Instructions for use

LiverPRO IVD medical software

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Contents

1 Instructions for use

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 fatty 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 fatty 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 fatty liver disease.

1.4 Definitions

Individuals at risk of fatty liver disease can be divided into two groups:

1. Alcohol-related liver disease (ArLD): 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. Non-alcoholic fatty liver disease (NAFLD): individuals with type-2 diabetes, and/or obesity, and/or metabolic syndrome, without a former or current alcohol overuse.
   - NAFLD is defined based on current guidelines from the European Association for the study of the liver. These guidelines are:
   - Type-2 diabetes is defined as an HbA1C above 48 mmol/L, or antidiabetic medication.
   - Obesity is defined as a body mass index (BMI) above 30 kg/m2.
   - Metabolic syndrome is defined according to the International Diabetes Federation:
   - Central obesity + any two of the following:
     - Raised triglycerides: $\geq$ 1.7 mmol/l (150 mg/dl) or specific treatment for this lipid abnormality
     - Reduced HDL-cholesterol: $<$ 1.03 mmol/l (40 mg/dl) in males$<$ 1.29 mmol/l (50 mg/dl) in females or specific treatment for this lipid abnormality
     - Raised blood pressure: Systolic: $\geq$ 130 mmHg or diastolic: $\geq$ 85 mmHg or treatment of previously diagnosed hypertension
     - Raised fasting plasma glucose: Fasting plasma glucose $\geq$ 5.6 mmol/l (100 mg/dl) or previously diagnosed Type 2 diabetes. If $>$ 5.6 mmol/l or 100 mg/dl, oral glucose tolerance test is strongly recommended but is not necessary to define presence of the syndrome.

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 fatty 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	$\mu mol/L$ / 17,10

Parameter	Unit required in LiverPRO (SI units)	Conventional unit	Conversion
Platelets	10^9/L	-	
Sodium	mmol/L	-	
Cholesterol	mmol/L	-	

Failure to input 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 21766018

Email: hello@evido.health

1.7 Limitations and Contraindications

Please note that if network parameters are changed, LiverPRO will not work as intended.

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.
- Liver cancer due to metastasis.
- 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 will take this into precaution by refusing to count LiverPRO if the INR is above 2.0.

1.8 Analytical performance characteristics

LiverPRO has the following AUC performance in the following intervals. The presented 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)

Inputs	AUC
Age + 3 input biomarkers	0.54 – 0.82
Age + 4 input biomarkers	0.55 – 0.82
Age + 5 input biomarkers	0.55 – 0.82
Age + 6 input biomarkers	0.57 – 0.80
Age + 7 input biomarkers	0.64 – 0.80
Age + 8 input biomarkers	0.69 – 0.79
Age + 9 input biomarkers	0.76 – 0.77

1.8.2 AUC-intervals for Advanced Fibrosis (F3)

Inputs	AUC
Age + 3 input biomarkers	0.65 – 0.87
Age + 4 input biomarkers	0.68 – 0.87
Age + 5 input biomarkers	0.72 – 0.87
Age + 6 input biomarkers	0.74 – 0.87
Age + 7 input biomarkers	0.76 – 0.87

Inputs	AUC
Age + 8 input biomarkers	0.77 – 0.86
Age + 9 input biomarkers	0.80 – 0.81

1.8.3 AUC-intervals for Cirrhosis (F4)

Inputs	AUC
Age + 3 input biomarkers	0.66 – 0.91
Age + 4 input biomarkers	0.67 – 0.91
Age + 5 input biomarkers	0.67 – 0.91
Age + 6 input biomarkers	0.67 – 0.91
Age + 7 input biomarkers	0.76 – 0.88
Age + 8 input biomarkers	0.79 – 0.88
Age + 9 input biomarkers	0.80 – 0.81

1.9 Clinical performance characteristics

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

1.9.1 Performance targeting Significant Fibrosis

To rule out significant liver fibrosis (Low cut of 10%) - corresponding to a Liver Stiffness Measurement < 8kPa.

