



FULL SPECTRUM HPV AMPLIFICATION AND DETECTION SYSTEM

OPTIMIZED REAGENT SET FOR PCR AMPLIFICATION AND
DETECTION OF 49 HPV GENOTYPES
IN THE FOLLOWING GROUPS:
HIGH-RISK GROUP (16,18,31,33,35,39,45,51,52,56,58,59,66,68)
LOW-RISK GROUP (6,11,42,43,44/55)
GENERAL HPV GROUP WITH 29 ADDITIONAL, NOT YET
CLASSIFIED GENOTYPES (2,3,7,10,13,26,27,28,29,30,34,40,53,54,57,61,67,70,72,73,74,
81,82,83,84,85,89,90,91)
INTERNAL CONTROL DETECTED IN EACH SAMPLE.

INSTRUCTIONS MANUAL

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COMPONENTS (FOR 44 SAMPLES)

FULL SPECTRUM HPV AMPLIFICATION KIT	M20040
FULL SPECTRUM HPV DETECTION PROBE KIT	P20430
GENERAL DETECTION REAGENT KIT	H20012

STORAGE

FULL SPECTRUM HPV AMPLIFICATION KIT	-18 °C OR BELOW
FULL SPECTRUM HPV DETECTION PROBE KIT	-18 °C OR BELOW
GENERAL DETECTION REAGENT KIT	2 °C TO 8 °C

General Kit Description

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System developed by GenoID.

Cervical cancer is the second most common cancer in women worldwide, with an estimated 493,000 new cases and 274,000 deaths in 2002 ^[1]. It has been established that certain types of HPVs are associated with cervical cancer and it is estimated that HPV DNA is present in over 99% of these cancers. These HPV types are considered the cause of invasive cervical cancer ^[2,3]. More than 100 HPV types were identified, and approximately 40 types are considered genital HPVs. These were classified into two groups according to their relative risk of causing cancer: 'Low-Risk' and 'High-Risk' types ^[4]. Low- risk types can cause genital warts or benign low-grade abnormalities in cervical cells, but are not associated with cervical cancer. However, the 'High-Risk' genotypes induce cervical dysplasias and invasive cervical cancer. Thus HPV detection and typing methods have been proposed to enhance screening and detection efficiency. These methods, besides detecting the presence of the virus, allow typing and patient follow-up. When compared to Pap testing (Papanicolau test), HPV testing has greater sensitivity for the detection of cervical intraepithelial neoplasia (CIN) ^[5]. Moreover, the combination of Pap test and HPV testing reduced the incidence of grade 2 or 3 cervical intraepithelial neoplasia or cancer detected by subsequent screening examinations ^[6].

GenoID's Genital Human Papillomavirus PCR Amplification and Detection Kit is designed and optimized ^[7] to amplify the following genital HPV types:

- Low-Risk: 6, 11, 42, 43, 44/55
- High-Risk: 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66 and 68
- and previously not classified: 2, 3, 7, 10, 13, 26, 27, 28, 29, 30, 34, 40, 53, 54, 57, 61, 67, 70, 72, 73, 74, 81, 82, 83, 84, 85, 89, 90, 91 genotypes.

To exclude false negative results an internal control DNA is prepared parallel with the specimen and amplified concurrently in the reaction.

The amplification targets the L1 gene of HPVs and is designed to detect the non-integrated copies of HPV. The balanced amplification of all genotypes is important in order to achieve optimal clinical sensitivity.

The amplicons resulted by the amplification are detected by solid phased hybridization. The detection of General HPV, High-Risk HPV, Low-Risk HPV and the Internal Controls are carried out in four different reaction chambers (wells). The biotinilated PCR products (resulting from amplification with a biotinilated primer) are captured onto the surface of a microplate well coated with streptavidin. The complementary chain is eluted from the immobilized PCR product and hybridization is carried out in the presence of specific fluorescein labeled probes. The bound probes are reacted with anti-fluorescein-HRPO (horse-radish peroxidase) antibody. The HRPO chromogenic substrate (TMB) yields blue product in case of a positive reaction.

