MODAPLEX FGFR3 Mutation Kit

Handbook

RUO

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

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Notice of Change

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

Document code	Changes	Date
F3MUTHB01v1en	Initial release of the handbook	22.08.2024
F3MUTHB01v2en	Adjustment in the chapter Instrument, Software and associated files. Replacement of MODAPLEX Size Standard with MODAPLEX Size Standard 2.	02.10.2025

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Content

Product Description

The MODAPLEX FGFR3 Mutation Kit is a qualitative PCR-based multiplex assay for the detection of 13 mutations in the fibroblast growth factor receptor 3 (FGFR3) gene. The assay is designed to work with the MODAPLEX instrument using human RNA derived from formalin-fixed, paraffin-embedded (FFPE) samples. The kit was tested on bladder cancer samples during development.

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

The fibroblast growth factor receptors (FGFR) belong to the family of transmembrane receptors with intracellular tyrosine kinase domain. They get activated by fibroblast growth factors (FGFs) initiating intracellular signaling pathways that influence cell development, differentiation, cell survival, migration, angiogenesis, and carcinogenesis. Alterations in FGFR genes can cause the FGFR signaling pathway to become overactive, which can then result in cells turning cancerous [1]. Mutations in the FGFR3 gene are most prevalent in urothelial bladder cancer samples. [1]

The MODAPLEX FGFR3 Mutation Kit is a fluorescent multiplex assay intended to be used with the MODAPLEX platform, which combines PCR and capillary electrophoresis (CE) in a unique technology. A subset of 13 FGFR3 mutations are amplified using fluorescent-labeled primers. The resulting amplicons are separated by CE and analyzed through qualitative endpoint detection using the MODAPLEX Reporter software.

The functionality of the assay is controlled by internal and external controls. Table 1 summarizes the list of FGFR3 mutation targets.

Table 1: List of detected FGFR3 mutations based on the FGFR3-IIIc splicing variant

Target Gene	AA Change	CDs Mutation	COSMIC legacy ID	Exon
FGFR3	R248C	c.742C>T	COSM714	7
	S249C	c.746C>G	COSM715	7
	G370C	c.1108G>T	COSM716	10
	S371C	c.1111A>T	COSM17461	10
	Y373C	c.1118A>G	COSM718	10
	G380R	c.1138G>A	COSM24842	10
	A391E	c.1172C>A	COSM721	10
	K650E	c.1948A>G	COSM719	15
	K650Q	c.1948A>C	COSM726	15
	K650M	c.1949A>T	COSM720	15
	K650T	c.1949A>C	COSM731	15
	K650N	c.1950G>T c.1950G>C	COSM1428730 COSM3993567	15

Principle of the Procedure

The MODAPLEX platform is a multiplex PCR benchtop system that merges PCR with a capillary electrophresis (CE) based detection of amplification products in an automated process. This technology enables the simultaneous detection and differentiation of multiple targets in two fluorescence channels through a single reaction.

Oligonucleotide primers are designed to produce PCR products with unique CE mobility. The primer mix includes primers for the 13 FGFR3 targets, 12 of which are differentiated, and three internal controls. A size standard, which is used for aligning and assigning CE peaks, is added to each test. At the end of the run, the amplified PCR products are sized, assigned, and evaluated.

Control Concept

The MODAPLEX FGFR3 Mutation Kit provides a comprehensive control concept. It consists of internal and external controls to evaluate the functionality of the PCR reaction as well as potential RNA fragmentation and FGFR3 expression. The control concept is described in detail below:

Template-independent PCR controls: MODAPLEX Size Standard 2

The MODAPLEX Size Standard 2 consists of four amplifying size standard peaks (SST-A, SST-B, SST-C and SST-D), all of which are detected in the blue channel. The artificial DNA template enables the template-independent control of the PCR reaction in each reaction. The assay-specific migration sizes of the MODAPLEX Size Standard 2 components are listed in Table 2 below.

Table 2: Migration sizes of the MODAPLEX Size Standard 2

Size Standard Peaks	Length (bp)	Channel
SST-A	66	blue
SST-B	107	blue
SST-C	169	blue
SST-D	261	blue

NOTE

The MODAPLEX Size Standard 2 must be added to all sample, no template control and positive control wells.

Internal Controls (IC)

The three internal controls, CALM2, FGFR3 and β-Actin (ACTB) serve as template-dependent PCR controls in sample wells.

- CALM2: stabely expressed FGFR3-independent gene (“housekeeper”)
- FGFR3: Gene expression level of FGFR3
- ACTB: Additional internal control with a longer amplicon that can indicate RNA fragmentation

Table 3: List of template-dependent internal controls with corresponding names and lenghts

Name of amplicon	Length (bp)	Channel
CALM2	87	blue
FGFR3	73	blue
ACTB	197	red

The internal controls are detected as amplicons of the respective sizes which are labelled via a flourescent primer. All primer designs are RNA-specific by spanning at least one intron, therefore the expected amplicon sizes of the control targets cannot be detected on genomic DNA. In the case of FGFR3 the included intron is short and the larger gDNA-dependent amplicon is detectable at 287 bp. In the MODAPLEX Reporter software an information is displayed when this gDNA-dependent FGFR3 signal is detected as the assay was not verified in the presence of genomic DNA.

