HepQuant & NASH:

Complementary Diagnostics for Drug Development and the Clinic

HepQuant Tests as Aids to Drug Development

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HepQuant – Filling an Unmet Need

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Assessing the Liver Patient – What’s Missing?

Standard Laboratory Tests – AST, ALT, Alk Phos, Bili, INR, Albumin, Platelet Count

Fibrosis Assessment – Biomarkers, Panels, Liver stiffness measurement, biopsy

Pressure Measurement - HVPG

What’s the Answer?

Function – What’s my Liver Score?

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“...... the development of collateral blood flow may alter hepatic drug metabolism without directly reflecting the metabolic or synthetic capacity of the liver. These issues have been addressed in the HepQuant® test by using two different stable isotope-labeled bile acids to simultaneously measure clearance from portal and systemic circulation as well as portal-systemic shunting.(50)
Preliminary data indicate this assessment of liver impairment correlates with hard endpoints.....”


The FDA explicitly encouraged the use of function testing in NASH Cirrhotics trials for both safety and efficacy. The following is from lines 169 – 172 of the Guidance: "The FDA encourages the sponsor to develop a specific approach (e.g., an algorithm) for monitoring liver function in patients with abnormal liver function at baseline, including criteria for drug discontinuation for individual patients and trial stopping rules (temporary or permanent).” The FDA has asked sponsors to create their own approach to measuring safety in NASH Comp Cirrhosis Trials. Sponsors protocol’s need to have, “guidelines for monitoring liver function,” (line 173).

The Liver “Functional Paradigm”

Surrogates for Liver Health
- Inflammation
  - ALT, AST
  - Biomarkers, NAS Score
  - Biopsy
- Fibrosis
  - Biomarkers, NFS Score
  - Elastography
  - Biopsy

Measures of Liver Health
- Hepatocyte Function
- Portal Circulation

Personal Health
- Feels
- Functions
- Survives

Defines how a Person Feels, Functions, and Survives

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The HepQuant Tests

STAT and SHUNT

Function: Cholate Uptake by Hepatocytes

Physiology: Flow-dependency, portal and systemic inflows
**Products**

**STAT: Potential for Broad application, POC**
- No Indwelling catheter
- Oral dosing only, single blood draw at t = 60 minutes
- **Estimates Disease Severity Index (DSI)**
- Scalable to any clinic

**SHUNT: Infusion Facility or Capability**
- Indwelling peripheral venous catheter
- IV and Oral dosing, blood sampling, 0,5,20,45,60,90 minutes
- **Measures Disease Severity Index (DSI)**
- Assesses the liver’s circulation and liver cell function

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Dual Cholate Clearance Test Administration

Simultaneous PO and IV Administration of Cholate Compounds

- 40 mg d4-Cholate mixed with juice
- 20 mg 13C-Cholate mixed with human albumin

Peripheral Blood Sampling at 5, 20, 45, 60, 90 min.

- Indwelling intravenous catheter for timed blood draws
- Serum samples shipped to HQ lab for LC-MS/MS

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Simultaneous Dual Cholate Clearances

Blood Samples (3 mL) at 0, 5, 20, 45, 60, 90 min

- Syst HFR 2.58 mL kg⁻¹ min⁻¹
- Port HFR 4.96 mL kg⁻¹ min⁻¹
- SHUNT 52.1%
- DSI 28.7
- STAT 1.44 µM (blue dot)

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Cholate Clearances assess the Functional Unit of the Liver

In Health, the First-pass Extraction of PO Cholate is $\approx 0.80$

Figure of Hepatic Acinus from Iwakiri Y, Shah V, Rockey DC. J Hepatology 2014;61:912-924

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Cholate Clearances Assess the Impact of Disease on Acinar Function

Portal Hypertension

Portal-Systemic Collaterals
Varices

↓Uptake + Collaterals
Decreases Extraction

Increases Spillover (SHUNT)

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DSI and STAT across the Spectrum of Disease
HepQuant Studies across Stages of Disease

