ChimerisMonitor IVD

Instructions for Use (IFU)

IVD CE 0483 For in vitro diagnostic use

CSMIFU01v3en
01.04.2026

REF 46-14800-0000

LOT 3.0.5 and higher (software version)

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Notice of Change

Please note the following adaptions compared to the previous IFU version:

Document code	Changes	Date
CSMIFU01v1en	Initial version	17.03.2025
CSMIFU01v2en	Change of odering number Mentype® DIPscreen PCR Amplification Kit	29.04.2025
CSMIFU01v3en	Addition of Swiss authorised representative and Swiss importer	01.04.2026

A printed version of this IFU can be provided free of charge within 7 days.

For this or for any further questions, please contact us:

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End User License Agreement (EULA)

for "ChimerisMonitor IVD", herein referred to as SOFTWARE

§ 1 Introduction

1) This End User License Agreement is a legal contract between you (either an individual or a single entity, herein referred to as the USER) and BIOTYPE GmbH.

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7) Unless otherwise noted, the USER authorizes BIOTYPE GmbH to collect and use data gathered within the scope of the provided product support. This also applies to data sent by the USER. BIOTYPE GmbH may use this information to advance the products and to provide services

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1) The licenses agreement according to these terms will be concluded indefinitely. For using product support services the USER must conclude a separate support contract.

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1) Both parties to the contract agree that according to the state of art it is not possible to develop data processing programs which are adequate for all user requirements. However, BIOTYPE GmbH guarantees that the SOFTWARE is adequate for the usage described in the user manual. BIOTYPE GmbH does not guarantee that the SOFTWARE will satisfy the requirements of the USER or that the SOFTWARE will work with other used programs.

2) BIOTYPE GmbH does not grant special properties of the SOFTWARE, neither explicit nor implicit. The USER is responsible for the selection of the SOFTWARE, its use and the achieved results. The user is responsible for all results which were generated with the SOFTWARE.

3) The USER is required to check the SOFTWARE and the enclosed documentation immediately and with a reasonable thoroughness. All deficiencies hereby recognized have to be reported to BIOTYPE GmbH in written form within fourteen days after starting to use the SOFTWARE. Latent deficiencies need to be reported similarly after their detection. If any deficiency is not reported as described above, any warranty by BIOTYPE GmbH is excluded.

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7) In case of unfounded notification of defects, BIOTYPE GmbH reserves the right to make a claim to the USER for the costs.

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3) In case of absence of warranted characteristics BIOTYPE GmbH is not liable for consequential damages, which the warranty does not contain.

4) BIOTYPE GmbH is only liable for data loss – with the exception of

deliberate action undertaken by the USER resulting in data loss – if the USER has carried out system audits and backups regularly and only to the extent to which data is reproducible with reasonable effort.

5) The liability of BIOTYPE GmbH as a commercial entitiy is limited to typical, forseeable events associated with a commercial enterprise and/or the use of the provided SOFTWARE when used only as intended as described in accompanying documentation.

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7) Claims for damages are subject to local national statutory provisions. Claims may only be submitted for events which fall into the statutory limits as they pertain to your local regulations or otherwise up to three years after the occurrence of the event.

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§ 8 Place of Jurisdiction/Final Clause

1) Any suit brought by BIOTYPE GmbH or the USER will be subject to the exclusive jurisdiction of Germany and venue of BIOTYPE GmbH.

2) The invalidity of single terms does not affect the validity of the contract as a whole.

3) There are no additional verbal agreements. Changes and additions to this contract require a written form.

October 2024

Content

Intended purpose

The software ChimerisMonitor IVD is an application that supports the data analysis of the IVD assays Mentype® Chimera® PCR Amplification Kit and Mentype® DIPscreen PCR Amplification Kit.

The software analyzes fsa-files generated on Genetic Analyzers of Thermo Fisher Scientific (Applied Biosystems division). These assay-specific data are used for the qualitative detection of the genotypes of patient and donor to identify patient specific alleles, prior to chimerism evaluation. After allogeneic hematopoietic stem cell transplantation (allo-HSCT), the informative patient-specific alleles are analyzed to perform a semi-quantitative chimerism monitoring. The software ChimerisMonitor IVD intended for professional laboratory users trained on molecular-genetic techniques, multiplex PCR, and the handling of Genetic Analyzers of Thermo Fisher Scientific (Applied Biosystems division).

Scientific Background

Allogeneic hematopoietic stem cell transplantation (allo-HSCT) is a treatment option to cure patients with non-malignant and malignant hematological diseases, such as leukemia. Chimerism analysis is used to determine the mixture of donor and recipient hematopoietic cells in allo-HSCT recipients to detect early signs of graft rejection. Human peripheral venous blood is used for genotyping and monitoring. According to the CLSI Guidelines (MM05-A2, 2nd edition) anticoagulants like EDTA and citrate are recommended for blood collection. Depending on the success of transplantation, different forms of hematopoietic chimerism (complete, mixed or loss) can develop. Different approaches are used for chimerism analysis, including fluorescence in situ hybridization (FISH), restriction fragment length polymorphism (RFLP), blood count analysis and PCR-based methods. Currently, PCR-based amplification of short tandem repeat (STR) polymorphisms is the golden standard for chimerism analysis. To detect early signs of graft rejection, chimerism analysis should be done at regular intervals and shortly after the allogeneic HSCT.

Product Description

ChimerisMonitor IVD is an advanced software for an automated data analysis, evaluation of electropherograms and chimerism calculation. The integrated Patient Management system allows to monitor chimerism kinetics in high resolution reports, but also in graphs and tabular visualization. Within each patient the transplantation history and chimerism kinetics over time can be assessed. Informative markers are logged prior the allo-HSCT according to the respective donor profile. After the allo-HSCT, a semiquantitative analysis of selected informative markers can be carried out and patient or donor chimerism [%] is calculated as mean and for each marker respectively.

All required analysis templates are included in the Test Kit Management system of ChimerisMonitor IVD. Those contain analysis methods as well as linked Bin and Panel templates. The software is performing a general, integrated run and sample validation during the batch import according to the requirements of Mentype® Chimera® PCR Amplification Kit and Mentype® DIPscreen PCR Amplification Kit. In addition, the quality of run and sample data can be assessed visually in 5 panels of electropherograms (6-FAM, BTG, BTY, BTO, BTR) as well as via size calling regression.

Materials provided

The ChimerisMonitor IVD Software is available for download via www.biotype.de/en/products/chimerismonitor.

It is strongly recommended to use ChimerisMonitor IVD for an accurate and simplified analysis of data obtained with Mentype® Chimera® PCR Amplification Kit or Mentype® DIPscreen PCR Amplification Kit.

Material and devices required

License keys

ChimerisMonitor IVD is a license-based software application. Trial licenses, 1-year or 3-year licenses can be ordered via sales@biotype.de (for details see Table 1). The local system-identificator, the order number, desktop or client application and desired type of license must be included when ordering.

For detailed information about how to activate the software with a license key, please refer to chapter Activating software with license.

NOTE

The validity of license keys is displayed in the bottom bar. If the license is expiring within the next two months, the days until expiration are counted down.

Table 1. Ordering information licenses ChimerisMonitor IVD

Licenses	Supplier	Order number
ChimerisMonitor IVD - Trial version - 1-year license - 3-year license	BIOTYPE GmbH	46-14800-0000

Kits intended to be analysed with ChimerisMonitor IVD

The software ChimerisMonitor IVD is an application that supports the data analysis of the IVD assays Mentype® Chimera® PCR Amplification Kit and Mentype® DIPscreen PCR Amplification Kit as described in Table 2.

Table 2. Assays intended to be analysed with ChimerisMonitor IVD

Reagent	Supplier	Order number
Mentype® Chimera® PCR Amplification Kit	BIOTYPE GmbH	45-12200-0025 45-12200-0100 45-12200-0400
Mentype® DIPscreen PCR Amplification Kit	BIOTYPE GmbH	45-12300-0025 45-12300-0100

System requirements desktop version/ database computer

Table 3. System requirements desktop version/ database computer

Specification	Requirements
Operating System	Windows 10 or 11
Free Harddisk	1 GB + Database
Processor	2 GHz Dual-Core
RAM	4 GB RAM

System requirements client computer

Table 4. System requirements client computer

Specification	Requirements
Operating System	Windows 10 or 11
Free Harddisk	1 GB
Processor	2 GHz Dual-Core
RAM	2 GB RAM

Input data

The software analyzes fsa-files generated on Genetic Analyzers of Thermo Fisher Scientific (Applied Biosystems division). The data import is carried out in batch. In the process the run evaluation is carried out according to the respective requirements of the test kit.

Warnings and Precautions

- Read the Instructions for Use carefully before using the product.
- Before the first use, check the system requirements. Consult your local IT for installation procedures and refer to chapter Installation. Administrator rights are needed for installation.
- The user is responsible for installing the application in a secure environment with regard to the operating system, network and data backup and for taking appropriate Cybersecurity measures.
- ChimerisMonitor IVD is a license based software application, please include the system-identificator, order number, use with local database or as network database and desired type of license in your order.
- If personalized access to the software is unauthorized or restricted, please contact the software administrator.
- There are no further residual risks for the intended user.

Notice to the user

Any problem that has occured in relation to the product shall be reported by the user to the manufacturer. Any serious incidents related with this software must be reported to the manufacturer and the appropriate authority of the member states in which the user and/or the patient is established.

A Summary of Safety and Performance (SSP) is created in accordance with Article 29 of Regulation (EU) 2017/746 and intended to provide public access via EUDAMED database to an updated summary of data on safety and performance of the device to intended user, in the case of this product laboratory professionals only.

Installation

Installation process

The present software can be installed either as a desktop or network version. Decide which version is needed, before the application is installed.

Within the desktop version the database is installed locally on a computer. Other users have no access to this database. Using a network version and a central database for several clients, no separate database is created on the individual computers in the network.

Before installing the software, please close all active applications to prevent potential conflicts or errors during the installation process.

NOTE

You need administrator rights to install the software. The installation of the present software is to be carried out only by IT personnel. For installation, data backup and validation of the software and therefore for the integration of the software into the existing software environment and in the applied quality management system, the user is responsible and accountable.

1. Start the installation by executing the ChimerisMonitor IVD.exe.
2. Choose your preferred installation language (English).
3. The installation assistant will guide you through the setup. Click ***Next*** to go on.
4. Read the license terms carefully and accept them by clicking on ***I Agree*** to continue with the setup.
5. Select a destination folder where the ChimerisMonitor IVD Client program will be installed into.
6. Select the Start Menu folder where the programm shortcuts will be created.

7. Select the type of installation of ChimerisMonitor IVD. The components to be installed will be pre-selected accordingly:
    a. Desktop (default): For single user installations. All components will be installed on the same computer.
    b. Client/-Database: For multi-user installation, if different users are working with separate client PCs and the database will be installed on a central server. Select ***Database*** when installing the database on the central server. Select ***Client*** to install the client application on the user computers.
8. Select ***Install*** to proceed. The installation progress will be shown in detail in the installer's console window.
9. During desktop or database installations, the installer verifies if a former ChimerisMonitor 2.1 database exists locally on the computer. The database can be selected for the import into ChimerisMonitor IVD.
10. After successful installation the installer allows the creation of an additional desktop shortcut.
11. If an error occurs during the installation, the process will be stopped and the installation is terminated by clicking on ***Cancel***. The console content can be copied by right-clicking and may be saved for further analysis.

Import of the ChimerisMonitor 2.1 database

The import of an existing ChimerisMonitor 2.1 database is handled by the installer during the installation process. The import is only possible during the first time installation of ChimerisMonitor IVD. The installer searches only in the ChimerisMonitor 2.1 default database folder C:\ProgramData\Biotype\ChimerisMonitor\database for an existing ChimerisMonitor 2.1 database.

