User manual for ADAPT

Version 1.0, February 2026, in English

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1. The Evidencio platform

The Evidencio platform facilitates the creation, use, validation and implementation of medical prediction algorithms and clinical decision support tools. This User Manual specifically relates to the ADAPT. The User Manual can also be referred to as the Instructions For Use (IFU). ADAPT meets the requirements laid down in: Regulation (EU) 2017/746 of the European Parliament and of the Council of 5 April 2017 on in vitro diagnostic medical devices and repealing Directive 98/79/EC and Commission Decision 2010/227/EU. Compliance with the applicable regulations is provided by means of declaration of conformity.

Throughout this manual CE-marked content and the term medical device are used interchangeably.

2. Disclaimer for CE-marked content

Evidencio provides certain CE-marked information, models, calculators, equations, and algorithms (tools) on any of its websites, applications, apps, or services. These tools may only be used in accordance with the intended use / intended purpose that has been published with the respective CE-marked tool.

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Your use of the websites, applications, apps, or services provided by Evidencio is subject to our Terms & Conditions, which can be found here: https://www.evidencio.com/terms-conditions.

3. Warnings

3.1. Warnings for CE-marked content

Calculations alone should never dictate patient care, and are no substitute for professional judgement. See our full disclaimer on: https://www.evidencio.com/disclaimer. This tool is only to be used by healthcare professionals in a clinical setting, and is not for patient use.

Always read the intended use before using this tool.

Always make sure the patient complies with the clinical indications and clinical contra-indications as stated on the Evidencio website, and in **sections 6.3.1** and **6.3.2** of this user manual respectively.

Before reading the result, double check the filled in values to prevent errors.

Results that concern risk percentages, do not guarantee certain outcomes. When there is a risk present, do not expect an event to not occur at all, even if the risk is very small. Conversely, a high risk does not guarantee that an event will occur.

This algorithm is only intended for use in settings where the usage and result of an algorithm are never immediately needed.

The data used to perform the calculations is stored by Evidencio to enhance algorithm function and allow issues to be traceable for further improvements. For details, see the privacy policy on our website at: https://www.evidencio.com/privacy-policy.

The ADAPT algorithm and its cut-off values are meant to be used specifically with Elecsys® PRO-C3 assays.

3.2. Notice to the user

Any serious incident that has occurred in relation to the device should be reported to the manufacturer and the competent authority of the country in which you, the reader, are established. A competent authority is the institute that governs all issues related to medical devices in a country.

Please contact Evidencio when you suspect any malfunction or changes in the performance of a medical device. Do not use the device, until Evidencio replies to your message that it is safe to start using it again.

4. Device description ADAPT

The ADAPT is an algorithm intended to use age, Pro-C3 (a marker of type III collagen formation), platelet count, and the presence of diabetes to estimate the severity of liver fibrosis in patients showing evidence or signs of metabolic dysfunction-associated steatotic liver disease (MASLD).

The Algorithm is Medical Device Software (MDSW), hosted on the Evidencio platform at www.evidencio.com. Local hosting of the algorithm is possible using Docker images. The algorithm is also accessible by 3rd party applications through the API and iFrame implementation. The Evidencio platform is managed under Evidencio's certified quality management system that ensures the correctness of calculations and availability of its services.

A summary of safety and performance (SSP) is made publicly available on the EUDAMED database. Information on publicly available CE-marked algorithms, including their corresponding SSP's, can be found on the manufacturer's page of Evidencio within the EUDAMED database.

4.1. Lifetime, residual risks and side effects

The ADAPT is software, and does not expire. The lifetime is initially set at 5 years from certification, if the state of the art does not change in such a way as to negatively affect the benefit-risk of the device, the lifetime can be extended.

No steps are required to be undertaken by the user to decommission a product when it is taken off the market. If the lifetime is not extended, a notice will be placed on the algorithm page on the platform. When a device is taken off the market, users may be informed about this (e.g. through e-mail).

Evidencio has identified a series of risks associated with the use of this algorithm.

The primary risk of the ADAPT relates to potential misinterpretation of the fibrosis score, which could lead to an incorrect assessment of liver fibrosis severity. All residual risks have been evaluated and are deemed acceptable. Most risks can be defined into two main groups, depending on their outcome.

a) The risk calculation was wrong or;
b) The MDSW prediction algorithm is inaccessible.

A wrong risk calculation can be the result of erroneous input values or an error in the mathematical calculation. Technical risks, including the erroneous calculations or the inaccessibly due to a technical error, have been mitigated when possible. These measures focussed on reducing the risks' probability and severity. Concluding that the risks could not be mitigated further, the residual risks were classified as *low-level and acceptable.* It should be noted that the use of Evidencio's Medical Device Software is itself a risk mitigation measure, as Evidencio's certified Quality Management System ensures and monitors the reliability of the calculations performed with its certified medical devices.

The ADAPT does not have any direct side effects.

5. Electronic label

The electronic label of this device contains the following information:

CE 2797	**Name of the device**	ADAPT
	Manufacturer information	Evidencio B.V., Irenesingel 19, 7481 GJ Haaksbergen, The Netherlands
LOT	**LOT number**	V-3.0-6094.25.03.27
UDI	**UDI number**	(01)08720938015298(8012)v3.0(4326)250327(240)6094
IVD	**IVD indication**	*In vitro* diagnostic medical device

The electronic label can be found on the Evidencio website, see also **section I** and **Figure 5** in **Chapter 9**.

The electronic label on the website further contains the option to download the **User Manual** and **Declaration of conformity** (DoC).

5.1. LOT number

The LOT number indicated the algorithm version, the algorithm identifier, and the algorithm publication date. Publication date is indicated as YY.MM.DD.

5.2. UDI number

Stands for Unique Device Identifier (UDI) number, which is an international tool that helps users identify and find information on products. Evidencio's UDI's have the following format:

(01)[UDI-DI number](8012)[versionnumber](4326)[releasedate](240)[identificationnumber]

The UDI-DI (Device Identifier) number is a unique numeric code. For each medical device of Evidencio, a unique UDI-DI is ascribed. This UDI-DI is used as an "access key" for information stored in a unique device identification database (UDID). Information on Evidencio's medical devices can be found by searching for the UDI-DI number in the following data base: https://gepir.gs1.org/index.php/search-by-gtin.

The version number within the UDI corresponds to the specific device version

6. Intended purpose

6.1. Intended medical use

ADAPT is an algorithm intended to combine age, diabetes status, Elecsys® PRO-C3 concentration and platelet count to assess the severity of hepatic fibrosis in patients showing evidence or signs of metabolic dysfunction-associated steatotic liver disease (MASLD). The ADAPT result must be interpreted in conjunction with other methods and in accordance with standard clinical management guidelines.

ADAPT is medical device software that automates the calculation of the formula. It requires quantitative and qualitative inputs to provide a semi-quantitative output.

ADAPT is not intended to replace clinical decision-making; it can only provide information to the healthcare professional on the estimation of the severity of liver fibrosis. The healthcare professional can use this information to support clinical decision-making.

Additional remarks on the intended use

The Pro-C3 concentrations and the platelet count have to be determined using a serum/plasma sample and the whole blood sample, respectively, from the same blood draw/sample collection.

