TREATMENT WITH HMG-CoA REDUCTASE INHIBITORS (STATINS) IS ASSOCIATED WITH PRESERVATION OF HEPATIC FUNCTION IN ADVANCED CHRONIC LIVER DISEASE (CLD): RESULTS FROM THE SHUNT-V STUDY

Robert S. Rahimi, MD, for the SHUNT-V Subjects, Investigators, and Coordinators
Disclosures

Robert Rahimi, MD
I have no financial relationship with a commercial interest

Steve M. Helmke, PhD: employee (CSO) HepQuant LLC; equity member HepQuant LLC; Intellectual property in HepQuant technology

Gregory T. Everson, MD: employee (CEO) HepQuant LLC; equity member HepQuant LLC; Intellectual property in HepQuant technology

The SHUNT-V Study was sponsored by HepQuant LLC
Aim

The primary aim of this analysis was to identify factors in patients with advanced chronic liver disease that are associated with severity of:

• Impairment of liver function
• Portal-systemic shunting

Specifically, we used the dual cholate test (HepQuant) to quantify liver function (Disease Severity Index, DSI) and shunting (SHUNT%) and define the impact of:

• Disease Etiology – NASH versus Other
• Coexistent disease – Diabetes versus No Diabetes
• Drug treatment – Diabetic and Lipid-lowering drugs
Background

• Etiology, coexistent disease, and concomitant drug therapy can influence the progression of chronic liver disease (CLD).

• With disease progression portal hypertension and portal-systemic shunting increase and liver function declines – leading to clinical complications, such as varices.

• The noninvasive DUAL CHOLATE test quantifies portal-systemic shunting (SHUNT%) and generates a Disease Severity Index (DSI) of global liver function.

• In the SHUNT-V Study, shunting (SHUNT%) and liver function (DSI) were characterized in subjects with suspected, compensated, or clinically-stable cirrhosis.

• SHUNT-V and other studies found that SHUNT% and DSI predicted likelihood for portal hypertension*, esophageal varices**, and risk for clinical outcome***.

The SHUNT-V Study Enrollment Criteria

• 27 US clinical centers from Feb 2019 through Dec 2020
• Adults undergoing screening or surveillance EGD for varices
• Included suspected or definite cirrhosis as determined by:
  • Prior liver biopsy
  • Radiologic (including elastography) or clinical criteria
  • Chronically abnormal liver tests with low platelet count
• Exclusions included:
  • Child-Pugh C cirrhosis
  • Refractory ascites or encephalopathy
  • Prior variceal hemorrhage, known large varices, or treatment of varices

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Dual Cholate Test Administration

**Simultaneous PO and IV Administration of Cholate Compounds**

- **Mouth**: 40 mg d4-Cholate mixed with juice
- **Blood stream**
- **Stomach**
- **Intestines**

**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

**Dissolved Active Pharmaceutical Ingredient (API)**

**20 mg 13C-Cholate mixed with human albumin**

**Entry of intravenously administered API into blood stream**

**Entry of orally administered API into blood stream**

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Example of Dual Cholate Clearances in a Subject with Liver Disease

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

DSI 28.7
(ULNI <12)

SHUNT 52.1%
(ULNI <30%)

[13C-cholate] after IV Injection

[d4-cholate] after PO Intake
Results: NASH versus NON-NASH Subjects
### Demographics by NASH Diagnosis

<table>
<thead>
<tr>
<th></th>
<th>Wt (kg)</th>
<th>Ht (cm)</th>
<th>BMI (kg m⁻²)</th>
<th>Obese (BMI &gt;30)</th>
<th>Diabetes Mellitus</th>
<th>Age (yr)</th>
<th>Men</th>
<th>Hispanic</th>
<th>White</th>
<th>Black</th>
</tr>
</thead>
<tbody>
<tr>
<td>NASH Mean (or %)</td>
<td>98.5</td>
<td>167.1</td>
<td>35.1</td>
<td>78.0%</td>
<td>66.7%</td>
<td>62.9</td>
<td>41.5%</td>
<td>10.6%</td>
<td>99.2%</td>
<td>0.8%</td>
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<tr>
<td>SD</td>
<td>20.8</td>
<td>9.6</td>
<td>6.3</td>
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</tr>
<tr>
<td>N</td>
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<td>147</td>
<td>147</td>
<td>79</td>
<td>33</td>
<td>147</td>
<td>83</td>
<td>25</td>
<td>131</td>
<td>13</td>
</tr>
<tr>
<td>Non-NASH Mean (or %)</td>
<td>93.1</td>
<td>170.2</td>
<td>32.0</td>
<td>53.7%</td>
<td>22.4%</td>
<td>60.3</td>
<td>56.5%</td>
<td>17.0%</td>
<td>89.1%</td>
<td>8.8%</td>
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<td>10.6</td>
<td>7.6</td>
<td></td>
<td></td>
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<td>p</td>
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<td>0.0130</td>
<td>0.0003</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
<td>0.0466</td>
<td>0.0150</td>
<td>0.16</td>
<td>0.0006</td>
<td>0.0040</td>
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Clinical Scores and Lab Tests by NASH Diagnosis