If a ChimerisMonitor IVD database is already existent, the import option is no longer available and the step is skipped during the installation.

Activating software with license

The software checks on login if a valid license is installed. If there is no valid license found, a dialog is presented showing the System-Identificator for the local system. The System-Identificator is necessary to order a license key. In order to activate the software, the purchased license key must be copied into the field ***License*** (see Figure 1). Click ***OK*** to unlock the application.

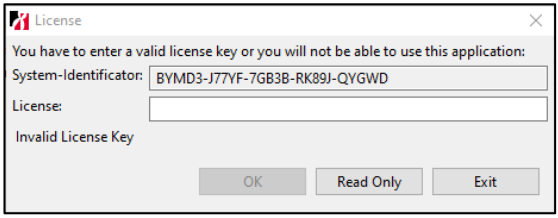


Figure 1. Licence key dialog

Alternatively, the application can be opened in read-only mode, where no changes to patient data is possible. The read-only mode allows only viewing and filtering within the Patient Management, opening the Patient Editor as well as Report generation and CSV export.

Login

ChimerisMonitor IVD is a password protected application. Thereby the software supports the setup of users with optionality of administrator rights.

User specific logins enable the traceabality of Batch Import and Report generation.

NOTE

For creation and management of user profiles please refer to chapter User Management.

It is recommend to add new users after the first login.

For the first login please use the following data:

Table 5 First login data

First user name	admin
First password	admin
Server	localhost resp. IP address*

*Select the server localhost if using the desktop version. If a central database is used in the network, the IP address of the database computer must be entered as server

Click ***Finish*** to login.

NOTE

The administrative user is responsible to change the generic first login password to a personal and secure one.

Overview of the Workflow - Quick Guide

Table 6. Quick guide for automated chimerism analysis

No.	Icon	Working step
1		Sample Import
		***Create new patient***. A database of all created patients is represented in the Patient Management
		***Batch Import:*** - Select the test kit ***Biotype Mentype Chimera*** or ***Biotype Mentype DIPscreen*** - All thresholds for the correct run and sample evaluation are linked to the respective analysis method. - Import a run containing fsa-files of the allelic ladder, positive control, no-template control, and the samples.

No.	Icon	Working step
		- Select sample types manually (essential for correct peak assignment and chimerism calculation) - General run evaluation is carried out by the software
		Open the ***Batch Import Management***
		***Assign Sample:*** Select a sample and assign it to the patient
2		Check controls – ChimerisMonitor IVD performs an integrated quality check and a run evaluation according to the test kit requirements
		Check the ***Allelic Ladder Electropherogram*** and ***Size Calling Regression*** Possible quality warnings are displayed… - Within tab ***Run Validation*** during the Batch Import - Within tab ***FSA Import Error and Warnings*** in the Patient editor
		Check the ***Positive Control Electropherogram*** and ***Size Calling Regression*** The ***Run Validation*** during the Batch Import displays possible quality warnings.
		Check the ***No-template Control Electropherogram*** and ***Size Calling Regression*** The ***Run Validation*** during the Batch Import displays possible quality warnings
3		Sample evaluation
		Check the ***Sample Electropherogram*** A correct peak assignment is essential for an accurate definition of informative markers and a robust chimerism calculation. The ***Sample Quality check*** during the Batch Import displays possible quality warnings

No.	Icon	Working step
		Check the ***Sample's Size Calling Regression*** The ***Sample Quality check*** during the Batch Import displays possible quality warnings
4		Definition of informative markers
		***Create a new transplantation:*** Predefined markers can be selected for patient monitoring
5		Chimerism Analysis
		***Calcalculate Chimerism:*** See preselected markers for chimerism analysis and carry out chimerism calculation (single marker chimerism, total chimerism and standard deviation)
6		Report
		***Create Report***: Single values and chimerism kinetics are displayed over time (table and graph, file format pdf or ***Export Patient*** function also in csv)
7		Build a database-driven system for ***Patient Management***

User Interface

The user interface of ChimerisMonitor IVD is organized in several sections. These display detailed patient information, Patient Management and detailed sample or transplantation information. The toolbar includes several general functions for the data and patient management. All sections are defined in Figure 2.

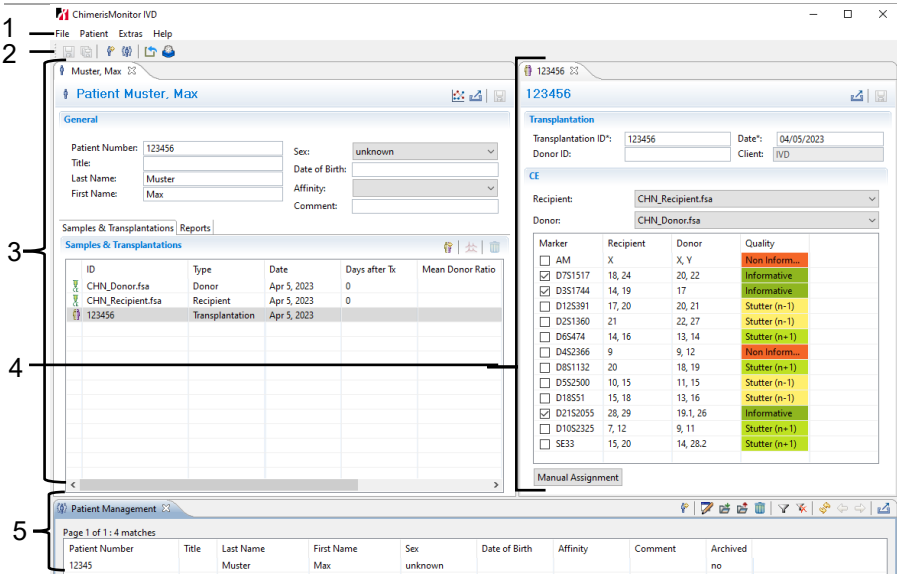


Figure 2. Sections of the user interface

Table 7. Description of the User Interface

No.		Description
1	Menu Bar	The menu bar is situated in the upper range of the main window directly below the title bar. It includes different menus, like ***File*** and ***Extras***, which give access to specific functions.
2	Toolbar	The toolbar consists of several buttons, tagged with icons. These buttons give access to functions of the program and can be active (coloured) or inactive (grey). Toolbars exist in many parts of the software, for instance within specific overviews or editors.
3	Patient Editor	The window Patient Editor can be displayed after a patient was created or opened from the ***Patient Management*** via double click on the selected patient in the table or the icon ***Show Patient***. The Editor displays general information on the patient and a tabular list of samples and transplantations.

No.		Description
		Within the Patient Editor the ***Sample- and Transplantation Editor*** is accessible via a double click on the respective line in the table.
4	Sample/ Transplantation Editor	Sample- and Transplantation Editor are windows, which display details of the specific dataset. The ***Sample Editor*** displays general information on the sample, a toolbar and depending on the sample type also detailed Chimerism calculation values. The ***Transplantation Editor*** displays general information on the event, an assignment of donor and recipient sample as well as the selection of informative markers. For detailed information please refer to chapter Sample Editor or Transplantation Editor.
5	Management	The Management section displays collections of specific datasets. ***Patient Management*** (see Figure 2) shows a collection of all patients and general information like name, sex or date of birth. ***Batch Import Management*** displays all imported run data, that passed the run and sample validation process. Within this overview single samples can be assigned to the respective patient. ***User Management*** displays an overview of all created user accounts with their respective rights and allows editing as well as creation of user accounts.

The user interface of ChimerisMonitor IVD offers extensive possiblities for rearrangement, allowing users to make adaptations to their personal preferences. Windows can be rearranged within the software by drag and drop.

Dialogs and Assistants

Dialogs are windows that are detached to the main window. They can be displaced from the main window and moved independently.

Assistants are dialogs with several steps through a workflow. Within this manual both terms will be used synonymously. Dialogs can be used for adding or visualizing data or they assist calculation or reporting procedures.

While a dialog is open or a process is ongoing, the access to the main window is locked.

Windows

Windows show data and enable its editing.

- Closing Windows

  Windows stay active until the window is closed or the program is exited. Individual windows can be closed by clicking the  ***Close*** button next to their window title. Alternatively, use the pop-up menu of the window title to close windows by right click. Windows are not closed automatically when a new one is opened. Tabs allow switching between different windows. The order of the tabs can be be changed by dragging and dropping.

Table 8. Functions within windows pop-up

Function	Description
Close	Closes the selected window
Close other	Closes all windows in the editor area but the one selected
Close all	Closes all windows in the editor area

- Adjusting width and height of a window

  To adjust the window size, place the mouse pointer onto the border of the window. A double-headed arrow allows changing of the window size to desired parameters. Use functions like  Minimize and  Maximize or double-click on on tabs to adapt the window size. After a window is maximized, the whole main window is occupied. This can be reversed by clicking on the  Restore button.

- Relocating windows

  To relocate windows, click on the corresponding tab and move it by dragging and dropping.

- Detaching windows/editors

  Editors can also be detached from the main window and the general user interface. To detach an overview, open the pop-up menu and select the item ***Detached***. Repeat the procedure to reverse the display.

Tables and sections

Tables and sections are displayed in different windows. They are used to collect detailed information about data or patients. To analyze your patient data as conveniently and effectively as possible, the following functions can be used:

- Fade in, fade out sections

  Labelled sections in editors show blue arrows. Sections can be faded in and out by clicking on the arrow icon.

- Adjusting width of table columns

  To adjust a column width, place the mouse pointer onto the border of the column. A double-headed arrow allows to change the column width.

- Selecting elements

- Several elements can be selected at once by clicking and holding the CTRL key while clicking on the desired elements. Within the Batch Import Mangement only single files can be assigned to each patient.Shortcuts

  Several shortcuts can be used to access several functions of ChimerisMonitor IVD. They are based on Windows standards and are listed in Table 9.

Table 9. Shortcuts for ChimerisMonitor IVD

Shortcut	Function
CTRL + A	Select all
CTRL + S	Save
CTRL + Shift + S	Save all
CTRL + F7	Change view

Functions of ChimerisMonitor IVD

Basic functions of the menu bar

File

Within ***File*** basic functions of the software can be controlled.

Table 10. Functions for menu bar - *File*

Function	Description
Logout	To log off the current user
Login	To log in a specific user
Exit	To terminate the program
Save	To save modifications
Save all	To save all modifications

Patient

Within the ***Patient*** menu, new patients can be created or existing patients can be displayed and edited within the ***Patient Management***. To create a new patient, go to ***Patient > Create New Patient*** within the menu bar or click on the icon  ***Create New Patient*** in the tool bar. A dialog to create a new patient data sheet will open (see Figure 3).

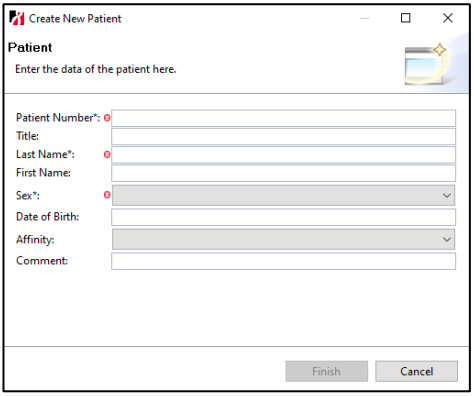


Figure 3. Create new Patient dialog

For detailed instructions for the Patient Management refer to chapter Functions within Patient Management.

Extras

This menu provides basic information and software settings which can be modified if necessary.

Reference data

Open ***Extras > Reference*** data to obtain information on Test Kit and Size Standard Management.

Test Kit Management

The Test Kit Management includes all Bin and Panel data for supported BIOTYPE test kits. These are important features to realize allele calling and to validate positive and no-template controls during the batch import according to the requirements of the test kit.

Details can be displayed by clicking on ***View***. Information about included markers, stutter limits, allele sizes, and tolerances are summarized within the overview. The history of test kits can be opened by clicking ***History***.

