IntelliPlex™ HPV Genotyping Kit User Manual

REF 82018 96 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 HPV Genotyping Kit, based on the πCode™ technology and PlexBio's instrument platform, is a molecular assay intended for qualitative identification of HPV infected cervical specimens including genotypes 16, 18 and 12 high-risk types (31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66 and 68) simultaneously. Together with the physician's assessment of cytology history, other risk factors, and professional guidelines, this result may be used to determine the need for referral to colposcopy.

2. INTRODUCTION

Human papillomavirus (HPV) infection found in the genital area of men and women is a common sexually transmitted disease. Certain types of HPV, known as high-risk types, may contribute to cervical cancer, its precursor lesion, high-grade cervical intraepithelial neoplasia (CIN 2/3) in women. Patients with persistent infection with one of the genotypes considered high-risk for cervical disease have higher risk for developing severe dysplasia or cervical carcinoma. However, the presence of HPV nucleic acid does not necessary mean that cervical dysplasia or cervical cancer is present. The IntelliPliex HPV Genotyping Kit based on the optimal probe design and πCode technology, will detect HPV DNA Type 16, 18 and other 12 high risk genotypes per reaction simultaneously in cervical specimens The IntelliPlex HPV Genotyping Kit identifies 14 HPV high-risk subtypes, as listed in Table 1.

Table 1: Genotypes of Detected HPV

Risk Level	Subtypes
High-risk	**16, 18, and other 12 high-risk types** (31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, 68)

3. TECHNOLOGICAL PRINCIPLES

πCode MicroDisc

πCode MicroDisc is designed 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 reaction.

Detection Principle

The test is based on five processes listed as follows:

I. DNA extraction from cervical samples
II. Genotype-specific multiplex PCR amplification
III. Hybridization of PCR amplicons with genotype-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.
- 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. PRODUCT USE LIMITATIONS

The test has only been validated for use with specimens collected in Hologic® ThinPrep® Pap Test PreservCyt® Solution or BD SurePath™ liquid-based Pap test (BD).

6. QUALITY CONTROL

The IntelliPlex HPV Genotyping Kit contains a series of internal control πCode MicroDiscs that monitor the specimen preparation, PCR amplification, SA-PE incubation procedure and background noise. These controls must always meet specification and should have approximately the same intensity in each test well in the same test run. Otherwise, the test is invalid. The external controls (positive control and negative control) monitor the whole testing procedure to prevent false positive or false negative results. If the external positive or negative control did not meet the specified value, the test is considered invalid.

7. KIT COMPONENTS

The IntelliPlex HPV Genotyping Kit contains sufficient reagents for up to 96 tests. The kit components supplied are listed as follows.

1. **HPV KIT Reaction Mix**
   Ref. No.: 20123-A
   Quantity & Volume: 1 vial, 576 uL/vial
   Description: For PCR amplification
   Contents: 1X GOLD Buffer
   <2 mM Magnesium chloride
   <0.5 mM dUTP Mix
   <0.3 U Super-Therm GOLD 250U

2. **HPV KIT Primer Mix**
   Ref. No.: 20123-B
   Quantity & Volume: 1 vial, 384 uL/vial
   Description: For PCR amplification
   Contents: 0.005-0.05 µM PCR primer
   Internal Control Plasmid DNA
   <0.001U UDG

3. **HPV KIT πCode MicroDisc**
   Ref. No.: 20402
   Quantity & Volume: 1 vial, 1.92 mL/vial
   Description: Control πCode and πCode conjugated with DNA probes for detection
   Contents: Glycerol
   Phosphate buffered saline
   0.1% Albumin, from bovine (Biological)
   <0.1% EDTA; <0.1% Sodium azide

4. **HPV KIT POS Control**
   Ref. No.: 20125
   Quantity & Volume: 1 vial, 80 uL/vial
   Description: Assay positive control
   Contents: HPV plasmid DNA
   Tris-EDTA Buffer

5. **HPV KIT NEG Control**
   Ref. No.: 20126
   Quantity & Volume: 1 vial, 80 uL/vial
   Description: Assay negative control
   Contents: AE Buffer

6. **SA-PE Solution**
   Ref. No.: 20320
   Quantity & Volume: 1 bottle, 10 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. **HPV KIT Hy Buffer**
   Ref. No.: 20124
   Quantity & Volume: 1 bottle, 9.6 mL/bottle
   Description: Buffered solution with preservative for hybridization
   Contents: Saline-Sodium Phosphate-EDTA

8. **HPV KIT 10X Wash Buffer**
   Ref. No.: 20118
   Quantity & Volume: 2 bottles, 50 mL/bottle
   Description: Concentrated buffered solution with preservative 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.

