IntelliPlex™ KRAS Mutation Plus Kit User Manual

REF 82022 24 Reactions

CE IVD For In-Vitro Diagnostic Use

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IMPORTANT:
Read the instructions carefully prior to use

1. INTENDED USE

The IntelliPlex KRAS Mutation Plus Kit, based on πCode™ technology and PlexBio's instrument platform, is an in-vitro molecular assay intended for qualitative identification of 25 single nucleotide changes on exons 2, 3 and 4 of the KRAS gene using DNA samples derived from formalin-fixed paraffin-embedded (FFPE) of colorectal cancer (CRC) tumor tissues. Results are intended to assist clinicians in identifying CRC patients who may benefit from Cetuximab or Panitumumab treatments, which are effective in patients with no KRAS mutation detected.

2. INTRODUCTION

A number of cancers have been associated with elevated activity of epidermal growth factor receptor (EGFR). EGFR and its signaling pathway is thus the targets in treatments for cancers such as metastatic colorectal cancer (mCRC) and non-small cell lung cancer (NSCLC). KRAS is a GTPase, tethered to cell membranes and functions in the downstream of the EGFR signaling network. Mutations to KRAS are often activating, which upregulating the EGFR-mediated signaling pathway and leading to cellular proliferation to the oncogenic process even in the absence of the EGF.

Cetuximab and Panitumumab are monoclonal antibodies targeting the EGFR and are approved for use in patients with mCRC. However, CRC patients who harbor KRAS mutations are unlikely to benefit from therapies with these agents. It is therefore critical to assess the mutation status of the KRAS gene for prediction of the efficacies of these treatments. Detection of 25 single nucleotide mutations of the KRAS gene in a single reaction from specimens with large amount of wild-type genomic DNA is feasible based on the SelectAmp and πCode technology. The IntelliPlex KRAS Mutation Plus Kit identifies 25 nucleotide changes on exons 2, 3 and 4 of the KRAS gene, as listed in Table 1.

Table 1: Mutations of the KRAS gene

Exon	Codon	Amino Acid Change	Nucleotide Change
2	12	G12A	GGT>GCT
		G12D	GGT>GAT
		G12V	GGT>GTT
		G12C	GGT>TGT
		G12R	GGT>CGT
		G12S	GGT>AGT
	13	G13A	GGC>GCC
		G13D	GGC>GAC
		G13V	GGC>GTC
		G13C	GGC>TGC
		G13R	GGC>CGC
		G13S	GGC>AGC
3	59	A59T	GCA>ACA
		A59E	GCA>GAA
		A59G	GCA>GGA
	61	Q61H	CAA>CAC
		Q61H	CAA>CAT
		Q61K	CAA>AAA
		Q61P	CAA>CCA
		Q61E	CAA>GAA
4	117	K117N	AAA>AAT
		K117N	AAA>AAC
	146	A146T	GCA>ACA
		A146P	GCA>CCA
		A146V	GCA>GTA

3. TECHNOLOGICAL PRINCIPLES

The IntelliPlex KRAS Mutation Plus Kit utilizes two technologies- SelectAmp and πCode - for detection of 25 KRAS gene mutations in one well reaction.

SelectAmp Technology

Mutation-specific multiplex PCR amplification is achieved by SelectAmp technology, which uses the Locked Nucleic Acid (LNA) to block the amplification of the wild-type sequence. Thus, a specific mutant sequence can be selectively amplified and dramatically increases the sensitivity and the specificity.

πCode MicroDisc

πCode MicroDisc is manufactured to generate up to 16,000 distinct circular image patterns for multiplexing applications. Each πCode has a distinct circular image pattern, which corresponds to a specific capture agent conjugated to the surface of the disc. All capture agent tagged πCode are pooled, enabling capturing and detection of specific analytes in one well reaction.

