User manual

for

INFLUENCE 3.0

Version 1, MAY 2024, in English

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 INFLUENCE 3.0. 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 here: https://www.evidencio.com/disclaimer

3. Warnings

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 professionals in a clinical setting, and is not for use by the patient on their own

Always read the intended use before using this tool.

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.

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

4. 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.

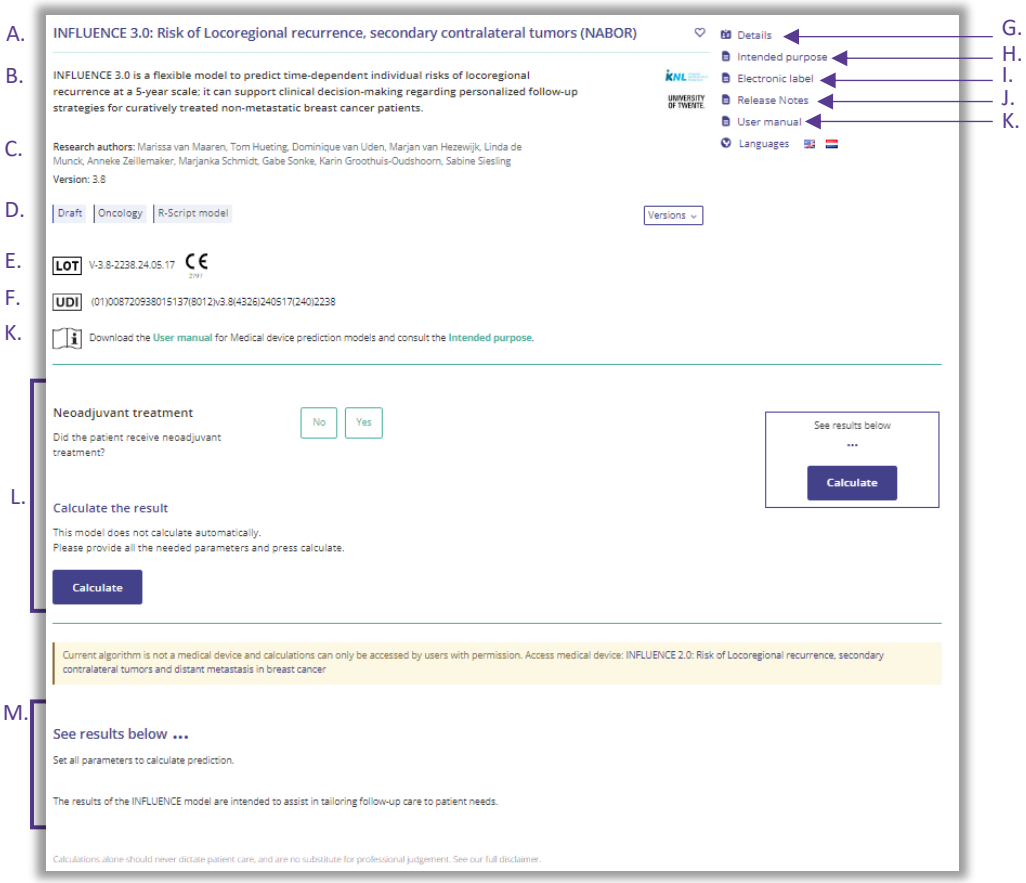

Figure 1. An example of a model landing page.

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 number

The UDI number is an international tool that helps users identify and find information on products. UDI stands for Unique Device Identifier. Evidencio's UDIs have the following format:

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

The UDI-DI 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

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.

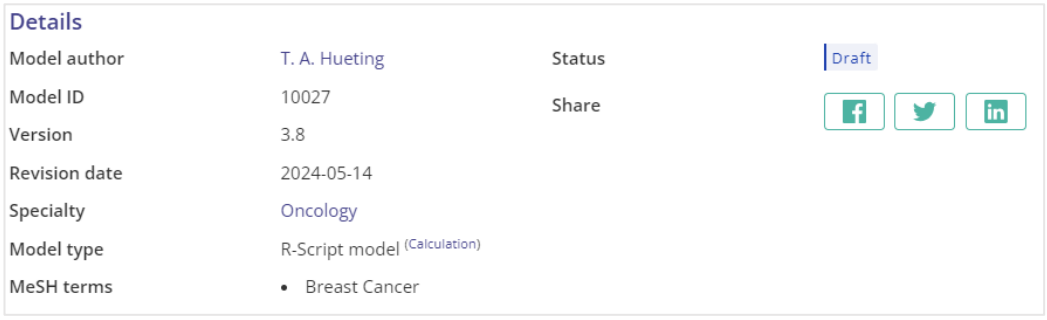

Figure 2. The model details.

