Non-invasive Testing for Fatty Liver Disease for Primary Care Providers

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ABSTRACT

Population data point to increasing prevalence of NAFLD worldwide. Emerging intervention strategies command development of more accessible diagnostic tools to identify individuals at early risk for morbidities associated with untreated NAFLD. While liver Bx is the diagnostic standard, patients & their clinicians need strong motivators to invoke the risk and uncertainty of biopsy; or even the expense and inconvenience of imperfect imaging technologies. We describe an inviting pathway to reliable diagnosis in a 2- stage process of risk assessment:

(1) The initial screening tool, LiverFASt Select, delivers a binary prediction of "Elevated" or "Low" Risk for steatosis; available to virtually any patient during an annual wellness or preventive visit.

"Elevated Risk" prediction justifies acquisition of a few strategic biomarkers for non-invasive quantitative risk assessment of steatosis, inflammation activity, & fibrosis.

(2) Using up to 9 biomarkers, the full LiverFASt algorithm predicts the likely degree of liver pathology, providing SAF scores: Steatosis S1-S3 ~ Activity/Inflammation A0 - A4 ~ Fibrosis F0 - F4

The algorithm is demonstrably close to biopsy predictions and can provide the critical diagnoses that motivate patient and physician to develop and implement the best available intervention strategies.

METHOD

- Interview IRB of Austin, TX approved the protocol to assess de-identified medical records containing multiple biomarkers and pathologists-determined SAF scores from liver biopsies.
- A database of 2862 unique medical assessments of biomarkers & biopsy reports was created: 1027 assessments were used to train the algorithm, 1835 constituted the validation set.
- ML developed the complex quantitative algorithm utilizing 3 anthropometrics: age, gender BMI; & up to 9 biomarkers to accurately predict level of steatosis, inflammation activity and fibrosis (comparable to biopsy SAF score).
- Previously, Assistance Publique (AP-HP) compiled 3 sets of markers to create algorithms to assess severity of the 3 lesions of NAFLD biopsy-demonstrated pathologies: age & gender plus 5 biomarkers for fibrosis; 1 additional biomarker for inflammation activity; and another 4 biomarkers for steatosis. For the creation of LiverFASt, three neural networks (1 each for S, A, and F) were developed and aligned against the AP-HP determinations for accuracy relative to Bx.
- Subsequently a LiverFASt Select algorithm was trained from 1678 medical records to make a binary decision for the (ELEVATED/LOW) probability of NAFLD/ NASH based on age, gender, BMI & 1 or more biomarkers out of 6 frequent tests. Patients predicted at ELEVATED risk require follow-up quantitative diagnostic prediction.

The ML algorithm created new SAF scoring using the markers below. LiverFASt uses one less biomarker than the AP-HP algorithm.

Fibrosis: Age, Gender, α 2 Macroglobulin, Apolipoprotein A1, Bilirubin, GGT, Haptoglobin
Inflammation: Age, Gender, α 2 Macroglobulin, Apolipoprotein A1, Bilirubin, GGT, Haptoglobin, ALT
Steatosis: Age, Gender, α 2 Macroglobulin, Apolipoprotein A1, Bilirubin, GGT, Haptoglobin, ALT, BMI, Total Cholesterol, Fasting Glucose, Triglycerides

BACKGROUND

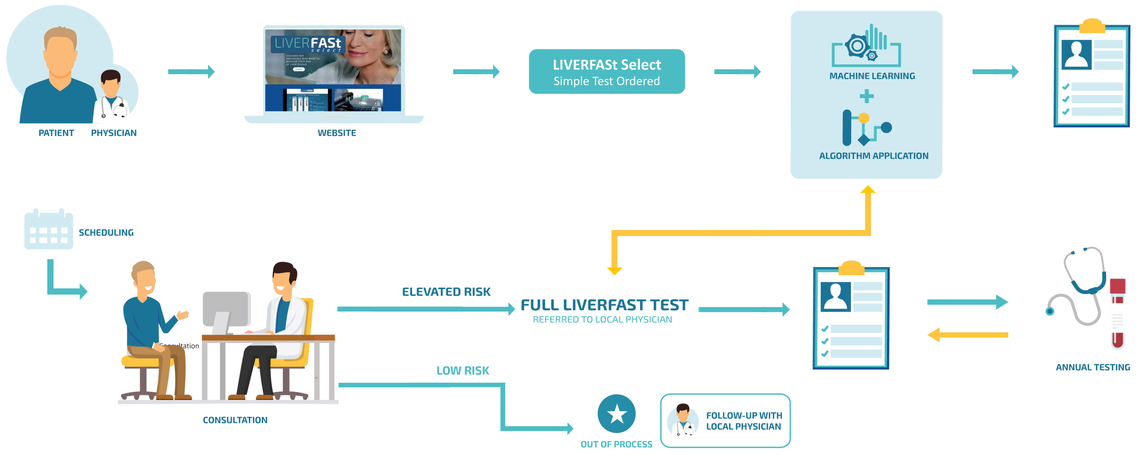

TABLE 1 RESULTS OF STAGE 1 FOR BINARY (ELEVATED/LOW) RISK ASSESSMENT

Statistical values related to LIVERFASt Select Risk Assessment based on increasing application of specific, selected biomarkers. (See Methods)

Gender	Age	BMI	FBG	Trig	ALT	GGT	a2 mac	APO A1	Precision	Sensitivity	Specificity	Clinical Value
X	X	X	X	X					0.82	0.94	0.54	+
X	X	X	X	X	X				0.88	0.93	0.72	++
X	X	X	X	X	X	X			0.93	0.94	0.84	+++
X	X	X	X	X	X	X	X	X	0.97	0.98	0.92	++++

Even when less than the optimal number of blood biomarkers are available for the LiverFASt Select algorithm (E.g.: only FBG and Trig) the algorithm provides useful information to inspire physician and/ or patients to investigate without causing unnecessary apprehension. Adding the readily available biomarkers ALT and GGT provide good sensitivity and specificity.

