User manual for the ROMA™

ROMA™ (for postmenopausal patients)
ROMA™ (for premenopausal patients)

Version 8, September 2024, in English

Table of Contents

1. The Evidencio platform

The Evidencio platform facilitates the creation, use, validation and implementation of medical prediction models and clinical decision support tools. This User Manual specifically relates to the ROMA™, which covers the ROMA™ (for postmenopausal patients) and the ROMA™ (for premenopausal patients). The User Manual can also be referred to as the Instructions For Use (IFU).

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

2. Disclaimer

Evidencio provides information, models, calculators, equations, and algorithms (tools) intended for use by healthcare professionals. Some of these tools have been certified as CE-medical devices. For such CE-marked content the 'Official Legal Disclaimer for CE-marked content' applies. All other content and tools provided by Evidencio are explicitly only covered by the 'Official Legal Disclaimer for non-CE-marked content. Both are available on the Evidencio website: https://www.evidencio.com/disclaimer.

The name ROMA™, derived from Risk of Ovarian Malignancy Algorithm, is a registered trademark by Fujirebio Diagnostics, Inc.

3. Warnings

⚠ 3.1. Warnings for CE-marked content

Calculations alone should never dictate patient care, and are no substitute for professional judgement. This tool is only to be used by physicians 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 Evidenico website, and in **paragraphs 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 model is only intended for use in settings where the usage and result of a model are never immediately needed.

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

The data used to perform the calculations is stored by Evidencio to enhance model 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.

4. Device Description ROMA™

The ROMA™ is a collective name used here to refer to two related medical devices, which can be used independent. Both the ROMA™ (for premenopausal patients) and the ROMA™ (for postmenopausal patients) can be used to estimate the risk of ovarian malignancy in premenopausal and postmenopausal patients who present with an ovarian adnexal mass. The model combines a patient's serum concentration of Elecsys HE4 assay, Elecsys CA125 II assay and menopausal status to calculate the risk of ovarian malignancy.

4.1. Lifetime, residual risks and side effects

The ROMA™ 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 model 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 model.

The ROMA™ is a low-risk device, there are no noticeable risks involved outside of possible mis-estimation of a patient's risk of malignancy, and all residual risks are accepted.

Most identified risks can be defined into two main groups, depending on their outcome.
a) The risk calculation was wrong or;
b) The MDSW prediction model 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 inaccessibility 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 ROMA™ does not have any direct side effects relevant for the patient.

5. Electronic Label

The electronic label of this device contains the following information:

Name of the device:	ROMA™
Manufacture information:	Evidencio B.V., Irenesingel 19, 7481 GJ Haaksbergen, The Netherlands
LOT number:	
ROMA™ (for premenopausal patients)	V-1.31-9927.24.08.19
ROMA™ (for postmenopausal patients)	V-1.32-9927.24.08.19
UDI-PI number:	
ROMA™ (for premenopausal patients)	(01)08720938015151(8012)v1.31(4326)240819(240)9927
ROMA™ (for postmenopausal patients)	(01)08720938015168(8012)v1.32(4326)240819(240)9927

The electronic label can be found on the Evidencio website, see also **Section I** and **Figure 5**.

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 model version, the model identifier, and the model publication date. Publication date is indicated as YY.MM.DD.

5.2. UDI-PI number

Stands for Unique Device Identifier Production Identifier (UDI-PI) number is an international tool that helps users identify and find information on products. Evidencio's UDI-PIs 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, also part of the UDI-PI, is linked to one of the 2 device sub-models. Version 1.31 for ROMA™ (for premenopausal patients) and Version 1.32 for the ROMA™ (for postmenopausal patients).

6. Intended Purpose

6.1. Intended Medical Use

The ROMA™ is intended to be used by professional users who are capable of operating the device and interpreting its results.

It combines menopausal status, i.e. by separate formulas for pre- and postmenopausal patients, with HE4 and CA-125 values obtained from an Elecsys HE4 assay and an Elecsys CA 125 II assay, respectively, to provide an estimate on the risk of malignancy in patients presenting with an ovarian adnexal mass.

The device is intended to be used for patients with an ovarian adnexal mass for whom a surgical intervention is planned. The result is intended to be reviewed and interpreted by qualified medical specialists only. The device is not intended for use by patients on their own.

The ROMA™ is not intended to replace clinical decision-making, it can only provide information to the user on the estimation of malignancy risk. The user can use this information to support decision-making regarding optimal clinical management of the patient.

6.2. Clinical Benefit

Correct functioning of the ROMA™ can result in these clinical benefits:

- It can assist in risk stratification for patients who present with an ovarian adnexal mass.
- Risk stratification can reduce the burden of (invasive and intensive) medical procedures such as tests on patients with low risks, reducing, shortening or avoiding stays in hospitals or other care facilities.
- Risk stratification can reduce the unnecessary consumption of (scarce) medical resources, decreasing costs and increasing their availability for high-risk patients.

6.3. Indented target population and exclusion

The ROMA™ on Evidencio is intended to be used only for a specific group of patients, corresponding to the below indications and contra-indications.