External Control 1: no template control (NTC)

The user must set up a NTC (no template control) for each run to assess if the master mix has potentially been contaminated while setting up the measurement. Nuclease-free water is used instead of a template in the NTC well.

The NTC is valid if only expected signals are present (size standard peaks). If mutation or internal control targets are detected, the NTC will be displayed as invalid. Consequently, the NTC ensures that the kit performs within the stated performance characteristics. The validity of the NTC is assessed by and displayed in the MODAPLEX Reporter software.

External Control 2: positive control (PC)

The FGFR3 Mutation Positive Control consists of both artificial templates containing 12 missense mutations as well as the three internal controls. The amplification and detection of the targets serves as a control for the funcionality of the primer mix and consequently ensures the kit performance as all targets must be amplified during the PCR reaction.

NOTE

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

Platform and Software

MODAPLEX Instrument

The MODAPLEX FGFR3 Mutation 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 and RNA targets in a single well and run. As a result, it allows the parallel run of tests for fragment analysis, mutational analysis, gene expression, copy-number variation, and more.

MODAPLEX Reporter Software

The MODAPLEX FGFR3 Mutation Kit must be analyzed using BIOTYPE's MODAPLEX Reporter software. The MODAPLEX Reporter, the FGFR3 Mutation 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 FGFR3 Mutation Kit.

Materials Provided

Kit content

The MODAPLEX FGFR3 Mutation Kit contains reagents that can be used to perform up to 50 reactions. It includes the following components:

Table 4: Content of the MODAPLEX FGFR3 Mutation Kit

Reagent	Cap Color	Volume per kit	Storage
Nuclease-Free Water	Light blue	1 x 1.5 mL	
FGFR3 Mutation Primer Mix	Red	1 x 125 µL	−25 °C to
FGFR3 Mutation Positive Control	White	1 x 80 µL	−15 °C,
One-Step Master Mix (2x)	Black	1 x 625 µL	protected
RT Enzyme Mix (20x)	Orange	1 x 62.5 µL	from light
MODAPLEX Size Standard 2	Green	1 x 25 µL	
Barcode of Assay Definition		1 x	-

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

NOTE

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

Description of Components

FGFR3 Mutation Primer Mix

This tube contains oligonucleotide primers specific to the 13 FGFR3 mutations and three internal control gene targets, as shown in Table 1.

One-Step Master Mix (2x)

This solution is supplied at 2x concentration and contains Hot-Start Taq DNA Polymerase, dNTPs, and all required buffer components for the PCR reaction. It also contains dUTP for carryover prevention as well as a non-fluorescent visible dye for monitoring reaction setup.

RT Enzyme Mix (20x)

The MODAPLEX FGFR3 Mutaion Kit contains a WarmStart Reverse Transcriptase enzyme for the reverse transcription in addition to RNase inhibitor to aid in preventing RNA degradation.

MODAPLEX Size Standard 2

The MODAPLEX Size Standard 2 is a template-independent PCR control and an internal length standard.

FGFR3 Mutation Positive Control

The FGFR3 Mutation Positive Control is described in detail in chapter Control Concept.

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 lengths. 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.

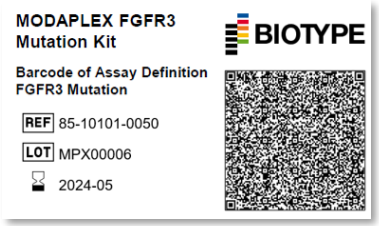


Figure 1: **Example of Barcode**

Reagent storage and handling

The kit is shipped on dry ice. The components of the kit shall arrive frozen, except the RT Enzyme Mix (20x), 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 shipping. Do not use kits that have been thawed upon arrival.

Store all components at -25 °C to -15 °C without light exposure. Especially the FGFR3 Mutation Primer Mix and MODAPLEX Size Standard 2 must be stored protected from light.

