Instructions for use (EU)

LiverPRO IVD medical software

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Contents

1 Instructions for use (EU)

1.1 Introduction

This is the Instruction for use for the LiverPRO in vitro diagnostic medical device software. LiverPRO is a clinical decision support tool with the purpose of identifying individuals at risk of steatotic liver disease.

1.2 Product Description and Intended use

LiverPRO is an In Vitro Diagnostic (IVD) software as medical device (SaMD) for automatically predicting the probability that patients suffer from steatotic liver disease based on standard blood sample biomarkers. The LiverPRO software consists of:

- Core module: Calculates LiverPRO scores based on biomarker inputs.
- Integration modules: Provide system-to-system integration with laboratory information systems and others.
- Licensing module: Ensures license validity.

LiverPRO is intended for use by healthcare professionals only.

1.3 Intended purpose

LiverPRO is intended to assess the likelihood of having liver fibrosis among adult individuals at risk of steatotic liver disease.

1.4 Patient population

The target patient population for LiverPRO are individuals at risk of steatotic liver disease, categorized into the following:

1. Alcohol-related liver disease (ALD): individuals with alcohol overuse.

- Alcohol overuse is defined based on the healthcare professional's discretion. But a rule of thumb would be an intake of more than 21/14 units of alcohol a week for men/women for more than 5 years.

2. Metabolic dysfunction-associated steatotic liver disease (MASLD): encompasses patients who have heaptic steatosis and have at least one of five cardiometabolic risk factors:

- BMI ≥ 25 kg/m² OR waist circumference (WC): ≥ 94 cm (M), 80 cm (F)
- Fasting serum glucose ≥ 5.6 mmol/L (100 mg/dL) OR serum glucose ≥ 11.1 mmol/L (200 mg/dL) OR 2-hour post-glucose ≥ 7.8 mmol/L (140 mg/dL) OR HbA1c ≥ 5.7% (39 mmol/mol).
- Blood pressure ≥ 130/85 mmHg OR specific antihypertensive drug use.
- Plasma triglycerides ≥ 1.7 mmol/L (150 mg/dL) OR lipid-lowering treatment.
- Plasma HDL cholesterol < 1.0 mmol/L (40 mg/dL) (M) OR < 1.3 mmol/L (50 mg/dL) (F) OR lipid-lowering treatment.

3. MASLD and increased alcohol intake (MetALD):

- MetALD: Represents an overlap of MASLD and ALD, based on alcohol consumption thresholds.
- Weekly alcohol intake (grams):

a) MASLD predominant: 140/210 (female/male)

b) Overlap: 210–280 (female), 280–350 (male)

c) ALD predominant: 350/420 (female/male)

LiverPRO can be calculated in individuals regardless of the numbers of risk factors, meaning patients can have both alcohol overuse, and non-alcoholic risk factors (obesity, type-2-diabetes, and/or metabolic syndrome).

1.5 Application

LiverPRO software is used by healthcare professionals both in the primary and secondary care sector. It is not intended to be used by lay users and ambient temperature and humidity do not affect the performance of the device.

There are no restrictions on the frequency of use i.e. it can be used whenever there is a suspected risk of having steatotic liver disease.

1.6 Warnings

The LiverPRO software cannot be used for other purposes than described in this Instruction for Use.

LiverPRO is NOT intended for a final diagnosis and should not be used solely as an indication to perform a liver biopsy. The indication for liver biopsy will always be given from a physician.

To ensure the accurate functioning of the LiverPRO software, it is essential to input the following nine biochemistry analyses in their respective SI units. During the installation phase the input parameter units will be checked, to make sure that all parameters are in the required units before the installation is complete. The means that the input parameters for LiverPRO will always be using the correct units. If the parameters are not obtainable in the right units, the installation cannot be completed.

Parameter	Unit required in LiverPRO (SI units)	Conventional unit	Conversion
Aspartate transaminase (AST)	U/L	-	
Alkaline phosphatase (ALP)	U/L	-	
Gamma-glutamyl transferase (GGT)	U/L	-	
International normalized ratio (INR)	-	-	
Albumin	g/L	g/dL	g/L /10
Bilirubin	µmol/L	mg/dL	µmol/L / 17,10
Platelets	10^9/L	-	
Sodium	mmol/L	-	
Cholesterol	mmol/L	-	

Failure to input any of the nine biochemistry analyses in their designated SI units may result in the software's inability to calculate accurately.