6.2. Clinical benefit

The benefits and risks associated with the use of ADAPT for the patient are indirect. The benefits arise from clinical decisions made using ADAPT in combination with other clinical and patient-specific factors.
ADAPT can result in the following clinical benefit:

- ADAPT can assist in risk stratification of patients with (signs or evidence of) MASLD based on the severity of liver fibrosis.

6.3. Intended target population and exclusion

ADAPT is intended to be used for patients who fit the indications and contra-indications listed below.

6.3.1. Clinical indications

ADAPT algorithm should be used for patients who meet the following inclusion criteria:

- Patients should be at least 18 years or older.
- Patients should be referred for investigation due to abnormal biochemical tests (e.g. abnormal alanine aminotransferase (ALT) or γ-glutamyltransferase (GGT) levels or FIB-4 Index score) or an ultrasonographically detected bright liver associated with features of metabolic syndrome.
- Patients should show signs or evidence of MASLD.

6.3.2. Clinical contra-indications

ADAPT algorithm should not be used for patients who meet the following exclusion criteria:

- Patients younger than 18 years (see also the inclusion criteria).
- Patients in a primary care population without prior confirmatory tests (see inclusion criteria).
- Patients with other chronic liver diseases, including hepatitis B or C, or patients with excessive alcohol consumption.

6.4. User profile

The result of ADAPT is intended to be reviewed and interpreted by healthcare professionals, i.e. qualified medical specialists, capable of operating the device and interpreting its results. It is intended to be used in two ways; by healthcare professionals using the algorithm interface on the Evidencio website or an image of the algorithm hosted by a distributor, or by using an automatic calculation through Evidencio's API. Results shall always be reviewed and interpreted by healthcare professionals, in the context of the patient's clinical history and other diagnostic test results. Healthcare professionals do not require additional training prior to the use of the medical device. The device is not intended for use by patients on their own.

6.5. Intended use environment

The MDSW can be used as made available on the Evidencio platform in any actively supported web-browser on personal computers, mobile devices, or tablet PCs, and on the mobile app provided by Evidencio. The MDSW can also be used through Evidencio's iFrame representation as an embedded view, provided that the specific Evidencio guidelines for iFrame implementations of this MDSW are adhered to. Automated calculation of the device is enabled through Evidencio's API. The device is only intended for use in healthcare settings where the immediate application and outcomes of the device are not required.

6.6. Physical interaction

The MDSW is stand-alone software and does not come into contact with any bodily or other material of the patient, user or otherwise.

6.7. Versions of the MDSW

The version of the ADAPT concerns the initial version of MDSW of which Evidencio is the manufacturer.

The 3.0 version is the first generation of this product to be developed as a medical device. Before the development of this version, the device has never been marketed anywhere in the world. Previous versions have been available on the Evidencio platform for informational purposes only, not as a medical device or in vitro diagnostic medical device.

7. Result interpretation

Primary outcome

The primary output of this device is given as the ADAPT score, a number between 2.19 and 78.44 rounded to 2 decimals.

Conditional information

The ADAPT outcome is a numeric score that can be interpreted as the severity of liver fibrosis. More precisely, based on cut-off values, outcomes of ADAPT can be interpreted as different severities of fibrosis or cirrhosis (stages F0 to F4). According to a study of the Elecsys® Pro-C3 assay from Roche Diagnostics, ADAPT scores can be interpreted as provided in **Table 1**.

Table 1. Outcome and corresponding interpretation of the ADAPT.

Outcome	Interpretation
ADAPT score < 9	The patient is not considered to be at risk of having significant liver fibrosis or worse (i.e. the liver fibrosis is considered a stage F0-F1 (no or early/mild fibrosis)).
ADAPT score ≥ 9	The patient is considered to be at risk of having significant liver fibrosis or worse (i.e. the liver fibrosis is considered a stage F2-F4).
ADAPT score ≥ 10	The patient is considered to be at risk of having advanced liver fibrosis or worse (i.e. the liver fibrosis is considered a stage F3-F4).
ADAPT score ≥ 11	The patient is considered to be at risk of having liver cirrhosis (i.e. the liver fibrosis is deteriorated to cirrhosis stage F4).

Calculations alone should never dictate patient care, and are no substitute for professional judgement. See the Evidencio website for the full disclaimer; https://www.evidencio.com/disclaimer.

8. Additional information

8.1. Details

Algorithm author	T. A. Hueting
Root model ID	6094
Version	3.0
Revision date	19-DEC-2025
Speciality	Hepatology
Algorithm type	Custom Model / R-Script model
MeSH terms	• Fibrosis, Liver • NAFLD

8.2. Input variables

To perform the calculations successfully, the ADAPT requires the input variables as listed in **Table 2**.

Table 2. Variables used as input for the ADAPT.

Name	Description	Type	Range (step size)	Units
Age	The age of the patient Ages of 100-150 years should be set to 100 years. The ADAPT is not meant for patients below 18 or above 150 years.	Continuous	18-100 (1.0)	Years
Elecsys® Pro-C3 assay result	The Pro-C3 level of the patient ⚠ The ADAPT algorithm is meant to be used specifically with the Elecsys® Pro-C3 assay and the risk stratification and cut-off values are based on this assay.	Continuous	20-500.0 (0.1)	ng/mL
Platelet count	The platelet count of the patient	Continuous	5-3500 (1.0)	× 10^9/L
Diabetes	Whether a patient has diabetes	Categorical	Yes/No (1/0)	N/A

8.3. Algorithm

The algorithm of ADAPT is as follows:

$$ADAPT = e^{log_{10}\left(\frac{Age \times Elecsys^{®}\ Pro{-}C3\ assay\ result}{\sqrt{Platelet\ count}}\right)} + Diabetes$$

Algorithm of the ADAPT.

8.4. Study characteristics

The ADAPT algorithm was developed by Daniels *et al*. (2019) with a cohort that consisted of 431 biopsy-confirmed NAFLD patients. A total of 150 NAFLD patients from the Storr Liver Centre, Sydney, Australia were included in the derivation cohort and 281 NAFLD patients from four international sites (Nottingham University Hospitals NHS Trust, United Kingdom (n=42); Kurume University School of Medicine, Kurume, Japan (n=48); University of Western Australia, Nedlands, Australia (n=144) and 47 additional patients from the Storr Liver Centre) were included in the validation cohort.

External validation was performed in a study from Nielsen *et al*. (2021) where 517 biopsy proven patients from the CENTAUR study were used to validate the ADAPT algorithm. The ADAPT had an area under the curve (AUC) of 0.80 (95% CI: 0.76-0.84), a sensitivity of 78% and a specificity of 69%. Moreover, it outperformed the other non-invasive diagnostic tests (NITs), such as the FIB-4, APRI, AST/ALT ratio and PRO-C3 alone.
Information on the characteristics of the patient data used to derive and validate the algorithm is provided in **Table 3**.

Table 3. Patient characteristics of the derivation and validation cohort.

