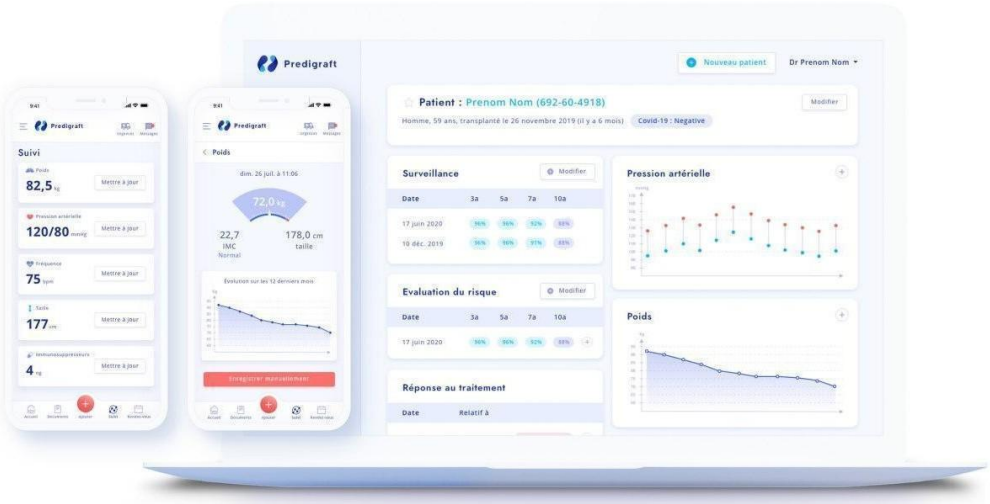
Predigraft v.1.0.0
User Manual

Healthcare Professional



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

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CE 2797

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

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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.

Note: 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 passwords.

- 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:

Symbol/Text	Meaning
	Manufacturer's address
Predigraft v1.0.0	Device name and version identification
	UDI barcode
	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 States.

4.2. Mode of action

Predigraft is used as a risk monitoring/assessment tool.

During patient follow-up, the healthcare professional uses Predigraft as a tool to be informed of the long-term survival probabilities of the allograft. The risk of allograft loss is assessed based on the biological parameters used in clinical follow-up during routine care, namely: creatinine (to estimate glomerular filtration rate according to the MDRD formula; in ml/min/1.73 m^2) and the ratio of proteinuria to urinary creatinine on a sample (in g/g).

Healthcare personnel are informed of the long-term survival estimates for kidney allograft transplants at the time of each patient visit and can decide to follow-up the patient's evaluation with additional information from an allograft biopsy and measurement of donor-specific anti-HLA antibodies. This decision may be made on the basis of:

- Survival probabilities of the kidney allograft,
- Other parameters non captured in Predigraft,
- Preset alerts.

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 79.0.3945.130
Firefox	Version 72.0.2
Safari	Version 13.0.5 (15608.5.11)

The use of Predigraft does not require any training.

6. Authentication/Account creation

When an account is created, the Cibiltech team configures access to the application for two profiles:

1. Team owner
2. Team member

Access rights and functionalities are different for these profiles.

The Cibiltech team creates the "owner" user account and then the team associated with this user. The Cibiltech team creates as many teams as needed. There is one owner per team.

6.1. You are the team owner

When you subscribe, you will receive a link to the "Reset Password" page via email. On this page, enter your email address to receive a reset link. By clicking on the link from your email, you will be redirected to a page where you can enter your password and a confirmation of the password. You are then connected to the application as the "team owner".

6.2. You are a team member

The team owner sends an invitation email to members via the Predigraft interface. If you are in the list of users authorized to create an account on Predigraft, you will receive an invitation link by email.

Click on this link to be redirected to the Account Creation page. You must enter your name, email address (identical to the address to which the invitation was received), password, and password confirmation. You are then connected to the application as a “team member".

6.3. You are a Predigraft user (owner/member)

To activate your account (owner or member), you must:

- Confirm your email by clicking on a link sent to you by email,
- Read and accept the General Terms and Conditions of Use (GTCU).

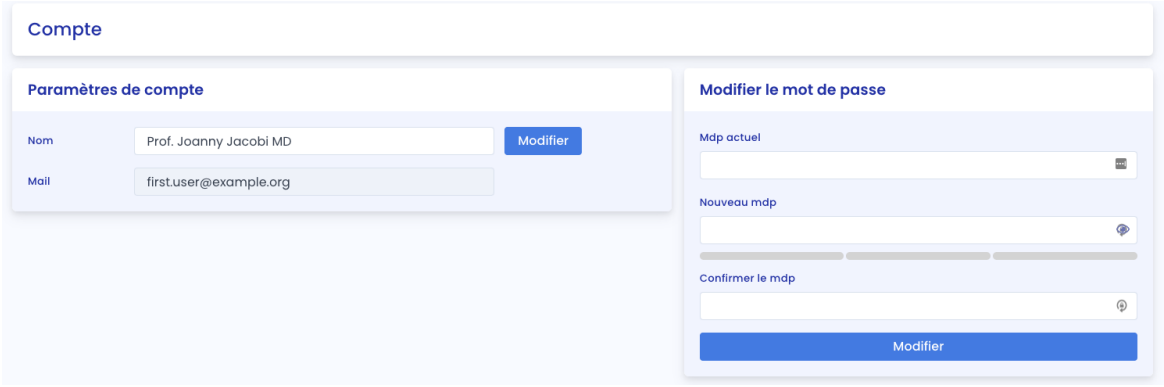
Forgot your password?

If you have forgotten your password, you can click on "Forgot your password?" on the login page. On the password reset page, enter your email address to receive a reset link. By clicking the link from your email, you will be redirected to a page where you can enter your new password and a confirmation of the password.

Warning: Passwords are personal and confidential. They must not be shared with a third party. They are governed by a confidentiality policy.

Account Setup:

Once logged in, you can go to your personal space in the "Account" tab. Here, you have the option to update account details, including your name and password.



7. Team Management

This module allows healthcare professionals to be part of a (hospital) department. The team owner and members have access to the patients of the team or department. The owner and members of the department have access to the Predigraft reports created for each patient in the department. At the time of subscription, the owner will be assigned to a team.

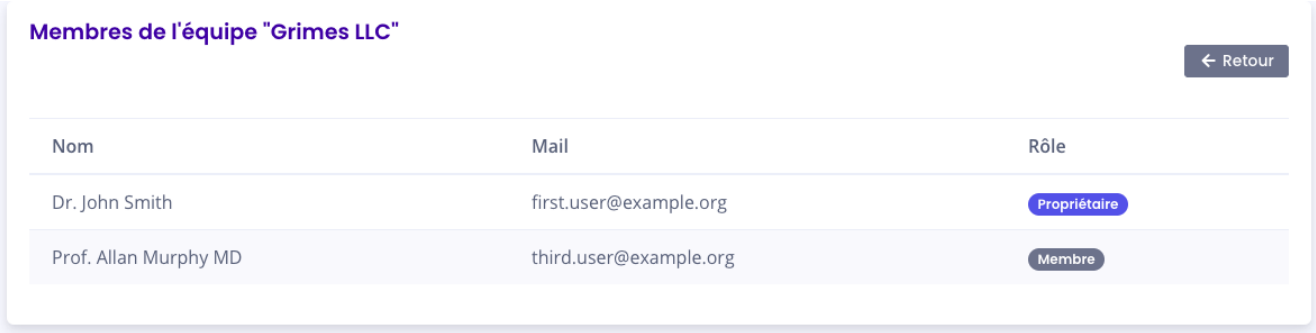
7.1. Team administration

You are a team member

To view the other members of your team, click on your name in the top right corner, click on "My Team" in the drop-down menu, and then click on your team.

On the "Members" page, you can consult the list of team members, including:

- The full name and email address of the member,
- The "owner" badge next to the name of the team owner,
- The "member" badge next to the name of each team member.



You are the team owner

To access the members of your team, click on your name in the top right corner, click on "My Team" in the drop-down menu, and then click on your team.

