# Hepatocellular Carcinoma – From Screening to Treatment

## Current Practice, Pearls, and Puzzles

***UTHSC 4TH ANNUAL CURRENT PERSPECTIVES IN HEPATOLOGY***

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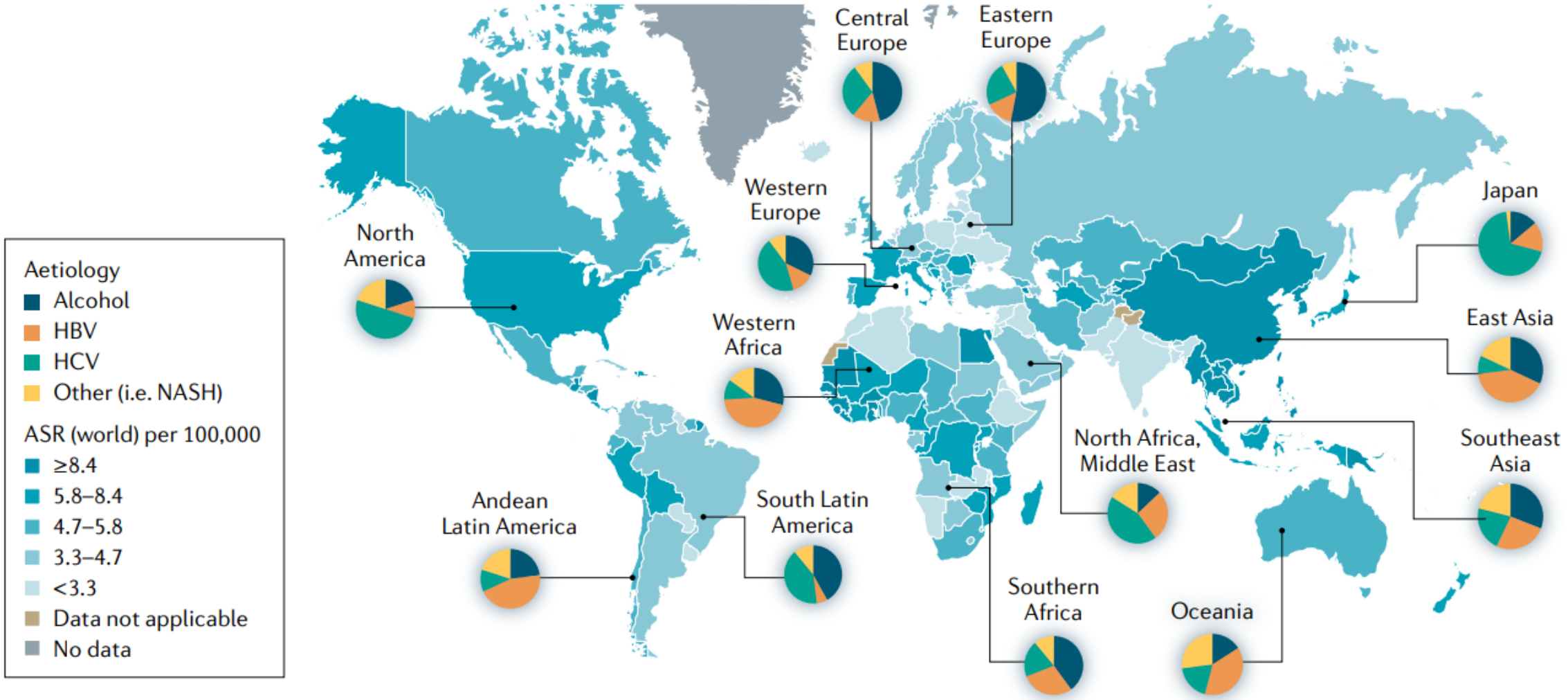
VA HEALTH CARE | Defining EXCELLENCE in the 21st Century

# I HAVE NO DISCLOSURES

# Objectives

- Understand the present state of HCC management, including areas with emerging data such as biomarker development.
- Identify at-risk populations, order appropriate screening and diagnostic tests, understand when to refer and how to treat HCC.
- Appreciate the cutting edge by exploring new therapeutics and treatment paradigms for HCC.
- Implement multidisciplinary management with the key stakeholders involved in decision-making.

# HCC is a global health problem.




Llovet et al. *Nat Rev Dis Primers* 2021

# HCC is a leading cause of liver-related and cancer-related mortality.

- HCC is the leading cause of death in cirrhosis.
- 3rd leading cause of cancer-related deaths worldwide in 2020 (830,180 deaths).
- Chronic liver disease (HBV/HCV/ALD/NASH) is a prerequisite in 90% of cases.
- Hepatocellular carcinoma (HCC) incidence tripled in the US from 1990-2020.

Mittal et al. *J Clin Gastro* 2013
Ryerson AB et al. *Cancer* 2016
Bray F et al. *Cancer* 2018
Globocan (https://gco.iarc.fr/today/data/factsheets/cancers/11-Liver-fact-sheet.pdf)

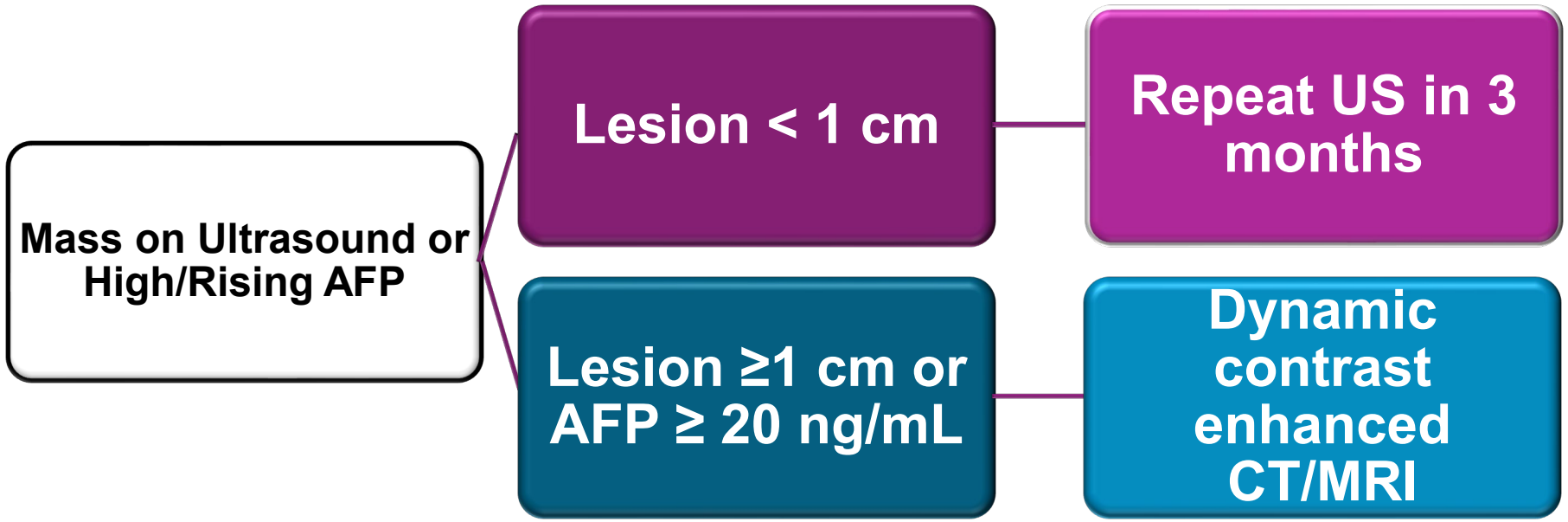
# Who should get surveillance?

**Liver US+AFP every six months in:**

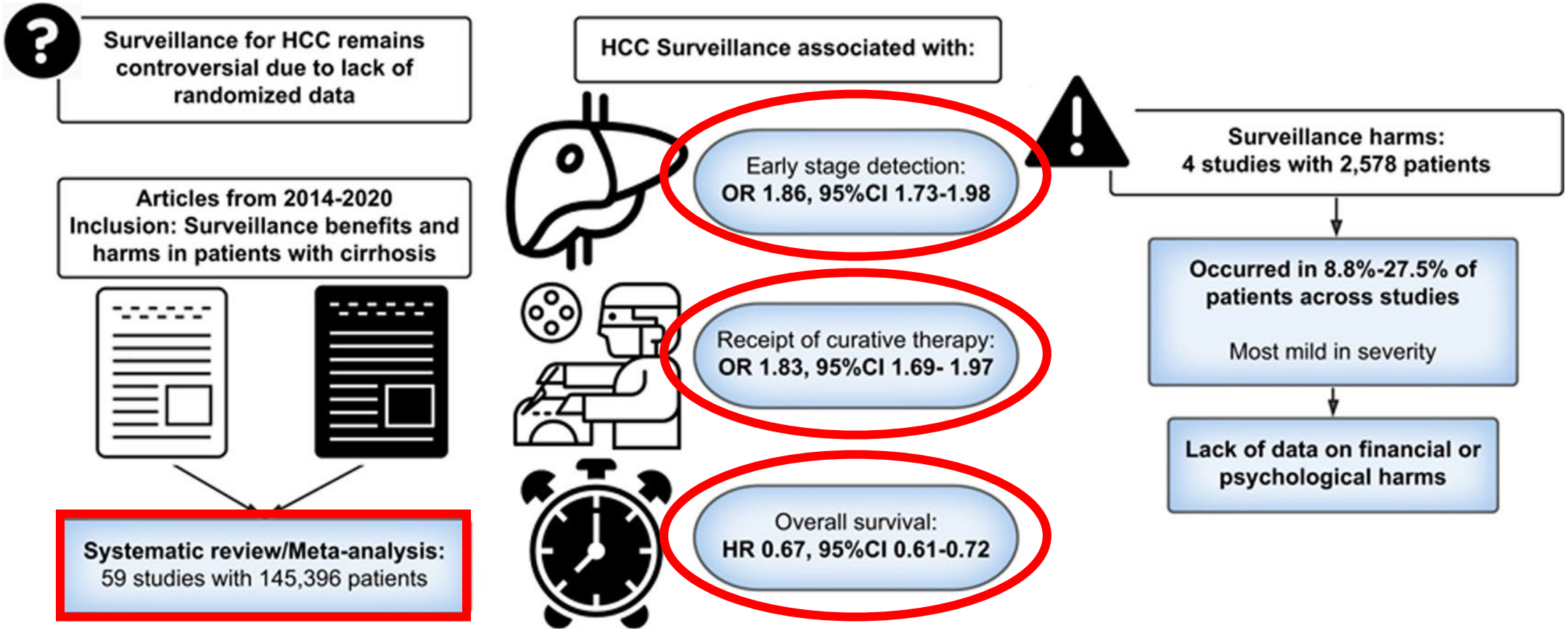
- **All patients with cirrhosis**
- **Patients with chronic hepatitis B (regardless of cirrhosis)**

**Gray areas**

- Patients with Child Pugh C cirrhosis (non-transplant candidates)
- NAFLD without cirrhosis
- HCV after SVR in patients without cirrhosis or FIB-4 ≥ 3.25



