# XXII Hepatology Meeting

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## "A global strategy for preventing HCC in the hepatitis C elimination era"

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Geneva,Switzerland

EASL INTERNATIONAL LIVER FOUNDATION

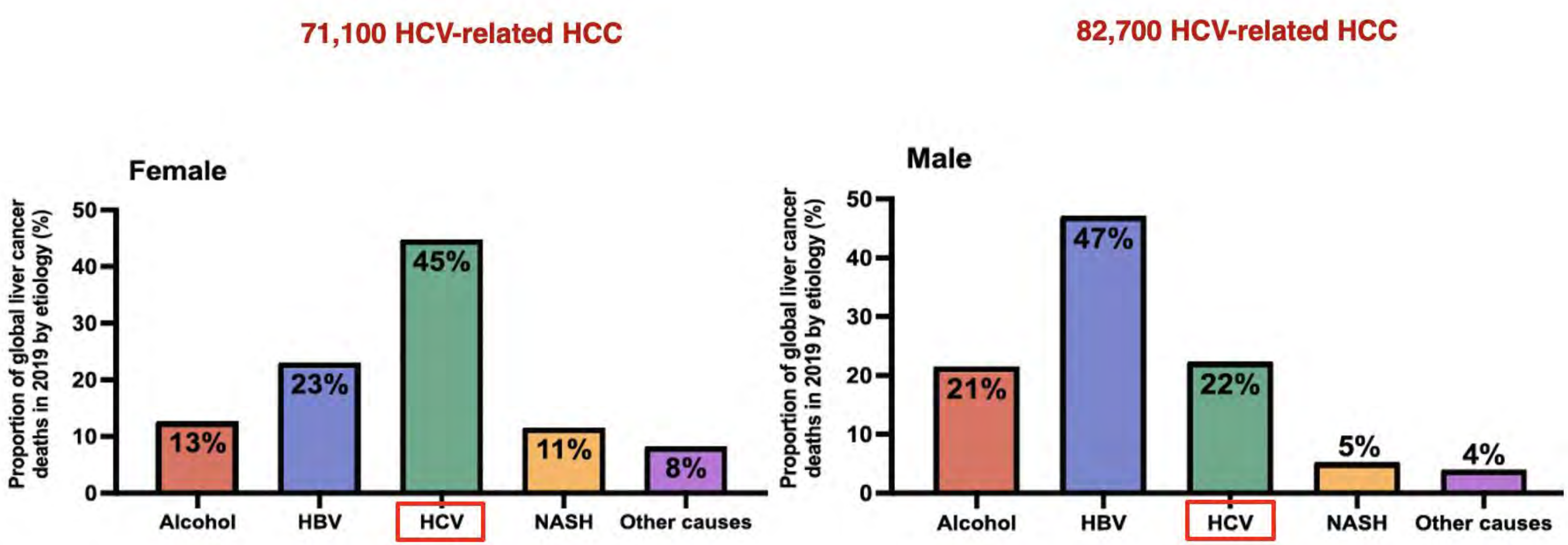
# Financial Disclosures

**Advisory committees** Merck, Roche, Novartis, Bayer, BMS, Gilead Sciences, Tibotec, Vertex, Janssen Cilag, Achillion, Lundbeck, GSK, GenSpera, AbbVie, Alfa Wasserman, Intercept COST,Target HCC,Exelixis,Galapagos.

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

# Contribution of Global Liver Cancer Deaths by Etiology of Liver Disease 2019

**2019 Global burden :** 376,483 incident cases of HCC in males and 157,881 in females causing 484,000 deaths and 12,5 mio. DALYs




Tan DJH et al Hepatology 2023

# The WHO Target to Eliminate HCV as a Global Health Threat by 2030
## Where Do We Stand

### The HCV burden

- 2020 : 58.5 millon viraemic infections estimated globally, 23% identified,1.5 million new infections/yr, 300,000 deaths.[1]
- 2015–2019 : 9.5 million people (36% in Egypt) initiated DAA therapy.
- 2020 : 641k estimated to have initiated DAA.

### Unrealistic to achieve the WHO target by 2030

- Efficient,curative and safe DAA have so far had limited effect on global HCV prevalence.
- The impact of PWIDs : left untreated,1 person actively injecting potentially will infect up to 20 others with HCV within the first 3 years of diagnosis.[2]
- Without population screening programs > 80% of chronic infections are underdiagnosed.