In the **"Invite to the team"** section you can:

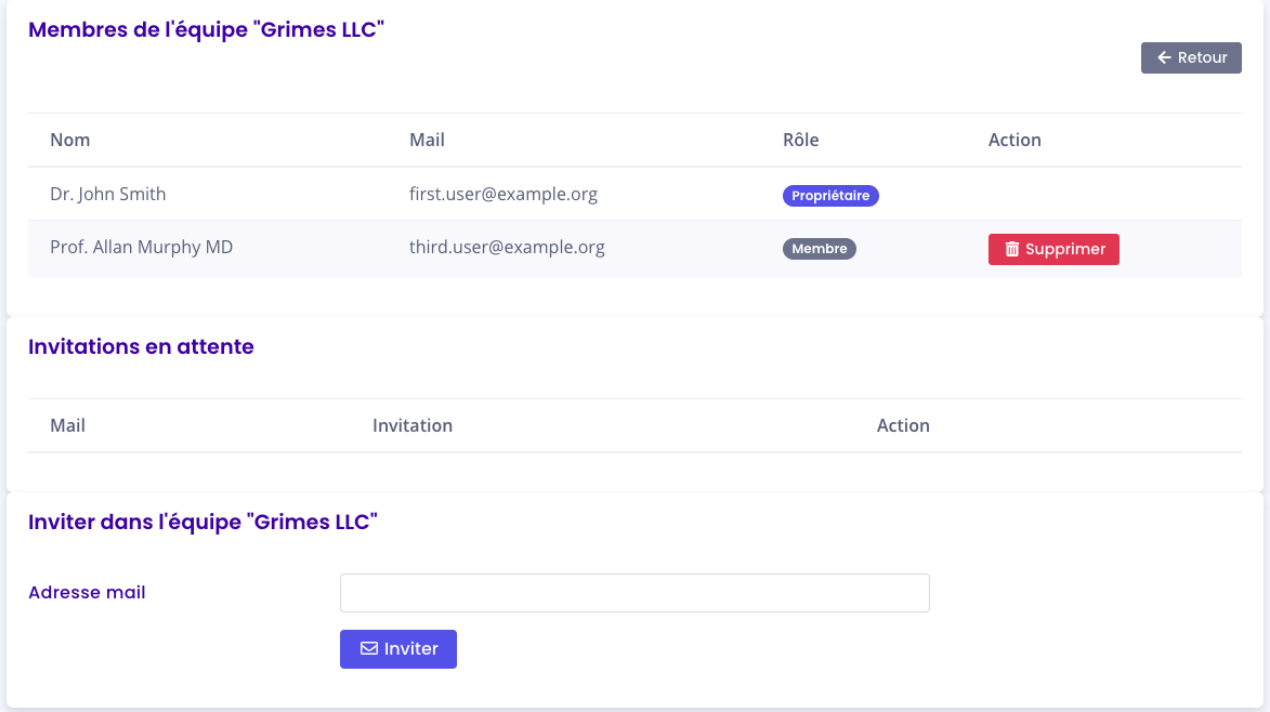
- Enter the email address of a collaborator and click on "send" to send an invitation email to this user. If the user is already part of another team, you cannot invite him/her to an additional team.

In the **"Pending Invitations"** section, you can:

- View the email addresses of all collaborators invited join the team,
- Delete the invitation: the invited collaborator will no longer be allowed to create an account on Predigraft and will not be able to join your team.

In the **"Members"** section, you can consult the list of team members and:

- See the full name and email of the member,
- Click on the "delete" button to remove a member from the list of team members. You cannot remove yourself from the team.

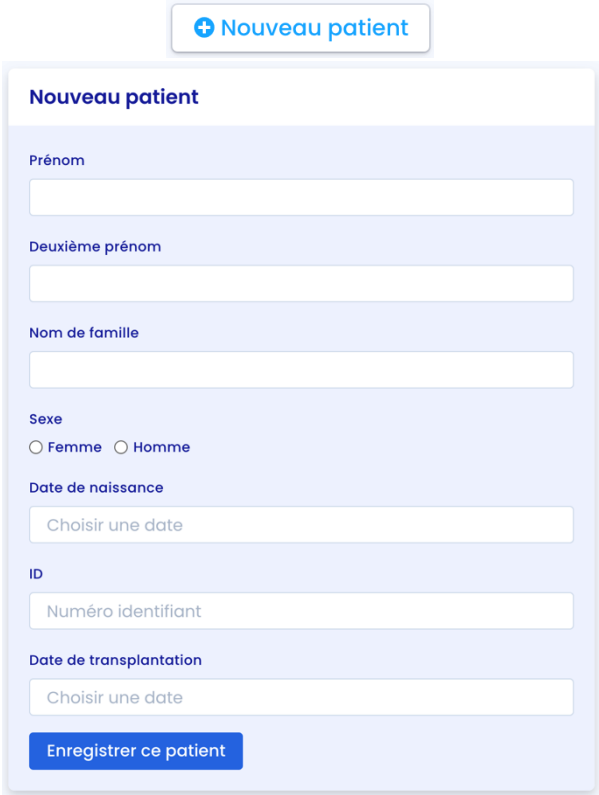


8. Patient Management

8.1. Patient file

8.1.1. Creation of a patient file

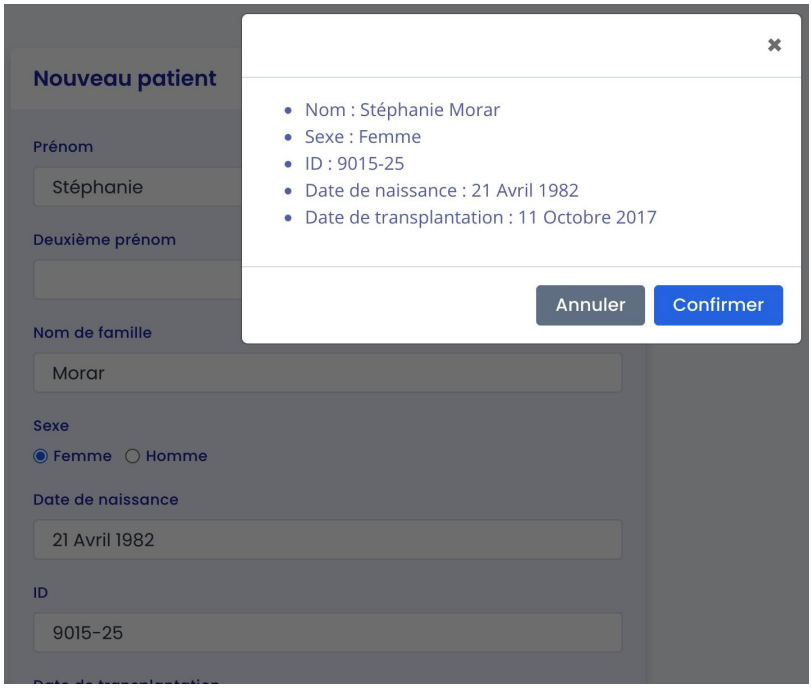
By clicking on the top right button "new patient", the user can create a new patient.



The following information must be completed in order to create the patient record:

- First name,
- Middle name (optional),
- Last name,
- Sex,
- Date of birth,
- ID (must be unique within a team/department),
- Date of transplant.

Click on "Register this patient". A window appears to confirm the information that will be entered into the patient record. Click "Confirm" to create the patient. Click "Cancel" to make changes to the patient information.



8.1.2. Modification of a patient record

To edit a patient record, click on the patient from the patient list to access his or her record. Click on "Modify" in the title bar. You can modify the following information in the patient record:

- First name,
- Middle name (optional),
- Last name,
- Sex,
- Date of birth,
- ID (must be unique within a team/department),
- Date of transplant.

Click "Save Changes". A window will appear to confirm the information that will be entered into the patient record. Click "Confirm" to apply the changes. Click "Cancel" to continue editing the form.

8.1.3. Deleting a patient record

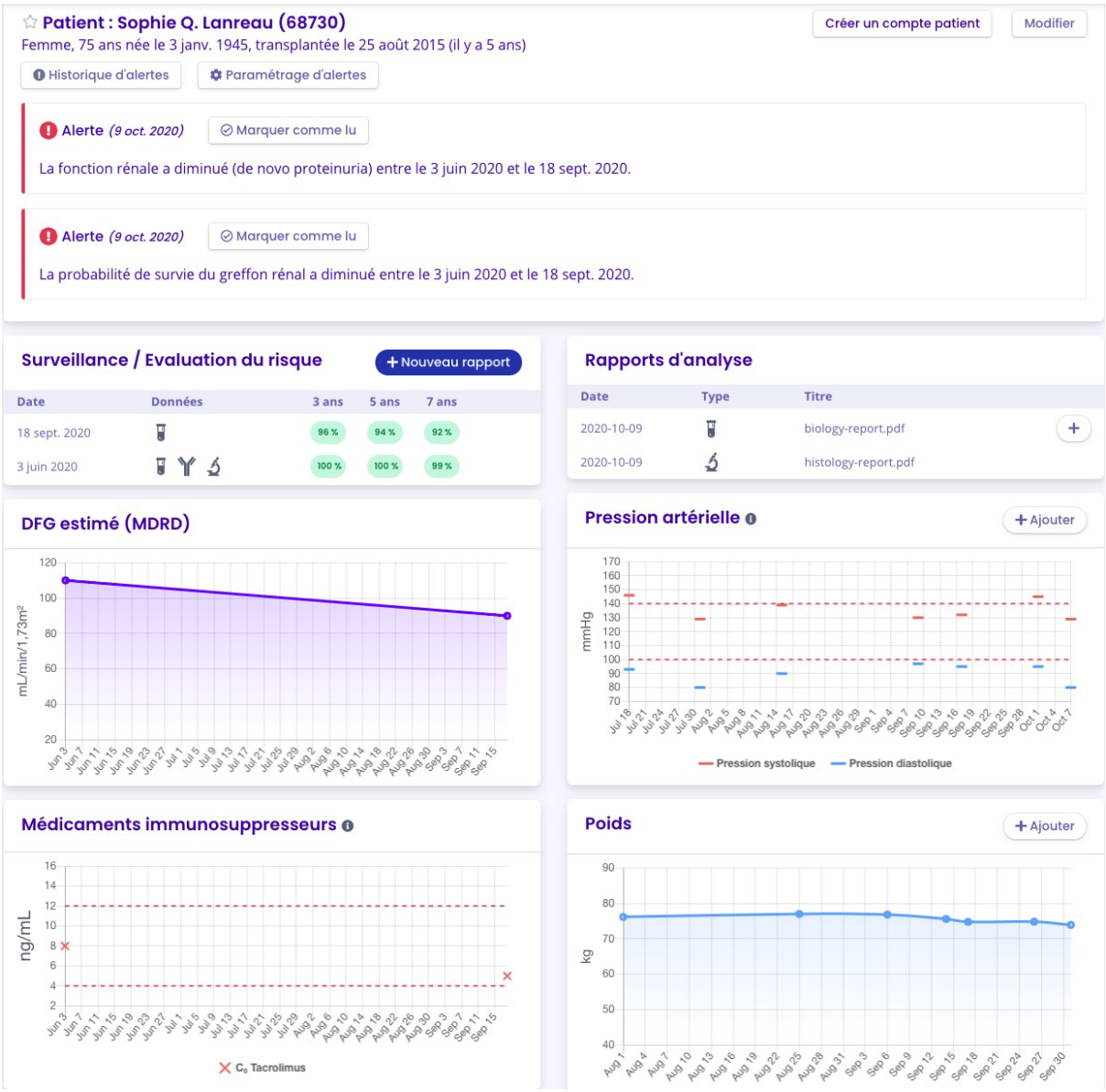
To delete a patient record, click on the patient from the patient list to access his or her record. Click on "Modify" in the title bar.