The expiration date is stated on the kit box label. Do not exceed a maximum of 10 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
- 96-well cooling racks and/or ice

NOTE

All material to be used for PCR shall have appropriate quality (DNA and RNA 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 5: Reagents required, but not provided

Reagent	Supplier	Order number
MODAPLEX PCR Plate	BIOTYPE GmbH	84-20102-0025
Aluminium Sealing Film	BIOTYPE GmbH	00-14X04-0100

Reagent	Supplier	Order number
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
RNeasy FFPE Kit	QIAGEN	73504
Deparaffinization Solution	QIAGEN	19093
Nuclease-Free Water	QIAGEN	129114, 129115
Qubit™ RNA HS Assay **or**	Thermo Fisher Scientific	Q32852, Q32855
Qubit™ RNA BR Assay	Thermo Fisher Scientific	Q10210, Q10211

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 v3.0.x (BIOTYPE GmbH)

Table 6: Assay-specific components

Component	Version	ID
Assay Definition	Lot-dependent	N/A
PCR-CE Protocol	Beta	aoHnJeXLS3uYJzhViWcT7A
Analysis Protocol	See Download Area	N/A
MODAPLEX Reporter Plugin	See Download Area V2.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 FGFR3 Mutation Kit has been verified using in-vitro transcripted RNA spiked into formalin-fixed paraffin-embedded (FFPE) RNA background for each target to be detected.

In addition, clinical FFPE RNA samples from bladder cancer tissue have been tested for use with the MODAPLEX FGFR3 Mutation Kit.

For long-term storage, the produced RNA should be kept undiluted at -80 °C.

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 Materials 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 FGFR3 Mutation Kit has been verified using in-vitro transcripted RNA spiked into formalin-fixed paraffin-embedded (FFPE) RNA background for each target to be detected.

In addition, RNA samples extracted from FFPE bladder cancer tissue have been tested for use with the MODAPLEX FGFR3 Mutation Kit. RNA samples to be used with the kit should ideally be freshly prepared. Prolonged storage of FFPE tissue material or an inadequate fixation may decrease the assay performance.

RNA extraction

It is recommended to isolate RNA using the RNeasy FFPE Kit (including the DNAse digestion step) and Deparaffinization Solution following the supplier's protocol. RNA isolation should be carried out from macro-dissected FFPE tissue or FFPE tissue sections. Up to 2 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 RNA isolation procedure and prior to storage, the RNA concentration must be promptly measured.

NOTE

The performance of the MODAPLEX FGFR3 Mutation Kit depends on the RNA quality. Heavily fragmented RNA can significantly influence the analysis and result interpretation.

RNA quantification and dilution

Quantification of the RNA should be carried out by fluorometric quantitation using the Qubit™ Fluorometer 3.0 or higher. For low FFPE tissue input (e. g. tissue biopsies) use the Qubit™ RNA HS Assay according to the manufacturer's protocol. Otherwise, the usage of the Qubit™ RNA BR Assay is recommended.

Set up the reactions with the MODAPLEX FGFR3 Mutation Kit using **20 ng (4 ng/µL)** of RNA template. Using a RNA amount below 20 ng could result in low PCR yields and the signal might fall below the target-specific detection limits. Using a RNA amount above 20 ng could cause signal background and therefore false-positive results.

NOTE

For sample dilution we recommend the use of nuclease-free water (i.e. provided with the RNA isolation kit or separately ordered) and a pipetting volume > 1.5 µL.

RNA storage

Store the RNA samples at -25 °C to -15 °C for short-term. For long-term storage RNA samples may be stored at -80 °C.

Component preparation

Positve control (PC)

Add the FGFR3 Mutation Positive Control included in the kit as template instead of a sample.

No template control (NTC)

Add the included Nuclease-Free Water to the reaction 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 FGFR3 Mutation Kit assay set-up

PCR master mix setup

Thaw the following components from the MODAPLEX FGFR3 Mutation Kit:

- Nuclease-Free Water (light-blue cap)
- One-Step Master Mix (2x) (black cap)
- FGFR3 Mutation Primer Mix (red cap)
- FGFR3 Mutation Positive Control (white cap)
- RT Enzyme Mix (20x) (orange cap)
- MODAPLEX Size Standard 2 (green cap)

During the PCR master mix setup, it is recommended to keep the RT Enzyme Mix in a cooled environment (e. g. on a cooling rack). All frozen components need to be thawed at room temperature (15 °C to 25 °C, ca. 30 min, protected from light) except the One-Step Master Mix must be thawed on ice. Homogeniz the components by inverting the tubes, pipetting, or gently vortexing. Do not vortex the RT Enzyme Mix. The reagents should be then briefly centrifuged (approx. 10 s) and placed on ice.

Prepare the PCR master mix according to Table 7 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 7: PCR master mix reaction setup

	Volume		
Component	**# 1**	**# 5**	**# 10**
One-step Master Mix (2x)	12.5 µL	62.5 µL	125 µL
Nuclease-Free Water	3.25 µL	16.25 µL	32.5 µL
FGFR3 Mutation Primer Mix	2.5 µL	12.5 µL	25 µL
RT Enzyme Mix (20x)	1.25 µL	6.25 µL	12.5 µL
MODAPLEX Size Standard 2	0.5 µL	2.5 µL	5 µL
Total volume	**20 µL**	**100 µL**	**200 µL**
RNA 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 into the designated wells of the MODAPLEX PCR Plate.