1.WHO Report on Viral Hepatitis 2022 ; 2.NIH on Drug Abuse Report 2022

# The Five Pillars to Reduce HCC-related Mortality
## ILCA Recommendations

1. Prevention of liver disease

2. Recognizing liver disease in individual patients

3. Recognising who among those with liver disease are at risk of developing HCC

4. Providing surveillance to those who are at significant risk

5. Providing treatment at a stage when cure is still possible

Allaire M et al J Hep Report 2022

# Elimination of VH as a Public Health Threat Challenge
## The EASL Recipe

- Reinvigorate political will : getting out of the hepatitis niche by positioning of viral hepatitis in the context of EU efforts to prevent cancer
- Expanding national plans of viral hepatitis testing beyond high-risk groups
- Establish mechanisms for prescription of HCV therapy in primary care and community services
- Optimizing care delivery : decentralization,integration,task-shifting and simplification of care pathways
- Increase access to harm reduction for PWIDs combining packages of OATs / NSPs

Karlsen T et al J Hepatology 2022

# Expanding National Plans of Viral Hepatitis Testing
## The UK Recipe

- **Old infections (general population)**

  Test for liver disease

  - Community vans with fibroscan to screen for cirrhosis (pick up 10%)

  Test for blood borne viruses

  - Emergency departments testing for HCV,HIV and HBV

- **High-risk populations**

  Delivery of easy tests, easy treatments and support (peers)

- **HCV burden in England 2019** : 40% reduction of HCV-related ESLD and HCC

NHS Viral Hepatitis Elimination Report 2022 ; Foster G Milan 16 May 2023

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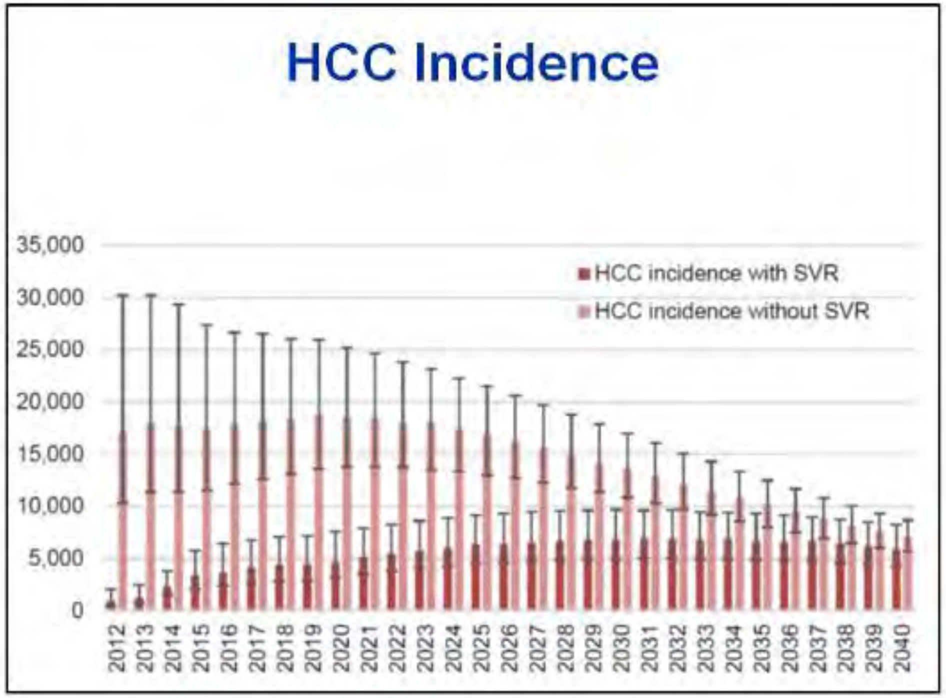
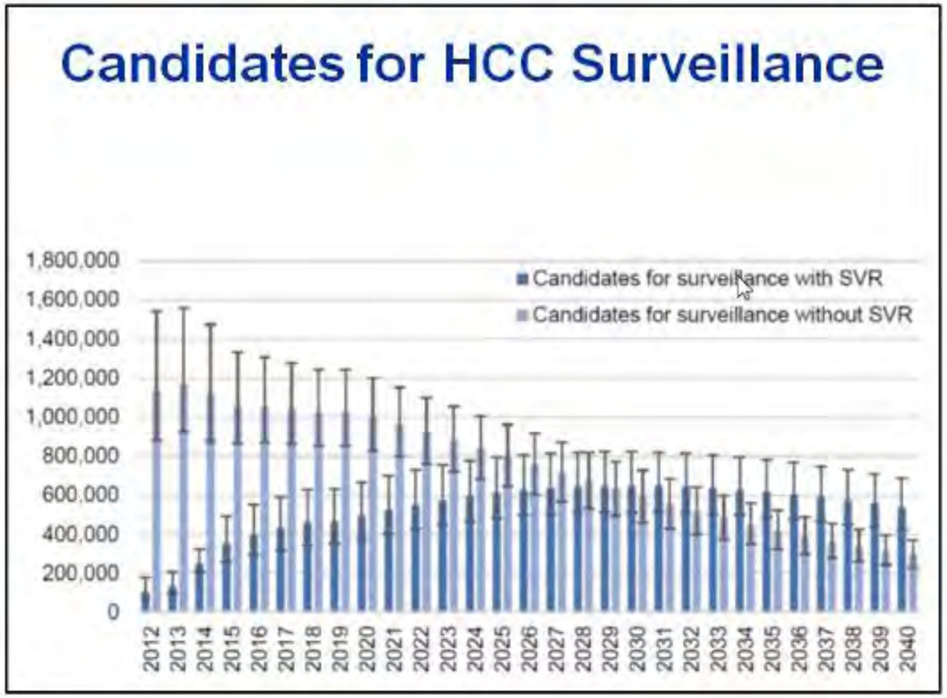
# HCC Burden in the Era of Growing SVR Patients
# A Simulation Study in the US