Study characteristics

Below the 'Details section' the section labeled '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. As of the writing of this manual, the paper describing the derivation of the INFLUENCE 3.0 has not yet been published, once it has been published, it will be added in the section on supporting publications. Currently, the document for the INFLUENCE 2.0 is shown.

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 3.

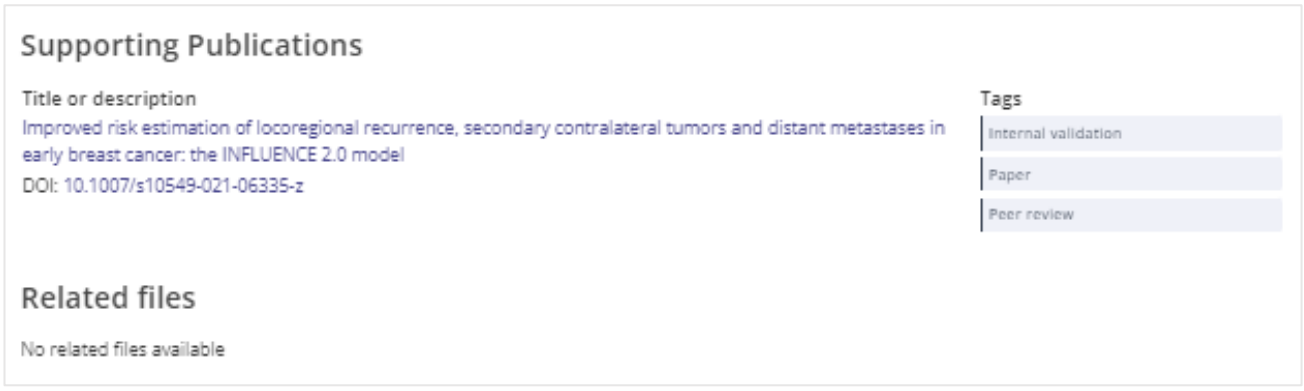

Figure 3. An example of Supporting publications & related files.

H. Intended use button

Intended medical use

The INFLUENCE 3.0 is intended to be used by professional users who are capable of operating the device and interpreting its results. It can be used to estimate the time-dependent risk of locoregional recurrence and second primary contralateral breast cancer for curatively treated non-metastatic breast cancer patients.

The INFLUENCE 3.0 consists of two somewhat different models, for patients who had neoadjuvant systemic treatment (NST) patients and patients who did not have neoadjuvant systemic treatment (non-NST).

For the NST patients, the INFLUENCE 3.0 combines Age, method of detection, DCIS component, axillary lymph node dissection, pathologic complete response, sublocation, Differentiation grade, HER2 status, hormone receptor status, hormonal therapy status and relapse free time.

For the non-NST patients, the INFLUENCE 3.0 combines Age, Method of detection, Clinical tumor Stage, Clinical nodal stage, Sublocalisation, Histological tumor type, Differentiation grade, HER2 status, Hormone receptor storage, Surgery type, Direct reconstruction status, Chemotherapy use, Radiotherapy use, Hormonal Therapy Use, Anti-HER2 Therapy use and Relapse free time.

In both cases, the algorithm uses the inputs to provide an estimate of the time-dependent risks for Locoregional recurrence and contralateral breast cancer in patients with curatively treated non-metastatic breast cancer.

The device is intended to be used for curatively treated non-metastatic breast cancer patients. The result of the INFLUENCE 3.0 is intended to be reviewed and interpreted by/together with a qualified medical specialists, as well as being used for a patient selection aid, to allow patient and physician to come to an informed decision regarding the planning of follow-up care.

The INFLUENCE 3.0 is not intended to replace clinical decision-making, it can only provide information to the user on the estimation of the risks of locoregional recurrence and Second primary contralateral breast cancer. The user can use this information to support clinical decision-making regarding personalised surveillance. In practice, this typically entails decisions surrounding time between follow-up meetings.

Clinical Benefit

The INFLUENCE 3.0 is intended to assist patients with relevant and specified clinical outcome parameters. Concretely, this is achieved by estimating a risk in order to support clinical decision-making aimed at curatively treated non-metastatic breast cancer patients, in order to support clinical decision-making regarding patient prognosis. Correct functioning of the INFLUENCE 3.0 can result in these clinical benefits:

- The INFLUENCE 3.0 can assist in risk stratification for patients
- Risk stratification can reduce the burden of medical follow-up procedures by helping in the individualisation of the follow-up plan.
- Risk stratification can reduce the unnecessary consumption of (scarce) medical resources, decreasing costs and increasing their availability for high risk patients.

