CIBILTECH

Predigraft v1.21

User guide
Healthcare Professional
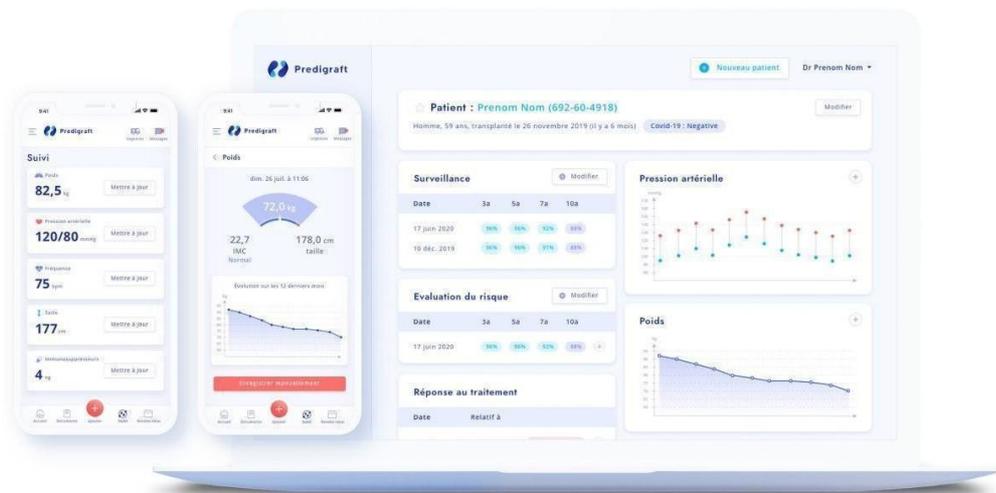
Please read this entire manual carefully before using Predigraft software, a class IIa medical device.

CIBILTECH

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English version

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$C\epsilon$ **2797**

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This manual complies with **EU** Medical Device **Regulation 2017/745.**

Table des matières

1. About this manual

This manual is an integral part of the Predigraft software. It details the presentation of the application, its configuration, and its use.

The electronic version of this manual is available online at www.cibiltech.com. If required, a printed version can be provided upon request at the following address: contact@cibiltech.com.

Note: The screenshots shown in this user manual are examples only, they are not exhaustive and may differ slightly from the views available in the user interface.

Intended Audience: This manual is intended for healthcare professionals.

2. Security Information

Only healthcare personnel who have read these instructions in full are authorized to use Predigraft. For correct and safe use and for all maintenance interventions, it is essential that personnel follow standard safety procedures.

2.1. Primary risks related to the use of Predigraft

The main risks identified are related to the input of data that can result in:

- **An overestimation of the patient's current or expected state of health:**

When an input is erroneous (i.e., falsely reassuring) and an alert is not sent to the healthcare professional, the chances of graft survival are higher than expected.

- **An underestimation of current or expected health status:**

When an input is erroneous (i.e., falsely critical) and an alert is sent to the healthcare professional, the probabilities of graft survival are lower than expected.

Warning: Predigraft is a decision support tool. The clinical assessment of health status by the health professional is not based solely on the prognosis of Predigraft.

2.2. Warnings

- Always ensure that you only open websites via a secure SSL/TLS connection. In this case, the Internet address starts with "https". Simple connections that only start with "http" are a security risk.
- Make sure you are using the latest version of your web browser (compatible with Predigraft *as per the technical specifications chapter*) and regularly update your operating system.
- Keep your passwords up to date. Use a separate password for each application and do not use previous password.
- Do not click on links in emails from unknown senders, as this could direct you to a website containing malware.

2.3. Description of product labeling

The following symbols may be visible in the application or in the documentation:

![CIBILTECH logo]

Symbol/Text	Meaning
🏭	Manufacturer's address
Predigraft v1.21	Device name and version identification
📖	Consult the user manual
CE 2797	CE Marking 2797: identification of the notified body

3. Intended use

Predigraft is a medical device intended to be used as a predictive tool to inform healthcare professionals of the probability of survival of allograft kidney transplants following kidney transplantation. These probabilities, along with available standard clinical data, help describe the condition of the allograft, and provide additional information concerning the patient's care and treatment decisions. Specifically, Predigraft provides probabilities of allograft survival at +3 / +5 / +7 years after evaluation, based on the combination of a set of clinical, biological, and histological parameters.