Application of RNA 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 RNA sample (4 ng/µL) to the corresponding sample well(s)

NTC: add 5.0 µL of Nuclease-Free Water

PC: add 5.0 µL of FGFR3 Mutation Positive Control

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	Sample 09	Sample 17	Sample 25	Empty 1x CPB	Empty 1x CPB	unused					
B	Sample 02	Sample 10	Sample 18	Sample 26	Empty 1x CPB	Empty 1x CPB						
C	Sample 03	Sample 11	Sample 19	Sample 27	Empty 1x CPB	Empty 1x CPB						
D	Sample 04	Sample 12	Sample 20	Sample 28	Empty 1x CPB	Empty 1x CPB						
E	Sample 05	Sample 13	Sample 21	Sample 29	Empty 1x CPB	Empty 1x CPB						
F	Sample 06	Sample 14	Sample 22	Sample 30	Empty 1x CPB	Empty 1x CPB						
G	Sample 07	Sample 15	Sample 23	**PC**	Empty 1x CPB	Empty 1x CPB						
H	Sample 08	Sample 16	Sample 24	**NTC**	Empty 1x CPB	Empty 1x CPB						

Figure 2: Example for a plate map set-up with 30 samples. Grey: 1x CPB: 1x Capillary Protection Buffer, yellow: well type "SAMPLE", 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 at least 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 run.

Preparing the MODAPLEX run

Recheck plate filling.
Before setting up the MODAPLEX run please recheck that the plate contains a PC and NTC. Also check whether all empty wells have been filled with 25 µL 1x Capillary Protection buffer.

Add the Assay Definition to the MODAPLEX instrument.
Scan the provided lot-dependent barcode to import the Assay Definition. The Assay Definition is then 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 FGFR3 Mutation 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, the 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
Sample well:	Well type: SAMPLE

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, SAMPLE). If no well types are assigned, the MODAPLEX Reporter software will not be able to evaluate the run results!

NOTE

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

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

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 FGFR3 Mutation Kit data must be analyzed using the following procedure:

1. Data transfer to the MODAPLEX Reporter software
2. Data analysis
3. Create FGFR3 Mutation report

Please refer to the MODAPLEX Reporter handbook for general instructions and details for 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 the run was already exported into 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 FGFR3 Mutation Kit run.

Start the MODAPLEX Reporter software with the installed FGFR3 Mutation Assay Plugin (for details see the MODAPLEX Reporter handbook). Click the "**Open Completed Run**" button, select the appropriate 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 . 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.

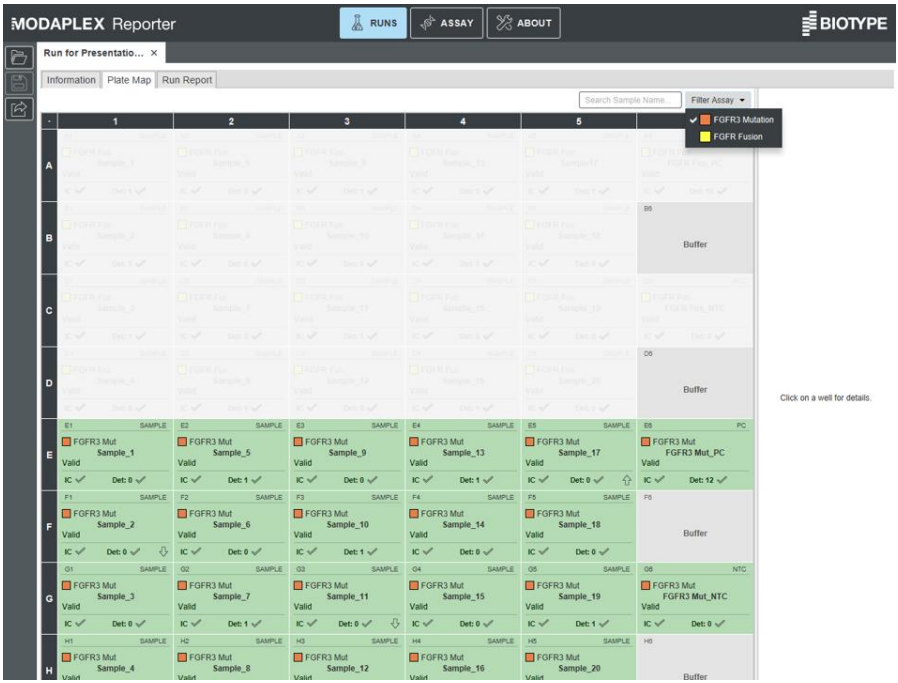


Figure 3: Plate map overview.

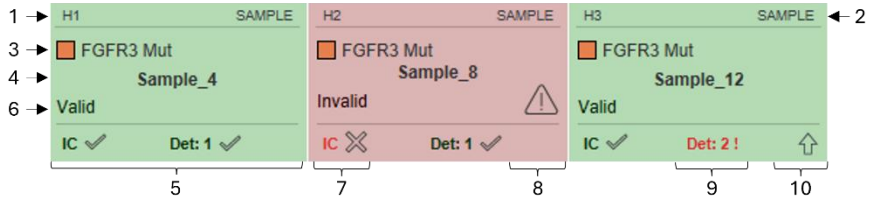


Figure 4: Well information.

