How HepQuant Tests May Aid Drug Development

HepQuant’s products are not FDA-approved. They are for investigational use only under FDA IDE guidelines.
How to Assess NASH Drug Efficacy?

NASH
Fat
Other Liver Diseases
Alcohol
HCV
HBV

Inflammation ➔ Fibrosis ➔ Cirrhosis

Clinical Outcomes
Morbidity
Mortality
How to Assess NASH Drug Efficacy?

NASH
Fat
Other Liver Diseases
Alcohol
HCV
HBV

Clinical Outcomes
Morbidity
Mortality

Inflammation
Fibrosis
Cirrhosis

Liver Dysfunction!!
HepQuant Liver Function Diagnostic Tests

**HepQuant-SHUNT**

- Simultaneous
  
  IV $^{13}$C-Cholate (20 mg)
  Oral d4-Cholate (40 mg)

- d$_4$-Cholate enters Portal Vein via multiple Enteric Bile Salt Transporters

- Multiple Hepatic Bile Salt Transporters clear the dual cholates from the Portal and Systemic circulation

- 5 blood draws used to measure liver blood flow, perfusion, and processing (Hepatic Filtration Rates)

- Portal and Systemic HFRs determine SHUNT and Disease Severity Index (DSI)

**HepQuant-STAT**

- Oral d4-Cholate (40 mg)

- Single blood draw used to calculate STAT value

- Estimates Portal HFR and DSI ($r^2 = 0.88$)

- Simpler, cost-effective, but
  
  STAT 20% CV vs DSI 10% CV
The HepQuant-SHUNT Liver Diagnostic Kit

Sites receive kits containing sterile solutions of labeled cholates, stable at ambient temperature.

Patient serum samples are shipped ambient back to the HepQuant Laboratory for LCMS.
HepQuant Liver Function Diagnostic Tests

HepQuant-SHUNT

5 Time Points Define Clearance Curves

- IV Dose / Area under IV Curve = IV Clearance
- IV Clearance / Body Weight = Systemic HFR

HepQuant-STAT

Single Time Point Estimates Oral Clearance

- Oral Dose / Area under Oral Curve = Oral Clearance
- Oral Clearance / Body Weight = Portal HFR
- Oral d4-Cholate concentration at 60 minutes normalized to body weight = STAT

Systemic HFR / Portal HFR = SHUNT fraction

DSI from Systemic HFR & Portal HFR Function Map
Function Map of Controls and NASH Patients
Data from HCV Patients

1. SHUNT DSI and STAT Correlate with Fibrosis
2. Predict Risk of Future Outcomes (Average Follow-up of 5.5 years)

Pearson Correlations are using all data points. Symbols are the mean ± SD.
Cutoffs for High Risk of Outcomes are DSI ≥ 19 and STAT ≥ 1.1 µM
Data from Multiple Variable Analysis of Predicting Future Clinical Outcomes in HCV Patients

1. SHUNT DSI and STAT are the Strongest Predictors
2. DSI and STAT are Independent Predictors (Cirrhosis drops from significance)

### HepQuant SHUNT DSI

<table>
<thead>
<tr>
<th>Variable</th>
<th>Hazard Ratio</th>
<th>Lower 95% CI</th>
<th>Upper 95% CI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>DSI tertile 15.395-19.898</td>
<td>2.40</td>
<td>0.64</td>
<td>9.04</td>
<td>0.196</td>
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<tr>
<td>DSI tertile &gt;19.898</td>
<td>14.01</td>
<td>3.84</td>
<td>51.08</td>
<td>&lt;0.001</td>
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<tr>
<td>Fibrosis ISHAK 5,6 vs 2,3,4</td>
<td>1.15</td>
<td>0.52</td>
<td>2.54</td>
<td>0.730</td>
</tr>
<tr>
<td>Platelets per unit</td>
<td>0.99</td>
<td>0.99</td>
<td>1.00</td>
<td>0.117</td>
</tr>
<tr>
<td>Age per year</td>
<td>0.98</td>
<td>0.94</td>
<td>1.02</td>
<td>0.300</td>
</tr>
<tr>
<td>Gender Male vs Female</td>
<td>1.23</td>
<td>0.64</td>
<td>2.38</td>
<td>0.538</td>
</tr>
<tr>
<td>Race Black vs Non-Hispanic, White</td>
<td>0.48</td>
<td>0.18</td>
<td>1.26</td>
<td>0.136</td>
</tr>
<tr>
<td>Race Hispanic/other vs Non-Hispanic, White</td>
<td>0.97</td>
<td>0.47</td>
<td>2.00</td>
<td>0.940</td>
</tr>
</tbody>
</table>