6.3.1. Clinical Indications

It is intended for:

- Patients of 18 years or older
- Patients whose menopausal status corresponds to that of the version of the model, who present with an ovarian adnexal mass for which surgery is planned
- Patients who are not yet referred to an oncologist

6.3.2. Clinical contra-indications

The MDSW should not be used for patients that do not fulfil the inclusion criteria, i.e. it is not intended for:

- Patients who are pregnant

- Patients who have had a prior bilateral oophorectomy

6.4. User profile

The ROMA™ is intended to be used by Healthcare Professionals or automatically calculated through Evidencio's API. Results shall always be reviewed and interpreted by qualified medical specialists only, 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 current version of the MDSW concerns the ROMA™ (for premenopausal patients) and ROMA™ (for postmenopausal patients), which comprise the ROMA™ (i.e. as of 1.31 and 1.32, respectively, and higher) of which Evidencio is the manufacturer.

6.8. Functioning, physical principle

The MDSW's underlying mathematical formulas concern two logistic regression models. The acquisition and processing of the data, the analyses to assemble the relevant criteria for the MDSW as well as the setup and refinement of the ROMA™ are provided in the instructions for use. Entering the details for an individual in the MDSW initiates the estimation of ovarian malignancy risk.

7. Result interpretation

The primary output of this device is given as a percentage of the estimated risk of ovarian malignancy.

This percentage allows risk stratification into **Low Risk** and **High Risk**. Evidencio uses a cutoff value based on a specificity of 75%.

For the ROMA™ (for premenopausal patients) patients are classified as **Low Risk** at **<11.4%** and **High Risk** at **≥11.4%**.

For the ROMA™ (for postmenopausal patients) patients are classified as **Low Risk** at **<29.9%** and **High Risk** at **≥29.9%**.

Conditional information

These cutoff values are based on a specificity of 75%, which is dependent on the essay used to determine the concentration of biomarkers in the patient's blood. Assays other than the Elecsys™ assays provided by Roche will have other specificities, requiring different cutoff values, and thus should not be used as input in the ROMA™ as implemented by Evidencio.

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

Model author	Romee Oonk	
Root model ID	9927	
	Version number	**Revision date**
ROMA™ (for premenopausal patients)	1.31	19 August 2024
ROMA™ (for postmenopausal patients)	1.32	19 August 2024
Speciality	-	
Model type	Custom model	
MeSH terms	-	

8.2. Input variables

To perform the calculations successfully, both models comprising the ROMA™ requires the input variables as listed in **Table 1.**

Table 1. Variables used as input for the both models of the ROMA™.

Name	Description	Type	Range (step size)	Units
Elecsys HE4 assay result	Concentration of human epididymis protein 4 in patient's blood measured with the Elecsys HE4 assay (including 1:20 dilution)	Continuous	15-30000 (0.1)	*pM*
Elecsys CA 125 II assay result	Concentration of carbohydrate antigen 125 in patient's blood measured with the Elecsys CA125 II assay (including 1:5 dilution)	Continuous	2-15000 (0.1)	*IU/mL*

8.3. Formula

ROMA™ (for postmenopausal patients) the predictive Index (PI) is calculated by the following formula;

$$\left(-12 + 2.38 \times ln(\boldsymbol{Elecsys\ HE4\ assay\ result}) + 0.0626 \times ln(\boldsymbol{Elecsys\ CA\ 125\ II\ assay\ result})\right)$$

ROMA™ (for postmenopausal patients) the predictive Index (PI) is calculated by the following formula

$$\left(-8.09 + 1.04 \times ln(\boldsymbol{Elecsys\ HE4\ assay\ result}) + 0.732 \times ln(\boldsymbol{Elecsys\ CA\ 125\ II\ assay\ result})\right)$$

For both models the Predictive Probability (PP) in percentages can be calculated by; $$\frac{e^{\min((PI),7.5)}}{1 \times e^{\min((PI),7.5)}} * 100\%$$

8.4. Study characteristics

In the development paper by Moore *et al.* (2009) the derivation of the ROMA™ is described. In summation; total of 566 patients were enrolled from 12 different geographic sites across the United States. Of the 566 patients enrolled onto the trial, 531 patients were evaluable, with 283 postmenopausal women and 248 premenopausal women. A total of 54 women had menopausal status determined by plasma FSH levels, 47 of which had a prior hysterectomy with preservation of at least one ovary. The mean age of the evaluable study cohort was 54 years old (range: 18 to 87), with a mean age for postmenopausal women of 65 years old (range: 42 to 87) and for premenopausal 41 years old (range: 18 to 59). There were 352 women with benign disease (150 postmenopausal and 202 premenopausal) and 179 women with a malignancy diagnosed in the study group.

For the implementation of the ROMA™ on the Evidencio website, its performance was assessed with data from a total of 22.599 patients gathered through literature research.