Name	Population size	Mean (±SD)	Unit
Derivation cohort	**151**		
Age	150	50.85 (±12.13	Years
PRO-C3	150	20.92 (±15.48)	ng/mL
Platelet count	148	244.4 (±73.53)	$\times 10^9$ /L
Diabetic	56		N/A
Validation cohort	**281**		
Age	277	52.9 (12.38)	Years
PRO-C3	279	19.93 (18.04)	ng/mL
Platelet count	270	229.7 (79.49)	$\times 10^9$ /L
Diabetic	105		N/A

The cut-offs that are used for ADAPT are derived from a study of the Elecsys® Pro-C3 assay from Roche Diagnostics. 683 patients showing evidence or signs of MASLD were included in a multicentric EU validation cohort (with 84 patients in the F0 fibrosis stage, 140 in the F1 stage, 207 in the F2 stage, 179 in the F3 stage, and 73 in the F4 stage. ADAPT performed well on the discrimination of Advanced Fibrosis with an AUC of 0.803 (95% CI: 0.771-0.835). The Sensitivity and Specificity for significant fibrosis, advanced fibrosis and cirrhosis, as well as the relevant cut-off values, are shown below in Table 4. These correspond with the conditional information in the result interpretation.

Table 4. Sensitivity and Specificity at cut-off values.

Cut-off	Sensitivity	Specificity
≥cut-off 9 Significant Fibrosis (F2-F4)	0.53 (0.48, 0.57)	0.80 (0.75, 0.85)
≥cut-off 10 Advanced Fibrosis (F3-F4)	0.50 (0.43, 0.56)	0.89 (0.86, 0.92)
≥cut-off 11 Cirrhosis (F4)	0.53 (0.41, 0.65)	0.90 (0.87, 0.92)

8.5. Supporting publication & Related files

Several relevant studies, such as the original derivation study by Daniels *et al*. (2019) are contained in **Table 5**. These publications have tags to identify their link with the algorithm. Examples of relevant tags are; "Peer review", "Internal validation", "External validation", and "TRIPOD". Publications that have the tags: "Internal validation" or "External validation", contain data on the performance characteristics of the device.

Table 5. Overview of selection of supporting publications & Related files.

Original calculator Information on topic Algorithm formula Risk factors ROC curve	**ADAPT: An Algorithm Incorporating PRO-C3 Accurately Identifies Patients With AFLD and Advanced Fibrosis** (2019) *Daniels, Samuel J.; Leeming, Diana J.; Eslam, Mohammed; Hashem, Ahmed M.; Nielsen, Mette J.; Krag, Aleksander; Karsdal, Morten A.; Grove, Jane I.; Neil Guha, Indra; Kawaguchi, Takumi; Torimura, Takuji; McLeod, Duncan; Akiba, Jun; Kaye, Philip; de Boer, Bastiaan; Aithal, Guruprasad P.; Adams, Leon A; George, Jacob* DOI: 10.1002/hep.30163
External validation	**Comparison of ADAPT, FIB-4 and APRI as non-invasive predictors of liver fibrosis and NASH within the CENTAUR screening population** (2021) *Nielsen M.J.; Leeming D.J.; Goodman Z.; Friedman S.; Frederiksen P.; Rasmussen D.G.K.; Vig P.; Seyedkazemi S.; Fischer L.; Torstenson R.; Karsdal M.A.; Lefebvre E.; Sanyal A.J.; Ratziu V.* DOI: 10.1016/j.jhep.2021.08.016

External validation	**Among simple non-invasive scores, Pro-C3 and ADAPT best exclude advanced fibrosis in Asian patients with MAFLD** (2022) *Tang L.J.; Ma H.L.; Eslam M.; Wong G.L.H.; Zhu P.W.; Chen S.D.; Leeming D.J.; Karsdal M.; Li G.; Huang O.Y.; Leung H.H.W.; Zhou Y.J.; Feng Q.; Jiang P.; Gao L.M.; Byrne C.D.; Targher G.; George J.; Wong V.W.S.; Zheng M.H.* DOI: 10.1016/j.metabol.2021.154958
External validation	**Obesity Modifies the Performance of Fibrosis Biomarkers in Nonalcoholic Fatty Liver Disease** *Quadri S.; Ahlholm N.; Lønsmann I.; Pellegrini P.; Poikola A.; Luukkonen P.K.; Porthan K.; Juuti A.; Sammalkorpi H.; Penttilä A.K.; D'Ambrosio R.; Soardo G.; Leeming D.J.; Karsdal M.; Arola J.; Kechagias S.; Pelusi S.; Ekstedt M.; Valenti L.; Hagström H.; Yki-Järvinen H.* DOI: 10.1210/clinem/dgab933
External validation Calibration plot	**PRO-C3 and ADAPT algorithm accurately identify patients with advanced fibrosis due to alcohol-related liver disease** *Madsen B.S.; Thiele M.; Detlefsen S.; Kjaergaard M.; Møller L.S.; Trebicka J.; Nielsen M.J.; Gudmann N.S.* DOI: 10.1111/apt.16513

8.6. Analytical performance characteristics

To demonstrate the analytical performance of ADAPT, evidence was collected based on five requirements. This led to the following results:

- A code review and functional test showed that the calculation of the online tool provides the exact same results as described in the paper by Daniels *et al*. (2019).
- Monthly uptime reports show that the device is available online with an uptime of at least 99%.
- The calculation time is within 2 minutes, otherwise an error is given to the manufacturer, this is analysed each 6 months in the analysis of quality data.
- Absence of unacceptable cybersecurity vulnerabilities.
- On a scale from 1 to 5, where 5 means that users trust the implementation very much, the reliability score was 4.44, and the accuracy score was 4.56 on average.

8.7. Clinical performance characteristics

In literature, the use and performance of ADAPT has been studied using a heterogeneous set of cut-off values. This results in a broad set of performance characteristics which cannot be directly compared between the different interpretations of ADAPT and between ADAPT and other non-invasive tests (NIT's). The FIB-4 Index is generally the recommended first-line test in the state of the art, with other NIT's, such as ADAPT, APRI, NFS or ELF allowing for further testing in a more specific population. ADAPT uses more direct markers of fibrosis than the FIB-4 index, and is intended to be used with a high specificity, rather than a high sensitivity, as is generally the case for the FIB-4 Index. However, overall, the FIB-4 Index is regarded as the state of the art for NIT's in the field of liver fibrosis and as such, generally all NIT's in the field are compared to it. Therefore, ADAPT was compared to the FIB-4 Index, using among other, C-statistics and Decision Curve Analysis (DCA).

Statistic performance characteristics

ADAPT, as implemented on Evidencio, is primarily focused on distinguishing patients in four groups, i.e. those with early/mild, significant or advanced liver fibrosis, or liver cirrhosis. As such, parameters of performance data that rely on cut-off values are not necessarily relevant to the manner in which ADAPT is intended as most studies investigated the performance of identifying patients at risk of advanced liver fibrosis and those who are not.

To directly compare ADAPT and the FIB-4 Index on discrimination, the identified performance on C-statistics were pooled in a meta-analysis to obtain an overall performance measure. This showed a good discriminatory performance for ADAPT (C-statistic = 0.85 (95% CI: 0.83 - 0.87)) which was better than that of the FIB-4 Index (C-statistic = 0.78 (95% CI: 0.74 - 0.82)) in identifying advanced fibrosis (≥ F3).

For an algorithm to be used as a rule-out decision support, the sensitivity and negative predictive value (NPV) are seen as the most important factors.