Predigraft is also intended to be used as a telehealth tool after kidney transplantation to facilitate communication between clinicians and patients by providing a customizable alert system.

Warning: Remote monitoring is not an emergency response system. In the event of a medical problem, patients should contact a healthcare professional or Emergency Medical Services.

3.1. Intended users

The Predigraft solution is intended to be used by:

- Healthcare professionals involved in the treatment and follow-up of kidney transplant patients such as nephrologists, nurses, etc.
- Kidney transplant patients.

3.2. Intended patient population

Patient selection criteria:

- Patient having received a kidney transplant from a living or deceased donor,
- Patient must be at least 18 years old.

3.3. Contraindications

Predigraft cannot be used for the follow-up of patients who have had:

- Previous non-functional kidney transplantation,
- A combined transplant (e.g., kidney - heart transplant, kidney - liver transplant).
- A transplant within the past month.

4. Operating principle and mode of action

4.1. iBox technology

Predigraft was developed using the "integrative BOX" (iBox) technology. The iBox is a predictive algorithm developed by the Paris Transplant Group (INSERM UMR 970; Principal Investigator: Professor Alexandre LOUPY). The algorithm predicts allograft survival at 3, 5, and 7 years after risk assessment with accurate calibration and discrimination (concordance index 0.81; 95% confidence interval - 0.79 to 0.83). It was developed in a cohort of 4000 kidney transplant patients in France and validated in a cohort of 2129 patients in Europe and a second cohort of 1428 patients in three centers in the United State.

4.2. Mode of action

Predigraft is used as a monitoring/risk assessment tool for kidney transplant patients.

During patient follow-up, the healthcare professional uses Predigraft as a tool to monitor his patients. He or she can collect clinical, biological, and histological information and can be informed about the long-term survival probabilities of allografts. The risk of allograft loss is assessed based on biological parameters used in clinical monitoring during standard care, namely: creatinine (to estimate glomerular filtration rate according to dietary modification in renal disease; unit ml/min/1.73 m2) and urine protein to urine creatinine ratio (unit g/g). A report is generated that helps describe the status of the allograft, thus providing additional information in the patient's care and treatment decision.

Predigraft is also used as a remote monitoring tool after kidney transplantation to facilitate communication between the healthcare professional and the patient by providing a customizable alert system. The patient can send clinical information (blood pressure, weight) and biological information (biological and histological reports) to the healthcare professional.

Patient ayant reçu une greffe de rein → Analyse biologique → Télécharger les résultats d'analyse via l'application patient → Réception des analyses sur l'application du professionnel de santé → Création du rapport par le professionnel de santé → Predigraft rapport (web, mobile) → Le professionnel de santé comprend mieux le risque de perte de greffe du patient

5. Technical data/Prerequisites

The Predigraft tool for healthcare professionals is available in SaaS (Software as a Service) mode via the web.
It is compatible with devices supporting the following browsers:

Browser	Compatible version
Chrome	≥ Version 81
Firefox	≥ Version 75
Safari	≥ Version 14
Edge	≥ Version 91

Note: An internet connection is required to use Predigraft. The use of Predigraft does not require any training.

6. iBox Evaluation

Predigraft offers three ways to generate iBox assessments:
 - Manually:
 - Without a biological analysis,
 - From a biological analysis.
 - Automatically.

6.1. Generating an iBox assessment manually

To create an iBox assessment, select a patient and open his patient record.

To generate a new iBox assessment, click on the "New iBox assessment" button in the "Monitoring/Risk assessment" block.

The Monitoring/Risk Assessment item lists the patient's iBox assessments. You can click on one of the rows in the list to access the corresponding iBox assessment. The date corresponds to the date entered in the first step "eGFR" when creating the assessment. The data correspond to:

- Biological data. This icon is always present. It corresponds to the steps 1 and 2 of the iBox evaluation creation.

- Anti-HLA antibody data specifically directed against the graft (DSA). This icon is present if you entered data in step 3 when creating the iBox evaluation.

