MODAPLEX MSI Analysis Kit

Handbook

RUO For research use only. Not for use in diagnostic procedures. Designed for use with the MODAPLEX instrument.

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BIOTYPE GmbH
Moritzburger Weg 67
01109 DRESDEN
GERMANY
Website: www.biotype.de
Support: support@biotype.de
Ordering: sales@biotype.de

BIOTYPE

Notice of Change

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

Document code	Changes	Date
MSIHB01v1en	Initial release of the handbook	11.10.2023
MSIHB01v2en	Corrections in chapter ‘Data Analysis’, result evaluation.	27.11.2023
MSIHB01v3en	Adjustments to the chapter "Instruments, software and associated files”, update of pictures and and changes to the wording.	14.08.2024
MSIHB01v4en	Adjustments to the chapter "Instruments, software and associated files”, update of pictures and and changes to the wording.	26.06.2025

For any further questions, please contact us:

at +49 351 8838 400 or

support@biotype.de

Content

Product Description

The MODAPLEX MSI Analysis Kit is a qualitative and comprehensive polymerase chain reaction (PCR)-based multiplex assay for the detection of microsatellite instability in human DNA derived from formalin-fixed, paraffin-embedded (FFPE) tissue on the MODAPLEX instrument.

The assay must be used by qualified and trained personnel in a professional laboratory environment only. Results are intended solely for research use and not for diagnostic procedures.

Summary and Explanation

Scientific Background

During replication and recombination, DNA mismatch repair (MMR) gene products identify and repair the misincorporation of bases as well as the short erroneous insertion and deletion loops[(1)]. Irreversible mutations in DNA MMR genes such as MLH1, MSH2, PMS2, and MSH6 are associated with a loss of DNA mismatch repair activity and cause genomic instability. A prominent consequence of a damaged DNA repair system is that repetitive sequences known as microsatellites become unstable and vary in length[(2)]. Thus, the presence of microsatellite instability (MSI) represents evidence that MMR is impaired[(3)].

The MODAPLEX MSI Analysis Kit is a fluorescent PCR-based multiplex assay intended for use with the MODAPLEX instrument. With a combination of five quasi-monomorphic mononucleotide markers (Bat-25, Bat-26, NR-21, NR-24, Mono27) and two dinucleotide repeat markers (D5S346, D17S250), the assay supports the identification of MSI-H status in clinical research based to standardized clinical guidelines[(4)]. The resulting amplicons are separated by capillary electrophoresis (CE) and analyzed through qualitative endpoint detection using the MODAPLEX Reporter software.

Table 1: List of assay markers

Quasi-monomorphic mononulcleotide markers	Gene loci
Bat-25	c-Kit, intron 16
Bat-26	hMSH2 gene, intron 5
NR-21	*SLC7A8*, 5_UTR
NR-24	*ZNF2*, 3_UTR
Mono27	*MAP4K3*, intron 13
Dinucleotide markers	**Gene loci**
D5S346	*APC*
D17S250	*Mfd15*
Controls	**Gene loci**
HLD131	*SHH*
HLD133	*ULK4*

Principle of the Procedure

The MODAPLEX MSI Analysis Kit is to be used with the MODAPLEX instrument. The microsatellite markers are amplified through fluorescent-labelled sequence-specific primers. During PCR, amplification products are injected electrokinetically and separated in an automated CE process. Electrophoresis is performed periodically every second cycle.

The microsatellite stability status is assessed using the MODAPLEX Reporter by comparing the fragment length profiles of matching tumor and normal tissue. A deviation in length of the entire peaks or change in shape of the peaks in the tumor sample relative to the normal adjacent sample indicates MSI.

Control Concept

The MODAPLEX MSI Analysis Kit provides a comprehensive control concept. It consists of internal and external controls that are used to evaluate the functionality of the PCR reaction as well as identify potential error sources such as contaminations. The control concept is described below:

Template-independent PCR control: MODAPLEX Calibrator 2

The MODAPLEX Calibrator 2 serves both as a template-independent PCR control and an internal length standard. It comprises six amplicons of various lengths which are listed in Table 2 below.

Table 2: List of MODAPLEX Calibrator 2 amplicons with corresponding names and lengths.

Name of amplicon	Length (nt)	Channel
C110	110	blue
C249	249	blue
C306	306	blue
C113	113	red
C251	251	red
C309	309	red

NOTE

The MODAPLEX Calibrator 2 must be added to all samples, no-template control and positive control wells.

Internal Controls (IC): Human Locus Deletion/Insertion (HLD) polymorphism

These forensically accepted human deletion/insertion polymorphisms support the genetic discrimination of human individuals. The MODAPLEX MSI assay contains two HLD markers: HLD131 and HLD133. They are amplified within every sample and positive control well serving both as a template-dependent PCR control as well as a sample mix-up control. Additionally, they can be used to identify contamination with human sample material.

External Control 1: No template control (NTC)

The user must set up a NTC (no template control) for each run to assess the potential contamination which might occur while setting up the assay. Nuclease-Free Water serves as a template for the NTC well. In addition, the NTC needs to be set up to assess the validity of the whole run.

The NTC is valid if no signals are present (ICs and targets). Consequently, the NTC ensures that the kit performs within the stated performance characteristics. The validity of the NTC is proven by the MODAPLEX Reporter software.

External Control 2: positive control (PC)

Human gDNA serves as PC for the MODAPLEX MSI Analysis Kit. Therefore, the PC shows a similar peak pattern as sample wells. All targets must be detectable within acceptable ranges, which confirms the proper functioning of the MSI Primer Mix. Consequently, the PC ensures that the kit performs within the stated acceptance criteria. To confirm the proper functioning of all assay components, one PC needs to be set up for each run. The PC does not indicate instability of the microsatellite marker. Instability is a result of polymerase slippage during replication and is genetically indicated by fragment-length shifts. The primer binding site is identical for unstable and stable microsatellite markers.

NOTE

The user needs to set up a **NTC and PC** for each MODAPLEX run.

Platform and Software

MODAPLEX Instrument

The MODAPLEX MSI Analysis Kit is designed to be used with the MODAPLEX instrument (MODAPLEX Controller software version 12.1.x). The platform is a benchtop system for molecular profiling and comprehensive multi-marker testing. It combines PCR with capillary electrophoresis (CE) in an automated workflow and enables the detection, differentiation, and quantification of DNA or RNA targets in a single well and run. As a result, it enables the combination of tests for fragment analysis, mutational analysis, gene expression, copy-number variation, and more.

MODAPLEX Reporter Software

The MODAPLEX MSI Analysis Kit must be analyzed using BIOTYPE´s MODAPLEX Reporter software. The MODAPLEX Reporter software, the MSI Assay plugin and the MAC (MODAPLEX Analysis Configuration) must be downloaded and installed separately.
Please refer to chapter Data Analysis for detailed information on the use of the MODAPLEX Reporter software for analysing the MODAPLEX MSI Analysis Kit.

Data Analysis

Material Provided

Kit content

The MODAPLEX MSI Analysis Kit contains reagents that can be used to perform 50 reactions (25 sample pairs). It includes the following components:

Table 3: Content of the MODAPLEX MSI Analysis Kit

Reagent	Cap color	Volume per kit	Storage
Nuclease-Free Water	Light blue	1 x 1.5 mL	-25 °C to -15 °C, protected from light
MSI Primer Mix	Red	1 x 125 µL	
MSI Positive Control	White	1 x 65 µL	
PCR Buffer 10	Black	1 x 625 µL	
MODAPLEX Polymerase P	Orange	1 x 25 µL	
MODAPLEX Calibrator 2	Yellow	1 x 25 µL	
MODAPLEX MSI Analysis Kit Barcode of Assay Definition		1 x	-

Additional digital components required for analysis are provided in the online download area and listed under Instruments, software and associated files

NOTE

Please note that the packaging size describes the number of testings **without** taking into account the number of required controls or the required excess for pipetting.

Description of Components

MSI Primer Mix

This tube contains the oligonucleotide primers specific to seven targets (Bat-25, Bat-26, NR-21, NR-24, Mono27, D5S346, D17S250) and two internal controls (HLD131 and HLD133), as shown in Table 1.

