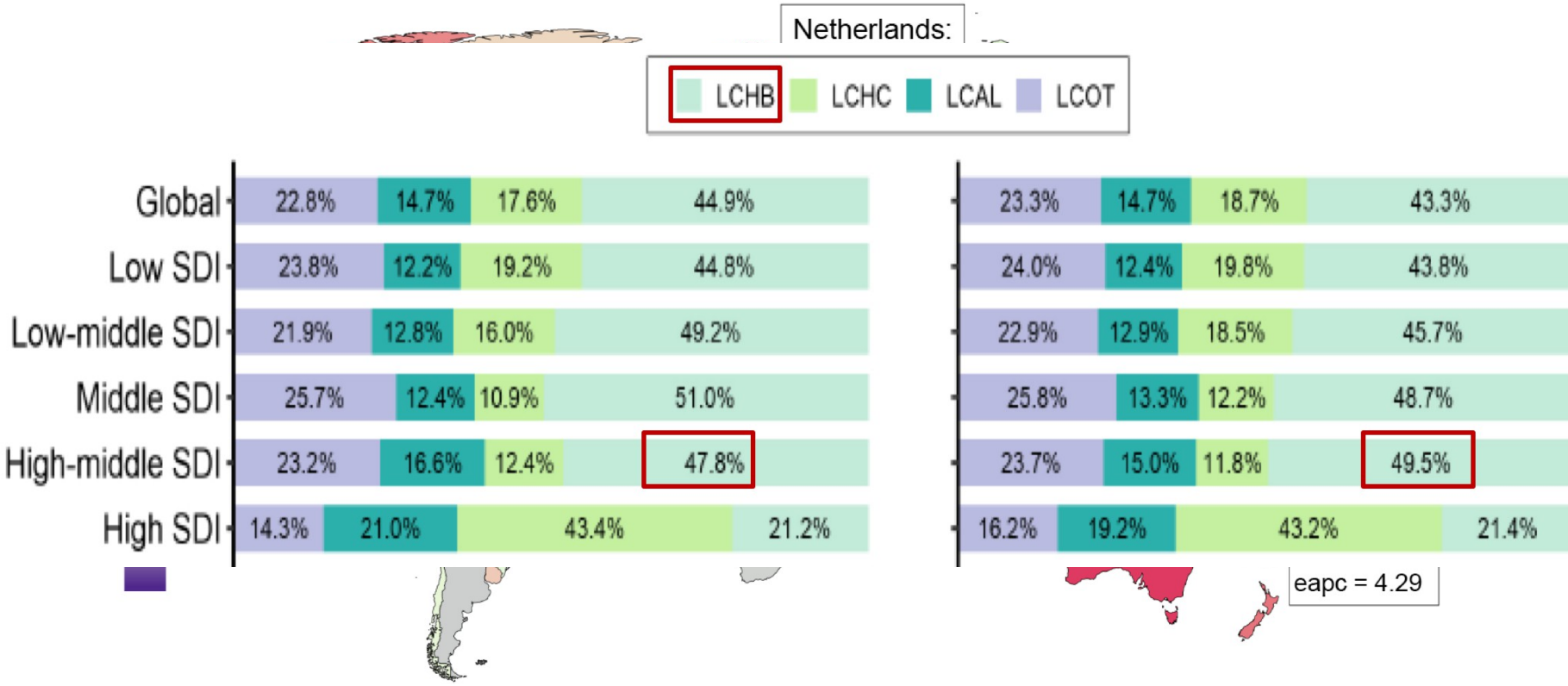
- The EAPC for HBV was 0.22 (95% CI 0.08−0.36), 0.57 for HCV (95% CI 0.48−0.66), and 0.51 for other causes (95% CI 0.41−0.62), respectively.

- The most pronounced increases were generally observed in countries with high socio-demographic index including the Netherlands, the UK, and the USA.

Zhenqiu L et al. J Hepatol in press ; *Fitzmaurice C et al . JAMA Oncol.2018 ;* Akinyemiju T et al. JAMA Oncol.2017