Note to EU-based users: in case any serious incident occurs in relation to LiverPRO, report it to the manufacturer and the competent authority of the Member State you are established in.

The incidents can be reported to Evido by phone or email at:

Phone: +45 23 91 11 89

Email: hello@evido.health

1.7 Limitations and Contraindications

There are no direct contraindications, but LiverPRO is not indicated in the following diseases:

- Viral hepatitis
- Autoimmune liver diseases: Autoimmune hepatitis, primary biliary cholangitis (PBC) and primary sclerosing cholangitis (PSC)
- Inherited diseases: Wilson disease, alfa-1-antitrypsin deficiency, and hemochromatosis.
- Budd-Chiari syndrome and portal vein thrombosis.
- Non-primary liver cancer.
- Decompensated liver cirrhosis (liver fibrosis is evident at this stage)

Direct Oral Anticoagulants are not considered contraindications for the use of LiverPRO since INR is only slightly increased by these pharmaceuticals. LiverPRO should be used with caution in patients prescribed Vitamin-K antagonists, due to the elevation of INR which may lead to an (falsely) elevated LiverPRO score. LiverPRO rejects requests which include an INR value above 2.0.

Patients with chronic kidney disease, hepatorenal syndrome or reduced clearance should have their results interpreted with caution.

1.8 Analytical performance characteristics

LiverPRO has the following ROC AUC performance in the following intervals. The presented ROC AUC performance intervals are split based on disease progress stage (F2, F3 and F4) and the number of input variables.

1.8.1 AUC-intervals for Significant Fibrosis (F2)

- Age + 3 input biomarkers: AUC 0.56 – 0.81
- Age + 4 input biomarkers: AUC 0.57 – 0.81
- Age + 5 input biomarkers: AUC 0.59 – 0.81
- Age + 6 input biomarkers: AUC 0.62 – 0.81
- Age + 7 input biomarkers: AUC 0.66 – 0.81
- Age + 8 input biomarkers: AUC 0.74 – 0.81
- Age + 9 input biomarkers: AUC 0.81(only one algorithm)

1.8.2 AUC-intervals for Advanced Fibrosis (F3)

- Age + 3 input biomarkers: AUC 0.61 – 0.86
- Age + 4 input biomarkers: AUC 0.68 – 0.86
- Age + 5 input biomarkers: AUC 0.71 – 0.86
- Age + 6 input biomarkers: AUC 0.73 – 0.86
- Age + 7 input biomarkers: AUC 0.75 – 0.86
- Age + 8 input biomarkers: AUC 0.80 – 0.86
- Age + 9 input biomarkers: AUC 0.86(only one algorithm)

1.8.3 AUC-intervals for Cirrhosis (F4)

- Age + 3 input biomarkers: AUC 0.64 – 0.89
- Age + 4 input biomarkers: AUC 0.72 – 0.89
- Age + 5 input biomarkers: AUC 0.75 – 0.89
- Age + 6 input biomarkers: AUC 0.76 – 0.89
- Age + 7 input biomarkers: AUC 0.79 – 0.89
- Age + 8 input biomarkers: AUC 0.84 – 0.89
- Age + 9 input biomarkers: AUC 0.89(only one algorithm)

1.9 Clinical performance characteristics

LiverPRO has the following clinical performance in the different disease stages targeted.

1.9.1 Performance targeting Significant Fibrosis (F2)

To rule out significant liver fibrosis (Low cut-off 13%) - corresponding to a Liver Stiffness Measurement < 8kPa.