A study performed by Roche Diagnostics, of which the data has not been publicly published, reported distinguished patients in four groups. Specificities were obtained of around 90% for advanced fibrosis and cirrhosis, and 80% for significant fibrosis, while sensitivities were obtained of about 50%.

Benefit assessment

Several studies have been performed on the potential clinical benefit of the ADAPT using DCA. In these studies ADAPT was compared to at least the FIB-4 Index and was found to show a higher net benefit in all compared to the what is considered to be the state of the art. In a study by Tang *et al*. (2023) it was also found to show a higher clinical benefit compared to PRO-C3, APRI, NFS, and BARD. An earlier study by Tang *et al*. (2022) also showed a higher net benefit for ADAPT when compared to reference NIT's.

8.8. Release notes

The release notes for each publicly available version of the device can be found on the Evidencio website pages for the ADAPT:

https://www.evidencio.com/models/show/6094?v=3.0

Simply select the "Release notes" on the right side of the screen. It is recommended to read these notes after a version update to see if these changes are relevant to you. Please make sure the correct algorithm version is selected.

9. Using the algorithm on the Evidencio website

Using the tool on the Evidencio website requires a stable internet connection. The tool was developed to work on the four most commonly used internet browsers; Google Chrome (version 135.0.7049.96 and higher), Mozilla Firefox (version 137.0.2 and higher), Microsoft Edge (version 135.0.3179.73 and higher), and Apple Safari (version 18.3.1 and higher). The medical device cannot be used in combination with Internet Explorer.

Use of the Evidencio platform is always encrypted through the https protocol.

The tool can also be accessed on mobile devices via their internet browsers running the most recent versions of the Android (version 14 and higher) and iOS (version 18.3.1 and higher) operating systems.

Correct functioning of the tool with earlier versions of these browsers cannot be guaranteed.

The personal computers, laptops, tablets or smartphones used should at least be able to have an internet connection and use one of the browsers mentioned above.

Furthermore, the algorithm may be used through the Evidencio iFrame representation of the calculator, as an embedded view, provided that the specific Evidencio guidelines for iFrame implementations of that algorithm are adhered to.

The Evidencio MDSW algorithms can be used with any browser settings that don't distort the regular display of websites, with a 50% to 500% zoom rate, and at a display minimal screen resolution starting from 800x600. However, factory recommended browser settings, 100% zoom rate and regular display resolution are recommended.

The MDSW is intended for authorised users only, and should not be used by unauthorised personnel.

This algorithm is only intended for use in settings where the usage and result of an algorithm are never immediately needed.

9.1. General algorithm landing page

An example of a medical device algorithm interface on the Evidencio platform is shown in **Figure 1**. The different sections indicated are explained in this chapter.

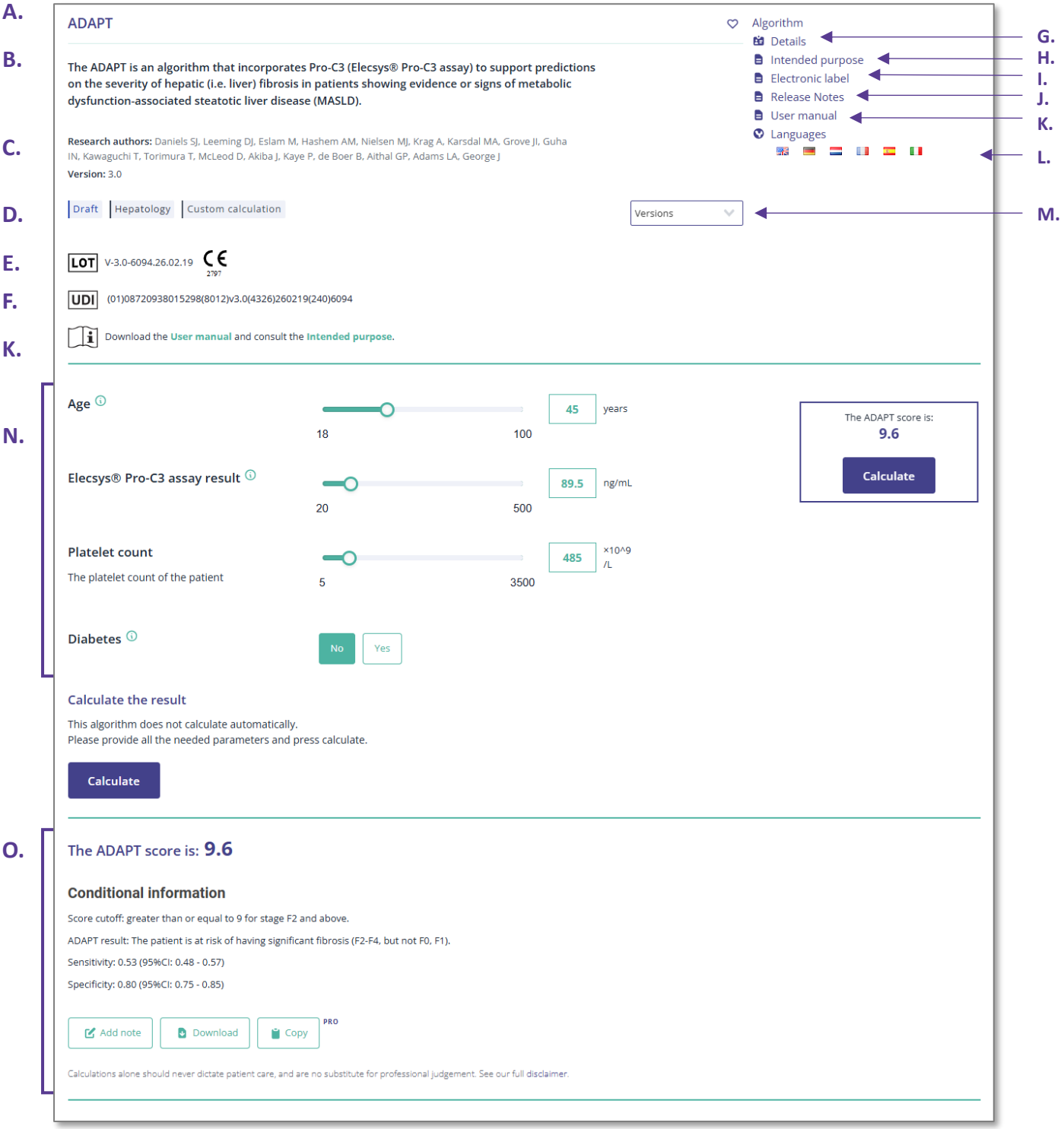

Figure 1: Graphical user interface of ADAPT

A. Algorithm title

This is the title and name of the algorithm.

B. Algorithm description

This is a short description of the algorithm.

C. Research authors

These are the research authors of the paper that originally described the development of the algorithm.

D. Algorithm tags

These are the tags that are assigned to the algorithm. Evidencio has the following status tags: “Draft”, “Public”, “Private”, “Under review”. Evidencio has the following algorithm type tags: “Composite model”, “Sequential model”, “API model”. Evidencio has the following calculation method tags: “Linear model”, “Logistic regression”, “Cox regression”, “RScript” and “Custom model”. Next to this, there are tags that indicate the specialty e.g. “Cardiology”.