PCR Buffer 10

This solution is optimized to promote enzyme activity for the PCR in the MODAPLEX MSI Analysis Kit.

MODAPLEX Polymerase P

The MODAPLEX MSI Analysis Kit contains a DNA Polymerase (2 U/µL).

MODAPLEX Calibrator 2

The size standard is a template-independent PCR control and an internal length standard.

Assay Definition: digital version and barcode printout

The assay-specific Assay Definition is required for each MODAPLEX run and provides the PCR protocol and the assay-specific information for the data analysis including for example target names as well as fragment lenghts. Additionally, the Assay Definition represents the kit lot and enables the lot-dependent documentation of results. The Assay Definition is provided as a barcode printout within the kitbox. Alternatively it is available as a digital file which can be imported.

Assay Definition upload in MODAPLEX software

- Import the Assay Definition for every new kit lot within the Protocol Definitions menu

- Barcode scan procedure:
    - Scan the provided barcode with the implemented barcode scanner at the MODAPLEX instrument within the Protocol Definitions menu
- Download of digital file:
    - Download the Assay Definition file via the online download area and import the file into the MODAPLEX Design and Analysis Software or MODAPLEX Controller software for preparing a run draft

For further information refer to the MODAPLEX manual.

Figure 1: Example of barcode

Reagent storage and handling

The kit is shipped on dry ice. The components of the kit must arrive frozen, except the MODAPLEX Polymerase P, which is provided in a buffer that prevents freezing of the reagent.

Check the kit to ensure it is complete upon receipt. Immediately contact BIOTYPE GmbH if one or more components are not frozen, or if tubes, barcode or the packaging have been compromised during the shipment. Do not use kits that have been thawed upon arrival.

Store all components at -25 °C to -15 °C without light exposure. Especially the MSI Primer Mix and MODAPLEX Calibrator 2 must be stored protected from light.

The expiration date is stated on the kit box label. Do not exceed a maximum of 5 freeze-thaw cycles.

Material and devices required but not provided

General laboratory equipment

- Benchtop centrifuge with a rotor for 2 mL reaction tubes
- Centrifuge with a rotor for microtiter plates
- Vortex mixer
- Calibrated adjustable pipettes with disposal aerosol tight filter tips
- Suitable racks for 2 mL reaction tubes and 96-well microtiter PCR plates
- Disposable powder-free gloves
- Qubit™ Fluorometer (cat. no. Q33238, Thermo Fisher Scientific)
- PCR workstation or clean bench

NOTE

All material to be used for PCR shall have appropriate quality (DNA free and for molecular biology). Please ensure that all instruments used have been installed, calibrated, checked and maintained according to the manufacturers' instructions and recommendations.

Reagents, kits and consumables

Table 4: List of reagents, kits and consumables with BIOTYPE GmbH Order number

Reagent	Supplier	Order number
MODAPLEX PCR Plate	BIOTYPE GmbH	84-20102-0025
Aluminium Sealing Film	BIOTYPE GmbH	00-14X04-0100
10X Capillary Protection Buffer Kit	BIOTYPE GmbH	85-21001-1800
Mineral Oil	BIOTYPE GmbH	00-04301-0025
MODAPLEX Cartridge	BIOTYPE GmbH	84-20101-0048
MODAPLEX Buffer	BIOTYPE GmbH	00-14302-2000
MODAPLEX Decon	BIOTYPE GmbH	00-14303-2000
MODAPLEX CE Gel	BIOTYPE GmbH	00-04305-0028
MODAPLEX CE Plates	BIOTYPE GmbH	00-14306-0020
MODAPLEX Hold Down Plate	BIOTYPE GmbH	84-20002-0001
QIAamp DNA FFPE Tissue Kit	QIAGEN	56404

Reagent	Supplier	Order number
Deparaffinization Solution	QIAGEN	19093
RNase A (100 mg/mL)	QIAGEN	19101
Qubit™ dsDNA HS Assay	Thermo Fisher Scientific	Q32851
Qubit™ ds DNA BR Assay	Thermo Fisher Scientific	Q32850

Instruments, software and associated files

- MODAPLEX instrument (BIOTYPE GmbH)
- MODAPLEX Controller v12.1.x (BIOTYPE GmbH)
- MODAPLEX Design and Analysis Software v12.1.x (BIOTYPE GmbH)
- MODAPLEX Reporter Software v3.0.x (BIOTYPE GmbH)

Table 5: Assay-specific components

Component	Version	ID
Assay Definition	Lot-dependent	N/A
PCR-CE Protocol	N/A	FcrZXjCGTKG07rxowgkOXQ
Analysis Protocol	See Download Area	N/A
MODAPLEX Reporter Plugin	See Download Area V3.x.x	N/A
MAC (MODAPLEX Assay Configuration) for MODAPLEX Reporter	See Download Area	N/A

NOTE

The suitable software and associated files are available as download via https://download.biotype.de.

Samples and Specimen

The MODAPLEX MSI Analysis Kit has been verified with human gDNA and DNA samples extracted from formalin-fixed, paraffin-embedded (FFPE) colorectal cancer (CRC) tissue.

In addition, DNA samples extracted from FFPE endometrial cancer tissue have been tested for use with the MODAPLEX MSI Analysis Kit.

Warnings and Precautions

- For research use only. Not for diagnostic use.
- Designed for use with the MODAPLEX instrument.
- Read the instructions carefully before using the product.
- Read the safety data sheets (SDS) and Non-Hazardous Statements (NHS) for all BIOTYPE products, which are available on request via support@biotype.de. For products that do not require a SDS as they do not contain an SVHC or are subject to other restrictions of Regulation 1272/2008 (CLP), BIOTYPE provides the SDS upon request.
- Please contact the respective manufacturers for copies of the SDS for any additionally needed reagents.
- Any wells in the PCR plate, that are not being used for testing a sample (including no-template control and positive control samples), must be filled with 25 µL of 1x Capillary Protection Buffer included in the 10X Capillary Protection Buffer Kit, and overlaid with mineral oil.
- Kit components of different kit lots must not be mixed.
- Aliquoting the kit components into other reaction vessels is not permitted.
- Do not use a kit that has passed its expiration date.
- Do not substitute the reagents with equal reagents from other manufacturers.
- Follow the instructions for reagent storage and handling.
- Ensure that the reagents are not exposed to light during storage.
- Before the first use, check the product and its components for:
    - Integrity
    - Completeness with respect to number, type and filling (see chapter Material Provided
    - Correct labelling
    - Frozenness upon arrival.
- Clean and disinfect all surfaces according to the laboratory's standard operating procedure (SOP) guidelines.

- Specimens should always be treated as infectious and/or biohazardous in accordance with safe laboratory procedures.
- Discard samples and assay waste according to your local safety regulations.
- All instruments used must have been installed, calibrated, checked and maintained according to the manufacturer´s instructions and recommendations. Follow the instructions in the MODAPLEX User Manual for the proper operation of the MODAPLEX instrument.

NOTE

Due to the high voltage required for the CE separation, failure to fill all wells is a general safety threat that may cause damage to the MODAPLEX instrument.

Procedure

Sample Preparation

Raw sample requirements

The MODAPLEX MSI Analysis Kit has been verified with human gDNA and DNA samples extracted from formalin-fixed, paraffin-embedded (FFPE) colorectal cancer (CRC) tissue. In addition, DNA samples extracted from FFPE endometrial cancer tissue have been tested for use with the MODAPLEX MSI Analysis Kit. DNA samples to be used with the MODAPLEX MSI Analysis Kit should ideally be freshly prepared. Prolonged storage of FFPE tissue material or an inadequate fixation may decrease the assay performance.

DNA extraction

It is recommended to purify extracted DNA using the QIAamp DNA FFPE Tissue Kit, Deparaffinization Solution and RNase A (100 mg/mL) following the supplier's protocol. Improved yield may be achieved by prolonged Proteinase K sample lysis overnight. DNA purification should be carried out from macro-dissected FFPE tissue. Up to 3 sections, each with a thickness of up to 10 µm and a surface area of up to 250 mm^2, can be combined in one preparation. After the DNA isolation procedure and prior to storage, the DNA concentration must be promptly measured.