The ROMA™ (for premenopausal patients) C-statistic = 0.83 (95%CI: 0.78 - 0.87) and the ROMA™ (for postmenopausal patients) C-statistic = 0.89 (95%CI: 0.79 - 0.94) performed better than the CA125 for premenopausal C-statistic = 0.81 (95%CI: 0.76 - 0.84) and postmenopausal C-statistic = 0.87 (95%CI: 0.84 - 0.90).

The ROMA™ achieved a specificity of at least 75.0% in almost all studies.

8.5. Supporting publication & Related files

Several relevant studies, such as the original derivation study by Moore *et al.* (2009) are contained in **Table 2**. These publications have tags to identify their link with the model. 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 2. Overview of selection of supporting publications & Related files.

Derivation study ROMA™	**A novel multiple marker bioassay utilizing HE4 and CA125 for the prediction of ovarian cancer in patients with a pelvic mass** (2009) *Richard G. Moore, D. Scott McMeekin, Amy K. Brown, Paul DiSilvestro, M. Craig Miller, W. Jeffrey Allard, Walter Gajewski, Robert Kurman, Robert C. Bast, Jr, and Steven J. Skatesh* DOI: *10.1016/j.ygyno.2008.08.031*
Validation study	**Validation of the Cut-points Recommended for ROMA Using the Roche Elecsys CA125 and HE4 Assays** (2018) *Kendall W Cradic, Michael A Lasho, and Alicia Algeciras-Schimnich* PMID: 29531002

8.6. Release notes

The release notes for each publicly available version of the device can be found on the Evidencio website page for the ROMA™: https://www.evidencio.com/models/show/9927 selecting the correct device, and clicking on Release Notes. It is recommended to read these notes after a version update to see if these changes are relevant to you.

9. Implementation of the model through an API

The ROMA™ can be used through Evidencio's API to allow for (automated) calculation of the risk of ovarian malignancy. In the case of use of the MDSW through the API, the user should take into account the different inputs for the model, in order to properly interpret the results.

Instruction 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.

When using the MDSW through the API, the warnings and descriptions given in this document all apply, as does the additional information. The information for use included in this document regards both use through the website as well as use through the API, as long as the API is properly implemented. The API is only intended for authorized users.

10. Using the model on the Evidencio website

Using the tool on the Evidencio website, requires a stable internet connection. The tool was tested on the following browsers and will run on these versions and higher;

- Personal computers or laptops using the following browsers:
  - Safari (version 17.5 and higher)
  - Chrome (version 126.0.6478.127 and higher)
  - Firefox (version 128.0 and higher)
  - Edge (version 126.0.2592.102 and higher)
- Tablets or smartphones running on the next operating systems:
  - IOS (version 17.5.1 and higher)
  - Android (version 13 and higher)

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

The medical device cannot be used in combination with Internet Explorer. The personal computers, laptops, tablets or smartphones used should at least be able to have an internet connection and use the browsers mentioned above. The minimal screen resolution should be 800x600.

Furthermore, the model 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 model are adhered to.

The Evidencio MDSW models 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 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 model is only intended for use in settings where the usage and result of a model are never immediately needed.

10.1. General model landing page

The medical device model on the Evidencio platform is shown in **Figure 1**. The model landing page contains the following sections, that are indicated in **Figure 1**.