Detection Principle

The test is based on five processes listed as follows:

I. DNA extraction from FFPE specimens
II. Mutation-specific multiplex PCR amplification
III. Hybridization of PCR amplicons with mutation-specific probes tagged πCode in one well reaction
IV. Incubation with SA-PE for fluorescent labelling
V. Image pattern decoding and fluorescent signal detection by the PlexBio™ 100 Fluorescent Analyzer

4. WARNINGS AND PRECAUTIONS

- For in-vitro diagnostic use.
- This assay kit should be used by qualified laboratory personnel only.
- Do not use a kit or reagent past its expiration date.
- Note that tumor samples are non-homogeneous and may also contain non-tumor sections from a same sample to cause false-negative results.
- Component reagents have been diluted optimally. Further dilution of the component reagents is not recommended.
- Specimens should be handled as infectious material. Please follow universal precaution for safe use.
- Store assay kits and reagents according to the product label and instructions.
- Do not mix reagents from different lots.
- Dispose of unused reagents, specimens and waste according to applicable central/federal, state, and local regulations.
- Wear powderless gloves and do not touch and make any markings on the bottom of the plate at any time, as fingerprints and markings would interfere with decoding and signal acquisition.
- General laboratory precautions should be taken:
  - Do not pipette by mouth.
  - Wear protective clothing (e.g., disposable powderless gloves and laboratory coats) and eye protection.
  - Do not eat, drink or smoke in the laboratory.
  - Wash hands thoroughly after handling samples and reagents.
- The workspace including racks and pipettes should be thoroughly cleaned and wiped with 0.5% sodium hypochlorite solution followed by wiping with a 70% ethanol solution. A 1:10 dilution of household bleach will produce a 0.5% sodium hypochlorite solution.
- Material Safety Data Sheets (MSDS) are available upon request from PlexBio Customer Service.

5. KIT COMPONENTS

The IntelliPlex KRAS Mutation Plus Kit contains sufficient reagents for up to 24 tests. The kit components supplied are listed as follows.

1. **KRAS Plus KIT Reaction Mix**
   Ref. No.: 20188
   Quantity & Volume: 1 vial, 264 µL/vial
   Description: For PCR amplification
   Contents: 36.4% MyFi 5X Reaction Buffer
   Magnesium chloride
   dNTPs and Enhancer
   3.6% MyFi DNA polymerase (Microbial)

2. **KRAS Plus KIT Primer Mix**
   Ref. No.: 20187
   Quantity & Volume: 1 vial, 120 µL/vial
   Description: For PCR amplification
   Contents: <0.01% Forward Primer
   <0.01% Reverse Primer (biotin labeled)
   <0.1% Locked Nucleic Acid

3. **KRAS Plus KIT πCode MicroDisc**
   Ref. No.: 20191
   Quantity & Volume: 1 vial, 480 µL/vial
   Description: For PCR amplicon capture
   Contents: Glycerol
   Phosphate buffered saline
   0.1% Albumin, from bovine (Biological)
   <0.1% EDTA, <0.1% Sodium azide

4. **KRAS Plus KIT POS Control**
   Ref. No.: 20189
   Quantity & Volume: 1 vial, 20 µL/vial
   Description: Assay positive control
   Contents: KRAS exon 2 plasmid DNA (Microbial)
   Tris-EDTA Buffer

5. **KRAS Plus KIT NEG Control**
   Ref. No.: 20190
   Quantity & Volume: 1 vial, 20 µL/vial
   Description: Assay negative control
   Contents: ddH_2O

6. **SA-PE Solution**
   Ref. No.: 20007
   Quantity & Volume: 1 bottle, 7 mL/bottle
   Description: Streptavidin-phycoerythrin for fluorescent signal acquisition
   Contents: Phosphate buffered saline
   0.5% Streptavidin-phycoerythrin
   1% Albumin, from bovine
   <0.1% Sodium azide

7. **KRAS Plus KIT Hy Buffer**
   Ref. No.: 20192
   Quantity & Volume: 1 bottle, 2.4 mL/bottle
   Description: For hybridization
   Contents: Saline-Sodium Phosphate-EDTA

8. **KRAS Plus KIT 10X Wash Buffer**
   Ref. No.: 20194
   Quantity & Volume: 1 bottle, 50 mL/bottle
   Description: For πCode washing
   Contents: Phosphate buffered saline
   1% Tween-20
   <0.1% Sodium azide

NOTE: POS Control, NEG Control and Hy Buffer stand for positive control, negative control and hybridization buffer, respectively.