Incidence Changes of Liver Cancer 1990-2016
Global Burden of Disease

Global Health Data Exchange (GHDx) from 195 countries and territories



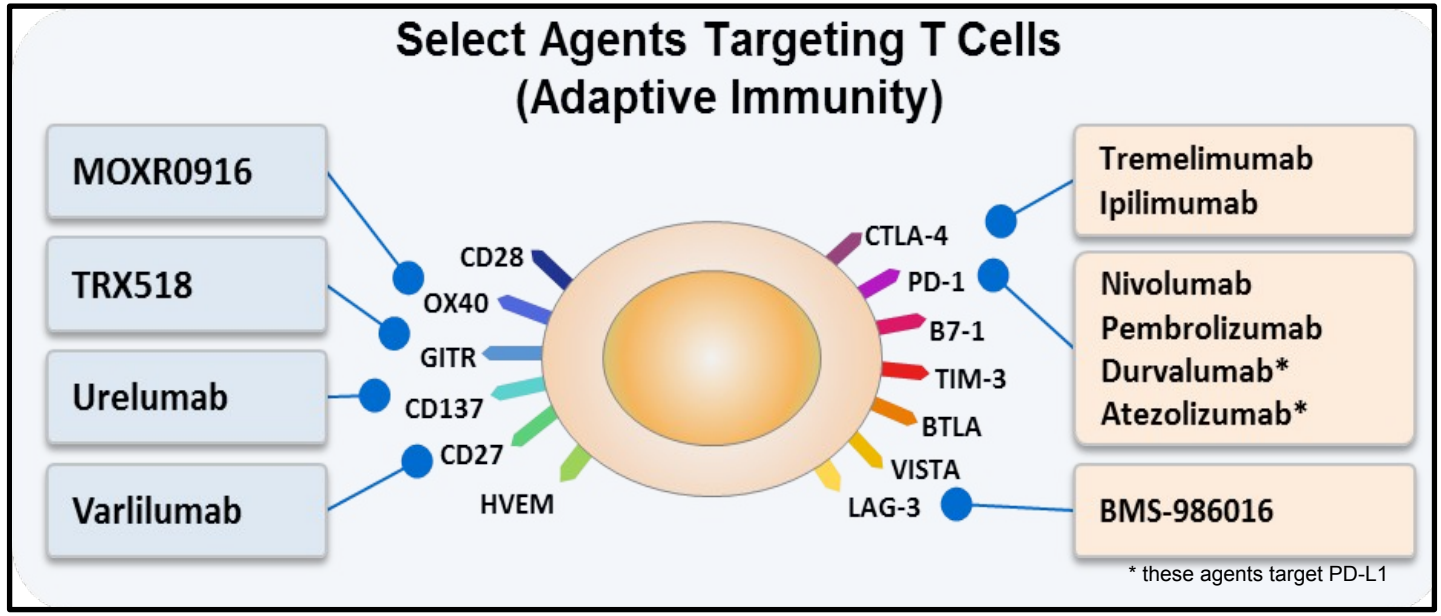
Zhenqiu L et al J Hepatol in press

Treatment Approach to HCC by Disease Stage Migration. The Sequential Concept

TREATMENT	BCLC	SURVIVAL
Resection/Transplantation/Ablation	Liver only disease Limited tumor burden	> 5 years
Chemoembolization	Liver only disease No vascular invasion PS 0 Selective approach	>2.5 years
Sorafenib / Lenvatinib	No tumor burden limit Preserved liver function PS 0-2	+/- 10 mo.
Rego / Cabo / Ramu (high AFP) Nivolumab	No tumor burden limit Preserved liver function PS 0-2	up to 16 mo.

EASL CPG HCC J Hepatol 2018, adapted from Forner A et al Lancet 2018

The "Gold Rush" of Cancer Immunotherapy Trials Triggering a Reversal of T Cell Exaustion



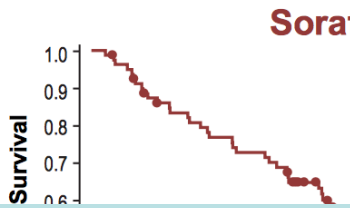
Stimulating Agents **Blocking Agents**

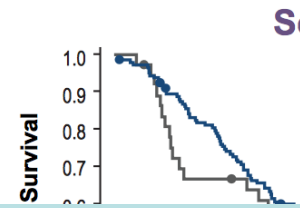
Checkpoint inhibitors approved in : Melanoma, NSCLC, renal cell ca., Merkel cell ca, bladder ca.

SCCHN, Hodgkin's lymphoma, MSI-high tumors & HCC

Pardoll DM. *Nat Rev Cancer*. 2012;12:252-64. Mellman I et al. *Nature*2011;480:480-9.