Hepatitis C Disease Burden Simulation model(HEP-SIM) to simulate the population with HCV who would be considered candidates for HCC surveillance in the era of DAAs in the US




**1,000 in 2012, 7,000 in 2031, 6,000 in 2040 (estimates)**




**From 8.5% in 2012 up to 64.6% in 2040 (estimates)**

Chen Q et al JAMA Network Open 2020

# Scientific Societies Recommendations for Surveillance of HCV Patients Achieving an SVR

is C

**Advanced fibrosis (F3)**

Definition of F3

HCC surveillance recomme

**Cirrhosis (F4)**

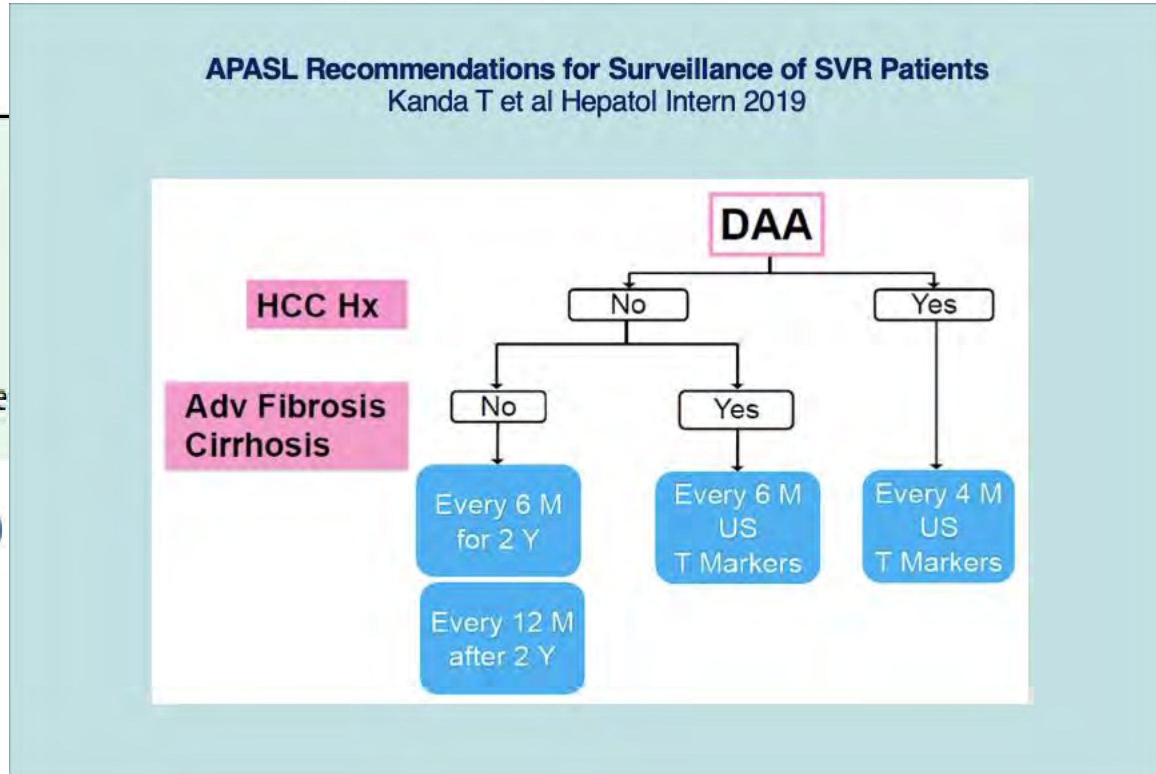
Definition of cirrhosis (F4)

12.5 kPa

raphy test indicating cirrhosis

F* above "threshold"

• APRI >2




| | | |
|---|---|---|
| HCC surveillance recommended after SVR? | YES<br>Ultrasound every 6 months "indefinitely" | YES<br>Ultrasound ± AFP every 6 months "Indefinitely" |
| | **EASL CPG J Hepatol 2018** | **Ghany MC et al Hepatology 2019** |

Ioannou GN et al J Hepatology 2021;74:458–465

# Limitations of the Current Surveillance Strategies

**Barriers to screening effectiveness in clinical practice**

- Inadequate risk stratification
- Underuse of surveillance
- Suboptimal accuracy of screening tests.

