

Risk Stratification for HCC

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Disclosure

Research support

Allergan

Kyowa Hakko Kirin

Morphic Therapeutics

Roche

Consultancy

Ferring Pharmaceuticals

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Ownership

Alentis Therapeutics

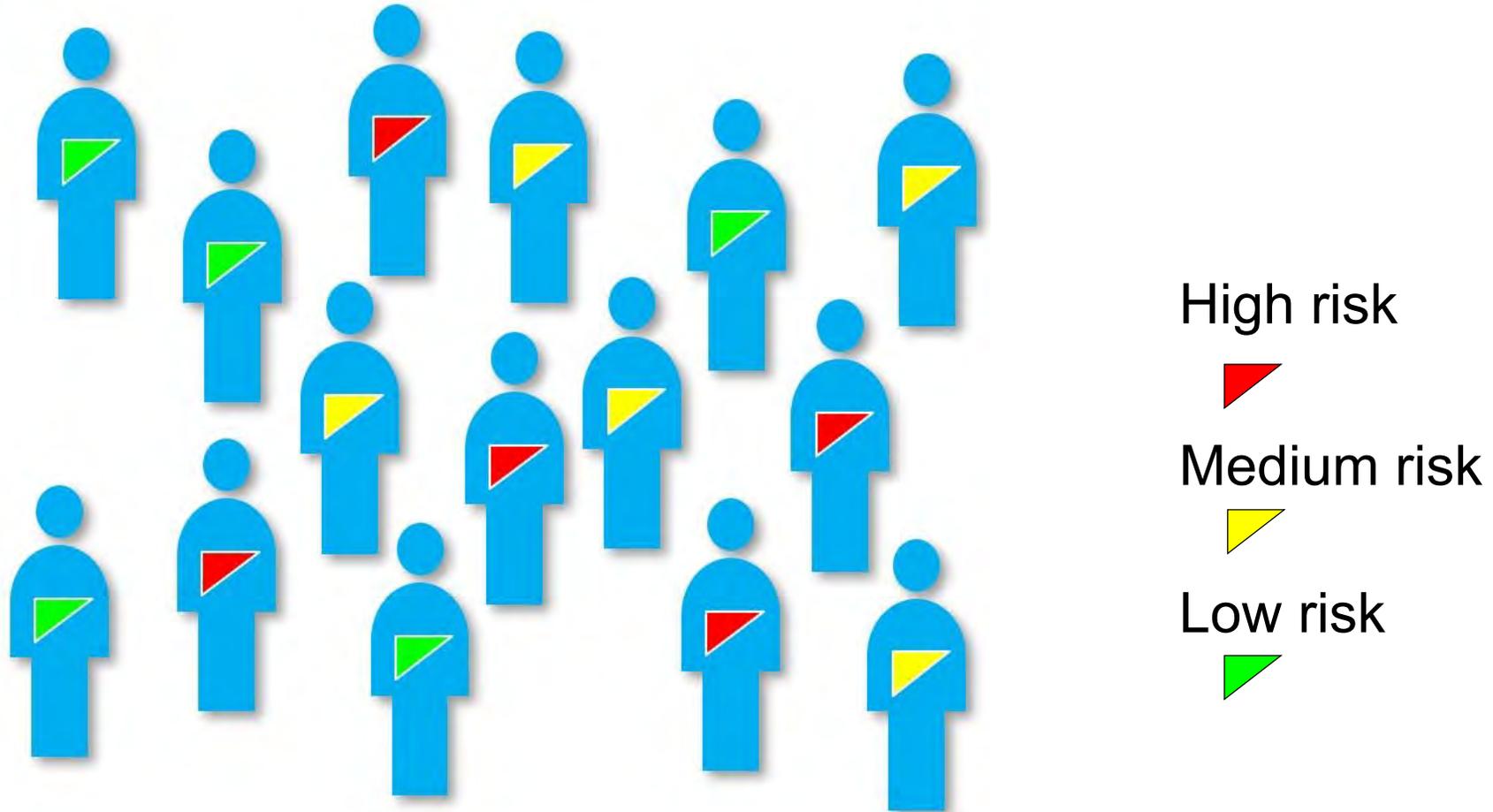
Outline

1. Why HCC risk stratification?
2. Clinical HCC risk indicators
3. Molecular HCC risk indicators
4. Benefit of risk-stratified HCC surveillance: *cost-effective?*

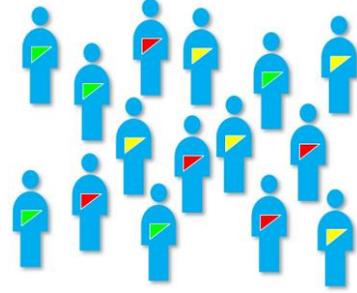
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Heterogeneous HCC risk across “at-risk” patients