The training dataset (n=1027) included 60% male, was slightly older (mean age ~51 yrs) and with a lower BMI. The validation dataset (n=1835) was 77% males, mean age ~45 years, and higher BMI.

Following algorithmic assignment of disease diagnoses, 235 medical assessments yielded simultaneously negative diagnosis predictions for steatosis, inflammation activity, and fibrosis. These "S0A0F0" patients were therefore considered to have a functionally "healthy liver". The training dataset and the validation dataset included 192 and 43 healthy liver assessments respectively

TABLE 2 CLINCAL CHARACTERISTICS OF INDIVIDUAL ASSESSMENTS IN THE DATASETS FOR THE QUANTITATIVE ALGORITHM:

Feature	Training Set Mean	Training Set STD	Validation Set Mean	Validation Set STD
Age (years)	50.96	12.91	45.10	15.38
a2 macroglobulin (g/L)	1.83	0.70	2.03	0.70
ApoA1 (g/L)	1.48	0.25	1.39	0.24
Bilirubin (µmol/L)	12.67	8.56	17.19	10.50
Haptoglobin (g/L)	1.18	0.57	1.09	0.66
GGT (IU/L)	67.84	91.47	98.11	88.76
ALT (IU/L)	52.83	47.57	55.76	46.79
BMI (kg/m²)	26.09	3.30	27.40	4.71
Cholesterol (total) (mmol/L)	4.92	1.05	5.40	1.28
Glucose (fasting) (mmol/L)	5.63	1.24	8.42	2.87
Triglycerides (mmol/L)	1.51	0.79	3.89	1.63

DESIGN OF THE STUDY

High sensitivity/specificity indicating "Elevated" or "Low" risk for NAFLD can be achieved using a simple algorithm based on minimal information from patients seeking routine check-ups from PCPs. The algorithmic result is significantly more precise than current reliance on identification of outlier values for standard individual liver function biomarkers. Furthermore, most patients at elevated risk can be evaluated for quantitative SAF score prediction using additional biomarkers - without undergoing expensive or invasive procedures of elastography, imaging or biopsy. This simplified process may be helpful in securing the attention and therapeutic compliance of patients at risk for or experiencing severe forms of NAFLD.

FIGURE 1 DISTRIBUTION OF THE INDIVIDUAL ASSESSMENT SCORES TEND TO REPRESENT EARLIER STAGES OF FIBROSIS AND INFLAMMATION ACTIVITY

Unlike some other non-biopsy diagnosis tools, the majority of the assessments were in early stages of fibrosis and inflammation activity; steatosis assessments, however, were more balanced across the range of scores.

Histograms of: (left to right) Steatosis, Inflammation Activity, & Fibrosis scores (Training and validation datasets are similar; only the training set shown)

TABLE 3 COMPARISON TO THE AP-HP TEST ACCURACY

Standard metrics used to describe the accuracy of regression models were computed to assess the performance of the new models: MAE, MaxAE and R2 (Coefficient of Determination) for the prediction of Fibrotest, ActiTest and SteatoTest biopsy-validated scores with the new SAF prediction models. On average, the new models make predictions that are very close to the AP-HP derived scores.

AP-HP Test	FibroTest	ActiTest	SteatoTest
Mean Absolute Error	1.30E-03	3.40E-03	1.10E-03
Max Absolute Error	3.20E-02	5.20E-02	2.40E-02
R^2	0.99992	0.99952	0.99991
CI (95%)	[1.2E-3, 1.4E-3]	[3.2E-3, 3.6E-3]	[1.0E-3, 1.2E-3]

For the three new models, the order of magnitude of the MAE is 1E-3.
This is satisfactory since AP-HP-derived scores are given with a precision of 1E-2.

TABLE 4 CORRELATION BETWEEN THE ESTIMATED SAF SCORE AND THE PREDICTED NAFLD/NASH DIAGNOSIS

The algorithm retrieves 3 separate scores to create the composite LiverFASt SAF score – SxAyFz – to determine probable outcome in FLIP biopsy scoring. (X, Y, and Z are integers as [0-3], [0-4] and [0-4] respectively)

Estimated SAF score	Diagnosis
S0 Ay Fz	No NAFLD
Sx>0 Ay<2 Fz	NAFLD
Sx>0 A2 Fz	NAFLD or NASH
Sx>0 Ay>2 Fz	NASH

Diagnoses are unambiguous except for Sx>0 A2 Fz. When the steatosis stage is at least 1 and the activity stage is 2, the patient is more likely to be labelled NAFLD (probability of 2/3) than NASH (probability of 1/3). In this specific case the LiverFASt algorithm is only able to provide an open diagnosis: NAFLD or NASH.

DISCLOSURE

Fibronostics provided the financial support for this study

FIBRONOSTICS