**Proposed way out**

- Risk stratification algorithms
- Biomarkers to better identify at-risk individuals
- Interventions to increase surveillance
- Emerging imaging- and blood-based surveillance tests

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Allaire M et al J Hep Report 2022

# Cost Effectiveness AS a Driver of of HCC Surveillance

<u>**Cost effectiveness(C/E)**</u> : analysis used to compare the cost of an intervention with a non-monetary measure of its effectiveness i.e. DALYs averted

<u>**HCC surveillance**</u>

<u>**AGA** criteria</u> : willingness-to-pay 50,000 USD/QUALY gained

C/E threshold : HCC incidence of 1.32 % x yr

<u>**WHO** criteria</u> : cost of DALY averted based on per capita GDP

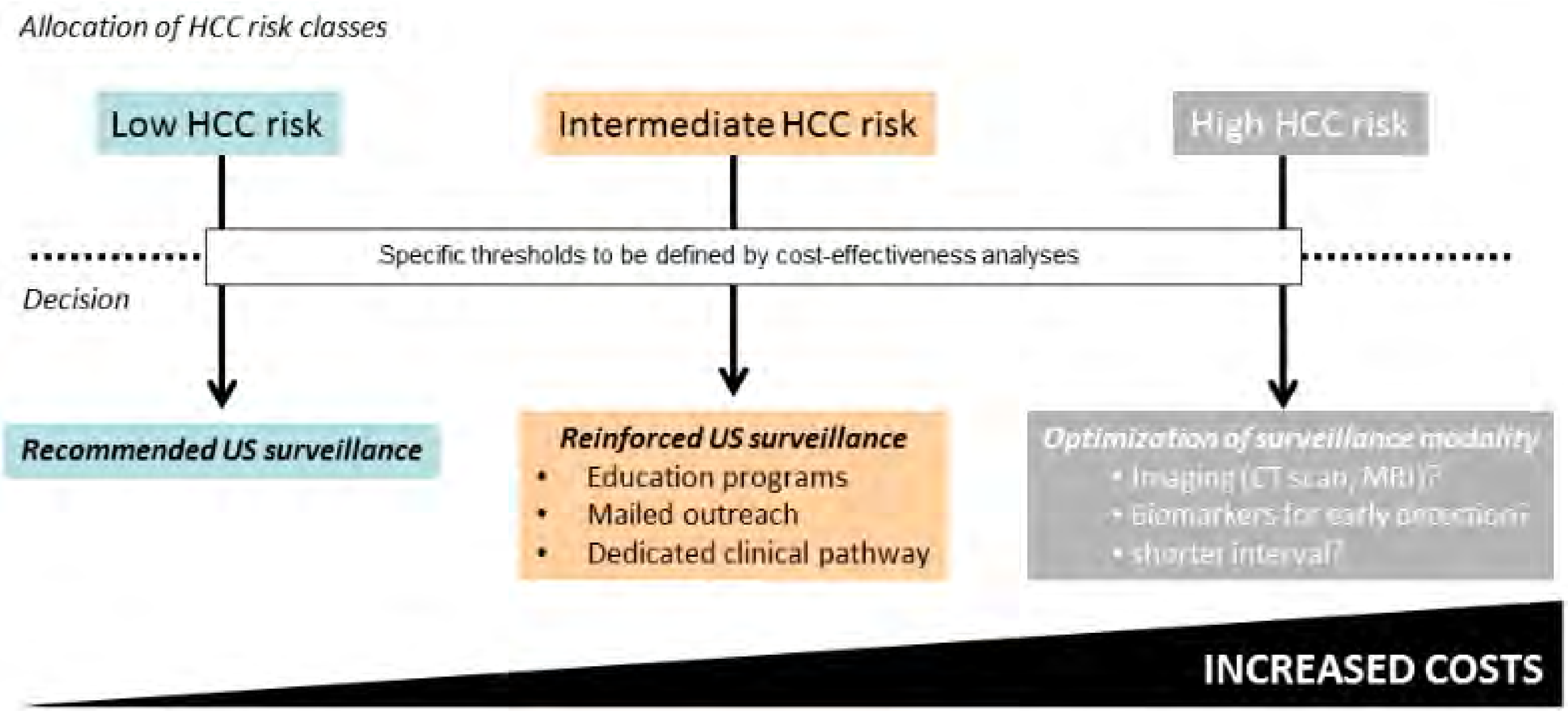
very C/E < GDP

C/E 1-3 times GDP

not C/E >3 times GDP

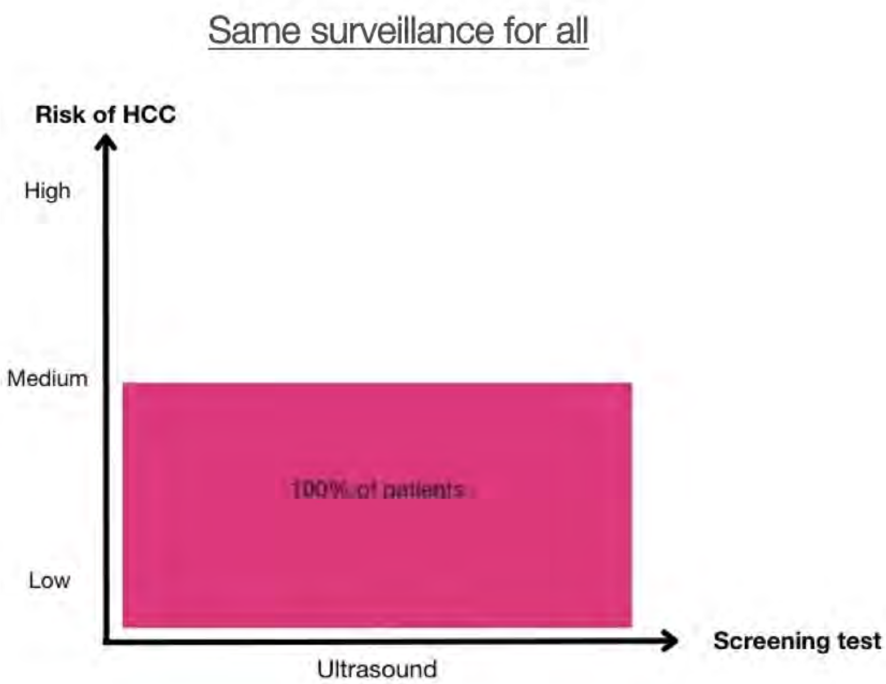
* Farhang Zangneh H et al. Clin Gastroenterol Hepatol 2019; 17:1840- 1849.e1816.

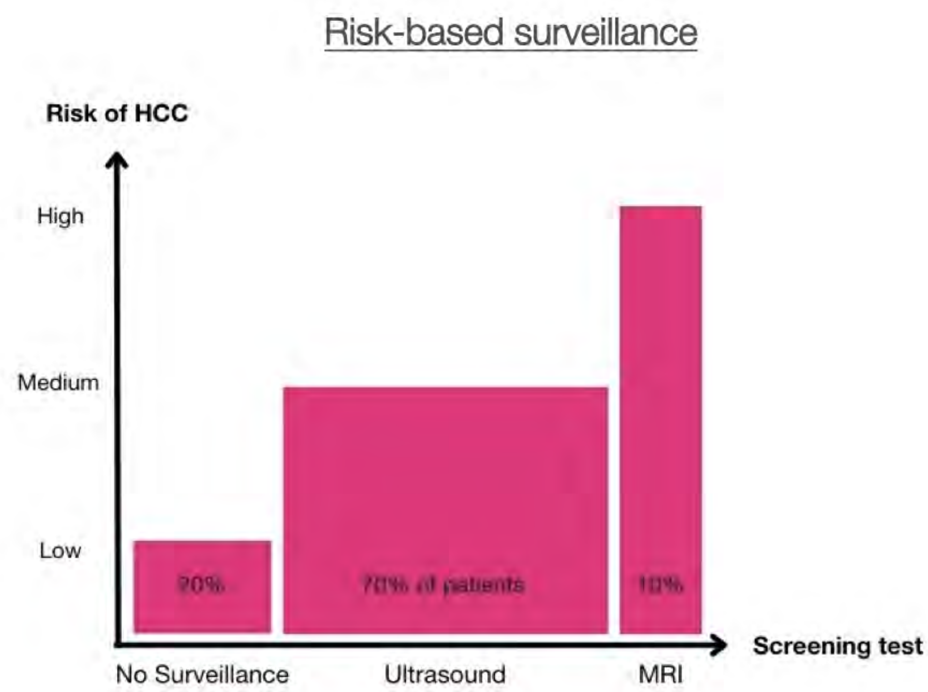
# Potential Application of HCC Risk Stratification Using Scoring Systems




Nahon P et al J. Clin. Med. 2021;10: 353.