Open the Test Kit Management within the menu bar under ***Extras > Reference data > Test Kit Management.***

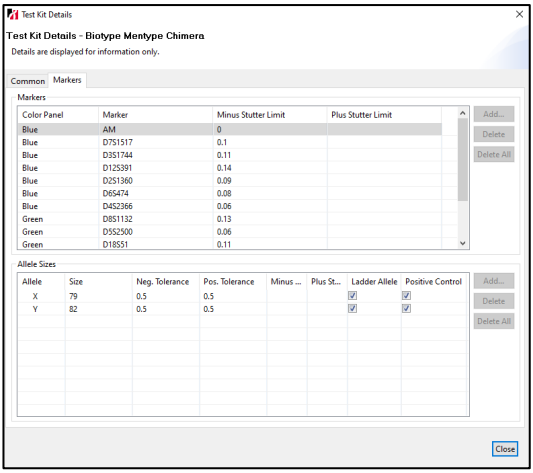


Figure 4. Test Kit Management details of e. g. Mentype® Chimera® PCR Amplification Kit

Size Standard Management

Size standards are required for the exact size calling of raw data. Open the Size Standard Management within the menu item ***Extras > Reference data > Size Standard Management***. All required definitions for the application of Mentype® Chimera® PCR Amplification Kit and Mentype® DIPscreen PCR Amplification Kit are listed and can be displayed in detail by clicking on ***View***.

Overwrite Password

Users with administrator rights within the application can change passwords and assign new ones. Please enter the new password. Then please retype the new password. Click ***Finish*** to save or ***Cancel*** to reject the changes.

User Management

To open User Management select the menu item ***Extras > User Management.*** It contains a table showing the user names of all user accounts including their role (e. g. administrator). All functions required for user administration by an admin can be accessed using the buttons in the tool bar (see Table 11).

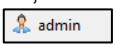
NOTE

User accounts can only be edited by administrators

Table 11. Functions within the User Management

Icon	Function	Description
	Create User	Specify information to set up a new user
	Edit User	Change the status or information about the selected user
	Overwrite Password	Change the password of the selected users by an admin
	Delete	Delete the selected user

NOTE

The user, who is currently logged in is displayed in the bottom bar. 

License Management

To open the License Management select the menu item ***Extras > License Management***. The overview contains information of all installed licenses for ChimerisMonitor IVD. The active license is displayed with a golden key icon, whereas inactive licenses are marked with a silver key icon.

The installation and expiry date can be tracked in the displayed table. If required, new license keys can be added after the first login. Click ***Add License*** and enter the new license key.

NOTE

New licenses can be orderd via sales@biotype.de with the following order number 46-14800-0000. Please include the validity period, when ordering - trial versions, 1 year or 3 year licenses can be purchased. The local system identifier and desktop or client application must also be specified.

NOTE

Within the bottom bar notes for expiring licenses are displayed. License expires in 24 days

Preferences

To open the user preferences select the menu item ***Extras > Preferences*** (see Figure 5). Within the preferences users can specify their preferred settings for the bioinformatic analyses, resulting reports and visualization of electropherograms.

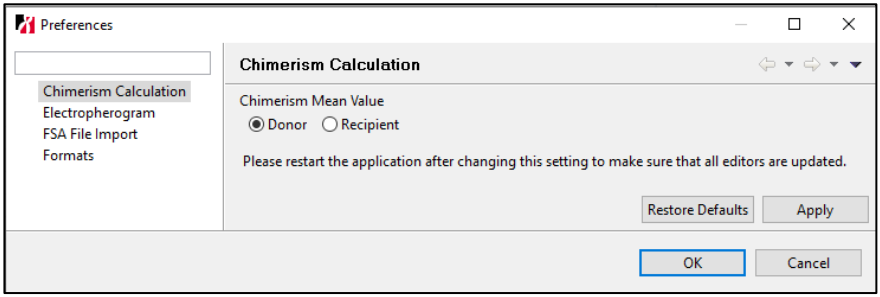


Figure 5. Preferences that can be adapted by users

- **Chimerism calculation**

  The output for chimerism calculations can be specified within Chimerism Calculation (***Extras > Preferences > Chimerism Calculation***). The output option for chimerism mean and single values in % Donor or % Recipient can be selected.

- **Electropherogram**

  Users can specify their preferred display settings for the electropherogram within this dialog.

  Use the button ***Restore Defaults*** to reset all modifications to default settings. Click ***Apply*** to save changes and keep preferences menu open or ***OK*** to save settings and close preferences. Click ***Cancel*** to close preferences and discard the changes.

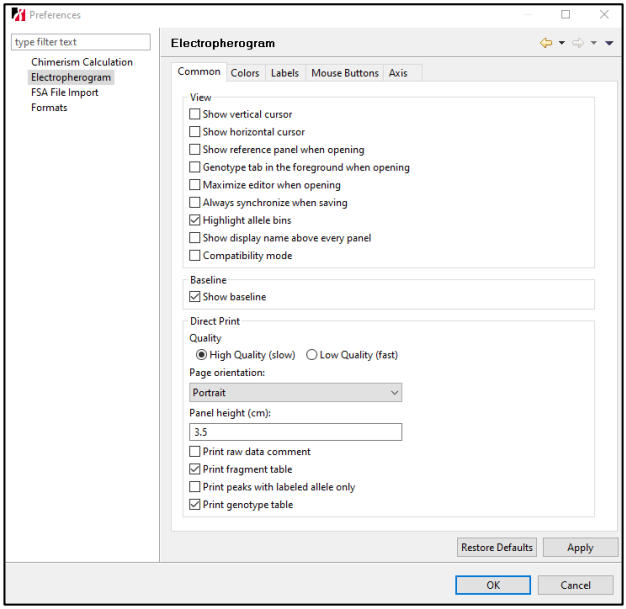


Figure 6. Electropherogram display settings

The settings can be modified within different tabs (see Table 12).

Table 12. Functions for editing electropherograms

Tab	Function	Description
Common	Show vertical/ horizontal cursor	By activating these functions vertical and/or horizontal cursors will indicate the position of the mouse pointer within the coordinate system. Select the color of the cursors within the tab ***Colors.***
	Show reference panel when opening	Select this option to fade in or out the reference color panel (color of the size standard) when opening an electropherogram.
	Genotype tab in the foreground when opening	Select this option to see the genotype tab in front instead of the fragment tab when opening an electropherogram.

Tab	Function	Description
	Maximize editor when opening	Check this box to maximize electropherogram and size standard regression views while opening.
	Always synchronize when saving	Select this option for automatic synchronization of changes within the electropherogram-coordinate system and the fragment/genotype table.
	Highlight allele bins	Deactivate this option if allele bins should not be highlighted in grey within the electropherogram
	Show display name above every panel	Select this option to display the name of the raw data file above every panel within the electropherogram. This setting might be important when printing the electropherogram.
	Compatibility mode	Activate it, if problems occur while viewing an electropherogram. In most cases problems will be fixed by this option
	Show baseline	This option determines whether or not the baseline is displayed.
	Quality	Select if direct prints of electropherograms should be done with high (slow printing) or low/medium quality (fast printing).
	Page orientation	This setting affects the orientation of the electropherograms within the print. Choose between ***Portrait*** or ***Landscape.***
	Panel height (cm)	Defines the height of the panel (cm) within the print.
	Print raw data comment	Select this option if comments imported from raw data should be included in the

Tab	Function	Description
		print (displayed above the coordinate system).
	Print fragment table	Select this option to print the electropherogram and the corresponding fragment table.
	Print peaks with labeled alleles only	Select this option if the print of the table information should be restricted to labeled alleles only.
	Print genotype table	Select this option to print electropherogram and the corresponding genotype table.
Color	Specify colors for cursors, peak height, size and area as well as for artefacts.	
Labels	Choose individual colors for the labels. Specify fonts for different elements and select to which sample type labels should be assigned. Furthermore you can decide which peak information should be indicated in a coordinate system.	
Mouse Buttons	Different functions to mouse buttons can be assigned to work within electropherograms. By choice, a mouse click could assign or delete an allele, open the pop-up menu of a specific peak or select a peak. All four options could be assigned to a desired mouse button and the operation mode could be switched between single or double click. Please notice that changes made here will become active only for electropherograms opened after saving.	
Axes	Specify axes and scaling of axes within the electropherogram.	
	Position of the X/Y-axis scale	Select where axes will be displayed in the coordinate system (bottom or/and top or left or/and right of the coordinate system).
	Unit of the X-axis:	Choose the unit of the X-axis: data point or (calculated) base pairs. By default, base pairs will be displayed.
	Use equal RFU scale for all panels by default	Select this option to decide whether RFU scale of all panels is in the same range

Tab	Function	Description
		by default or RFU scale of panels is adapted to the respective peak heights. Equal scaling can also be directly switched on and off by clicking ***Equalize Zoom*** within the electropherogram editor.
	Show this range of the electropherogram	Select this option to define which range is displayed in the electropherogram. The X-axis will be adjusted to this range. By default whole area of data points above the cut off will be displayed. Please notice that changes made here will become active only for electropherograms opened after saving.

- **Data Analysis**

  ChimerisMonitor IVD supports the import and evaluation of raw data of different sequencer formats (fsa files). The program identifies peaks and artefacts as part of the process and is also capable of assigning peaks to alleles and, thus, to generate DNA profiles. For a detailed description of raw data analyses of fragment analysis data, please refer to chapter Analysis of Electropherograms and Procedure for chimerism analysis. Find Analysis Methods within the path ***Extras > Preferences > Data Analysis > Analysis Methods.*** Detailed parameters of the Analysis Methods ***Chimera IVD*** and ***DIPscreen IVD*** can be displayed by clicking ***Show***.

NOTE

Analysis methods are part of the IVD certified process and therefore they can not be adjusted. For assistance within data analysis and run validation please contact support@biotype.de.

- **Formats**

  The preferred date format can be edited: e. g. yyyy-mm-dd

NOTE
Coherent dates are important to create transplantations and to define sample types.

Functions within editors

Patient Editor

The ***Patient Editor*** represents the central overview for patient-specific data management and subsequent calculations within the software.

All ***Samples & Transplantations*** of the patient are displayed in tabular form. In addition, results of conducted chimerism calculations can be reviewed within the overview or reports can be generated and will be collected in the tab ***Reports***. All possible functions within the ***Patient Editor*** are summarized in Table 13.

Table 13. Functions within the Patient Editor

Icon	Function	Description
	Create Report	Create a monitoring report for chimerism analysis
	Export Patient	Detailed patient information is exported in csv
	Save	Save changes
	Delete	Delete a sample or transplantation. To delete a transplantation no recipient or donor files should be selected within the transplantation
	Open Electropherogram	Open the Panel Editor: All electropherograms of selected CE-samples are displayed
	Create new Transplantation	Create a new transplantation. For details refer to chapter Transplantation Editor.

Create Report

To record the monitoring of a patient, a report function is available. This report contains results of the most recently performed calculations that are depicted in tabular form (see Figure 7, a) and are sorted with respect to the used method. Moreover, the report displays the overall monitoring course of the patient in a graph (see Figure 7, b).

To create a report, click on the icon  ***Create Report*** in the upper rigth part of the ***Patient Editor***.

You may fill in respective free text fields (Subject, Comments). This information will be incorporated in the report.

Click ***OK*** to start automated compiling.