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 or SAMPLE

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 additionally 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 bottom 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. Number of detected targets is displayed. Additionally a checkmark indicates that the correct number of targets was detected for the well type. An exclamation mark indicates that the incorrect number of targets was detected for the well type. Additional verification is recommended.
10. If the FGFR3 gene expression level in a sample is high or low in relation to CALM2 expression, it will be indicated by an arrow. This is calculated using the Delta Ct of FGFR3/CALM2. Overexpression of FGFR3 in the sample is marked by an up arrow and underexpression of FGFR3 is marked by a down arrow. This arrow should be taken as an indication only, as this is not a quantitative assay.

Well details

For detailed information about a well, click on it 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 four sections (e.g. see Figure 5):

1. Notes: Warnings and comments related to the well validity are displayed here. Please refer to the chapter Troubleshooting if notes with code “F:*number*” are displayed.
2. Results: This section shows a table with all tested targets as well as size standards and controls. If a mutation was found and is assessed as valid, a Ct value is reported.
3. Electropherograms: In this section the electropherograms of the respective sample are shown. Buttons above the graph allow changing between the red and the blue channel (A). Above the electropherogram, four additional buttons are located: the graph can be opened in a separate window (B), scales for the x and y axes can be adjusted (C), the legend can be hidden/shown (D) and a screenshot of the electropherogram can be saved (E).

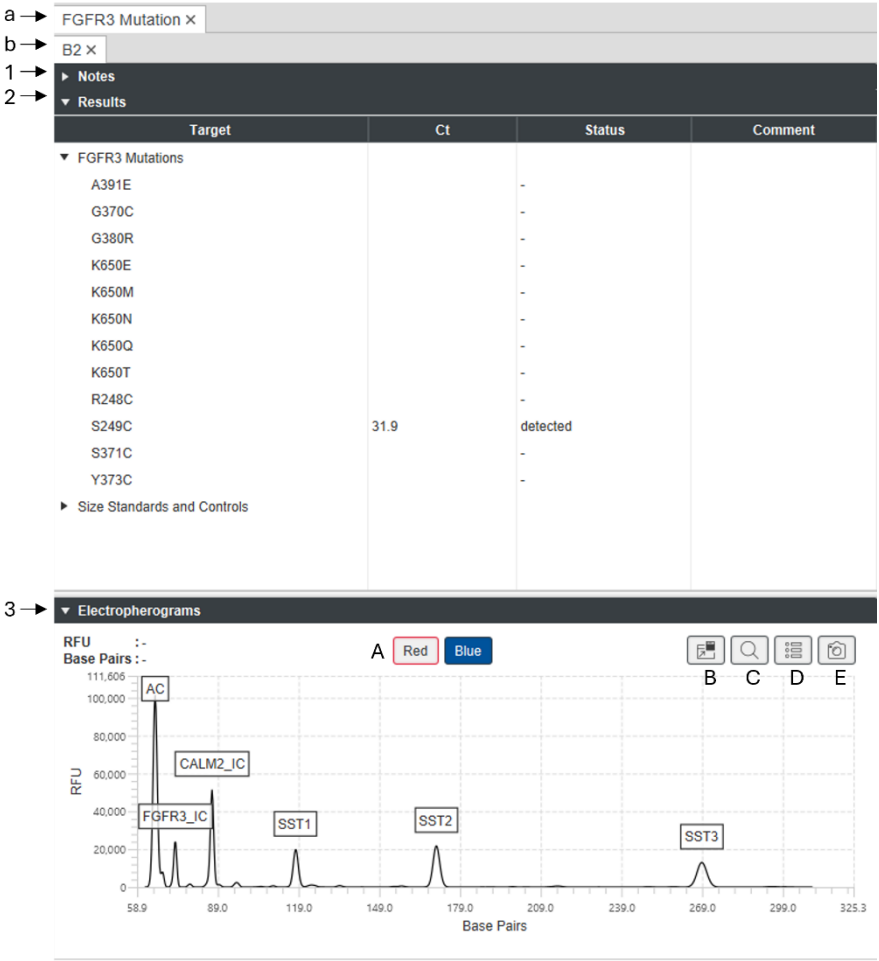


Figure 5: Well details view.

B. Quality control: Analysis of the NTC and PC

Each MODAPLEX FGFR3 Mutation 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 summary.

NOTE

The validity of the run controls is not connected to the validity of the sample wells. 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 and target is detected. It is reported as invalid if at least one internal control or target is detected, or if one or more peaks of the size standard are out of range. For guidance on invalid NTC results, refer to the Troubleshooting chapter.