Metric	Formula	Result
Sensitivity	= TP/(TP + FN)	= 82%
NPV	= TN/(TN +FN)	= 98%

To rule in significant liver fibrosis (High cut-off 36%) - corresponding to a Liver Stiffness Measurement > 8kPa

Metric	Formula	Result
Specificity	= TN/(TN + FP)	= 91%
PPV	= TP/(TP + FP)	= 26%

1.9.2 Performance targeting Advanced Fibrosis (F3)

To rule out advanced liver fibrosis (Low cut-off 6%) - corresponding to a Liver Stiffness Measurement of <12 kPa

Metric	Formula	Result
Sensitivity	= TP/(TP + FN)	= 81%
NPV	= TN/(TN +FN)	= 99%

To rule in advanced liver fibrosis (High cut-off 11%) - corresponding to a Liver Stiffness Measurement of >12 kPa

Metric	Formula	Result
Specificity	= TN/(TN + FP)	= 91%
PPV	= TP/(TP + FP)	= 13%

1.9.3 Performance targeting Cirrhosis (F4)

To rule out cirrhosis (Low cut-off 13%) - corresponding to a Liver Stiffness Measurement of <15kPa

Metric	Formula	Result
Sensitivity	= TP/(TP + FN)	= 82%
NPV	= TN/(TN +FN)	= 99%

To rule in cirrhosis (High cut-off 16%) - corresponding to a Liver Stiffness Measurement of >15 kPa

Metric	Formula	Result
Specificity	= TN/(TN + FP)	= 91%
PPV	= TP/(TP + FP)	= 9%

1.10 Requirements for installation and Laboratory Information System (LIS) operation

The LiverPRO software is designed to operate on off-the-shelf x86/ia64 compatible hardware. Please refer to the table below for detailed minimum soft- and hardware requirements when operating the LiverPRO software for clinical use.

1.10.1 Requirement

1.10.1.1 Operating system One of the following:

- Windows Server 2016 (native or docker install)
- Windows Server 2019 (native or docker install)
- Windows Server 2022 (native or docker install)
- Ubuntu Linux 22.04 (preferred) (docker install)
- Red Hat Enterprise Linux 9 (preferred) (docker install)
- Red Hat Enterprise Linux 8.6 (preferred) (docker install)

1.10.1.2 Software All of the following:

- Docker version 20.10.17 or newer (preferred) for docker container installation

1.10.1.3 CPU One of the following:

- Intel Core i9 9900k or equivalent
- Intel Xeon E-2300 or equivalent

1.10.1.4 RAM $\geq$ 16 GB

1.10.1.5 Persistent storage $\geq$ 50 GB

1.10.1.6 Network All the following:

- 10 Mbit/s bandwidth
- Permitted outgoing traffic on port 443/TCP to internet for licensing and error reporting. (Optional in case of local file licensing)
- Permitted incoming/outgoing traffic on port 443/TCP

1.11 Product features (Functional description)

LiverPRO features include:

- Fully automated, high precision prediction and stratification of patient risk of being affected by steatotic liver disease.
- Seamless integration into existing clinical workflows using system-to-system LIS integration.
- Full compatibility with existing graphical user interfaces.

1.12 Use Scenario

LiverPRO is intended for use by healthcare professionals only.

Specifically:

- Medical doctors at hospitals (secondary care sector) regardless of specialization.
- General Practitioners (GPs) (primary care sector).

When a healthcare professional is in consultation with an individual at risk of having steatotic liver disease, they will order a LiverPRO calculation through the regular biochemical ordering system, and the required blood samples will be drawn from the patient. When the calculation is performed by LiverPRO, the healthcare professional will be given the result through/or in the Laboratory Information System (LIS), as a percentage risk prediction for the given individual's risk of having the configured level of liver fibrosis (E.g. Significant fibrosis (F2), Advanced fibrosis (F3) or Cirrhosis (F4)). In other words, LiverPRO does not detect or measure anything directly but rather processes already measured parameters as inputs and transforms them into outputs by using an IP-protected algorithm.

Meanwhile, the clinician will receive a clinical recommendation for which actions to take.

LiverPRO is not involved in handling any types of specimens and does not measure or detect any specific analytes so we cannot say that the terms ‘‘qualitative, semi-quantitative and quantitative" are applicable per se. However, the LiverPRO score itself represents a numerical value which correlates to a certain risk of having liver fibrosis displayed in percentages which could classify it as quantitative.

The clinical recommendations are: (using significant fibrosis as an example)

1. LiverPRO < low cut-off:

“Liver Fibrosis test result: Low risk.