The report will subsequently be converted to PDF format for printing or saving the results. Already compiled reports will be saved in the tab ***Reports*** in the ***Patient Editor*** and can be opened with a double click or deleted with a click on the icon  ***Delete File***.

a

This report was created using an IVD analysis kit and analysis software. ChimerisMonitor IVD

Chimerism Report

Patient Information	
Name	Muster, Max
Patient ID	123456
Date of Transplantation	04/05/2023
Donor ID	

Report Information	
Days after Transplantation (Tx)	2
Calculation	% Donor
Subject	
Comments	

Current Test Result

Sample ID	Days after Tx	Sample Material	Marker	Chimerism
CHN_postTx2.fsa	2	PB	D7S1517	34.074%
			D3S1744	28.449%
			D6S474	22.540%
			D10S2325	30.808%
			SE33	34.157%
			Mean:	**30.005%**
			SD:	**4.811%**

b

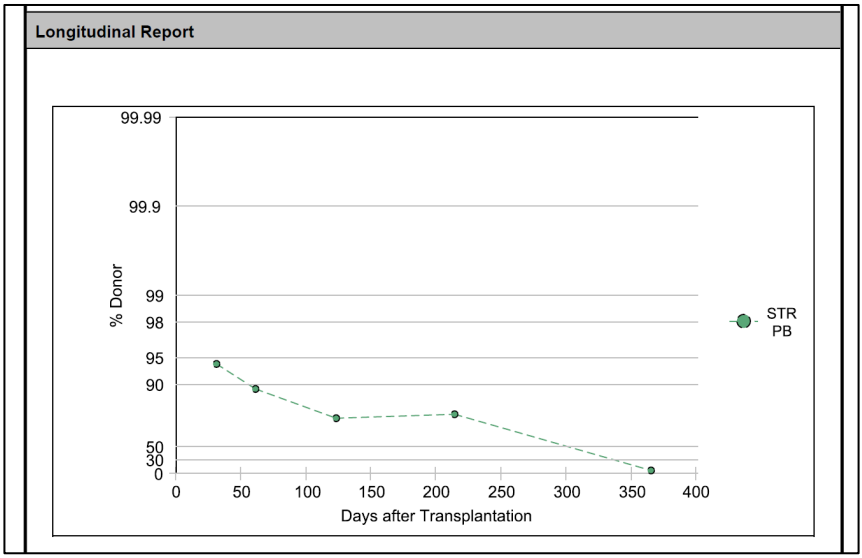


Figure 7. Chimerism report in (a) tabular form and (b) as longitudinal report

Export Patient

To generate the monitoring of a patient as a processable csv file, an export function is available. This export contains the general patient information as well as all information displayed in the ***Samples & Transplantations*** table.

The export will be generated as a csv file via file explorer in a selectable location.

NOTE

Please note that depending on the settings of the operating system or used spreadsheet software, additional steps to separate information in different cells might be necessary.

Sample Editor

The ***Sample Editor*** (see Figure 8) can be opened by double-clicking on single CE-samples in the tabular display of the ***Patient Editor***. The overview contains general sample information and a table of chimerism values for each marker after the calculation has been performed.

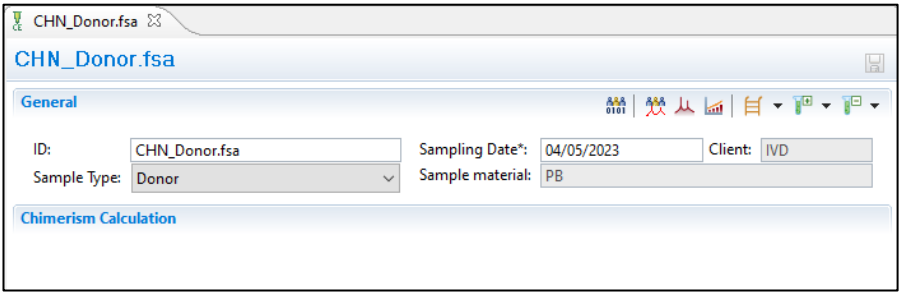


Figure 8. Section of the Sample Editor

The ***Sample Editor*** is divided into three sections. Within the ***General*** section further parameters (see Table 14) are defined for each sample. Define respective parameters as they are necessary for successful transplantation setups or chimerism calculations.

Table 14. Information defined within the general tab of the Sample Editor

Information	Description
Sample Type	Defining the ***Sample Type*** is essential for setting up transplantations or chimerism calculation, choose between ***Recipient*** (prior allo-HSCT), ***Donor*** or ***PostTx*** (Monitoring sample after allo-HSCT)
Sampling date	Define the date of sampling. Samples with the type ***Recipient*** and ***Donor*** must have a date prior to transplantation date. Samples with type ***PostTx*** must have a date after transplantation date

Information	Description
Sample material	Defines tissue or origin of the sample. For the application of Mentype® Chimera® PCR Amplification Kit and Mentype® DIPscreen PCR Amplification Kit ***PB*** as peripheral blood is preselected for the IVD Client and cannot be changed
Client	Describes the software status. *IVD* is defined according to Regulation (EU) 2017/746 (IVDR). Samples processed in The ChimerisMonitor RUO application display the *RUO* as client. Database entries imported from ChimerisMonitor 2.1 application display the Client *Transfer*

Confirm all modifications within the Sample Editor by clicking  ***Save*** within the menu bar of the main window. Otherwise, you will be asked to confirm your changes when closing the ***Sample Editor*** or when starting certain calculations. To confirm, click ***Yes***. To close the Sample Editor without saving the changes click ***No*** or click ***Cancel*** to return to the ***Sample Editor***.

NOTE

Changes to samples will not be automatically applied to already finished calculations or transplantations which are associated with these samples. Therefore all calculations and transplantation settings have to be repeated or reset if used retrospectively.

The section ***Chimerism Calculation*** within the ***Sample Editor*** serves as a tabular overview for the calculation results of monitoring samples. The section is active after a successful calculation. Subsequently, the calculated values will also be summarized within the ***Samples & Transplantations*** view of the ***Patient Editor***.

The section ***FSA Import Errors and Warnings*** shows all possible warnings regarding sample or run quality. Before further processing check electropherograms and size calling regressions.

Several functions of the Sample Editor can be selected via the toolbar. For detailed descriptions see Table 15.

Table 15. Functions within the Sample Editor

Icon	Function	Description
	Calculate Chimerism	Guided process with display of detected markers, marker selection for chimerism analysis and chimerism calculation (single marker chimerism, total chimerism and standard deviation)
	Open Chimerism Panel	Display of electropherograms from postTx- samples, donor and recipient profiles. Compare profiles and check possible positions for recipient-specific alleles
	Open Electropherogram Editor	Display of the Sample Electropherogram Sample validity is checked within the batch import, but always perform a plausibility check. A correct peak assignment is essential for an accurate definition of informative markers and a robust chimerism calculation
	Open Size Calling Regression	Sample's Size Calling Regression Display of the size calling regression line and quality value. Additionally a table with details on the peaks and their quality is shown. The Sample Quality Check during the Batch Import displays possible quality warnings
	Open Allelic Ladder Electropherogram	***Allelic Ladder Electropherogram*** and its ***Size Calling Regression*** Possible quality warnings are displayed… Within tab ***Run Validation*** during the Batch Import Within tab ***FSA Import Warnings*** in the Patient View
	Open Positive Control Electropherogram	***Positive Control Electropherogram and Size Calling Regression*** The Evaluation of Positive Controls during the Batch Import displays possible quality warnings

Icon	Function	Description
	Open No Template Control Electropherogram	***No Template Control Electropherogram*** and ***Size Calling Regression*** The Evaluation of No Template Controls during the Batch Import displays possible quality warnings.
	Save	Save all modifications made

NOTE

Formulas for chimerism calculation can be reviewed within chapter Semi-quantitative analysis – chimerism analysis

Analysis of Electropherograms

The analysis of sample and control electropherograms is an important part for a reliant quality assessment.

NOTE

Even though a general run and sample vaidation is performed automaticially during the Batch Import, always check results for plausibility. Reviewing electropherograms is an important part to assess sample and device performance

All electropherograms represent a graphical output of analysed raw data from capillary gel electrophoresis. ChimerisMonitor IVD offers a special graphic user interface for the visualization of electropherograms. For the assessment of the selected sample electropherogram click on ***Open Electropherogram Editor***, for the Positive Control choose ***Open Positive Control Electropherogram*** via the icon and for the No Template Control ***Open No Template Control Electropherogram*** via the icon .

For possible adaptions of the visualization according to the users preferences please select ***Extras > Preferences > Electropherogram*.**

The Electropherogram Editor (see Figure 9) contains a menu bar including several functions (see Table 16) and analyzed raw data of the capillary gel electrophoresis displayed in preselected panels. The unit of the Y-axis of the coordinate system is RFU, whereas the shared X-axis uses *base pairs* or *data points*.The coordinate systems do always display the same range of the X-axis. Additionally, detailed information about ***Fragments***, that includes absolute values like data points, alleles, marker, size, height, area and QC flags, but also the ***Genotype*** are displayed in tables below the electropherograms.

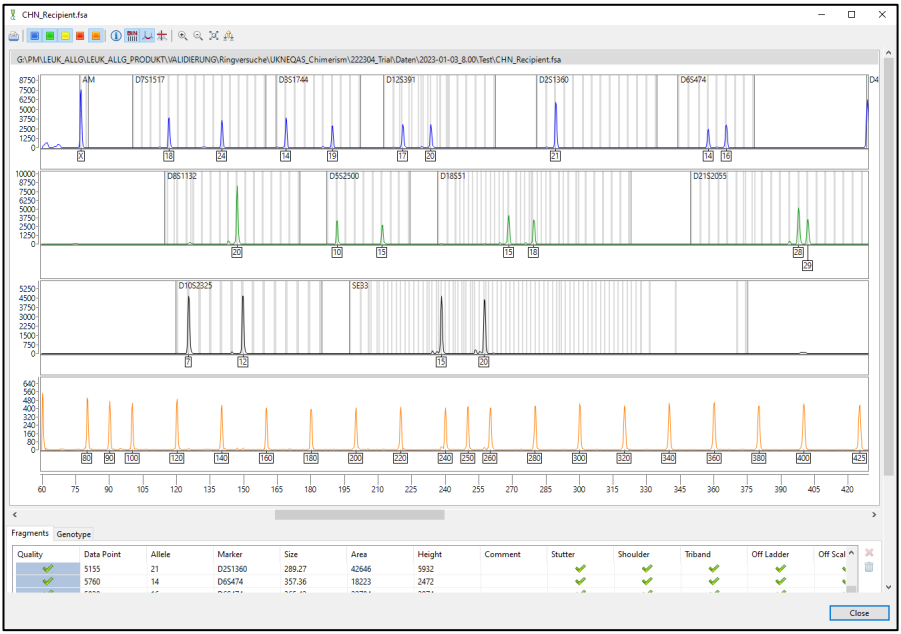


Figure 9. Electropherogram Editor, e.g. sample from Mentype® Chimera® PCR Amplification Kit Analysis

The following functions can be used, when working with the ***Electropherogram Editor*** (see Table 16).

Table 16. Function within Electropherogram Editor

Icon	Function	Description
	Print	Print the electropherogram in its current state, including the current scaling, the panel and label selection as well as the two tables. To change the printing preferences, go to Extras > Preferences > Electropherogram > Direct Print.
	Dye Selection	Select any desired color to show or hide the referring color panels.
	Display Name Above Every Panel	The sample name can be displayed permanently above the panels. This has no impact on the printing preferences.
	Show/Hide Allele Bins	Deactivate or activate allele bins, that are represented by grey stripes in the coordinate systems.
	Show/Hide Baseline	For a simplified analysis the baseline can be displayed or not.
	Show/Hide Cursor	The position of the mouse pointer can be indicated by cursors in a color of choice (see preferences).
	Zoom In	Change the Panel view by zooming in.
	Zoom Out	Change the Panel view by zooming out.
	Fit	Come back to the complete representation of the active panel.
	Equalize Zoom	Determine, whether the Y-range of all panels shall always be the same, meaning if you zoom into one panel, the other ones will be magnified as well or whether the zoom into one panel should work independently.