At the bottom of the Edit Patient Record page, click on "Delete". You must confirm the deletion by pressing the "Delete patient" button.

8.2. Managing a patient

Each department has its own patient list. The information below can be consulted in the patient file:

- Patient information,
- Patient alerts,
- Monitoring / Risk Assessment: link to patient's Predigraft reports,
- Estimated glomerular filtration flow rate (eGFR) according to MDRD: graph of visualization of eGFR values,
- Immunosuppressive drugs: immunosuppressive drug visualization chart,
- Analysis reports: histological or biological test reports,
- Blood pressure: blood pressure visualization graph,
- Weight: weight display graph.



8.2.1. Marking a patient as a starred

In the patient file, the star button ☆ allows you to star the patient or remove the label.
A solid star ⭐: the patient is on the list.

An empty star ☆: the patient is not on the list.

Note: *Each user has their own list of priority patients. This list belongs to the user and not to the team.*

8.2.2. Granting patient access

From each patient record, you can invite a patient to use the Predigraft Patient Application. Click on the "Create a patient account" button in the title bar and enter the patient's email address.

The button "Create a patient account" is replaced by the text "Patient account created".
The patient will receive an email explaining the steps to follow to finalize the creation of the account.
See the Patient Application Chapter for more information about the data exchanges between the doctor interface and the patient interface.

8.2.3. Alerts

Details of the alerts are available in chapter 10.

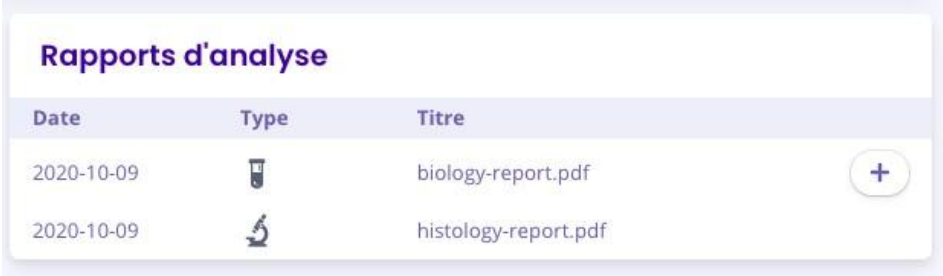
8.2.4. Monitoring/Risk Assessment

Click on "New Report" to create a new Predigraft report. The Monitoring/Risk Assessment section lists the patient's Predigraft reports. You can click on one of the lines in the list to access the Predigraft report. The date corresponds to the date entered at the "eGFR" step when creating a report.
The data correspond to:

- Biological data. This icon is always present. It corresponds to the report creation steps: 2) eGFR and 3) Proteinuria.
- Graft-specific anti-HLA antibody (DSA) data. This icon is present if you entered data in step 4) DSA when creating the report.
- Histology data. This icon is present if you filled in data in step 5) Histology when creating the report.

8.2.5. Analysis reports

You can view the list of biological or histological analysis reports recorded in the patient record.



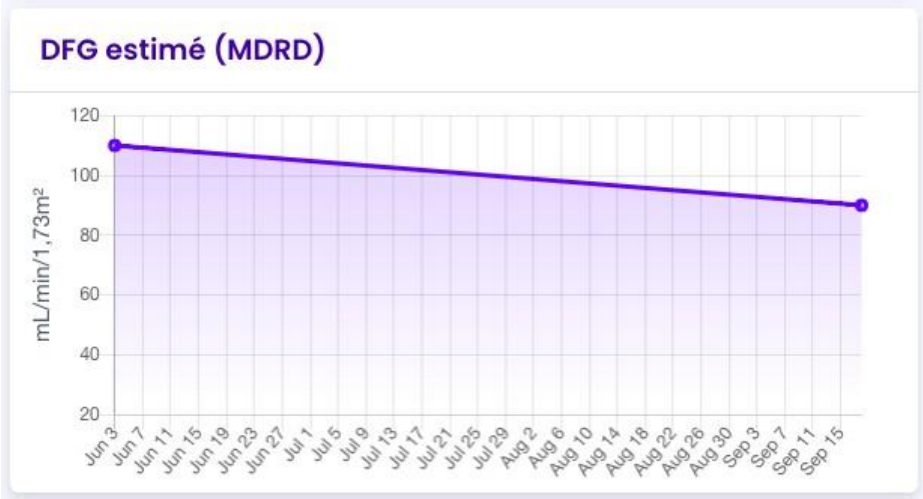
The date is the date the report is added to the patient record.

Report types include histology or biology .
The title is the title of the file name when it is saved.

You can create a Predigraft report from a biological report document by clicking on the button . See Chapter 9 for more information on creating a report.

8.2.6. Estimated GFR

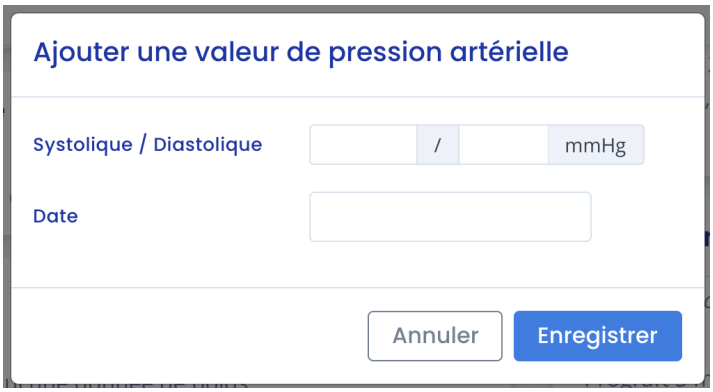
You can view the Estimated Glomerular Filtration Flow Rate (eGFR) value calculated using the MDRD formula. This value comes from the patient's Predigraft reports, step "eGFR".
You can hover your mouse cursor over the points on the graph to see more detailed information.



8.2.7. Blood pressure

You can view the patient's systolic and diastolic pressures over time. The dotted red lines are indicative of the recommended minimum and maximum systolic pressure values. You can hover your mouse cursor over the points on the graph to see more detailed information.

Click the "Add" button to enter systolic and diastolic pressure values for a given date.



8.2.8. Immunosuppressive drugs

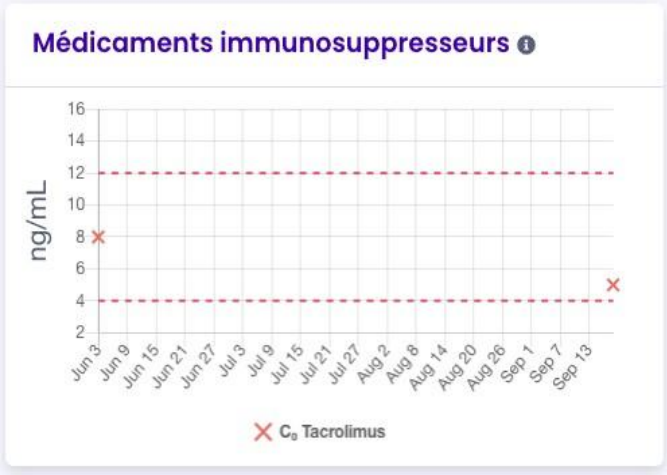
You can view the concentrations of immunosuppressive drugs (C_0 Tacrolimus, C_0 Ciclosporin, C_2 Ciclosporin, C_0 Everolimus, C_0 Sirolimus). The dotted red lines indicate the recommended minimum and maximum values for C_0 Tacrolimus.

- Patient values corresponding to C_0 Tacrolimus, C_0 Everolimus, C_0 Sirolimus are indicated on the left y axis.
- If the patient has values corresponding to C_0 Cyclosporin, C_2 Cyclosporin, an additional y axis will appear on the right.

You can hover your mouse cursor over the points on the graph to see more detailed data.

You can add data when creating a Predigraft report. (see chapter Creating a report).

Example of a patient with values from C_0 Tacrolimus :



8.2.9. Weight

You can view the patient's weight over time. Hover your mouse cursor over the points on the graph to see more detailed data.

Click on the "Add" button to enter a weight value for a given date.