<table>
<thead>
<tr>
<th></th>
<th>CTP Score</th>
<th>MELD Score</th>
<th>MELD Na Score</th>
<th>Creatinine (mg/dL)</th>
<th>Bilirubin (mg/dL)</th>
<th>INR</th>
<th>Sodium (meq/L)</th>
</tr>
</thead>
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<tr>
<td><strong>NASH</strong></td>
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<td></td>
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<td></td>
<td></td>
<td></td>
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<tr>
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<td>117</td>
<td>118</td>
<td>116</td>
<td>114</td>
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<tr>
<td>SD</td>
<td>5.33</td>
<td>8.51</td>
<td>8.55</td>
<td>0.91</td>
<td>0.82</td>
<td>1.15</td>
<td>140</td>
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<tr>
<td><strong>Non-NASH</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>Mean</td>
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<td>129</td>
<td>134</td>
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<td>SD</td>
<td>5.49</td>
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<tr>
<td>t-test p</td>
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NASH and NON-NASH subjects had similar clinical scores and standard laboratory tests.
Results of the Dual Cholate Test by NASH Diagnosis

<table>
<thead>
<tr>
<th>NASH</th>
<th>Systemic HFR</th>
<th>Portal HFR</th>
<th>SHUNT</th>
<th>DSI</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>mL min⁻¹ kg⁻¹</td>
<td>mL min⁻¹ kg⁻¹</td>
<td>%</td>
<td>Score</td>
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<td>147</td>
<td>147</td>
<td>147</td>
</tr>
<tr>
<td>N</td>
<td>3.16</td>
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<tr>
<td>SD</td>
<td>1.10</td>
<td>6.76</td>
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<td>8.5</td>
</tr>
<tr>
<td>t-test</td>
<td>p</td>
<td></td>
<td>0.0256</td>
<td>0.0375</td>
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UNEXPECTED FINDING: Thus, it was surprising that NASH subjects had better liver function (lower DSI) and less portal-systemic shunting (lower SHUNT%).
Results: Diabetic versus NON-Diabetic Subjects
Demographics by Diabetes Diagnosis

<table>
<thead>
<tr>
<th></th>
<th>Wt (kg)</th>
<th>Ht (cm)</th>
<th>BMI (kg m(^{-2}))</th>
<th>Obese (BMI &gt;30)</th>
<th>NASH</th>
<th>Age (yr)</th>
<th>Men</th>
<th>Hispanic</th>
<th>White</th>
<th>Black</th>
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</thead>
<tbody>
<tr>
<td>Diabetic</td>
<td>N</td>
<td>Mean (or %)</td>
<td>SD</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>115</td>
<td>98.3</td>
<td>20.6</td>
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<tr>
<td></td>
<td>115</td>
<td>168.3</td>
<td>9.1</td>
<td>115</td>
<td>82</td>
<td>63.9</td>
<td>47.0%</td>
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<td>94.8%</td>
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<tr>
<td></td>
<td>155</td>
<td>169.2</td>
<td>11.1</td>
<td>155</td>
<td>93</td>
<td>59.7</td>
<td>51.6%</td>
<td>13.5%</td>
<td>92.9%</td>
<td>5.8%</td>
</tr>
<tr>
<td>Non-Diabetic</td>
<td>N</td>
<td>Mean (or %)</td>
<td>SD</td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td></td>
<td>115</td>
<td>93.5</td>
<td>25.1</td>
<td>115</td>
<td>93</td>
<td>59.7</td>
<td>51.6%</td>
<td>13.5%</td>
<td>92.9%</td>
<td>5.8%</td>
</tr>
<tr>
<td></td>
<td>116</td>
<td>169.2</td>
<td>11.1</td>
<td>93</td>
<td>41</td>
<td>59.7</td>
<td>51.6%</td>
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<td>92.9%</td>
<td>5.8%</td>
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<tr>
<td></td>
<td>155</td>
<td>169.2</td>
<td>11.1</td>
<td>155</td>
<td>41</td>
<td>59.7</td>
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<tr>
<td></td>
<td>155</td>
<td>169.2</td>
<td>11.1</td>
<td>155</td>
<td>41</td>
<td>59.7</td>
<td>51.6%</td>
<td>13.5%</td>
<td>92.9%</td>
<td>5.8%</td>
</tr>
</tbody>
</table>