# Liver cancer surveillance saves lives.

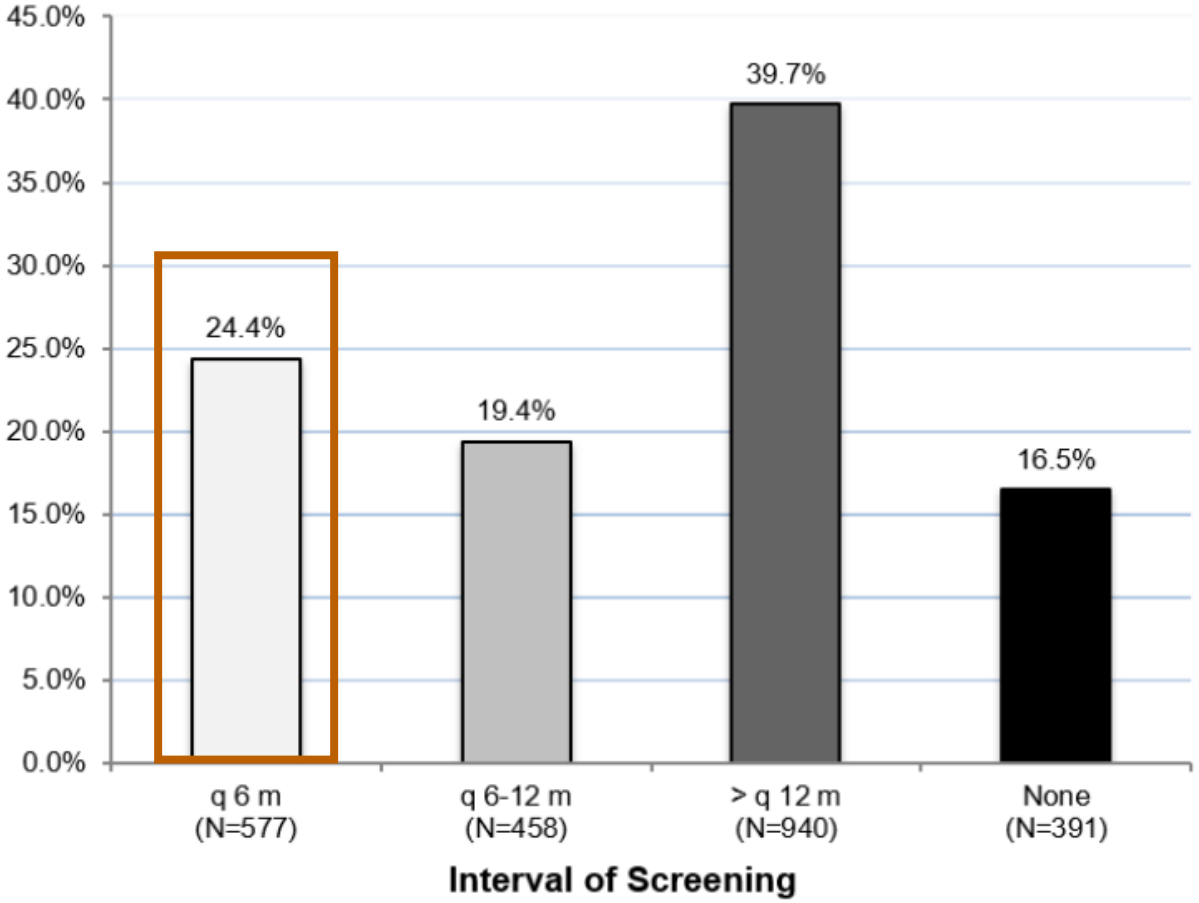



Surveillance is advised by all GI/Liver Societies and NCCN,
But ASCO and USPSTF do not advise surveillance

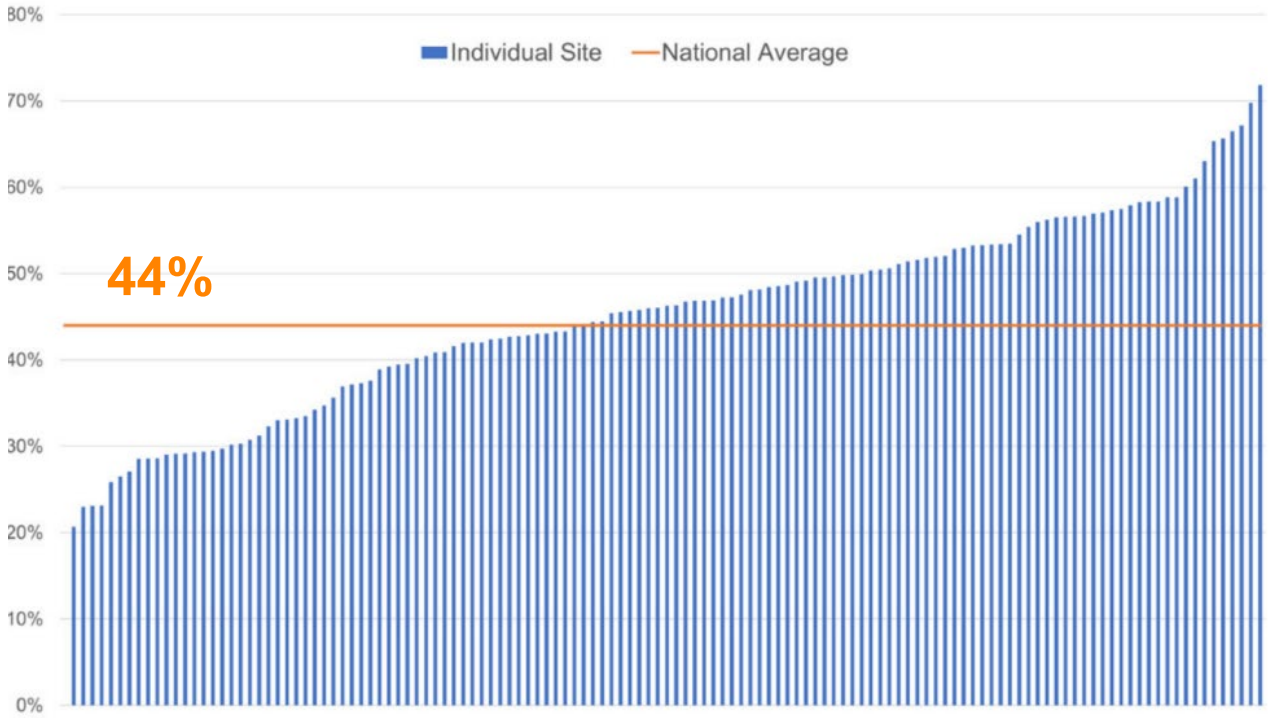
Singal et al. *J Hepatol* 2022

# Surveillance rates are poor.

Private Sector HCV Cohort



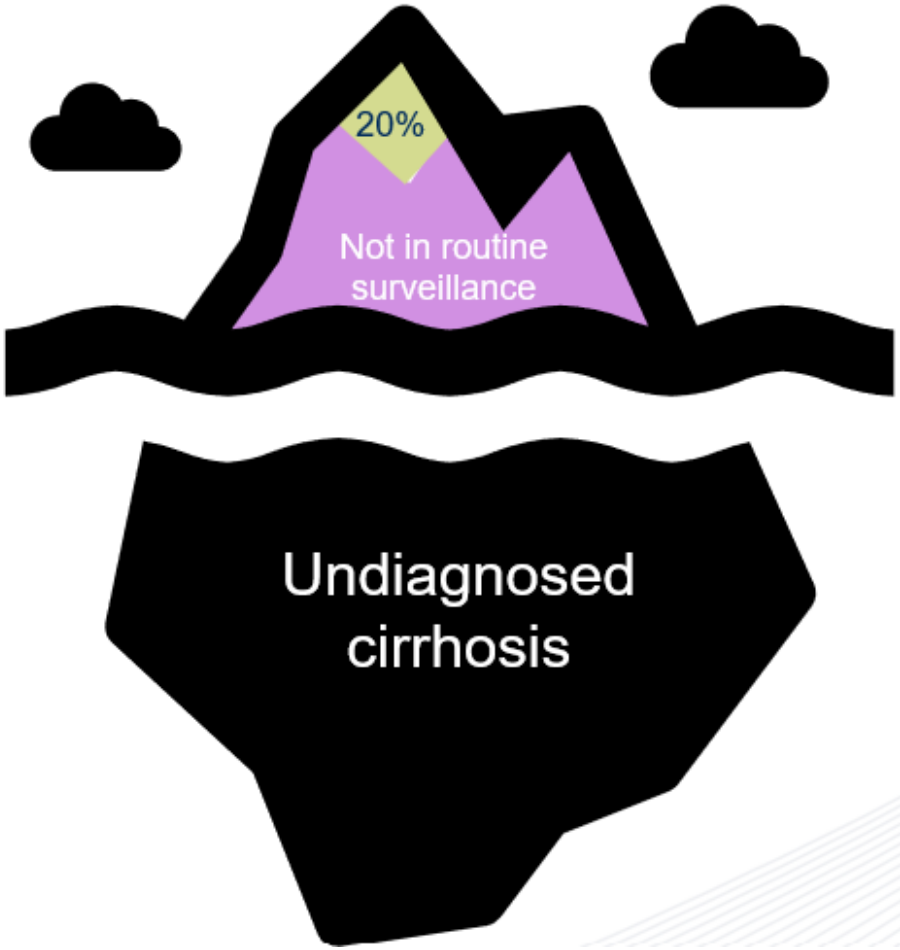

National VA Data




**Proportion of Veterans Receiving HCC Surveillance (FY18) by Facility**

Tran et al. *BMJ Open Gastroenterology* 2018
Rogal et al. *Cancers* 2021

# We only see the tip of the iceberg.




- Linkage to liver cancer care starts with identifying cirrhosis and starting surveillance
- Primary care providers need to be educated to suspect cirrhosis
- **Surveillance needs a mandate**

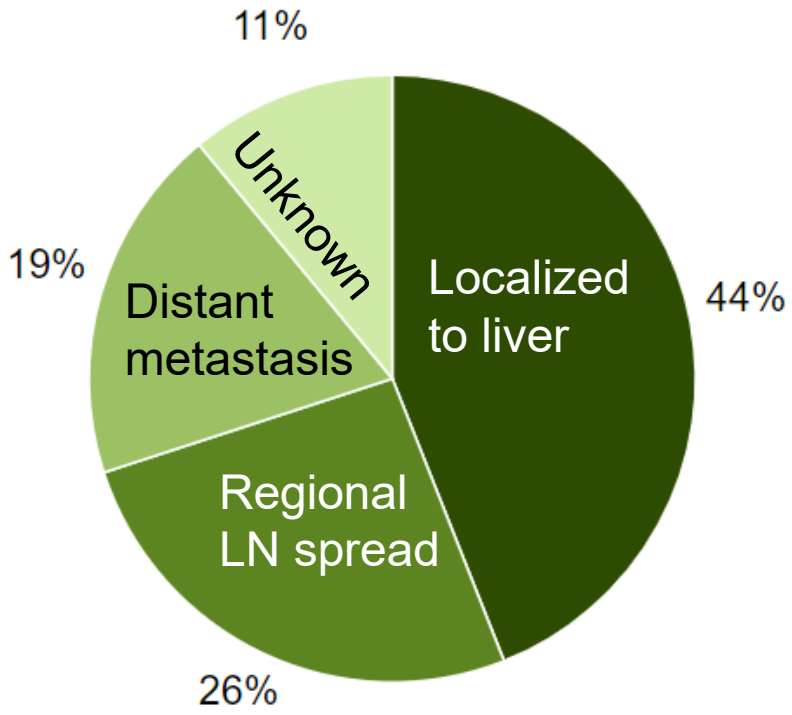
# At risk populations are changing with the changing natural history of liver disease.