“One-size-fits-all” HCC surveillance



Under-surveillance

Late HCC diagnosis

Over-surveillance

Physical, psychological,
& financial harms



High risk



Medium risk

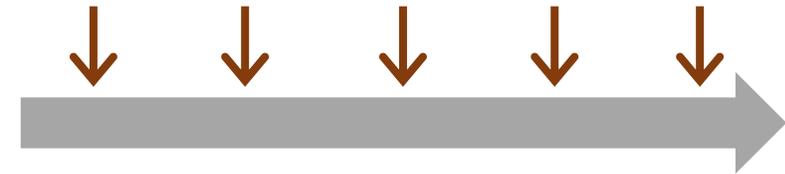


Low risk

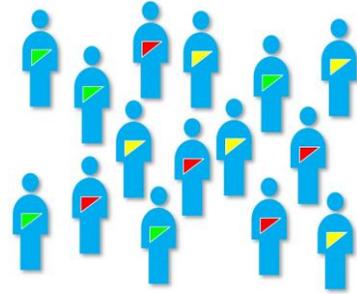


Semi-annual HCC surveillance

Ultrasound +/- AFP (every 6 months)



Risk-stratified HCC surveillance



Under-surveillance

Late HCC diagnosis

Over-surveillance

Physical, psychological,
& financial harms



High risk



Medium risk



Low risk



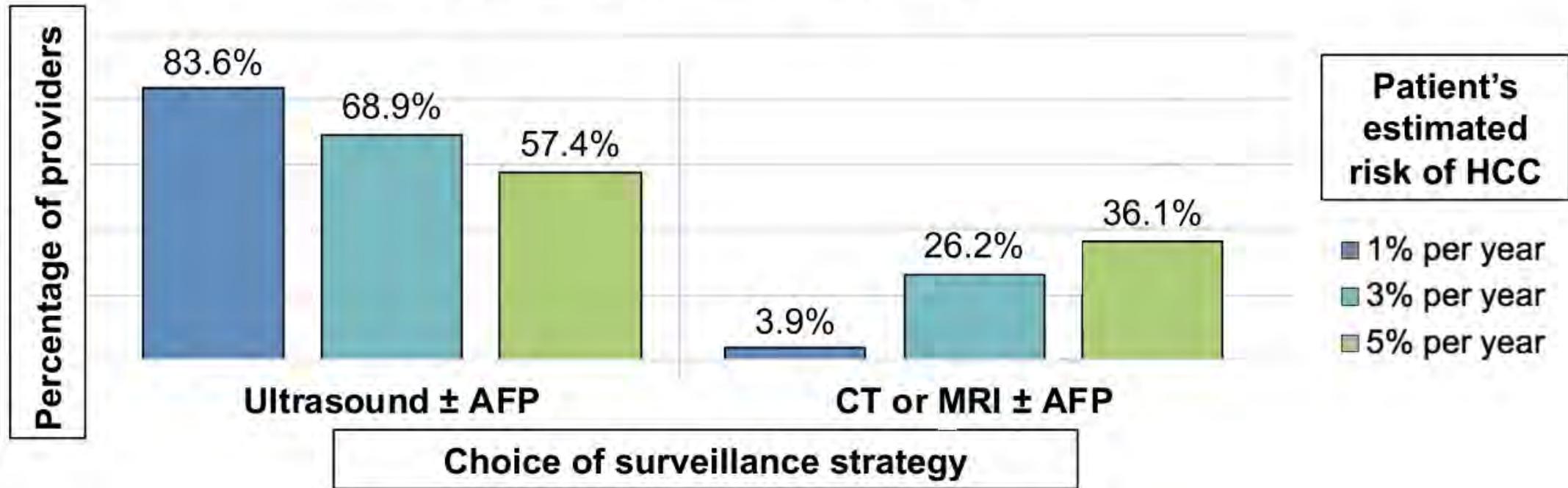
- High-performance & costly imaging, biomarkers
- More frequent exam



- Low-performance & cheap tests
- Less frequent exam

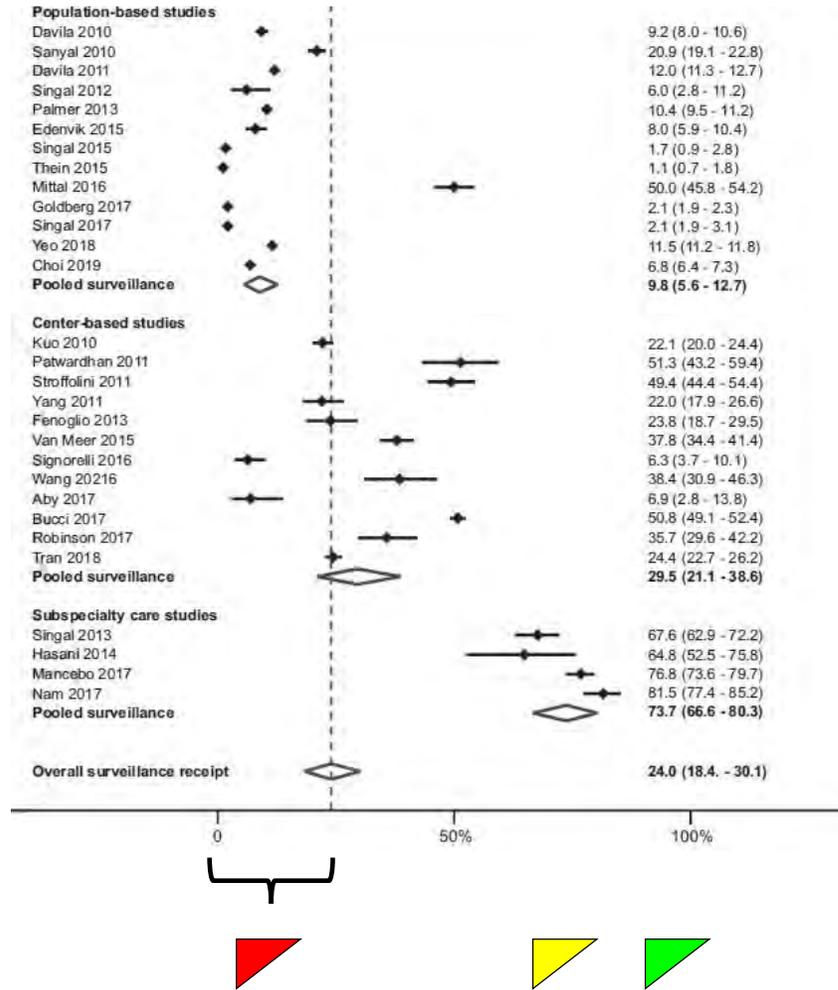
Physicians are receptive to risk-based tailoring