**DSI**
- Early HCV F0-F2 (N=23)
- HALT-C F1-F2 (N=111)
- NASH F0-F2 (N=28)
- PSC early stage (N=47)
- Controls (N=50)
- CU HVPG (N=20)
- NIDDK dPP (N=28)

**STAT**
- Baylor cirrhosis study (N=71),
- REPRO (N=48)
- HQ-US-SHUNT-1701 (N=17)
- PSC (N=47)

<table>
<thead>
<tr>
<th>Stage of Disease</th>
<th>DSI Cutpoints</th>
<th>STAT Cutpoints</th>
</tr>
</thead>
<tbody>
<tr>
<td>Early Disease</td>
<td>~ 12.5</td>
<td>~ 0.5</td>
</tr>
<tr>
<td>Portal Hypertension</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any Varices</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Large Varices</td>
<td>~ 25</td>
<td>~ 1.5 – 2.0</td>
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<tr>
<td>Decompensation</td>
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</table>

*Cutpoints will be estimated from AUROC analysis and Plots of Sensitivity and Specificity vs Test Results

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STAT for Early Detection; SHUNT for Defining Severity and Monitoring

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Quantifying Liver Function

Further defines the health of the liver at baseline prior to instituting treatment

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HepQuant Model: The Complementary Function Test

- Greater risk for progression and clinical outcome
- Lower risk for progression and clinical outcome

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<table>
<thead>
<tr>
<th>C-P Class (categorical)</th>
<th>C-P Score</th>
<th>DSI (Continuous, 0 → 50)</th>
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<tbody>
<tr>
<td><strong>A</strong></td>
<td>5</td>
<td>17 ± 5 (HALT-C Adv Fibrosis, N=67)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>20 ± 5 (HALT-C Cirrhosis, N=40)</td>
</tr>
<tr>
<td></td>
<td>6</td>
<td>21 ± 5 (HALT-C Adv Fibrosis, N=24)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>24 ± 7 (HALT-C Cirrhosis, N=40)</td>
</tr>
<tr>
<td><strong>B</strong></td>
<td>7 – 9</td>
<td>33 ± 8 (HALT-C Cirrhosis, N=15)</td>
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<tr>
<td></td>
<td></td>
<td>35 ± 2 (TURQUOISE CPB, N=8)</td>
</tr>
<tr>
<td><strong>C</strong></td>
<td>10 – 15</td>
<td>39 ± 5 (SOLAR-1, N=6, CP 10-12)*</td>
</tr>
</tbody>
</table>

Data from QLFT Ancillary Study of HALT-C Trial M24, ABBVIE-sponsored TURQUOISE CPB Study, and GILEAD-sponsored SOLAR-1 Study.


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Antipyrine Clearance by Child-Pugh and DSI

Changes in PK of 5 Diverse Drugs by DSI

Quantifying Liver Function

Assesses change in liver health with natural disease progression and in response to treatment

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Serial Testing Quantifies Risk more Accurately

Baseline DSI

AUROC 0.827

1 - Specificity

Sensitivity

Clinical Followup and Retesting

MODEL D - DSI + ΔDSI

AUROC 0.874

1 - Specificity

Sensitivity

Data from QLFT Ancillary Study of HALT-C Trial: Baseline and M24

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ΔDSI after SVR

Data from subjects experiencing SVR from peginterferon/ribavirin in the QLFT Ancillary Study of HALT-C Trial: Baseline and M24

FUNCTIONAL IMPROVEMENT MEASURED BY A REDUCTION IN HEPQUANT’S DISEASE SEVERITY INDEX (DSI) AFTER SUSTAINED VIRAL RESPONSE (SVR) IN ADVANCED HEPATITIS C IS RELATED TO SEVERITY OF HEPATIC IMPAIRMENT AS DETERMINED BY BASELINE DSI. Helmke SM, Everson GT. Hepatology 2019;70:335A.