# Risk-based Surveillance for HCC Among Patients with Cirrhosis
## EASL Policy Statement



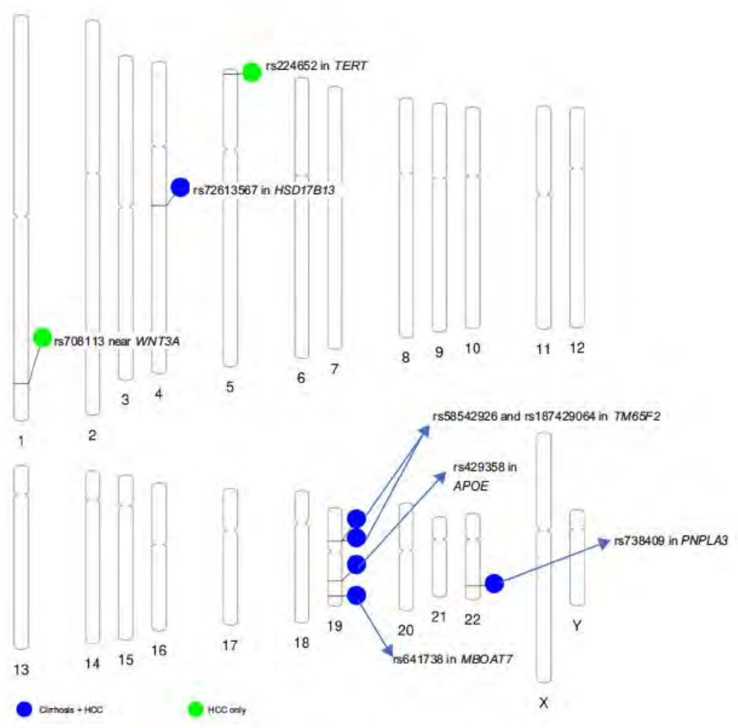
# Emerging Biomarkers for HCC Surveillance
# ILCA White Paper

| SCORE name or first author | Biomarker | Biomarker phase | Number patients | Sensitivity (%) | Specificity (%) |
|---|---|---|---|---|---|
| **GALAD** | Gender, age, AFP-L3%, AFP, and DCP levels | 3 | 1550 with liver cirrhosis | 65 | 82 |
| **Von Fielden J** | Extracellular vesicles (small RNA clusters) | 2 | 105 HCC and 185 non-HCC | 86° | 91 |
| **HelioLiver** | Methylation markers (28 genes), AFP, AFP- L3%, and DCP, combined with age and sex | 2 | 122 HCC and 125 non-HCC | 76 ° | 91 |
| **Mt-HBT methylated DNA panel** | Methylation markers (HOXA1, TSPYL5, and B3GALT6) combined with AFP, and sex | 2 | 135 HCC and 302 non-HCC | 74° | 90 |
| **HCC-screen** | Cell free DNA (TP53, CTNNB1, AXIN1, TERT promoter, and HBV integration breakpoint) with gender, age, AFP, and DCP | 2 | 24 HCC and 307 non-HCC) | 100 | 94 |
| **Methylation signature** | Ten methylation markers | 2 | 1,098 HCC and 835 non-HCC | 83.3 | 90.5 |

Singal AG et al J Hepatol 2022

**A look at the future…..**

# Integrating Polygenic Scores into Clinical Algorithms for HCC Risk Stratification




**aMAP multivariable regression model**

(age,sex,al-bi,platelets)

- aMAP +/- 7 SNIPs ( 6 lipid turnover and 1 Wnt-B-catenin)
- 1,145 alcoholic and cured HCV cirrhosis
- 86 with HCC in 43.7 months of prospective surveillance

<u>Five yr risk of HCC</u>

G1(n.627) = 5.4%

G2(n.276) = 10.7%

G3(n.232) = 15.3% $p<0.001$

**aMAP + SNIPs vs. aMAP – SNIPs** : C-index 0.786 vs. 0.783

Nahon P et al J Hepatology 2023;78:584-595

# The Future of Infectious-disease Surveillance
# Emerging Forms of Technology

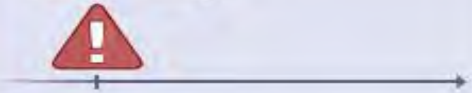
- Biosensors
- Quantum computing
- Augmented intelligence
- e language models e.g., Generative Pre-trained Transformer 4 (GPT-4)

**Likely advances** : - can process and analyze vast amounts of unstructured text

- may enhance our ability to streamline labor intensive processes and spot hidden trends