Providers' choice of HCC surveillance strategy by patient's estimated risk of HCC



Kim, *CGH* 2020

Allocate limited medical resources to high-risk patients?



HCC surveillance utilization rate

Community clinics: 9.8%

Specialized centers: 29.5%

Overall: 24%

High risk

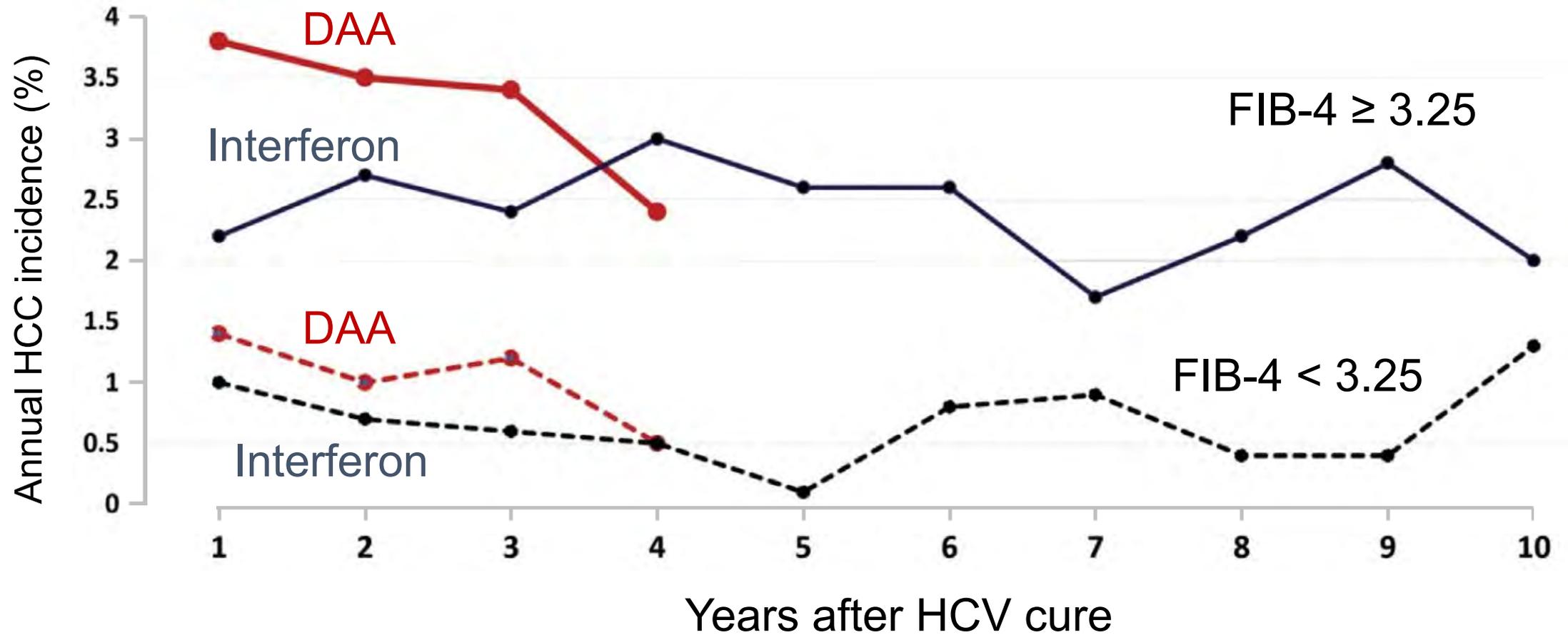
Medium/low risk

Wolf, *Hepatology* 2020

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Clinical HCC risk indicator: FIB-4 index