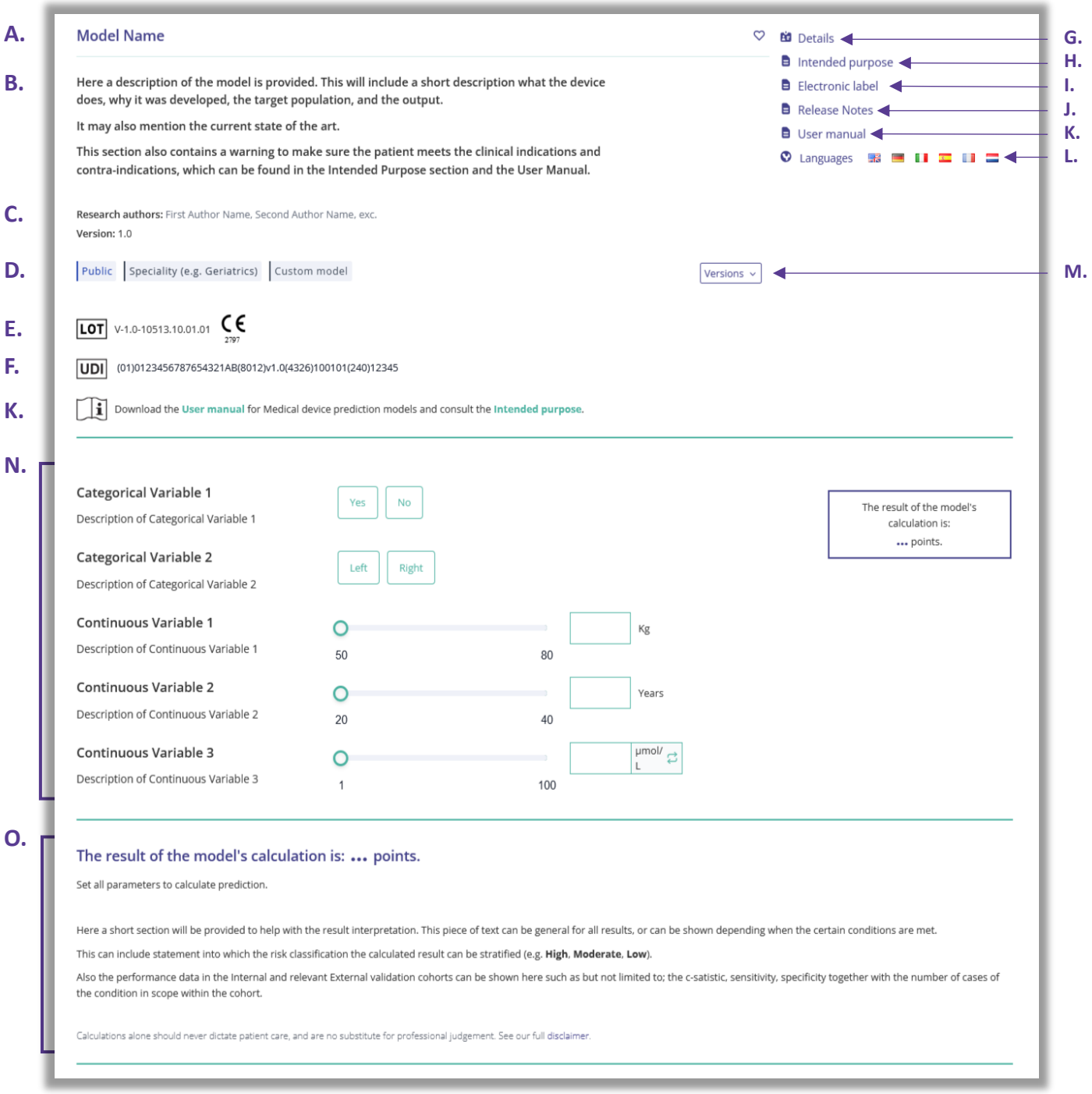

Figure 1. Example of a model landing page on the Evidencio website.

A. Model title

This is the title and name of the model

B. Model description

This is a short description of the model.

C. Research Authors

These are the research authors of the paper that originally published the model.

D. Model tags

These are the tags that are assigned to the model. Evidencio has the following status tags: “Draft”, “Public”, “Private”, “Under review”. Evidencio has the following model 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 model version, the model identifier, and the model 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-PI number

For a description of the UDI-PI number; see **section 5.2** on **page 5** of this manual.

G. Details button

On the top right of the model 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 model. 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 model 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.

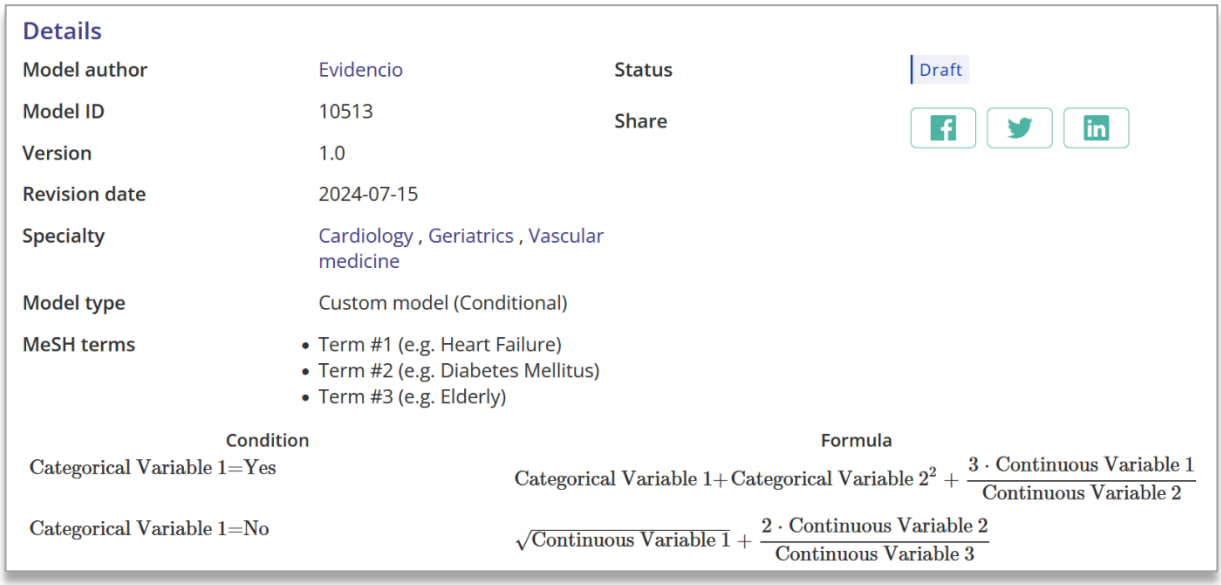

Figure 2. Example of first part of detail section.