Protocol

The Genital Human Papillomavirus amplification and detection procedure consists of three main steps:

1. DNA extraction from samples - sample preparation
2. DNA amplification by PCR
3. Detection of PCR amplicons by solid phase hybridization

Attention!

- Work carefully to avoid contamination of the samples with each other or with the amplified product.
- Wear powder-free examination gloves during PCR set-up.
- Centrifuge briefly the reagents before use.
- Use DNA and DNase-free tips with filters.
- Use dedicated equipment in dedicated areas for
 - mastermix preparation,
 - reaction set-up, and
 - post PCR processing.

1. Sample Preparation

Only specimens collected in PreservCyt Solution may be used with the GenoID FULL SPECTRUM HPV AMPLIFICATION AND DETECTION SYSTEM®. Collect samples according to the manufacturer's instructions. Do not process samples having inadequate quality or insufficient volume. Too frequent sampling could result in false negative tests. Specimens collected in PreservCyt Solution can be transported at 2-30 °C. Specimens collected in PreservCyt Solution may be stored at room temperature for up to 21 days or at 2-8 °C for up to 12 weeks.

Perform DNA isolation using one of the recommended kits: ROCHE AmpliLute Liquid Media Extraction Kit or ROCHE High-Pure PCR Template Preparation Kit (use "Isolation of Nucleic Acids from Mammalian Tissue" protocol). (Not provided by GenoID.)

1. Prepare IC Solution by adding 10 µl of **HPV-IC DNA (R3)** to 20 ml of Cytic PreservCyt Solution (one full vial). Prepare it freshly.
2. Transfer 1250 µl of specimen to Eppendorf tubes and centrifuge at 4000 g, for 10 min., at room temperature using a fixed angle rotor.
3. Discard the supernatant, do not disturb the pellet.
4. Add 250 µl of IC Solution to the pellet. Vortex and proceed with sample preparation using ROCHE AmpliLute Liquid Media Extraction Kit or ROCHE High-Pure PCR Template Preparation Kit.

2. Performing the PCR

The Full Spectrum HPV Amplification Kit is sufficient for the simultaneous examination of **44 samples** and 2 controls (a positive and a negative control, respectively).

The following components of the PCR are included in the Full Spectrum HPV Amplification Kit (M20040):

Vial	Cap Color	Label	Content and usage
R1	Green	Master Mix	980 µl Master Mix
R2	Pink	Control DNA for HPV LR, HR	65 µl HPV positive DNA (genotypes 6, 16)
R3	Red	HPV-IC DNA	100 µl HPV Internal Control DNA

ADDITIONALLY REQUIRED MATERIALS AND INSTRUMENTS (not provided with the kit):

- Thin-walled 0.2ml PCR tubes, or 96 well PCR plates (thermocycler compatible)
- Adjustable pipettes with aerosol barrier or positive displacement, DNA and DNase-free tips with filters
- GeneAmp® PCR System 9700 (Applied Biosystems) or other compatible thermocycler
- Exclusively AmpliTaq Gold polymerase (Applied Biosystems: Cat.No.: 4311806 (250U))

2 A. PCR Setup

1. Add **20 µl AmpliTaq Gold enzyme** (Applied Biosystems) to the **“Mastermix” reagent (R1)**. If you would like to prepare less than 44 reactions, both master Mastermix (**R1**) and enzyme can be scaled down proportionally.
2. Vortex reagents.
3. Aliquot **20-20 µl of reaction mixture** into the PCR tubes prepared in advance.
4. Add **5-5 µl template** DNA to the PCR tubes.
5. Set up two reactions for controls: a positive control (using reagent **R2**) and a negative control “no template control” (add 5µl of PCR grade water instead of sample). See [Recommended PCR Plate Design](#) on p6.
6. Close the tubes and place them into the thermocycler, programmed in advance as described ([Thermocycling parameters](#) see below).

Perform the programmed thermocycling.