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Decrease in DSI and Estimated Reduction in Clinical Risk after SVR

Baseline

- Baseline DSI: 17.06
- Annual Risk of Clinical Event (Model A): 2.4%

Post SVR

- Repeat DSI (2 yr): 15.08
- Annual Risk of Clinical Event (Model D): 1.1%

54% Reduction in Annual Risk of a Clinical Outcome

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Relating Decrease in DSI to Reduced Risk for Clinical Outcome


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Quantifying Liver Function

Value as an endpoint for efficacy, or, in hepatic impairment studies, for detecting toxicity, defining severity of injury, and measuring recovery.
Effect of HCV Rx in Advanced Disease

**Results:**
Functional Changes ($\Delta$DSI) after SVR in Advanced HCV

FUNCTIONAL IMPROVEMENT MEASURED BY A REDUCTION IN HEPUQUANT’S DISEASE SEVERITY INDEX (DSI) AFTER SUSTAINED VIRAL RESPONSE (SVR) IN ADVANCED HEPATITIS C IS RELATED TO SEVERITY OF HEPATIC IMPAIRMENT AS DETERMINED BY BASELINE DSI. Helmke SM, Everson GT. Hepatology 2019;70:335A.
RESPONDERS


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Overview of Pharma and Research Studies and Collaborations

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HepQuant R&D Spans the Spectrum of Liver Research

34 Trials Completed, Ongoing and Projected

- CLD (includes NASH)
- NASH
- HCV
- Hepatic Impairment
- PBC
- PSC
- HCC
- Portal Hypertension
- TIPS
- Congenital Heart FONTAN

3162 Tests
1534 Subjects

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HepQuant R&D Spans all Disease Stages

Disease Stages Studied by Trial

Cirrhotics Studied
- Comp F4
- Portal Hypertension
- Decomp F4
- CTPA
- CTPB
- CTPC
- End-Stage

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Research (Non-Pharma) Collaborations

Experience
- 16 Total Trials
- 5 Current Ongoing and Projected Trials
- Spans all areas of liver research

Current Activity
- Working with key centers in multicenter proposals
- Incorporate as line item into any academic study
- Advance research with function testing

Research Trials Tests and Subjects

- Total Tests: 1609
- Total Subjects: 975

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Pharma Collaborations

Experience

- 18 Total Trials
- 10 Current Ongoing and Projected Trials
- Heavy Focus on NASH, Hepatic Impairment and HCC

Current Activity

- Working with leading companies in all phases of development
- Onboarding new partners
- Strategic discussions

Pharma Trials Tests & Subjects

- Ongoing / Projected
- All Trials

<table>
<thead>
<tr>
<th>TOTAL TESTS</th>
<th>TOTAL SUBJECTS</th>
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<tbody>
<tr>
<td>1138</td>
<td>415</td>
</tr>
<tr>
<td>1553</td>
<td>559</td>
</tr>
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</table>

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• **114** HepQuant sites and growing
  • New pharma trials train new sites

• **63** active sites in 1801 and pharma trials

• **51** projected to be trained for upcoming studies

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The SHUNT-V Pivotal Study
Current Status of the SHUNT-V Study

Original Design
Validation of DSI 18.3 for Likelihood of Large Esophageal Varices
420 Subjects

Interim Analysis
COVID Pandemic
251 Subjects

Based on preliminary findings at the Interim Analysis we are filing a PMA application

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HepQuant the Company
Greg Everson, M.D., FACP  
CEO, Technology Inventor

Dr. Everson is a director of HepQuant and is the inventor of the HepQuant technologies. Dr. Everson is Past Director of Hepatology at the University of Colorado, Denver where he worked for over 40 years.

Dr. Everson received his MD degree from Cornell Medical College, NY, NY. He is a distinguished Fellow of several professional societies and has published over 300 original papers, books and book chapters in peer-reviewed journals that include Hepatology, Clinics in Liver Disease, Gastroenterology, Journal of Hepatology, New England Journal of Medicine, The American Journal of Gastroenterology, Alimentary Pharmacology and Therapeutics, and Expert Reviews in Gastroenterology and Hepatology. He has authored several "self-help" books on a variety of liver diseases: Living with Hepatitis C: a Survivor’s Guide, Curing Hepatitis C, Living with Hepatitis B: A Survivors Guide, and Living with Hemochromatosis: Answers to Your Questions About Iron Overload.