8. 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
- Pap smear collection kit (Hologic Ref. 70097-005)
- 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)

* Pipettes should be accurate within 3% of stated volume. Aerosol barrier or positive displacement DNA- and DNase-free tips must be used where specified to prevent sample and amplicon cross-contamination.

9. STORAGE, STABILITY AND TRANSPORTATION

Storage

All kit components of the IntelliPlex HPV Genotyping Kit should be stored at 2°C to 8°C. Once opened, the reagent components are stable for one year or until the expiration date, whichever comes first.

Stability

Do not use the IntelliPlex HPV Genotyping 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 HPV Genotyping Kit is at 2-8°C. If the kit is broken or has components missing, please contact the PlexBio Customer Service.

10. 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 HPV 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/ HPV 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.

11. SPECIMENS

Specimen Collection

Cervical specimens should be collected with the Pap smear sample collection kit. DNA sample extracted from cervical specimens by using the QIAamp DNA Blood Mini kit (Qiagen, Cat. No. 51104 for 50 Rxn or Cat. No. 51106 for 250 Rxn) is recommended for use with the IntelliPlex HPV Genotyping Kit.

Specimen Transportation and Storage

The shipping and storage conditions as specified in the Pap smear sample collection kit should be strictly followed.

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.

12. ASSAY PROCEDURE

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

12.1 DNA Extraction

Follow the instructions provided by the DNA extraction kit manufacturer. It is recommended to use the QIAamp DNA Blood Mini kit (Qiagen, Cat. No. 51104 for 50 Rxn or Cat. No. 51106 for 250 Rxn) to extract DNA from cervical samples.

12.2 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
HPV KIT Reaction Mix	6
HPV KIT Primer Mix	4
Extracted DNA/PC/NC	10
Total	20

***Note:**

- *The amount of PCR reaction mix and primer mix required depends on the number of reactions.*
- *Both POS Control and NEG Control reactions should be included in every run of the assay.*
- *Vortex POS and NEG for 5-10 seconds before adding to PCR tube, then pipet to mix.*

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
37	10 min	1
95	10 min	1
95	8 sec	5
55	5 sec	
95	20 sec	35
47	30 sec	
72	30 sec	
72	5 min	1
4	∞	1

**Note: Ramp rate: 1°C/sec*

12.3 DNA Hybridization and SA-PE Reaction

1. Transfer 50 mL 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.*

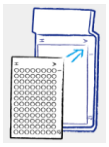
3. Mix by vortexing the HPV πCode for 10 seconds, and dispense 20 µL of HPV πCode to each well without further pipetting (96-well plate). Vortex the HPV πCode every 4 wells to ensure homogeneous suspension of the HPV πCode.
4. Dispense 100 µL of HPV Hy Buffer to each well.
5. Spin down the PCR products.
6. Denature the PCR products on the thermocycler by heating up to 95˚C for 5 minutes then cooling down to 4˚C or place on ice 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/ HPV/ 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.*

12.4 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.

13. DISCLAIMERS

Negative test result

A negative test result means that no HPV was detected by IntelliPlex HPV Genotyping kit. It does not preclude an infection with HPV types 16, 18, and other 12 high-risk genotypes (31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, 68). Moreover, false negative test results may be due to experimental errors or other causes.

Positive test result

A positive test result means that HPV types 16, 18, or other 12 high-risk genotypes (31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, 68) was detected by IntelliPlex HPV Genotyping kit. It does not preclude the possibility that the specimen did in fact not contain HPV DNA. False positive test results may be caused by experimental errors or other causes.