6. MATERIALS AND EQUIPMENT REQUIRED BUT NOT SUPPLIED

- 96-well plate (Greiner Bio-one; Cat. No. 655101)
- Clean tubes for PCR reaction
- Dedicated micropipette
- Filter tips for micropipette
- ddH2O for dilution of 10X Wash Buffer
- FFPE DNA extraction kit (QIAamp DNA FFPE Tissue Kit, Qiagen; Cat. No. 56404)
- Vortex mixer
- Microcentrifuge
- U Tray (PlexBio; Cat. No. 80023)
- V Tray (PlexBio; Cat. No. 80024)
- DigiPlex™ Thermocycler (PlexBio; Cat. No. 80018)
- IntelliPlex 1000 πCode Processor (PlexBio; Cat. No. 80033)
- PlexBio 100 Fluorescent Analyzer (PlexBio; Cat. No. 80000)
- Industrial Computer (PlexBio; Cat. No. 80002)
- DeXipher™ MD (PlexBio; Cat. No. 80051)

7. STORAGE, STABILITY AND TRANSPORTATION

Storage

All kit components of the IntelliPlex KRAS Mutation Plus Kit should be stored at 2°C to 8°C.

Stability

Do not use the IntelliPlex KRAS Mutation Plus Kit when it is expired. All components are stable up to the expiration date on the label if handled and stored under the recommended conditions.

Transportation

The shipping temperature for the IntelliPlex KRAS Mutation Plus Kit is at 2-8°C. If the kit is broken or has components missing, please contact the PlexBio Customer Service.

8. INSTRUMENT AND SOFTWARE

Instrument

Refer to the instrument user manual for complete installation and operation instructions (Thermocycler, IntelliPlex 1000 πCode Processor and PlexBio 100 Fluorescent Analyzer).

Software Installation

NOTE:

- ***For the first time assay operation, please make sure the KIT APP is installed into DeXipher.***
- ***The ENC file contains the information of kit lot no. and expiration date.***

KIT APP Installation

1. Open the KRAS Plus KIT APP from the USB drive provided and run “Installer.exe”.
2. Click on “Install” from the pop up window and finish the APP installation.

Note: The KIT APP only needs to be installed for the first time running until the new version release.

ENC File Installation

1. Download the corresponding ENC File from PlexBio’s website (Homepage/ Download/ ENC Files/ KRAS Plus Kit/ Corresponding Kit Lot no.)
2. Save to the computer and make sure the ENC file matches the lot no. of the assay kit.
3. Click on the button as shown below on the DeXipher homepage.

4. Click on the button as shown below to import kit.

5. Select and import the corresponding ENC file into the software.

9. SPECIMENS

Specimen Collection

The colorectal cancer (CRC) formalin-fixed paraffin embedded (FFPE) tissue have been validated to use with the IntelliPlex KRAS Mutation Plus Kit. It is recommend to use the QIAamp DNA FFPE Tissue Kit (50) (Qiagen; Cat. No. 56404) for DNA extraction.

Specimen Transportation and Storage

FFPE specimens can be transported and stored at 15-30°C for over 12 months.

Storage of Extracted DNA

Extracted DNA can be stored at 2°C to 8°C for immediately use, or at -15°C to -25°C for long-term storage.

10. ASSAY PROCEDURE

Warning:
Read the instructions carefully and follow every step of the assay protocol correctly.

10.1 DNA Extraction

1. Follow the instructions provided by the DNA extraction kit manufacturer. It is recommended to use QIAamp DNA FFPE Tissue Kit for FFPE section specimens with the elution volume of 50 µL.
2. Quantify the DNA using a Nanodrop UV-Vis Spectrophotometer or Qubit Fluorometer according to the manufacturer's protocol.
3. The DNA Stock concentration from the specimens must be ≥ 2.5 ng/µL to perform the IntelliPlex KRAS Mutation Plus Kit. Each amplification per specimen is run by using 4 µL of a 2.5 ng/µL DNA Stock (total of 10 ng DNA).

