Cardio Explorer

Instructions for use

Cardio Explorer®
Software version 2.0

CE

Legend

Symbol	Definition
CE	CE mark
	Manufacturer
	Caution: A potentially hazardous situation which could result in minor or moderate injury or material damage
IVD	In-vitro diagnostic medical device
EC REP	Authorized Representative in the European union

Abbreviation	Term
AUC	Area Under the Receiver Operating Characteristic Curve
ROC	Receiver Operating Characteristic
CCS	Chronic Coronary Syndome
CAD	Coronary Artery Disease
ESC	European Society of Cardiology
PPV	Positive Predictive Value
NPV	Negative Predictive Value
SaMD	Software as a Medical Device

Table of Contents

1. Cardio Explorer

1.1. Intended purpose

Cardio Explorer is an IVD Software as a Medical Device (SaMD) intended to assist healthcare professionals in the diagnostic assessment and risk stratification of adult patients evaluated for suspected chronic coronary syndrome (CCS). For this purpose, it requires as an input routinely collected clinical and biological markers. The result is provided as a numerical estimate of the clinical likelihood of the patient having obstructive coronary artery disease (CAD), in line with medical guidelines for the management of CCS.

1.2. Intended users and use environment

The Cardio Explorer is intended to be used by healthcare professionals for evaluating patients suspected of having CCS, typically in a professional healthcare environment.

A healthcare professional that has basic IT knowledge and has read these Instructions for Use does not need any additional training to use Cardio Explorer.

1.3. Intended patient population

Cardio Explorer is intended to be used in adult patients (18 years of age or older) undergoing evaluation for suspected CCS, in whom the physician seeks to estimate the clinical likelihood of obstructive coronary artery disease (CAD) prior to diagnostic imaging or invasive testing.

The device is suitable for patients presenting in primary care, outpatient cardiology, or emergency department settings that represent a low- to intermediate-risk population with symptoms such as chest pain, dyspnea, or cardiovascular risk factors suggestive of stable CAD, where obstructive CAD is clinically suspected in accordance with current guidelines.

Cardio Explorer is not validated for acute coronary syndrome, pediatric patients, or patients with previous known CAD.

1.4. Contraindications

There are no known specific patient situations that contraindicate the use of the device.

1.5. Limitations of use

Cardio Explorer is intended as an adjunct diagnostic tool and does not replace the clinical judgment of a qualified healthcare professional. The output must not be used as the sole basis for diagnosis or clinical decision-making.

1.6. Adverse events

If any serious incident occurs with Cardio Explorer or that can be related or relevant to it, immediately inform the manufacturer and the competent authority in your Member State.

2. Getting Started with Cardio Explorer

Access Cardio Explorer through a web browser (e.g., Edge, Safari, Chrome) using the link provided by Exploris Health. No installation is required.

2.1. Registration

For first-time access:

1. **Enter** a valid e-mail address and select **Continue**.
2. **Complete** the user registration form.
3. **Enter** the one-time authentication code sent to your e-mail.
4. **Review and accept** the license agreement, and **confirm** your healthcare professional status.

2.2. Authentication

To log in:

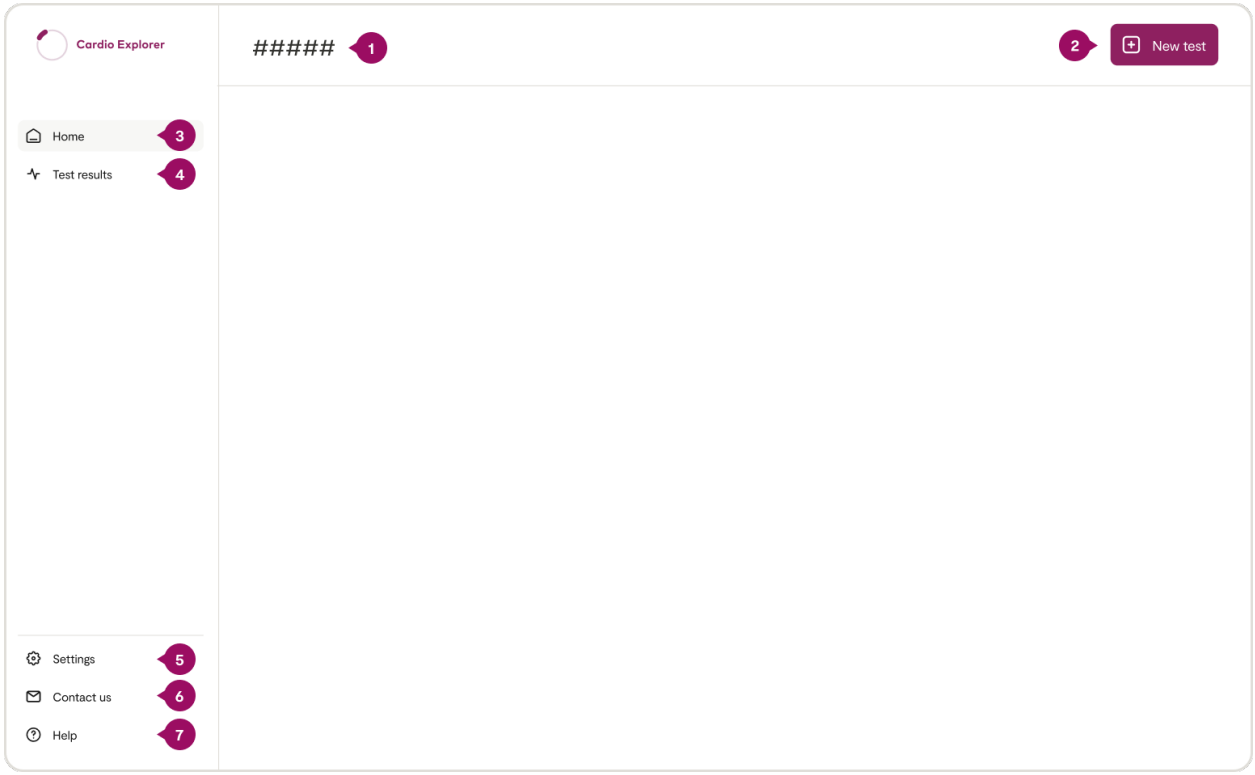
1. **Enter** your registered e-mail address.
2. **Open** the secure authentication (“magic link“) sent to your e-mail.
3. **Enter** the one-time authentication code sent to your e-mail.
4. **Review and accept** the license agreement, and **confirm** your healthcare professional status.

CAUTION

Do not share your authentication link and ensure your e-mail account is secure.

3. Working with Cardio Explorer

After logging in, use the main menu on the left to navigate the application. The New test button is always available in the top-right corner. The numbered elements in the image correspond to the following functions:



1. **Page header** – View the title of the current page.
2. **New test button** – Start a new test.
3. **Home** – Return to the Home page.
4. **Test results** – Access completed and draft tests.
5. **Settings** – Adjust general and account settings.
6. **Contact us** – Reach Exploris Health support.
7. **Help** – Open clinical resources and FAQs.

3.1. Home page

On the **Home** page, you can:

- **Add** a new member to your workspace.
- **Start** a test by clicking **Start your first CAD-CL test**.
- **Watch** the introductory video to learn how to use Cardio Explorer.

3.2. New test

Click **New test** to open the draft form. Complete the required fields as described below.

3.2.1. Input clinical and laboratory values

To input data:

1. **Select** SI units, conventional units, or customized units for each parameter.
2. **Enter** the patient's identification, demographics (age, sex, height, weight), and the required clinical and laboratory values.
3. **Cardio Explorer automatically validates** all input ranges. When connected to a laboratory system, predefined ranges are applied.
4. **Ensure** that all inputs are current and within the specified validity intervals.

CAUTION

Selecting an incorrect unit of measure for the required fields can result in incorrect test results, which could lead to a **delayed or wrong diagnosis** and progression of the disease. Please verify the selected units and entered values.