14. INTERPRETATION OF RESULTS

Table 4: Result Interpretation

Test Result	Report Result	Interpretation
HPV Detected	HPV 16, HPV 18, Others	HPV is detected with HPV type 16 or type 18 or any one of, or combination of, the following high risk types (31, 33. 35, 39, 45, 51, 52, 56, 58, 59, 66, 68)
HPV Not Detected	None	HPV are undetectable
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

15. TROUBLESHOOTING

Table 5: Troubleshooting Guide

Problem	Possible Cause	Recommendations
Positive or Negative Control Fail	Contamination or operation mistake during assay procedure.	Start over from the PCR amplification
Reference Gene Control Fail	1. The low quality or inadequate amount of extracted DNA. 2. Operation mistake during DNA extraction procedure	Start over from the DNA extraction. If reference gene control still remains failed, collect the sample again.

Internal Control Fail	1. Operation mistake during the assay or DNA extraction procedure 2. HPV PCR Reagent inactivation	1. If only one of the samples fails, please run the DNA extraction again. 2. If all samples fail, please make sure the correct storage condition of PCR Reagent.
Blank Fail	The detection well is not clean	Run the Wash Program again
SA-PE Monitor Control Fail	Operation mistake during the assay procedure or SA-PE solution inactivation	1. Make sure all the assay procedures are followed correctly. 2. Make sure the correct storage condition of SA-PE.
No report or Low πCode Disc Count	1. πCode discs were lost during washes 2. Overlapping of πCode	1. Make sure the recommended procedures for all washes are followed. 2. Run the "Disperse" program and decoding again

16. PERFORMANCE

Limit of Blank (LoB)

The limit of blank (LoB) values were determined by 15 negative cervical specimens across 3 days using two reagent lots for a total of 60 replicates valid runs. Based on the results, the maximum analytical signal intensity values for each genotypes were used as the LoB cutoff values for each targeted genotypes of the assay.

Limit of Detection (LoD)

The limit of detection of IntelliPlex HPV Genotyping Kit was determined for 14 high risk HPV genotypes. Each type of DNA was serial diluted ranging from 1000 to 20 copies per reaction or 500 to 10 copies per reaction, respectively. 21 replicates of each copy level were tested using two reagent lots across 3 days for a total of 42 replicates. The limit of detection of each genotype was shown in the table below.

Table 6: Summary of Limit of Detection Tested

Target	Limit of Detection* (95% CI)
HPV 16	10
HPV 18	10
HPV 31	73
HPV 33	113
HPV 35	62
HPV 39	46
HPV 45	26
HPV 51	22
HPV 52	105
HPV 56	257
HPV 58	30
HPV 59	19
HPV 66	41
HPV 68	121

*Copies per reaction

Analytical Specificity

A panel of microorganism that includes those commonly found in the female urogenital tract were tested to evaluate the analytical specificity. The tested inactivated bacteria, viruses or nucleic acid of microorganism with high titers were spiked into HPV negative samples (HEK293) in PreservCyt Solution or into PreservCyt Solution with HPV type 18 infected HeLa cells. Results indicated that the IntelliPlex HPV Genotyping Kit was not affected by any of the organisms tested.

Table 7: Microorganism Tested for Analytical Specificity

Microorganism	Test Concentration with No Cross-Reactivity
Neisseria gonorrhoeae	2 x 10^4 copies/µL
Chlamydia trachomatis	2 x 10^4 copies/µL
Bacteroides fragilis genomic DNA	2 ng/µL
Proteus vulgaris genomic DNA	2 ng/µL
Herpes simplex virus I (HSV-I)	1 x 10^4 copies/µL
Herpes simplex virus II (HSV-II)	1 x 10^4 copies/µL
Cytomegalovirus (CMV)	1 x 10^4 copies/µL

Repeatability

The repeatability of IntelliPlex HPV Genotyping Kit was demonstrated with four positive clinical specimens, two negative clinical specimens and four high-risk HPV genotypes (HPV 16, 52, 56 and 58) at different concentration levels (High, Moderate, Low and Constant). Each sample was evaluated across three reagent lots, two operators, three sets of instrument and 12 non-consecutive testing days with a total of 58 replicates. The result of repeatability accuracy in each type was shown in the table below.