- HCV post-SVR patients without cirrhosis
  - Incidence is significantly lower
  - Surveillance is not cost-effective
- Non-cirrhotic NAFLD
  - Up to one third of NAFLD-related HCC occurs in the absence of cirrhosis
  - Annual HCC incidence of 0.008 per 100 person-years
- Risk stratification tools to identify those at highest risk
- Surveillance on a case-by-case basis

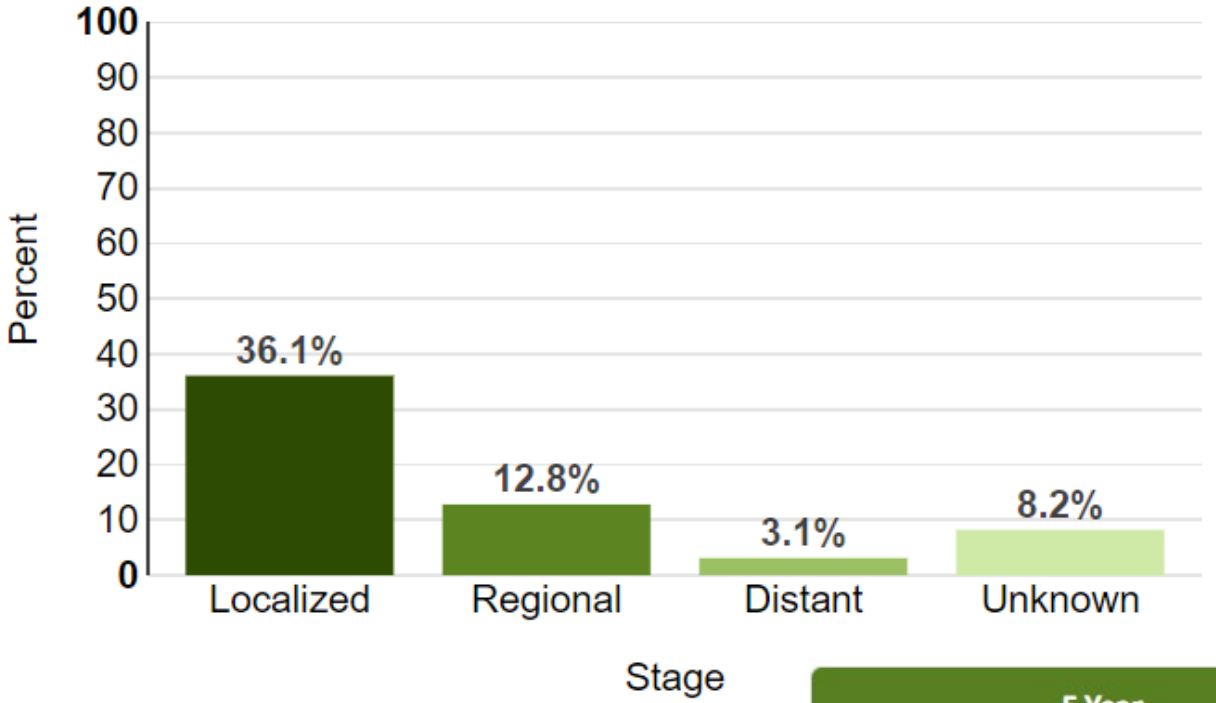
Farhang Zangneh et al. *Clin Gastroenterol Hepatol* 2019
Orci et al. *Clin Gastroenterol Hepatol* 2022

# HCC is diagnosed late.

**Percent of Cases by Stage**



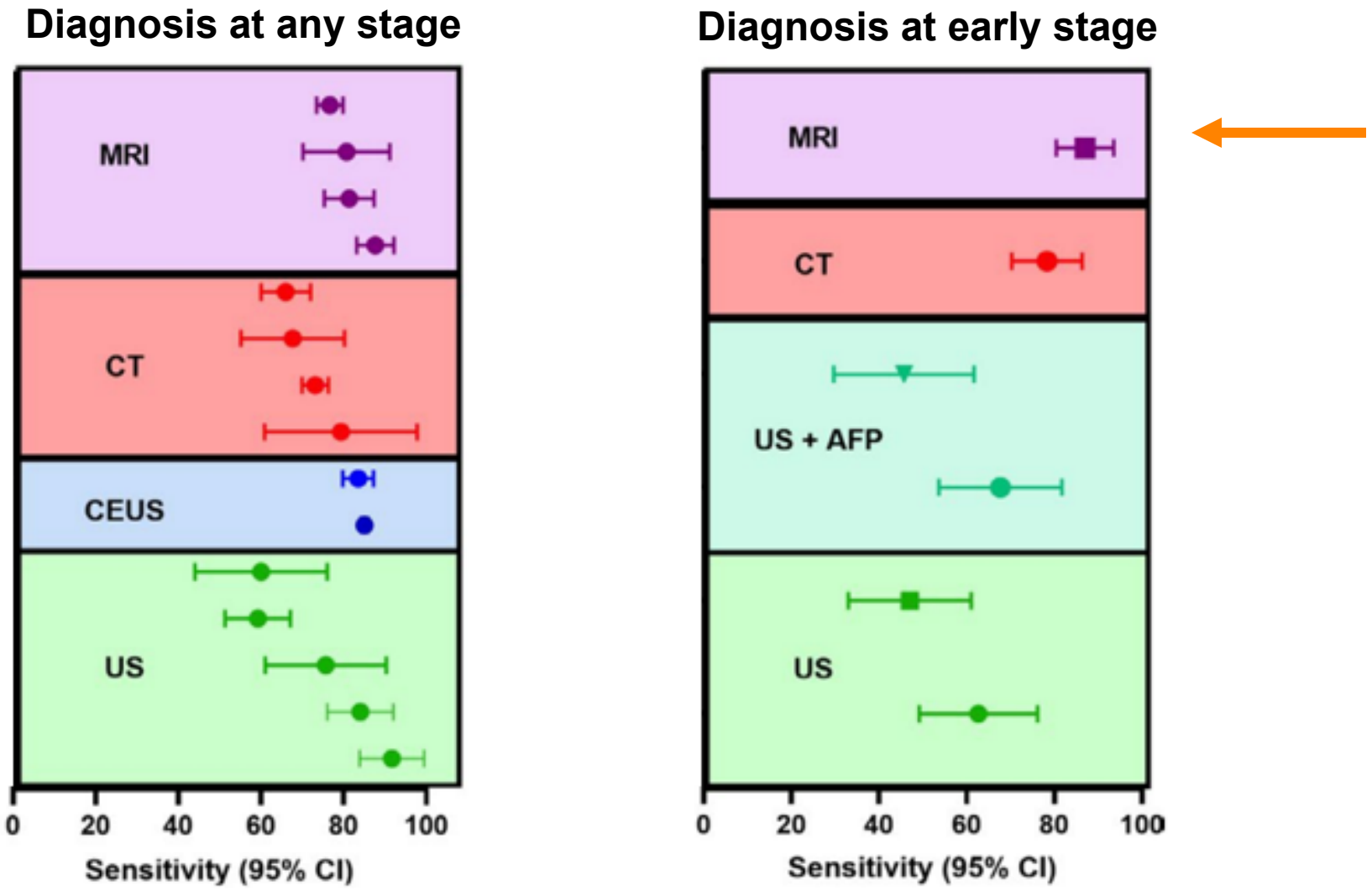

**5-year Relative Survival**




| 5-Year Relative Survival |
| --- |
| 20.8% |
| 2012–2018 |

SEER 17 2012–2018, Liver and Intrahepatic Bile Duct Cancer, All Races, Both Sexes by SEER Combined Summary Stage, Liver and Intrahepatic Bile Duct Cancer — Cancer Stat Facts

# Ultrasound lacks sensitivity for early stage detection of HCC.




Adeniji and Dhanasekaran, *Hepatology Communications* 2021

# Could we move the needle on early detection?

| Imaging | Pros | Cons | Emerging Innovations |
|---|---|---|---|
| 1. US scan | Easy to perform, accessible, Cost-effective | Lower sensitivity than MRI Interobserver variablity | Contrast enhanced US Standardization of reporting |
| 2. CT scan | Higher sensitivity than US, Faster and less expensive than MRI | Need for IV contrast Exposure to radiation | Contrast and Radiation dose reduction strategies |
| 3. MRI scan | Higher sensitivity than US | Expensive, not widely available, takes long time | Abbreviated MRI with shorter imaging times |

Adeniji and Dhanasekaran, *Hepatology Communications* 2021

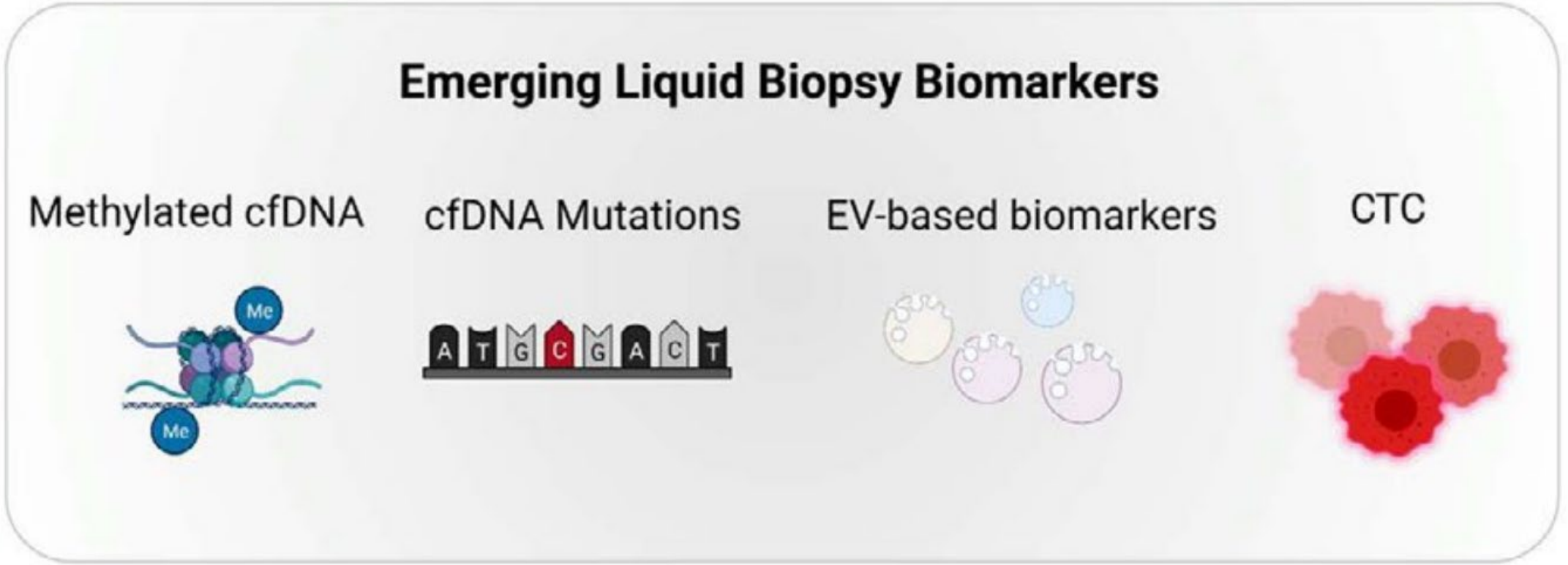
# Biomarkers for early detection vary in performance and readiness

| Test | EDRN phase of validation | Performance characteristics | |
|---|---|---|---|
| **US plus AFP** | **5** | Sensitivity<br>Specificity | 61%<br>92% |
| **AFP-L3%** | **3** | Sensitivity<br>Specificity | 62%<br>90% |
| **DCP** | **3** | Sensitivity<br>Specificity | 40%<br>81% |
| **Multitarget algorithm** | **2** | Sensitivity<br>Specificity | 82%<br>87% |
| **GALAD** | **2/3** | Sensitivity<br>Specificity | 54–72%<br>90% |
| **Doylestown plus** | **2/3** | Sensitivity<br>Specificity | 90%<br>95% |