ANAMNESIS

Variable	Description	Justification	Validity interval
Angina	Classify chest pain based on characteristics and relief.	Symptom classification (typical/atypical) is central to CCS assessment. [ESC Guidelines, 2024]	Up to 24 hours
Nicotine Consumption (NC)	Smoking status defined by recent and past use.	Smoking is a major modifiable cardiovascular risk factor strongly influencing prognosis. [ESC Guidelines, 2024]	Last 30 days
Systolic blood pressure	Latest resting SBP after ≥5 min seated rest.	Hypertension is a key determinant in cardiovascular risk assessment and treatment planning. [ESC Guidelines, 2024]	Up to 30 days
Diastolic blood pressure	Latest resting DBP after ≥5 min seated rest.	Blood pressure measurement is fundamental for assessing cardiovascular health and guiding management. [ESC Guidelines, 2024]	Up to 30 days
Q-wave status in resting ECG	Presence of pathological Q-waves.	Resting ECG findings such as Q-waves provide evidence of prior myocardial infarction. [ESC Guidelines, 2024]	Up to 3 months

MEDICATION

Variable	Description	Justification	Drug classes	Validity interval
Lipid-lowering therapy	Use of statins or non-statin LDL-lowering agents.	Lipid-lowering therapy is a cornerstone in reducing cardiovascular risk in CCS. [ESC Guidelines, 2024]	Statins, Ezetimibe, PCSK9 inhibitors, Bempedoic acid, Inclisiran	Last 3 months
RAAS-inhibiting therapy	ACE inhibitor or ARB.	RAAS inhibitors reduce cardiovascular events in hypertension, HF, and post-MI patients. [ESC Guidelines, 2024]	ACE inhibitors, ARBs	Last 3 months
Beta blocker therapy	Any beta blocker.	Beta blockers reduce myocardial oxygen demand and improve symptoms in CCS. [ESC Guidelines, 2024]	Beta blockers	Last 3 months
Calcium channel blocker therapy	Any calcium channel blocker.	Calcium channel blockers relieve angina and control heart rate or blood pressure. [ESC Guidelines, 2024]	Dihydropyridines (DHP), Non-DHP (rate-limiting)	Last 3 months
Diuretic therapy	Any diuretic.	Diuretics manage blood pressure and symptoms of heart failure or volume overload. [ESC Guidelines, 2024]	Thiazides, Loop diuretics, MRAs	Last 3 months

MEDICATION (CONT'D)

Anti-anginal nitrate therapy	Nitrates for angina.	Nitrates provide rapid relief of angina by vasodilation and reducing myocardial oxygen demand. [ESC Guidelines, 2024]	Organic nitrates	Last 3 months
Anti-platelet therapy	Any antiplatelet agent.	Antiplatelet agents reduce the risk of thrombotic cardiovascular events. [ESC Guidelines, 2024]	Aspirin and P2Y12 inhibitors	Last 3 months
Glucose-lowering therapy	Any glucose-lowering medication.	Glucose-lowering therapy reduces cardiovascular complications in diabetes. [ESC Guidelines, 2024]	Insulin, Metformin, SGLT2 inhibitors, GLP-1 RAs, Sulfonylureas, DPP4 inhibitors	Last 3 months

LAB VALUES

Variable	Description	Justification	Validity interval
Total cholesterol	Total cholesterol from lipid panel.	Total cholesterol is part of lipid profile assessment for cardiovascular risk. [ESC Guidelines, 2024]	Up to 3 months
HDL cholesterol	HDL-C from lipid panel.	HDL cholesterol is inversely associated with cardiovascular risk. [ESC Guidelines, 2024]	Up to 3 months
LDL cholesterol	Direct or calculated LDL-C.	LDL cholesterol is the primary target for lipid-lowering therapy. [ESC Guidelines, 2024]	Up to 3 months
High-sensitivity troponin T	Must be hs TnT, not other forms.	hs TnT detects low-level myocardial injury and provides prognostic information. [ESC Guidelines, 2024]	Up to 24 hours
ALAT	Also ALT or SGPT; liver enzyme.	ALT is a marker of liver function and metabolic health, and is used to monitor statin safety. [J Hepatol, 2005]	Up to 3 months
Pancreatic amylase	Pancreatic-specific isoenzyme of amylase.	Pancreatic amylase helps diagnose and monitor pancreatic disorders. [Yadav et al., Gastroenterology, 2007]	Up to 3 months
Total bilirubin	Total serum bilirubin.	Bilirubin has antioxidant properties and low levels have been linked to higher cardiovascular risk. [Framingham Offspring Study]	Up to 3 months
Albumin	Serum albumin only.	Albumin reflects nutritional status and inflammation; low levels predict worse cardiovascular outcomes. [ARIC Study]	Up to 3 months