NOTE

The performance of the MODAPLEX MSI Analysis Kit may depend on the DNA quality. Heavily fragmented DNA can significantly influence the analysis and result interpretation.

DNA quantification and dilution

Quantification of the DNA should be carried out by fluorometric quantitation using the Qubit™ 3.0 Fluorometer. For low FFPE tissue input (e. g., tissue biopsies) use the Qubit™ dsDNA HS Assay according to the manufacturer's

protocol. Otherwise, the usage of the Qubit™ ds DNA BR Assay is recommended.

Set up the MODAPLEX MSI Analysis Kit using **10 ng input DNA (2 ng/µL)**. It is not advised to use less than 2 ng/µL. An insufficient amount of DNA could lead to low PCR yields and the peak heights may fall below the target-specific detection limits. Excessive amounts of DNA > 20 ng may lead to peak heights with a disturbed migration size resulting in incorrect assignments of calibrators, control amplicons, and MSI targets.

NOTE

For sample dilution we recommend the use of 1 x TE (Tris-EDTA)- Buffer, pH value 8.0 and a sample volume > 1.5 µL

DNA storage

Store the DNA samples at -25 °C to -15 °C. Undiluted DNA samples can be stored for 4 weeks at 2 °C to 8 °C or at -25 °C to -15 °C for long-term storage.

Component Preparation

Positive Control (PC)

Apply the MSI Positive Control included in the kit as positive control PC instead of a sample.

No template control (NTC)

Apply the Nuclease-Free Water included in the kit as no template control NTC instead of a sample.

1x Capillary Protection Buffer (not included in the kit)

Calculate the number of empty wells of the PCR plate based on the cartridge size. Dilute the 10X Capillary Protection Buffer according to the instructions (1:10 dilution with Nuclease-Free Water).

NOTE

Using the 48 capillary cartridge, 48 wells of the 96-well plate are used. Therefore, calculate the number of empty wells:

48 – 2 (PC, NTC) – (number of sample wells) = number of empty wells

MODAPLEX MSI Analysis Kit assay set-up

PCR master mix setup

Remove and thaw the following components from the MODAPLEX MSI Analysis Kit:

- Nuclease-Free Water (light-blue cap)
- PCR Buffer 10 (black cap)
- MSI Primer Mix (red cap)
- MSI Positive Control (white cap)
- MODAPLEX Polymerase P (orange cap)
- MODAPLEX Calibrator 2 (yellow cap)

During the PCR master mix setup, it is recommended to keep the MODAPLEX Polymerase P in a cooled environment (e. g., on a cooling rack). All frozen components need to be thawed at room temperature (15 °C to 30 °C, ca. 30 min, protected from light) and homogenized by inverting the tubes, pipetting, or gently vortexing. The reagents should be then briefly centrifuged (approx. 10 s).

Prepare the PCR master mix according to Table 6 for the total number of samples to be tested, in an appropriately sized microcentrifuge tube, in a dedicated clean area. Include at least one PC and one NTC for each MODAPLEX run.

Table 6: PCR master mix reaction set-up.

Component	Volume #1	#5	#10
PCR Buffer 10	12.5 µL	62.5 µL	125 µL
Nuclease-Free Water	3.5 µL	17.5 µL	35 µL
MSI Primer Mix	2.5 µL	12.5 µL	25 µL
MODAPLEX Calibrator 2	1 µL	5 µL	10 µL
MODAPLEX Polymerase P	0.5 µL	2.5 µL	5 µL
Total Volume	20 µL	100 µL	200 µL
DNA template or control sample	5 µL	5 x 5 µL	10 x 5 µL

NOTE

As a rule of thumb, if you are testing fewer than 10 samples, use enough master mix for one extra sample. If you are testing 10 or more samples, use an excess reagent master mix volume of +10 %.

Mix the master mix by gentle vortexing, then briefly centrifuge the mix. Aliquot 20 µL of the master mix to the designated wells in MODAPLEX PCR Plate.

Application of DNA templates and controls

Add 5.0 µL of the following sample types to the prepared PCR plate containing the master mixes.

Sample: add 5.0 µL of the prepared, diluted DNA samples (2 ng/µL) to the corresponding sample well(s)

NTC: add 5.0 µL of Nuclease-Free Water instead of a sample

PC: add 5.0 µL of MSI Positive Control instead of a sample

Add 25 µL of the prepared 1x Capillary Protection Buffer (CPB) dilution to the remaining empty wells that are not being used for a sample well, NTC or PC. Please refer to the plate map set-up in the MODAPLEX User Manual for further explanation.

NOTE

Due to the high voltage required for the CE separation, failure to fill all wells is a general safety threat that may cause damage to the MODAPLEX instrument.

	1	2	3	4	5	6	7	8	9	10	11	12
A	Sample 01 TUMOR	Sample 01 NATIVE	Sample 09 TUMOR	Sample 09 NATIVE	Empty 1 x CPB	Empty 1 x CPB	unused					
B	Sample 02 TUMOR	Sample 02 NATIVE	Sample 10 TUMOR	Sample 10 NATIVE	Empty 1 x CPB	Empty 1 x CPB						
C	Sample 03 TUMOR	Sample 03 NATIVE	Sample 11 TUMOR	Sample 11 NATIVE	Empty 1 x CPB	Empty 1 x CPB						
D	Sample 04 TUMOR	Sample 04 NATIVE	Sample 12 TUMOR	Sample 12 NATIVE	Empty 1 x CPB	Empty 1 x CPB						
E	Sample 05 TUMOR	Sample 05 NATIVE	Sample 13 TUMOR	Sample 13 NATIVE	Empty 1 x CPB	Empty 1 x CPB						
F	Sample 06 TUMOR	Sample 06 NATIVE	Sample 14 TUMOR	Sample 14 NATIVE	Empty 1 x CPB	Empty 1 x CPB						
G	Sample 07 TUMOR	Sample 07 NATIVE	Sample 15 TUMOR	Sample 14 NATIVE	Empty 1 x CPB	Empty 1 x CPB						
H	Sample 08 TUMOR	Sample 08 NATIVE	**PC**	**NTC**	Empty 1 x CPB	Empty 1 x CPB						

Figure 2: Example for a plate map for 30 samples. Grey: 1x CPB: 1x Capillary Protection Buffer, white: well type “NATIVE”, yellow: well type “TUMOR”, blue: well type “PC”, green: well type “NTC”.

Seal the PCR plate with aluminum sealing film. Spin the PCR plate in a table-top centrifuge.

Remove the seal and overlay all 48 wells on the PCR plate with one drop of mineral oil. Ensure that each reaction is fully covered by oil.

Seal the PCR plate again with aluminum sealing film. Spin the PCR plate and the MODAPLEX CE Plate in a table-top centrifuge. Proceed to the MODAPLEX and prepare for the following run.

Preparing the MODAPLEX run

Recheck plate filling
Before setting up the MODAPLEX run please recheck whether the plate contains a PC and NTC.Also check whether all empty wells (based on the used cartridge size) have been filled with 25 µl 1x Capillary Protection buffer.

Add the Assay Definitions to the MODAPLEX instrument.
Scan the MODAPLEX Barcode of Assay Definition provided with the MODAPLEX kit. The Assay Definition is automatically added to the MODAPLEX System. See the MODAPLEX User Manual for further instructions.

NOTE

The barcode of the Assay Definition needs to be imported every time a new lot of the MODAPLEX MSI Analysis Kit is used.

Check the operational capability of the device.
Before setting up the MODAPLEX assay the following conditions regarding the consumables should be met for the planned MODAPLEX run:

- At least one remaining run in the MODAPLEX Cartridge
- All consumables must be sufficient for the run

To replace the MODAPLEX Cartridge or other consumables, please refer to the MODAPLEX user manual for further instructions.

Create a run draft and a plate map on the MODAPLEX instrument.
A run draft can be created in the MODAPLEX Design and Analysis Software at the workstation or alternatively, in the MODAPLEX Controller directly on the instrument. The Assay Definition must be assigned to a run draft after file import or by scanning the QR code of Assay Definition, Analysis Protocol and PCR-CE Protocol.

Enter basic information to complete the run information and define the plate map by selecting the size of the used cartridge and well type for each well.