- US, ultrasound
- AFP-L3%, *Lens culinaris* lectin binding subfraction of AFP
- DCP, des-gamma carboxyprothrombin
- Multitarget algorithm: information from 3 **methylation markers** (*HOXA1*, *TSPYL5*, *B3GALT6*), AFP, and **patient sex**
- GALAD: **gender**, **age**, AFP-L3%, AFP, and DCP
- Doylestown Plus: **age**, logAFP, PEG-precipitated IgG, and **fucosylated kininogen**

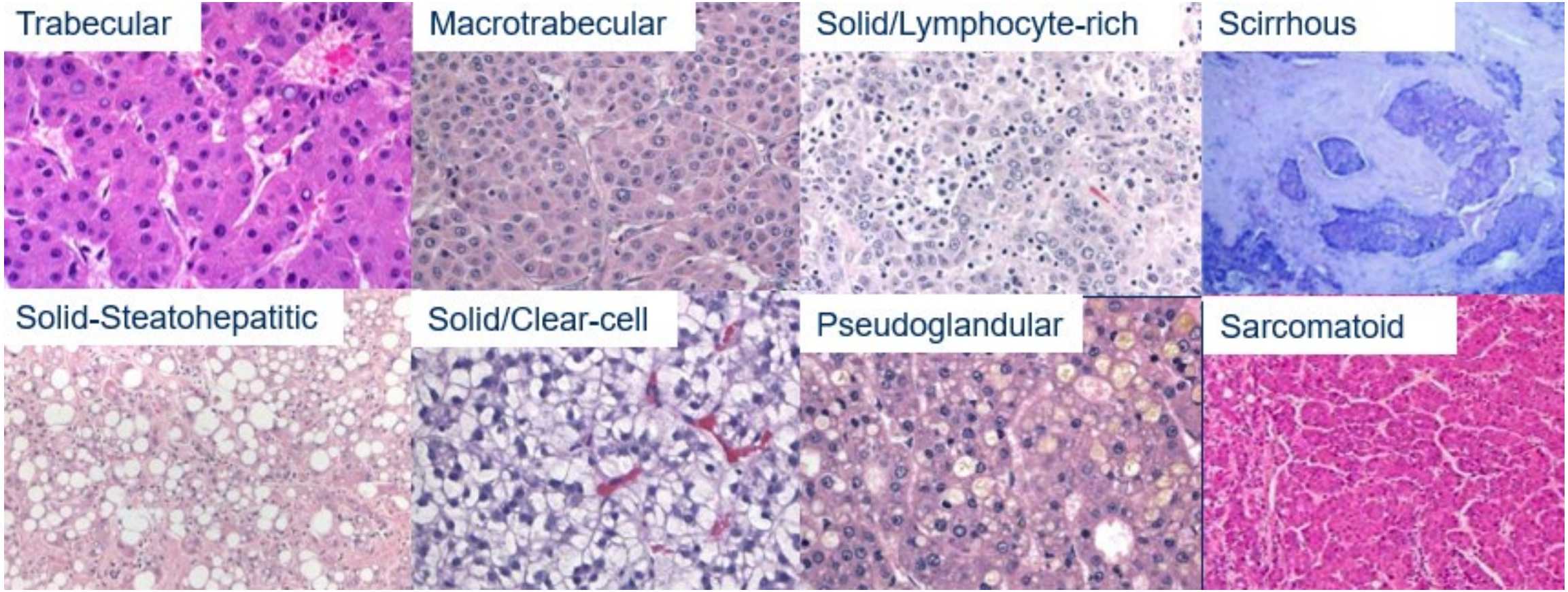
Parikh et al. *Cancer Epidemiol Biomarkers Prev*. 2020