LAB VALUES (CONT'D)

Total protein	Total serum protein.	Total protein indicates nutritional and immune status and can reflect chronic disease burden. [Bano et al., J Am Heart Assoc, 2018]	Up to 3 months
Urea	Serum urea (or BUN).	Urea reflects renal function, which is an important prognostic factor in cardiovascular disease. [REACH Registry]	Up to 3 months
Uric acid	Serum uric acid.	Uric acid is associated with hypertension, renal dysfunction, and adverse cardiovascular outcomes. [ESC Guidelines, 2024]	Up to 3 months
Alkaline phosphatase	Serum ALP.	ALP is associated with vascular calcification and adverse cardiovascular events. [Rotterdam Study]	Up to 3 months
Glucose	Fasting or non fasting plasma glucose.	Glucose levels are critical for detecting and managing diabetes, a major cardiovascular risk factor. [ESC Guidelines, 2024]	Up to 3 months
Leucocytes	WBC count from CBC.	Elevated WBC count reflects systemic inflammation, which contributes to atherosclerosis. [ARIC Study, JAMA 2001]	Up to 3 months
MCHC	Mean corpuscular hemoglobin concentration.	MCHC reflects red blood cell hemoglobin concentration; abnormal values can indicate anemia affecting prognosis. [Tkaczyszyn et al., Eur J Heart Fail, 2018]	Up to 3 months

3.2.2. Save an incomplete test as a draft

If you cannot complete the form in one session:

1. **Click Save** (next to **Run test**) to save to progress.
2. **Resume** later by opening the draft from the **Test results** page.

3.2.3. Submit the test form

To submit:

1. **Click Run test** in the top-right corner.
2. Ensure all required fields are complete and valid. Incorrect or missing values will be flagged for correction.

> INFO
>
> Cardio Explorer stores and processes pseudonymized data only in the country-specific Azure Cloud. Data does not leave the country.

3.3. Test results

The **Test results** page lists all completed and draft tests linked to your profile. Each test is associated with a unique patient ID. From this page you can:

- **Open** a completed report by selecting **See report**.
- **Delete or complete** a draft test by selecting it from the list.
- **Search or filter** results using the search bar and filter options.

INFO
If no tests are available, a message prompts you to create a new test.

3.4. Settings

The **Settings** page allows you to adjust preferences and manage your account.

- In **General**, select the application language, default measurement units, and view manufacturer/economic actors' information.
- In **Account**, update your account details or manage workspace members.

INFO
To save your changes, click **Save** in the top-right corner. To exit your session, select **Log out**.