If you use a thermocycler other than GeneAmp® PCR System 9700, it is recommended to carry out an experiment with a series of dilutions of the positive control prior to the first experiment.

Recommended PCR Plate Design

0	3	3	3	3	3	0	0	0	0	0	0
0	3	3	3	3	3	0	0	0	0	0	0
1	3	3	3	3	3	0	0	0	0	0	0
2	3	3	3	3	3	0	0	0	0	0	0
3	3	3	3	3	3	0	0	0	0	0	0
3	3	3	3	3	3	0	0	0	0	0	0
3	3	3	3	3	3	0	0	0	0	0	0
3	3	3	3	3	3	0	0	0	0	0	0

0 Empty
 1 PCR negative control
 2 PCR positive control
 3 Samples

This design allows the direct transfer of PCR products to the hybridization plate using an 8-channel pipette.

2 B. Thermocycling Parameters

Temperature (°C)	Time	Number of Cycles
95	10 min	1
95	30 sec	10
45 increment +0,3°C/cycle	30 sec	
72	30 sec	
95	30 sec	35
48	30 sec	
72	30 sec	
72	4 min	1
4	∞	

3. Detection of PCR Amplicons by Solid Phase Hybridization

The following bottles and vials are the components of the hybridization reaction:

Full Spectrum HPV Detection Probe Kit P20430

Vial	Cap Color	Label	Content and usage
H1	Yellow	HPV-High-Risk Probe Mix	40 µl Hybridization probe for HPV-HR
H2	Orange	HPV-Low-Risk Probe Mix	40 µl Hybridization probe for HPV-LR
H3	Pink	HPV-IC Probe	40 µl Hybridization probe for HPV-IC
H4	White	General HPV Probe mix	40 µl Hybridization probe for HPV-HR;-LR and IC
H5	Black	HPV High-Risk, Low-Risk and IC hybridization Positive Control mix	100 µl Hybridization positive control mix for HPV HR LR and IC

General Detection Reagent kit H20012

Vial	Cap Color	Label	Content
H6		Binding buffer	10 ml binding buffer
H7		Elution buffer	15 ml elution buffer
H8		Hybridization buffer	15 ml hybridization buffer
H9		Conjugation buffer	25 ml conjugation buffer
H10	Blue	Detection reagent	12.5 µl HRPO conjugated anti-florescein antibody
H11	Brown	Substrate solution	30 ml ready to use stabilized TMB substrate for HRPO
H12		Washing solution 1	2x50 ml concentrated (10xcc.) washing solution 1
H13		Washing solution 2	60 ml concentrated (10xcc.) washing solution 2
H14		Hybridization plate 24X8 strips	Streptavidin coated plate: 2 "eggcrate" holder frame, 24 (transparent) strip

Additionally required reagents and equipments (should be provided by user)

- DNase free PCR-grade water
- 8-channel pipette (20-200 µl)
- Adjustable pipettes with aerosol barrier or positive displacement (1-10 µl, 20-200 µl, 100-1000 µl)
- 1-10 µl, 20-200 µl and 1000 µl DNA and DNase-free pipette tips with filters
- Reagent reservoirs
- Microplate reader (optional) with detection capability at 360 nm or 655 nm
- Sealing film

Prepare the following solutions before the procedure:

- Add 50 ml washing solution 1 (H12) to 450 ml distilled water and mix thoroughly.
- Add 60ml washing solution 2 (H13) to 540 ml distilled water and mix thoroughly.
- Incubate the hybridization buffer (H8) at 55 °C until use.

The detections of HPV-**HR**, HPV-**LR**, HPV-**Internal Control** and **General HPV** from one sample are carried out in four separate wells. For 44 samples use 6 strips of wells for each probe, which will take up a half plate. Altogether the four hybridization reactions of 44 samples take two whole plates.