8.2.10. Patient list management

Click on "Patients" in the main menu on the left to view a list of patients in the team/department. The list contains the following information:

- A clickable star to add the patient to the list of favorites,
- Patient's full name,
- Patient's date of birth,
- Patient ID,
- Last evaluation date (indicated in Step 2, eGFR when creating a Predigraft report),
- Date of transplant,
- Time since Transplant (the difference between today's date and the transplant date),
- Date of creation of the patient file.

When the page loads, the list is ordered by the last evaluation date column.

8.2.11. Search options:

In the search field, you can enter:

- All or part of the patient's name,
- All or part of an ID,
- A date (corresponding to the columns "Last evaluation", "Transplant date", "Created on") in the format dd/mm/yyyy or /mm or /yyyy.

The list of patients corresponding to the entry is displayed by pressing the "Enter" key on your keyboard.

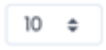
8.2.12. List of favorites:

Click on ☆ to add the patient to your favorites.

Click ★ to remove the patient from the favorites.

Click Patients favoris ☆ to display the list of patients saved in the favorites list.

8.2.13. Display filter:

Click the scroll box on the top right  to change the number of patients displayed on a page. You can display 10, 25, 50, or 100 patients.

8.2.14. Order the list:

Click on the column header to change whether the list is displayed in ascending or descending order.

Example: Order names in ascending alphabetical order.

A second click on the Name column allows you to order the list in descending order.

8.2.15. Browse the list:

To browse the list, click on one of the numbers, "Previous" or "Next" from the list.

9. Report generation

To create a Predigraft report:

- Select a patient from the list to open his or her record.

If the patient has an account on the Predigraft Patient Application and has uploaded biological analysis reports, you can view one of these documents when you create a Predigraft report:

- From the patient record, in the "Analysis reports" item, click on the "+" button of the biological analysis report you want to view.

You can also create a Predigraft report without viewing patient documents:

- From the patient record, click on the "New report" button of the Monitoring / Risk Assessment item.

You will then be directed to the page "New Predigraft report".

9.1. Creating a report

Fill out all required fields in the form in order to proceed to the next step.

1. Clinical Parameters
2. Estimated glomerular filtration flow rate value (eGFR)
3. Proteinuria value
4. DSA value if available, if not check "Not available".
5. Histology information if available, if not check "Not available".

Steps 1), 2) and 3) if you have chosen to view a biological analysis document:

In step 1, from the drop-down list, you can choose the document to display from the list of documents uploaded by the patient through the Predigraft Patient Application.

During steps 1, 2, and 3 of the report creation, you can view the selected document on the left side of the screen. Fill in the patient's Clinical parameters, eGFR, and proteinuria.

Steps 1), 2) and 3) if you create a Predigraft report *without* viewing a biological analysis document:

Fill in the patient's Clinical Parameters, eGFR, and proteinuria.

Step 4):

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

Step 5):

Click on "Import a histology report" on the left side of the report creation screen. You can then import a histology report from your computer and view it next to the form. You can also save the histology report in the patient record. Fill in the Histology information. You can check "Not available" for any information you do not have.

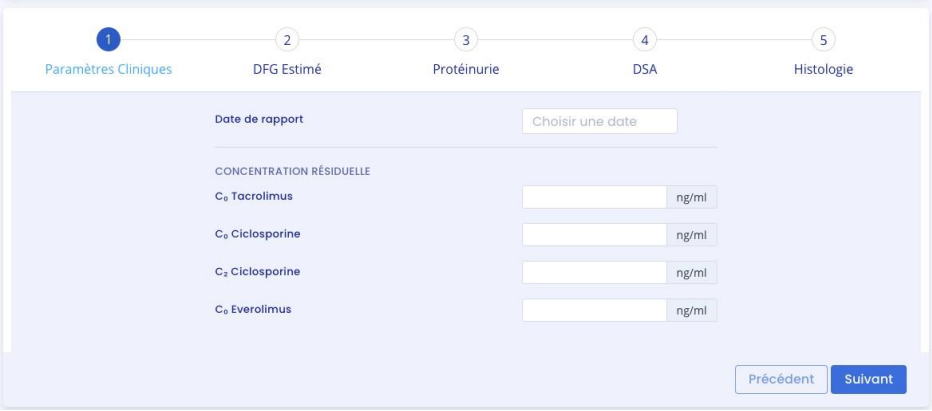
Dates

The date for steps 2, 3, 4, and 5 is mandatory and it cannot be prior to the date of transplantation. You can view the clickable calendar to enter the date:

For step 2, you can click on a date in the calendar or on the "Today" button.

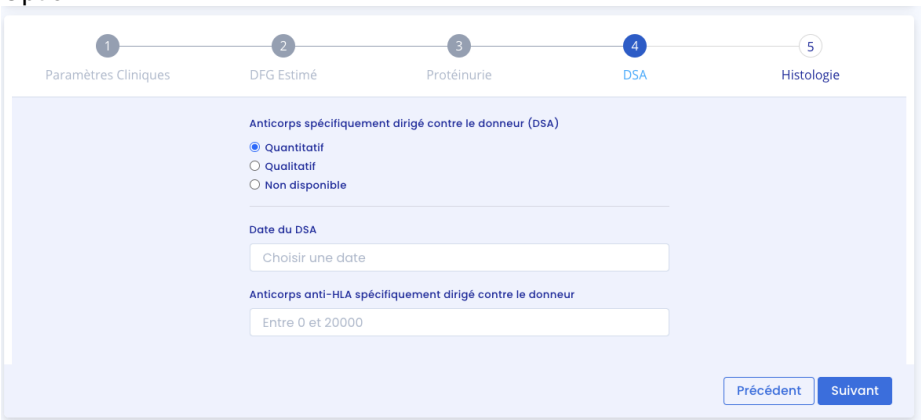
In steps 3, 4, and 5 you can click on a date in the calendar, on the "Today" button or on the "GFR/Creatinine Date" button (date from step 2).

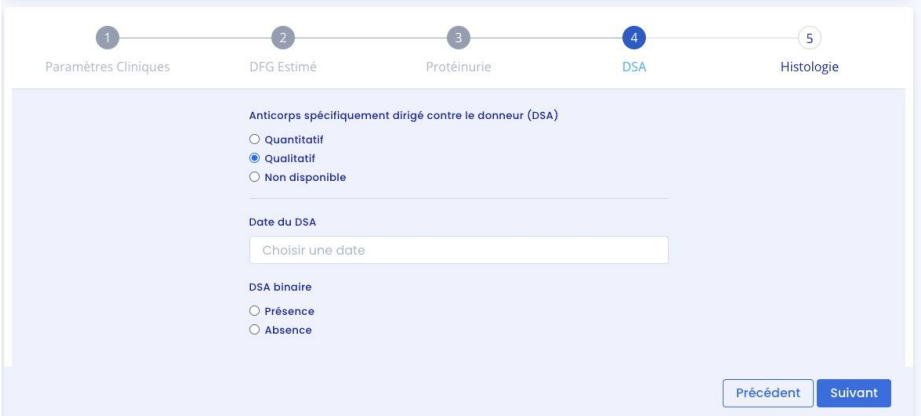
The following screenshots show the necessary steps to create a report without viewing biological analysis reports.

Title banner	The title banner is available on all report creation pages. You will see the following patient information: - Name, - ID, - Sex, - Age and date of birth, - Date of transplant.
1) Clinical parameters (Optional)	
2) Estimated glomerular filtration rate value (eGFR)	Option 1: The estimated GFR value should be between 0 and 120. Error message: `The estimated GFR must be between 0 and 120.` Option 2:

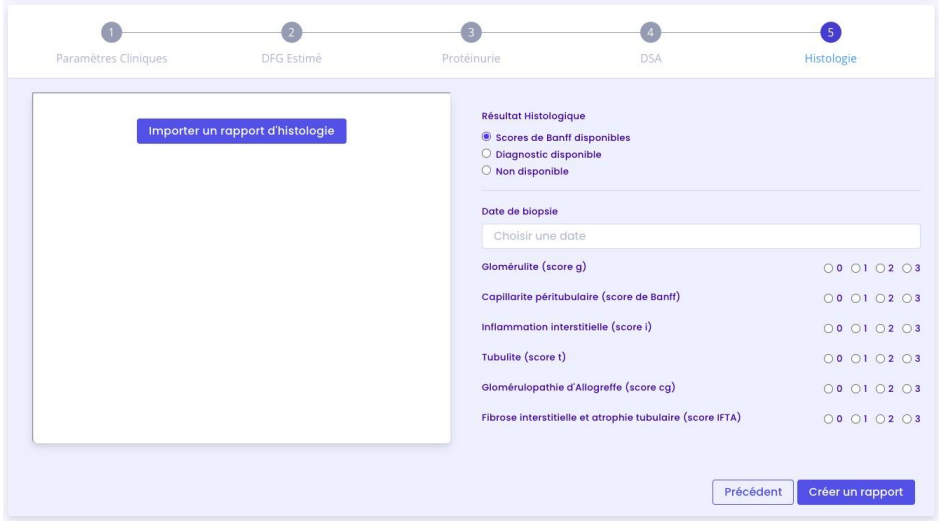
	 Predigraft applies the MDRD formula based on creatinine: Success Message: `The estimated GFR is <value> mL/min/1.73m² according to the MDRD equation.` Error Message: `Estimated GFR is greater than 120 mL/min/1.73m².` Error Message: `Estimated GFR is less than 0 mL/min/1.73m².` <u>Note:</u> The upper limit of 120 ml/min has been applied for the following reasons: - Reduced risk of input error (eg. 140 micromole/l of creatinine entered as eGFR), - The calculation of iBox probabilities and the expected survival benefit at 3, 5, 7 years are unchanged above 120 ml/min. - We, therefore, recommend entering a value of 120 ml/min in case of eGFR higher than 120 ml/min.
3) Proteinuria value	Option 1: The proteinuria value should be between 0 and 12. Error message: `Proteinuria must be between 0 and 12 g/g.` Option 2:

	Predigraft calculates proteinuria based on the ratio of urine protein to urine creatinine.
	Success Message: `The urine protein/creatinine ratio is <value> g/g.`
	Error message: `The urine protein/creatinine ratio should not exceed 12 g/g.`
	Error Message: `The urine protein/creatinine ratio cannot be negative.`
	
	<u>Note on the date of proteinuria:</u>
	Predigraft recommends measuring GFR and proteinuria a maximum of 15 days apart.
	Warning Message:
	`The time between estimated GFR and proteinuria is greater than the recommended 15 days.`
	Error Message:
	`The time from estimated GFR to proteinuria is greater than 30 days.`

4) DSA value	Option 1:  The anti-HLA antibody value should be between 0 and 20000.