3.5. Contact Us

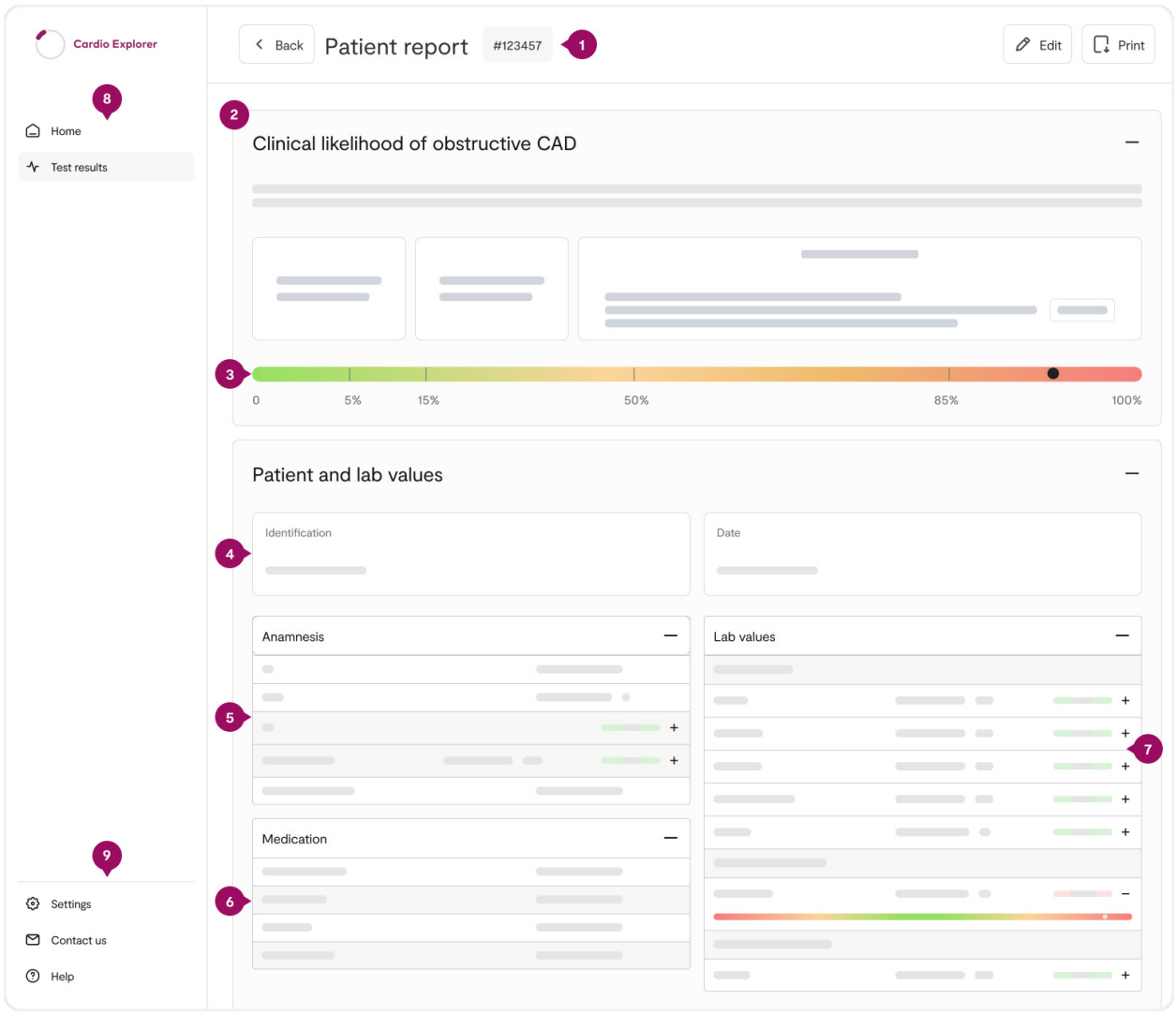
Select **Contact us** to open the Exploris Health website contact section and send a support request.

3.6. Help

Select **Help** to access clinical resources, including FAQs, this Instructions for Use, scientific publications, and other guidance.

3.7. Patient report and results interpretation

3.7.1. Patient report



Once the test is submitted, Cardio Explorer generates a patient report available on the Test results page. The report includes:

1. **Header and navigation** – View the page title, report ID, and control buttons (Edit, Print, Back).
2. **Clinical assessment panel** – See CAD risk class, pre-test likelihood, and recommendations.
3. **Risk indicator bar** – Check the visual marker showing the patient's CAD risk level.
4. **Patient identification and date** – View the anonymized patient ID and report creation date.
5. **Anamnesis section** – Review patient vitals and symptom data (age, sex, blood pressure, BMI, etc.).
6. **Medications section** – Review current therapies (e.g., statins, ACE inhibitors).
7. **Lab values section** – View lab results by system (cardiovascular, liver, kidney) with reference ranges.

8. **Navigation menu** – Move between report pages using the sidebar.
9. **Settings and support section** – Access application settings and support resources.

3.7.2. Results interpretation

The output of Cardio Explorer is expressed as the **clinical likelihood (pre-test probability, PTP) of obstructive coronary artery disease (CAD)**.