- Histology data. This icon is present if you filled in data in step 4 when creating the iBox evaluation.

You will then arrive on the "New iBox evaluation" creation page.

Fill in the form step by step, making sure that all required fields are filled in, and then proceed to the next step.
1. Estimated glomerular filtration rate (GFR-e) value,
2. Proteinuria value,
3. DSA value if available, if not check "Not available",
4. Histology information if available, if not check "Not available".

The dates to be filled in during these steps are mandatory. They cannot be earlier than the date of transplantation of the patient. You can choose the date through a calendar.

6.1.1 Without biological analysis

Step 1
If you have chosen to create an iBox assessment for a patient who does not have an imported biology report, click on "Not Available" in the drop-down list.
You must then fill in the patient's eGFR.

Choice 1:
The estimated GFR value must be between 0 and 500. Beyond 120, a message informs you that the iBox calculation will be done with a GFR equal to 120: "Are you sure that the estimated GFR is above 120mL/min/1.73m²? The iBox calculation will use a GFR equal to 120 mL/min/1.73m²."
Error message: "The estimated GFR must be between 0 and 500."

Choice 2:
Predigraft applies the MDRD formula based on creatinine.
The creatinine value is limited:
- Error messages "Creatinine value must be between 1 and 1300 µmol/L." OR "Creatinine value must be between 0.02 and 33.92 mg/dL."
GFR is calculated:
- Success messages: "Estimated GFR is <value> mL/min/1.73m² based on MDRD equation" or if GFR is between 120 and 500: "Estimated GFR is <value> mL/min/1.73m² based on MDRD equation. The iBox calculation will use an estimated GFR equal to 120 mL/min/1.73m²."
- Error messages: "The estimated GFR is greater than 500 mL/min/1.73m²." OR "The estimated GFR is less than 0 mL/min/1.73m²."

Step 2
Next, you must enter the patient's proteinuria.

Choice 1:
Proteinuria value is limited:
- Error message: "Proteinuria must be between 0 and 12 g/g."

Choice 2:
Predigraft calculates proteinuria by the ratio of urine protein to urine creatinine.
Proteinuria is limited:
- Error messages "Proteinuria value must be between 0 and 30 g/L." OR "Proteinuria value must be between 0 and 30,000 mg/L."
Creatinine is limited:
- Error messages: "Creatinine value must be between 0 and 35 mmol/L." OR "Creatinine value must be between 0 and 3959.27 mg/L."
The ratio is then calculated:
- Success message: "The urine protein/creatinine ratio is <value> g/g."
- Error messages: "Urine protein/creatinine ratio must not exceed 12 g/g" OR "Urine protein/creatinine ratio cannot be negative."

Proteinuria date: Predigraft recommends measuring GFR and proteinuria 15 days apart.
Warning message: "The time between the estimated GFR and proteinuria is longer than the recommended 15 days."
Error message: "The time between estimated GFR and proteinuria is greater than 30 days".

Step 3
You can fill in the information about the patient's DSA. If you do not have this information, you can check the "Not available" box.

Choice 1:
Anti-HLA antibody value is limited:
- Error message: "MFI must be between 0 and 20000."

Choice 2:
You must select "Presence" or "Absence".

Choice 3:
You must select "Not Available."

DSA Date: Predigraft recommends measuring GFR and DSA 2 months apart.
Warning message: "The delay between the estimated GFR and the ASD is greater than the recommended 2 months".
Error message: "The time between the estimated GFR and the ASD is greater than 4 months".

Step 4
You can import a histology report from your computer by clicking on "Import a histology report". This histology report will be saved in the patient record.
Then you can fill in the patient's histology information. If you do not have this information, you can check the box "Not available".

Choice 1:
You must select "0", "1", "2" or "3" for each Banff score.

Choice 2:
You must select at least one diagnosis.
The choice "Other" corresponds to any other diagnosis including "Healthy".

Choice 3:
You must select "Not Available".

Histology date: Predigraft recommends measuring GFR and histology at 2 months interval.
Error message: "The delay between the estimated GFR and the biopsy must be less than 2 months".