Nivolumab in the Treatment of HCC. CheckMate 040



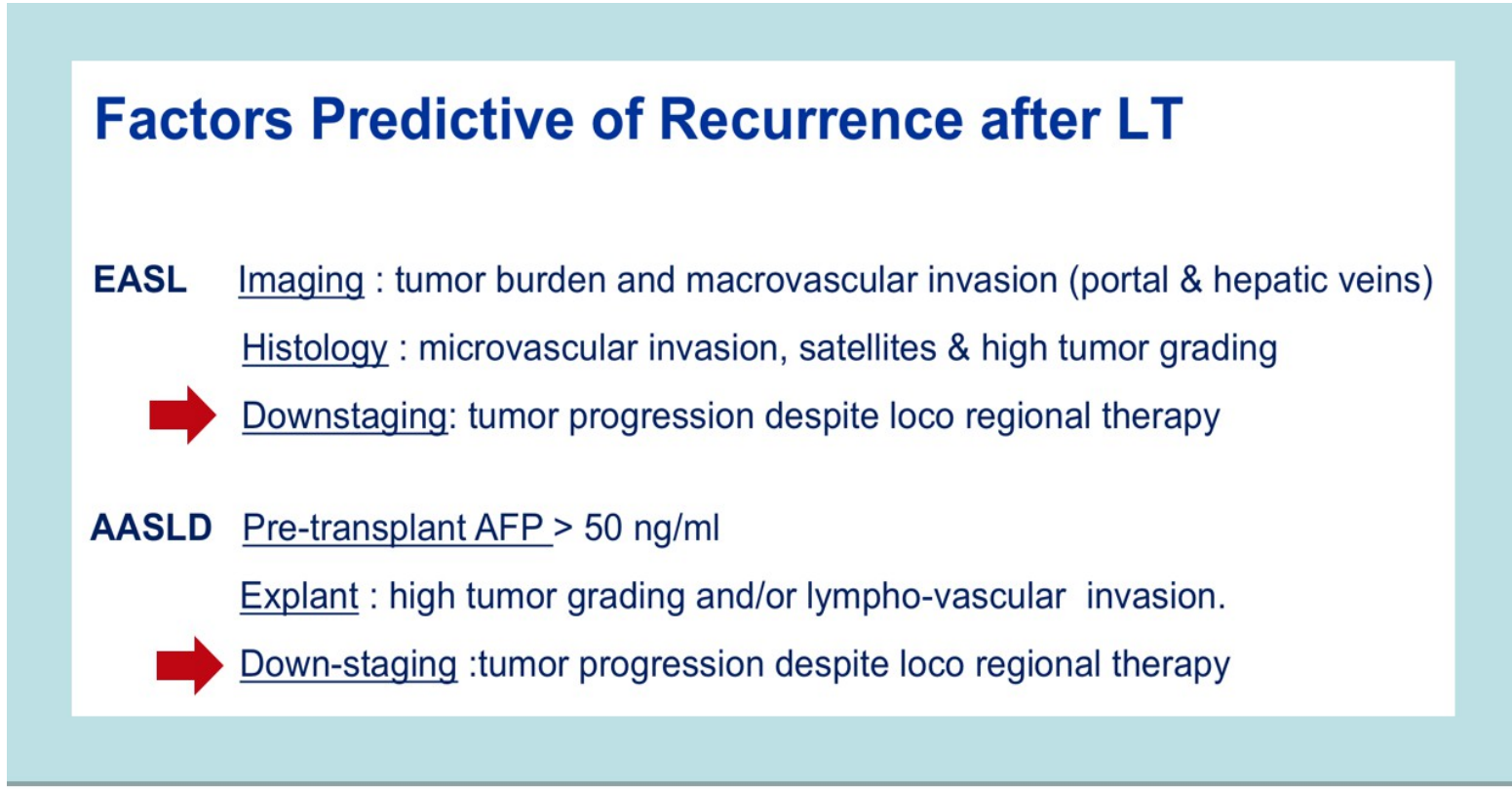


2nd line therapy		Patients	Months	95% CI
RESORCE	Placebo	193	7.8	6.3-8.8
CheckMate 040	**Nivolumab**	145	15.6	13.2-18

Courtesy of Prof. B.Sangro

Trojan et al 2018 www.professionalabstracts.com/dgho2017/pdf/open.php?id=773&system=list

LT for HCC.Expanding Beyond Milan Criteria Respecting the Paradigm of Utility



gest

TTV, total tumor volume

Reviewed by J.Bruix et al, Gut. 2014;63:844-55

Beyond Milan Criteria. Integrating Transplant Benefit Criteria into Societies Guidelines

EASL

- LT is the first-line option for unresectable HCC within Milan criteria(MC).

  (Level of evidence high, strenght of recommendation strong)

- Patients outside MC considered after successful down-staging to within MC.

  (Level of Evidence moderate, strenght of recommendation weak)

AASLD

- LT is the treatment of choice for patients with early stage HCC and clinically significant portal hypertension and/or decompensated cirrhosis.

- Patients outside MC considered after successful down-staging to within MC.

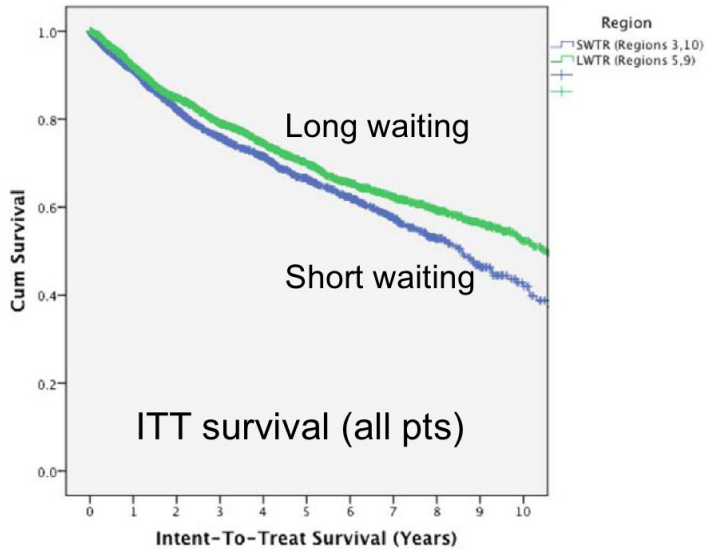
  (Level of evidence very low, strenght of recommendation conditional)

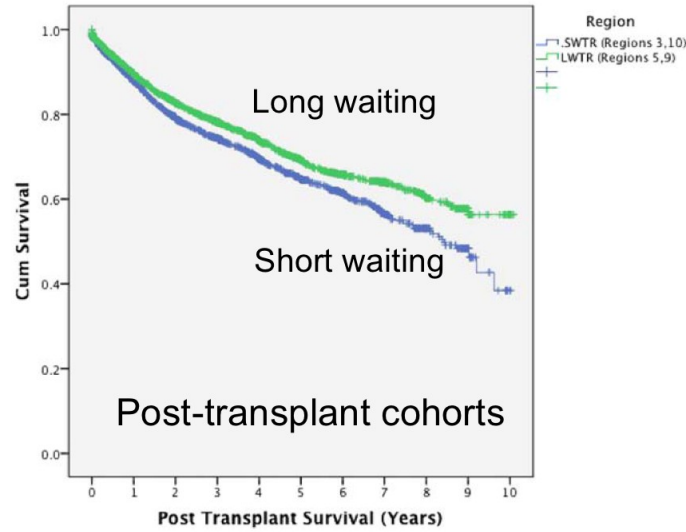
EASL CPG HCC J Hepatol 2018; AASLD PG HCC Hepatology 2018

Prioritizing Patients with HCC.Results of the UNOS Natural Geographic Experiment

Long-waiting time regions (median 7.6 mo.) *vs* short waiting time regions (median 1.6 mo.)