1. **Risk classification**

   a. **Very low** (≤5%) – **Defer further cardiac testing**. If clinically relevant **risk factors** (e.g., elevated glucose, lipids, blood pressure) are present, consider **appropriate modification or treatment** in line with preventive care guidelines.
   b. **Low** (>5-15%) - **Defer further cardiac testing**. If clinically relevant **risk factors** (e.g., elevated glucose, lipids, blood pressure) are present, consider **appropriate modification or treatment** in line with preventive care guidelines.
   c. **Moderate** (>15-50%) - Coronary CT angiography (CCTA) for diagnosis and risk stratification is recommended
   d. **High** (>50-85%) - Functional imaging (e.g. stress echocardiography, SPECT, PET or stress CMR) is recommended.
   e. **Very high** (>85%) - Direct invasive coronary angiography is recommended, particularly in the presence of high-risk features or limiting symptoms.

2. **Use of the risk indicator bar**

   a. The color-coded probability bar and marker display the patient's estimated likelihood.
   b. Interpret the patient's value in the context of the thresholds above.
   c. Always cross-check highlighted abnormal lab values that may explain the risk estimate.

3. **Integration with clinical context**

   a. Compare Cardio Explorer results with the patient's symptoms, history, and exam findings.
   b. Do not use Cardio Explorer as the sole basis for diagnosis or treatment.
   c. Adjust decisions if important risk factors not included in the model (e.g., family history of premature CAD, imaging evidence of calcification) are present.

CAUTION

Performing diagnostic decisions based on the wrong results can result in harm to the patient in the form of a delayed or wrong diagnosis and progression of the disease.

Always verify the patient ID in the report. Always compare the test results with the patient's apparent condition and your clinical judgment.

4. Maintenance, updates & requirements

Cardio Explorer requires no user-performed maintenance. Updates are deployed automatically.

Minimum system requirements:

- A stable internet connection
- Latest version of Google Chrome, Safari, or Microsoft Edge
- Device with minimum 2 GB RAM and 1 GHz processor