# Liquid biopsy is encouraging, but requires cross validation and better precision

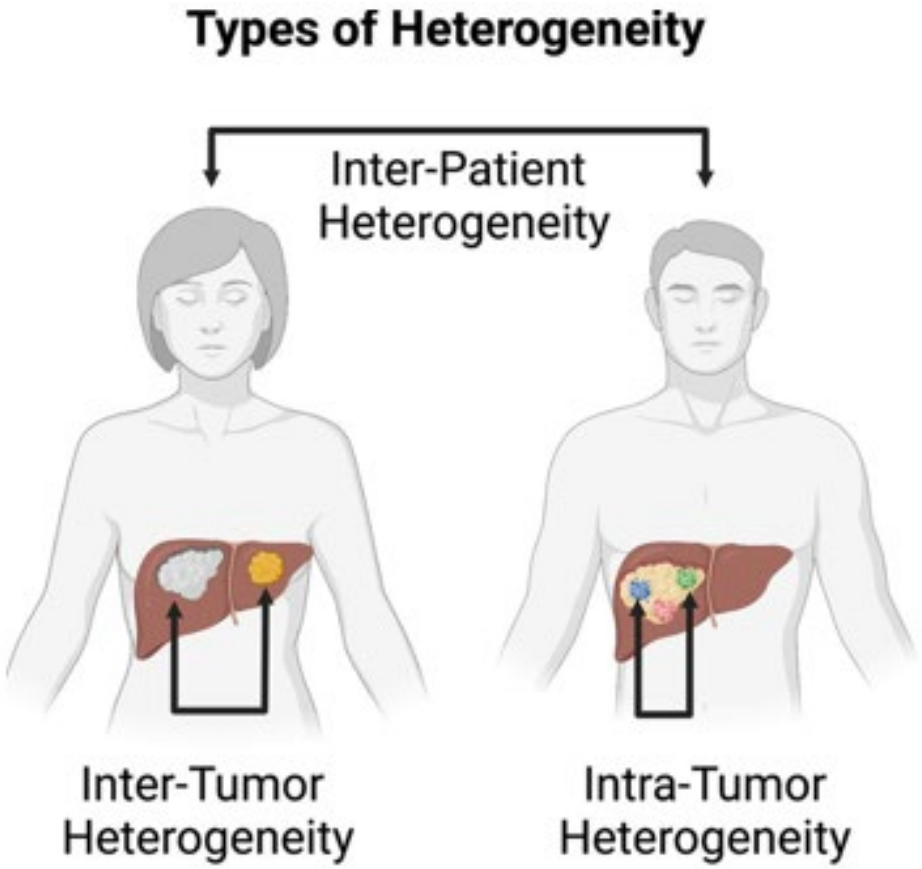


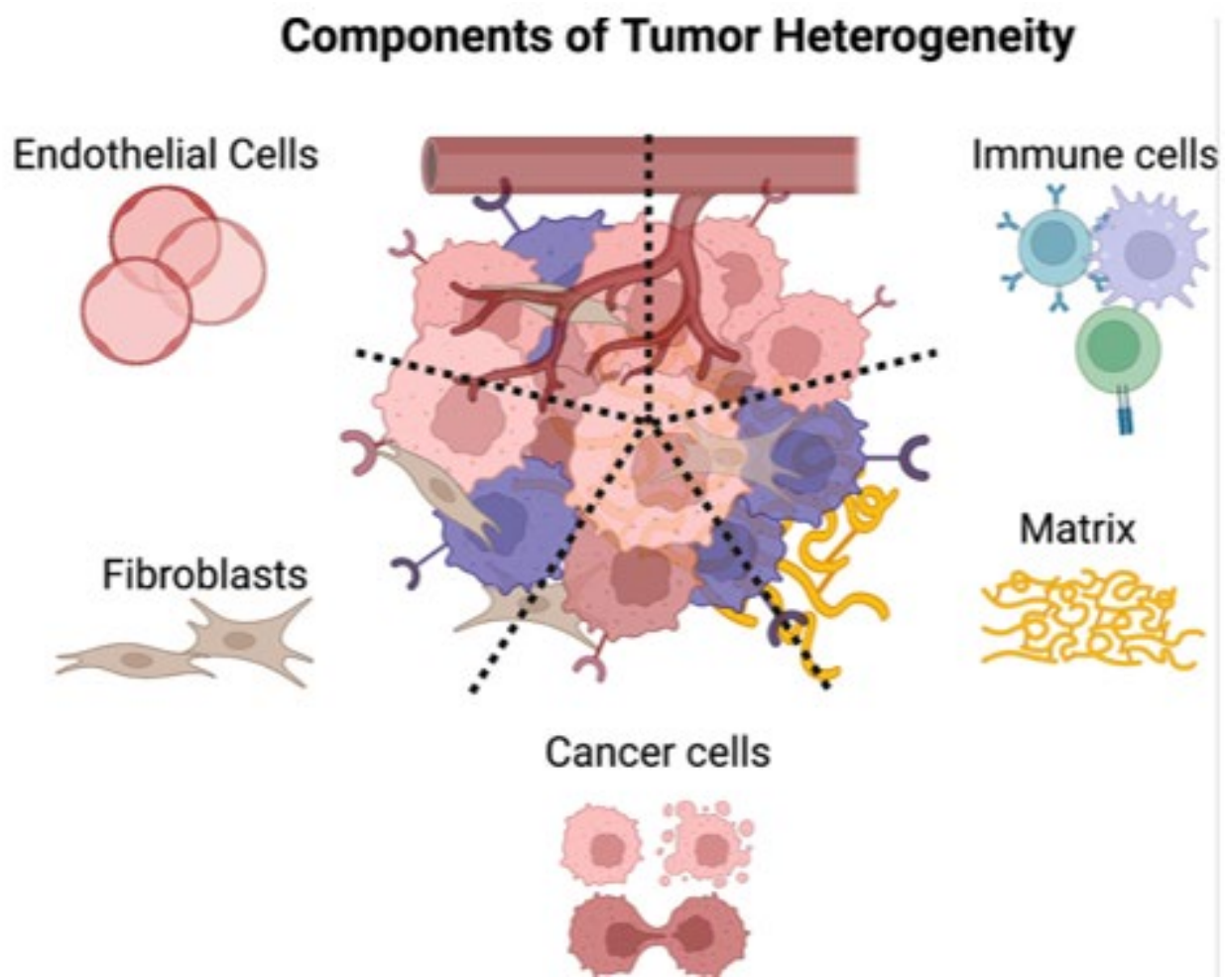

Adeniji and Dhanasekaran, *Hepatology Communications* 2021

# HCC is a heterogeneous cancer.



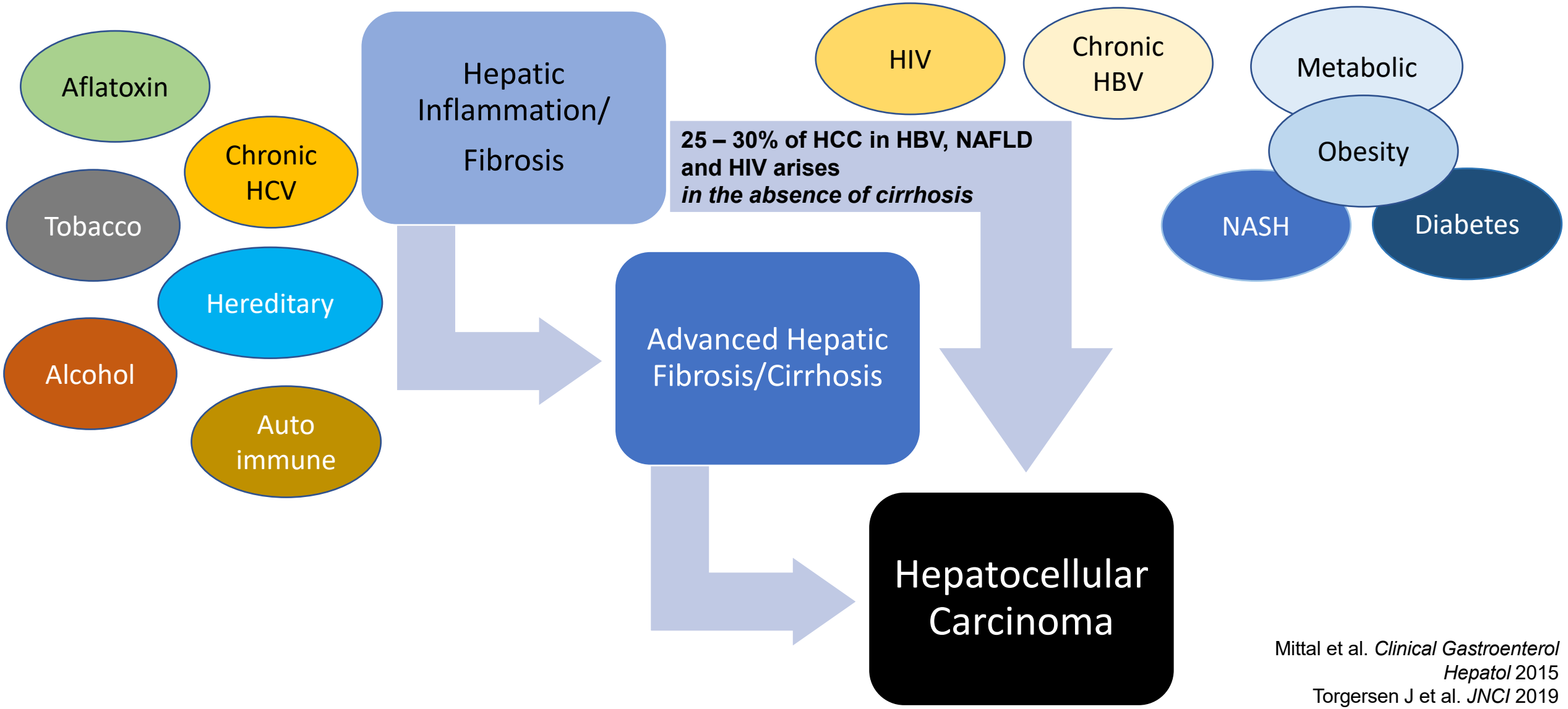
# It gets even more complicated.




Suresh and Dhanasekaran, *Adv Cancer Res* 2022

# Teasing out oncogenic pathways from hepatic injury and repair is complex (and not linear).



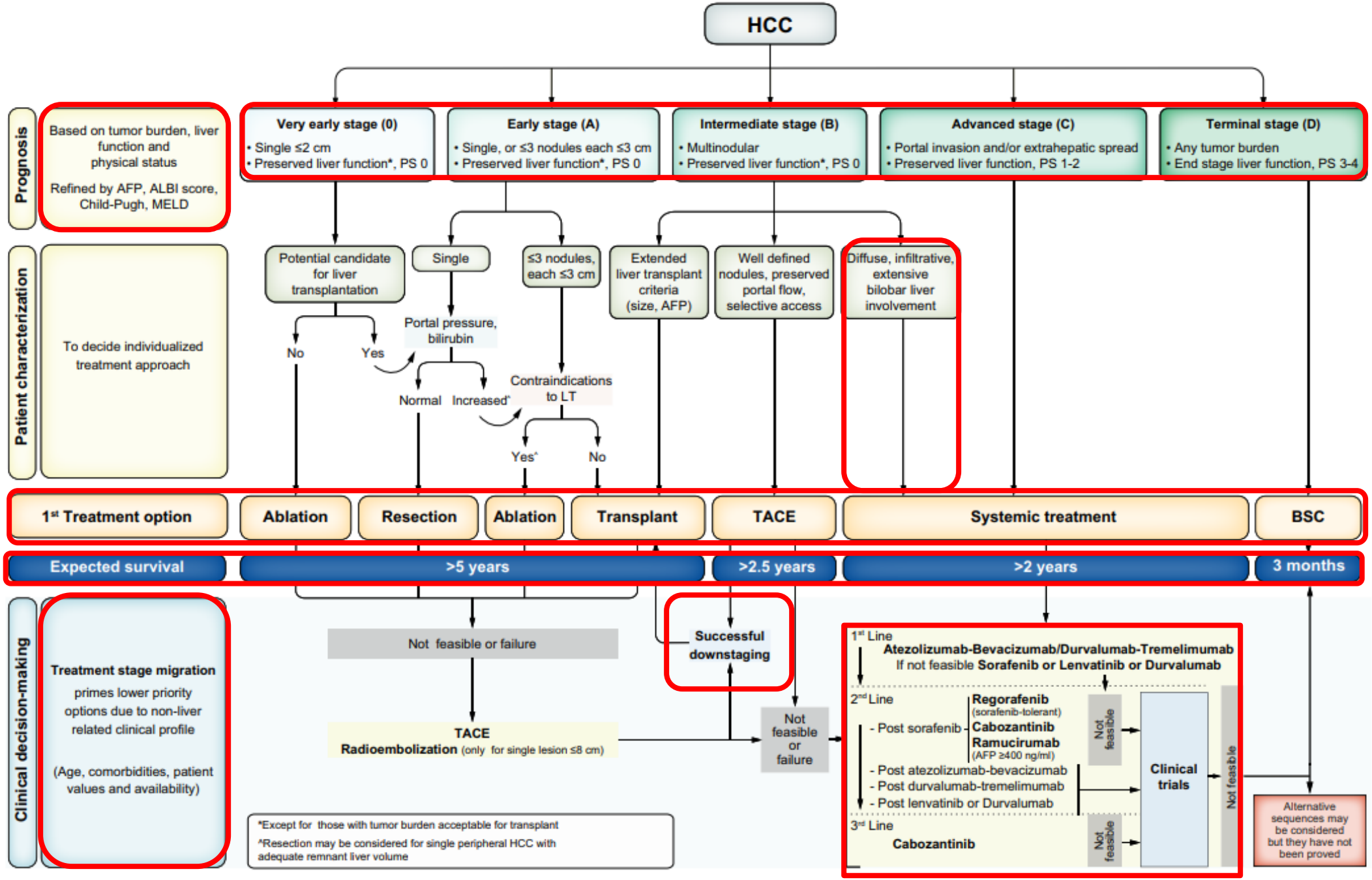

Mittal et al. *Clinical Gastroenterol Hepatol* 2015
Torgersen J et al. *JNCI* 2019

# HCC is clinically complicated, because it is unique among cancers.

- 1 patient, 2 diseases
  - Cirrhosis leads to
    - **multifocal** liver cancer
    - **high recurrence** rates
  - Cirrhosis complicates treatment and trial design
- HCC can be diagnosed by **imaging alone**
- HCC is the only solid organ malignancy for which **transplantation offers a cure**

# Treatment of HCC has followed a linear pathway from early to advanced disease.

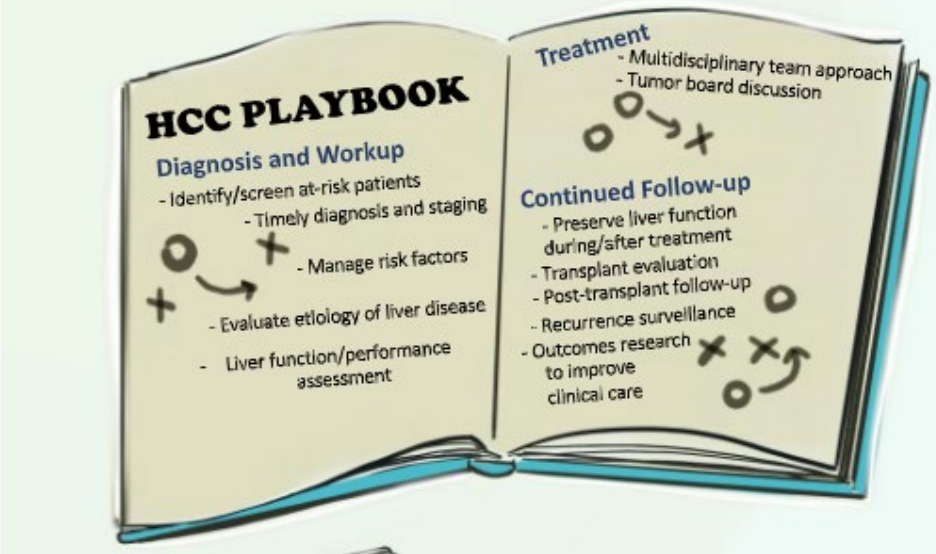
- Hepatology, surgery (surgical oncology and transplant surgery) and interventional radiology dominate early-stage disease
- Oncology is usually consulted only in diffuse, infiltrative intermediate-stage disease or in advanced disease (vascular invasion or extrahepatic metastases)
- The advent of new therapies is challenging this paradigm, not only the timing of specialty involvement but the types of specialists involved