For overall evaluation and data assignment, plate map must contain well name, Assay Definition and well type as listed below:

Positive control:	Well type: PC
No template control :	Well type: NTC
Tumor tissue (= tumor):	Well type: TUMOR
Normal adjacent tissue (= native):	Well type: NATIVE

NOTE

It is required to use the same name for tumor tissue and native tissue from the same patient. This is a prerequisite for the MODAPLEX Reporter software to be able to align the electropherograms of the two samples automatically.

The sample name can be any name, number, or code that can identify a sample.

Avoid special symbols like double quotes (“), brackets (< or >), ampersands (&), etc.

NOTE

Wells are automatically defined as “Buffer” wells as long as they have not been assigned with a name, an Assay Definition or a well type. Wells filled with Capillary Protection Buffer shall not be assigned.

Each well not containing buffer, must be assigned with a name, an Assay Definition and a well type (PC, NTC, TUMOR, NATIVE). If no well types are assigned, the MODAPLEX Reporter software will not be able to evaluate the run results!

Open the run draft in the MODAPLEX Controller and start the run by completing the run start wizard in the software.

After setting up the MODAPLEX instrument, briefly centrifuge the PCR and CE plates, then place the prepared PCR plate and the MODAPLEX CE Plate in the MODAPLEX instrument and start the run.

NOTE

The plate cover seals must be removed from the PCR plate and the MODAPLEX CE Plate before they are placed on the MODAPLEX instrument.

Check status of completed run and access the results.

Check if the run was completed properly and remove the plates. Seal the PCR and MODAPLEX CE Plates with aluminum sealing film before disposing of them. Decontaminate the MODAPLEX Hold Down Plate. For further instructions refer to the MODAPLEX user manual.

Interpretation of the Results

After the MODAPLEX run is completed, the MODAPLEX MSI Analysis Kit data must be analyzed using the following procedure:

1. Data transfer to the MODAPLEX Reporter software
2. Data analysis
3. Create a MSI report

Please refer to the MODAPLEX Reporter handbook for general instructions and details to the software.

Data transfer to the MODAPLEX Reporter software

For initial installation of the MODAPLEX Reporter software, please follow the installation instructions provided with the installer.

After the completion of the MODAPLEX run, the instrument creates a run folder, containing all the run-related data. The folder is automatically generated and named by date, serial number and a sequential number, e. g. 20230904_D12345_01 for the first run on September 4, 2023 on the

instrument with serial number D12345. Copy the run folder to your computer either using a USB stick, or the MODAPLEX Hub, as described in the MODAPLEX manual.

If your run is already available in the MODAPLEX Design and Analysis Software, you must export the run from within this software for use with MODAPLEX Reporter.

NOTE

The MODAPLEX Reporter software should not be installed on the MODAPLEX instrument.

Open the MODAPLEX Reporter software and select ***Import MODAPLEX Run***. Select your run folder and click ***Select folder***. Ensure that the MODAPLEX Reporter software contains the assay-specific Plugin and MAC.

This loads the MODAPLEX data into the MODAPLEX Reporter software. The quality control for all wells is performed automatically during import. After the data transfer, the 'Information' window opens for data analysis.

NOTE

The suitable software plugins are available as download via https://download.biotype.de.

Data Analysis

This section also contains detailed information about the result interpretation of the control and the sample wells, including the comments and recommendations pertaining to all possible results. This section is divided into the following subsections:

A. Interface overview: General display of analyzed data

B. Quality control: Analysis of the NTC and PC

C. Result interpretation: Analysis of the sample wells

Open a MODAPLEX MSI Analysis Kit run.

Start the MODAPLEX Reporter software with the installed MSI Assay Plugin (for details see the MODAPLEX Reporter handbook). Click the "***Open Completed Run***" button, select the MODAPLEX run folder and click "***OK***".

A. Interface overview: General display of analyzed data

Run information

General information about the run such as instrument status, consumables/reagents or applied overrides can be found in the tab "Run Report". Information about used protocols for the run (Assay Definition, PCR-CE protocol, Analysis Protocol) can be found in the tab "Information".

Plate map overview

The tab "Plate Map" shows the samples loaded on the MODAPLEX plate. A color code is used to display the validity of each well. The applied color code displays the following information:

1. QC information: Independent determination of the validity of each well
2. Internal control information: The validity of the detected internal controls

The plate summary is illustrated in Figure 3. The color code is explained in detail in the chapters Quality Control: Analysis of the NTC and PC, and Result interpretation of the sample wells.

The plate map includes a filter for the loaded assays on the plate (1) above the plate map on the right side. The filter function includes a text-based sample name filter (2) to easily search a specific sample name.

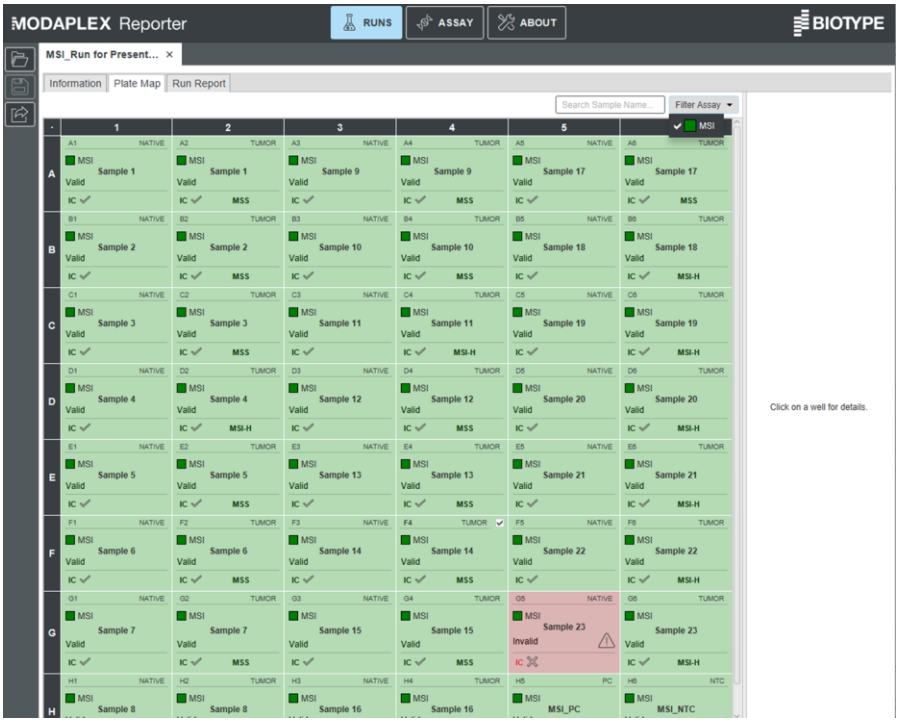


Figure 3: Plate map overview

Each well shows the following information (e.g. see Figure 4):

1. Well localization: Combination of a capital letter (A to H) and a number (1 to 6).
2. Well type: PC, NTC, TUMOR or NATIVE
3. Assay name with assay-specific colour-coded square in the upper left
4. Sample name
5. Background color indicating the well validity: green (valid well) or red (invalid well).
6. Well validity is aditionally indicated as either “Valid” or “Invalid”. Validity criteria are dependent on well types described in the subsequent chapters B and C.
7. Validity of internal controls (IC) indicated in the bottm left of the well though either a checkmark (valid) or a cross (invalid)
8. Symbols indicating warnings or comments. If symbols are visible they are explained in the Notes section of the details view (see below).
9. Status of Microsatelite instability.
   MSS (stable), MSI-L (low), MSI-H (high)

Figure 4: Well information

Well details

For detailed information about a well, click on the well to open the details view on the right side. The details view opens within an assay tab displayed with the assay short name (a) and a well tab displayed with the corresponding well ID (b). Furthermore, the details view contains two sections (e.g. see Figure 5):

1. Notes: Warnings and comments related to the well validity are displayed here. Additionally, a note is given if no overall evaluation has been made.
2. Results: In the left panel the marker group can be set using a dropdown menu (A). For wells with a tumor sample (well type TUMOR), the corresponding native sample (well type NATIVE) can be manually linked by using the dropdown menu “Linked Sample” (B). The dropdown menu “Overall Evaluation” (C) allows the selection of the MSI status of the tumor sample. The right part of the results section shows a table with the markers as well as size standards and controls. For details on performing the MSI evaluation please see chapter “Result evaluation”.
3. Electropherograms: In this section the electropherograms of the respective sample are shown. Wells with a tumor sample show two lines, one for the tumor sample (green) and one for the native sample (black). Buttons above the graph allow change between the red and the blue channel (D). Above the electropherogram, four additional buttons are located: the graph can be opened in a separate window (E), scales for the x and y axes can be adjusted (F), the legend can be hidden/shown (G) and a screenshot of the electropherogram can be saved as .png file (H).