Intended target population and exclusion

The INFLUENCE 3.0 is intended to be used only for a specific group of patients, corresponding to the below indications and contra-indications.

Clinical indication

The INFLUENCE 3.0 should be used for patients who meet the following inclusion criteria:

- Women surgically treated for primary invasive nonmetastatic breast cancer
- Patients should be at least 18 years or older

Contra-indications

The INFLUENCE 3.0 should not be used for patients who meet one or more of the following exclusion criteria:

- Patients with synchronous breast cancer
- Male patients
- Patients whose breast cancer was detected through incidental findings
- Patients with positive tumor margins after surgery
- Patients with Hereditary Breast Cancer
- Patients younger than 18 years old

NST Group:

- Patients who only received neoadjuvant radiation therapy or targeted therapy without chemotherapy

The INFLUENCE 3.0 is explicitly not meant to be used for treatment decision-making, because information on treatment in the model was derived from a retrospective database, meaning that treatment allocation was not random.

User profile
The INFLUENCE 3.0 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.

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.

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.

Functioning, physical principle
The MDSW's underlying mathematical formula is a combination of Random Survival Forest models and Cox 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 INFLUENCE 3.0 are provided in the instructions for use. Entering the details for an individual in the MDSW initiates the estimation of the risks of locoregional recurrence and second primary contralateral breast cancer.

I. Electronic label button

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 4.

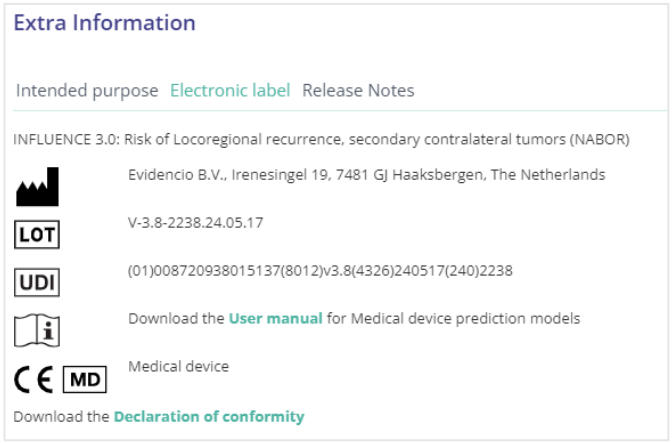

Figure 4. Example of the electronic label

J. Release notes

The 'Release Notes' button opens a pop-up with the latest release notes of the model. Here you can find what has changed over the last versions of the model. Additionally, if there are any known residual anomalies the user should be aware of, they are listed here.

K. User Manual

This user manual can be found in three places: 1) under the short description, 2) on the right of the model page, and 3) in the electronic label. 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 5. The user manual page is shown in Figure 6.

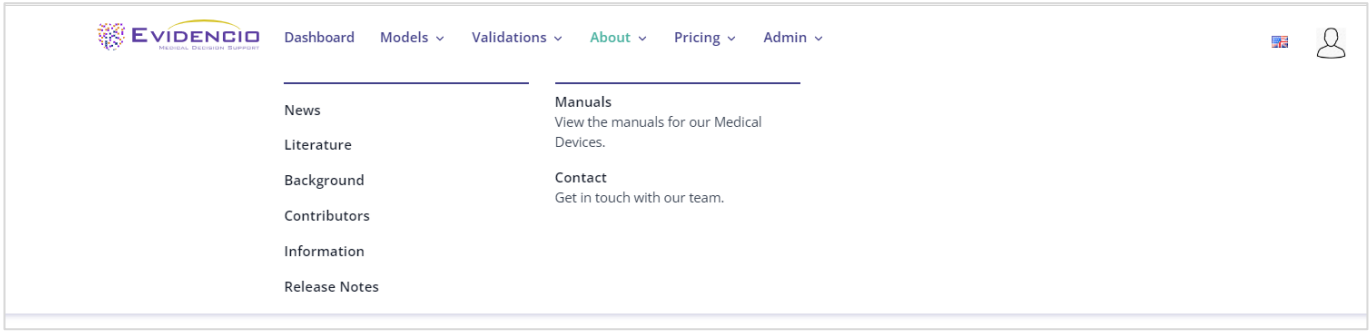

Figure 5. The drop-down menu where the user manual page can be found.