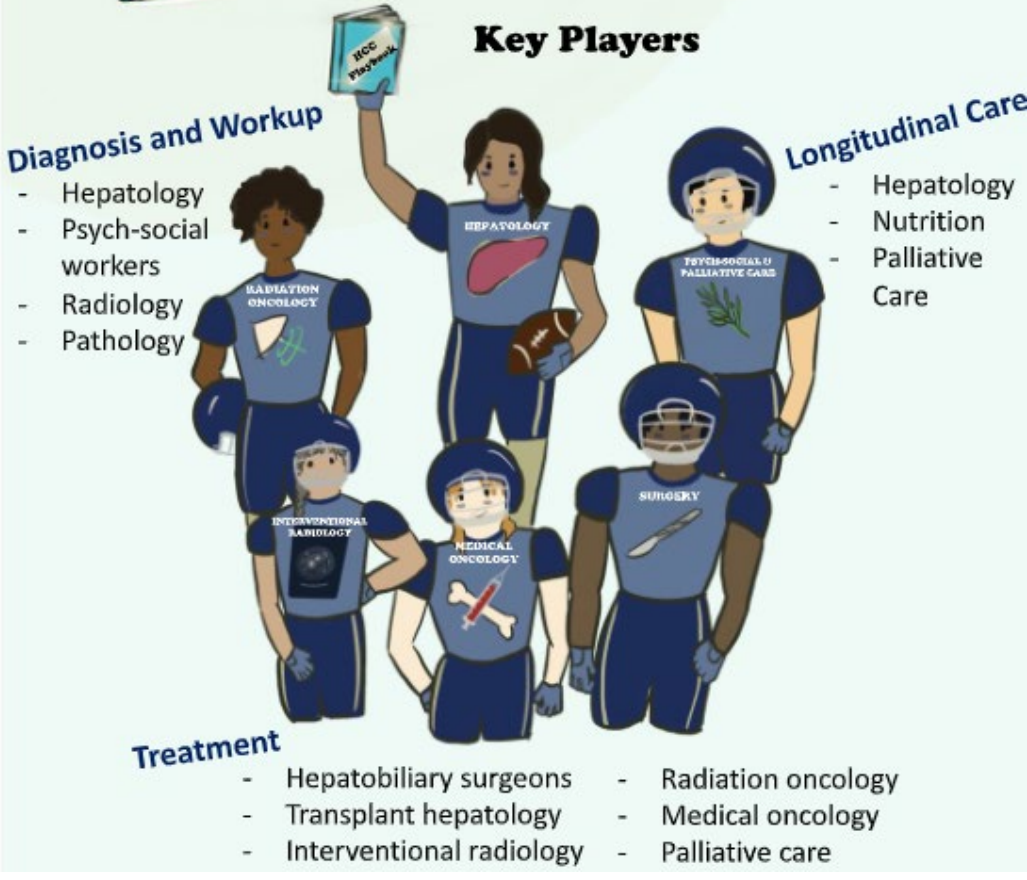



Reig et al. J Hepatol 2021

# Multidisciplinary care is essential.

- Defining the endpoint
  - Improve survival (survival is relative!)
  - Proper selection and risk assessment
- Setting standards
  - Variations among disciplines
  - Variations among programs/regions
- Identifying optimal candidates
- Identifying contraindications
- Considering the continuum




Jaffe et al. *Liver International* 2022

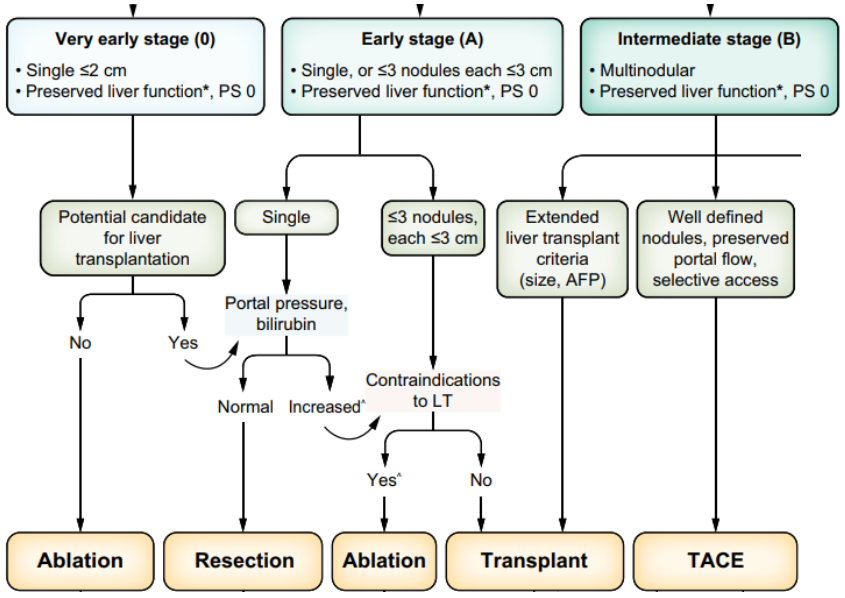
# Specialist seen within 30 days of diagnosis and MDTB associated with better overall survival.

| Provider factors | HR for Mortality | 95% CI | P value |
|---|---|---|---|
| Specialist seen within 30 days of diagnosis | | | |
| **Hepatology** | **0.7** | **0.63-0.78** | **<0.001** |
| **Medical oncology** | **0.82** | **0.74-0.91** | **<0.001** |
| **Surgery** | **0.79** | **0.71-0.89** | **<0.001** |
| Gastroenterology | 1.02 | 093-1.13 | 0.673 |
| **Palliative care** | **2.1** | **1.87-2.36** | **<0.001** |
| No specialist | 0.89 | 0.65-1.21 | 0.447 |
| Evaluation by ≥ 1 specialist | 1.09 | 0.96-1.23 | 0.187 |
| **Multidisciplinary Tumor Board** | **0.83** | **0.77-0.90** | **<0.001** |

Hepatology care, while not associated with higher odds of receiving active therapy, was associated with a 30% mortality reduction.

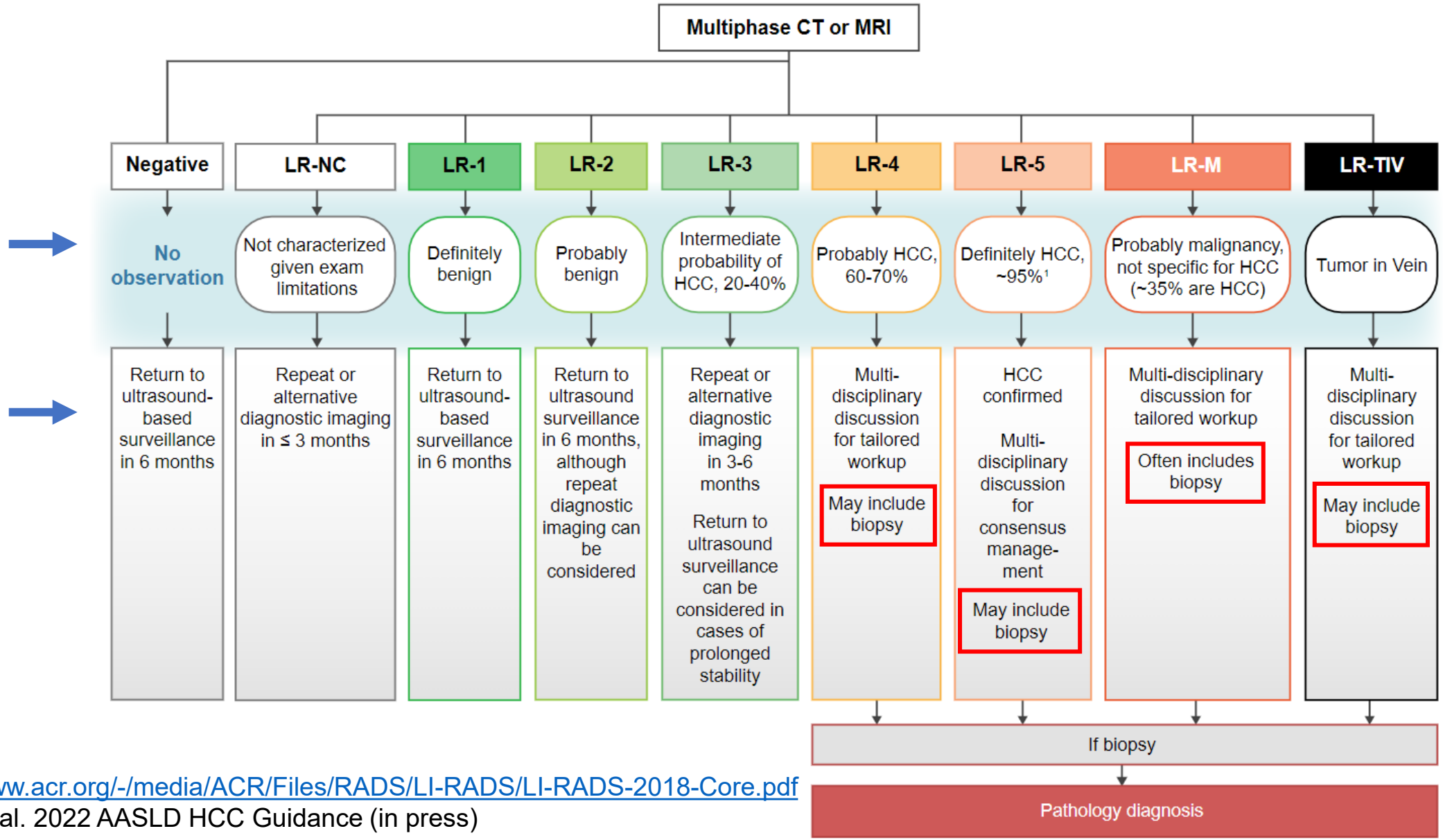
Serper et al. *Gastroenterology* 2017

# There are many options for locoregional therapy in early and intermediate stage disease




| | Surgical Options | Locoregional Therapies |
|---|---|---|
| CURATIVE INTENT | • Liver resection<br>• Liver transplantation | • Ablation<br>  • Radiofrequency<br>  • Microwave<br>  • Cryoablation<br>  • Chemical (EtOH)<br>  • Irreversible electroporation<br>  • Histotripsy<br>  • SBRT? |
| PALLIATIVE INTENT | | • Trans-arterial (palliative)<br>  • Chemoembolization (TACE)<br>  • 90Yttrium microspheres<br>• SBRT |