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 model. Additional information is provided on the methods used to develop and/or validate the model. An example of the Study characteristics section can be seen in **Figure 3**.

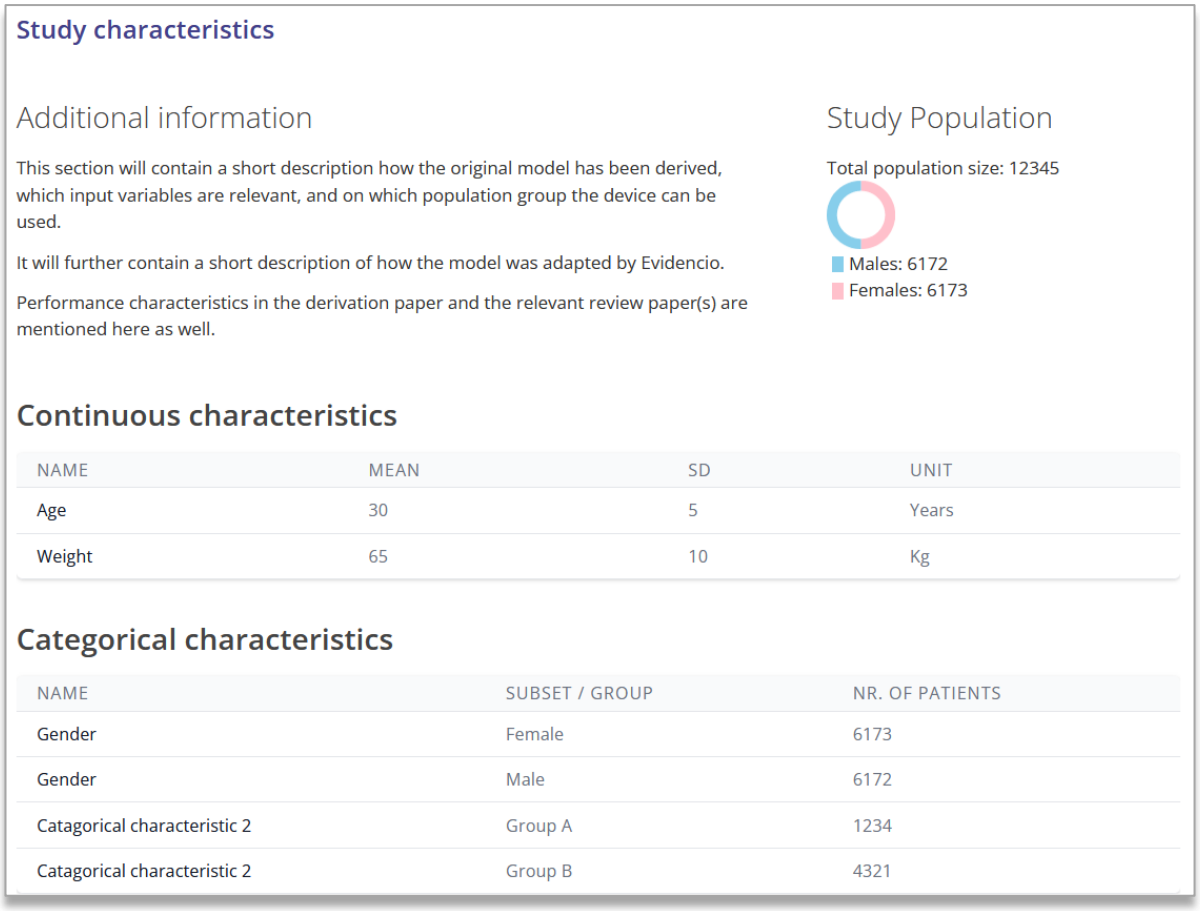

Figure 3. Example of the study characteristics section under the Details tab.