10.2 Multiplex PCR Amplification

1. Vortex mix each sample before use.
2. Spin down and keep samples on ice.
3. Prepare PCR Reaction Mix as follows for each sample:

Table 2: PCR Reaction Mix Preparation*

Material	Vol. (µL) per reaction
KRAS Plus Reaction Mix	11
KRAS Plus Primer Mix	5
Extracted DNA/PC/NC	4
Total	20

***Note:**

- *The amount of PCR reagent required depends on the number of reactions.*
- *Both POS Control and NEG Control reactions should be included in every run of the assay.*

4. Mix by tapping the tubes and spin down before placing the tubes on the thermocycler. Set up the PCR program conditions as shown in Table 3:

Table 3: PCR Program Conditions#

Temp. (˚C)	Time	Cycles
95	5 min	1
95	20 sec	36
70	20 sec	
60	60 sec	
4	Hold	1

#*Note: Ramp rate: 1°C/sec*

10.3 DNA Hybridization and SA-PE Reaction

1. Transfer the 10X Wash Buffer to 1L Wash Buffer bottle of the IntelliPlex 1000 πCode Processor supplied and add 450 ml ddH2O to prepare 1X Wash Buffer for use.
2. Pipet the desired volume of SA-PE solution into SA-PE solution tank (V-tray). Please note that the dead volume of V-tray is **500 µL** and the minimum usage of SA-PE is **one row**.

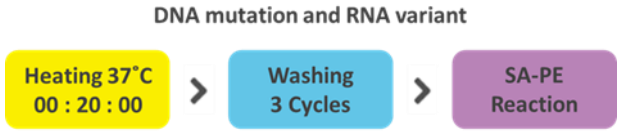
Calculation Example:
For 3 rows reaction, the SA-PE solution needed is **400 µL x 3 rows + 500 µL = 1.7mL (at least)**.
In order to ensure the instrument has sufficient solution to dispense, pipet extra volume into the solution tank is recommended.

***Note:**

- *SA-PE solution should be kept in the dark.*
- ***Do not** reuse the leftover of SAPE solution and the V-tray tank.*

3. Mix by vortexing the KRAS Plus πCode for 10 seconds, and add 20 µL of KRAS Plus πCode to each well directly without further pipetting. Vortex the KRAS Plus πCode every 4 wells to ensure homogeneous suspension of the πCode.

4. Add 100 µL of KRAS Plus Hy Buffer to each well.
5. Spin down the PCR products.
6. Denature the PCR products on the thermocycler by heating up to 95˚C for 5 minutes then cooling down to 4˚C without delay.
7. Spin down the PCR products, and keep PCR products on the ice before adding to wells.
8. Add 10 µL of the denatured PCR products to each well.
9. Refer to IntelliPlex 1000 πCode Processor operation manual and follow the instructions for built-in assay program as described (Homepage/ Molecular Assay/ Select well rows/ DNA&RNA/ Confirm procedure conditions as figure shown below/ Start Running). The plate will be ready for decoding once program finished.

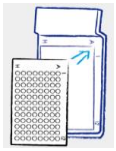


***Note:**

- ***Do not*** *open the door during the instrument operation.*

10.4 Image Decoding and Fluorescent Detection

1. Place the plate on the PlexBio 100 Fluorescent Analyzer as shown below.



2. Click on the button as shown below on the DeXipher homepage.

3. Select the well for detection and import the needed information of each detection samples. Click next step as figure shown as below.

4. Enter the “Assay Name” for the assay and click icon as shown below for image pattern decoding and fluorescent signal acquisition.

5. Export the results for data analysis or calculation or the PDF report.

11. DISCLAIMERS

Negative test result

A negative test result means that the nucleotide changes in exons 2, 3 and 4 of the KRAS gene is not detected by the IntelliPlex KRAS Mutation Plus Kit. It does not preclude the nucleotide changes in exons 2, 3 and 4 of the KRAS gene. Moreover, false negative test results may be due to experimental errors or other causes. Clinical interpretation of the results should be made in combination with all other clinical findings.

Positive test result

A positive test result means that the nucleotide changes in exons 2, 3 and 4 of the KRAS gene are detected by IntelliPlex KRAS Mutation Plus Kit. It does not preclude the possibility that the specimen did not have mutation in exons 2, 3 and 4 of the KRAS gene. False positive test results may be caused by experimental errors or other causes. Clinical interpretation of the results should be made in combination with all other clinical findings.