### HepQuant STAT

<table>
<thead>
<tr>
<th>Variable</th>
<th>Hazard Ratio</th>
<th>Lower 95% CI</th>
<th>Upper 95% CI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>STAT tertile 0.73-1.19</td>
<td>2.59</td>
<td>0.70</td>
<td>9.56</td>
<td>0.154</td>
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<tr>
<td>STAT tertile &gt;1.19</td>
<td>9.82</td>
<td>2.82</td>
<td>34.22</td>
<td>&lt;0.001</td>
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<tr>
<td>Fibrosis ISHAK 5,6 vs 2,3,4</td>
<td>1.58</td>
<td>0.79</td>
<td>3.17</td>
<td>0.199</td>
</tr>
<tr>
<td>Platelets per unit</td>
<td>0.99</td>
<td>0.99</td>
<td>1.00</td>
<td>0.059</td>
</tr>
<tr>
<td>Age per year</td>
<td>0.98</td>
<td>0.94</td>
<td>1.02</td>
<td>0.263</td>
</tr>
<tr>
<td>Gender Male vs Female</td>
<td>1.10</td>
<td>0.58</td>
<td>2.08</td>
<td>0.771</td>
</tr>
<tr>
<td>Race Black vs Non-Hispanic, White</td>
<td>0.69</td>
<td>0.26</td>
<td>1.81</td>
<td>0.451</td>
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<tr>
<td>Race Hispanic/other vs Non-Hispanic, White</td>
<td>1.01</td>
<td>0.49</td>
<td>2.05</td>
<td>0.987</td>
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</table>
Using HepQuant Tests to Identify NASH Patients

Sens. Spec.
87% 98%
PPV NPV
97% 91%

Sens. Spec.
69% 98%
PPV NPV
96% 80%
Using HepQuant Tests to Identify NASH F3/comp F4 Patients

<table>
<thead>
<tr>
<th>Histology</th>
<th>DSI &lt;17.2</th>
<th>17.2 &lt; DSI &lt;30.0</th>
<th>DSI &gt;30.0</th>
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<tbody>
<tr>
<td>Decompensated Cirrhosis (F4)</td>
<td>0</td>
<td>0</td>
<td>9</td>
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<tr>
<td>Compensated Cirrhosis (F4)</td>
<td>3</td>
<td>18</td>
<td>1</td>
</tr>
<tr>
<td>Advanced Fibrosis (F3)</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Early Fibrosis (F1-2)</td>
<td>5</td>
<td>3</td>
<td>0</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Histology</th>
<th>STAT &lt;0.81</th>
<th>0.81 &lt; STAT &lt;2.5</th>
<th>STAT &gt;2.5</th>
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</thead>
<tbody>
<tr>
<td>Decompensated Cirrhosis (F4)</td>
<td>0</td>
<td>0</td>
<td>9</td>
</tr>
<tr>
<td>Compensated Cirrhosis (F4)</td>
<td>9</td>
<td>13</td>
<td>0</td>
</tr>
<tr>
<td>Advanced Fibrosis (F3)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Early Fibrosis (F1-2)</td>
<td>6</td>
<td>2</td>
<td>0</td>
</tr>
</tbody>
</table>

Sens.  Spec.  PPV  NPV
82%     82%     86%     78%
59%     88%     87%     63%
Results from the HepQuant Substudy of Gilead SOLAR-1: Curing HCV Improves Liver Graft Function

Cirrhotic Grafts (0 → 4 → 24 weeks) N=11

Healthy Control Function
Early Fibrosis (Ishak F0-2)
Moderate Fibrosis (Ishak F3-4)
Compensated Cirrhosis (Ishak F5-6)
 Decompensated Cirrhosis (Ishak F5-6)

Fibrotic Grafts (0 → 4 weeks) N=10
Ideal Diagnostic for Assessing Efficacy of Drugs for NASH and Fibrosis

- Reproducible
- Plausible link to pathogenesis of the disease
- Assess the whole organ
- Minimally invasive, well-tolerated
- Measure effectively all stages of disease
- Work in relevant populations (NASH/Fibrosis)
- Standardized
- Apply across centers

HepQuant Tests

- ✔ Reproducible
- ✔ Plausible link to pathogenesis of the disease
- ✔ Assess the whole organ
- ✔ Minimally invasive, well-tolerated
- ✔ Measure effectively all stages of disease
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- ✔ Standardized
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Thank You for your attention!!

Any Questions?