NOTE

Quality Flags summarize whether artefacts have been detected or not or if the identification is not safe and need to be checked . This includes: Stutter, Shoulder, Tri-Band, Off-ladder, Off-scale and Spectral Overlap and if maximum peak height (MPH) and maximum peak width (MPW) were overstepped or not.

Analysis of Size Calling Regression

The Size Calling Regression is an important method for an exact length assignment of amplicons in each panel. Next to the allelic ladder performance, it is one of the prerequisites for exact allele assignments.

The analysis of size standards can be assessed within each sample, allelic ladder, positive and no template control by clicking the respective icons (see Table 15) within the ***Sample Editor***. The ***Quality of Regression*** should not exceed 0.995 for the application of the DNA Size Standard 550 (BTO) within the Mentype® Chimera® PCR Amplification kit or Mentype® DIPscreen PCR Amplification Kit analysis.

NOTE

The size standard validity is checked as part of the sample and run validity test within the batch import.

Similar functions as for the analysis of electropherograms (see Table 16) can be used within the tool bar of the Size Calling Regression Editor (see Figure 10).

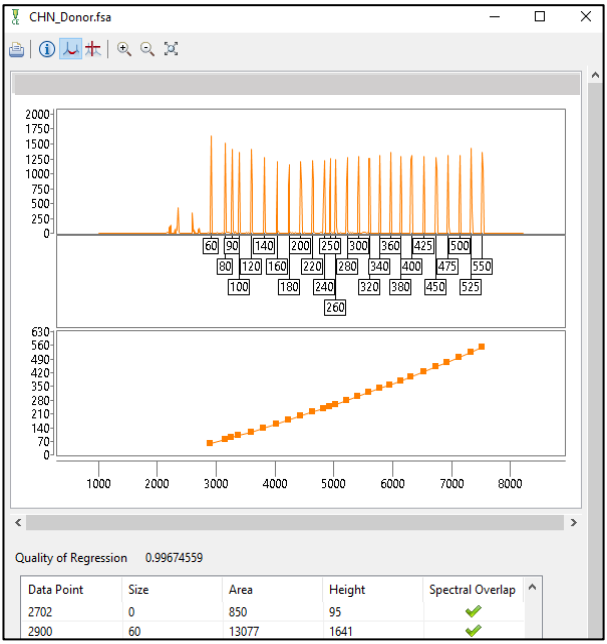


Figure 10. Size Calling Regression for DNA Size Standard 550 (BTO)

Transplantation Editor

After having successfully defined donor and recipient samples, a transplantation can be set up to which these can be assigned.

To assign the transplantation to a patient, click on the icon  ***Create new Transplantation*** in the ***Sample Editor***. In Figure 11 an exemplary transplantation setup is shown. Perform the following steps to create a transplantation:

1. Assign a ***Transplantation ID***.
2. Assign the ***Date*** of the transplantation. This entry is mandatory in order to select recipient and donor samples.

3. Optional: Assign a ***Donor ID*** for an unambiguous definition of the transplantation.

4. Choose respective donor and recipient (Pre Tx) samples in the ***CE***-section.

NOTE

Only sample types defined as Recipient and Donor and with a date of sampling prior to the date of transplantation are depicted.

5. After the selection of the reference data, the genotype of all markers for donors and recipients enclosed in the kit will appear in the ***Transplantation Editor*** (see Figure 11).

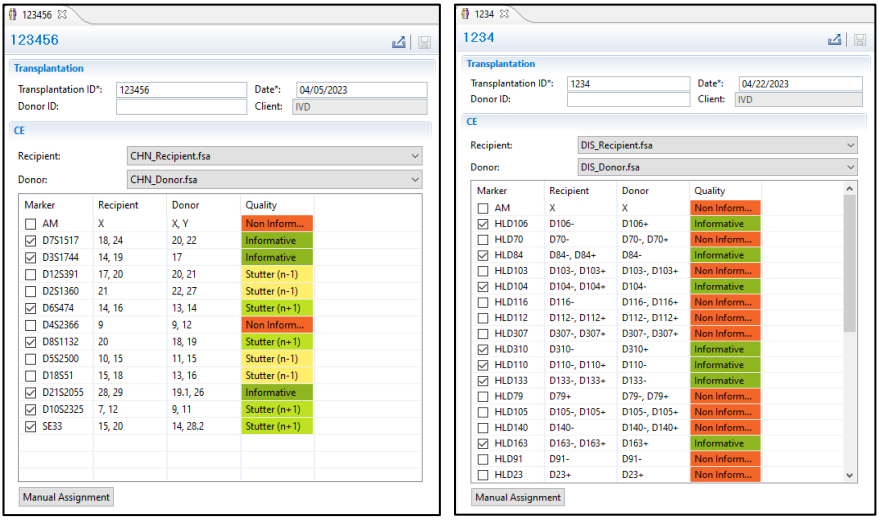


Figure 11. Transplantation Editor with the exemplary application Mentype® Chimera® PCR Amplification Kit on the left and Mentype® DIPscreen PCR Amplification Kit on the right.

6. Determine which markers should be chosen as standard to calculate the chimerism status of the respective transplantation. Please refer to

the instructions for use of Mentype® Chimera® PCR Amplification Kit or Mentype® DIPscreen PCR Amplification Kit. Please refer also to chapter Setting up a transplantation.

If no donor or recipient sample is available, it is also possible to choose ***Manual Assignment***. By selecting the respective button it is possible to choose the assay and add the known genotype.

NOTE

Marker selection is solely in the responsibility of the user.

Calculate Chimerism

Before starting the calculation, please determine whether the results shall appear as % recipient or % donor chimerism in ***Extras > Preferences > Chimerism Calculation***. After the transplantation is set up and informative markers are preselected the chimerism calculation can be started within the ***Sample Editor***. Click on ***Calculate Chimerism.***

A dialog appears. First a window containing all detected alleles of the monitoring sample assigned to the donor and the recipient of the respective transplantation is displayed. Alleles of unknown origin (neither donor nor recipient) will likewise be depicted but can be faded out by a click on the button ***Hide alleles of unknown origin.***

NOTE

Only alleles that clearly originate from donor or recipient will be included in the calculation.

Click ***Next*** to confirm the donor and recipient assignment or click ***Cancel*** to return to the ***Sample Editor***.

The next window shows the input values for the chimerism calculation (see Figure 12). Markers preselected within the Transplantation Editor are shown in the table. These can either be used or deselected while others can be added. This function is especially helpful, when excluding single outliers from

one analysis. Furthermore, you can select either height or area as the parameter to be used for the calculation.

NOTE

Settings for the marker selection will only be active for the current calculation. The pre-settings of the transplantation will not be changed.

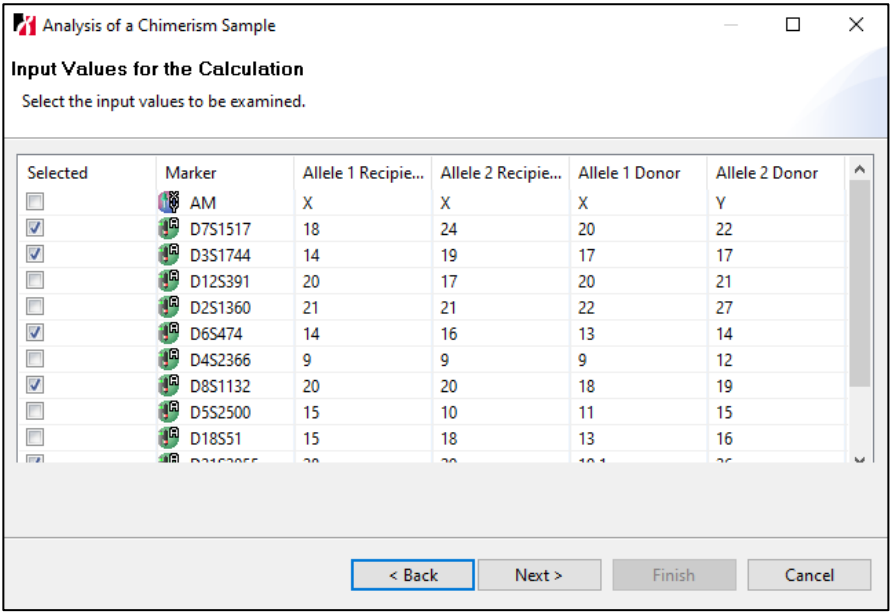


Figure 12. Input values for chimerism calculation, e. g. STR- alleles with Mentype® Chimera® PCR Amplification Kit

NOTE

After the chimerism calculation is successfully completed, a report can be issued within the ***Patient Editor***.

Click ***Next*** to confirm the input values and to see an overview of all detected alleles (see Figure 13). By clicking ***Finish*** all single marker chimerism values and the mean chimerism with standard deviation is displayed within the ***Sample Editor***.

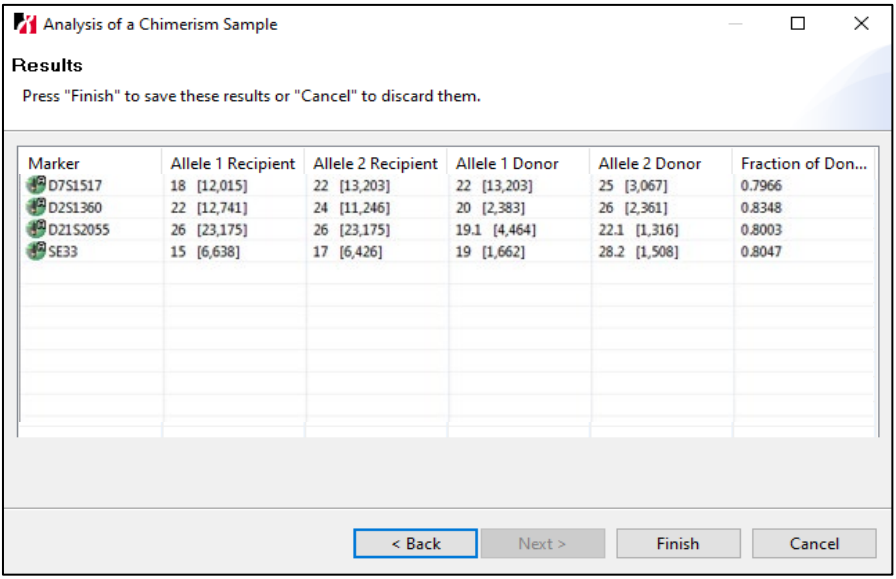


Figure 13. Result window

Functions within the Patient Management

The Patient Management represents a database of all created patients. The tabular overview contains a list of all patients as well as a specific tool bar with functions to edit them. The functions within Patient Management are listed in Table 17. The tabular visualization can be edited according to the requirements of the user. To add or delete single columns, click the right mouse button.

Table 17. Function of the Patient Management

Icon	Function	Description
	Create new patient	Create a new patient
	Show patient	Open the patient editor
	Archive Patient	The patient is archived and not listed within the active Patient Management. Archived patients can be displayed after setting the filter respectively
	Reopen Patient	The archived patient is reopened within the active Patient Management
	Delete Patient	Delete a patient from the database
	Filter	Filter for specific attributes (detailed patient information) within the patient data base.
	Reset Filter	Reset the filter to display all active patients.
	Turn Pages	Show previous or next page
	Export Patients	Detailed patient information is exported as csv file
	Refresh	Refresh the page to show all recent adaptions

Create new patient

To create a new patient, go to ***Patient > Create new Patient*** within the menu bar, click on the icon  ***Create new Patient*** in the tool bar or in the Patient Management. A dialog to create a new patient data sheet will open (see Figure 14). Information on Patient Number, Last Name and Sex are mandatory. Sex hereby refers to the biological sex determination.

