Introduction
While liver biopsy is currently considered the ‘gold standard’ for the diagnosis of nonalcoholic steatohepatitis (NASH) and advanced fibrosis, it has significant limitations, including sampling error, and potentially serious complications including pain, bleeding, injury to other organs, and, rarely, death.

Due to these risks, noninvasive dynamic markers represent a large, unmet medical need.

To date, biomarkers for NASH have been evaluated primarily by univariate analysis or as composite scores.

GNS Healthcare’s Reverse Engineering and Forward Simulation (REFS®) proprietary machine learning platform allows complete and unbiased integration of all available markers into a single predictive measure, allowing for quantification and evaluation of predictive performance provided by noninvasive markers alone compared with complete measures, including invasive testing.

Objectives
To identify key noninvasive or invasive factors, combinations of factors, and subpopulations that impact progression to cirrhosis and cirrhosis-related clinical events

To determine the extent to which only noninvasive measures of fibrosis can be used to predict these outcomes

Methods
Study population:
– 219 adults with NASH and bridging fibrosis (modified Ishak Stages 3–4), and 258 adults with NASH and compensated cirrhosis (modified Ishak Stages 5–6) were enrolled in a Phase 2b placebo-controlled trial of simtuzumab (GS-US-321-0105 [ClinicalTrials.gov identifier NCT01672968]) and GS-US-321-0106 (NCT01672878) for bridging fibrosis and cirrhosis patients, respectively, a monoclonal antibody directed against lysyl oxidase-like 2.

– Analyses included 475 patients with available data: 381 in the training cohort and 94 in the validation cohort.

– The trials were stopped at Week 96 due to lack of efficacy, so treatment groups were combined for this analysis

Outcome measures:
– We performed survival modeling of time to progression to cirrhosis in patients with bridging fibrosis or advanced fibrotic clinical events (eg, ascites, newly diagnosed varices, variceal hemorrhage, hepatic encephalopathy, ≥2-point increase in Child-Pugh-Turcotte score). Model for End-stage Liver Disease score ≥15, liver transplantation, and death) in patients with cirrhosis

Predictors:
– 2 sets of models were run for each outcome: 1st, a full model incorporating all available baseline clinical, histologic, and serum fibrosis marker data; and 2nd, a noninvasive model excluding measures obtained from invasive procedures

Modeling Approach and REFS Analytic Platform
Visualization of REFS Enumeration of Model Fragments and Reverse Engineering of Prediction Model Ensemble

REFS was used to build the survival models using a Weibull distribution

Selection of a single model underestimates prediction error; thus REFS learns an ensemble of the most probable models (N=256) given the data

– Ensemble constructed via Monte Carlo sampling of the posterior model landscape

– Model additions/subtractions scored based on a maximum entropy structural prior, with complexity also penalized by the Bayesian information criterion

– Linear, additive, and quadratic terms allowed to accommodate nonlinear effects and subpopulations

– Confidence of the importance of a given predictor towards predicting the outcome determined by selection frequency among ensemble

Model evaluation:
– The predictive performance of the survival model ensembles was assessed in-sample and by internal 3-fold cross validation (CV) in the training set, and further validated in a test sample (20% of cohort)

– The performance measure used is the Concordance index (C-index): probability that for a pair of randomly selected patients, the patient with the higher risk prediction will experience an event before the other sample

Results

Noninvasive Models Performed As Well As Full Models Including Liver Histology

Modeling Approach and REFS Analytic Platform
Visualization of REFS Enumeration of Model Fragments and Reverse Engineering of Prediction Model Ensemble

Outcomes

<table>
<thead>
<tr>
<th>Predictor Set</th>
<th>Full model</th>
<th>Noninvasive</th>
</tr>
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<td>Predictor Set</td>
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<td>95% CI</td>
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Disease Progression

Time to Onset of Cirrhosis: Study 105

<table>
<thead>
<tr>
<th>Predictor Set</th>
<th>Term Ensemble</th>
<th>% Ensemble</th>
<th>C-index (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
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Time to Onset of Clinical Events: Study 106

<table>
<thead>
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Conclusions

Models generated using machine learning utilizing only noninvasive data can accurately predict the risk of clinical disease progression in patients with advanced fibrosis due to NASH

References


Acknowledgments

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