Supporting publications & Related files

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

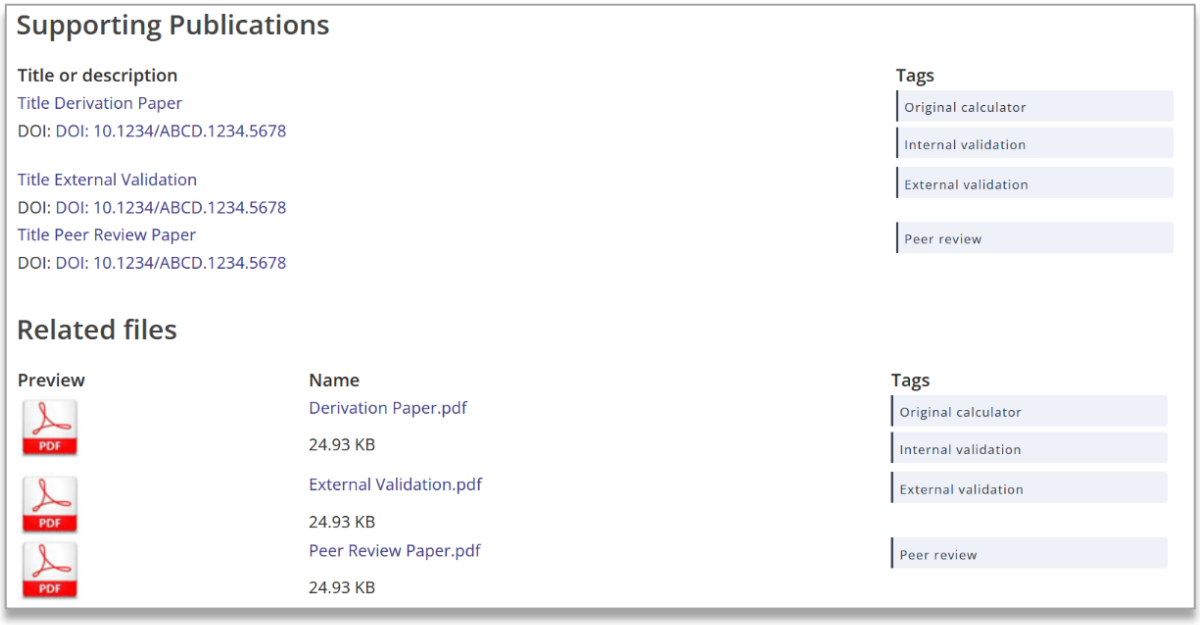

Figure 4. Example of the Supporting publication & Related files section under the Details tab.

Tags are attached to the different files to identify their link with the model. Examples of relevant tags are a.o.; “Peer review”, “Internal validation”, “External validation”, and “TRIPOD”. Publications that have the tags: “Internal validation” or “External validation”, contain the performance characteristics of the device. Figures and tables which help to interpreted the results may also be provided here.

H. Intended purpose

Under this tab, the intended purpose can be found, containing a lot of information regarding the model, 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**.

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 example of the electronic label is shown in **Figure 5**. The electronic label is unique for each model comprising the ROMA™.

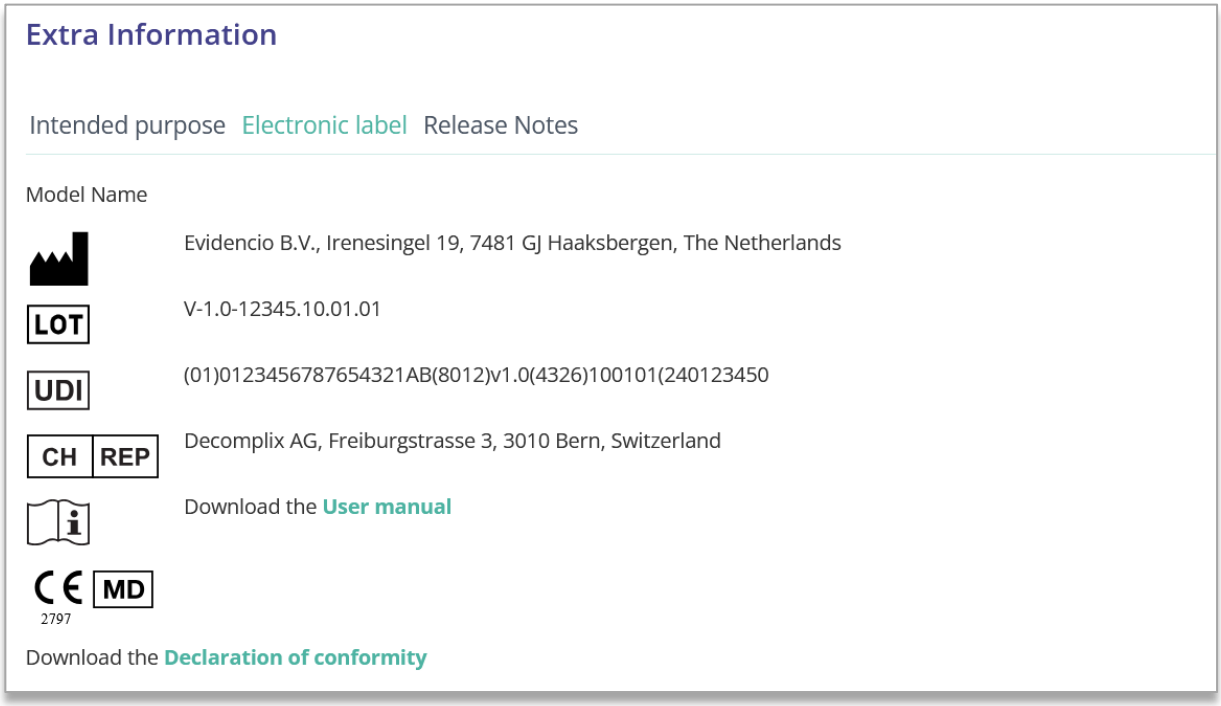

Figure 5. Example of an electronic label under the Electronic Label tab.

J. Release notes

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

The ‘Release Notes’ button opens a pop-up with the latest release notes of the model. Here you can find a list of the most significant changes over the different versions of the model. 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 model on the Evidencio model page, 2) on the right of the model 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.