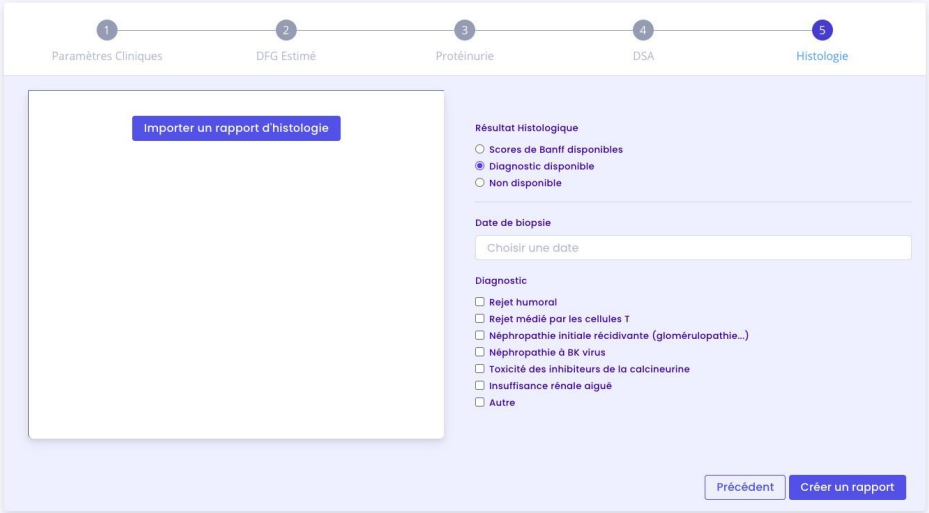
	Error message: `The MFI must be between 0 and 20000.`
	
	Option 2:
	 
	
	"Presence" or "Absence" must be selected.
	
	Option 3:
	
	<u>Note on DSA date:</u>
	Predigraft recommends measuring GFR and DSA at 2-month intervals.
	Warning Message:
	`The time between the estimated GFR and DSA is more than the recommended 2 month interval.`
	
	Error Message:
	`The time between the estimated GFR and DSA is more than 4 months.`

5) Histology information	Option 1:



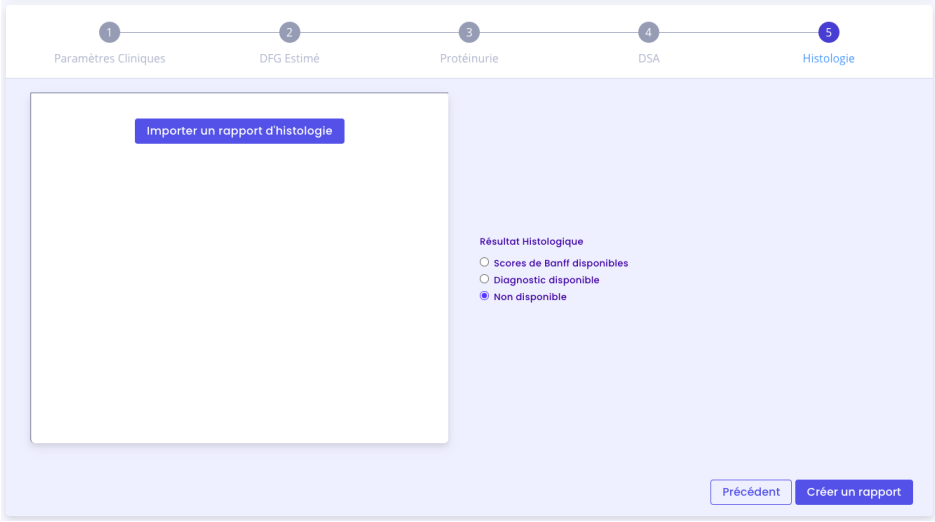
A value of "0", "1", "2" or "3" must be selected for each Banff score.

Option 2:



At least one diagnosis must be selected. "Other" corresponds to any other diagnosis.

Option 3:



Note on histology date:
Predigraft recommends measuring GFR and histology at 2-month intervals.
Error Message:
`The time between estimated GFR and biopsy must be less than 2 months.`

Predigraft applies the iBox algorithm to the input data. The "Create Report" button checks the input data for errors. The generated Predigraft report contains the results of the iBox calculation: the probability of survival at 3, 5, and 7 years after the evaluation date (date of step 2).

9.2. Visualization of results

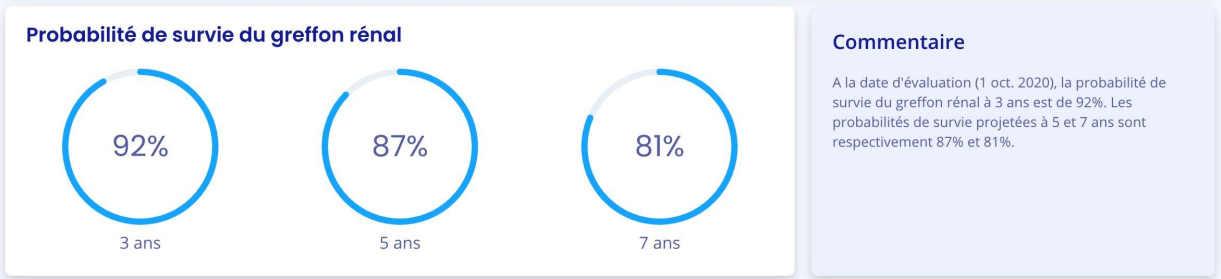
The title banner displays the patient's name, the date of assessment (date of step 2) eGFR), and the date of the patient's transplant.

You can print the Predigraft report by clicking on "Print". If you have created the Predigraft report by viewing a bioanalysis report, you can also download the bioanalysis report.

You can delete the report by clicking on "Delete" and specifying the reason in the confirmation window that appears:

- Incorrect data,
- The record is for a different patient,
- The report is a duplicate.

You can visualize the results of the iBox calculation: the probability of kidney graft survival projected at 3 years, 5 years, and 7 years from the evaluation date. The "comments" panel describes the probabilities.



You can view the iBox results of the current report compared to the results of the most recent previous report. The comment panel describes whether the survival probabilities are better or worse since the previous report.

You can visualize the input data that were used to generate the report: date and value for each step of the report creation (Clinical Parameters, Estimated GFR, Proteinuria, DSA, Histology). In the Comment panel, you can find the probability of agreement of the iBox model based on the input data (C-stat). Click on the "publication" link to access the Paris Transplant Group publication about the iBox.

9.3. Managing the list of reports

Click on "Predigraft Reports" on the left sidebar to view a list of reports for all patients in the team/department. The list contains the following information:

- Report: report of <full name of patient> (born on <patient date of birth>),
- Evaluation date: date of step 2) "Estimated GFR" when creating the report,
- Time after Tx: the time between transplant date and evaluation date,
- 3 years, 5 years, 7 years: the probability of renal graft survival at 3 years, 5 years, and 7 years after the evaluation date,
- Created on: the date the report was created.

When the page loads, the list is automatically ordered by the Evaluation Date column.

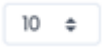
9.3.1. Search for:

In the search field, you can enter:

- All or part of a patient's name
- A date corresponding to the columns "Evaluation date", "Time after Tx", "Created on" in the format dd/mm/yyyy or /mm or /yyyy

The list of reports corresponding to the search entry is displayed by pressing the "Enter" key on your keyboard.

9.3.2. Display filter:

Click on the scroll box on the upper right 

to change the number of reports displayed on a page. You can display 10, 25, 50, or 100 reports.

9.3.3. Order the list:

Click on the column header to change whether the list is displayed in ascending or descending order.

9.3.4. Browse the list:

To browse the list, click on one of the numbers, "Previous" or "Next" from the list.

You can click on Previous or Next.