Positive control (PC)

The PC is reported as valid if all markers and internal controls are detected, and all peaks of the size standard are within range. If the PC is invalid, refer to the Troubleshooting chapter.

Table 8: MODAPLEX Reporter: Validity of PC and NTC wells

Background color of control well	Description	Criteria
	Valid MODAPLEX run for NTC	▪ All size standard peaks (SST-A, SST-B, SST-C, SST-D) are detected ▪ No target detected in NTC ▪ No internal control detected in NTC
	Valid MODAPLEX run for PC	▪ All size standard peaks (SST-A, SST-B, SST-C, SST-D) are detected ▪ All targets detected in PC ▪ All internal controls detected in PC
	Invalid MODAPLEX run for NTC	▪ One or more size standard peaks (SST-A, SST-B, SST-C, SST-D) are missing ▪ 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	▪ One or more size standard peaks (SST-A, SST-B, SST-C, SST-D) are missing ▪ Not all 12 targets detected in PC ▪ Not all internal controls detected in PC ▪ Additional information in the single well view under “Notes” explaining the failed well validity

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

Color code for the PC	Description	Criteria
	Complete detection of internal control	All internal controls detected
	Incomplete detection of internal controls	Not all internal control detected Or no internal control detected

Table 10: MODAPLEX Reporter: Number of FGFR3 mutation targets in PC

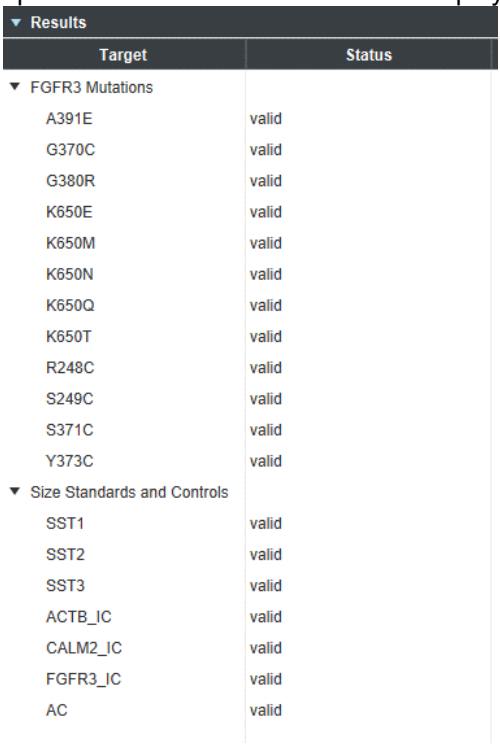
Detection view	Description
	Complete detection of FGFR3 Mutation targets (12)

Det: 11	Incomplete detection of FGFR3 Mutation targets (0-11)

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 must not be detected to achieve the „valid“ status. For PC wells all mutation targets and ICs must be detected to be valid.

C. Result interpretation of the sample wells

The background color of each well on the plate map indicates the well validity. The MODAPLEX Reporter software automatically performs assay-specific evaluation of the wells and displays the wells/sample as either valid



Results	
Target	**Status**
▼ FGFR3 Mutations	
A391E	valid
G370C	valid
G380R	valid
K650E	valid
K650M	valid
K650N	valid
K650Q	valid
K650T	valid
R248C	valid
S249C	valid
S371C	valid
Y373C	valid
▼ Size Standards and Controls	
SST1	valid
SST2	valid
SST3	valid
ACTB_IC	valid
CALM2_IC	valid
FGFR3_IC	valid
AC	valid

Figure 6 : Single well view – PC and NTC.

or invalid. If a sample well is invalid, the user should refer to the BIOTYPE GmbH troubleshooting guide. Table 11, Table 12 and

Table 13 describe the color coding in detail.

If the sample well is invalid because no FGFR3 IC was detected, note that no Ct value is calculated and displayed for any other mutation target, as the target evaluation is performed using delta Ct FGFR3 IC/target. The delta Ct cutoffs are implemented in the MODAPLEX Reporter software.

Table 11: MODAPLEX Reporter: The QC information for the sample wells.

Background color of sample well	Description	Criteria
	Valid sample well	▪ All size standard peaks (SST-A, SST-B, SST-C, SST-D) are detected ▪ Internal controls detected
	Warning Sign shown for highly unlikely detection of more than one mutation	▪ > 1 FGFR3 Mutation target detected within assay specifications ▪ Please refer to the troubleshooting section
	Invalid sample well	▪ One or more size standard peaks (SST-A, SST-B, SST-C, SST-D) are missing ▪ 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 12: MODAPLEX Reporter: Detection of the internal controls in sample wells

Color code for sample wells	Description	Criteria
	Complete detection of internal control	All internal controls detected

IC ✕	Incomplete detection of internal controls	Not all internal controls detected Or no internal control detected

Table 13: MODAPLEX Reporter: Detection of targets in sample wells

Color and number code for FGFR3 mutation targets (examples) in sample wells	Description	Criteria
Det: 0 ✓ Det: 1 ✓	Displays the number of detected FGFR3 Mutation targets	Detection within assay specifications
Det: 2 !	Displays the number of detected FGFR3 Mutation targets	Detection of more than one mutation is very unlikely

For more information about the sample well, click on the well. The detail view will appear, on the right side of the plate map and shows information about notes, list of targets and electropherograms.