12. INTERPRETATION OF RESULTS

Table 4: Interpretation of Result

Test Result	Report Result	Interpretation
Mutation Detected	Refer to Table 1	Mutation detected on the specified targeted KRAS region
Mutation Not Detected	None	Mutation not detected on the targeted KRAS regions
Invalid Assay	Invalid	**Possible Cause:** 1. PCR Inhibition 2. SAPE Reaction Failed 3. Low Input or Low Quality of Sample DNA 4. Low πCode Disc Count 5. No πCode Detected 6. Blank πCode Control Failed

13. PERFORMANCE EVALUATION

Limit of Blank (LoB)

The limit of blank (LoB) values were determined by 12 replicates of wild-type KRAS cell line (K562) across 3 days and 4 replicates of 12 wild-type KRAS FFPE specimens across 3 days. Based on the results, the maximum analytical signal intensity values for each mutation were used as the cutoff values for each targeted mutation of the assays.

"No Mutation Detected" results were only observed in the samples presence of KRAS wild type DNA or samples without any DNA templates.

Limit of Detection (LoD)

The limit of detection (LoD) of IntelliPlex KRAS Mutation Plus Kit was determined for six mutations in codon 12, six mutations in codon 13, three mutations in codon 59, 5 mutations in codon 61, 2 mutations in codon 117 and 3 mutations in codon 146. DNA tested by plasmid blended DNA which is the DNA from mutant plasmid blended with wild-type KRAS cell line DNA (K562).

Each mutant DNA containing sample were serially diluted from 5% to 0.05% mutation level (5%, 2.5%, 1%, 0.5%, 0.25%, 0.1%, and 0.05%). The LoD was performed by using 2 lots of IntelliPlex KRAS Mutation Plus Kit to test various mutation level for each mutation site, respectively. Each level of DNA was tested with 21 replicates across 3 days per reagent lot. The LoDs of each lot were determined based on a positive hit rate at 95% in PriProbit analysis as shown in table 5.

Table 5. Limit of Detection (LoD) of each KARS Mutation

Target	Nucleotide Change	LoD (% Mutation)
G12A	GGT>GCT	0.82
G12D	GGT>GAT	0.59
G12V	GGT>GTT	1.02
G12C	GGT>TGT	1.83
G12R	GGT>CGT	0.49
G12S	GGT>AGT	0.73
G13A	GGC>GCC	1.29
G13D	GGC>GAC	1.14
G13V	GGC>GTC	1.58
G13C	GGC>TGC	0.92
G13R	GGC>CGC	1.71
G13S	GGC>AGC	0.5
A59T	GCA>ACA	1.56
A59E	GCA>GAA	1.63
A59G	GCA>GGA	1.4
Q61H	CAA>CAC	1.02
Q61H	CAA>CAT	1.44
Q61K	CAA>AAA	1.1
Q61P	CAA>CCA	0.48
Q61E	CAA>GAA	0.64
K117N	AAA>AAT	0.61
K117N	AAA>AAC	0.57
A146T	GCA>ACA	1.17
A146P	GCA>CCA	0.36
A146V	GCA>GTA	0.64

Method Comparison

The performance of IntelliPlex KRAS Mutation Plus Kit was evaluated in comparison with the Sanger sequencing which as the Gold Standard. A total of 43 FFPE colon cancer specimens were conducted and summarized in the table. Concordance between the KRAS kit and Sanger sequencing was 88% positive agreement (sensitivity) and 96% negative agreement (specificity). The overall agreement was 93%.

Table 6. Comparison of the IntelliPlex KRAS Mutation Plus Kit with the Sanger Sequencing

		Sanger Sequencing	
		Mutation Detected	Mutation Not Detected
IntelliPlex KRAS Mutation Plus Kit	Mutation Detected	15	1
	Mutation Not Detected	2	25
Positive agreement = 88%			
Negative agreement = 96%			
Overall agreement = 93%			

Repeatability and Reproducibility

The repeatability and reproducibility of IntelliPlex KRAS Mutation Plus Kit was evaluated across two reagent lots, 2 operators, 2 sets of instrument and 5 non-consecutive testing days. Four replicate runs were performed per reagent lot per day for a total of 40 valid runs at one site. The repeatability and reproducibility of IntelliPlex KRAS Mutation Plus Kit was demonstrated with low level

mutant (2x LoD) and high level mutant (6x LoD). The accuracy of the all testing level was at least 98% (39/40) across all variance combined (i.e., site/instrument, operator, and day).