E. LOT number

The LOT number indicated the algorithm version, the algorithm identifier, and the algorithm publication date. Publication date is indicated as YY.MM.DD.

Additionally, the CE mark is displayed next to the LOT number. This way, medical devices can be easily recognized.

F. UDI Number

For information on the UDI Number see **Section 5.2** of this user manual.

G. Details button

On the top right of the algorithm page, several clickable buttons are displayed that show a pop-up when clicked. The first button opens a pop-up concerning additional information about the algorithm. This pop-up has three sections: Details, Study characteristics and Supporting publications & related files.

Details

The first part of the additional information concerns the details of the algorithm as shown in **Figure 2**. This section may show the calculation if it is built as a mathematical formula and, if applicable, shows the conditions at which certain formulas are used.

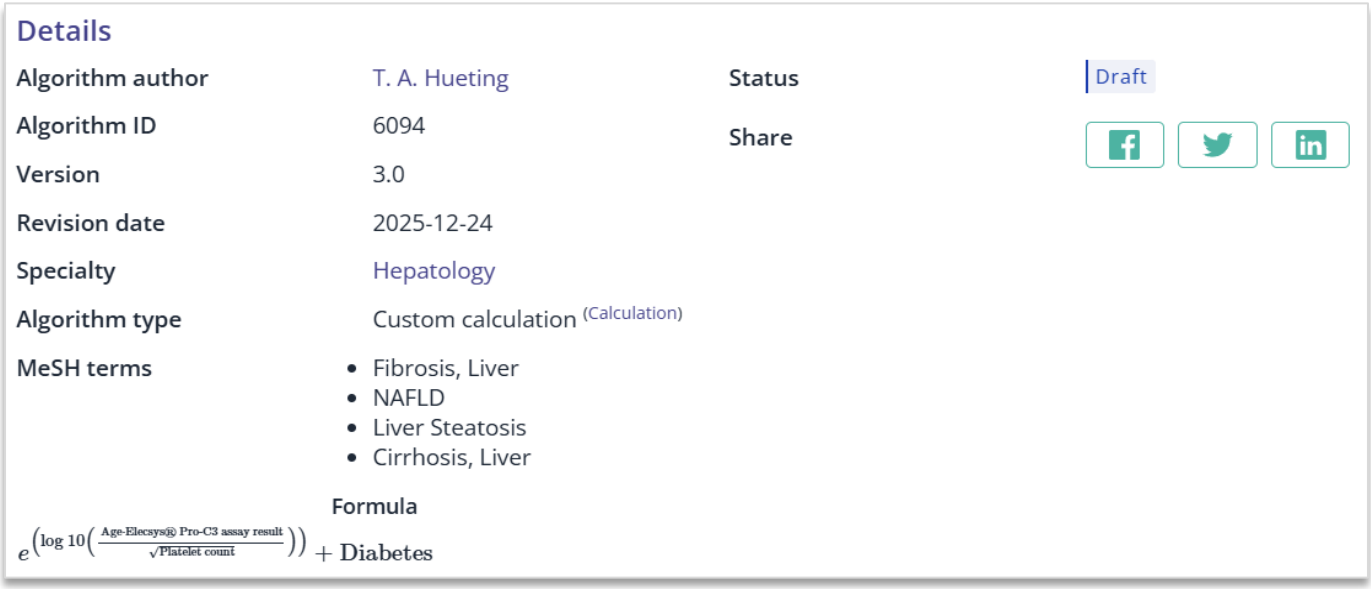

Figure 2. Example of the first part of the Details section.

Study Characteristics

Below the 'Details section' the section labelled "Study characteristics" provides information on the characteristics of the patient data used to derive and validate the algorithm. Additional information is provided on the methods used to develop and/or validate the algorithm. An example of the Study characteristics section can be seen in **Figure 3**.

Study characteristics

Additional information

The ADAPT was developed within a study cohort with a total of 431 well phenotyped patients with biopsy confirmed NAFLD. The algorithm was first developed by Daniels et al. in 2019. The ADAPT combines Age, Elecsys® Pro-C3, Platelet count, and Diabetes to assist in risk stratification of patients with (signs or evidence of) MASLD (formerly NAFLD/MAFLD) based on the severity of liver fibrosis. The ADAPT is externally validated in many studies and demonstrated better performance in risk stratification of patients with MASLD based on the severity of liver fibrosis compared to the FIB-4 Index.

Study Population

Total population size: 431

Continuous characteristics

NAME	MEAN	SD	UNIT
Age (Derivation cohort) (n=150)	50.85	12.13	Years
PRO-C3 (Derivation cohort) (n=150)	20.92	15.48	ng/mL
Platelet count (Derivation cohort) (n=148)	244.4	73.53	x 10^9/L
Age (Validation cohort) (n=277)	52.9	12.38	Years
PRO-C3 (Validation cohort) (n=279)	19.93	18.04	ng/mL
Platelet count (Validation cohort) (n=270)	229.7	79.49	x 10^9/L

Categorical characteristics

NAME	SUBSET / GROUP	NR. OF PATIENTS
Cohorts	Derivation cohort	150
Cohorts	Validation cohort	281
Diabetic	Derivation cohort	56
Diabetic	Validation cohort	105

Figure 3: Study characteristics for ADAPT.

Supporting publications & Related files

An important part of the Study characteristics is the information on Supporting publications and related files. The list of related files and relevant tags can also be found in **Paragraph 8.5**. These sections can be found at the bottom of the Details-pop-up as shown in **Figure 4**.