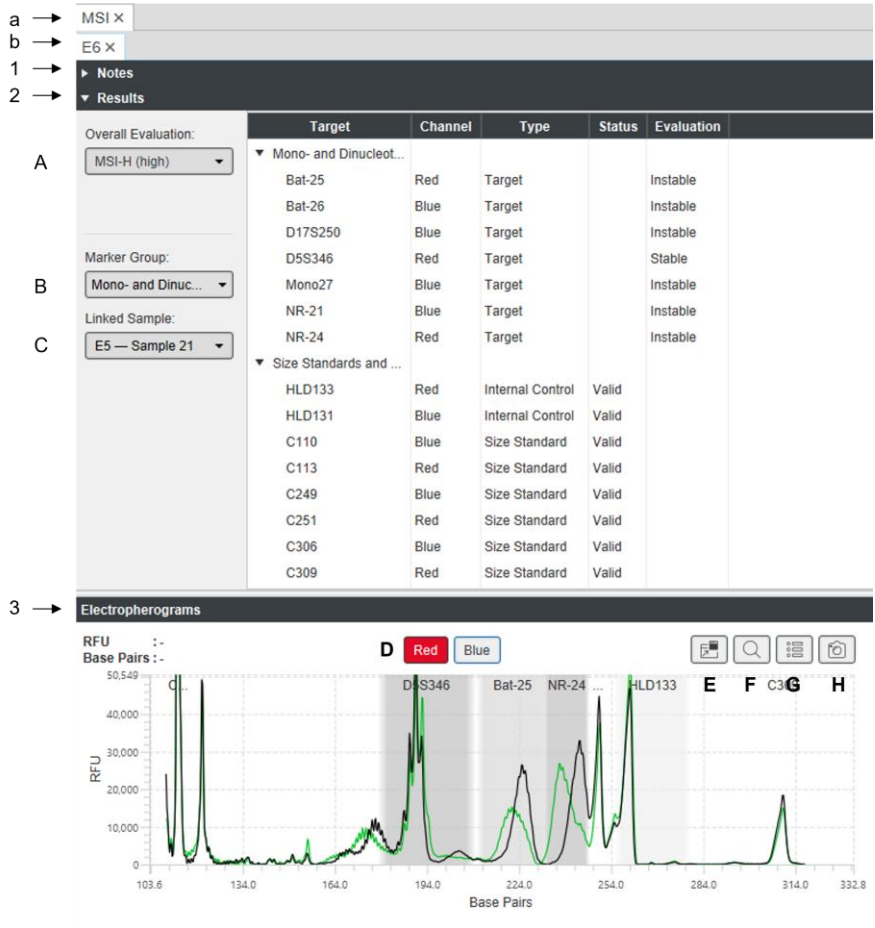


Figure 5: Well details view.

B. Quality control: Analysis of the NTC and PC

Each MODAPLEX MSI Analysis Kit run shall include the run controls NTC and PC. A MODAPLEX run is valid if the PC and the NTC wells are valid. The results of the run controls are displayed through changes in the background color of each well on the plate map.

NOTE

The validity of the run controls is not connected to the validity of the sample wells (TUMOR and NATIVE). A sample well can be valid even when there are invalid run controls. In such cases, the reason behind the invalid controls should be investigated and BIOTYPE GmbH should be contacted for technical assistance, if required.

The background color of the wells do not display the run validity of the complete run.

No template control (NTC)

The NTC is reported as valid if no internal control (IC1 and IC2) and target is detected. It is reported as invalid if at least one internal control or target is detected or at least one size standard is out of range. Please refer to the troubleshooting guide in case of invalid NTC.

Positive control (PC)

The PC is reported as valid if all markers and internal controls are detected and the size standards are in range. If the PC is invalid, the user should refer to the troubleshooting guide.

Table 7: MODAPLEX Reporter: Validity of PC and NTC wells

Background color of control well	Description	Criteria
	Valid MODAPLEX run for NTC	▪ All size standard peaks in the blue channel (C110/ C249/ C306) and the red channel (C113/ C251/ C309) detected. ▪ No target detected in NTC ▪ No internal control detected in NTC

Background color of control well	Description	Criteria
	Valid MODAPLEX run for PC	▪ All size standard peaks in the blue channel (C110/ C249/ C306) and the red channel (C113/ C251/ C309) detected ▪ All markers detected in PC ▪ All internal controls (HLD131 and HLD133) detected in PC
	Invalid MODAPLEX run for NTC	▪ Not all size standard peaks in the blue channel (C110/ C249/ C306) and the red channel (C113/ C251/ C309) detected. ▪ Target detected in NTC. ▪ Internal control detected in NTC. ▪ Additional information in the single well view under “Notes” explaining the failed well validity
	Invalid MODAPLEX run for PC	▪ Not all size standard peaks in the blue channel (C110/ C249/ C306) and the red channel (C113/ C251/ C309) detected. ▪ Not all targets detected in PC ▪ Less than two internal controls detected in PC. ▪ Additional information in the single well view under “Notes” explaining the failed well validity

Table 8: MODAPLEX Reporter: Detection of the internal controls in PC

Color code for the PC	Description	Criteria
	Complete detection of internal control	Both internal controls detected
	Incomplete detection of internal controls	One internal control detected Or no internal control detected

Table 9: MODAPLEX Reporter: Detection of the internal controls in NTC

Color code for the PC	Description	Criteria
	Expected detection of internal control	No internal controls detected
	Detection of internal control	Minimum one internal control detected

For more information about the NTC or PC well, click on the well. The detail view will be displayed on the right side of the plate map and shows information about notes and validity of each target. For NTC wells, target and ICs should not be detected to achieve the „valid“ state. For PC all targets and ICs need to be detected to be valid.

C. Result interpretation of the sample wells

Each well on the plate map displays well validity by the background color. The MODAPLEX Reporter software automatically performs assay-specific evaluation of the wells and displays results as either valid or invalid. If the sample well is invalid, the user should refer to the BIOTYPE GmbH troubleshooting guide.

Table 10: MODAPLEX Reporter: The QC information for the sample wells (TUMOR and NATIVE)

Background color of sample well	Description	Criteria
	Valid sample well	▪ All size standard peaks in the blue channel (C110/ C249/ C306) or the red channel (C113/ C251/ C309) detected. ▪ Internal controls (HLD131 and HLD133) detected
	Invalid sample well	▪ Not all size standard peaks in the blue channel (C110/ C249/ C306) and the red channel (C113/ C251/ C309) detected. ▪ Not all internal controls detected. ▪ Additional information in the single well details view as “Notes” explaining the failed well validity. ▪ Please refer to the troubleshooting section

Table 11: MODAPLEX Reporter: Detection of the internal controls in sample wells (TUMOR and NATIVE)

Color code for sample wells	Description	Criteria
IC ✓	Complete detection of internal control	Both internal controls detected
IC ✗	Incomplete detection of internal controls	One internal control detected Or no internal control detected

1. Open the details view of a well with a tumor sample (well type TUMOR).

   Well Linking

   Wells with a tumor sample (well type TUMOR) need to be linked with the well of the corresponding non-tumor material (well type NATIVE). If the sample name for both wells is identical, the software performes the linking automatically. In case the sample names are not identical, a manual linking is necessary: use the “Linked Sample” drowpdown menu in the results section to select the well with the non-tumor material (well type NATIVE) that shall be linked.

2. Confirm that the TUMOR and NATIVE electropherograms are aligned. Inspect the size standards C110 (blue channel) and C113 (red channel) and affirm that the lines for TUMOR (green) and NATIVE (black) are aligned and of similar height.

