and without T2DM. Finally, using the cut-off of ELF ≥ 9.8 for prediction of advanced fibrosis in NAFLD, observed accuracy was as follows: histologic advanced fibrosis - sensitivity 54%, specificity 89%, positive predictive value (PPV) 67%, negative predictive value (NPV) 83%; advanced fibrosis by TE - sensitivity 59%, specificity 86%, positive predictive value (PPV) 46%, negative predictive value (NPV) 91%. On the other hand, the cut-off of ELF ≥ 11.3 returned specificity 99.0%, sensitivity 18%, PPV 88%, NPV 75% for histologic advanced fibrosis; specificity 99.6%, sensitivity 20%, PPV 91%, NPV 86% for advanced fibrosis by TE. **Conclusion:** The ELF test performs well in identifying high risk NAFLD patients with or without T2DM. The ELF test can be used in clinical practice to assess advanced fibrosis in NAFLD.

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PERFORMANCE OF NONINVASIVE TESTS IN PATIENTS WITH LIPODYSTROPHY

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Background: Inherited and acquired lipodystrophies are disorders characterized by variable loss of adipose tissue resulting in leptin deficiency and metabolic complications such as insulin resistance, hypertriglyceridemia and progressive nonalcoholic steatohepatitis (NASH). The clinical performance and utility of non-invasive assessments of liver fibrosis validated in obesity-associated NASH have never been assessed in lipodystrophy. **Methods:** The aim of this study was to assess the utility of biochemical and radiological noninvasive fibrosis tests (NITs) in patients with lipodystrophy. Data regarding demographics, laboratory, imaging, vibration-controlled transient elastography (VCTE) and shear wave elastography (SWE) were collected. NITs including the APRI, BARD score, Fibrosis-4 (FIB-4) index and Non-Alcoholic Fatty Liver Disease Fibrosis Score (NFS) were calculated. The performance of each modality to diagnose cirrhosis (defined by histology or imaging and platelet counts) was assessed by area under receiver operating characteristics (AUROC). **Results:** Eighty-one patients with lipodystrophy (congenital generalized 28%; familial partial 54%; acquired generalized 14%; acquired partial 4%) were evaluated: 79% female, 85% diabetic, mean age 32.9 (SD, 17.9) years, BMI 23.4 (SD, 6.2) kg/m2. ALT 25.0 (IQR, 21.3) U/L, AST 24.0 (IQR, 12.8) U/L, VCTE 5.5 (IQR, 3.3) kPa and SWE 1.5 (IQR, 0.3) m/s. 21% patients had cirrhosis. Moderate correlations were demonstrated between VCTE and SWE (r_s 0.4820, p-value < 0.001) and SWE and APRI (r_s 0.5162, p-value < 0.001); weak correlations were demonstrated between VCTE and APRI (r_s 0.2725, p=0.01) and SWE and FIB-4 (r_s 0.2716, p-value 0.0142). Of all modalities, APRI performed best in detecting cirrhosis (AUROC=0.72) followed by VCTE (AUROC=0.71), NFS (AUROC=0.70), SWE (AUROC=0.68), FIB-4 (AUROC=0.62) and BARD (AUROC=0.59) (Table 1). By Youden's index, the optimal cutpoint for identifying cirrhosis in lipodystrophy patients by APRI was 0.968 and VCTE was 12.4 kPa. **Conclusion:** In patients with inherited and acquired lipodystrophies who have evidence of NASH, APRI and VCTE demonstrate the best performance, as noninvasive fibrosis tests, for determining cirrhosis. These tests may provide clinical utility for monitoring progression of liver disease in this unique patient population.

Table 1: Performance of noninvasive tests in detection of cirrhosis.

	AUROC	Cutpoint	Sensitivity	Specificity	PPV	NPV
Noninvasive Imaging Modalities						
VCTE	0.7132	12.4	0.412	0.953	0.7	0.859
SWE	0.6847	1.61	0.529	0.859	0.5	0.873
Noninvasive Serologic Tests						
Corrected APRI	0.7229	0.473	0.647	0.844	0.524	0.900
BARD	0.5873	2	0.529	0.594	0.257	0.826
FIB-4	0.6213	0.787	0.529	0.703	0.321	0.849
NFS	0.6976	-2.72	0.941	0.422	0.302	0.964

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PLASMA AND STOOL METABOLOMIC BIOMARKERS FOR NON-ALCOHOLIC FATTY LIVER DISEASE IN ARGENTINA

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Background: Non-invasive biomarkers are urgently needed to identify patients with non-alcoholic fatty liver disease (NAFLD) at risk of disease progression, particularly in high prevalence areas such as Latin America. In this regard, targeted metabolomics is a powerful technology for discovering new gut microbiome-derived metabolites. Thus, we aimed to identify potential metabolomic biomarkers related to NAFLD stage in Argentina, and to assess their relationship with clinical and host genetic factors. **Methods:** Adult healthy