Well specific notes are displayed in the first section in the details view. The main section shows a list of targets, controls, size standards and the detected Ct values and corresponding comments. In the bottom section the electropherogram of the sample is shown.

Notes are listed in the troubleshooting chapter. Valid sample wells might contain a comment in the Notes section, if increased attention is required.

NOTE

The following “Comments” will be displayed when a mutation target is detected outside of the verified range which occurs in samples with unusually high or low target abundance. Evaluate results with caution.

- Out of verified range

A detection of more than one mutation is a highly unlikely event, however the presence of more than one mutation in a single tissue sample can occur due to the presence of different tumor cell populations within the same sample. This tumor heterogeneity is known so far for the driver mutations R248C and S249C in bladder cancer. Nevertheless, it is recommended to verify the results by e.g. NGS.

Special attention is required if the DNA target was detected. A note will be displayed including the code [F:13]. All primer designs in this assay are RNA-specific by spanning at least one intron, therefore the expected amplicon sizes of the control targets cannot be detected on genomic DNA. In the case of FGFR3 the intron is relatively small, and a larger amplicon is detectable at 287 bp in case of gDNA contamination. The note will be displayed in the MODAPLEX Reporter software if a strong FGFR3 signal specific for genomic DNA is detected as the assay was not verified using DNA in the background material. There is a minimal risk of false positive results in samples with a high genomic DNA concentration.

Create a FGFR3 Mutation report

This protocol shall be used to generate a report after the FGFR3 Mutation data has been analyzed and classified as valid. The report contains the following information:

- The result of the sample
- Sample information
- MODAPLEX FGFR3 Mutation 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 the 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. The number of detected mutations is reported as well. The following pages display detailed information of each sample including Ct values of detected mutations and potential notes.

JSON File

Run results can also be exported as JSON format for later import into third party tools, such as a LIMS system. If you need assistance with the integration of this data into your workflow, please contact our customer support (support@biotype.de).

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 Specificity	A Basic Local Alignment Search Tool (BLAST) analysis has been performed. The primers of the MODAPLEX FGFR3 Mutation Kit only amplify human FGFR3 sequences without cross-reactions to non-FGFR3 sequences. Furthermore, the assay was tested successfully on more than 200 pre-characterized urothelial bladder cancer samples for unspecific amplifications.
Sample Material	The MODAPLEX FGFR3 Mutation Kit has been verified using artificial RNA material spiked into the formalin-fixed paraffin-embedded (FFPE) RNA background for each target to be detected. In addition, RNA samples extracted from FFPE urothelial bladder cancer tissue have been tested for use with the MODAPLEX FGFR3 Mutation Kit.
Input Amount	20 ng (4 ng/ µL) Tested with up to 100 ng RNA per reaction.
LOD	The assay sensitivity (limit of detection) was defined as the lowest amount of in-vitro-transcripted RNA template (artificial template) in a wild type FFPE RNA background that was detected in at least 95 % of the reactions tested. The table below shows the verified LOD levels for each of the targets.

Assay Performance	Result/Description	
	AA Change	LOD (copies RNA/µl)
	R248C	120
	S249C	309,6
	G370C	192,8
	S371C	120
	Y373C	309,6
	G380R	120
	A391E	120
	K650M	120
	K650Q	309,6
	K650T	120
	K650E	120
	K650N	120

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).

Failure	Comments and suggestions
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. The NTC well was incorrectly assigned on the plate map (wrong well type). Correct the well type in the plate set-up in the MODAPLEX Design and Analysis Software and re-analyze the run. After this, import again into the MODAPLEX Reporter.
Invalid positive control (PC)	1. Incomplete detection of targets, size standards 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 assigned on the plate map (wrong well type). Correct the well type in the plate set-up in the MODAPLEX Design and Analysis Software and re-analyze the run. After this, import again into the MODAPLEX Reporter. 4. In case the PC is only positive for these targets: FGFR3_IC, CALM2_IC and ACTB_IC, the FGFR Gene Fusion Primer Mix was used in the PCR master mix. Repeat the whole plate with the FGFR3 Mutation Primer Mix.
The storage conditions for one or more kit components do not comply with the instructions given in	1. Check the storage conditions and the expiration date (see the kit label). Please use a new kit if the reagents were stored improperly.