Table 7. Accuracy of Each KRAS Mutation

No.	Target	Mutation (%)	Mutation Detected	Mutation Not Detected	Accuracy (%)
1	G12A	1.64	40	0	100%
		4.92	39	1	98%
2	G12D	1.18	40	0	100%
		3.54	39	1	98%
3	G12V	2.04	40	0	100%
		6.12	40	0	100%
4	G12C	3.66	40	0	100%
		10.98	40	0	100%
5	G12R	0.98	40	0	100%
		2.94	40	0	100%
6	G12S	1.46	40	0	100%
		4.38	40	0	100%
7	G13A	2.58	39	1	98%
		7.74	40	0	100%
8	G13D	2.28	40	0	100%
		6.84	40	0	100%
9	G13V	3.16	40	0	100%
		9.48	40	0	100%
10	G13C	1.84	40	0	100%
		5.52	40	0	100%
11	G13R	3.42	40	0	100%
		10.26	39	1	98%
12	G13S	1	40	0	100%
		3	40	0	100%
13	A59T	3.12	40	0	100%
		9.36	40	0	100%
14	A59E	3.26	40	0	100%
		9.78	39	1	98%
15	A59G	2.8	40	0	100%
		8.4	39	1	98%
16	Q61H	2.04	40	0	100%
		6.12	40	0	100%
17	Q61H	2.88	40	0	100%
		8.64	40	0	100%
18	Q61K	2.2	40	0	100%
		6.6	40	0	100%
19	Q61P	0.96	40	0	100%
		2.88	40	0	100%
20	Q61E	1.28	40	0	100%
		3.84	40	0	100%
21	K117N	1.22	40	0	100%
		3.66	40	0	100%
22	K117N	1.14	40	0	100%
		3.42	40	0	100%
23	A146T	2.34	40	0	100%
		7.02	40	0	100%
24	A146P	0.72	40	0	100%
		2.16	40	0	100%
25	A146V	1.28	40	0	100%
		3.84	40	0	100%
26	WT FFPE	-	3	77	96%

Cross-Reactivity

The cross-reactivity was evaluated by testing the KRAS homolog plasmids (NRAS exon2, exon3 and exon4). The tested plasmids were blended with 5% of NRAS codon 12, codon13, codon59, codon61, codon 117 and codon 146 in a background of wild-type cell line DNA. The results demonstrated that there was no cross reactivity with any of the tested samples.

Cross-Contamination

The test is designed to access the cross-contamination during the washing steps which may lead to the false positive results. The tested wild-type FFPE samples and KRAS G12D mutation FFPE samples were placed in rotated order between wells in the 96-well plate. The results demonstrated that there was no cross-contamination during the washing steps.

Interference

The test is designed to evaluate the impact of potentially carrying over substances from QIAamp DNA FFPE Tissue Kit. The KRAS G12C mutation FFPE samples and each potential interference substances (Listed as table 8) were tested in three replicates. The result indicated the interference substances will not interfere the performance of the Intelliplex KRAS Mutation Plus Kit.

Table 8. The tested interfering substances

Interfering Substance	Assumed Interference Residue Volume (ul / 20ul DNA)
Xylene	$4*10^{-5}$
Ethanol	$2.7*10^{-4}$
Buffer ATL	$1.08*10^{-4}$
Proteinase K	$2.64*10^{-6}$
Buffer AL	$2.66*10^{-4}$
Wash Buffer AW1	0.1
Wash Buffer AW2	1

14. SYMBOLS

Symbol	Explanation	Symbol	Explanation
IVD	In-vitro diagnostic use	REF	Catalog number
LOT	Batch number		Consult instructions for use
	Manufacturer		Use by Date
	Temperature limitation		Caution
	Contains sufficient for <n> tests		Date of Manufacture
CE	European Union Conformity	EC REP	European Authorized Representative

15. REFERENCES

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