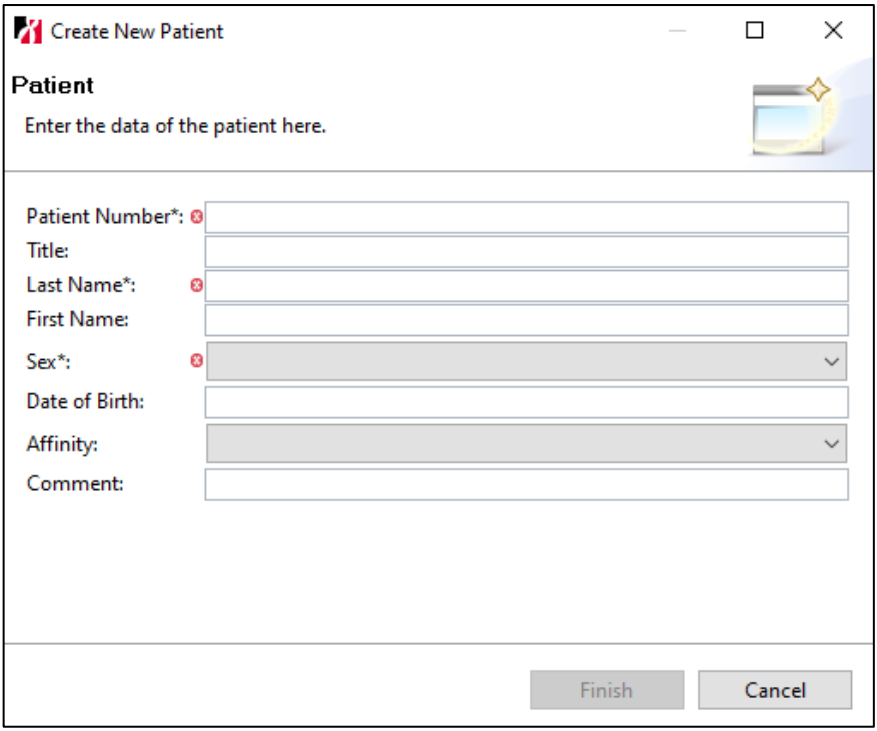


Figure 14. Create new Patient wizard

Show Patient

To open the Patient Editor select a patient within the Patient Management by double-clicking or select the icon ***Show Patient***. The Patient Editor contains all detailed patient information and assigned samples and transplantations.

Delete Patient

Select the respective patient from the Patient Management and choose the icon ***Delete Patient***. In order to delete patients all connected transplantations must be deleted within the ***Patient Editor***. A window will ask to confirm the deletion. Press ***Finish*** to delete the patient from the list or ***Cancel*** to abort the procedure.

Filter

The function ***Filter*** is helpful to search for patients from the data base. Click on the icon  ***Filter*** to open a filter mask (see Figure 15). Choose your respective criteria within the mask. Use the filter function to enter the archive (Status: archived), because the default Patient Management shows active patients only.

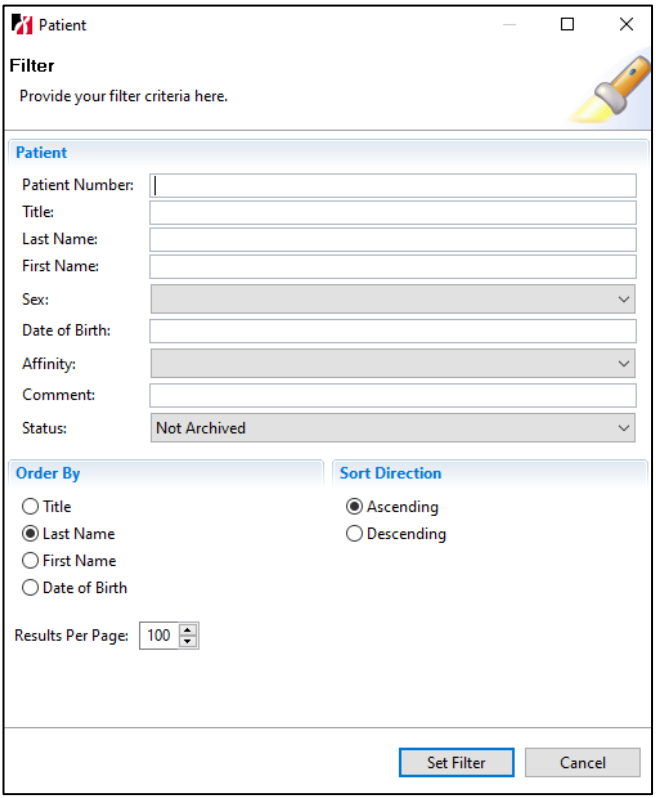


Figure 14. Filter mask within *Patient Management*

Archive

For an easy access and simplified overview within the data base, patients can be archived by clicking the icon  ***Archive Patient***. To reopen a patient and change the status to active, select the icon  ***Reopen Patient***.

Archived patients can be opened in the Patient Editor read-only as well as to generate a csv export.

Functions within the Batch Import Management

Fsa-files of a capillary gel electrophoresis run are imported in batch, meaning a whole folder is selected for the primary run validation, including sample files and control files (positive control, no-template control, allelic ladder).The Batch Import Management provides an overview of all performed Batch Imports. Therby information about the processing user, date, time, and type or amount of imported samples is summarized within the management (see Figure 16). The table can be sorted by import date by clicking on the date column.

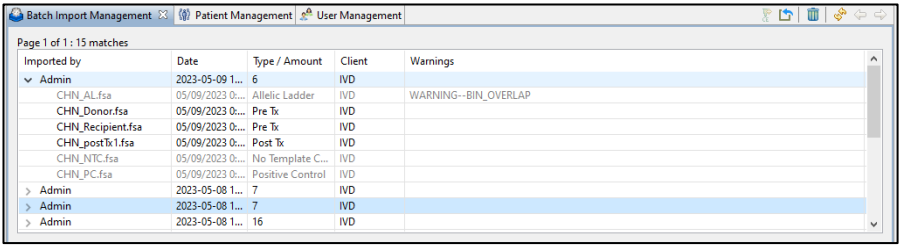


Figure 15. Batch Import Management

After the successful Batch Import, single files can be assigned to the desired ***Patient Editor***. See functions of the ***Batch Import Management*** below in Table 18.

Table 18. Functions of the Batch Import Management

Icon	Function	Description
	Assign CE sample	Assign the selected sample file to the recently opened ***Patient Editor. Allelic ladders, Positiv and No template Controls cannot be assigned.***
	Delete Batch	Delete a Batch from the database
	Refresh	Refresh the page to show all recent adaptions
	Turn Pages	Show previous or next page

NOTE

Control files are a mandatory part for the run validation process during the ***Batch Import.*** They are assessed according to the requirements of the test kit used. The CE-files of controls remain within the ***Batch Import Management***: they are already assigned to the specific ***Sample Editor*** and available for visual analysis within the toolbar.

Procedure for chimerism analysis

Run/Batch Import

ChimerisMonitor IVD supports the import and evaluation of raw data of different sequencer formats (fsa files). The program identifies peaks and artifacts as part of the process and is also capable of assigning peaks to alleles and, thus, to generate DNA profiles. During import an automated validation process is started according to the requirements of the applied kit.

To start the Batch Import click  ***Batch Import*** within the menu bar or Batch Import Management. After defining the specific properties of the imported files like the applied ***Size Standard*** and ***Test Kit***, choose ***Add***

Folder to search for saved runs (see Figure 17). Now adapt single sample types for the imported files by clicking in the respective table cell and select from the drop down menu. Selecting an ***Allelic Ladder***, a ***Positive Control*** and a ***No Template Control*** is mandatory to perform the Batch Import and a Run Validation.

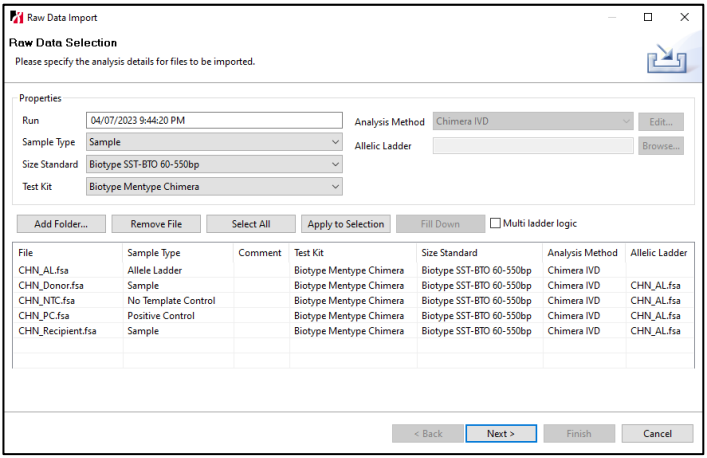


Figure 16. Raw Data Selection within the Batch Import

Click ***Next*** to proceed.

The window ***Run Validation*** provides a status of the Batch Import (Figure 18). The quality of all run controls, including the ***Allelic Ladder***, ***Positive Control*** and ***No Template Control*** is assessed.

NOTE

All passed quality criteria are marked with ☑

Possible warnings are marked with ⚠. Some criteria are not fulfilled. However, an analysis of the raw data is possible. Please review sample warnings within the ***Sample Editor***.

If quality criteria are not fullfilled, messages are marked with ✖

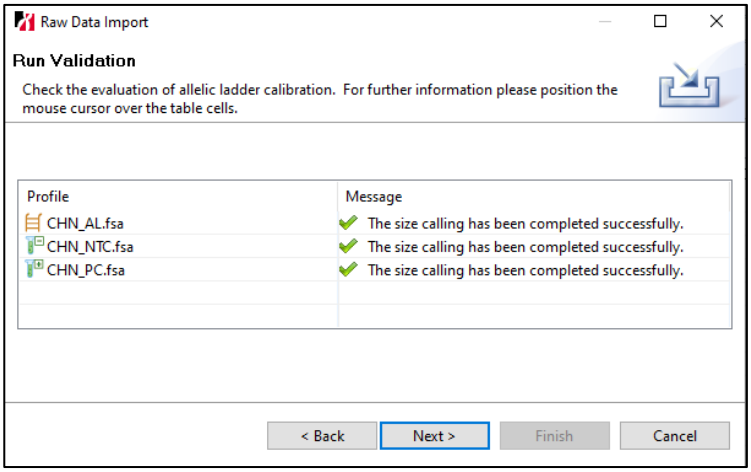


Figure 17. Run Validation within the Batch Import

The following criteria are checked within the Run Validation:

1. Valid DNA Size Standard 550 (BTO) of all controls
2. Valid peak heights in all control samples
3. Suitable number of allele peaks per loci, or no peak detection for No Template Control.

NOTE

For detailed information about the validation requirementents and criteria of Mentype® Chimera® PCR Amplification Kit and Mentype® DIPscreen PCR Amplification Kit, please refer to the kit specific instructions for use. Settings for the applied analysis method can be displayed via ***Extras > Preferences > Data Analysis > Analysis Methods.***

Click ***Next*** to proceed with the assessment of the ***Sample Quality***. The same general criteria as described above are used for the validity evaluation.

Make sure, that the correct sample type is selected for each sample (see Figure 19). In order to change the sample type, select the respective sample and click either in the tabel cell and select from the drop down menu or change by selecting the button ***preTx Sample*** or ***postTx Sample*** below the table.

An error explanation can be expanded for samples assigned as failed by clicking on the arrow in the Sample/Warnings column. In case of failed sample validity the respective sample needs to be deleted from the file table on page 1 of the wizard to finish the import.