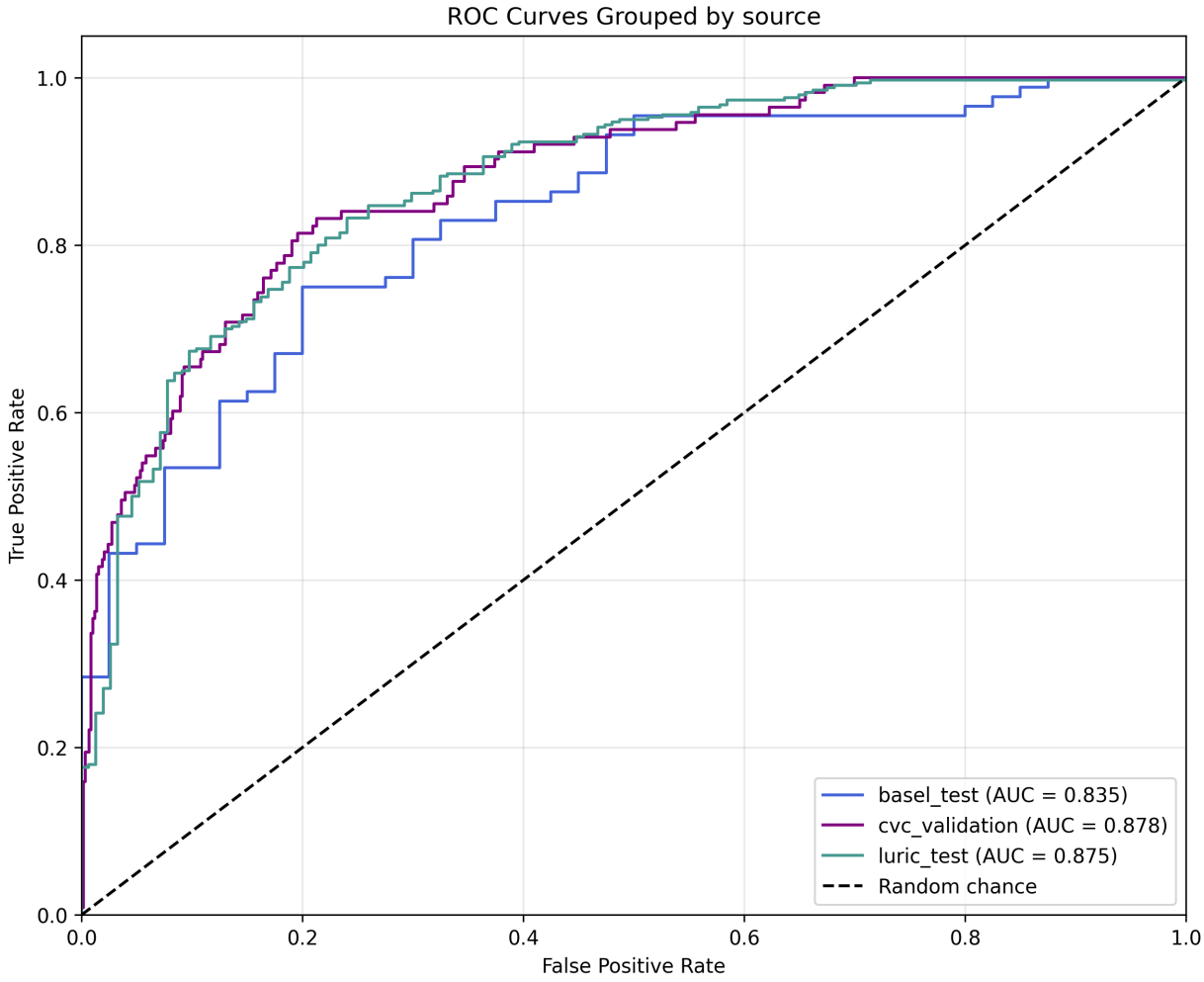
5. Performance characteristics

This section summarizes the performance of the diagnostic algorithm in accordance with IVDR Annex I.

The evidence hierarchy is as follows: Maastricht is the pivotal cohort and matches the intended-use population. BASEL I and LURIC are not pivotal for threshold-based claims but support the generalizability of discrimination (AUC) across different centres and different CAD prevalence and risk spectra. Intended-use sensitivity, specificity, PPV, and NPV at the 15% threshold remain anchored to Maastricht.

To evaluate the algorithm's analytical and clinical performance, three independent clinical studies were conducted. BASEL I and LURIC, evaluating high-risk patients; and Maastricht, focusing on a low- to intermediate-risk outpatient cohort (intended-use population). The algorithm demonstrated consistently high discriminative ability.

AUC values ranged from 0.835 (BASEL I) to 0.878 (Maastricht), indicating strong overall accuracy across diverse settings.



5.1. Performance metrics

Key classification metrics are summarized in Table 1. In the Maastricht cohort (CAD prevalence 16.2%), sensitivity and specificity were well-balanced (83.2% and 78.6%), yielding a negative predictive value (NPV) of 96.0%, which supports safe rule-out in lower-risk patients.