Diabetic subjects had higher BMI and were older; 71.3% had NASH.
Clinical Scores and Lab Tests by Diabetes Diagnosis

<table>
<thead>
<tr>
<th></th>
<th>CTP Score</th>
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<th>Bilirubin (mg/dL)</th>
<th>INR</th>
<th>Sodium (meq/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Diabetic</strong></td>
<td>N</td>
<td>113</td>
<td>111</td>
<td>107</td>
<td>111</td>
<td>112</td>
<td>111</td>
</tr>
<tr>
<td></td>
<td>Mean</td>
<td>5.27</td>
<td>8.25</td>
<td>8.60</td>
<td>0.91</td>
<td>0.79</td>
<td>1.14</td>
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<tr>
<td></td>
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<td>0.65</td>
<td>3.04</td>
<td>3.97</td>
<td>0.27</td>
<td>0.68</td>
<td>0.35</td>
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<tr>
<td><strong>Non-Diabetic</strong></td>
<td>N</td>
<td>142</td>
<td>139</td>
<td>135</td>
<td>140</td>
<td>141</td>
<td>140</td>
</tr>
<tr>
<td></td>
<td>Mean</td>
<td>5.54</td>
<td>8.80</td>
<td>8.73</td>
<td>0.87</td>
<td>1.03</td>
<td>1.23</td>
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<tr>
<td></td>
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<td>2.88</td>
<td>3.96</td>
<td>0.32</td>
<td>0.89</td>
<td>0.88</td>
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<tr>
<td><strong>t-test</strong></td>
<td>p</td>
<td><strong>0.0121</strong></td>
<td>0.15</td>
<td>0.80</td>
<td>0.30</td>
<td><strong>0.0196</strong></td>
<td>0.30</td>
</tr>
</tbody>
</table>

Preserved function in diabetic subjects is suggested by the slightly lower CP score and mean bilirubin.
## Results of the Dual Chololate Test by Diabetes Diagnosis

<table>
<thead>
<tr>
<th></th>
<th>Systemic HFR</th>
<th>Portal HFR</th>
<th>SHUNT</th>
<th>DSI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>mL min⁻¹ kg⁻¹</td>
<td>mL min⁻¹ kg⁻¹</td>
<td>%</td>
<td>Score</td>
</tr>
<tr>
<td><strong>DM</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>115</td>
<td>115</td>
<td>115</td>
<td>115</td>
</tr>
<tr>
<td>Mean</td>
<td>3.38</td>
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<td>22.63</td>
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<td>7.46</td>
</tr>
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<td><strong>No-DM</strong></td>
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<td></td>
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<td>155</td>
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<tr>
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<td>3.10</td>
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<td>0.0325</td>
<td>0.0004</td>
<td>0.0013</td>
<td>0.0008</td>
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</table>

**UNEXPECTED FINDING:** Since diabetes is a risk factor for progression of liver disease, it was surprising that liver function was better (lower DSI) and Portal-Systemic Shunting Less (lower SHUNT%) in DIABETIC Subjects.
Results: Drug Treatment
Effect of Diabetic and Lipid-lowering Drugs

Diabetic and Lipid-lowering drug use is associated with less portal-systemic shunting (lower SHUNT%) and better liver function (lower DSI). *p value for change from treatment with neither to both classes of drug.
In Multivariable Analysis the Use of STATINs or METFORMIN were Independently Associated with Lower SHUNT% and Lower DSI

<table>
<thead>
<tr>
<th></th>
<th>Impact on SHUNT%</th>
<th>Impact on DSI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Decline in SHUNT%</td>
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</tr>
<tr>
<td>Statin</td>
<td>-6.3%</td>
<td>0.0132</td>
</tr>
<tr>
<td>Metformin</td>
<td>-5.9%</td>
<td>0.0475</td>
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<tr>
<td>Diabetes Diagnosis</td>
<td>-1.4%</td>
<td>0.64</td>
</tr>
<tr>
<td>NASH Diagnosis</td>
<td>-1.3%</td>
<td>0.61</td>
</tr>
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</table>

The combined effect of the use of STATINs plus METFORMIN was 20% less portal-systemic shunting (lower SHUNT%) and 20% better function (lower DSI).
Summary

• This study highlights the potential utility of the sensitive and reliable dual cholate test of liver function for detecting treatment effects.

• STATINS and Metformin were independently associated with preserved hepatic function and reduced portal-systemic shunting.

• Improved liver function and reduced portal-systemic shunting should reduce risk for clinical outcome.