Drazen JM et al N Engl J Med 2023

# Various Functions of Artificial Intelligence (AI) for Infectious-Disease Surveillance

| Function | Examples |
|---|---|
| **Early warning**  | • Natural-language processing of news sources to identify outbreaks (Freifeld et al., *JAMIA* 2008)<br>• Unsupervised machine learning of social media data to detect unknown infections (Lim, Tucker, and Kumara, *J Biomed Inform* 2017) |
| **Pathogen classification**  | • Convolutional neural network model for reading antibiograms (Pascucci et al., *Nat Commun* 2021)<br>• Convolutional neural network model to automate malaria microscopy and diagnosis (Liang et al., *IEEE* 2016) |
| **Risk assessment**  | • Reinforcement learning of Covid-19 positivity rates to target limited testing in Greece (Bastani et al., *Nature* 2021)<br>• Machine-learning models including random forest and extreme gradient boosting to use syndromic surveillance for Covid-19 risk prediction (Dantas, *PLoS One* 2021) |
| **Source identification**  | • Automated data mining of electronic medical records to uncover hidden routes of infection transmission (Sundermann et al., *Clin Infect Dis* 2021)<br>• Supervised machine learning in combination with digital signal processing for genomic tracing of Covid-19 (Randhawa et al., *PLoS One* 2020) |
| **Hotspot detection**  | • Neural computing engine to correlate sound from hospital waiting rooms with influenza spikes (Al Hossain et al., *Proc ACM Interact Mob Wearable Ubiquitous Technol* 2020)<br>• Multilayer perceptron artificial neural network model to detect spatial clustering of tuberculosis (Mollalo et al., *Int J Environ Res Public Health* 2019) |
| **Tracking and forecasting**  | • Real-time stacking of multiple models to improve forecasts of seasonal influenza (Reich et al., *PLoS Comput Biol* 2019)<br>• Machine learning to combine new data sources for monitoring Covid-19 (Liu et al., *J Med Internet Res* 2020) |

Drazen JM et al N Engl J Med 2023

# Does ChatGPT Empower Patients and Improves Health Literacy in HCC Domain?

A questionnaire-based study of accuracy and reproducibility of ChatGPT in answering Qs regarding cirrhosis and HCC

**Methods** ChatGPT responses to 164 Q independently graded by two transplant hepatologists.

**Findings** ChatGPT regurgitated extensive knowledge of HCC (74% correct) , 41.1% were considered comprehensive responses.

Responses on basic knowledge, lifestyle, and treatment showed better performance than those regarding diagnosis and preventive medicine.

**However** ChatGPT failed to specify decision-making cut-offs,treatment durations and differences in regional recommendations on HCC screening criteria.

Yeo YH et al Clin Molecular Hepatol 21 March 2023

# Is a Protective HCV Vaccine Needed for the Final Push to Eliminate HCV?

- **Why**

Despite progress in HCV therapeutics,new infections continue to outpace cure ➡ need for HCV vaccine

- **The starting point**

Chimps that produced a high level of anti-E1E2 abs were protected against challenge with homologous HCV strain (Choo et al 1994)

- **The way forward**

Increased understanding of HCV protective immunity and HCV envelop glycoprotein structure and function is paving the way toward rational vaccine design and evaluation

**Clinical protection studies**

One candidate vaccine only : in the phase I/II NCT01436357 in PWID a viral vector vaccine encoding NS3-NS5B induced HCV-specific T cells,did not protect against chronic HCV infection