1. Dilute each PCR product 10 times (25µl/225µl) in DNase free water and mix well.
2. Wash the hybridization wells once with the diluted **washing solution 1 (H12)**: pipette 200-200 µl **washing solution 1 (H12)** into each well using an 8-channel pipette. Dump out the washing solution and strike the inverted plate sharply on a clean absorbent paper to remove the rest of the washing solution.
3. Dispense 40-40 µl **binding buffer (H6)** into each well using an 8-channel pipette.
4. Add 10 µl of the 10 times diluted PCR product and the controls to the wells in the following order (see **Recommended Hybridization Plate Design** on p9). For each **half plate**:

well 1: Hybridization NTC: 10 µl DNase-free distilled water

well 2: Hybridization PC: 10 µl **hybridization positive control (H5)**

well 3: PCR NTC: 10 µl 10 times diluted PCR negative control (from the amplification reaction)

well 4: PCR PC: 10 µl 10 times diluted PCR positive control (from the amplification reaction)

well 5: 10 µl 10 times diluted PCR products of samples.

Replicate the same sample order on the other three half plates (order of the half plates is the following: LR, HR, general HPV, internal control). Incubate the plates for 10 minutes at room temperature with shaking.

5. Dispense 50-50 µl **elution buffer (H7)** into each well and incubate for 2-3 minutes at room temperature with shaking (do not remove the binding buffer and PCR product mix before this step).

6. Dump out the liquid and strike the inverted plate sharply on a clean absorbent paper. Wash **3 times** with 200-200 µl washing **solution 1 (H12)**.

7. Add 20 µl hybridization probe for HPV-**HR (H1)**, 20 µl hybridization probe for HPV-**LR (H2)**, 20 µl hybridization probe for HPV-**General (H4)** and 20 µl hybridization probe for HPV-**IC (H3)** into **four separated tubes** containing 3ml preheated (55°C) **hybridization buffer (H8)**. Mix well and dispense 50-50 µl hybridization solution into the wells according to sample distribution. (Dispense the hybridization solution containing **LR** probe mix into the first 6 strips, dispense the hybridization solution containing **HR** probe mix into the second 6 strips, dispense the hybridization solution containing **General** probe mix into the third 6 strips and dispense the hybridization solution containing **IC** probe into the fourth 6 strips).

8. Incubate for 20 minutes at **55°C**.

9. Dump out the washing solution and strike the inverted plate sharply on a clean absorbent paper. Wash the wells 6 times with 200 µl **washing solution 2 (H13)**.

10. Add 4 µl **detection reagent (H10)** in 12 ml **conjugation buffer (H9)**. Mix well. Dispense 50-50 µl solution into each well and incubate for 10 minutes at room temperature with shaking.

11. Dump out the washing solution and strike the inverted plate sharply on a clean absorbent paper. Wash **10 times** with 200 µl **washing solution 1 (H12)**.
 12. Dispense 140 µl **substrate solution (H11)** into the wells and incubate for 15 minutes at room temperature with shaking.
 13. Stop the reaction by adding 60 µl 1N HCl solution.
 14. Measure the absorbance of the samples by a microplate reader at 450 nm save the records (**optional**: without the HCl stopping step detected the absorbance at 370 nm or at 655 nm).
- Interpretation by simple visual inspection is also possible.** Wells displaying blue or yellow color are considered as positive reactions.

Recommended Hybridization Plate Design

1	5	5	5	5	5	1	6	6	6	6	6
2	5	5	5	5	5	2	6	6	6	6	6
3	5	5	5	5	5	3	6	6	6	6	6
4	5	5	5	5	5	4	6	6	6	6	6
5	5	5	5	5	5	6	6	6	6	6	6
5	5	5	5	5	5	6	6	6	6	6	6
5	5	5	5	5	5	6	6	6	6	6	6
5	5	5	5	5	5	6	6	6	6	6	6

1	7	7	7	7	7	1	8	8	8	8	8
2	7	7	7	7	7	2	8	8	8	8	8
3	7	7	7	7	7	3	8	8	8	8	8
4	7	7	7	7	7	4	8	8	8	8	8
7	7	7	7	7	7	8	8	8	8	8	8
7	7	7	7	7	7	8	8	8	8	8	8
7	7	7	7	7	7	8	8	8	8	8	8
7	7	7	7	7	7	8	8	8	8	8	8