6.1.2 With biological analysis

Steps 1 and 2
For steps 1 and 2, the biological analysis document is displayed on the left side of the evaluation creation.
You have to fill in the following patient information:
      - GFR-e,
      - Proteinuria.

Notes:
      - The biology report with the most recent date is displayed by default. To select another report, please click on the arrow, a drop-down menu will appear with all the patient's bioassay reports.

- The bioassay reports that appear in the drop-down menu are reports for which you have previously validated the data. In this case, the information in steps 1 and 2 of the iBox evaluation creation form will be pre-filled:

      - GFR date,
      - The estimated GFR,
      - The creatinine level in the blood,
      - Proteinuria date,
      - Protein to creatinine ratio in urine
      - The creatinine level in urine,
      - Protein level in urine.

Step 3

You can fill in the information about the patient's DSA. If you do not have this information, you can check the "Not available" box.

Step 4

You can import a histology report from your computer by clicking on "Import a histology report". This histology report will be saved in the patient's record.
Then you can fill in the patient's histology information. If you do not have this information, you can check the "Not available" box.

Predigraft chooses the iBox algorithmic model corresponding to the input data. The "Create Report" button checks the input data for errors. The generated iBox evaluation contains the results of the iBox algorithm calculation: survival probability at 3, 5 and 7 years post evaluation date (date of step 1).

6.2. Generating an iBox evaluation automatically

You have the possibility to create iBox assessments automatically. Indeed, the score of the iBox algorithm is calculated thanks to the proteinuria and the GFR (the calculation can be done automatically by the MDRD equation), the DSA and the histological data.
Thus, for each new biological report containing urine creatinine and urine protein or for each new value of proteinuria (and addition of DSA and histological data if any) that you will enter on your patient's chart, a new iBox evaluation is automatically created, only if an estimated GFR value is already present on your patient's chart and is less than one month old.
Similarly, for each new creatinine or estimated GFR value added to your patient's record (and DSA and histology data added if any), a new iBox assessment is created automatically, only if a proteinuria value is already present on your patient's record and is less than one month old.

Note: Each automatically created assessment is displayed in the same place as the manually created assessments.

6.3. Viewing the iBox Assessment Results

Once all steps have been completed, a report of the iBox evaluation is displayed.
You will see the results of the iBox calculation: the projected probability of renal graft survival at 3 years, 5 years and 7 years from the date of assessment. The "Comment" panel describes the probabilities.

You can also view the iBox results of the current report compared to the results of the previous report (with the

earliest evaluation date).

You can also view the input data that was used to generate the report. In the "Comment" panel, you can see the probability of agreement of the iBox model used given the input data (c-stat). You can click on the "publication" link to access the Paris Transplant Group publication about the iBox.

You can print or delete this report by clicking on "Delete" and specifying the reason in the confirmation window that appears:
- Incorrect data,
- The patient is not the right one,
- This report is a duplicate.

You can also generate a new iBox evaluation from the biological table. To do so, click on "Biological table" in the patient's record, then on the "New iBox evaluation" button located at the top right of the table.

7. Alerts

Predigraft calculates alerts on clinical, biological and immunological data of patients.

7.1.   Setting up alerts

Predigraft calculates alerts based on alert parameters. There are three levels of parameters:
- (Default) Predigraft level: Cibiltech sets the default values.
- Department level: the department manager can modify the department alert parameters. This setting is then valid for all patients in the department.
- Patient level: the members of the department can change the alert settings for each patient. This setting is only valid for the patient concerned.

7.1.1 Cibiltech settings: default settings

At Predigraft level, Cibiltech has defined default values that departments can modify as soon as they start using the solution.

Blood pressure
- Maximum systolic pressure value: 140 mmHg.
- Maximum diastolic pressure value: 90 mmHg.
- Systolic pressure value for hypertension (Grade 3): 180 mmHg.
- Diastolic pressure value for hypertension (Grade 3): 110 mmHg.

The maximum values for each parameter are:
- Maximum systolic pressure value: 250 mmHg.
- Maximum diastolic pressure value: 130 mmHg.

Weight
- Weight gain: 1 kg.
- Weight loss in one month: 5%.
- Weight loss in six months: 10%.