Law M Cold Spring Harb Perspect Med 2021;11:a036962 ; Page K et al NEJM 2021

# The Immunological Challenges that HCV Presents for Vaccine Development

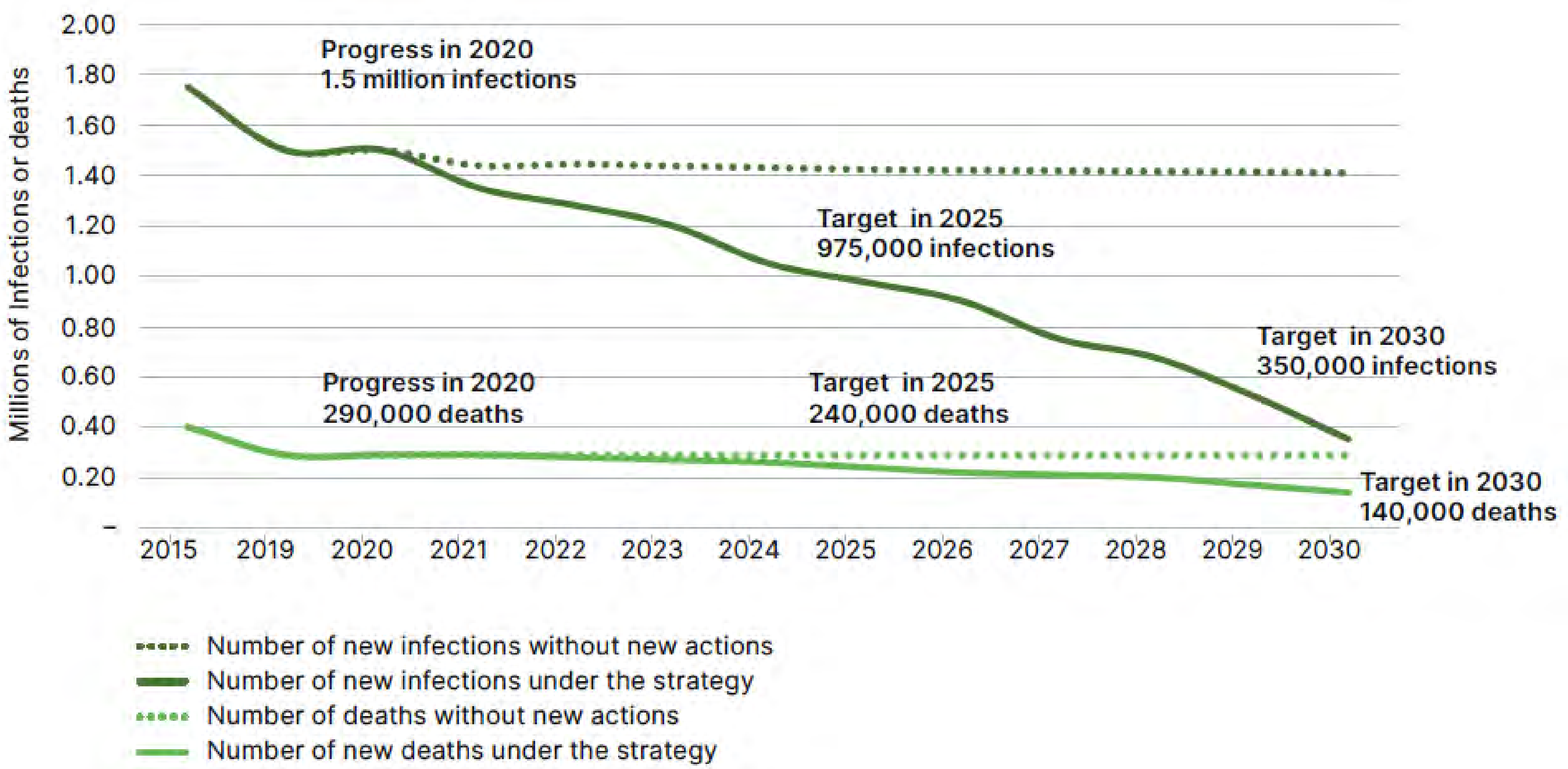
- Chronic HCV infection promotes pronounced T cell exhaustion.
- Antigen elimination alone is not enough to reverse exhaustion once chonicity is established, explaining the lack of protection against HCV reinfection after DAA cure.
- Vaccination of previously infected individuals might be challenging owing to persistence of HCV-specific CD8* cells that expand to produce only terminally exhausted T cells.
- The immunopathological events during HCV infection support  early treatment during acute infection,ie a difficult undertaking in real life practice.

Hensel N et al Nat.Immunol 2021;22:229-239

# Barriers to the Development of a HCC Biomarker

- Molecular and histological heterogeneity of the tumour.
- External validation is needed
- Time-dependent outcomes
- Assessment of calibration
- The linearity conundrum

# Hepatitis C Incidence and Mortality Trends from New Actions *vs.* No New Actions 2020-2030




WHO Report 2022

# International Liver Cancer Association(ILCA)Proposal for Adapted Surveillance

**Patients qualified for surveillance**

Cirrhosis

Stage 3 fibrosis

Long standing chronic hepatitis B

} **High risk scores** *

**Recommended tests**

US performed by specially trained technicians + AFP every 6 months

* *GALAD score blood test whenever available*

Allaire et al J Hepatol 2022

# HCC Prediction Models in Patients Who Achieved SVR

| Tools for HCC risk estimation | Examples | Predictor variables | Advantages | Disadvantages |
|---|---|---|---|---|
| Simplified HCC scoring systems | FIB-4 score cirrhosis[illegible] | Age, AST, ALT, platelet count | Readily available; easy to use. | Not specifically developed for HCC prediction; less accurate |
| Elastography | Fibroscan-derived elastography[11] | Liver stiffness (kPa) | Increasingly common; additionally, provides estimate of fibrosis | Not specifically developed for HCC prediction; less accurate, expensive |
| Multivariable regression models ("HCC risk calculators") | VA HCC model at hccrisk.com[illegible] and aMAP[illegible] | VA model: SVR, age, sex, BMI, race/ethnicity, HCV genotype, platelet count, AST, ALT, albumin, INR and haemoglobin. aMAP: age, male sex, albumin-bilirubin and platelet count | More accurate than simple scores or elastography | Require special tools to calculate (e.g. web-based or app-based calculators) |
| Deep learning HCC risk prediction models | Recurrent Neural Network (RNN) HCC model[illegible] | Age, sex, race, HCV genotype and 24 laboratory tests | More accurate than regression models | Hard to implement in clinical practice currently |

Ioannou GN J Hepatol 2020