3. Inspect the internal controls to confirm that TUMOR and NATIVE samples are from the same patient. Peaks of the TUMOR and NATIVE sample for HLD131 (blue channel) and HLD133 (red channel) should be aligned.

4. Choose the marker group that shall be used for the analysis. Two marker groups are available (table 1): five mononucleotide markers or seven mono- and dinucleotide markers.

5. Select a marker by clicking on the marker name in the results table. Automatically, the electropherogram focusses on this marker.

6. From the dropdown menu for the respective marker select either “Stable”, “Instable”, or “Uncertain”.

   Two criteria shall be applied for characterisation of instable targets. If one or both of the criteria are met, the respective target can be judged as instable.

   1. Shift of the whole peak. Please refer to the maximum of the individual peaks and assess whether migration length of tumor signal and native adjacent tissue signal differs by at least 2 bp. Peak height differences can occur and shall not be the basis for the evaluation.

   2. Emergence of a second peak maximum. The original peak can persist in this case and a new maximum arises. It is possible that instability manifests as a shoulder of the original peak or as a new signal.

   For target NR-21 no target below 5000 RFU shall be considered for evaluation. For the targets D17S250, Mono27, Bat-25 and NR-24, signals may be as low as 1000 RFU. Signals below 1000 RFU shall be ignored.

   If it cannot be clearly assessed whether one of the two criteria applies, the rating “uncertain“ should be assigned. It is recommended to repeat the run if two or more markers are evaluated as “uncertain“. In case of repetition, an increased DNA input of 20 ng should be used.

7. Repeat step 6 for all markers in the marker group.

8. Finally, set the overall evaluation based on the results of the evaluation of the individual markers. For this, use the “Overall Evaluation” dropdown menu and select either “MSI-L (low)”, “MSI-H (high)” or “MSS (stable)”. A suggestion for the interpretation of the individual marker evaluation is given by [5] (Table 12). In case of an unclear sample, select “Cannot be determined” from the dropdown menu.

Table 12: Interpretation of the MSI status of tumor samples. Adapted from [5].

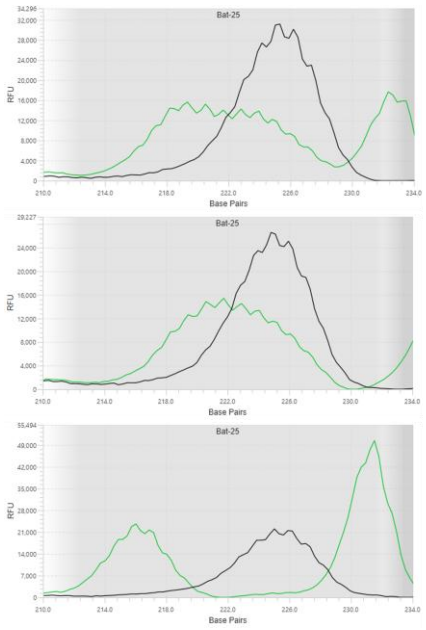
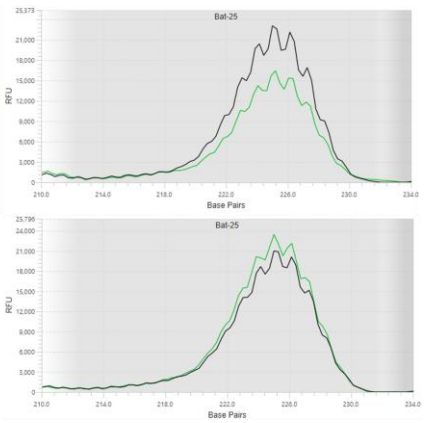
	Criteria for interpretation		
	5 loci analyzed	> 5 loci analyzed	Interpretation
No. of markers exhibiting instability length changes	≥ 2	≥ 30-40%	MSI-H
	1	< 30-40%	MSI-L
	0	0	MSS or MSI-L

9. Save the evaluation results by clicking the “Save” button in the left toolbar.

Examples for (un-) shifted markers

Bat-25

Table 13: Visual orientation of evaluation of "Stable" and "Instable" status of Marker Bat-25. The green curve represents the TUMOR sample, the black the NATIVE sample.

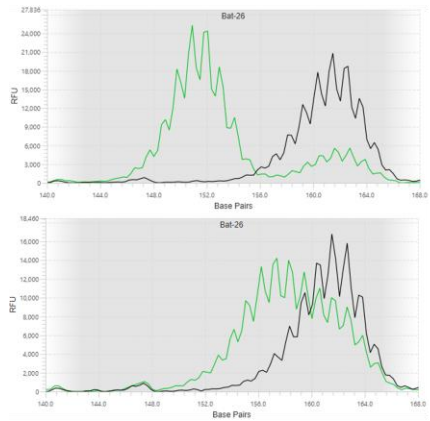
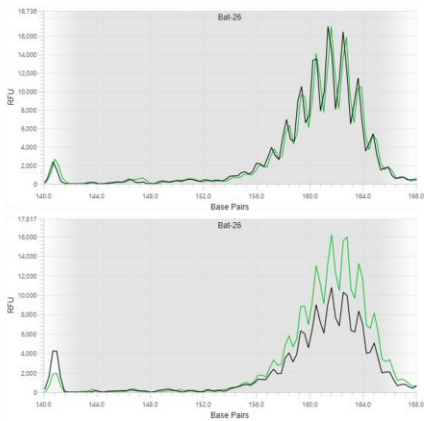
Mononucleotide Bat-25	
MSI 'Instable'	**MSS ‚Stable'**
	

NOTE

This target region includes known side products that can appear left and right of the Bat-25 signal. They can be easily distinguished from the spiky marker signal as they are flat and smooth. These side products should never be the basis for evaluation of Bat-25 stability or instability.

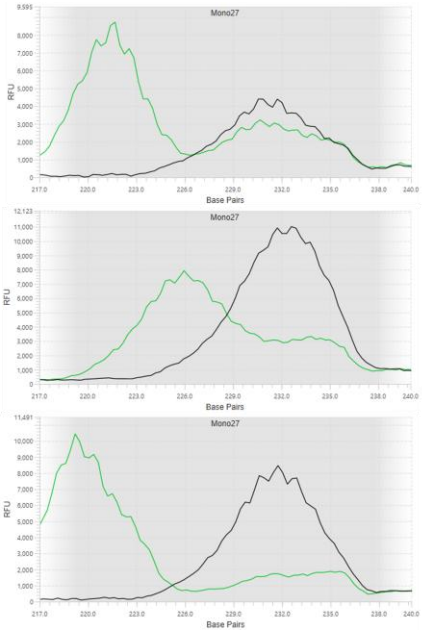
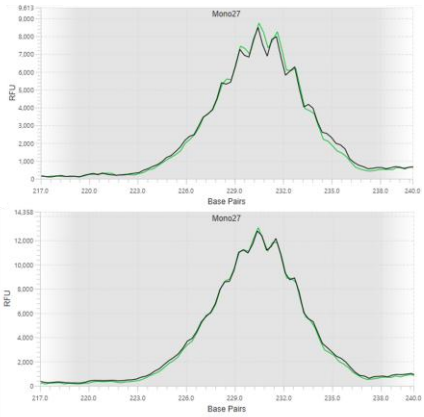
Bat-26

Table 14: Visual orientation of evaluation of "Stable" and "Instable" status of Marker Bat-26. The green curve represents the TUMOR sample, the black one the NATIVE sample.