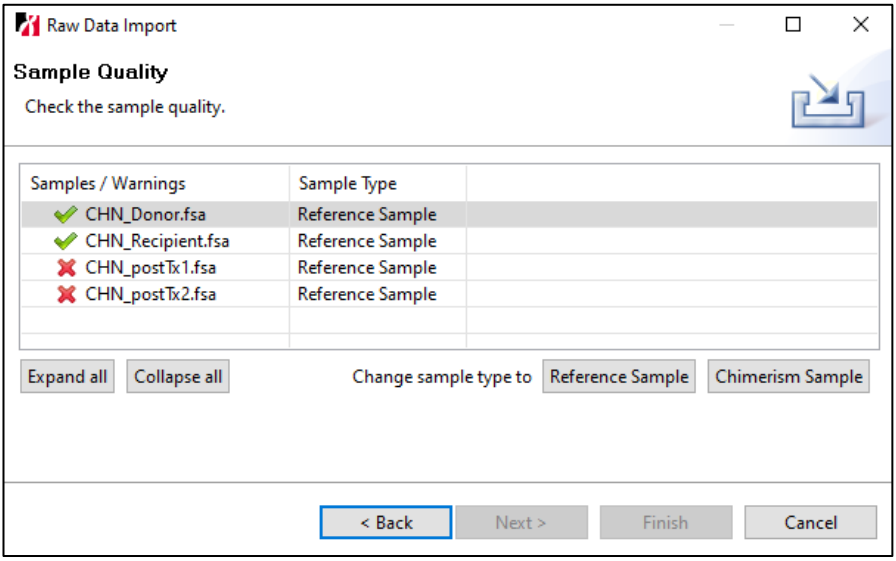


Figure 18. Sample Quality assessment within the Batch Import. e. g. sample type for postTX-samples must be changed.

Click ***Finish*** to complete the process. Click ***Cancel*** to abort.

The ***Batch Import Management*** will now open to assign validated samples to the ***Patient Editor***. Please refer to chapter Functions within the Batch Import Management.

Analysis of Electropherograms

ChimerisMonitor IVD is performing a general run and sample validation according to kit specific parameters and requirements. Nevertheless, each sample electropherogram should be evaluated by the user.

For detailed information about single functions within the Sample or Electropherogram Editors, please refer to chapter Sample Editor.

To assess the quality of a capillary gel electrophoresis run, please check the following parameters:

1. Correct allele assignments:

   Only alleles that are assigned are available for marker selection for preTx samples and only they are integrated within the chimerism calculation for postTx samples. A visual assessment of all electropherograms is higly recommended.

2. Evaluate all control samples:

   Including allelic ladder, positive control and no template control as well as their sizing quality. Check peak heights, correct allele assignment and peak shape according to the instructions for use of the respective test kit.

NOTE

Day to day fluctuations, environmental conditions, consumable status and DNA quality can effect the results of a capillary gel electrophoresis run. These effects include changing peak shapes with alterations like tailing, fronting, shoulder peaks or broadened peak basis, but also reduced or unbalanced peak heights.

3. Evaluate sample quality:

   By checking peak heights, allele assignments, peak shape and sizing quality according to the instructions for use of the respective test kit.

The number of called alleles should be plausible. When analysing postTx samples, DNA profiles should be comparable to donor or recipient samples. The software supports in filtering plausible donor- or patient-specific alleles. Any other additional peaks might be artefacts or contaminations, please refer to chapter Troubleshooting.

4. Evaluation of possible artifacts:

   Artifacts can be detected by ChimerisMonitor IVD. Please evaluate the quality section of each fragment table within the Electropherogram Editor.

   Stutters: The occurrence of stutter peaks depends on the sequence of the repeat structure and the number of alleles. n-4 peaks are caused by a loss of a repeat unit during amplification of tetranucleotide STR motives, caused by slippage effects of the Multi Taq 2 DNA Polymerase. Stutters are only relevant for the STR kit Mentype® Chimera® PCR Amplification Kit.

   Shoulder- und Split-Peaks: Shoulder and split peaks are double peaks with maxima, that are approximately one base pair apart. These peaks can be the result of inconsistent non-template addition, a consequence of the incomplete adenylation of PCR products by the polymerase during the PCR reaction.

   Off-ladder: Off-ladder peaks are located outside of allele bins. They can result either from very rare alleles or from other artifacts. Off-ladder peaks can be assigned to alleles (new or user-defined ones).

   Off-scale: The fluorescence (RFU) of off-scale peaks excesses the measurement range (up to 32,000 RFU).

   Tri-Band: Sometimes, an analysis apparatus might detect three signals, although there are only two PCR-fragments. This phenomenon is called tri-band pattern. The peaks of a tri-band pattern are all of the same height or two of the peaks cumulate to the height of the third one. Tri-band patterns are specific for analysis apparatuses and kits. A number of known tri-band patterns are already deposited in the reference database.

   Spectral Overlap: Spectral overlap artifacts are peaks resulting from overlapping emission spectra of fluorescent dyes, i. e. the signal of

one dye is mistakenly detected in another color panel, too. Hence, these pull-ups are situated at the same position (data point) as the larger causing peak, only in another color panel.

Peak height and width: Too large RFU values can indicate pull-ups. Furthermore, too wide peaks should also not be regarded as allele fragments. Hence, you can set maximum peak heights and widths.

Setting up a transplantation

In order to define informative loci via the ***Transplantation Editor***, all sample types must be assigned for both ***Donor*** and ***Recipient*** within each ***Sample Editor***. For detailed information about all functions within the Transplantation Editor please refer to chapter Transplantation Editor.

Click  ***Create new Transplantation*** Within the ***Patient Editor*** and define Date and Transplantation ID. After assigning Donor and Recipient sample to the Transplantation, informative loci can be selected as a general preselection for upcoming chimerism calculations.

Qualitative analysis – identification of informative loci

In the following, the identification and differentiation of patient specific loci is explained. Therefore, donor specific loci are defined as non-informative. The identification of informative loci is performed using data from patient and donor before the transplantation.

Informative Loci: At least one allele in the patient sample cannot be detected in the donor sample.

Only for Mentype® Chimera® PCR Amplification Kit: This allele shall not be in the stutter area of the donor sample.

Non-informative loci: Loci where the patient specific peak overlap with the donor specific peak, or donor-specific loci.

Only relevant for **Mentype® Chimera® PCR Amplification Kit:**

Stutter (n+1) loci: The patient specific peak is overlaping with the n+1 stutter of the donor specific peak. Such loci can be used if few informative loci are available.

Stutter (n-1) loci: The patient specific peak is overlaping with the n-1 stutter of the donor specific peak. Such loci should only be used if no other informative or stutter (n+1) loci are available.

The evaluation of the locus informativity is performed according to the published formulas described in: Nollet, F.; Billiet, J.; Selleslag, D.; Criel, A. (2001) *Standardisation of multiplex fluorescent short tandem repeat analysis for chimerism testing*, Bone Marrow Transplantation 28 (5), p. 511-518.[1]

NOTE

Using stutter (n-1) loci for the semi-quantitative monitoring, the sensitivity is decreased due to overlap of the patient specific allele and the stutter from the donor allele.

Chimerism Calculation

After the transplantation is set up and informative markers are preselected the chimerism calculation can be started within the ***Sample Editor***. Click on ***Calculate Chimerism.*** For detailed information on how to perform the chimerism calculation, please refer to chapter Calculate Chimerism.

NOTE

Only alleles that are assigned and selected within the transplantation or within the window Input Values for Transplantation will be included in the calculation.

Semi-quantitative analysis – chimerism analysis

A chimerism analysis is performed to monitor the success of the allo-HSCT. After transplantation, some of the patient's cells show the patient's native genotype **P** and some cells show the genotype of the donor's cells **D**. The patient shows characteristics of a chimerism. Ideally, the ratio of the native

patient cells will lower to zero in comparison to the donor cell ratio **D** that will steadily increase.

Chimerism analysis identifies the ratio of donor - and recipient genotype **F(D)** in a patient sample.

To analyse chimerism, the native genotypes **D** and **P**, thus the donor's and recipient's genotype, need to be known before the transplantation.

Chimerism analysis can either be performed on the peak area (recommended) or the peak height. Only peaks of alleles are considered for the calculation that can clearly be assigned to either the donor's **D** or the recipient's **P** genotype. All loci, in which the donor's or recipient's genotypes differ in at least one allele, can be included in the analysis.

The following formula is used to calculate the % donor ratio:

$$\boldsymbol{F(D) = 100\,\% * \frac{A(D)}{A(D)+A(P)}}$$

To calculate the % recipient ration F(P), the value of the donor chimerism will be subtracted from 100 %.

$$\boldsymbol{F(P) = 100\,\% - F(D)}$$

F(D) cell ratio of donor-genotype D in percent,

A(D) total peak area of donor alleles,

A(P) total peak area of native patient alleles,

For the overall evaluation of the sample, the average value of all marker-percentages that were included in the analysis, will be calculated. Moreover, the standard deviation will be assessed.

The evaluation of the chimerism calculation is performed according to the published formulas described in *Nollet et al. (2001).*[1]

Troubleshooting

Installation

Symptom	Answer
Installer shows a dialog requesting username and password.	Installation requires administrative permissions. Request an administrators assistance or to provide credentials of a privileged user.
An error shows up during installation.	Check the Installer console window for details. If necessary console output can be copied by right-click and may be saved into an file for further analysis.
Installation aborts before completion.	Check the Installer console window for details. If necessary console output can be copied by right-click and may be saved into an file for further analysis.
Installer doesn't prompt to import existing ChimerisMonitor 2.1 database.	The installer searches only in the ChimerisMonitor 2.1 *default database folder* C:\ProgramData\Biotype\ChimerisMonitor\database for an ChimerisMonitor 2.1 database. An import prompt is only shown, if the directory exists and the file PG_RELEASE is found there.
After canceling the database import dialog, the dialog is no longer shown.	Import of ChimerisMonitor 2.1 data is only possible on first time installations if no ChimerisMonitor IVD database exists already. Canceling the import dialog will create a new ChimerisMonitor IVD database. As the import into an existing ChimerisMonitor IVD database is not supported at all, the dialog is no longer shown.

Application

Symptom	Answer
User “admin” cannot be edited.	The user “admin” is built-in by the software and does not allow any modification.
The license is invalid.	The license key is incorrect or the license has timed out.
A problem occurred accessing the database	This can be caused by serveral problems, check: the server setting in the login dialog if the ChimerisMonitor IVD database service is running
The client won't start.	Try to start the client in “Safe mode” by selecting the relevant menu entry in Windows Start-Menu. Alternatively check the client logfile.
It is not possible to create patients, change samples or transplantations.	The software may be in read-only mode. To switch mode enter a valid license.

Batch Import

Symptom	Answer
The UUID of the Run is not unique.	Selected samples seem to belong to different analyzer runs. For quality reasons all samples should origin from the same run.
There are additional peaks after the assigned size standard peaks. Check the size standard.	More peaks than expected have been detected in the size standard. It is solely possible to use the in the Batch Import selected Size Standard. If artefacts are interfering with the size calling regression please repeat the capillary

Symptom	Answer
	gel electrophoresis. Make sure to use fresh consumables.
Ladder Calibration failed: No alleles detected.	Calibration of allelic ladder file seems unsuccesful as no alleles had been assigned to peaks. Please repeat the analysis. Make sure that the correct allelic ladder is added to the respective well and that all components are mixed sufficiently.
Could not detect an X allele for amelogenin in the marker.	The file contained no allele marked as gender determinand allele X. As the Genotype is not obtained completely, the analysis should be repeated. Allelic dropout or insufficient amplification could be a reason, if all other markers are detected.
The profile requires a Positive/ No Template Control associated with it.	There was no No Template Control or Positive Control in the list of files to import. This is mandatory for a successful run validation.
The profile needs an allelic ladder associated with it.	The imported file contains no reference about the ladder file it was called with. Please repeat the analysis with an Allelic Ladder included.
Not all expected ladder alleles were found in raw data.	The imported allelic ladder file doesn't contain all expected alleles of the selected test kit. Make sure that correct allelic ladder is added to the respective well and that all components are mixed sufficiently.
Additional alleles were found that are not in ladder.	Imported allelic ladder file contains more alleles than expected by testkit. If artefacts are interfering with the Allelic Ladder please repeat the capillary gel electrophoresis. Make sure to use fresh consumables.