Ioannou *Gastro* 2019

Clinical HCC risk scores

Risk indicator	Etiology	Race/ethnicity
LSM-HCC score	HBV	Asian
REACH-B	HBV	Asian
CU-HCC	HBV	Asian
Yang, et al.	HBV	Asian
Hung, et al.	HBV	Asian
PAGE-B	HBV	White
Sohn, et al.	HBV	Asian
FIB-4	HBV	Asian
GAG-HCC	HBV	Asian
Shin, et al.	HBV	Asian
Kim, et al.	HBV	Asian
Singal, et al.	HCV	White, black, Hispanic
REVEAL-HCV	HCV	Asian
Ganne-Carrié, et al.	HCV	n.a.
Lok, et al.	HCV	White, black, Hispanic
El-Serag, et al.	HCV	White, black
Huang, et al.	HCC	n.a.
Motosugi, et al.	HCV	Asian
Chang, et al.	HCV after IFN	Asian
Ikeda, et al.	HCV after SVR	Asian
scoreHCC	HCV after SVR	Asian
Wang, et al.	HCV after SVR	Asian
ADRESS-HCC	HCV, alcohol, NASH/crypt	White, Hispanic
Velázquez, et al.	Alcohol, HCV	n.a.
VFMAP	Non-viral, HCV	Asian
Wen, et al.	General population	Asian

HCC risk calculator

IFLM | ALD - Cirrhosis | NAFLD - Cirrhosis

Cirrhotic:

SVR:

Age:

Gender:

BMI:

Race/Ethnicity:

Genotype 3:

Platelet Count:

AST:

ALT:

Albumin:

Hepatocellular Carcinoma (HCC) Risk calculator

- These models were developed using data from the Veterans Affairs healthcare system in patients with hepatitis C (Ioannou J Hep 2018 (69): 1088-1098) and NAFLD/ALD-cirrhosis (Ioannou J Hep 2019 (71): 523-533)
- The aim of this tool is to estimate the 3-year risk of HCC in patients with hepatitis C virus (HCV) infection who have undergone antiviral treatment or in patients with cirrhosis caused by alcohol-related liver disease (ALD) or nonalcoholic fatty liver disease (NAFLD).
- Enter the patient's age and labs, using values obtained before the initiation of HCV treatment.
- 3 year risk refers to the 3 year period after SVR ascertainment
- This risk calculator should not be used in patients with a previously diagnosed HCC, prior liver transplant, or cirrhosis from other etiologies (e.g. alcoholic liver disease, non-alcoholic fatty liver disease, hepatitis B).
- This risk calculator has not been validated among patients without prior HCV treatment.
- **This tool is not designed for use by patients.**
- For patients with Child A or B cirrhosis or Child C cirrhosis on the transplant waiting list, it is recommended they receive screening with abdominal ultrasound with or without serum AFP every 6 months.