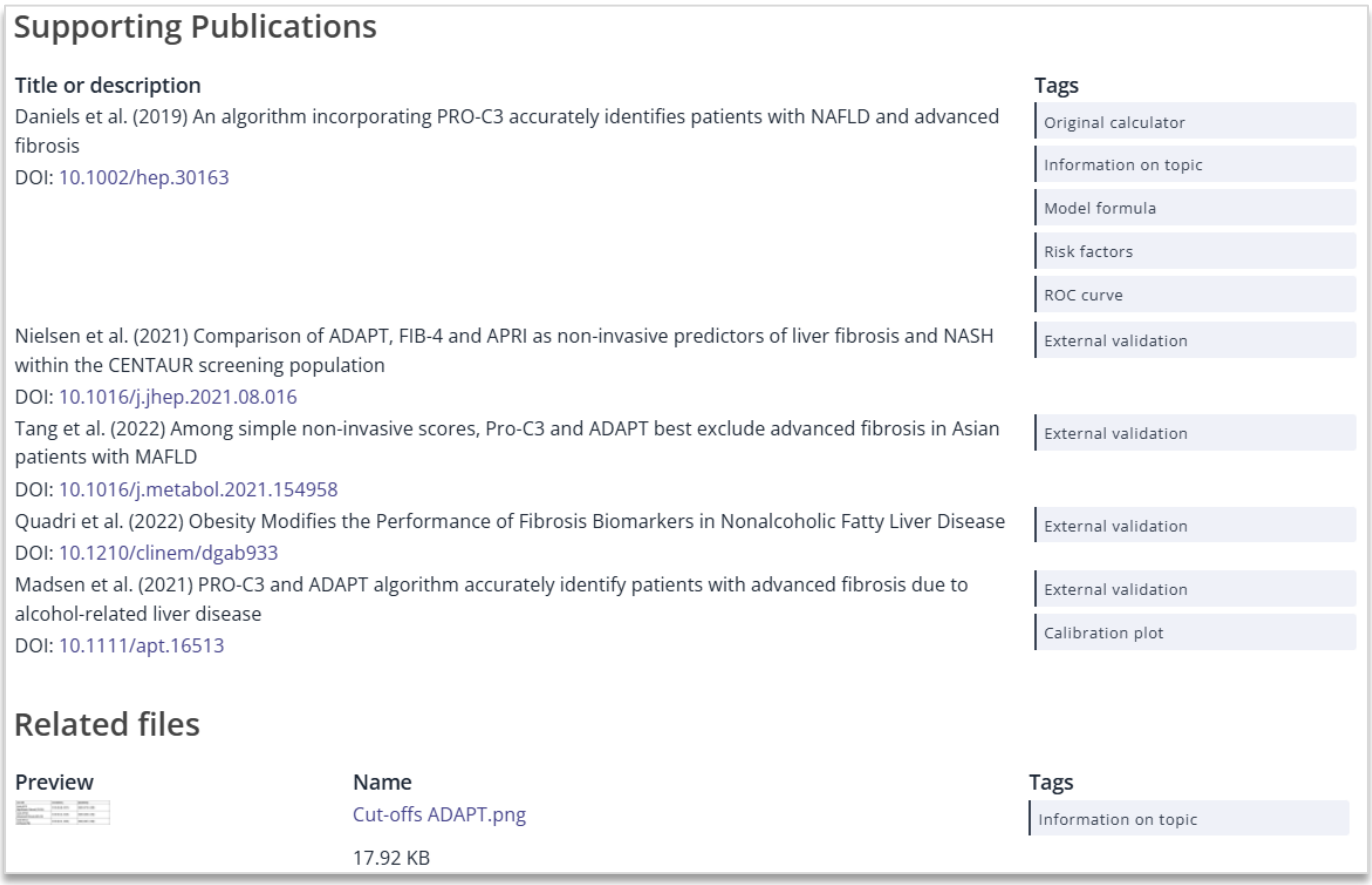

Figure 4. Supporting publication & Related files section under the Details tab.

H. Intended purpose

Under this tab, the intended purpose can be found, containing a lot of information regarding the algorithm, its user, target population, clinical benefit, etc. This information is also provided in this manual and can be found in **Chapter 6** on **page 5** and **6**.

I. Electronic label

The electronic label button opens a pop-up with the location and address of Evidencio, the LOT number, the UDI number, the CE-mark, the medical device logo and a download link for the declaration of conformity of the medical device. The electronic label can also be found in section 5 of this document. An example of the electronic label as presented on the Evidencio website is shown in **Figure 5**.

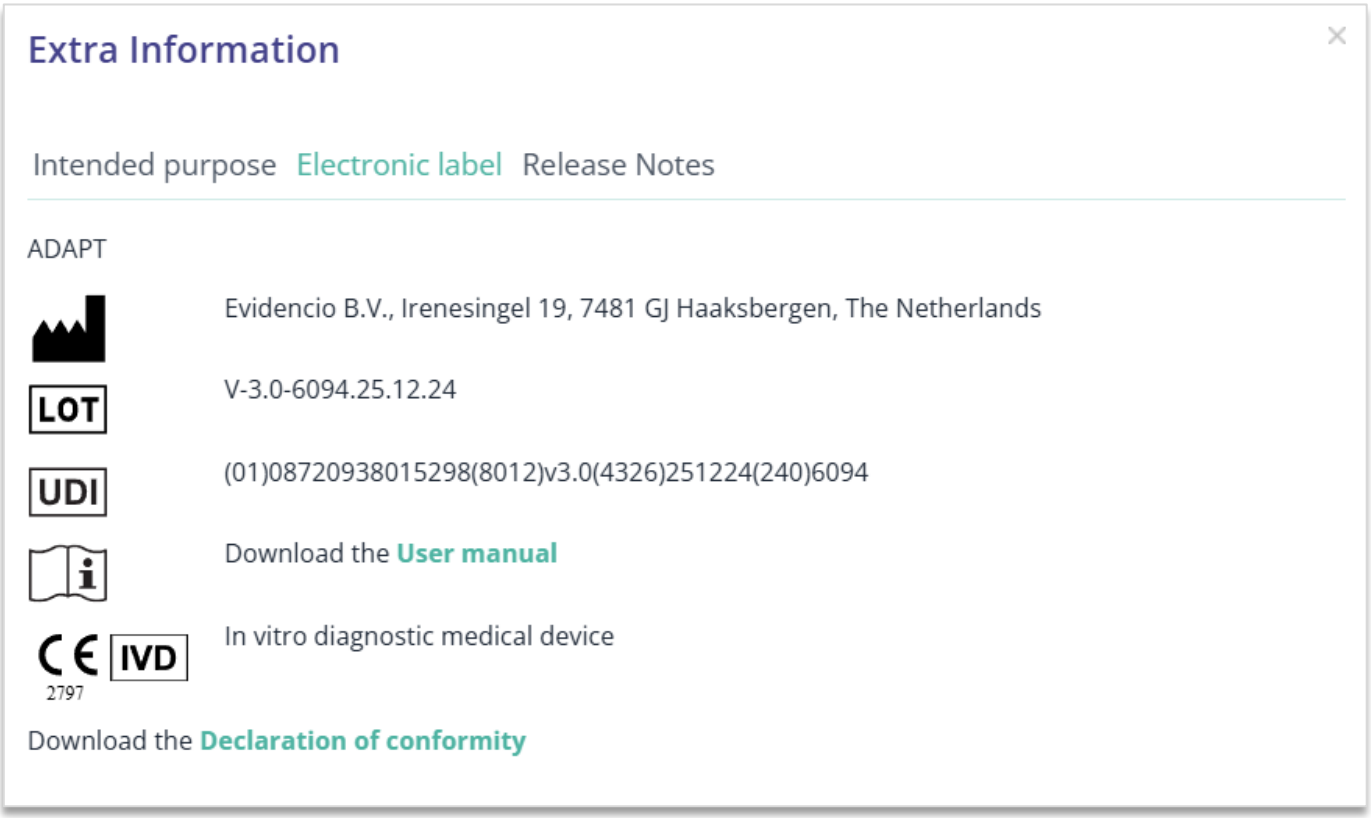

Figure 5. Electronic label under the Electronic Label tab.

J. Release notes

Under this tab the most recent release notes can be found, noting the most significant changes between the versions of the algorithm found on the Evidencio website.

The 'Release Notes' button opens a pop-up with the latest release notes of the algorithm. Here you can find a list of the most significant changes over the different versions of the algorithm. Additionally, if there are any known residual anomalies the user should be aware of, they are listed here. It is recommended to read these notes after a version update to see if these changes are relevant to you.