- 1 Hybridization negative control
- 2 Hybridization positive control (H5)
- 3 PCR negative control
- 4 PCR positive control
- 5 Samples - High-Risk group detection
- 6 Samples - Low-Risk group detection
- 7 Samples - Internal Control
- 8 Samples - General HPV detection

Interpretation of Results

Microplate Reader Protocol

Record the absorbance readings (optical density values of the reactions at 370 nm or 655 nm).

Determine the positive cut-off values for each probe: the positive cut-off value is 130% of the OD value of the PCR negative control, for the corresponding probe. Determine the negative cut-off values: the negative cut-off value is 110% of the OD value of the PCR negative control, for the corresponding probe.

For a valid assay, the ratio of the PCR negative controls and corresponding hybridization negative controls should be below 2 for each ratio. The ratio between values of the hybridization positive controls and PCR positive controls should be greater than at least 2 times the positive cut-off value.

If the assay is valid and the OD value of the sample shows a value greater than the positive cut-off of the given probe, the reaction is considered positive. If a sample shows a value between the positive and negative cut-off values for a given probe, the result is considered uncertain, please repeat the PCR. If the repeated reaction yields a value below the negative cut-off, the sample is negative. If the repeated reaction yields the same value, the reaction could be interpreted as weak positive, and repeated sampling is recommended.

For other details refer to the *Results Table*.

Visual Inspection Protocol

If you intend to interpret the result by simple visual inspection, you should take into consideration its possible lower sensitivity. A skilled investigator, however, could reliably interpret the results.

For a valid assay the hybridization negative controls and the PCR negative controls should be transparent and colorless. The hybridization positive controls and the PCR positive controls should develop intense color. If the assay is valid, even a faint blue color could be considered as positive reaction.

Result Table

Features				Results
HPV- HR	HPV- LR	HPV- General	IC	
-	-	-	-	Repeat the experiment.
-	-	-	+	Negative result.
-	-	+	-	Positive result, strong amplification, sample contains other genotype(s) than HR or LR genotypes.
-	-	+	+	Positive result, medium or weak amplification, sample contains other genotype/s than HR or LR genotypes.
-	+	+	-	Positive result for LR HPV genotypes, strong amplification.
-	+	+	+	Positive result for LR HPV genotypes, medium or weak amplification.
+	-	+	-	Positive result for HR HPV genotypes, strong amplification.
+	-	+	+	Positive result for HR HPV genotypes, medium or weak amplification.
+	+	+	-	Positive result for both HR and LR HPV genotypes, strong amplification.
+	+	+	+	Positive result for both HR and LR genotypes, medium and weak amplification.

Troubleshooting

No signal in the sample reactions.

Examine the control samples; if both the internal control and the positive controls produced satisfactory signals (and they are valid), template DNA purity or concentration could be inadequate.

Solution: Repeat sample preparation and PCR.

No signals can be detected in either of the control reactions.

The kits are quality controlled; if they are stored properly we guarantee satisfactory results prior to expiration.

Solution: Please repeat the experiment; follow the exact instructions of the manufacturers.

Signal is detected in the PCR negative control.

It is a sign of contamination during the set-up of the PCR. In this case results are unreliable. The source of contamination could be the pipettes, pipette tips, PCR tubes and the examiner as well.

Solution: Verify reaction conditions and correct individual steps, if necessary. Use filter pipette tips. Repeat the experiment with cleaned pipettes.

No signal detected in the positive control.

It can be caused by pipetting error, or degradation of control DNA.

Solution: Check your work steps by means of the pipetting scheme. If the positive control is not amplified after repeating the reaction, the DNA is degraded.

No internal control is amplified in a sample reaction.

If a specific LR, HR or general signal is detected, it does not influence the evaluation.

Solution: Repeat the sample preparation and the PCR.

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