Symptom	Answer
Ladder calibration warning : Bins are overlapping {0}	Bins of neighboring alleles are overlapping. Because of day-to-day interferences or different Genetic Analyzer performances it can happen, that peak bases of neighboring alleles merge, because of broader peak bases. Please visually assess the Allelic Ladder for the respective alleles.
Too many alleles found in marker	Imported profile contains more alleles than expected. The expected allele count is determined by sample type: reference or chimerism. The detection of additional alleles might also be caused by contaminations or CE-artefacts. Repeat PCR or capillary electrophoresis and ensure a clean working environment.
Not enough alleles found in marker	Imported profile has less alleles than expected. The expected allele count is determined by sample type: reference or chimerism. Alleles below the test kit specific thresholds are not assigned. Please refer to the test kits instructions to ensure the correct setup of the PCR reaction
Unable to assign sample from “Batch Import Management” to patient	Check selected sample type. Only reference- or chimerism samples can be assigned to a patient.
The import of more than one Allelic Ladder per run is not valid.	For processing of the run one Allelic Ladder is required. Please select one Allelic Ladder to proceed. If more than one Allelic Ladder was selected, deletion of the extra Allelic Ladder on page 1 is required via the button “Remove file”.

Performance Evaluation

The software ChimerisMonitor IVD has the evaluation of the locus informativity and the subsequent semi-quantitative chimerism analysis, which are described in detail in multiple publications from Clark et al. (2015)[2] or Nollet et al. (2001)[1], implemented in its own algorithm. This core function allows for the evaluation of clinical data/samples in the form of fsa-files generated by the Mentype® Chimera® PCR Amplification Kit and Mentype® DIPscreen PCR Amplification Kit.

The clinical performance of the software ChimerisMonitor IVD is demonstrated with external, independent, and qualified reference materials of the UK National External Quality Assessment Service (UKNEQAS) and Instand e.V (Gesellschaft für Förderung der Qualitätssicherung in medizinischen Laboratorien e. V.). Reference Materials are processed according to the requirements of the Mentype® Chimera® PCR Amplification Kit and Mentype® DIPscreen PCR Amplification Kit. EQA (external quality assessment) services are monitoring performance of samples processed and evaluated as if they were patient samples to certify testing is "[…] comparable, safe and clinically useful to a patient no matter where the testing is performed. EQA participation demonstrates that your laboratory is committed to providing the highest quality of analysis for all patients." (https://ukneqashandi.org.uk/schemes/). These EQA schemes are accredited according to DIN EN ISO/IEC 17043:2010. The software application is regarded as a supportive tool using established and standardized tests, principles, and formulas for chimerism calculation as well as for the identification of informative loci between donor and patient prior to the allo-HSCT (Nollet et al. (2001)[1], Thiede et al. (1999)[3]). Hence, the result evaluation shall be comparable to the current performance characteristics of EQA schemes.

Additionally, the data analysis and subsequent chimerism calculation of the generated fragment analysis files can be performed with the software GeneMapperTM ID-X. For the comparison of the data analysis and chimerism calculation, the fragment analysis data files from the executed performance evaluation experiments Robustness, Reproducibility as well as Linearity of the Mentype® Chimera® PCR Amplification Kit were analyzed with ChimerisMonitor IVD or GeneMapperTM ID-X.

For the comparison of the two software, a concordance with ≥ 0.95 R^2 was expected. A coefficient of determination ≤ 0.90 would lead to the rejection of the hypothesis that both software show concordant results. A coefficient of determination between 0.90 and 0.95 would lead to careful evaluation of the results and the determination of the degree of concordance e. g. for MC intervals.

The correlation of chimerism calculation on ChimerisMonitor IVD and GeneMapper™ ID-X is demonstrated based on the Deming-Regression as displayed in Figure 20. The regression curve fit with f(x) = 1.019 * X – 0.3598 as well as the Pearson coefficient of determination with 0.9962 (N = 300) confirm a high degree of correlation for the chimerism analysis with either ChimerisMonitor IVD or GeneMapper™ ID-X software. As the results generated with both software are concordant, no significant impact on the analytical assay performance is determined.

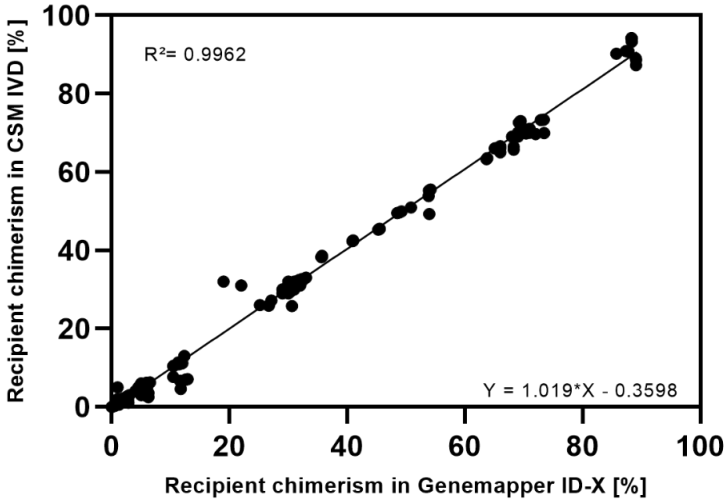


Figure 19. Deming-Regression of recipient chimerism calculation with ChimerisMonitor IVD vs. GeneMapper™ ID-X software. One sample set covering a recipient chimerism range from 1 %-90 % was analyzed with both software (N = 300).

References

[1] Nollet, F., Billiet, J., Selleslag, D., & Criel, A. (2001). Standardisation of multiplex fluorescent short tandem repeat analysis for chimerism testing. Bone marrow transplantation, 28(5), 511-518.

[2] Clark, J. R., Scott, S. D., Jack, A. L., Lee, H., Mason, J., Carter, G. I., ... & Barnett, D. (2015). Monitoring of chimerism following allogeneic haematopoietic stem cell transplantation (HSCT): technical recommendations for the use of short tandem repeat (STR) based techniques, on behalf of the United Kingdom National External Quality Assessment Service for Leucocyte Immunophenotyping Chimerism Working Group. British journal of haematology, 168(1), 26-37.

[3] Thiede, C., Florek, M., Bornhäuser, M., Ritter, M., Mohr, B., Brendel, C., ... & Neubauer, A. (1999). Rapid quantification of mixed chimerism using multiplex amplification of short tandem repeat markers and fluorescence detection. Bone Marrow Transplantation, 23(10), 1055-1060.

Cybersecurity

This chapter outlines necessary cybersecurity measures and guidelines to ensure the integrity and confidentiality of data handled by ChimerisMonitor IVD. As this software is employed in sensitive medical applications, protecting patient information and ensuring the reliability of data is our outmost concern.

System Requirements

Operating Systems: ChimerisMonitor IVD is compatible with the operating systems Windows 10 or 11.

Antivirus Software: Up-to-date antivirus software must be installed and running.

Firewall Settings: A configured firewall to protect data inflow and outflow.

Configure firewall rules to restrict access to only authorized IP addresses, protocols, and ports required for system functionality.

Implement rate-limiting to control the number of requests allowed per user or system within a specified time frame, preventing abuse or denial-of-service attempts.

Secure Installation and Configuration

Ensure that ChimerisMonitor IVD is installed by a qualified technician or an authorized representative. Set strong, unique passwords for accessing the software, and change them periodically.

Data Privacy

All patient data should be treated as confidential. Access should be restricted to authorized personnel only. This also applies to exported data and system backups. Ensure compliance with local and international data protection regulations (e. g., GDPR, HIPAA).

Regular Updates and Maintenance

Regularly update ChimerisMonitor IVD to the latest version to protect against vulnerabilities. Apply security patches and updates as soon as they are available. Maintain and regularly review system and access logs to monitor for any unauthorized access or anomalies.

Server Logs

Server logs are generated periodically and can be found at C:\ProgramData\Biotype\ChimerisMonitor 3\database\log. Regularly check these logs for any unusual activity or errors. These logs are crucial for troubleshooting and understanding the health of the server components.

Client Logs

Client application logs are incrementally generated and located in the directory %USERPROFILE%\ChimerisMonitor IVD\.metadata. Client logs provide insights into user operations and should be reviewed in response to user-reported issues or unexpected client behavior. These logs are essential for tracking user interactions and potential application issues.

Backups

Make sure, that backup routines are regularly performed for crucial data. Follow these steps:

Stop the "ChimerisMonitor-IVD-Database" service via the Windows Services Manager. Access the Database Folder: Open the Windows Explorer. Navigate to the ‘View’ tab and check the option for ‘Hidden Items’. Go to the directory C:\ProgramData\Biotype\ChimerisMonitor 3. Copy the database folder: Locate and select the ‘database’ folder within the directory. Right-click and choose ‘Copy’. Securely paste the copied folder to your designated backup location, ensuring it is outside the local drive for redundancy. Restart the "ChimerisMonitor-IVD-Database" service to resume normal operations.

Incident Response

If suspicious behavior is observed, users should consult their IT administrator or IT security officer immediately. Form an incident response team capable of responding to cybersecurity threats. Develop a comprehensive disaster recovery plan to restore functionality and data in the event of a cybersecurity incident.

Decommissioning

If the software needs to be taken out of operation, it is crucial not only to uninstall the application but also to ensure that all sensitive data is either securely erased from storage devices or archived according to the requirements of your organization. This process should follow a standard, verified data destruction protocol.

Training and Awareness

Conduct regular training sessions for all users to understand the cybersecurity policies and procedures related to ChimerisMonitor IVD.

Implement ongoing awareness campaigns to keep security at the forefront of operations.

Technical Assistance

For technical advice or assistance with cybersecurity issues please contact our Technical Support:

e-mail: support@biotype.de

phone: +49 (0)351 8838 400

Limitations of Use

- The procedures in this IFU must be followed, as described. Any deviations may result in error messages.
- ChimerisMonitor IVD is a software solution for automated analysis of capillary electrophoresis-data (fsa-files) using the Mentype® Chimera® PCR Amplfication Kit and Mentype® DIPscreen PCR Amplification Kit only.
- Use of this product is limited to professional laboratory users trained on molecular-genetic techniques, multiplex PCR, and the handling of Genetic Analyzers of Thermo Fisher Scientific (Applied Biosystems division).
- Results must be interpreted by clinicians in context with results of other therapy- or diagnostic relevant methods.
- Interpretation of results must account for the possibility of false negative and false positive results
- Monitoring of patients who have undergone multiple allo-HSCTs (e. g. double transplantation, that leads to more than 2 detectable genotypes) is not supported.
- Chimerism monitoring of patients whose donor is their identical twin is not possible.
- Foreseeable misuse is prevented by restrictions within the software, warning messages and appropriate selection options in analysis steps of the software.

Trademarks and Disclaimers

Mentype® and Chimera® are registered trademarks of BIOTYPE GmbH.

Other trademarks: Applied Biosystems® (Applied Biosystems LLC group)

The PCR is covered by patents. Patentees are Hoffmann-La Roche Inc. and F. Hoffmann-La Roche (Roche).

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ChimerisMonitor IVD is a CE-marked software according to the European in vitro diagnostic regulation (EU) 2017/746.

Product not licensed with Health Canada and not FDA cleared or approved.

Not available in all countries.

Explanation of Symbols

	Manufacturer
	Batch code
	Reference to eIFU
	Catalogue number
	In-Vitro-Diagnostics
	Swiss authorised representative
	Importer

Further marking used in this Instruction for Use:

	Useful tips
	Attention, be sure to follow this notice!
blue underlined text	Links leading to external content like homepages, e-mail adresses
black underlined text	Cross-links in the document for easy navigation

indented, cursive, bold text	Fields which are to be clicked or tabs/sections which are to be chosen in the software

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