Risk Stratification for HCC

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Disclosure

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  Morphic Therapeutics
  Roche

Consultancy
  Ferring Pharmaceuticals
  Kyowa Hakko Kirin
  Laboratory for Advanced Medicine

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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1. Why HCC risk stratification?
2. Clinical HCC risk indicators
3. Molecular HCC risk indicators
4. Benefit of risk-stratified HCC surveillance: cost-effective?
Heterogeneous HCC risk across “at-risk” patients

High risk

Medium risk

Low risk
“One-size-fits-all” HCC surveillance

Semi-annual HCC surveillance

Under-surveillance
- Late HCC diagnosis

Over-surveillance
- Physical, psychological, & financial harms

High risk
- Ultrasound +/- AFP (every 6 months)

Medium risk

Low risk
Risk-stratified HCC surveillance

Under-surveillance
- Late HCC diagnosis

Over-surveillance
- Physical, psychological, & financial harms

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

Medium risk

Low risk
- 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

- Ultrasound ± AFP
  - 83.6%
- CT or MRI ± AFP
  - 68.9%
  - 57.4%
  - 3.9%
  - 26.2%
  - 36.1%

Patient’s estimated risk of HCC:
- 1% per year
- 3% per year
- 5% per year

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%

Wolf, Hepatol 2020
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Clinical HCC risk indicator: FIB-4 index

- FIB-4 ≥ 3.25
- FIB-4 < 3.25

**Years after HCV cure**

**Annual HCC incidence (%)**

- DAA
- Interferon

Ioannou *Gastro* 2019
## Clinical HCC risk scores

<table>
<thead>
<tr>
<th>Risk indicator</th>
<th>Etiology</th>
<th>Race/ethnicity</th>
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<tbody>
<tr>
<td>LSM-HCC score</td>
<td>HBV</td>
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<td>REACH-B</td>
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<td>Yang, et al.</td>
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<td>FIB-4</td>
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<td>Shin, et al.</td>
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<td>Kim, et al.</td>
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<tr>
<td>Singal, et al.</td>
<td>HCV</td>
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<td>Lok, et al.</td>
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<td>Wang, et al.</td>
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<td>ADRESS-HCC</td>
<td>HCV, alcohol, NASH/crypt</td>
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<td>VFMAP</td>
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<td>Wen, et al.</td>
<td>General population</td>
<td>Asian</td>
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</tbody>
</table>

[www.hccrisk.com](http://www.hccrisk.com)

Fujiwara J *Hepatol* 2018
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Molecular HCC risk indicators may guide chemoprevention

Aspirin
- Simon *NEJM* 2020
- Malehmir *Nat Med* 2019

Lipophilic statins
- Simon *Ann Intern Med* 2019

Fujiwara *J Hepatol* 2018
## Molecular HCC risk indicators

<table>
<thead>
<tr>
<th>Omics technology</th>
<th>Biomarker</th>
<th>Biospecimens</th>
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<tbody>
<tr>
<td>Germline DNA variants</td>
<td><em>IFNL3</em> (rs12979860: C &gt; T, rs8099917: T &gt; G)</td>
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<td><em>MICA</em> (rs2596542: C &gt; T)</td>
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<td>Gene-expression signatures</td>
<td>Prognostic liver signature</td>
<td>Liver tissue</td>
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<td>HIR gene signature</td>
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<td>Activated HSC gene signature</td>
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<td>Immune-mediated cancer field signature</td>
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<td>Circulating nucleic acids</td>
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<td>5-genera microbiome signature</td>
<td>Serum</td>
</tr>
</tbody>
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Fujiwara *Hepatol Res* 2020
HCC risk molecular signature

Molecular HCC risk level

Liver gene expression, Serum proteins

Cirrhosis patients

All cirrhosis patients

High risk

Low risk

Hazard ratio

Pre-test annual HCC incidence

Post-test annual HCC incidence


Naoto Fujiwara
Outline

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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

HCC risk assessment

- High
  - US 4x MRI
  - AMRI

- Intermediate
  - US MRI
  - AMRI
  - None

- Low
  - US
  - None

Imaging modalities

AMRI: abbreviated MRI

Goossens, Clin Transl Gastro 2017
Risk-stratified HCC surveillance is cost-effective

Willingness-to-pay measure

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

\(<$50,000: \text{cost-effective}\)

<table>
<thead>
<tr>
<th>Strategy</th>
<th>ICER</th>
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<td>MRI - US2× - US2×</td>
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<td>AMRI - US2× - US2×</td>
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<td>US4× - US2× - none</td>
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<td>MRI - MRI - none</td>
<td>$31,500</td>
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<td>AMRI - US2x - none</td>
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<tr>
<td>MRI - none - none</td>
<td>Dominant</td>
</tr>
</tbody>
</table>

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, …)
- …

Goossens Clin Transl Gastro 2017
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