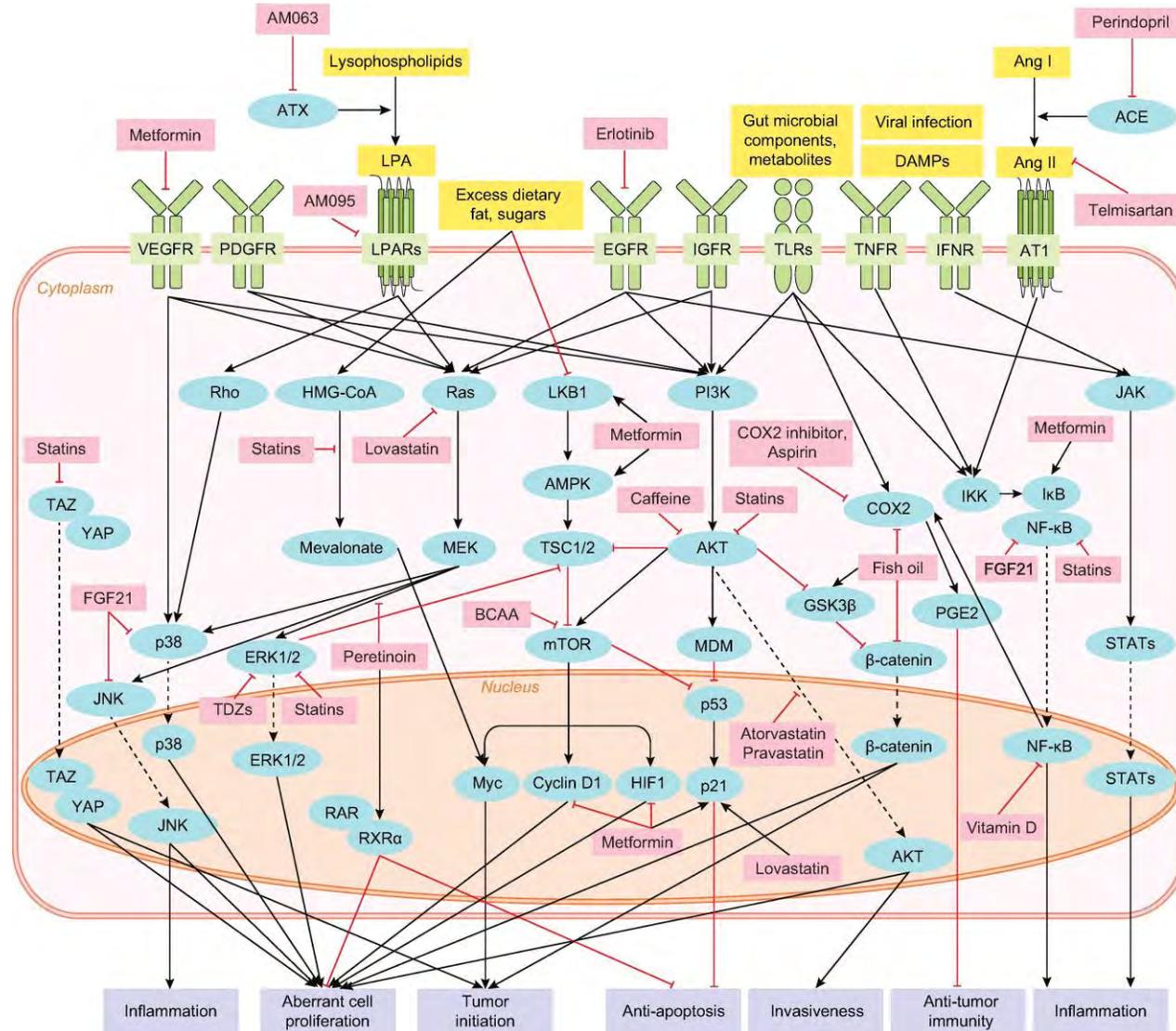
www.hccrisk.com

Fujiwara *J Hepatol* 2018

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Molecular HCC risk indicators may guide chemoprevention



Aspirin

(Simon *NEJM* 2020
Malemir *Nat Med* 2019)

Lipophilic statins

(Simon *Ann Intern Med* 2019)

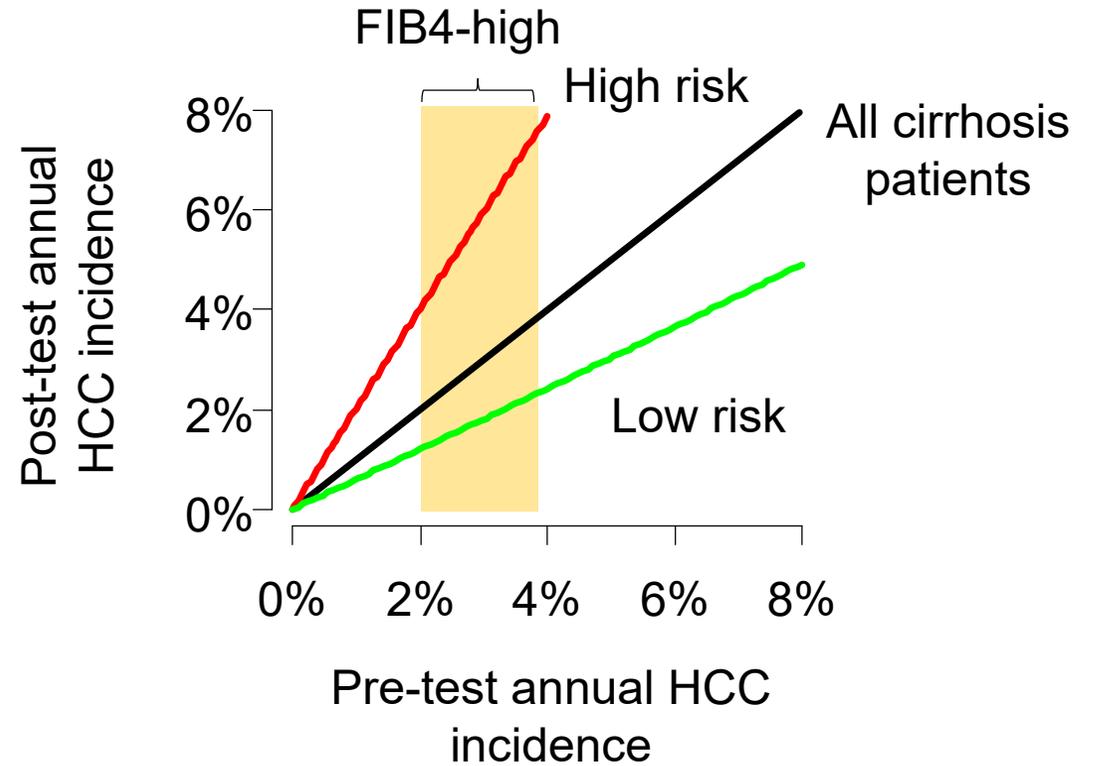
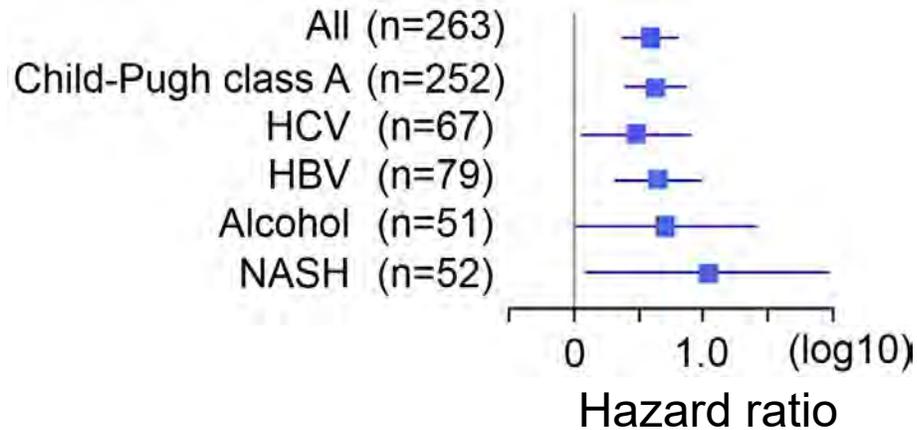
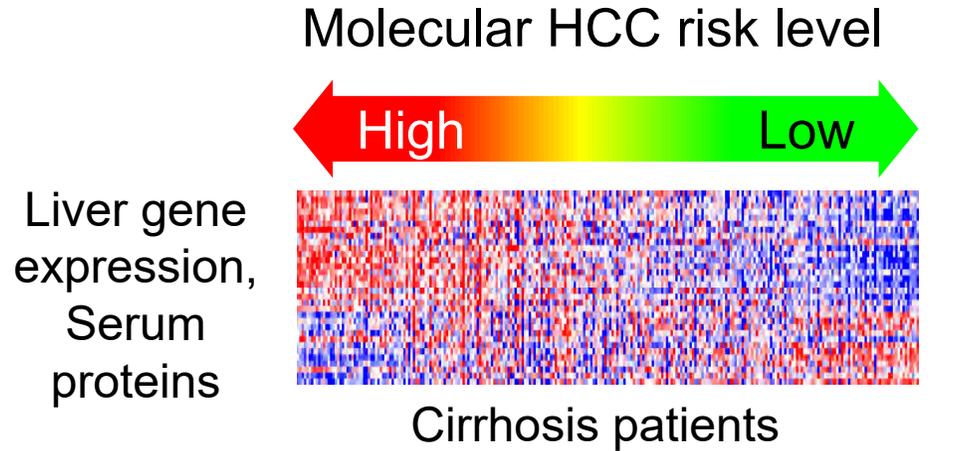
Fujiwara *J Hepatol* 2018