T2 HCCs (4,759 pts) and downstaged T3 who received exception points (1,387 pts)



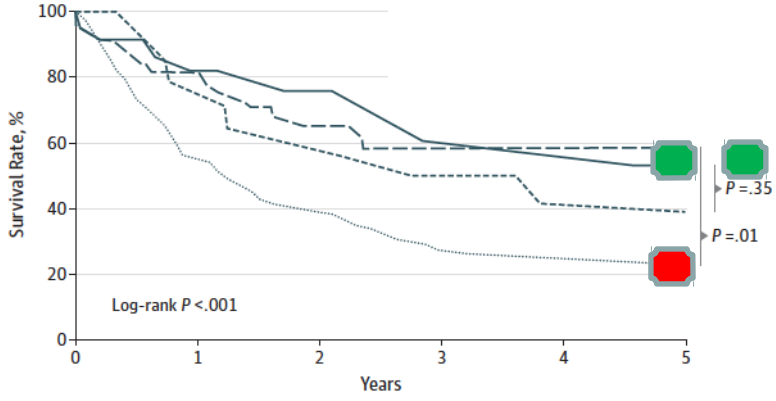


Listed/transplanted in an short-waiting time region was an independent predictor of poor patient survival.

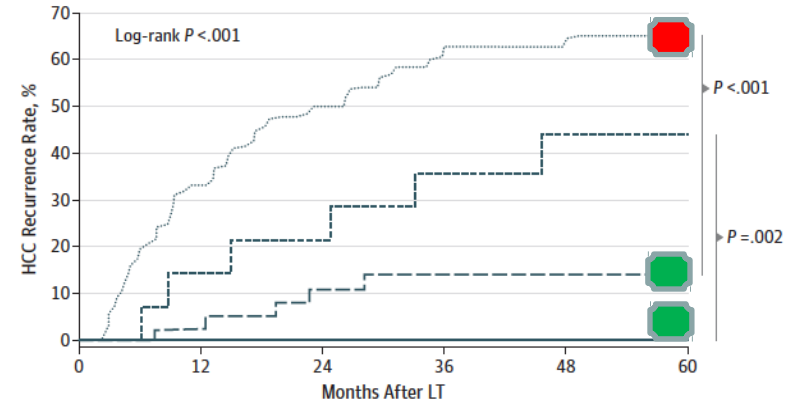
Halazun KJ et al Hepatology 2014

AFP Response to Downstaging Predicts Survival of HCC Patients Outside Milan Criteria