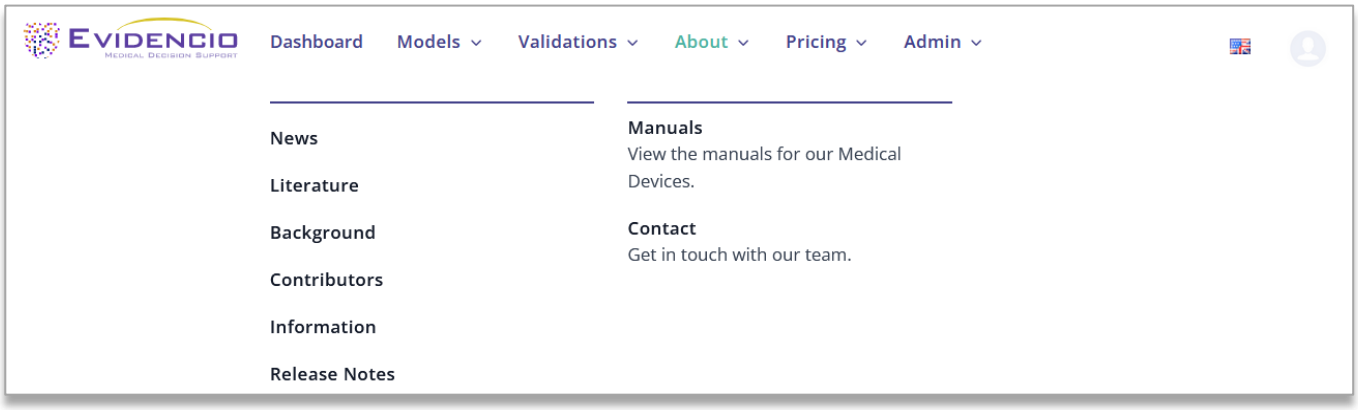

Figure 6. The drop-down menu where the user manual page can be found.

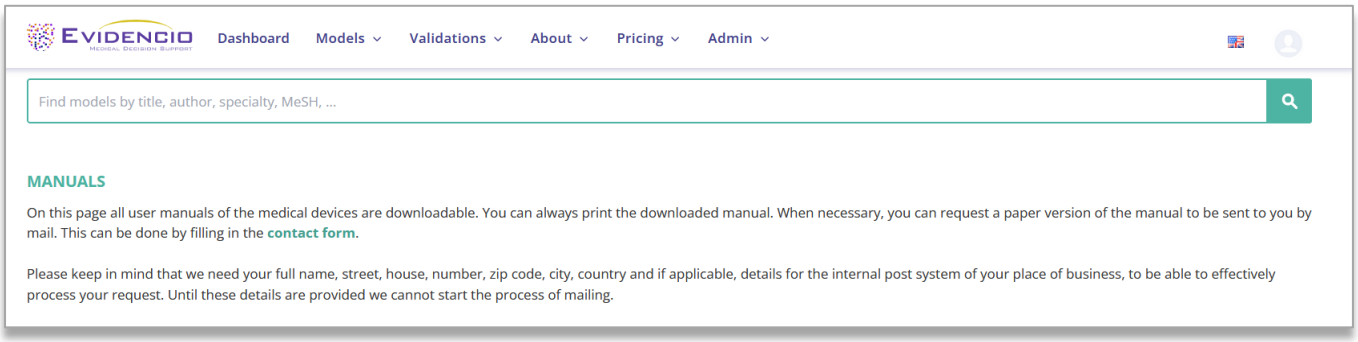

Figure 7. The user manual page for all user manuals.

L. Languages

The standard language on the Evidencio website is English. When other languages are available, these can be selected here. The list of languages may be different between models and may change when in time more languages will become available. Currently the ROMA™ and its user manual are available in German, French, Spanish, Italian, Dutch, and English.

Please note that, if a language is selected, only the user interface of the specific model 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. Model & version selection

Clicking on the Version tab allows the user to select the different model and version of the ROMA™ for a list as displayed in **Figure 8**. Please note that the model currently selected is not presented in the dropdown menu.

Figure 8. Example of the model selection tab.

N. Input section

The Evidencio platform allows two separate input variables; categorical variables and continuous variables.

Categorical variables

In the example shown in shown in **Figure 9** and **Figure 10**, the example **Categorical Variable 1** concerns a categorical variable. The input that is wished to be used can be entered by clicking on either button. The selected button changes to green, as seen in **Figure 10**.

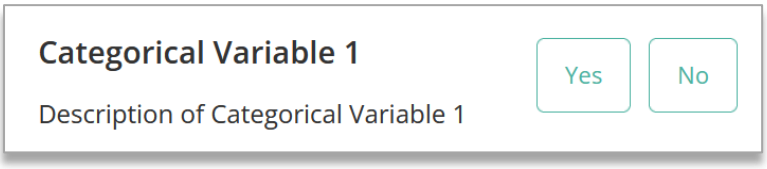

Figure 9. Example of a categorical variable, no button has been clicked and thus no input has been provided by the user.