This patient has a low risk of having fibrosis in the liver."

2. LiverPRO between low and high cut-off:

   “Liver Fibrosis test result: Moderate risk. Repeated tests and intervene on lifestyle.

   Based on the standard liver function tests, this patient had a LiverPRO calculation performed to assess the risk of having severe liver disease, corresponding to significant liver fibrosis. The result indicates that the patient has a moderate risk of having significant liver fibrosis. As long as the patient does not show obvious signs of cirrhosis or other severe liver disease, we suggest that the test is repeated in 6-12 months, and that lifestyle interventions towards obesity, type 2 diabetes, and excessive alcohol consumption are initiated."

3. LiverPRO > high cut-off:

“Liver Fibrosis test result: High risk - Consider referring the patient for specialist evaluation.

Based on the standard liver function tests, this patient had a LiverPRO calculation performed to assess the risk of having severe liver disease, corresponding to significant liver fibrosis. The result indicates that the patient has a high risk of having significant liver fibrosis. You should consider referring the patient for further examinations at the relevant Gastroenterology or Hepatology Department."

The healthcare professional will take the appropriate actions that they find relevant.

1.13 Residual Risks

After the risk management measures were applied, the residual risks, including cybersecurity risks were assessed according to criteria set by risk management planning. The assessment results were recorded in a risk analysis. The residual risk assessment was done for each risk. All risks were reduced to an acceptable level and no serious risks remained as residual.

1.14 Post-market obligations

In order to operate, LiverPRO requires a license which is renewed yearly. Upon non-renewal of the license, the software is no longer operable and in that sense can be considered “decommissioned/disposed of”.

Whenever a new release is out, Evido sends release notes to customers which inform them on versioning and what the release has included. This could e.g. be that bug fixes/new features/new IFU versions etc. have been introduced. If there is any impact on safety and/or security of the modified software, it has to be clearly communicated to users.

However, the decision of a user whether to install the updated version of LiverPRO is up to their discretion.

Please carefully read the full contents of this Instructions for use before using.

1.15 Symbols

1.15.1 Consult instructions for use

Figure 1: IFU

1.15.2 Mark of conformity according to the In Vitro Diagnostic Regulation 2017/746

Figure 2: CE mark

1.15.2.1 Meaning Title/meaning: Consult instructions for use or consult electronic instructions for use.

Function/description: To identify the location where the operator's manual is stored or to identify information that relates to the operating instructions. To indicate that the operating instructions should be considered when operating the device or control close to where the symbol is placed.

1.15.3 In Vitro Diagnostic Medical

Figure 3: IVD

1.15.3.1 Meaning Title/Meaning: In Vitro Diagnostic Medical device.

Function/description: To indicate that the software is an in vitro diagnostic medical device according to the European In Vitro Diagnostic Regulation 2017/746.

1.15.4 Unique device identifier

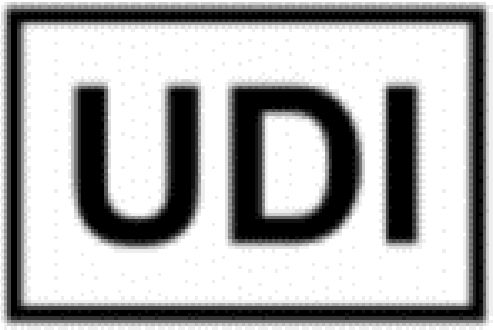

Figure 4: UDI

1.15.4.1 Meaning Title/Meaning: Unique Device Identifier.

Function/description: To indicate a carrier that contains unique device identifier information according to the European In Vitro Diagnostic Regulation 2017/746.

1.15.5 Company logo

Figure 5: Logo

1.15.5.1 Meaning Title/Meaning: Company logo.

Figure 6: Manufacturer

1.15.6 Manufacturer

1.15.6.1 Meaning Title/Meaning: Manufacturer.

Function/description: To identify the manufacturer of a product. It shall be used filled in all applications to differentiate it from ISO 7000-2497.