➢ Follow-up of the SHUNT-V cohort is planned.
Key Takeaways

• STATIN and Metformin use may slow the progression of chronic liver disease.

• These results provide support for a clinical trial of STATIN and Metformin in the treatment of chronic liver disease.

• The dual cholate test may detect the effects of treatments on liver function and physiology, and potentially provide new endpoints for clinical trials.
### SHUNT-V Investigators and Clinical Centers

<table>
<thead>
<tr>
<th>Institution</th>
<th>Investigator Name</th>
<th>Investigator Title</th>
</tr>
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<tbody>
<tr>
<td>Accel Research Sites</td>
<td>John M Hill, MD</td>
<td>Chair, Integrated Site Network</td>
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<tr>
<td>Arizona Liver Health</td>
<td>Anita Kohli, MD</td>
<td>Director of Research and Managing Partner</td>
</tr>
<tr>
<td>Baylor Scott and White</td>
<td>Robert Rahimi, MD</td>
<td>Transplant Hepatologist and Gastroenterologist</td>
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<td>Bon Secours Liver Institute of Richmond</td>
<td>Mitchell Shiffman, MD</td>
<td>Director, Liver Institute of Virginia, Bon Secours Virginia Health System</td>
</tr>
<tr>
<td>California Liver Research Institute</td>
<td>Edward Mena, MD</td>
<td>Medical Director &amp; CEO</td>
</tr>
<tr>
<td>Clinical Trials of Texas, Inc.</td>
<td>Douglas Denham, DO</td>
<td>Medical Director</td>
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<tr>
<td>Digestive Disease Associates</td>
<td>Natarajan Ravendhran, MD</td>
<td>Medical Director, Clinical Research Department</td>
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<tr>
<td>Gastroenterology Associates of Pensacola, PA</td>
<td>Frederic Newman, MD</td>
<td>Gastroenterologist</td>
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<td>Gastroenterology Consultants of Southwest Virginia</td>
<td>Vishal Bhat, MD</td>
<td>Director of Clinical Research</td>
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<td>Gastroenterology Health Partners, PLLC</td>
<td>James Strobel, MD</td>
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<td>Inland Empire Liver Foundation</td>
<td>Zeid Kayali, MD</td>
<td>Medical Director</td>
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<tr>
<td>Intermountain Medical Center</td>
<td>Richard Gilroy, MD</td>
<td>Medical Director of Hepatology and Liver Transplantation</td>
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<tr>
<td>Lucas Research</td>
<td>Kathryn Lucas, MD</td>
<td>Endocrinologist &amp; President</td>
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<tr>
<td>Mayo Clinic Florida</td>
<td>Andrew Keaveny, MD</td>
<td>Medical Director, Clinical and Transplant Hepatology</td>
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<tr>
<td>Mayo Clinic Rochester</td>
<td>Michael Leise, MD</td>
<td>Associate Professor of Medicine</td>
</tr>
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<td>McGuire VA</td>
<td>Michael Fuchs, MD</td>
<td>Professor of Medicine</td>
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<tr>
<td>Methodist Dallas Medical Center</td>
<td>Parvez Mantry, MD</td>
<td>Medical Director, Liver Institute Research</td>
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<td>Paul Hellstern, MD</td>
<td>Clinical Research Investigator Gastroenterology</td>
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<td>Peak Gastroenterology Associates</td>
<td>Bhaktasharan Patel, MD</td>
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</tr>
<tr>
<td>PMG Research</td>
<td>Brian Smith, MD</td>
<td>Clinical Investigator</td>
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<tr>
<td>Ralph H Johnson VAMC</td>
<td>Wing-Kin Syn, MBChB</td>
<td>Professor of Medicine &amp; Associate Research Program Director</td>
</tr>
<tr>
<td>Southern California Research Center</td>
<td>Tarek Hassanein, MD</td>
<td>Director</td>
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<tr>
<td>St. Louis University</td>
<td>Kamran Qureshi, MD</td>
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<td>Tandem Clinical Research</td>
<td>Gary Reiss, MD</td>
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<td>University of Mississippi</td>
<td>Sarah Glover, DO</td>
<td>Division Chief for Digestive Disease</td>
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<td>University of Pennsylvania</td>
<td>Rajender Reddy, MD</td>
<td>Director, Hepatology &amp; Medical Director, Liver Transplantation</td>
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<tr>
<td>University of Washington</td>
<td>Ethan Weinberg, MD</td>
<td>Assistant Professor in Clinical Medicine</td>
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<tr>
<td></td>
<td>Kiran Bambha, MD</td>
<td>Associate Professor of Medicine</td>
</tr>
</tbody>
</table>

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Thank you!