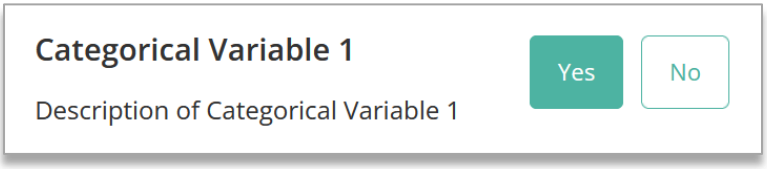

Figure 10. Example of a categorical variable, where the "Yes" button has been clicked.

Continuous variables

In the example shown in **Figure 11**, the **Continuous Variable 3**, exemplifies a continuous variable. The plausible ranges for which the model is tested and deemed valid are used.

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 10.2 mg/dL is entered for the **Continuous Variable 3**).

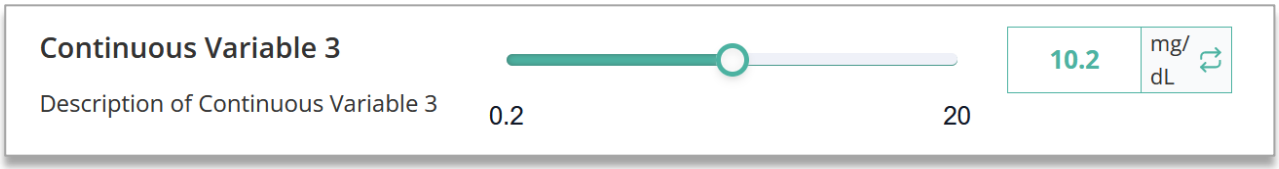

Figure 11. Example of a continuous variable, where "10.2 mg/dL" has been entered.

Unit conversion

Sometimes it is possible to use a unit conversion, by clicking on the unit when the green arrows are present. See **Figure 12** below where the unit has been clicked and switched.

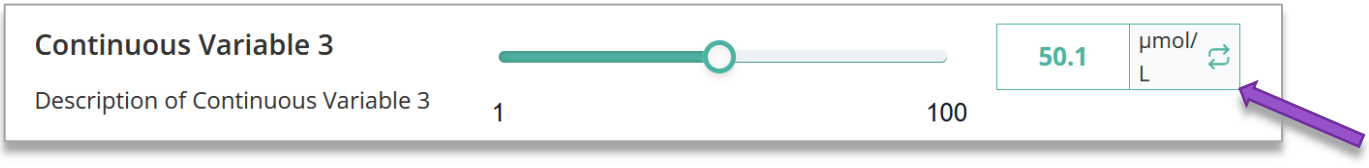

Figure 12. Example of a continuous variable where "50.1 $\mu mol/L$" has been entered.

Details on variable measurements

Directly underneath the name for each variable, additional details can be provided on the methods required to enter the correct value for each variable. Details may include but are not limited to; more detailed explanation of the variable, the ranges of the variables (for healthy individuals), or a description when a continuous variable should be true or false.

O. Result section

At the bottom of the page, the results of the model 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, a result will 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, a risk stratification is provided based on the calculated result. Additional information about this stratification and the classification as found in the derivation and important validation cohorts may also be provided. An example of the information is shown in **Figure 13**.

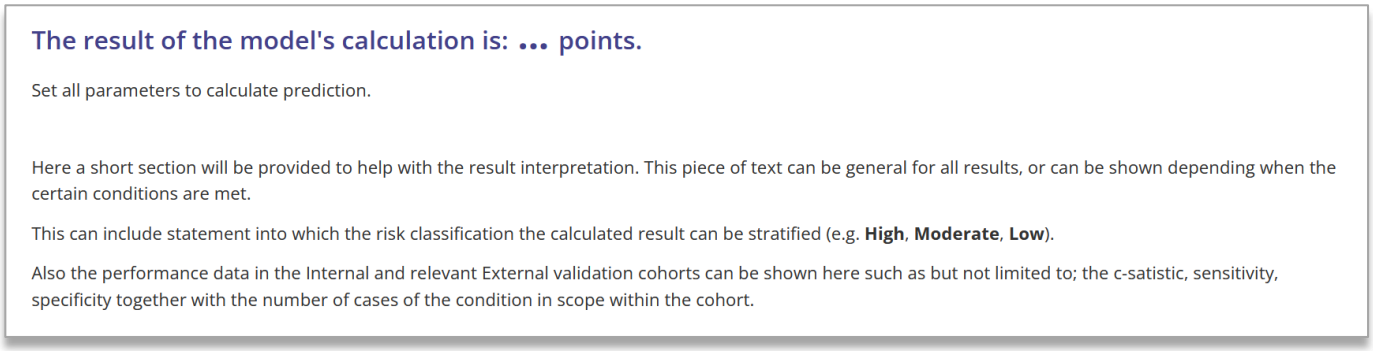

Figure 13. Example of the result display and information section.

11. Manufacturer details

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.

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