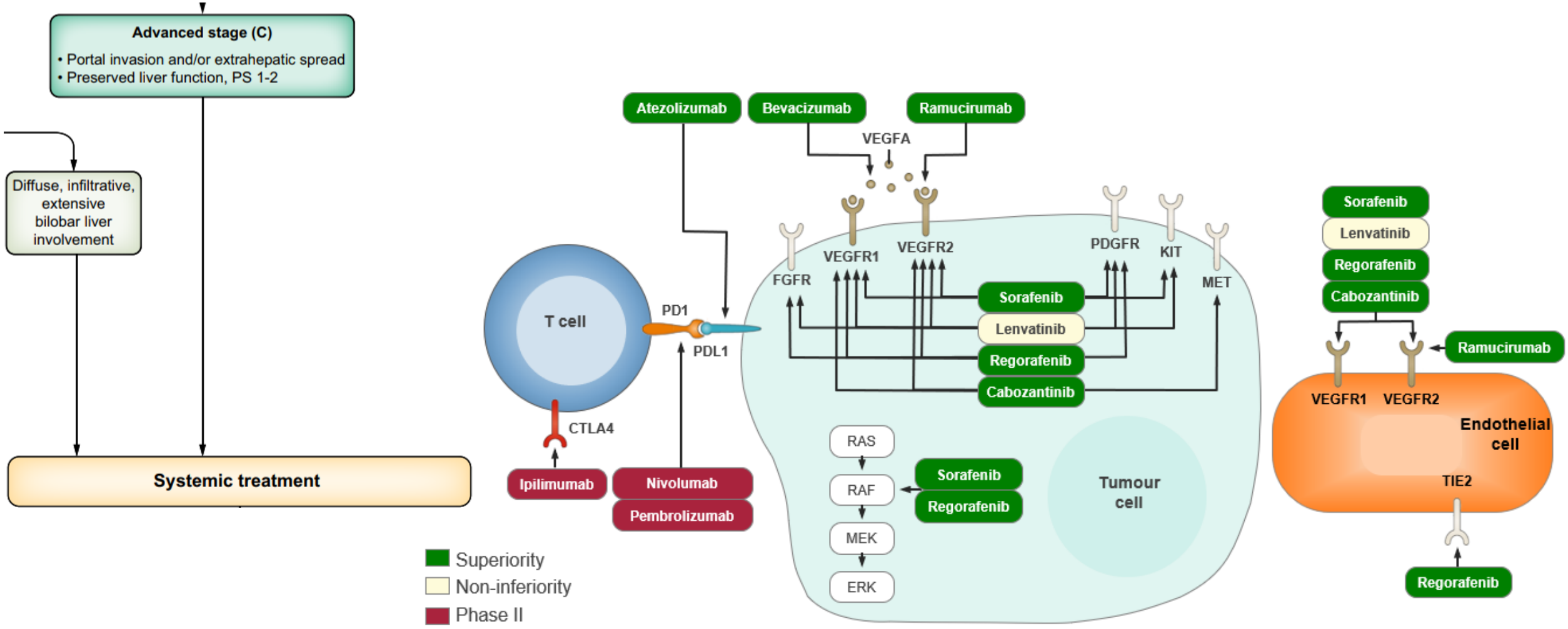
# We now advise a more liberal approach to biopsy.




https://www.acr.org/-/media/ACR/Files/RADS/LI-RADS/LI-RADS-2018-Core.pdf

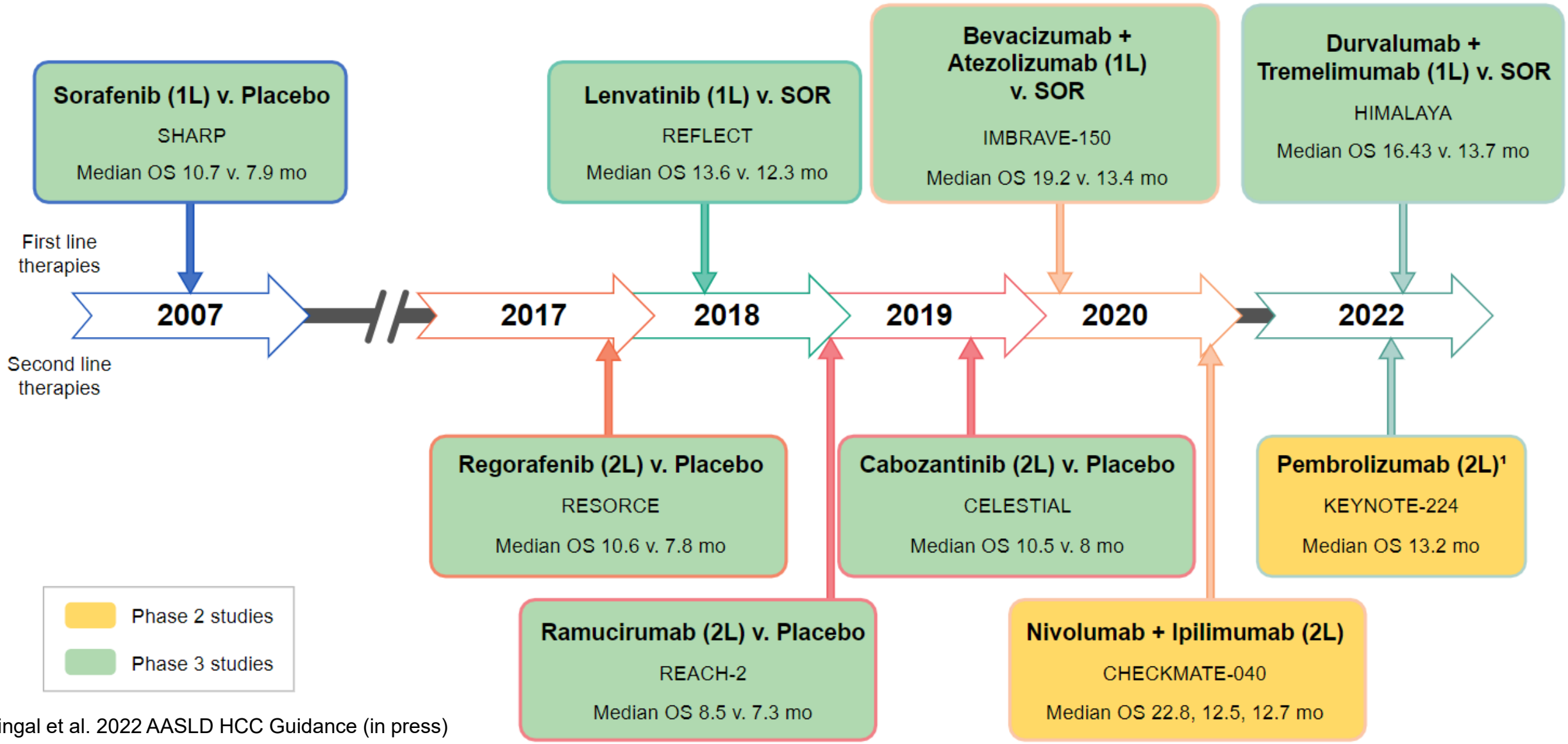
Singal et al. 2022 AASLD HCC Guidance (in press)

# The choice of systemic therapies is growing.



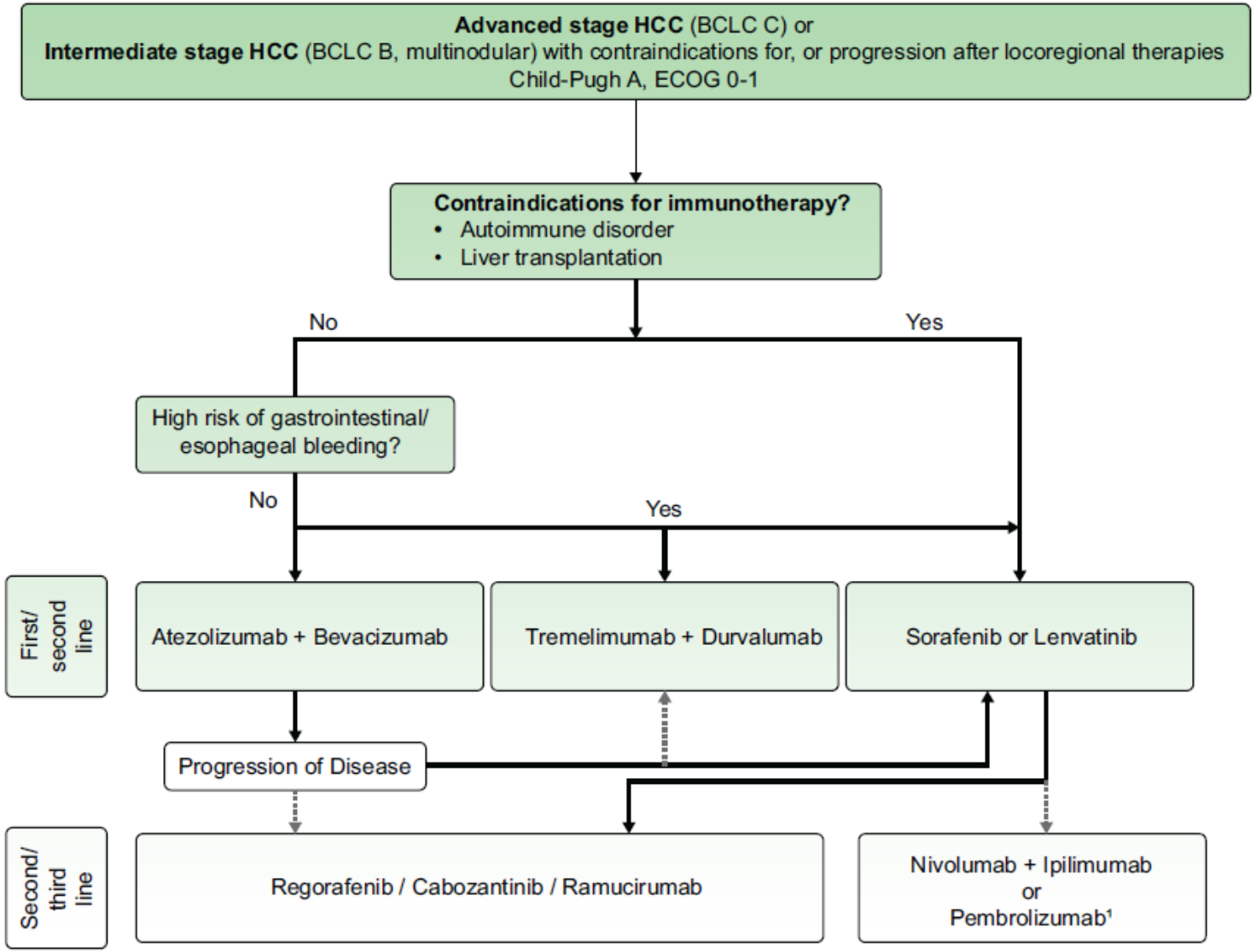

Llovet et al. *Nat Rev Dis Primers*. 2021

# The treatment landscape has changed dramatically in 5 years




Singal et al. 2022 AASLD HCC Guidance (in press)