Molecular HCC risk indicators

Omics technology	Biomarker	Biospecimens
Germline DNA variants	<i>IFNL3</i> (rs12979860: C > T, rs8099917: T > G)	Blood, buccal swab
	<i>MICA</i> (rs2596542: C > T)	Blood, buccal swab
	<i>DEPDC5</i> (rs1012068: T > G)	Blood, buccal swab
	<i>TLL1</i> (rs17047200: A > T)	Blood, buccal swab
	<i>1p36.22</i> (rs17401966: A > G)	Blood, buccal swab
	<i>STAT4</i> (rs7574865 G > T)	Blood, buccal swab
	<i>HLA-DQB1/HLA-DBA2</i> (rs9275319 A > G)	Blood, buccal swab
	<i>PNPLA3</i> I148M (rs738409: C > G)	Blood, buccal swab
	<i>TM6SF2</i> E167K (rs58542926: C > T)	Blood, buccal swab
	<i>MBOAT7</i> (rs641738: C > T)	Blood, buccal swab
	<i>HSD17B13</i> (rs72613567 TA)	Blood, buccal swab
Gene-expression signatures	Prognostic liver signature	Liver tissue
	HIR gene signature	Liver tissue
	Activated HSC gene signature	Liver tissue
	HSC signature	Liver tissue
	Ectopic lymphoid structure signature	Liver tissue
	Immune-mediated cancer field signature	Liver tissue
Circulating nucleic acids	cfDNA mutation	Plasma
	cd-score	Plasma
	15-miRNA risk score	Serum
	9 miRNAs	Serum
Circulating metabolites	2 metabolites	Serum
	5 metabolites	Serum
	Urinary metabolite panel	Urine
Microbiome	Gut microbiome	Stool
	5-genera microbiome signature	Serum

Fujiwara *Hepatol Res* 2020

HCC risk molecular signature



Naoto Fujiwara

NEJM 2008, *Gastro* 2013, *Gut* 2015, *Cancer Cell* 2016, *Hepatol* 2017, *CGH* 2017, *Gut* 2020

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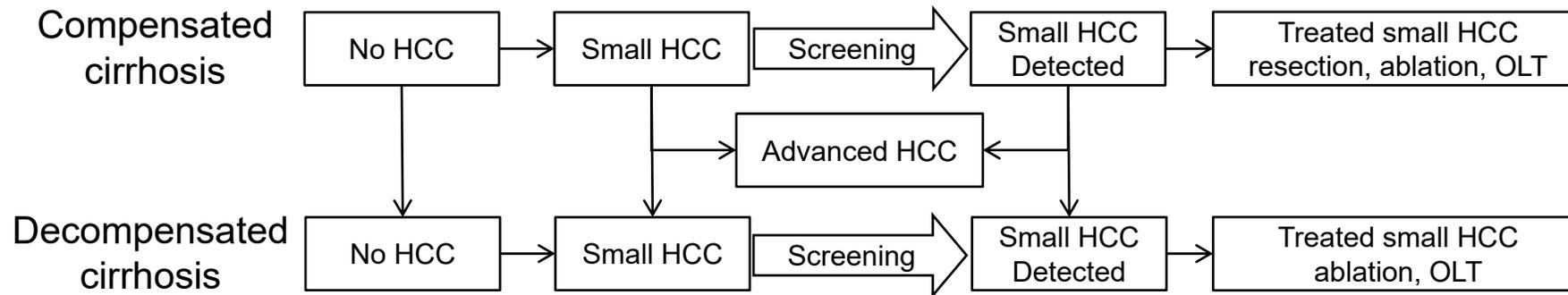
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Benefit of risk-stratified HCC surveillance

1. Potential strategies of risk-stratified HCC surveillance?
2. Magnitude of cost-effectiveness?
3. Desired performance/cost of risk stratification?