1.16 Regulations and standards

Medical software LiverPRO is classified according to IVDR (EU) 2017/746, Annex VIII: Class B, Rule 6. LiverPRO is classified as Class A according to IEC 62304:2006/A1:2015 - Medical device software — Software lifecycle processes. The device complies with the following product standards:

- IEC 62304:2006/A1:2015 - Medical device software – Software lifecycle processes
- EN ISO 13485:2016/A11:2021 - Medical devices - Quality management systems - Requirements for regulatory purposes
- IEC 82304-1:2016 - Health Software - Part 1: General requirements for product safety
- In Vitro Diagnostic Regulation IVDR (EU) 2017/746
- EN ISO 14971:2019/A11:2021 - Medical devices – Application of risk management to medical devices
- IEC 62366-1:2015/AMD1:2020 - Medical devices - Part 1: Application of usability engineering to medical devices

1.17 Contact information

If you have any questions or concerns about the use of LiverPRO, or if you experience any technical issues while using LiverPRO please contact Evido customer support at:

Table 8: Company sites

Site	Address
Main site	Evido ApS Danneskiold-Samsøes Allé 41 1434 København K Denmark Phone: +45 23 91 11 89 Email: hello@evido.health Website: evido.health

	
Manuf acturer	Evido ApS
	
2797	[IVD] (images/img_3.png “IVD”)

1.18 About this document

1.18.1 Terms and abbreviations

Term	Definition
Harm	Injury or damage to the health of people, or damage to property or the environment.
Hazard	Potential source of harm
Hazardous Situation	Circumstance in which people, property, or the environment is/are exposed to one or more hazards.
Reasonably foreseeable misuse	Use of a product or system in a way not intended by manufacturer, but which can result from readily predictable human behavior
Residual risk	Risk remaining after risk control measures have been implemented.
Risk	Combination of the probability of occurrence of harm and the severity of that harm
Risk analysis	Systematic use of available information to identify hazards and to estimate the risk.
Risk assessment	Overall process comprising a risk analysis and a risk evaluation
Risk control	Process in which decisions are made and measures implemented by which risks are reduced to, or maintained within, specified levels
Risk estimation	Process used to assign values to the probability of occurrence of harm and the severity of that harm
Risk evaluation	Process of comparing the estimated risk against given risk criteria to determine the acceptability of the risk
Risk management	Systematic application of management policies, procedures and practices to the tasks of analyzing, evaluating, controlling and monitoring risk
Risk management file	Set of records and other documents that are produced by risk management
Safety	Freedom from unacceptable risk
Severity	Measure of the possible consequences of a hazard
Clinical evidence	Clinical data and performance evaluation results, pertaining to a device of a sufficient amount and quality to allow a qualified assessment of whether the device is safe and achieves the intended clinical benefit(s), when used as intended by the manufacturer
Scientific validity of an analyte	The association of an analyte with a clinical condition or a physiological state

Analytical performance	The ability of a device to correctly detect or measure a particular analyte
Clinical performance	The ability of a device to yield results that are correlated with a particular clinical condition or a physiological or pathological process or state in accordance with the target population and intended user
Performance evaluation	An assessment and analysis of data to establish or verify the scientific validity, the analytical and, where applicable, the clinical performance of a device
Post-market surveillance	All activities carried out by manufacturers in cooperation with other economic operators to institute and keep up to date a systematic procedure to proactively collect and review experience gained from devices they place on the market, make available on the market or put into service for the purpose of identifying any need to immediately apply any necessary corrective or preventive actions
Recall	Any measure aimed at achieving the return of a device that has already been made available to the end user
Incident	Any malfunction or deterioration in the characteristics or performance of a device made available on the market, including use-error due to ergonomic features, as well as any inadequacy in the information supplied by the manufacturer and any harm as a consequence of a medical decision, action taken or not taken on the basis of information or result(s) provided by the device
Serious incident	Any incident that directly or indirectly led, might have led or might lead to any of the following: (a) the death of a patient, user or other person, (b) the temporary or permanent serious deterioration of a patient's, user's or other person's state of health, (c) a serious public health threat
Serious public health threat	An event which could result in imminent risk of death, serious deterioration in a person's state of health, or serious illness, that may require prompt remedial action, and that may cause significant morbidity or mortality in humans, or that is unusual or unexpected for the given place and time |
Field safety corrective action	Corrective action taken by a manufacturer for technical or medical reasons to prevent or reduce the risk of a serious incident in relation to a device made available on the market
Field safety notice	A communication sent by a manufacturer to users or customers in relation to a field safety corrective action