A Recurrence-free survival outside Milan criteria



B Incidence of HCC recurrence outside Milan criteria



Agopian VG et al JAMA Surgery 2017

HCC.Future Directions

2018 EASL Recommendations

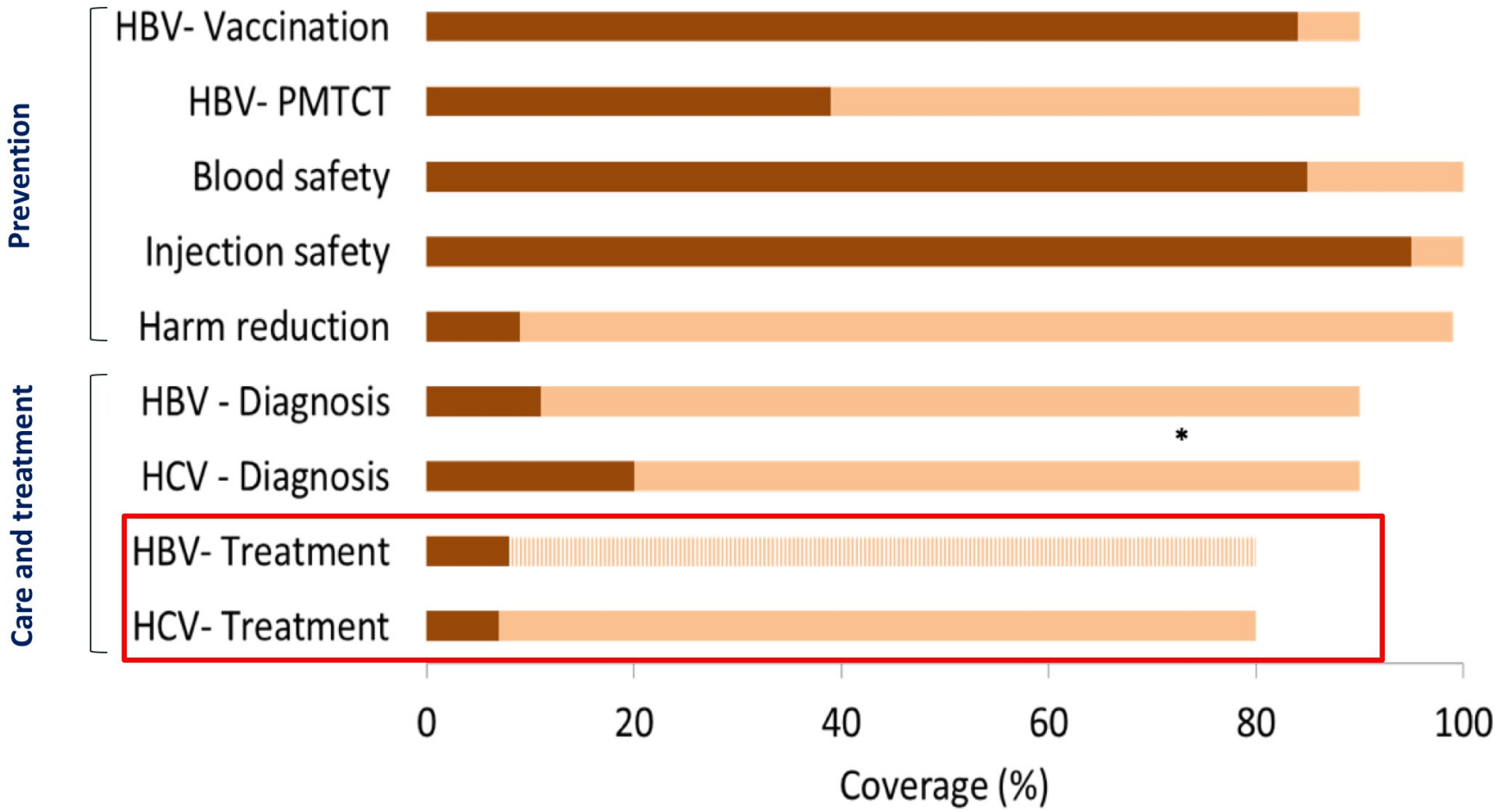
1. Public health policies to prevent, detect, and treat chronic liver disease

2. Appropriate cancer surveillance to detect HCC in a stage amenable to curative treatment

3. Link molecular subclasses in clinical trials to therapeutic response and outcome

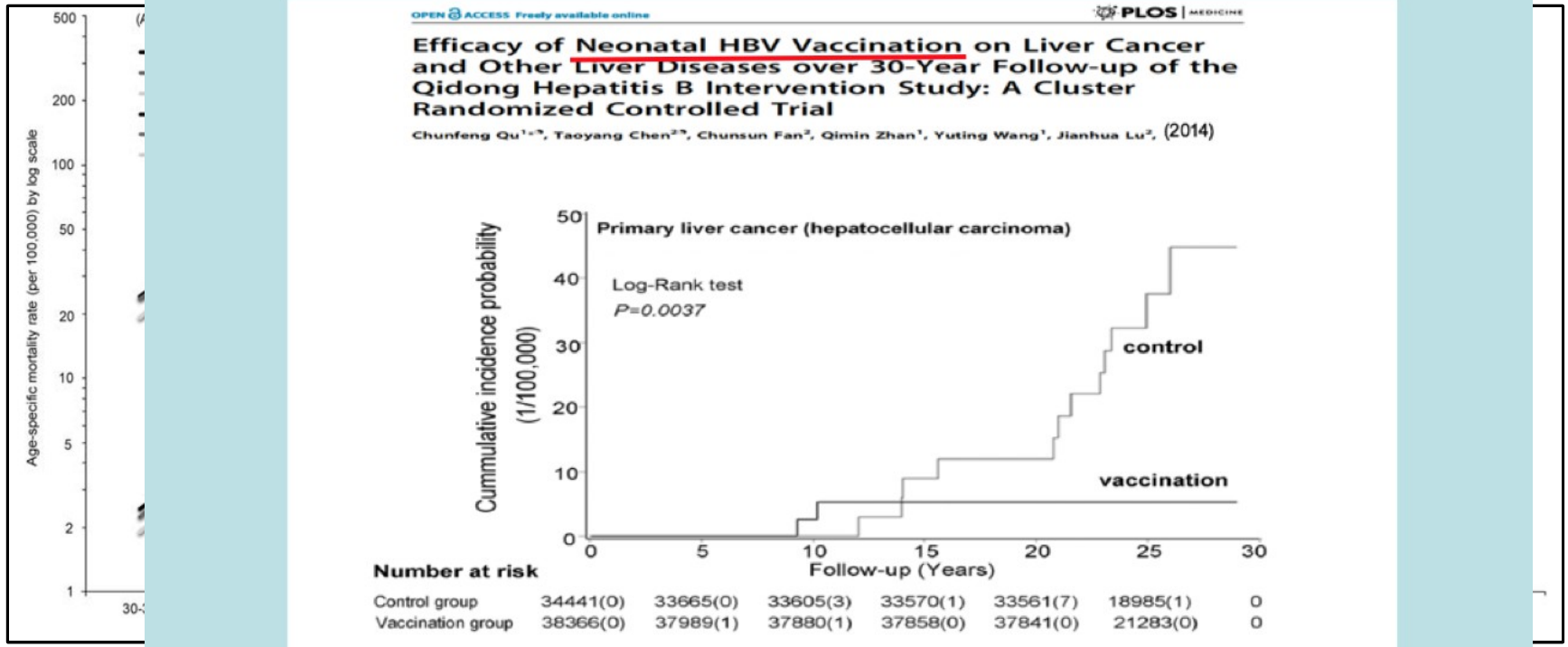
EASL CPG HCC J Hepatol 2018

Global Strategy of Viral Hepatitis Elimination 2015 BaselineTowards 2030 Targets



WHO Global Hepatitis Report 2017

The National Viral Hepatitis Program in Taiwan
Decline of HCC Following HBV Therapy