Metric	Formula	Result
Sensitivity	= TP/(TP + FN)	= 95.8%
Specificity	= TN/(TN + FP)	= 28.7%
PPV	= TP/(TP + FP)	= 8.12%
NPV	= TN/(TN +FN)	= 99.1%

To rule in significant liver fibrosis (High cut of 20%) - corresponding to a Liver Stiffness Measurement > 8kPa

Metric	Formula	Result
Sensitivity	= TP/(TP + FN)	= 87.2%
Specificity	= TN/(TN + FP)	= 55.1%
PPV	= TP/(TP + FP)	= 11.3%
NPV	= TN/(TN +FN)	= 98.5%

1.9.2 Performance targeting Advanced Fibrosis

To rule out advanced liver fibrosis (Low cut of 10%) - corresponding to a Liver Stiffness Measurement of <12 kPa

Metric	Formula	Result
Sensitivity	= TP/(TP + FN)	= 61.5%
Specificity	= TN/(TN + FP)	= 91.6%
PPV	= TP/(TP + FP)	= 14.4%
NPV	= TN/(TN +FN)	= 99.0%

To rule in advanced liver fibrosis (High cut of 20%) - corresponding to a Liver Stiffness Measurement of >12 kPa

Metric	Formula	Result
Sensitivity	= TP/(TP + FN)	= 44.6%

Metric	Formula	Result
Specificity	= TN/(TN + FP)	= 97.26%
PPV	= TP/(TP + FP)	= 26.6%
NPV	= TN/(TN +FN)	= 98.7%

1.9.3 Performance targeting Cirrhosis

To rule out cirrhosis (Low cut of 10%) - corresponding to a Liver Stiffness Measurement of <15kPa

Metric	Formula	Result
Sensitivity	= TP/(TP + FN)	= 66.3%
Specificity	= TN/(TN + FP)	= 93.1%
PPV	= TP/(TP + FP)	= 12.2%
NPV	= TN/(TN +FN)	= 99.5%

To rule in advanced liver fibrosis (High cut of 20%) - corresponding to a Liver Stiffness Measurement of >15 kPa

Metric	Formula	Result
Sensitivity	= TP/(TP + FN)	= 36.6%
Specificity	= TN/(TN + FP)	= 98.0%
PPV	= TP/(TP + FP)	= 30.2%
NPV	= TN/(TN +FN)	= 98.5%

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.

The current software version of LiverPRO is compatible with Unilab; future versions will be compatible with other Laboratory Information Systems, as well.

1.10.1 Requirement

1.10.1.1 Operating system One of the following:

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

1.10.1.2 Software One of the following:

- Docker version 20.10.17 or newer (preferred) for docker container installation
- Python version 3.10 for a native operating system 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 >= 16 GB

1.10.1.5 Persistent storage $>=$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
- Permitted incoming/outgoing traffic on port 443/TCP from/to LIS server

1.11 Product features (Functional description)

LiverPRO features include:

- Fully automated, high precision prediction and stratification of patient risk of being affected by fatty 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 fatty 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 confiFgured 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.

In short, the clinical recommendations are:

1. LiverPRO <10%: "Low risk = no further examination for now. Test again in 2-3 years if still showing risk factors."
2. LiverPRO 10-20%: "Moderate risk score, intervene on lifestyle, e.g. weight loss, alcohol abstinence, and repeat LiverPRO test in 6-12 months."
3. LiverPRO >20%: "High risk, intervene on lifestyle and refer to a specialist for further examination."

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 risks remained as residual.

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

1.14 Symbols

Symbol	Description
	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.
 2797	Mark of conformity according to the In Vitro Diagnostic Regulation 2017/746.
	Title/Meaning: Manufacturer. Function/description: To identify the manufacturer of a product. This symbol shall be used filled in all applications to differentiate it from ISO 7000-2497
	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.

Symbol	Description
	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.
	Title/Meaning: Company logo.

1.15 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

1.16 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:

Evido ApS

Erik Husfeldts Vej 7, 2630 Taastrup, Denmark

Phone: +45 21766018

Email: hello@evido.health

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2797

1.17 About this document

1.17.1 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

Abbreviation	Definition
RM	Risk Management
RMF	Risk Management File

Abbreviation	Definition
RMP	Risk Management Plan
RMR	Risk Management Report
FMEA	Failure Mode and Effect Analysis
RPN	Risk Priority Number

1.17.2 Revision history

Revision	Date	Author	Changes	Scope
8.0	2023-07-03	Søren Boll Overgaard (CTO, PRRC) soren@evido.health	Initial markdown version	Minor

1.17.3 Storage location

The original of this document is stored in GitHub.

Any print-out of this document or a document stored in different location is considered an “Uncontrolled Copy”.