Abbreviation	Definition
RM	Risk Management
RMF	Risk Management File
RMP	Risk Management Plan
RMR	Risk Management Report
FMEA	Failure Mode and Effect Analysis
RPN	Risk Priority Number
UDI	Unique Device Identifier
AUC	Area Under the (Receiver Operating) Curve
PPV	Positive Predictive Value
NPV	Negative Predictive Value
LIS	Laboratory Information System
IVD	In Vitro Diagnostic
FDA	Food and Drug Administration
ALD	Alcohol-Related Liver Disease
MASLD	Non-Alcoholic Steatotic Liver Disease

Abbreviation	Definition
MASH	Metabolic dysfunction-associated steatohepatitis
TE	Transient Elastography
LSM	Liver Stiffness Measurement
ELF	Enhanced Liver Fibrosis
INR	International Normalised Ratio
IFU	Instructions For Use
MDSW	Medical Device Software
SaMD	Software as Medical Device
SOUP	Software Of Unknown Provenance
MDCG	Medical Device Coordination Group
MEDDEV	Medical Devices Documents
EMDN	European Medical Device Nomenclature
GP	General Practitioner
GSPR	General Safety and Performance Requirements
IQ	Installation Qualification
OQ	Operational Qualification
PQ	Performance Qualification
PEP	Performance Evaluation Plan
LSP	Literature Search Protocol
PER	Performance Evaluation Report
SoA	State-Of-The-Art
PMS	Post-Market Surveillance
PMPF	Post-Market Performance Follow-Up
MAUDE	Manufacturer And User Facility Device Experience
DoC	Declaration of Conformity
SRN	Single Registration Number

1.18.2 Revision history

Revision	Date	Author	Changes	Scope
8.0	2023-07-03	Søren Boll Overgaard (CTO, PRRC) soren@evido.health	Initial markdown version	Minor
9.0	2024-04-21	Søren Boll Overgaard (CTO, PRRC) soren@evido.health	Clean up formatting	Cosmetic
10.0	2024-04-25	Søren Boll Overgaard (CTO, PRRC) soren@evido.health	Update Evidos phone number	Minor
11.0	2024-05-09	Søren Boll Overgaard (CTO, PRRC) soren@evido.health	Update company address	Minor
12.0	2024-05-09	Søren Boll Overgaard (CTO, PRRC) soren@evido.health	Update company address	Minor
13.0	2024-05-10	Søren Boll Overgaard (CTO, PRRC) soren@evido.health	Fix incorrect address include reference	Minor
14.0	2024-08-05	Søren Boll Overgaard (CTO, PRRC) soren@evido.health	Update terms and abbreviations	Minor
15.0	2024-08-07	Søren Boll Overgaard (CTO, PRRC) soren@evido.health	Updated hard- & software requirements	Minor
16.0	2025-01-09	Søren Boll Overgaard (CTO, PRRC) soren@evido.health	Updated ROC AUC values	Minor

Revision	Date	Author	Changes	Scope
17.0	2025-01-14	Søren Boll Overgaard (CTO, PRRC) soren@evido.health	Updated cut-off values and derived quality metrics	Minor
18.0	2025-02-26	Søren Boll Overgaard (CTO, PRRC) soren@evido.health	Make this IFU EU only. Only title change, no content updates.	Cosmetic
19.0	2025-02-27	Søren Boll Overgaard (CTO, PRRC) soren@evido.health	Patient population terminology updated,post-market obligations section added	Minor
20.0	2025-07-28	Søren Boll Overgaard (CTO, PRRC) soren@evido.health	Reformatting, no content change	Cosmetic
21.0	2025-09-29	Søren Boll Overgaard (CTO, PRRC) soren@evido.health	Updated performance of f4 model includes revision	Minor
22.0	2025-10-03	Søren Boll Overgaard (CTO, PRRC) soren@evido.health	Updates according to comments from Roche	Minor

1.18.3 Storage location

The original of this document is stored in GitHub.

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