Simulation-based cost-effectiveness assessment

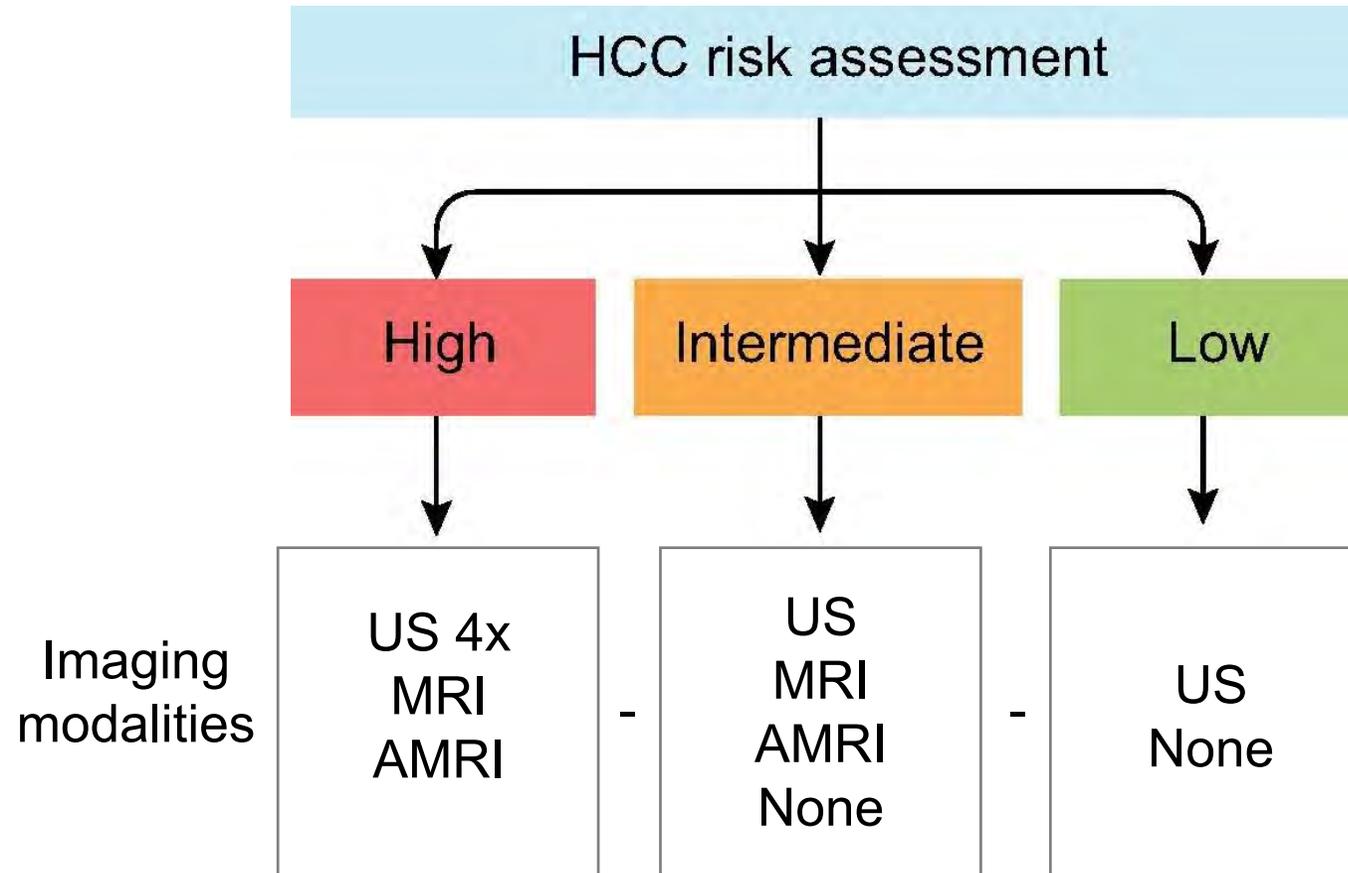
Markov model of HCC surveillance & natural history



- Health system perspective
- 50y compensated cirrhosis (n=10,000)
- Followed up with a 6-month cycle for 30 years
- Based on the costs, standard care in the U.S.