Failure	Comments and suggestions
'Reagent Storage and Handling'	
Error 01-02 (MODAPLEX Reporter)	Issue during data acquisition – please repeat the corresponding sample or contact the customer support.
Invalid amplifying Size Standard	Issue during data acquisition or issues during PCR master mix reaction setup. Please check that 0.5 µL MODAPLEX Size Standard 2 is added per reaction. If individual SST peaks are not detected, contact the customer support and repeat the run.
Detection of more than 1 mutation.	A detection of more than one mutation is a highly unlikely event, however the presence of more than one mutation in a single tissue sample can occur due to the presence of different tumor cell populations within the same sample. Detection of more than one mutation in one sample should be verified using independent methods.
F:01 Note: High FGFR3 target abundance.	The FGFR signal is outside of the verified range (Ct value < verified range). There is a very low risk of false positive signals.
F:02 High RNA fragmentation. See troubleshooting section in handbook.	The ACTB signal is outside of the verified range (Ct value > verified range). This indicates a potentially high fragmentation of the RNA. This can be due to incorrect handling. Longer amplicons might not be detected. In case the RNA sample is >3 months old, consider a new isolation from fresh FFPE sections to obtain potentially improved RNA quality samples.
F:03 Reduce RNA input. See troubleshooting section in handbook.	One or more internal controls are detected outside of the verified range (Ct value < verified range). This can be due to high RNA amount. Determine the sample concentration (20ng input) and use at least a 1:10 diluted sample.
F:04 Inconclusive control result. See troubleshooting section in handbook.	CALM2 detected outside of the verified range (Ct value < verified range). This indicates a high input amount. Additionally, both FGFR3 and ACTB are invalid. In case the RNA sample is >3 months old, consider a new isolation from fresh FFPE sections to obtain potentially improved RNA quality samples.
F:05 Inconclusive control result. See troubleshooting section in handbook.	The Ct values of the internal controls show an unexpected expression pattern. Please contact customer support.

Failure	Comments and suggestions
F:06 Insufficient RNA input. See troubleshooting section in handbook.	One or more internal controls are not detected or detected outside of the verified range (Ct value > verified range). This indicates low RNA input. Retest with undiluted sample.
F:07 FGFR3 signal too low. Increase tumor content. See troubleshooting section in handbook.	FGFR3 is not detected or detected outside of the verified range (Ct value > verified range). Low FGFR expression can potentially be due to insufficient tumor content. Check tumor content of your sample and consider RNA isolation from tumor material only.
F:08 FGFR3 signal too low. Increase RNA input. See troubleshooting section in handbook.	FGFR3 is not detected and ACTB is detected outside of the verified range (Ct value > verified range). Potentially low tumor content and additionally RNA quality might be compromised. Repeat RNA isolation from a section with high tumor content.
F:09 FGFR3 signal too high. See troubleshooting section in handbook.	FGFR3 and CALM2 are detected outside of the verified range (Ct value < verified range) indicating high gene expression. Determine the sample concentration (20ng input) and use at least a 1:10 diluted sample.
F:10 High RNA fragmentation and input. See troubleshooting section in handbook.	ACTB is not detected and CALM2 is detected outside of the measuring range (Ct value < measuring range) indicating high fragmentation. Repeat RNA isolation from a fresh prepared section.
F:11 Inconclusive ACTB result. See troubleshooting section in handbook.	ACTB is detected outside of the measuring range (Ct value < measuring range) indicating not verified sample material. Repeat RNA isolation from FFPE sample [Chapter: Sample preparation].
F:12 High RNA fragmentation with high FGFR3 abundance. See troubleshooting section in handbook.	ACTB is not detected and FGFR3 is detected outside of the measuring range (Ct value < measuring range) indicating high fragmentation. Repeat RNA isolation from a fresh prepared section.
F:13 Note: DNA detected.	DNA was detected. The assay is specific for RNA and was verified without DNA background. Consider sample digestion with DNase (see also Data Analysis C).

Limitations of Use

- For optimal results, strict compliance with the MODAPLEX FGFR3 Mutation 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 RNA in the sample are assessed and adjusted prior to performing a sample analysis using the MODAPLEX FGFR3 Mutation Kit.
- The kit has been verified using the kits described in chapter Reagents, kits and consumable for RNA extraction and purification.
- Verified for use with an optimum input of 20 ng RNA 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.

Technical Assistance

For technical advice, please contact our customer support team:

E-mail: support@biotype.de

Phone: +49 (0)351 8838 400

References

[1] Du, S. *et al.* Current progress in cancer treatment by targeting FGFR signaling. *Cancer Biol Med* **20,** 490–499; 10.20892/j.issn.2095-3941.2023.0137 (2023).

Ordering information

Direct your orders via e-mail to sales@biotype.de.

Product	Packaging size	Order number
MODAPLEX FGFR3 Mutation Kit	50 reactions	85-15601-0050
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

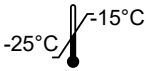
Manufacturer

Batch code

Contains sufficient reagents for <N> tests

Consult electronic instructions for use (eIFU)

Use-by date



Temperature limit

Catalogue number

Keep away from sunlight

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

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