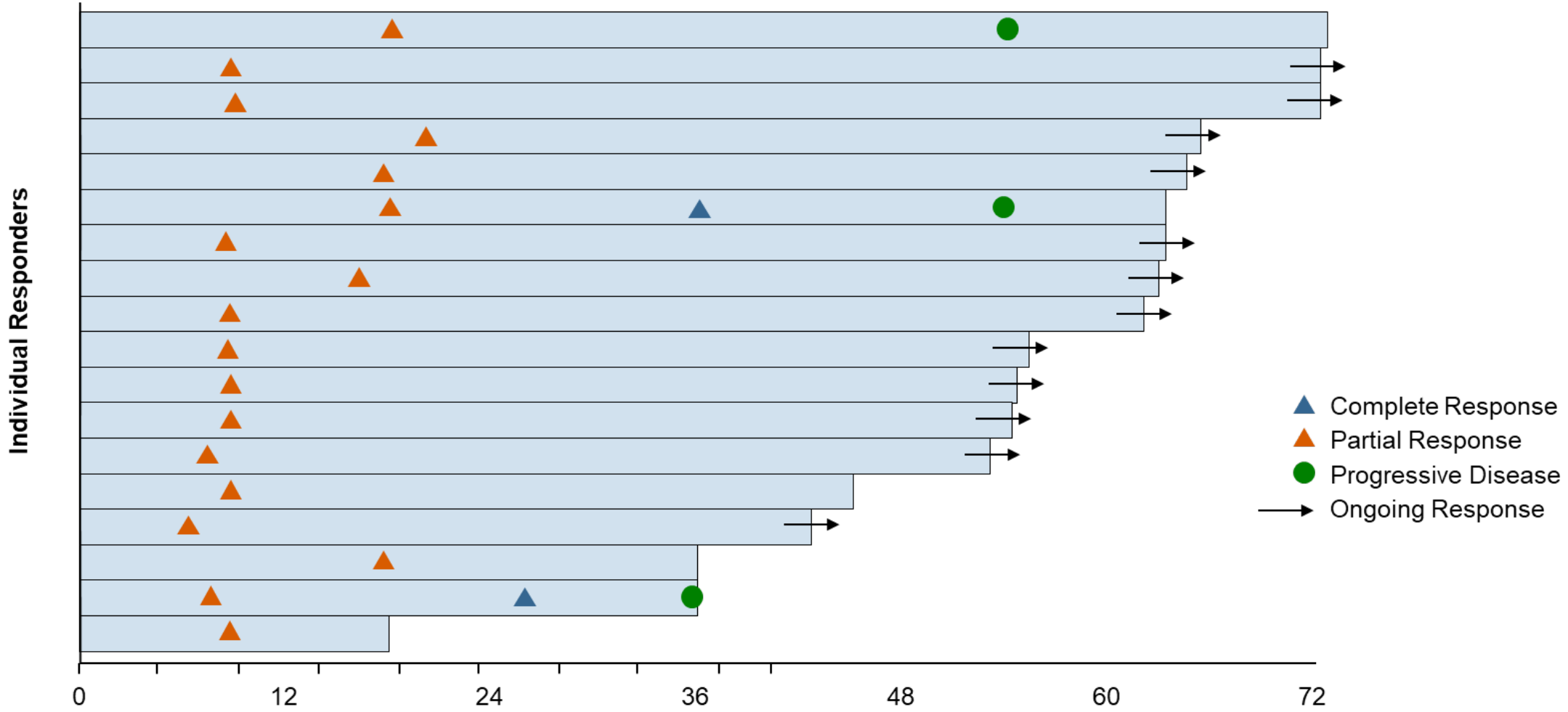
# The current paradigm is based on clinical characteristics




Adapted from Llovet et al, *Nature Cancer* 2022

Singal et al. 2022 AASLD HCC Guidance (in press)

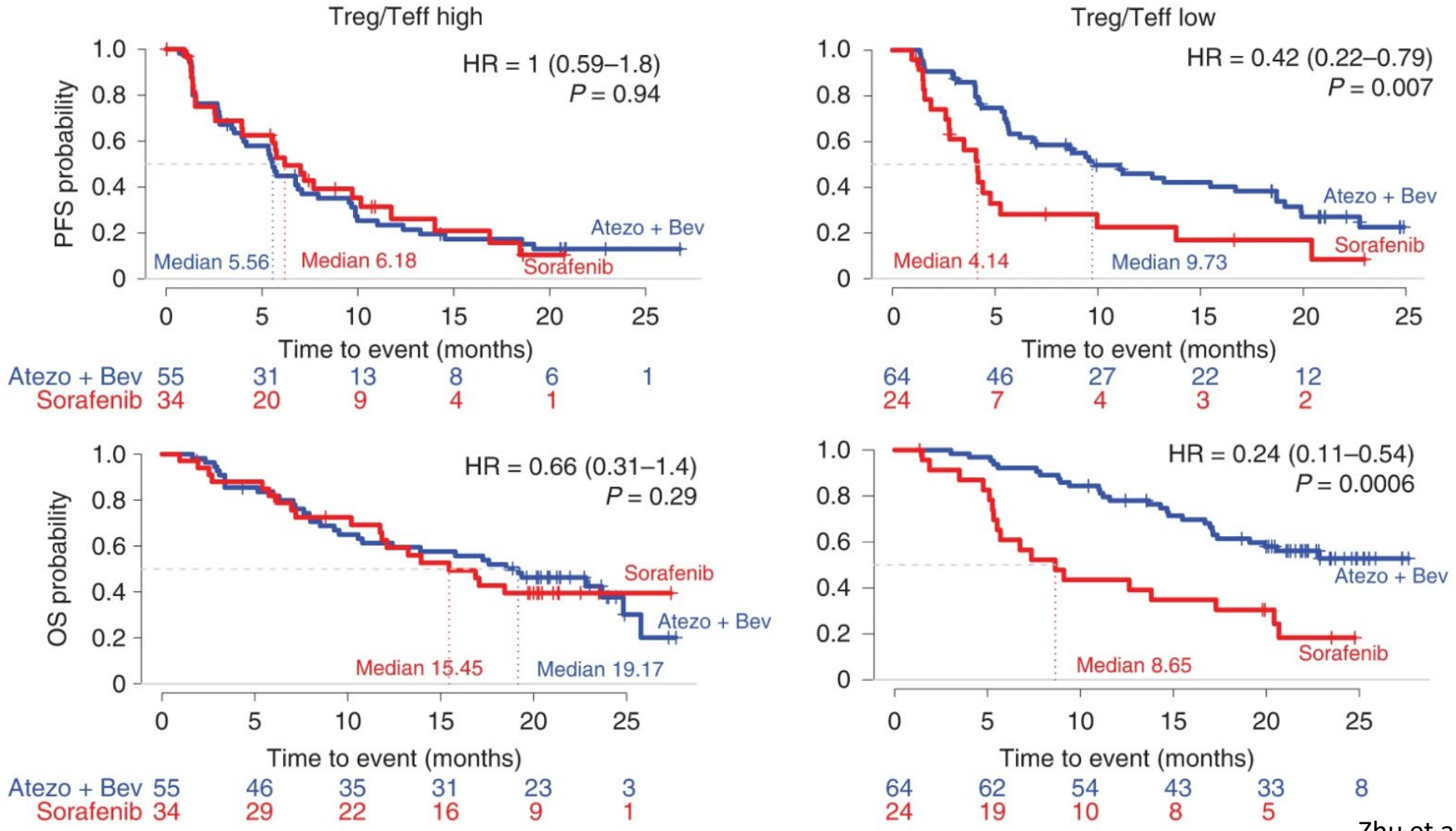
# Response is unpredictable, but some responses are very durable




Pembrolizumab: time to response and duration of response
(Keynote 224 – Pembrolizumab after PD with sorafenib)

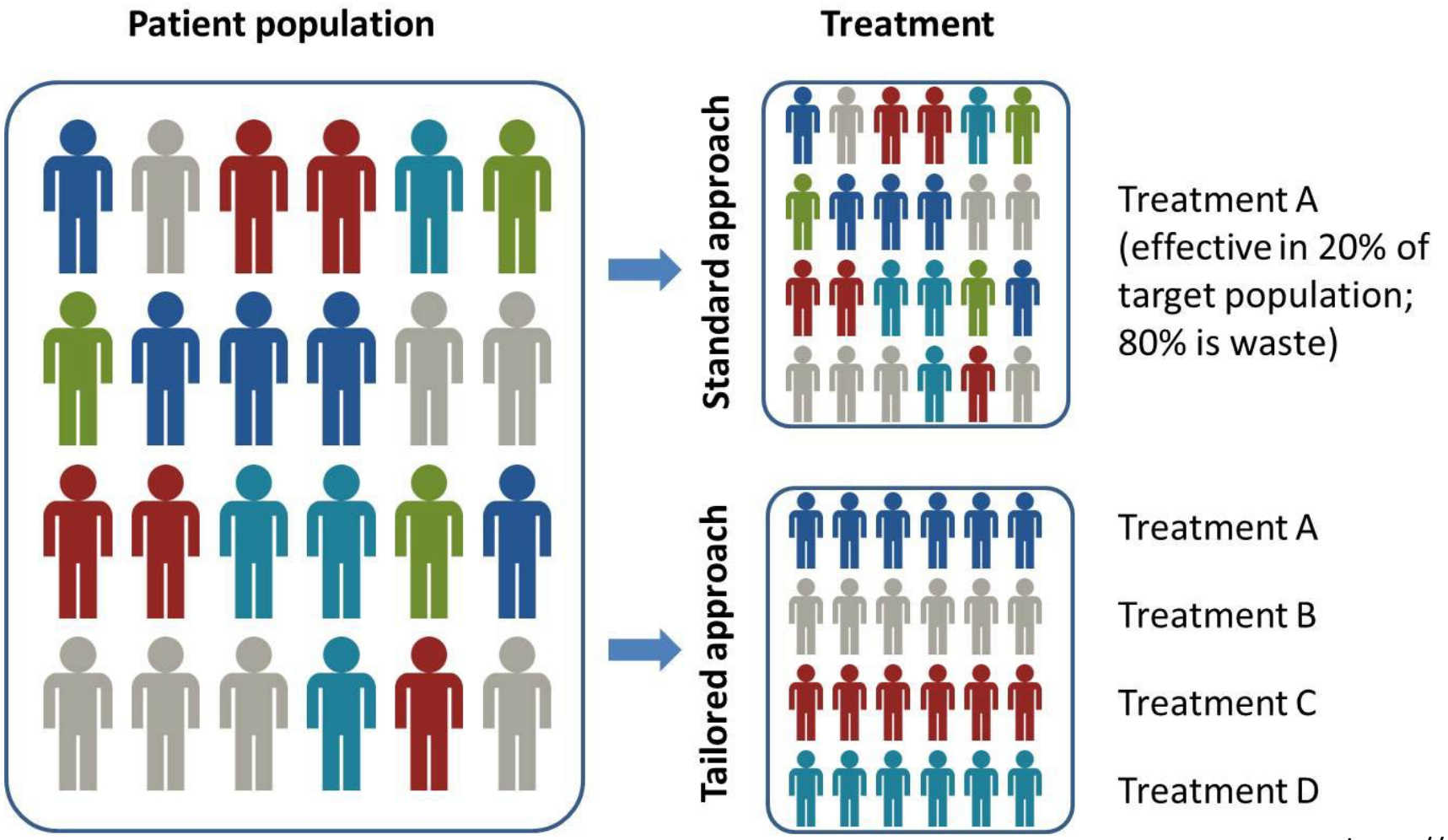
Zhu et al. *Lancet Oncol* 2018

# Understanding immune response in an immunosuppressive environment




Zhu et al. *Nature Medicine* 2022

# We need to collectively strive for a personalized approach.




https://www.acobiom.com/en/precision-medicine/

# The most pressing clinical- and research-related needs

- Access to care for prevention and screening
- Early diagnosis (imaging, “liquid biopsy”, tissue)
- Clinical, blood based, imaging, and tissue biomarkers for detection, prognosis, and response to treatment
- Mechanisms of pathogenesis and tumor behavior
- Order and timing of treatment(s) and sequential classification
  - across stage migration and stage shift
- Delivery of value-based care

# Key take aways

- The epidemiology of HCC is shifting.
- We need to embrace complexity, technology, and team-based care and science to offer our patients the best possible outcomes.
- A multidisciplinary approach is the mainstay for complex decision-making.
- Always push the envelope, most ideally in a clinical trial setting.
- The surge in large-scale observational and “omic” data should help inform large prospective trials.
- Systemic therapy options continue to grow for advanced HCC patients.
- We need a better understanding of when to introduce systemic therapies and how they affect other options (e.g. transplant after ICI therapy)
- Across all stages of HCC, over 150 clinical trials are ongoing and likely to reshape the field.