Maximum values for each parameter are:
- Weight gain: 20 kg

Immunosuppressive drugs
- T0 Tacrolimus minimum threshold: 4 ng/mL
- T0 Tacrolimus maximum threshold: 12 ng/mL
- T2 Ciclosporin minimum threshold: 600 ng/mL
- T2 Ciclosporin maximum threshold: 1200 ng/mL
- T0 Ciclosporin minimum threshold: 50 ng/mL
- T0 Ciclosporin maximum threshold: 150 ng/mL
- T0 Everolimus minimum threshold: 3 ng/mL
- T0 Everolimus maximum threshold: 8 ng/mL
- T0 Sirolimus minimum threshold: 4 ng/mL
- T0 Sirolimus maximum threshold: 12 ng/mL

The maximum values for each parameter are :
- T0 Tacrolimus minimum threshold: 12 ng/mL
- T0 Tacrolimus maximum threshold: 13 ng/mL
- T2 Ciclosporin minimum threshold: 1000 ng/mL
- T2 Ciclosporin maximum threshold: 1500 ng/mL
- T0 Ciclosporin minimum threshold: 250 ng/mL
- T0 Ciclosporin maximum threshold: 300 ng/mL
- T0 Everolimus minimum threshold: 12 ng/mL
- T0 Everolimus maximum threshold: 13 ng/mL
- T0 Sirolimus minimum threshold: 12 ng/mL
- T0 Sirolimus maximum threshold: 13 ng/mL

Blood biology data
- Potassium minimum: 3.2 mmol/L
- Potassium maximum: 5.3 mmol/L
- Minimum hemoglobin: 10 g/dL
- Hemoglobin maximum: 16.5 g/dL
- Minimum HbA1c: 4.5 %.
- Maximum HbA1c: 9 %.
- Platelets minimum: 80 000 /mm3
- Platelets maximum: 550 000 /mm3
- Neutropenia (minimum neutrophils): 1 000 /mm3
- Troponin maximum: 0.6 µg/L
- Minimum INR: 1
- Maximum INR: 5

The accepted thresholds for each parameter are:
- Potassium minimum: [3 - 3.5] mmol/L
- Potassium maximum: [4.8 - 5.5] mmol/L
- Hemoglobin minimum: [8.5 - 10] g/dL
- Maximum hemoglobin: [16 - 17.5] g/dL
- HbA1c minimum: [4 - 6] %
- HbA1c maximum: [6.5 - 13.5] %
- Platelets minimum: [10 000 - 150 000] /mm3
- Platelets maximum: [550,000 - 1,000,000] /mm3
- Neutropenia (minimum neutrophils) : [500 - 1,000] /mm3
- Troponin maximum: [0.6 - 2] µg/L

- INR minimum: [1 - 3.5]
- Maximum INR: [3.5 - 5]

Renal function (estimated GFR, proteinuria)
- Increase in serum creatinine: 50

Maximum values for each parameter are:
- Serum creatinine increase: 9999.99%.
Other parameters
- De novo proteinuria
- Systolic pressure for hypertension (Grade 3): ≥ 180 mmHg.
- Diastolic pressure for hypertension (Grade 3): ≥ 110 mmHg.
- Weight loss in one month: ≥ 5%.
- Weight loss in six months: ≥ 10%.
- Probability of graft survival at 7 years: ≥ 5%.

7.1.2 Service level settings

To set up alerts for the service, click on "Alerts" in the main menu on the left, then on "Alert settings".

Alertes

⚙ Paramétrage d'alertes

Nom	ID	Dernière évaluation	Date de transplantation	Créé le
Sophie Q. Lanreau	68730	26 août 2020	25 août 2015	9 oct. 2020

You arrive on the page "Service alert settings". To modify a parameter: modify the value in the corresponding field then click on the "Modify" button. A confirmation window appears and contains the following information
- The parameter value you have entered,
- The calculation that generates the alert.