Mononucleotide Marker Bat-26	
MSI 'Instable'	**MSS ‚Stable'**
	

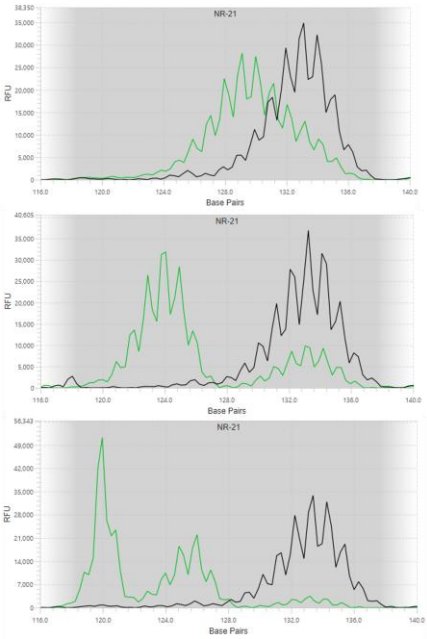
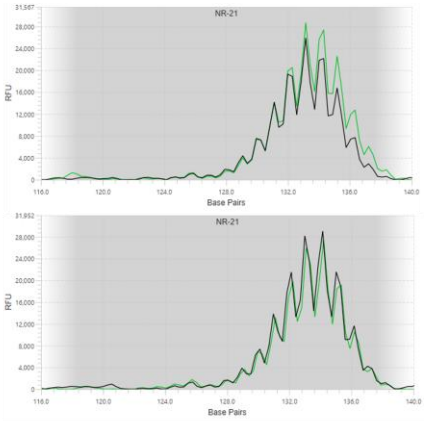
Mono27

Table 15: Visual orientation of evaluation of “Stable” and “Instable” status of Marker Mono27. The green curve represents the TUMOR sample, the black one the NATIVE sample.

Mononucleotide Marker Mono27	
MSI ‘Instable’	MSS ‚Stable‘
	

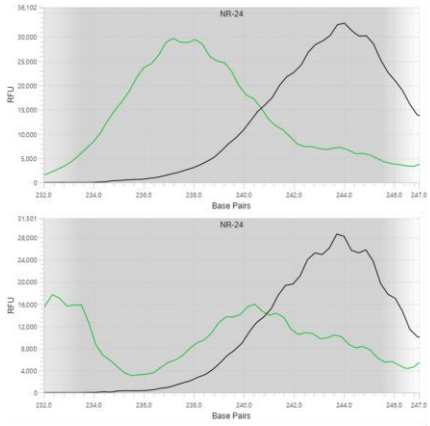
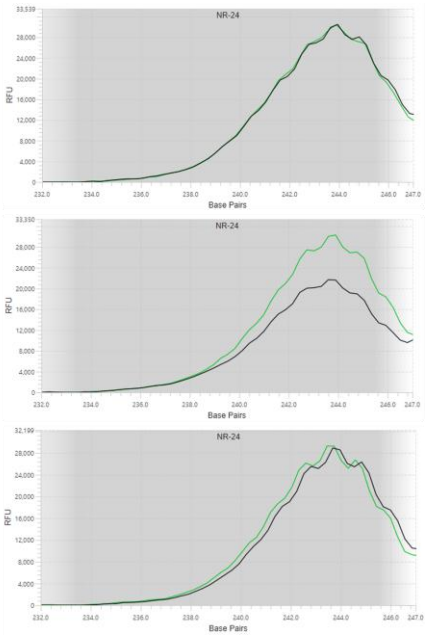
NR21

Table 16: Visual orientation of evaluation of 'Stable' and 'Instable' status of Marker NR-21. The green curve represents the TUMOR sample, the black one the NATIVE sample.

Mononucleotide Marker NR-21	
MSI 'Instable'	MSS ‚Stable'
	

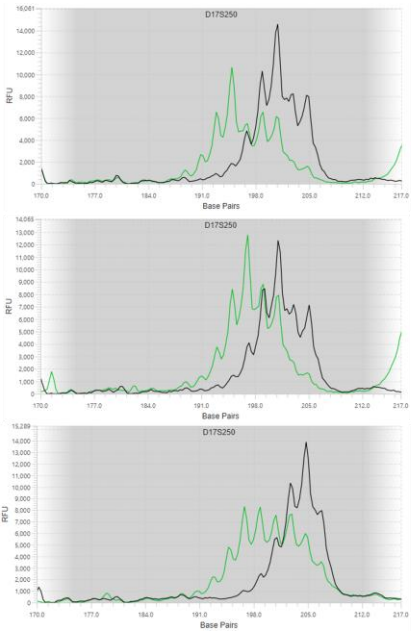
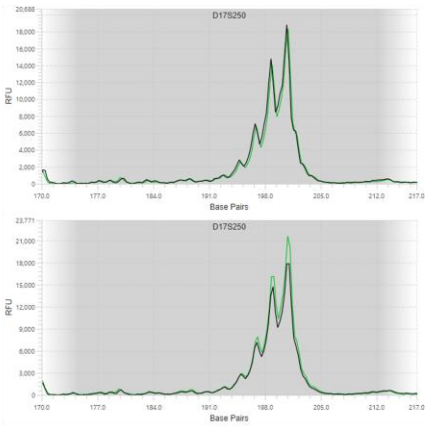
NR-24

Table 17: Visual orientation of evaluation of "Stable" and "Instable" status of Marker NR-24. The green curve represents the TUMOR sample, the black one the NATIVE sample.

Mononucleotide NR-24	
MSI 'Instable'	**MSS ‚Stable'**
	

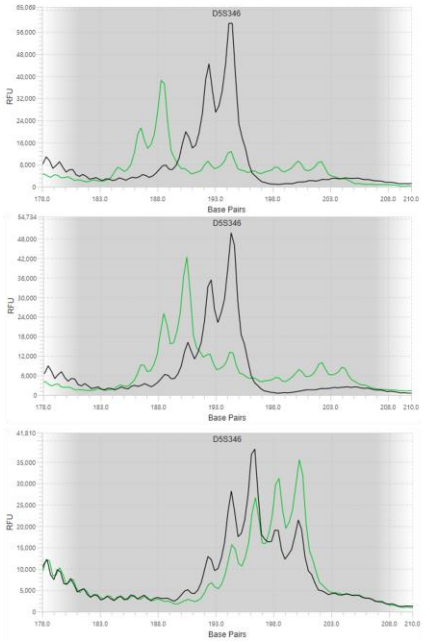
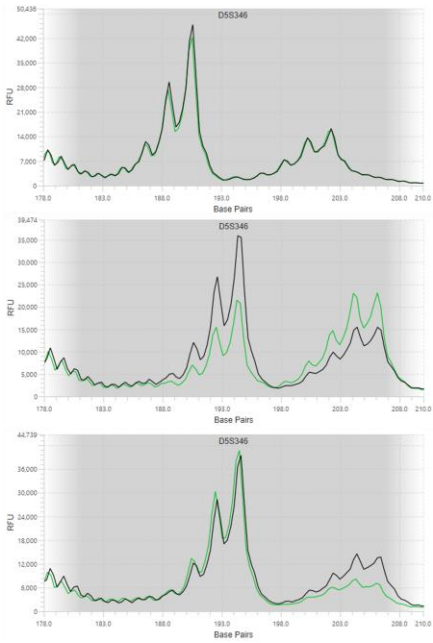
D17S250

Table 18: Visual orientation of evaluation of “Stable” and “Instable” status of Marker D17S250. The green curve represents the TUMOR sample, the black one the NATIVE sample.

Mononucleotide Marker D17S250	
MSI ‘Instable’	**MSS ‚Stable‘**
	

D5S346

Table 19: Visual orientation of evaluation of "Stable" and "Instable" status of Marker D5S346. The green curve represents the TUMOR sample, the black one the NATIVE sample.

Mononucleotide Marker D5S346	
MSI 'Instable'	MSS ‚Stable'
	

NOTE

This target region includes known side products that can appear left and right of the D5S346 signal. They can be easily distinguished from the spiky marker signal as they are flat and smooth. These side products should never be the basis for evaluation of D5S346 stability or instability.

Create a MSI report

This protocol shall be used to generate a report after the MSI data has been analyzed and classified as valid. The report contains the following information:

- The result of the sample
- Sample information
- MODAPLEX MSI Analysis Kit information, such as lot, assay ID, and expiration date
- Information about the MODAPLEX run, including consumable lots

Results can be exported either as printable PDF report or as text-based JSON file. If specific wells shall be exported, select them by checking the checkbox in the top right corner of each well. If data from the whole plate shall be exported, no selection is necessary.

1. Start the export wizard by clicking ***Export*** in the left toolbar.
2. Select the desired format (PDF or JSON).
3. Select if the whole plate (full report) or selected wells shall be exported.
4. Browse the directory name in which the file will be saved.
5. Click ***Export***.