K. User manual

This user manual can be found in three places: 1) under the short description of the algorithm on the Evidencio algorithm page, 2) on the right of the algorithm page, and 3) as a tab in the electronic label screen. Additionally, all versions of the user manual can be found in the general page for all user manuals for medical devices. The page can be found under the 'About' drop-down menu button as shown in **Figure 6**. The user manual page is shown in **Figure 7**. This version of the manual can be printed if required. If necessary, a paper version of the manual can be requested to be sent to you by mail. Evidencio's contact details are listed in **Chapter 11** of this user manual.

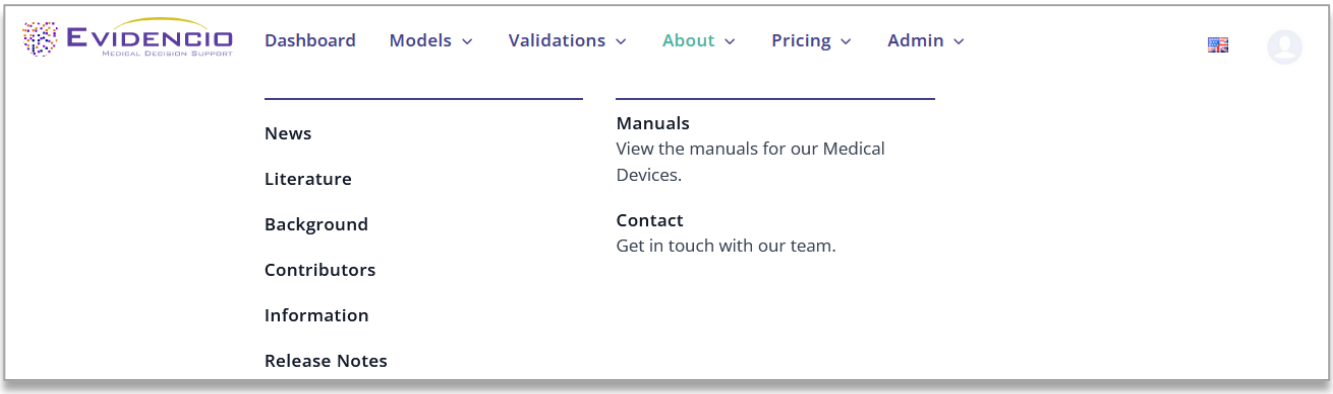

Figure 6. The drop-down menu where the user manual page can be found.

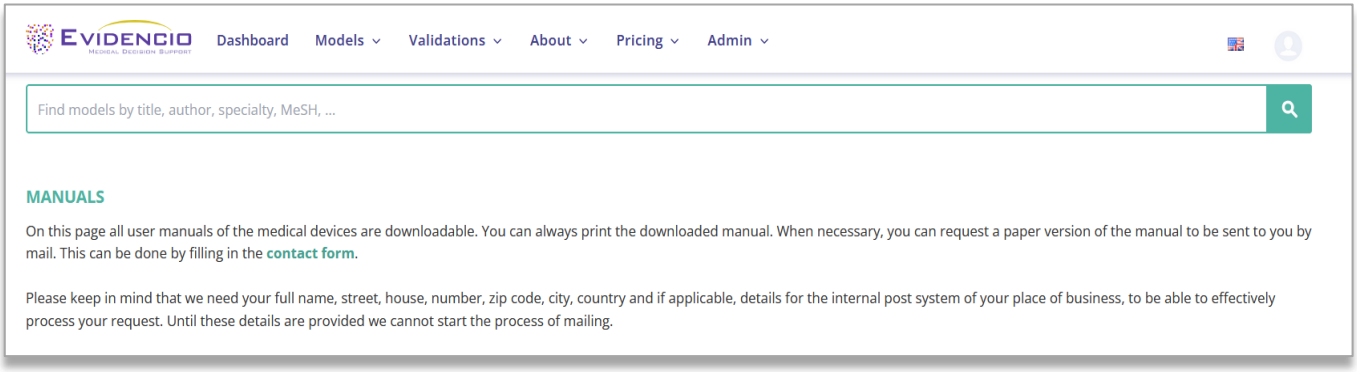

Figure 7. The user manual page for all user manuals.

L. Languages

Here an overview of languages in which the ADAPT is available is provided, any of which can be selected by clicking on the corresponding flag icon. The standard language on the Evidencio website is English.

Please note that, if a language is selected, only the user interface of the specific algorithm will be translated, other general features and information on the site might still be set to one of our primary languages English, German, and Dutch.

When you find mistranslations, irregularities, confusing or ambiguous use of language in English or any other language on the Evidencio website or in one of our manuals, please do not hesitate to contact us using the contact information provided at the end of this manual.

M. Version selection

If available, clicking on the Version tab allows the user to select a different version of the ADAPT from a list. Please note that the algorithm currently selected is not presented in the dropdown menu.

N. Input section

ADAPT utilizes two types of input variables; categorical and continuous variables.

Categorical variable

In **Figure 8** and **Figure 9**, the variable **Diabetes** is displayed. The correct value can be entered by clicking on either button. The selected button changes to green, as seen in **Figure 9**.

Figure 8. No button has been clicked and thus no input has been provided by the user.

Figure 9. Example of a categorical variable, where the "Yes" button has been clicked.

Continuous variables

In **Figure 10**, the Continuous Variable **Age** is displayed. The plausible ranges for which the algorithm is tested and deemed valid are displayed below the slider.

The details for a patient can be entered by sliding the button to the correct value, or by entering the correct value in the box on the right-hand side (i.e., where the 45 years is entered).

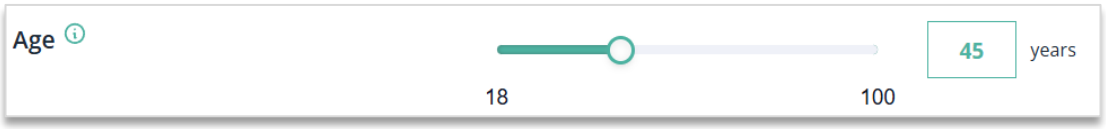

Figure 10. Example of a continuous variable, where “45 years” has been entered.

O. Result section

At the bottom of the page, the results of the algorithm are shown.

Calculations alone should never dictate patient care, and are no substitute for professional judgement. See our full disclaimer on: https://www.evidencio.com/disclaimer.

Result calculation

When all variables are filled in, and the user presses calculate, a result can be calculated. No result is displayed until all variables are filled in and the result section will indicate; *“Set all parameters to calculate prediction.”*

Result interpretation

In the result interpretation, the details will be displayed based on the calculated ADAPT score. This section always includes the following details:

- **Score cutoff**
- **ADAPT result**
- **Sensitivity**
- **Specificity**

Figure 11 displays an example of an output, and the associated interpretation shown by the device.

The user can add a specific note in the context of the values that have been entered and the results that are displayed by clicking on **Add note**.

The user can download the results in a PDF by clicking on **Download** or copy the results directly to the users' clipboard by clicking on **Copy.** The downloaded PDF contains the information that is displayed in figure 1 in sections A, B, C, M, and N. It also displays the electronic label of the device, and includes a timestamp. The copy button copies the following sections to the clipboard: Device title, URL to the device, device version, timestamp corresponding to when the copy button was used, Entered input parameters, result, conditional result information, disclaimer text.