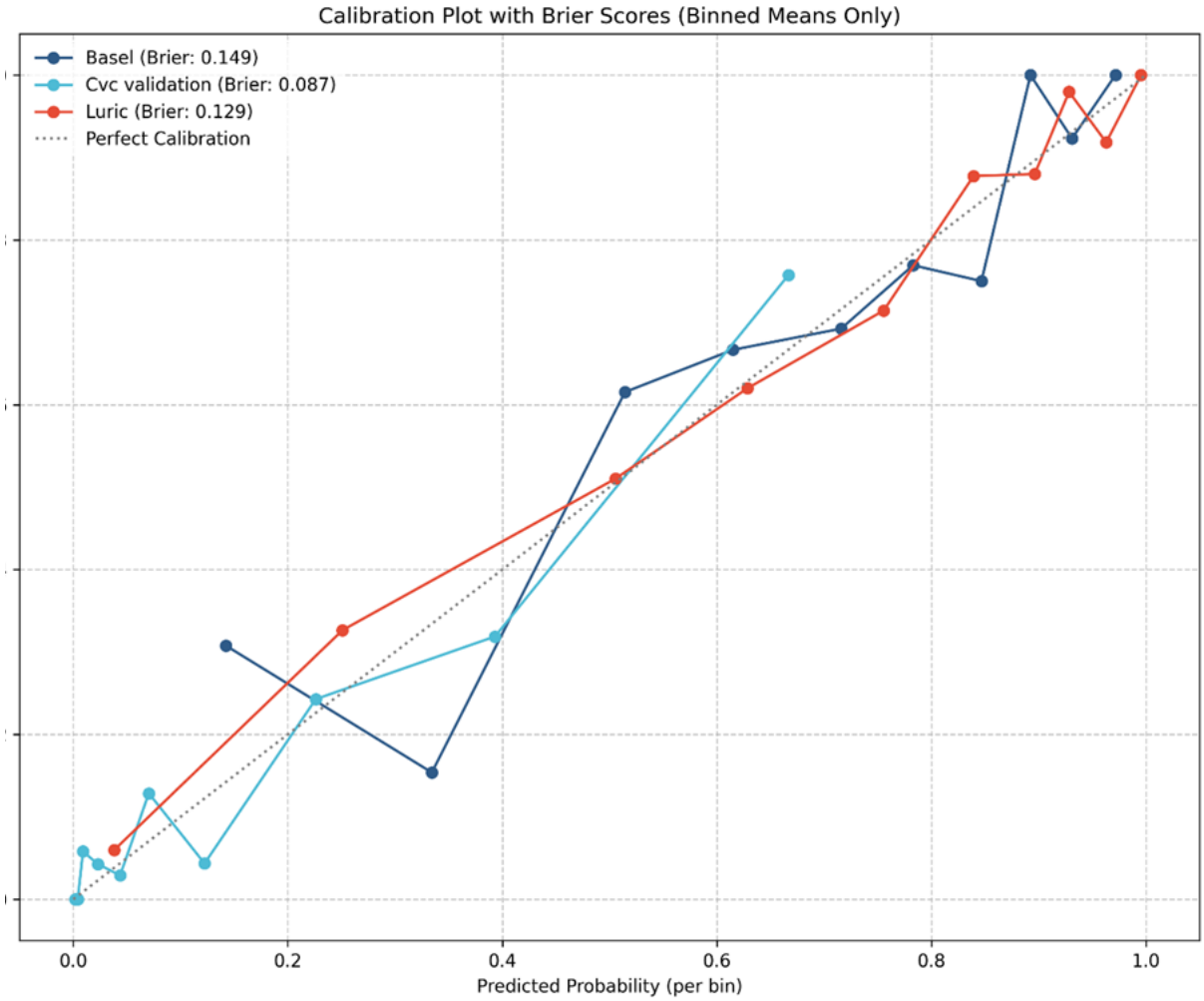
Metric	Basel I	LURIC	Maastricht
AUC	0.835 (0.770–0.895)	0.875 (0.847–0.902)	0.878 (0.848–0.905)
Accuracy	0.727 (0.664–0.789)	0.783 (0.751–0.816)	0.793 (0.767–0.818)
Sensitivity	0.989 (0.966–1.000)	0.979 (0.967–0.991)	0.832 (0.776–0.890)
Specificity	0.150 (0.057–0.245)	0.351 (0.284–0.418)	0.786 (0.757–0.813)
PPV	0.719 (0.653–0.783)	0.769 (0.734–0.805)	0.429 (0.376–0.483)
NPV	0.857 (0.600–1.000)	0.885 (0.815–0.950)	0.960 (0.946–0.975)
F1 score	0.833 (0.784–0.876)	0.862 (0.839–0.885)	0.566 (0.512–0.617)
CAD prevalence (%)	68.8	68.8	16.2
True positives	87	333	94
True negatives	6	54	458
False positives	34	100	125
False negatives	1	7	19

5.2. Calibration

Calibration, reflecting how well predicted probabilities match observed outcomes, was evaluated using Brier scores:

- Maastricht: 0.087
- LURIC: 0.129
- BASEL I: 0.149

These scores indicate good probability calibration, especially in the intended use population.



6. Contact information

Manufacturer:

Exploris Health AG
Industriestrasse 44, 8304 Wallisellen, Switzerland
Telephone number: +41 43 355 80 10
E-mail: info@explorishealth.com
Website: www.explorishealth.com

European Authorized Representative and Importer:

NEMIUS Medical Europe GmbH & Co. KG
Hauptstrasse 17 + 19, 55120 Mainz, Germany
Telephone number: +49 0800 13485 00
E-Mail: info@nemius.com
Website: www.nemius.com