PDF Report

The PDF report shows run and consumable information on page 1 (chapter 1). Details about used assay(s) including assay definition(s) can be found on the following pages (chapter 2). Chapter 3 gives an overview over all samples on the plate. The validity status is indicated by red (invalid) or green (valid) color. If an overall evaluation has been made, the result is shown for each sample. The following pages display detailed information of each sample including the marker evaluation, overall evaluation, potential notes and electropherograms for the red and blue channel.

JSON File

JSON is a text-based open standard derived from the format used to represent simple data structures in JavaScript. Most LIMS systems are able to import JSON files. It is also possible to open JSON files using Microsoft Excel. For detailed information, please refer to MODAPLEX Reporter handbook.

Performance Characteristics

Assay Performance	Result/Description
Primer Specifity	A basic local alignment search tool (BLAST) analysis was performed. The primer of the MODAPLEX MSI Analysis Kit only amplifies seven targets (Bat-25, Bat-26, NR-21, NR-24, Mono27, D5S346, D17S250) and two internal control targets (HLD131 and HLD133).
Sample Material	The MODAPLEX MSI Analysis Kit has been verified with human gDNA and DNA samples extracted from formalin-fixed, paraffin-embedded (FFPE) colorectal cancer (CRC) tissue. In addition, DNA samples extracted from formalin-fixed paraffin-embedded (FFPE) endometrial tissue have been tested for use with the MODAPLEX MSI Analysis Kit.
Input	10 ng (2 ng/µL)
Freeze Thaw Stability	Store all components at -25 °C to -15 °C and avoid repeated thawing and freezing. The MODAPLEX MSI analysis kit is verified to be stable for 5 freeze-thaw cycles.

Troubleshooting

The troubleshooting guide may be helpful for solving any problems that may arise. See also the MODAPLEX User Manual and Software Troubleshooting Guidance. For further information about protocols or if further support is needed, please contact our customer support (see Technical Assistance

Assay Performance	Result/Description
Invalid no-template control (NTC)	1. Targets and/or internal controls were detected in NTC. Contamination occurred during the preparation of the PCR. Repeat the PCR in replicates. If possible, close the PCR tubes directly after addition of the sample to be tested. Do not reseal the plates with the same plate seal. Ensure that the workspace and the instruments are decontaminated at regular intervals. If possible, use a different set of pipettes. 2. Check the maintenance interval for all used devices (e. g., pipettes) 3. NTC well was incorrectly labeled (wrong well type). Correct the well type in the plate set-up on the MODAPLEX and re-analyze the run. After this, load again into MODAPLEX Reporter.
Invalid positive control (PC)	1. Incomplete detection of targets, calibrators and/or internal controls. Incorrect handling occurred during the preparation of the PCR and/or positive control. Repeat the PCR in replicates. If possible, close the PCR tubes directly after addition of the sample to be tested. Do not reseal the plates with the same plate seal. Ensure that the workspace and the instruments are decontaminated at regular intervals. 2. Check the maintenance interval for all used devices (e. g. pipettes) 3. PC well was incorrectly labeled (wrong well type). Correct the well type in the plate set-up on the MODAPLEX and re-analyze the run. After this, load again into MODAPLEX Reporter..
The storage conditions for one or more kit components do not comply with the instructions given in ‘‘Reagent Storage and Handling’	Check the storage conditions and the expiration date (see the kit label). Please use a new kit if the reagents were stored improperly.
Incorrect overlay of peaks.	Calibrators have failed or assigned incorrectly. Please contact technical support.
Targets only present in one channel	1. Review all the run controls and the sample wells in the MODAPLEX Reporter software. If no well shows fluorescence in one channel, contact BIOTYPE GmbH

Assay Performance	Result/Description
IC not matching (MODAPLEX Reporter)	1. IC of tumor and native sample are not showing the same genotype. 2. Check the correct: • well linking – are the correct samples assigned together? • sample naming – are the wells named with the correct sample names? • Sample mix-up – were the correct samples added to the assigned wells? • Contamination – is the NTC valid? Was there a contamination of a sample with a second sample? 3. Repeat the affected samples.
Error 02 (MODAPLEX Reporter)	Issue during data acquisition – please repeat the corresponding sample

Limitation of Use

- For optimal results, strict compliance with the MODAPLEX MSI Analysis Kit handbook is required. The dilution of the reagents, other than as described in this handbook, is not recommended and will result in loss of performance.
- Use of this product is limited to personnel specially instructed and trained in PCR techniques and MODAPLEX technology.
- It is important that the amount and quality of the DNA in the sample are assessed and adjusted prior to performing a sample analysis using the MODAPLEX MSI Analysis Kit.
- The kit has been verified using the kits described in chapter Reagents, kits and consumables
- for DNA extraction and purification.
- Verified for use with an optimum input of 10 ng DNA per reaction.
- All results obtained with the product must be interpreted within the context of all relevant laboratory findings. The results are not to be used for diagnosis.
- Interpretation of results must account for the possibility of false negative and false positive results.

- Attention should be paid to expiration dates and storage conditions printed on the box and on the labels of all components. Do not use expired or incorrectly stored components.

Warranties and Disclaimer

This product is warranted to perform as described when used in strict conformity with the instructions given herein. The product has been designed for research use only and is to be used solely by qualified professionals. It is the user's responsibility to ensure that a given product is suitable for a given application.

BIOTYPE GmbH provides no other warranty, expressed or implied, and disclaims any implied warranty of merchantability or fitness for a particular purpose. Under no circumstances whatsoever shall BIOTYPE GmbH be liable for any indirect, special, or consequential damage.

Quality Control

All kit components undergo an intensive quality assurance process at BIOTYPE GmbH. Quality of the test kits is permanently monitored to ensure unrestricted usability. Please contact us if you have any questions regarding quality assurance.

References

[1] P. Peltomaki, "Role of DNA mismatch repair defects in the pathogenesis of human cancer", J Clin Oncol, vol. 21, pp. 1174–1179, 2003

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D5S346, D17S25) in Rectal Cancer.", ABCD Arq Bras Cir Dig. Vol. 25(4), pp. 240–244, 2012

[4] "Revised Bethesda Guidelines for Hereditary Nonpolyposis Colorectal Cancer (Lynch Syndrome) and Microsatellite Instability", J Natl Cancer, vol. 96(4), pp. 261–268, 2004.

[5] Boland, Clement Richard et al. "A National Cancer Institute Workshop on Microsatellite Instability for cancer detection and familial predisposition: development of international criteria for the determination of microsatellite instability in colorectal cancer." Cancer research 58 22 (1998): 5248-57

Technical Assistance

For technical advice, please contact our customer support team:

e-mail: support@biotype.de

phone: +49 (0)351 8838 400

Ordering information

Direct your orders via email to sales@biotype.de.

Product	Packaging size	Order number
MODAPLEX MSI Analysis Kit	50 reactions	85-10701-0050
MODAPLEX	1 instrument	84-20001-0001
MODAPLEX Hold Down Plate	1 plate	84-20002-0001
MODAPLEX Cartridge	1 cartridge (48 capillaries)	84-20101-0048
MODAPLEX Buffer	2 x 1 L	00-14302-2000
MODAPLEX Decon	2 x 1 L	00-14303-2000
MODAPLEX CE Gel	28 mL	00-04305-0028
MODAPLEX CE Plate	20 plates	00-14306-0020
10X Capillary Protection Buffer Kit	1800 reactions	85-21001-1800
Mineral Oil	5 x 5 mL	00-04301-0025
MODAPLEX PCR Plate	25 plates	84-20102-0025
Aluminium Sealing Film	100 pieces	00-14X04-0100

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Explanation of Symbols

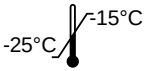
Manufacturer

Batch code

Contains sufficient reagents for <N> tests

Reference to eIFU

Use by



Storage temperature limitation

Catalogue number

Protect from light

Keep dry

Further marking used in this handbook:

	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
Cursive, bold text	Field which are to be clicked in a software

BIOTYPE GmbH

Moritzburger Weg 67
01109 DRESDEN
GERMAY

Tel.: +49 351 8838 400
Fax: +49 351 8838 403
info@biotype.de
www.biotype.de

Ordering
sales@biotype.de

Customer Service & Support
support@biotype.de