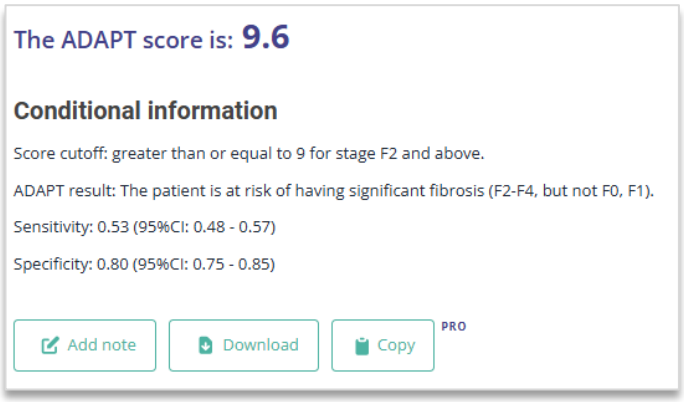

Figure 11. Example of the result interpretation of ADAPT.

10. Implementation of the algorithm through an API

The ADAPT can be used through Evidencio's API to allow for (automated) calculation of the ADAPT score, which can be used as an indicator of liver fibrosis severity in patients showing evidence or signs of MASLD. In the case of use of the MDSW through the API, the user should take into account the different inputs for the algorithm, in order to properly interpret the results.

The information provided over the API is the same as the information that is displayed in the graphical user interface on the web application provided by Evidencio. In **Box 1** below, an example of a result from ADAPT over the API is shown. The result concerns a JSON formatted text. The API for ADAPT leverages the generic API that is provided for the Evidencio platform and therefore contains information that may be applicable for different software algorithms and devices. This means that not all of the details provided over the API may be relevant for ADAPT.

```
{
   "CIPercentage": 0,
   "id": 6094,
   "author": "T. A. Hueting",
   "title": "ADAPT (Research Use Only)",
   "variables": {
      "8230549946": 45,
      "5632699332": 89.5,
      "6533462455": 485,
      "7138271474": 0
   },
   "min": 9.6,
   "max": 9.6,
   "additionalResultSet": [],
   "mintxt": "9.6",
   "maxtxt": "9.6",
   "result": "9.6",
   "resultText": "The ADAPT score is:",
   "postresultText": "",
   "formulaSegments": [],
   "conditionalResultArray": [
      "<p><p>Score cutoff: greater than or equal to 9 for stage F2 and above.</p><p></p></p>",
      "<p><p>ADAPT result: The patient is at risk of having significant fibrosis (F2-F4, but not F0, F1).</p></p>",
      "<p><p>Sensitivity: 0.53 (95%CI: 0.48 - 0.57)</p><p></p></p>",
      "<p><p>Specificity: 0.80 (95%CI: 0.75 - 0.85)</p></p>"
   ],
   "conditionalResultText": "<p><p>Score cutoff: greater than or equal to 9 for stage F2 and above.</p><p></p></p><p><p>ADAPT result: The patient is at risk of having significant fibrosis (F2-F4, but not F0, F1).</p></p><p><p>Sensitivity: 0.53 (95%CI: 0.48 - 0.57)</p><p></p></p><p><p>Specificity: 0.80 (95%CI: 0.75 - 0.85)</p></p>",
   "UDI": "(01)08720938015298(8012)v3.0(4326)260218(240)6094",
   "medicalDevice": "This is an in vitro diagnostic medical device. The electronic label is available at: https://www.evidencio.com/models/show/6094?v=3.0",
   "userManual": "Always refer to the user manual for correct use of the in vitro diagnostic medical device. The user manual can be found at: https://www.evidencio.com/manuals"
}
```


Box 1: Example of an API output for ADAPT.

Table 6 shows a match between the separately listed items in the API output with the items listed on the graphical user interface on the Evidencio website (elaborated in chapter 9).

API Item	GUI item	Comment
CIPercentage	N/A	Not applicable for ADAPT as this feature is not used for ADAPT
id	Algorithm ID under 'details' Id used in the URL (www.evidencio.com/models/show/6094)	The ID is the Evidencio specific identification number of the algorithm.
author	Algorithm author under 'details'	Name of the Evidencio user who created the algorithm on the Evidencio platform.
title	Title of the algorithm (part A of figure 1).	-
variables	Input variables and their entered value. (part N. of figure 1)	The API displays the variables as unique IDs.

min	N/A	Depicts the lowest value when the result of the algorithm is a range. Since ADAPT always displays a single value as a result, this value is the same as the 'result'.
max	N/A	Depicts the highest value when the result of the algorithm is a range. Since ADAPT always displays a single value as a result, this value is the same as the 'result'.
additionalResultSet	N/A	N/A
mintxt	N/A	Same as 'min', but as a string.
maxtxt	N/A	Same as 'max', but as a string.
result	The main result of the algorithm, the ADAPT score.	-
resultText	The text displayed in front of the main result	e.g. "The ADAPT score is:".
postresultText	The text displayed behind the main result	Not used for ADAPT.
formulaSegments	N/A	N/A
conditionalResultArray	Result interpretation displayed beneath "Conditional Information" (section O. in figure 1).	The API result shows the raw HTML text that is rendered by the software used for the graphical user interface.
conditionalResultText	Result interpretation displayed beneath "Conditional Information" (section O. in figure 1).	This section is the same as *'conditionalResultArray',* but displayed as a single string.
UDI	Same as the UDI displayed in the GUI (section F. in figure 1).	-
medicalDevice	The electronic label (section I. in figure 1).	The API refers to the electronic label on the graphical user interface.
userManual	The user manual (section K. in figure 1).	The API refers to the location of the user manual at the user interface & Evidencio website).

Instructions on how to implement the API within a system are included in a separate document that is made available to the party performing the technical implementation. The party performing the integration of ADAPT using the API should adhere to the requirements outlined in **6094-DOC-45 instructions for API integration ADAPT.**

11. Revision history user manual

Version	Revision notes
V1.0	Original version

12. Manufacturer details

Contact details of Evidencio:

Evidencio B.V., Irenesingel 19, 7481 GJ Haaksbergen, The Netherlands
www.evidencio.com
tel: +31 53 85195 08
e-mail: info@evidencio.com

13. ANNEX I: Different versions of ADAPT

To accommodate for specific implementation scenario's, separate sub-versions of ADAPT have been created. This is mainly due to the nature of the required inputs in ADAPT. The biomarker values (e.g. Pro-C3 & Platelet count) are collected by the lab, but the lab doesn't have knowledge on the Diabetic status of the patient. This could hamper automated calculation of ADAPT and therefore integration into the workflow of the health care professional. The different sub-versions of ADAPT were created to remove these potential barriers. Besides the main "ADAPT" algorithm, three other versions were created:

(1) **ADAPT for Diabetic patients**. This concerns a version of ADAPT where "*Diabetes*" status is always set to "*Yes*".
(2) **ADAPT for non-Diabetic patients.** This concerns a version of ADAPT where "*Diabetes*" status is always set to "*No*".
(3) **ADAPT for patients with unknown Diabetes status.** This concerns a version of ADAPT that provides two results, an ADAPT score for a diabetic patient, and an ADAPT score for a non-diabetic patient.

Please note that the current user manual and instructions for API only cover the main ADAPT algorithm. Additional instructions are available for the three other versions of ADAPT in separate documentation.