OPEN ACCESS Freely available online PLOS | MEDICINE

Efficacy of Neonatal HBV Vaccination on Liver Cancer and Other Liver Diseases over 30-Year Follow-up of the Qidong Hepatitis B Intervention Study: A Cluster Randomized Controlled Trial

Chunfeng Qu[1-3], Taoyang Chen[2,3], Chunsun Fan[2], Qimin Zhan[1], Yuting Wang[1], Jianhua Lu[2], (2014)

Number at risk

Control group	34441(0)	33665(0)	33605(3)	33570(1)	33561(7)	18985(1)	0
Vaccination group	38366(0)	37989(1)	37880(1)	37858(0)	37841(0)	21283(0)	0

mortality and 0.86 for HCC incidence *vs* 2000-2003

Chiang, C. J., et al.Hepatology,2015 : 61: 1154-1162.

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EASL CPG HCC J Hepatol 2018

Surveillance Increases Survival of Patients at Risk Suboptimal Uptake in Developed World

The lesson from Japan : Screening rose from 12.9% (1966-1979) to 77.6% (2000-2013) curative treatments from 3.3% to 62.8%. OS from 16.6 to 52 mo.

BUT

France < 25% of HCC are diagnosed in the context of cirrhosis surveillance
<30% are amenable to curative treatment .

Hong-Kong no screening, OS of HCC was 17.8 months during the period 2003-2014.

USA HCC patients missing US surveillance:HCV 13%,ETOH 40%,NAFLD 50%.
Meta-analysis by Singal(2012):18.4% uptake of surveillance in cirrhotics.

Costentin C et al Cancer 2018; Johnson P et al Br J Cancer 2017;Mittal et al Clin Gastroent Hepatol 2016

The Real-life Lesson from VA. Primary Prevention Outperformed Secondary Prevention

15,059 Patients with advanced HCV [1]

Death Rates* SVR (-)12.5 *vs* SVR (+) 2.4 , *p<0.001*

Incident HCC* SVR (-) 9.7 *vs* SVR (+) 2.4 , *p<0.001*

* x 100 patient/year

Case/control study of surveillance uptake in cirrhosis[2]

238 who died with HCC 52.9%

238 who died w/o HCC 54.2 %

BUT : 2.1 US exams in 4-yr study period >50% "Milan in" < 15% resected or ablated,only. None transplanted.