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volunteers (HV), biopsy-proven simple steatosis (SS) and non-alcoholic steatohepatitis (NASH) patients were recruited. Demographic, clinical and food frequency consumption data, as well as plasma and stool samples were collected. SNP rs738409 (PNPLA3 gene) was determined in all volunteers. HPLC and flow injection analysis with MS/MS in tandem was applied for metabolomic studies using the MxP Quant 500 Kit (Biocrates Life Sciences AG, Austria). Significantly different metabolites among groups were identified with MetaboAnalyst v4.0. Bivariate and multivariate analyses were used to identify variables that were independently related to NAFLD stage. Forward stepwise logistic regression models were constructed to design the best feature combination that could distinguish between study groups. Receiver Operating Characteristic (ROC) curves were used to evaluate models' accuracy. **Results:** 19 HV, 12 SS and 22 NASH patients were included in the study. Diet was similar between groups. The concentrations of 33 out of the 424 detected metabolites (25 in plasma and 8 in stool) were significantly different among study groups. Levels of triglycerides (TG) were higher among NAFLD patients, whereas levels of phosphatidylcholines (PC) and lysoPC were higher among HV. The PNPLA3 risk genotype for NAFLD and NASH (GG) was related to higher plasma levels of eicosenoic acid FA(20:1) ($p<0.001$). Plasma metabolites showed a higher accuracy for diagnosis of NAFLD and NASH when compared to stool metabolites (Table 1). Body mass index (BMI) and plasma levels of PC aa C24:0, FA(20:1) and TG(16:1_34:1) showed high accuracy for diagnosis of NAFLD; whereas the best AUROC for discriminating NASH from SS was that of plasma levels of PC aa C24:0 and PC ae C40:1 (Table 1). **Conclusion:** Gut microbiome-derived metabolomic biomarkers were identified in plasma and stool, but plasma metabolites were better diagnostic biomarkers of NAFLD and NASH in Argentina. Further validation studies are needed.

Table 1. Diagnostic performance of different models for NAFLD and NASH.

	Model	Variables	Model *p*-value	Specificity	Sensitivity	AUROC
HV vs. NAFLD	CLINICAL	PNPLA3 BMI	1.41E-09	0.89	0.91	0.95
	STOOL	Xanthine	5.20E-05	0.68	0.69	0.79
	PLASMA	FA(20:1) TG(16:1_32:1) lysoPC a C28:0 TG(16:0_34:2) TG(20:4_32:0)	2.57E-12	1.00	1.00	1.00
	ALL	BMI PC aa C24:0 (P) FA(20:1) (P) TG(16:1_34:1) (P)	9.08E-13	1.00	1.00	1.00
SS vs. NASH	CLINICAL	PNPLA3 BMI	0.0225	0.58	0.57	0.73
	STOOL	Xanthine Cysteine	0.0001	0.73	0.75	0.90
	PLASMA	PC aa C24:0 PC ae C40:1 PC ae C36:2	5.98E-09	1.00	1.00	1.00
	ALL	PC aa C24:0 (P) PC ae C40:1 (P)	5.09E-09	1.00	1.00	1.00

P: metabolites detected in plasma samples.

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PREDICTED LONG-TERM CLINICAL OUTCOMES OF OBETICHOLIC ACID (OCA) FOR THE TREATMENT OF PATIENTS WITH ADVANCED FIBROSIS WITHOUT CIRRHOSIS DUE TO NON-ALCOHOLIC STEATOHEPATITIS (NASH) COMPARED TO STANDARD OF CARE IN THE USA

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Background: NASH with fibrosis is a chronic liver disease that can progress to serious and costly clinical outcomes. Patients with Advanced Fibrosis without Cirrhosis due to NASH (Adv Fib; fibrosis stage 3, F3) are at high risk of progression to end-stage liver disease in the absence of specific treatment. Obeticholic acid (OCA) is the first treatment to demonstrate safety and efficacy in improving or stabilizing fibrosis in stage F2/F3 NASH patients in the Phase 3 REGENERATE (REGEN) trial. This study evaluated the long-term clinical and humanistic benefits of using OCA vs. standard of care (SOC) (life-style changes) in patients with Adv Fib due to NASH for preventing progression to compensated (CC) and decompensated cirrhosis (DCC), hepatocellular carcinoma (HCC), liver transplants (LT), and deaths in the US. **Methods:** A lifetime Markov-model followed Adv Fib due to NASH through 5 fibrosis (F0 to CC) and 4 clinical health states (DCC, HCC, LT, liver-related and all cause deaths) using transition probabilities including fibrosis progression and regression from the REGEN 18-month analysis for the OCA 25 mg and placebo treatment arms. Transitions from F0-F1 and CC came from two publications representing natural history populations. Progression to adverse outcomes and health state utilities also came from the literature. Results included: life years gained (LYGs), clinical events avoided, number needed to treat (NNT), changes in cumulative incidence and overall and liver transplant-free survival (OS, LTFS) over time, and quality-adjusted life years (QALYs). **Results:** The model included PP patients baseline characteristics from REGEN (54 years; 64% female). The model estimated that in comparison with SOC, OCA could decrease the 10-year cumulative incidences by ~50% for CC (35.2% to 17.7%), DCC (8.4% to 4.4%), HCC (6.2% to 3.7%), LT (3.9% to 2.3%), and liver-related deaths (8.9% to 5.3%). 10-year LTFS also improved from 80.3% to 85.3%. Data for NNTs and clinical events avoided over a lifetime are shown in Table 1. The model also estimated an incremental 1.61 QALYs and 1.17 LYGs vs. SOC. **Conclusion:** OCA has the potential to substantially improve the long-term clinical outcomes and survival of patients with Adv Fib due to NASH. Given the strong association between advanced fibrosis and risk of morbidity and mortality, the model predicts substantial clinical benefit due to OCA's ability to prevent progression to CC, DCC, HCC, LT, and liver-related deaths.

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