He is an advisor and consultant to foundations and industry. Dr. Everson is a member of the American Association for the Study of Liver Diseases (AASLD), American Gastroenterological Association (AGA), American Society of Transplantation (AST), and the International Liver Transplant Society (ILTS). He is past member of the Transplant Hepatology Committees of the American Board of Internal Medicine and Accreditation Council for Graduate Medical Education.

Randy Dietrich  
Co-Manager, Chief Commercial Officer  
CEO Republic Financial Corporation

Randy Dietrich is a director of HepQuant and CEO of Republic Financial Corporation. During his more than 35-year tenure with Republic Financial Mr. Dietrich has overseen the acquisition, start-up and the eventual sale of more than 20 companies in a variety of industries. He has been instrumental in developing and building the company’s Special Assets and Aviation divisions which have acquired more than $2 billion in assets.

A founding ambassador of the Hepatitis C Caring Ambassador Program, Mr. Dietrich is a strong advocate for raising public awareness of health issues. The Caring Ambassadors Program encourages individuals with a life changing or life-threatening disease to take an active role in managing their health care and in supporting others with similar health issues.

Mr. Dietrich holds a Bachelor of Science in accounting from Wittenberg University in Springfield, Ohio. Earlier in his career Mr. Dietrich was a CPA with Coopers and Lybrand.

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The HepQuant Team

Sean Bundy, RAC
Chief Operations Officer & Director of Regulatory
• Business Operations; Supply Chain Management
• Lab Operations – CAP, COLA, CLIA Certification & Compliance
• Oversight of Quality & Regulatory; Clinical Trial management

Brad Everson
Chief Business Development Officer
• Sales of Tests (Pharma, Institutions, etc.)
• CDAs, MSAs/WOs, Licensing
• Bus Dev and Commercialization

Andrea Herman RN and Elyse Handley – Pivotal Study (SHUNT-V), HepQuant Studies, and Pharmaceutical Clinical Trials Management

(Individual to Join Soon)
Director of Regulatory Affairs
• Direct SHUNT V PMA Submission
• Directs all Issues related to Quality and Regulatory
• Team building in Quality and Regulatory
• Regulatory matters related to R & D

Steve Helmke
Chief Scientific Officer
• Scientific and technical oversight – Lab operations
• Lab technology – quality controls
• Data and Analysis
• High Quality publications and presentations; R & D

Matt Lauer
Director of Finance
• Financial Modeling
• Commercialization
• Capital Raising

Sarah Downing
Senior Manager, Quality Affairs
• QMS Management
• DHF Compliance
• Implementation of Quality Initiatives

Keith Hoffman
Laboratory Manager
• Lab Management
• Improve efficiencies
• Managing and directing Lab personnel
• Calibration management

Dziuleta Cepeniene
Laboratory Technician

Lisa Goggin
Managing Director of Business Operations
• Cash Forecast / Cap Table
• Treasury, AP, AR, Contracting / Budgeting
• Royalty reporting, Inventory ERM System
• Human Resources, Insurance

Rochelle Keffler
Administration

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Board of Advisors

Lloyd Everson, MD  
*Healthcare Entrepreneur*  
*Former CEO Molecular Health*  
Former President and COO of American Oncology

Robert Gish, MD  
*Leading Hepatologist*  
Formerly Adjunct Professor of Medicine at Stanford University

Bob Possehl  
*Serial Entrepreneur in numerous industries*  
*President, Republic Financial*

David Brunel  
*Diagnostic Executive*  
*Chairman, Biodesix*

Byron Hewett  
*Diagnostic Executive*  
*CEO Brava Diagnostics*  
Former CEO of 3 Diagnostic companies  
Executive positions at Abbott Labs, Qiagen, Bayer Diagnostics, Chiron Diagnostics

Charlie Henry  
*Diagnostic Entrepreneur*  
*CEO, President & Founder Op-T and Opt-Mune*  
Former CEO of 2 Diagnostic companies

David Brunel  
*Leading Hepatologist*  
*Liver Consultants of Texas*

James Trotter, MD  
*Leading Hepatologist*  
*Liver Consultants of Texas*

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