10. Alerts

10.1. Definition of alerts

Predigraft calculates patient alerts when the following data are added to a patient record:

- Weight data
- Blood pressure data
- Values for immunosuppressive drugs C_0 Tacrolimus, C_2 Ciclosporin, C_0 Everolimus or C_0 Sirolimus when creating a Predigraft report
- Kidney function values for estimated GFR and proteinuria when creating a Predigraft report
- Kidney Graft Survival Probability during Predigraft Report creation and iBox calculation

10.2. Alert settings

Predigraft calculates patient alerts based on alert settings. There are three parameter categor:

- Predigraft-level (default): Cibiltech sets the default values
- Team level: the team owner can modify the alert settings for the team. This setting is then applied to all patients in the team.
- Patient-level: department members can change alert settings for each patient. this setting is only valid for the specified patient.

10.2.1. Cibiltech settings: default setting

For the Predigraft level, Cibiltech has defined default values that teams can modify as they see fit.

1) 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 setting are:

- Maximum systolic pressure value: 250 mmHg
- Maximum diastolic pressure value: 130 mmHg

2) Weight

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

The maximum values for each setting are:

- Weight gain: 20 kg

3) Immunosuppressive drugs

- C0 Tacrolimus minimum threshold: 4 ng/mL
- C0 Tacrolimus maximum threshold: 12 ng/mL
- C2 Ciclosporin minimum threshold: 600 ng/mL
- C2 Ciclosporin maximum threshold: 1200 ng/mL
- C0 Everolimus minimum threshold: 3 ng/mL
- C0 Everolimus maximum threshold: 8 ng/mL
- C0 Sirolimus minimum threshold: 4 ng/mL
- C0 Sirolimus maximum threshold: 12 ng/mL

4) Renal function (estimated GFR, proteinuria)

- Decrease in estimated GFR: 30%.
- Increase in serum creatinine: 50%.
- *de novo* proteinuria

There are no maximum values for "Estimated GFR Decrease" or "Serum Creatinine Increase".

5) Probability of kidney graft survival

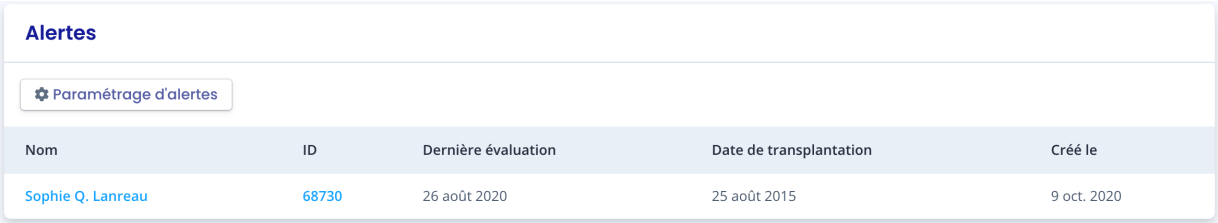
- Decrease in the probability of survival at 3 years: 1%.
- Decrease in the probability of survival at 5 years: 1%.
- Decrease in the probability of survival at 7 years: 1%.

Settings that cannot be changed are:

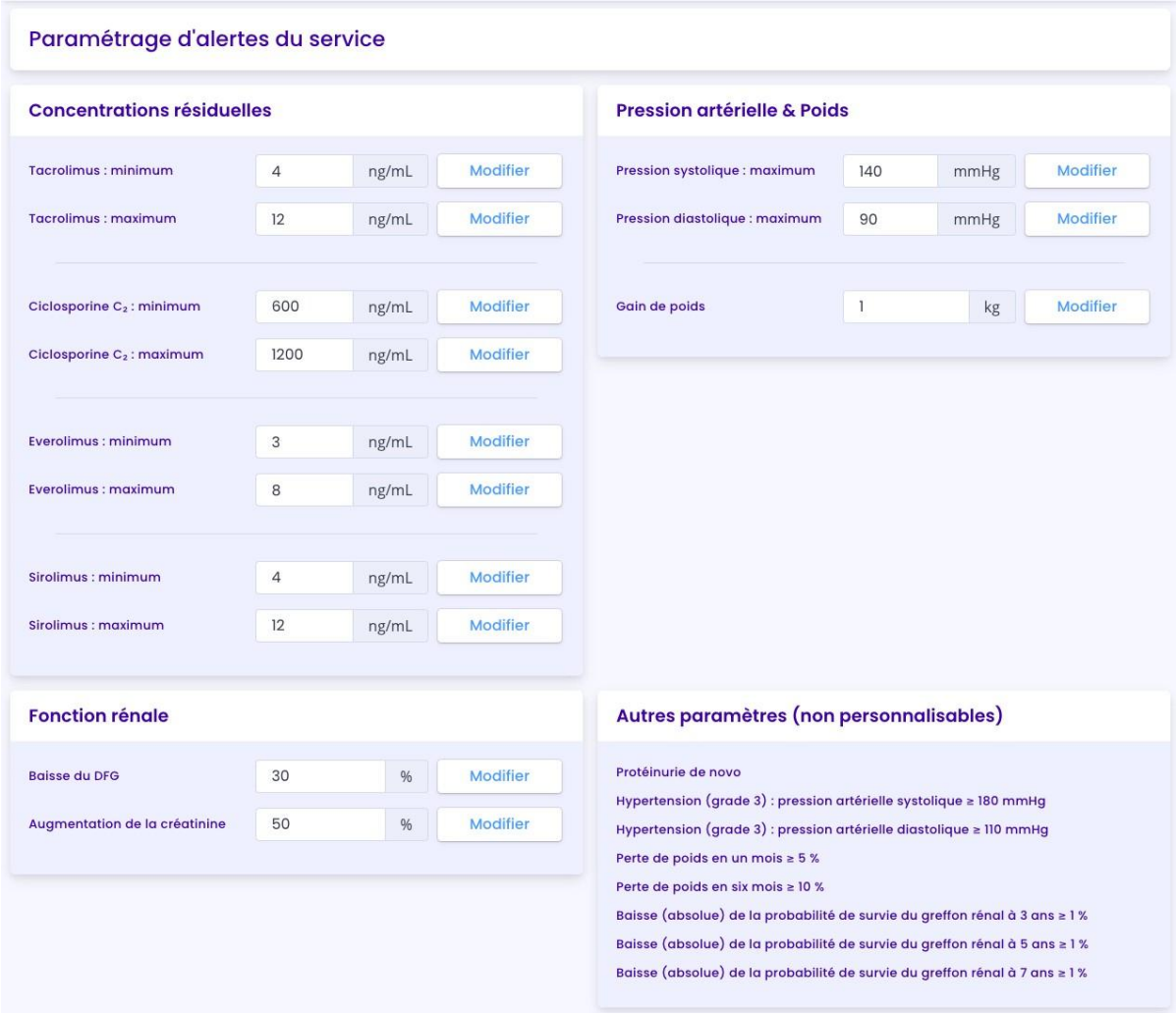
- *de novo* proteinuria
- Systolic pressure for hypertension (Grade 3)
- Diastolic pressure for hypertension (Grade 3)
- Weight loss in one month
- Weight loss in six months
- Decrease in the probability of survival at 3 years
- Decreased probability of survival at 5 years
- Decreased probability of survival at 7 years

10.2.2. Team-level configuration

To set up the team alerts, click on "Alerts" in the left sidebar, then click on "Alert Setup".



You will then be taken to the "Team Alert Settings" page.



To modify a parameter: change the value in the corresponding field and then click on the “Modify” button. A confirmation window will display the following information:

- The parameter value entered,

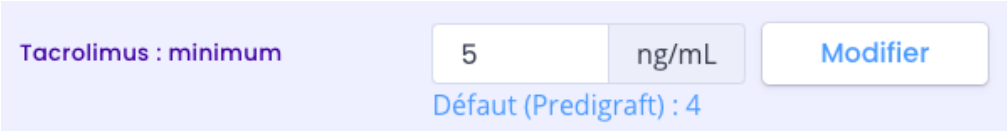
- The calculation that generates the alert.

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

Click on "Modify for all patients" to confirm, or on "Cancel" to cancel the update.

Once you have updated a parameter, a "Parameter History" button allows you to access the history of changes. Next to the history button, a message indicates the date of the last parameter update as well as the name of the user who performed the action.

For each parameter that does not apply the default value, the default value will be displayed below: "Default (Predigraft): <Predigraft setting value>".