Table 8: Repeatability Accuracy of Each Target Tested

Target	Concentration Level (Copies/reaction)	Number of Positive/ Total Tests	Hit Rate (%)
HPV 16	High (500)	58/58	100%
	Moderate (100)	58/58	100%
	Low (30)	58/58	100%
	Constant (200)	58/58	100%
HPV 52	High (5250)	58/58	100%
	Moderate (1050)	58/58	100%
	Low (315)	58/58	100%
	Constant (200)	57/58	98.3%
HPV 56	High (8550)	58/58	100%
	Moderate (1710)	58/58	100%
	Low (513)	58/58	100%
	Constant (200)	57/58	98.3%
HPV 58	High (1500)	58/58	100%
	Moderate (300)	58/58	100%
	Low (90)	53/58	91.4%
	Constant (200)	58/58	100%
P1	Clinical Positive	58/58	100%
P2		58/58	100%
P3		58/58	100%
P4		58/58	100%
N1	Clinical Negative	58/58	100%
N2		58/58	100%

Reproducibility

The reproducibility of IntelliPlex HPV Genotyping Kit was demonstrated with four positive clinical specimens, two negative clinical specimens and four high-risk HPV genotypes (HPV 16, 52, 56 and 58) at different concentration levels (High, Moderate, Low and Constant). Each sample was evaluated in triplicates across three reagent lots, three sites, two operators, three sets of instrument and 5 non-consecutive testing days with a total of 90 valid tests listed as table below.

Table 9: Reproducibility Accuracy of Each Target Tested

Target	Concentration Level (Copies/reaction)	Number of Positive/ Total Tests	Hit Rate (%)
HPV 16	High (500)	90/90	100%
	Moderate (100)	90/90	100%
	Low (30)	90/90	100%
	Constant (200)	90/90	100%
HPV 52	High (5250)	90/90	100%
	Moderate (1050)	90/90	100%
	Low (315)	90/90	100%
	Constant (200)	89/90	98.9%
HPV 56	High (8550)	90/90	100%
	Moderate (1710)	90/90	100%
	Low (513)	90/90	100%
	Constant (200)	89/90	98.9%
HPV 58	High (1500)	90/90	100%
	Moderate (300)	90/90	100%
	Low (90)	85/90	94.4%
	Constant (200)	90/90	100%
P1	Clinical Positive	90/90	100%
P2		90/90	100%
P3		90/90	100%
P4		90/90	100%
N1	Clinical Negative	90/90	100%
N2		90/90	100%

Cross-Contamination

The test is designed to access the cross-contamination during all assay operation steps which may lead to the false positive results. The tested HPV negative samples (HEK293) and HPV positive samples (HPV type 18 infected HeLa cells) were placed in rotated order between wells in the 96-well plate. The results demonstrated that there was no cross-contamination during all assay operation steps.

Interference

The test is designed to access the analytical specificity by testing the impact of potentially interfering substances (List as table below). The substances were spiked at highest concentration into HeLa cells with HPV type 18 positive infected and into HPV negative HEK293 cells in PreservCyt Solution, respectively. Each sample was tested in four replicates at least. Rest potentially interfering substances will not interfere with the performance of the Intelliplex HPV Genotyping Kit.

Table 10: Interfering Substance Tested

Interfering Substance	PreservCyt Solution
Buffer only	13/13 (100%)
Lubricating Gel	4/4 (100%)
Personal Lubricating Jelly	7/7 (100%)
Whole Blood	8/8 (100%)
Statin Vaginal Tablets 100000 Units “Standard” (NYSTATIN)	4/4 (100%)
Fortin Suppositories	4/4 (100%)
Kanezin Vaginal Tablets 100MG “SWISS” (CLOTRIMAZOLE)	4/4 (100%)
Jslady Spray Solution 3MG/ML (POVIDONE-IODINE)	6/6 (100%)
Feminine Cleansing Mist Sensitive Skin	4/4 (100%)
Feminine Cleansing Mist	4/4 (100%)

17. SYMBOLS

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

18. REFERENCES

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