Goossens, *Clin Transl Gastro* 2017

Strategies of risk-stratified HCC surveillance



AMRI: abbreviated MRI

Goossens, *Clin Transl Gastro* 2017

Risk-stratified HCC surveillance is cost-effective

Willingness-to-pay measure

$$\text{ICER} = \frac{\text{Additional cost required}}{\text{Quality-adjusted life year gained}}$$

<\$50,000: cost-effective

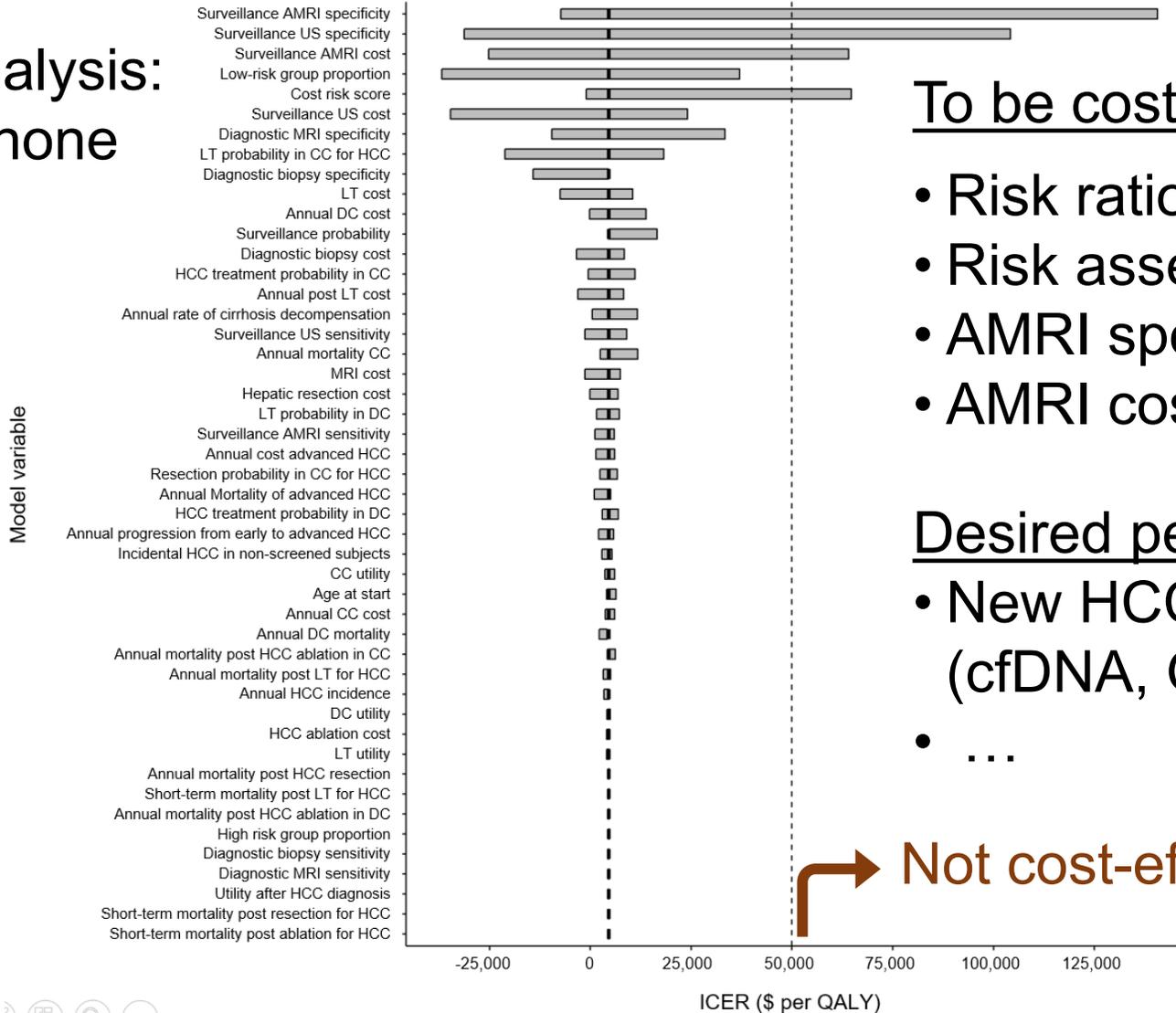
Strategy	ICER
MRI - US2x - US2x	\$89,367
AMRI - US2x - US2x	\$83,800
US4x - US2x - none	\$53,900
MRI - MRI - none	\$31,500
MRI - US2x - none	\$9,475
AMRI - AMRI - none	\$2,100
US2x - US2x - none	Dominant
AMRI - US2x - none	Dominant
MRI - none - none	Dominant

ICER: Incremental Cost-Effectiveness Ratio

Goossens, *Clin Transl Gastro* 2017

Factors influencing cost-effectiveness

Sensitivity analysis: AMRI-AMRI-none



To be cost-effective

- Risk ratio > 2x
- Risk assessment cost < \$3,400
- AMRI specificity > 89%
- AMRI cost < \$532

Desired performance/cost for

- New HCC detection test (cfDNA, GALAD, ...)
- ...

Not cost-effective

Summary

- Risk stratification will enable rational & more effective HCC surveillance
- Clinical and molecular HCC risk indicators can identify high-risk individuals
- Risk-stratified HCC surveillance is cost-effective
- Cost-effectiveness guides desired performance/cost of HCC risk stratification & surveillance modalities