10.2.3. History of team-level configuration

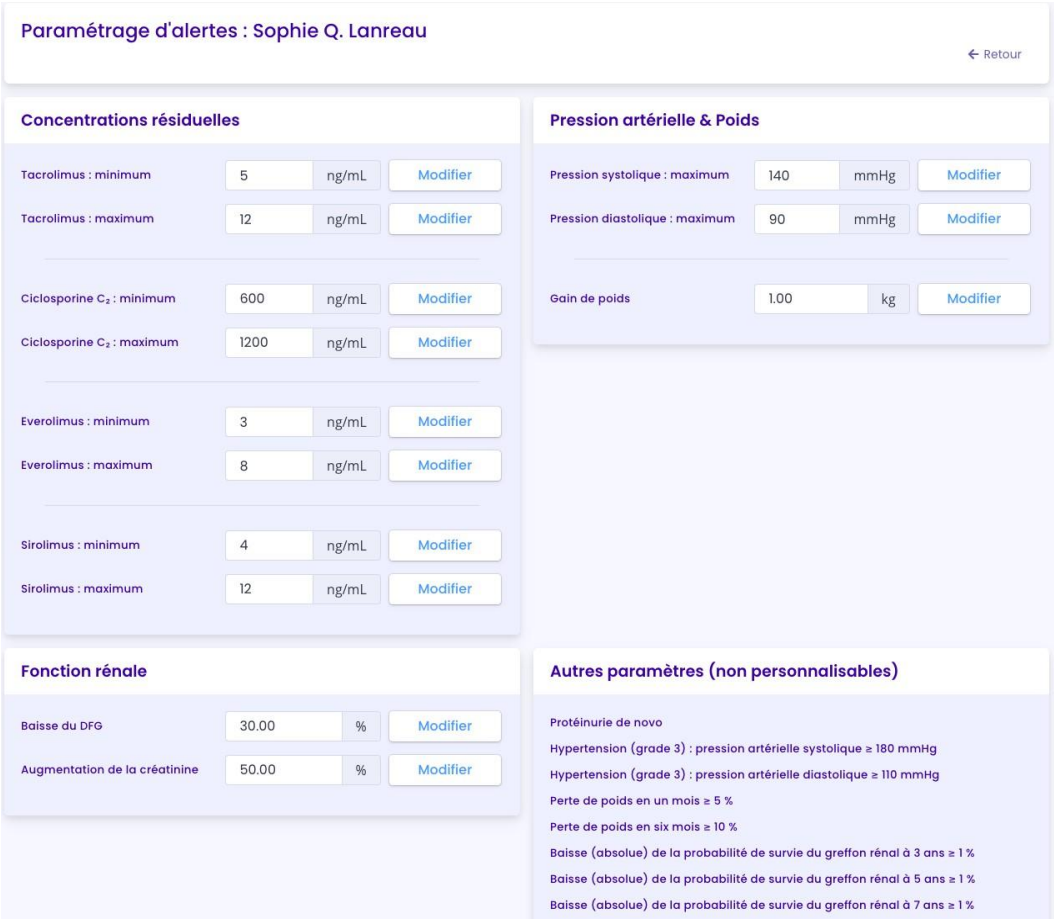
You can access settings history via the left sidebar: "Alerts" > "Alert Settings" > "Settings History".

The history is displayed in descending order from the most recent to the oldest. In the history you will see:

- The name of the user who changed the settings,
- The date of the change,
- The list of each alert parameter and corresponding value.

10.2.4. Patient-level configuration

To set up patient alerts, access the patient record and click on "Alert settings" to navigate to the "Alert Settings" page: <patient's full name>".

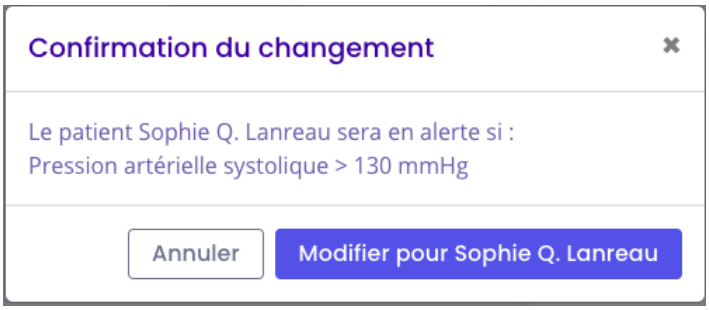


To modify a parameter: change the value in the corresponding field and then click on the “Modify” button. A confirmation window will display the following information:

- The parameter value entered,
- The calculation that generates the alert.

Click on "Modify for <full patient name>" to validate, or on "Cancel" to cancel the update.

Example of changing the Maximum Systolic Pressure threshold at the patient level:



Once you have updated an alert parameter at the patient level, a "Parameter History" button allows you to access the modification history. The button does not appear if the parameter has only been changed at the team level.

Next to the history button, a message will display the date of the last update to the patient's alert settings as well as the name of the user who performed the action.

For each parameter that does not apply the default value, the default value will be displayed below: "Default (Predigraft): <Predigraft setting value>".

10.2.5. History of patient-level settings

From the Patient Alert Settings page, click on "Settings History".

The history is sorted with the most recent modification at the top of the page. The history is a list containing:

- The category of the setting: team/department or patient,
- The name of the user who changed the settings,
- The date of the change.

10.3. Alert calculation for a patient

Alerts are based on the following information (calculations are available in the Appendix).

1) Blood pressure

The software calculates blood pressure alerts from:

- the most recent date of blood pressure and associated systolic and diastolic pressure values

2) Weight

The software calculates weight alerts from:

- the most recent date of weight and the corresponding value
- the previous weight date and the corresponding value

3) Immunosuppressive drugs

The software calculates immunosuppressive drug alerts from a Predigraft report:

- the most recent date of immunosuppressive drugs (the date of step 1 of Predigraft report creation or the date of step 2 if not filled in) and corresponding values: C_0 Tacrolimus, C_2 Ciclosporin, C_0 Everolimus, C_0 Sirolimus.

4) Kidney function

The software calculates kidney function alerts from two Predigraft reports:

- Predigraft reports are ordered by evaluation date (date from Step 2) estimated GFR)
- The most recent report is selected: “report in progress".
- The previous report Is selected: "previous report".

The software selects from both reports: estimated GFR date, DFG value, creatinine value if entered, proteinuria date, proteinuria value.

5) Probability of kidney graft survival

The software calculates kidney function alerts from two Predigraft reports:

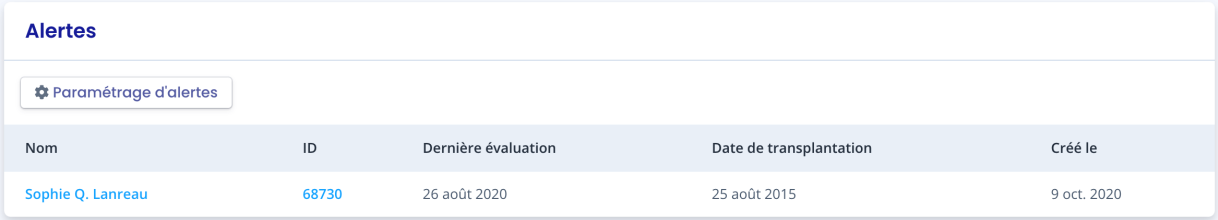
- Predigraft reports are ordered by evaluation date (date from Step 2) estimated GFR)
- The most recent report is selected: “report in progress".
- The previous report Is selected: "previous report".

The software selects from the two reports: projected survival probabilities at 3 years, 5 years, and 7 years.

10.4. Management of the list of patients on alert

Click on "Alerts" on the left sidebar for a list of patients on alert.

A counter of patients on alert is displayed on the left sidebar Alerts 1. If the counter is not visible, there are no patients on alert.



The list of patients on alert contains:

- Patient's full name
- Patient ID
- Latest assessment date: last date of the "Estimated GFR" stage entered during creation of a Predigraft report for this patient
- Patient transplant date
- Date of creation of the patient record

You can click on one of the lines in the list of patients on alert to access the corresponding patient record.

10.5. Managing an alert

If a patient is on alert, the alerts are visible from the patient record.

Each alert contains:

- The date of creation of the alert
- Details of the alert
- A "Mark as read" button

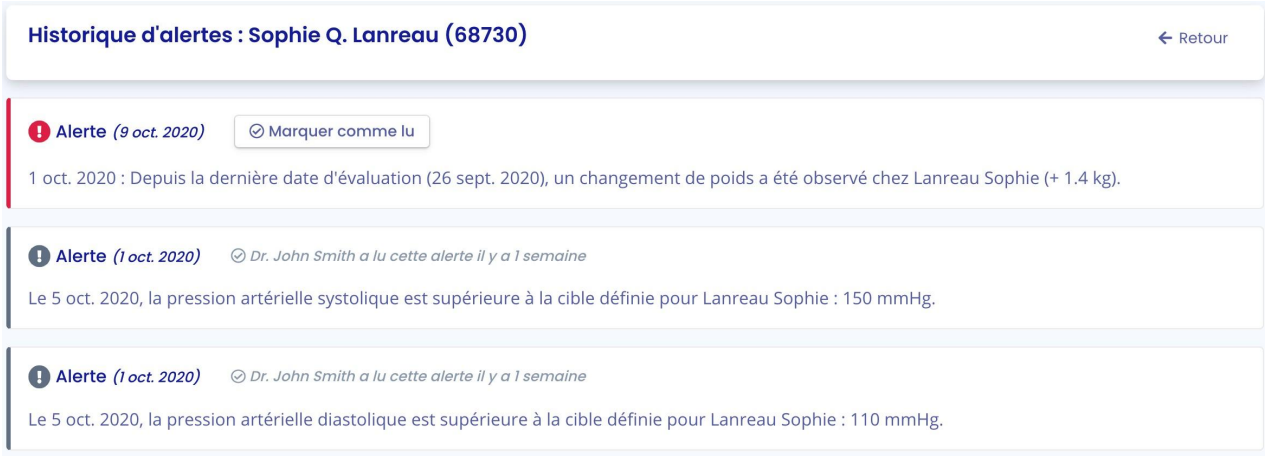
Mark as read

If you click on "Mark as read", this action is recorded in the database and means that you are aware of the alert. The button is changed to "Read on <date and time> by <user>" and this message is visible to all team members.

An alert marked as read is moved to the alert history page, accessible through the "Alert History" button on the patient page.