1 Backus LI et al AASLD Washington 2017 abs # 78 ;Moon et al Gastroenterol ogy2018

HCC.Future Directions

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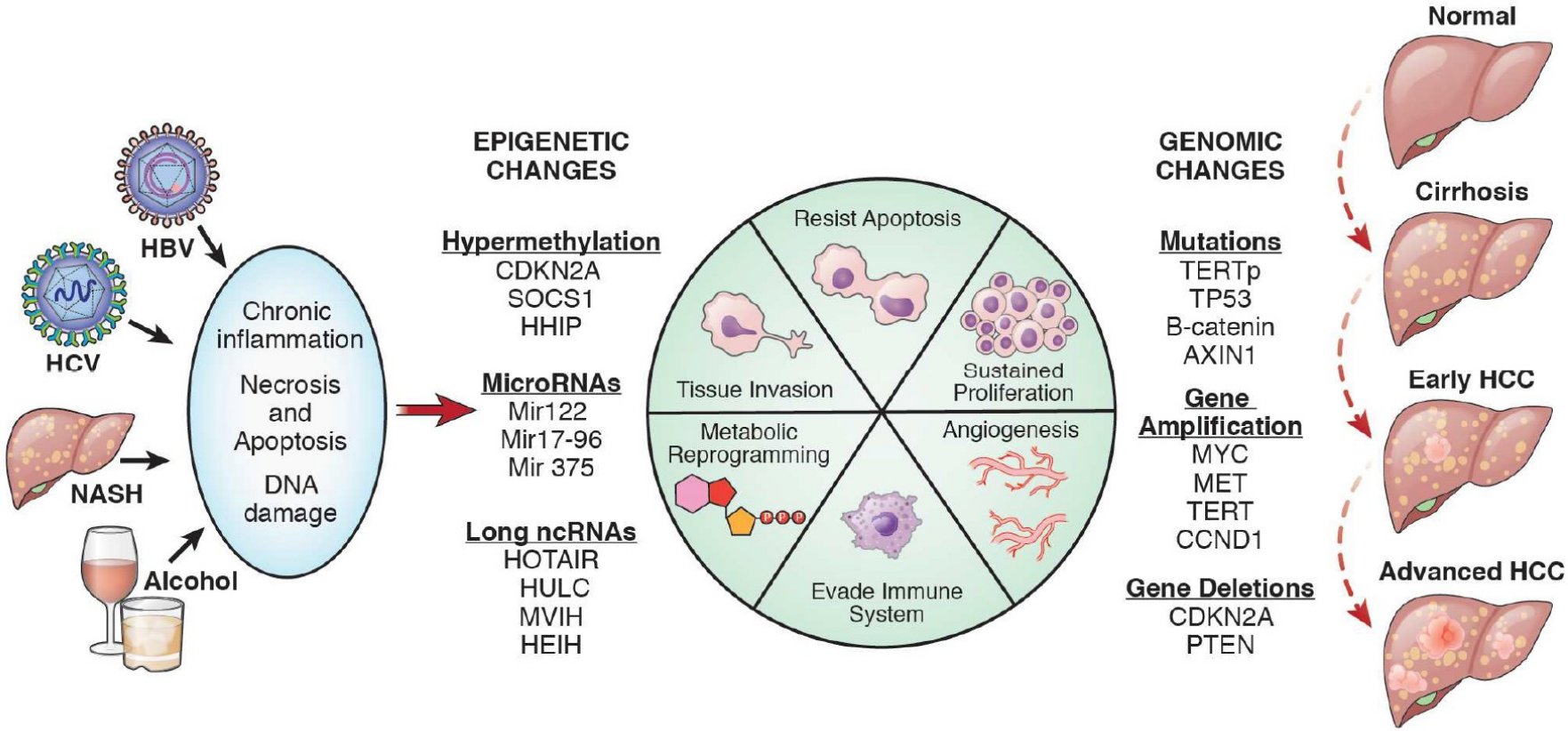
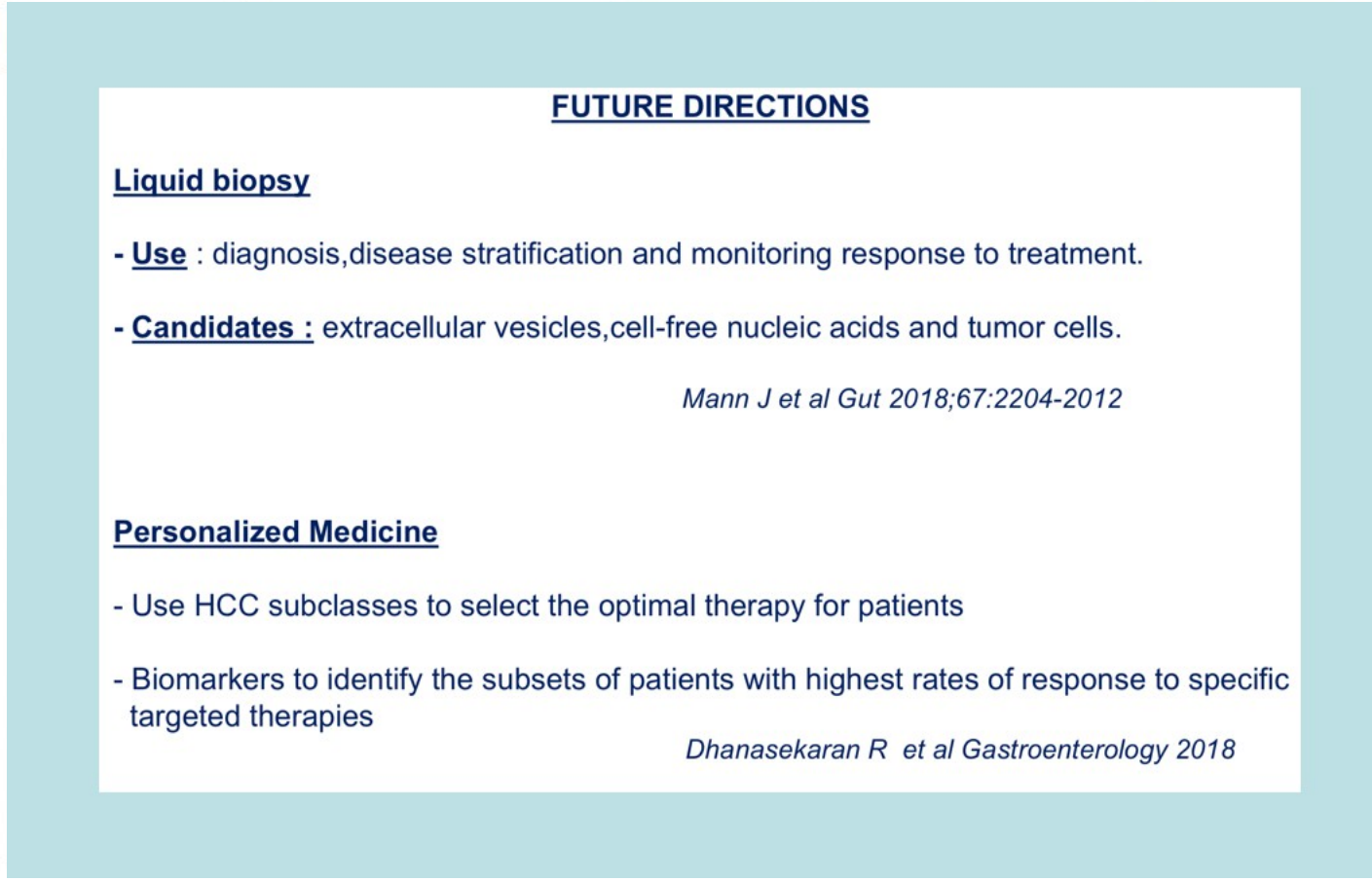
Epigenetic and Genomic Changes in the Pathogenesis of HCC