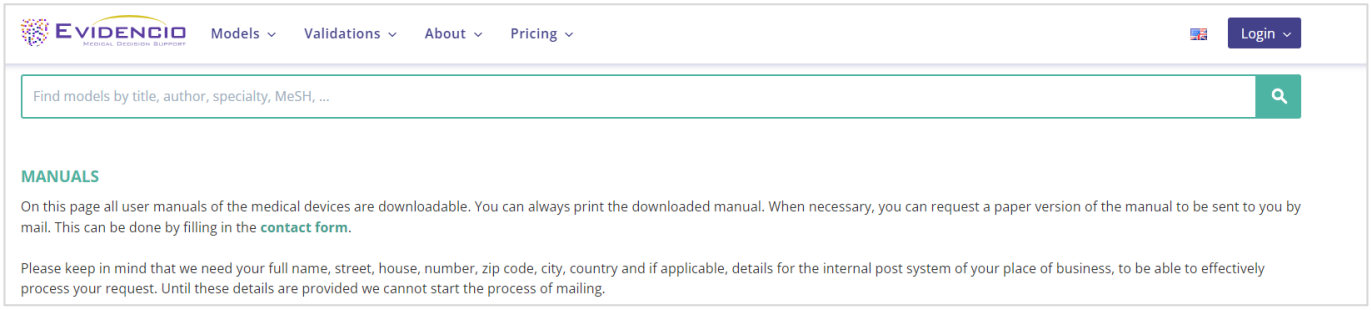

Figure 6. The user manual page for all user manuals.

You (The user) can always print this downloaded manual. When necessary, you can request a paper version of the manual to be sent to you by mail. Evidencio's contact details are listed in Chapter 6 of this user manual.

L. Input section

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

Categorical variables

In the example shown in Figures 7 and 8, the **Neoadjuvant treatment** variable concerns a categorical variable. The version that is wished to be used can be entered by clicking on either button. The selected button changes to green, as seen in Figure 8.

Figure 7. The variable for Neoadjuvant treatment, where no button has been clicked, and thus no input has been provided by the user.

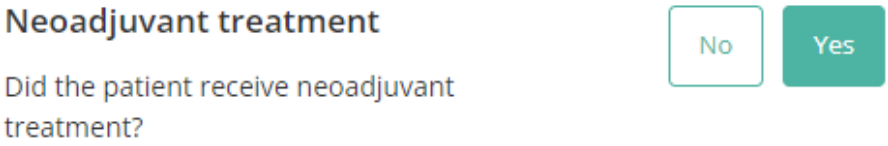

Figure 8. The variable for Neoadjuvant treatment, where the "Yes" button has been clicked.

Continuous variables

In the example shown in Figure 9, the **Age** variable, exemplifies a continuous variable. The plausible ranges for the variables are used for the model.

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 50 is entered for **Age**).

Figure 9. The variable for Age, where "50" 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. In Figure 10, the details below **Hormone receptor status** explains how the variable should be interpreted.

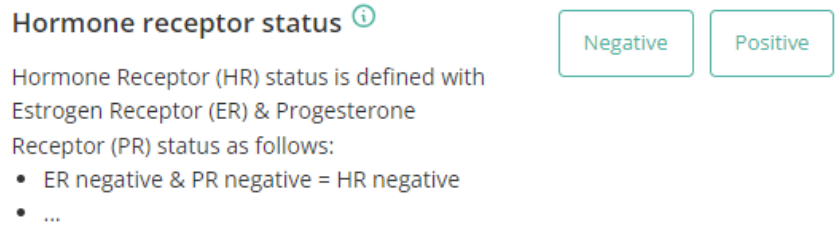

Figure 10. An example on how additional information can be provided for a variable.

M. Result section

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

Result calculation

When all variables are filled in, a result will be calculated. No risk is displayed until all variables are filled in. The result section indicates *"Set all parameters to calculate prediction."*

Result interpretation

In the result interpretation, a risk stratification is given based on the risk score. An example of the information is shown In Figure 11.

Figure 11. The result information

Relevant information for correct use of the model

At the bottom of the page, there is a link to Evidencio's terms and conditions of use, the privacy policy, and the disclaimer.

5. Use of Medical devices

In general, and unless explicitly stated otherwise, CE-marked tools on Evidencio are only to be used by professionals in a clinical setting, and are not for patient use. For the INFLUENCE 3.0, the results can be used by a professional together with their patient, as long as the medical professional provides the proper medical context to understand and interpret the result.

To use the tool, Evidencio requires a stable internet connection and runs on the following devices:

- Personal computers or laptops using the following browsers:
  - Safari (the latest three versions)
  - Chrome (the latest three versions)
  - Firefox (the latest three versions)
  - Edge (the latest three versions)
- Tablets or smartphones running on the next operating systems:
  - IOS (the latest three versions)
  - Android (the latest three versions)

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 SaMD 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.

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

6. 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.
Contact details of your competent authority can be found here: https://www.ema.europa.eu/en/partners-networks/eu-partners/eu-member-states/national-competent-authorities-human

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:

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