Alert History

The Alert History page lists a patient's alerts, displaying the most recent first. The history page lists read alerts (gray) and unread alerts (red). You can read an alert from this page.



11. 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: materiovigilance@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.pdf

12. Personal data

The use of the Predigraft application requires you to fill in certain personal data necessary for its operation. In the context of your professional activity, you are required to provide us with your surname, first name, date of birth, gender, title, language, e-mail address, business telephone number, mobile telephone number, the care center to which you are affiliated or employed. Entering this personal data allows us to establish a regular means of communication with a given patient, while securing the transfer of that patient's personal data. We verify your identity, for example, using your e-mail address and phone number. Collecting your personal data also allows us to communicate with you for information on the use of the application itself, in the event of security issues related to the application and may be used for commercial purposes (manufacturer-healthcare center communication).

When you contact our technical support, you are also informed that the call is likely to be recorded and we inform you that we also collect data. The purpose is to be able to improve the technical support. The technical, regulatory, quality and sales departments are the recipients of this information. Your personal data is kept for the time you use the application, for a given care center. As the Predigraft application is a regulated medical device, this information is then archived for regulatory traceability purposes for 10 years**.**

In accordance with the Data Protection Act and the European Regulation 2016/679 (GDPR) you have the following rights regarding your personal data:

- Right to access,
- Right to rectification,
- Right to erasure,
- Right to restriction of processing,
- Right to object,
- Right to data portability.

In order to request the exercise of your rights, you can contact our data protection officer at: privacy@cibiltech.com. In this request, please specify your surname, first name, e-mail address, institution/facility and the nature of the right(s) you wish to exercise, accompanied by a copy of your identity card in order to authenticate your identity. We make every effort to comply with Data Protection Regulations to ensure the security of your data and your rights. Nevertheless, in the event that you notice a breach of this regulation, you are entitled to file a complaint with the supervisory authority (the CNIL, www.cnil.fr, or the Data Protection Officer (DPP or DPO in English) of the person responsible for processing your data (DPO of the health establishment or DPO of the manufacturer of the application).

1. Appendix 1: Input Parameters

1. Transplant and evaluation date

The transplant date must be filled in with the day, month and year.

The evaluation date is the date on which the creatinine measurement was performed. This date may be different from the date of the medical appointment. This date is used as a reference for all other measurements taken. It must be completed with the day, month and year.

2. Estimated glomerular filtration rate (eGFR)

Glomerular filtration rate (GFR) is the primary measure of kidney function. It can be measured or estimated from validated formulas that have been published in scientific journals. The equation that was used to develop and validate the iBox is the one used in the Modification of Diet in Renal Disease (MDRD) study:

Estimated GFR (mL/min/1.73 m²) = $186 \times (Scr/88.4)^{-1.154} \times (Age)^{-0.203} \times$ (0.742 if female) (International Unit)

3. Proteinuria

Proteinuria is a marker of kidney damage. It can be tested with a urine test strip. If positive, it is confirmed and quantified on a 24-hour urine collection (result in mg/24h), or when 24-hour urine collection is not possible, on a urine sample taken at any time of day and by the proteinuria/creatinuria ratio (result in mg/g or mg/mmol).

Proteinuria is measured on the same day as creatinine. A delay of up to 15 days between the measurement of creatinine and the estimation or measurement of proteinuria is tolerated.

4. anti-HLA donor specific antibodies

The presence of donor-specific anti-HLA antibodies (DSA) is assessed regularly after a kidney transplant. The measurement is carried out by solid phase analysis. The current preferred method is flow cytometry using fluorescent microbeads. The result is provided by the HLA laboratory. It can be qualitative (positive or negative) or quantitative. The mean value of the fluorescence intensity (MFI) of the immunodominant DSA (i.e. DSA with the highest MFI) should be reported. The date of the DSA test should not be more than 2 months from the evaluation date.

5. Histology

A pathology report is provided after a kidney transplant biopsy. This report provides a histological description with a diagnostic result as well as a semi-quantitative description of the basic histological lesions according to the Banff classification system. The clinician has the option to enter the reported diagnoses or the Banff histological scores. The date of biopsy should not exceed 2 months from the date of assessment.

2. Appendix 2: Calculation of alerts

1) Blood pressure

The software calculates blood pressure alerts from:
- the most recent date of blood pressure and corresponding systolic and diastolic pressure values

Systolic blood pressure is referred to as "SP" below. Diastolic blood pressure is referred to as "PAD".

Calculation of alerts:

IF SP > blood_pressure_high_systolic: "On the <DATE>, systolic blood pressure is above the target set for <NAME> FIRST NAME>: <PAS VALUE> mmHg. »
IF DP > blood_pressure_high_diastolic: "On the <DATE>, diastolic blood pressure is above the target set for <NAME> <FIRST NAME>: <PAD VALUE> mmHg. »

IF PAS >= 180 OR PAD >= 110: "On <DATE>, a grade 3 blood pressure was observed for <NAME> <FIRST NAME> (<PAS VALUE> / <PAD VALUE> mmHg)".

2) Weight
The software calculates Weight alerts from:
- the most recent date of weight and corresponding value
- the previous weight date and the corresponding value

Calculation of alerts:

IF Weight_gain >= Weight_gain_kg:
"< RECENT DATE>: Since the last evaluation date (<PREVIOUS DATE>), a change in weight has been observed for <NAME> <FIRST NAME> (+ <DIFFERENCE BETWEEN WEIGHTS> kg)".
ELSE IF
Difference between dates is one month or less AND Weight loss >= Weight_loss_percentage_one_month_ago (5%)
OR
The difference between the dates corresponds to one month to six months AND Weight Loss >= Weight_loss_percentage_six_months_ago (10%):
"< RECENT DATE> : Since the last evaluation date (<PREVIOUS DATE>), weight loss has been observed in <NAME> <FIRST NAME> (- <DIFFERENCE BETWEEN WEIGHTS> kg)".

3) Immunosuppressive drugs

The software calculates immunosuppressive drug alerts from a Predigraft report:
- the most recent date of immunosuppressive drugs (the date corresponding with step 1 of Predigraft report creation or the date from step 2 if not available from step 1) and associated values: C_0 Tacrolimus, C_2 Ciclosporin, C_0 Everolimus, C_0 Sirolimus

Calculation of alerts:

IF C_0 Tacrolimus < trough_levels_low_tacrolimus OR > trough_levels_high_tacrolimus: "<DATE>: The residual tacrolimus concentration is outside the target defined for <NAME> <FIRST NAME> (C0: <VALUE> ng/mL).

IF C_2 Cyclosporine < trough_levels_low_cyclosporine OR > trough_levels_high_cyclosporine: "<DATE> : The concentration of cyclosporine 2 hours after dosing (C2) is outside the target defined for <NAME> <FIRST NAME> (C2: <VALUE> ng/mL).".

IF C_0 Sirolimus < trough_levels__low_everolimus OR > trough_levels__high_everolimus: "<DATE>: The residual concentration of sirolimus is outside the target defined for <NAME> <FIRST NAME> (C0: <VALUE> ng/mL).".

IF C_0 Everolimus < trough_levels_low_sirolimus OR > trough_levels_high_sirolimus: "<DATE>: The residual concentration of everolimus is outside the target defined for <NAME> <FIRST NAME> (C0: <VALUE> ng/mL).

4) Kidney function

The software calculates kidney function alerts from two Predigraft reports:

- Orders Predigraft reports by valuation date (date from Step 2) Estimated DFG)
- Selects the most recent report: "report in progress".
- Selects the previous report: "previous report".

The software selects in both reports: estimated DFG date, DFG value, creatinine value if filled in, proteinuria date, proteinuria value

Calculation of alerts :

IF the DFG value of the current report is reduced by "kidney_function_egfr_reduction" or more, compared to the DFG value of the previous report:
"Kidney function decreased (decrease in estimated GFR) between <PREVIOUS REPORT DATE> and <CURRENT REPORT DATE>".

IF the creatinine serum value of the current report is increased by "kidney_function_serum _creatinine_increase" or more, compared to the creatinine serum value of the previous report:
"Renal function decreased (decrease in serum creatinine) between the <PREVIOUS REPORT DATE> and the <CURRENT REPORT DATE>."

IF the proteinuria value was 0 in the previous report and is greater than 0 in the current report: "Renal function decreased (de novo proteinuria) between the <PREVIOUS REPORT DATE> and the <CURRENT REPORT DATE>".

5) Probability of kidney graft survival

The software calculates kidney function alerts from two Predigraft reports:

- Predigraft reports are ordered by evaluation date (date from Step 2) estimated GFR)
- The most recent report is selected: "current report".

- The previous report Is selected: "previous report".

The software selects from the two reports: projected survival probabilities at 3 years, 5 years, and 7 years.

Calculation of alerts:

IF probability of survival at 3 years from the current report < probability of survival at 3 years of the previous report with an accuracy of survival_probability_3y_reduction (1%)
OR
Probability of survival at 5 years of the current report < probability of survival at 5 years of the previous report with an accuracy of survival_probability_5y_reduction (1%)
OR
Probability of survival at 7 years of the current report < probability of survival at 7 years of the previous report with an accuracy of survival_probability_7y_reduction (1%) :
"The probability of renal graft survival decreased between <PREVIOUS REPORT DATE> and <CURRENT REPORT DATE>."