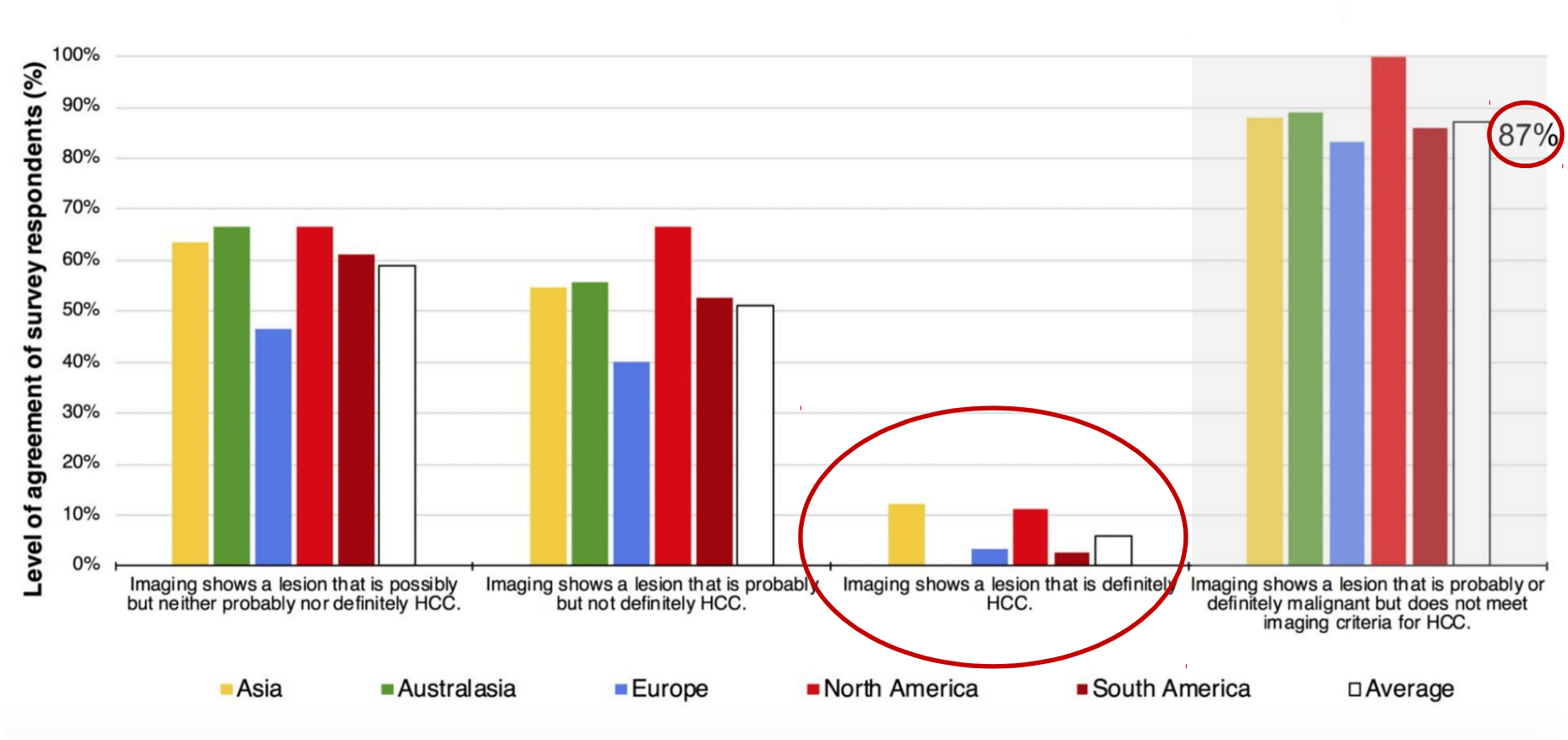
Dhanasekaran R et al Gastroenterology 2018

Genotype and Phenotype Classification of HCC



Dhanasekaran R et al Gastroenterology 2018

Diagnostic Biopsy Indications for Lesions by Region
More 'Routine' Biopsies to Confirm HCC ?



hould We Use More Routine Liver Biopsies o Diagnose HCC in Cirrhosis?

- EASL,AASLD & APASL recommend multiphase CT or multiphase MRI because of similar performance characteristics.
- Radiological diagnosis of HCC (wash-in / wash-out) : 100% specificity and PPV, 71% sensitivity for 1-2 cm tumors.

Wash-in / wash-out in iCCA

- CCA and HCC in cirrhotic livers may share similar enhancement patterns at multiphase dynamic MR imaging(Huang et al Radiology 2016)
- Prevalence and clinical significance of iCCA with radiological enhancement patterns mimicking HCC (Viganò et al submitted)

1 Forner A et al.,Lancet 2012

EASL Consortium for Regenerative Hepatology Aiming at a Bioengineered Liver

Editorial

JOURNAL OF HEPATOLOGY

The EASL International Liver Foundation: A growing pup with missions that are distinct yet integrated with those of its mother

Massimo Colombo[1,2,*], Tom Hemming Karlsen[3,4]

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