Example of modification of the minimum Tacrolimus threshold, at the department level:

Confirmation du changement ✖

Tous les patients du service seront en alerte si :
Concentration résiduelle de Tacrolimus < 5 ng/mL

Annuler   **Modifier pour tous les patients**

Click on "Modify for all patients" to validate or on "Cancel" so that the update of the parameter is not effective.
Once you have updated a parameter, a "Parameter history" button allows you to access the modification history. In this history, you can see the name of the user who modified the parameters, the date of the modification and the list of each alert parameter with its value.
Next to the history button, a message shows the date of the last update of the parameters and the name of the user who performed the action.
Under each parameter that does not have the default value, a text indicates: "Default (Predigraft): <value of Predigraft parameter>".

Tacrolimus : minimum	5	ng/mL	Modifier
	Défaut (Predigraft) : 4		

7.1.3 Patient level settings

To set up alerts for a patient, access the patient record and click on the three small dots next to the patient's name, then click on "Alert settings". This will take you to the "Alert settings: <full name of patient>".
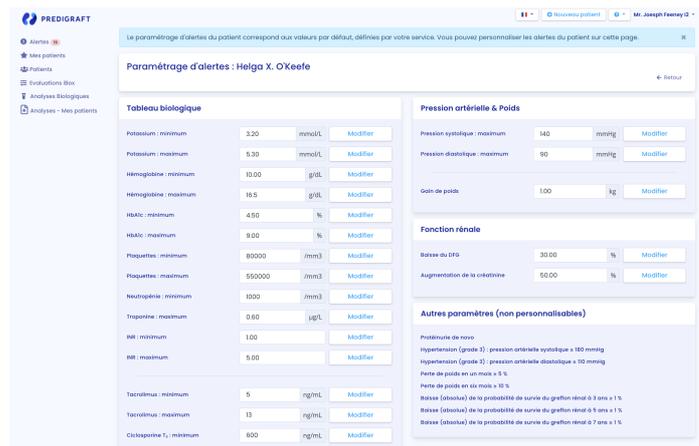
Note: modifying a parameter is done in the same way as modifying a parameter of a service.

You can view the history of the alert settings of a patient by clicking on the three small dots next to the patient's name from his file, then click on "History of settings". In this history, you can see the name of the user who modified the parameters, the date of the modification and the list of each alert parameter with their value.

7.2.   Alert management

If a patient has a data outside the pre-defined alert thresholds, an alert is triggered and is then visible from the patient record.

Each alert contains the date of creation of the alert, the details of the alert and a button "mark as read".
You have the possibility to click on the button "Mark as read", this action means that you have taken into account the alert. The button is changed to "Read at <date and time> by <user>" and this message is visible to all members of the service.
An alert marked as read is moved to the alert history page and accessed by the "Alert History" button on the patient page.

The alert history page lists a patient's alerts in order of most recent first. The history page lists the alerts that have been read (in gray) and the alerts that have not been read (in red). You can read an alert from this page.

8. Notification of your patients' activity

If you are a member of a team, you will receive a daily email about the Predigraft activity of your patients in your "My Patients" list.
This email contains in particular:
        - The number of your patients in the "My Patients" list who have a weight or blood pressure alert.

If you are a department manager, you will receive a daily email about the Predigraft activity of all the patients in your department. This email contains the following information:
        - The number of patients in your "My Patients" list who have a weight or blood pressure alert,
        - The number of your patients not on any of your team members' "My Patients" list who have weight and blood pressure alerts.

Notes: Clinical and biological data are not contained in the email.

If you are a member of a team (with patients in the "My patients" list) or if you are a department head, an email will be automatically sent to you, if one of your patients has an alert on the probability of graft survival at 5 years (decrease in the probability of survival being greater than 5% between two reports).

9. Support/Maintenance

For any questions, requests, or reports of malfunction, please send an email to support@cibiltech.com

MATERIOVIGILANCE: Any incident or risk of serious incident (defined according to article L5212-2 of the Public Health Code) detected during the use of the medical device Predigraft must be reported to the manufacturer at the following address: contact@cibiltech.com

You must report any event to the competent authority of the Member State in which you are established: https://ec.europa.eu/health/sites/health/files/md_sector/docs/md_vigilance_contact_points.pd

10. Personal data

For any questions, requests or statements regarding your personal data, please refer to Cibiltech's Privacy Policy, available online on the company's website: www.cibiltech.com.