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INFINITI® HPV-HR QUAD

Directional Package Insert (DPI)

For *In Vitro* Diagnostic Use

CE

FOR EXPORT ONLY

Manufactured by AutoGenomics, Inc.,1600 Faraday Avenue, Carlsbad, CA USA 92008

Authorized EU Agent: Medical Device Safety Service GmbH (MDSS)
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INTENDED USE

The INFINITI® HPV-HR QUAD is indicated for use to detect the presence of 14 high risk DNA types in women with abnormal Pap smear results (i.e., atypical squamous cells of undetermined significance, ASCUS). Together with the patient's cytology history, other risk factors and relevant clinical information, the information from the INFINITI® HPV-HR QUAD may be used to guide patient management.

The INFINITI® HPV-HR QUAD results may not be used to prevent women from proceeding to colposcopy.

The INFINITI®HPV-HR QUAD is a qualitative assay for use in clinical laboratories upon prescription by the attending physician.

BACKGROUND INFORMATION

Genital HPV infection is caused by human papillomavirus (HPV), a group of viruses that include more than 100 different strains or types. More than 30 of these viruses are sexually transmitted and can infect the genital area of men and women. At least 50% of sexually active men and women acquire genital HPV infection at some point in their lives. By age 50, at least 80% of women will have acquired genital HPV infection. About 6.2 million Americans get a new genital HPV infection each year. [(1)]

Human papillomaviruses are composed of an icosahedral viral particle (virion) containing an 8000 base pair double-stranded circular DNA molecule surrounded by a protein capsid. Following infection of epithelial cells, the viral DNA becomes established throughout the entire thickness of the epithelium, but intact virions are found only in the upper layers of the tissue. Thus, viral DNA can be found either in virions or as episomal or integrated HPV sequences, depending upon the type and grade of lesion.[(9, 10, 11, 12)]

Epidemiological studies demonstrate that persistent infection with certain types of human papillomaviruses (HPVs) are a necessary risk factor for the development of invasive cervical cancer.[(2,8)] Based on such studies, genital HPV types were grouped into high risk, probable high risk and low risk types, reflecting their risk potential to induce invasive cancer. HPV types are classified as high risk types (16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, and 68), probable high risk types (26, 53, 67, 69, 73, and 82) and low risk types (6, 11, 30, 34, 40, 42, 43, 44, 54, 61, 70, 72, 81, 85 and 89).[(2,8,9,10)]

High-risk HPV types are those associated with cervical intraepithelial neoplasia (CIN 2/3) and are thought to be responsible for approximately 70% of all invasive cervical cancers, although the relationship of HPV type to risk of cancer appears to vary geographically.[(2,3)] In addition to cervical cancer, high risk HPV types may lead to cancer of the vulva, vagina or anus. The presence of certain HPV types in the female genital tract is also associated with other diseases, including Bowenoid papulosis, and cervical, vaginal and vulvar intraepithelial neoplasia. Certain low-risk HPV types 6 and 11 may be associated with the presence of genital warts (condyloma), but have been infrequently linked with precancerous or cancerous cervical changes.[(4,5,6,7)] It is not completely understood how HPV infection progresses to cancer.

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TEST PRINCIPLE/ASSAY OVERVIEW

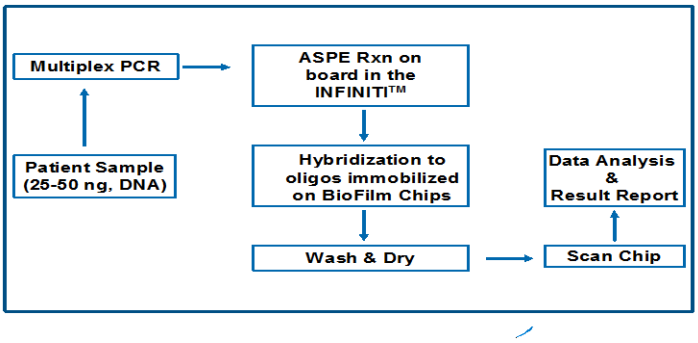
The INFINITI® HPV-HR QUAD utilizes AutoGenomics' proprietary film-based microarray technology combined with process automation, reagent management and software technology for multiplex detection of the presence of HPV genotypes in deoxyribonucleic acid (DNA) obtained from cervical specimens.

The INFINITI® HPV-HR QUAD is based on the following processes:

a) PCR amplification of purified DNA.
b) Labeling of the amplified product (analyte specific primer extension).
c) Hybridization of the fluorescent labeled product to a microarray.
d) Scanning of the microarray.
e) Detection of fluorescence (identification of HPV types).
f) Signal detection and analysis.

Steps (b) through (f) are automated by the CE marked INFINITI ®Analyzer or INFINITI® PLUS Analyzer.

A schematic overview of the assay is shown below.



DEVICE DESCRIPTION

The INFINITI® HPV-HR QUAD is an *in vitro* diagnostic device that consists of reagents and instrumentation which includes polymerase chain reaction (PCR) primers, microarrays, a thermal cycler, an imager, and software designed to detect the presence of fourteen (14) high risk HPV types (and identify HPV Types (16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, and 68) in cervical specimens.

Cervical specimen types may include:

- Specimens collected using a broom type collection device and placed in Cytyc ThinPrep® Pap Test™ PreserveCyt® Solution.

The INFINITI® HPV-HR QUAD is comprised of the BioFilmChip® Microarray, the Intellipac® Reagent Module, and the PCR Amplification Mix. The instrumentation for the INFINITI® HPV-HR QUAD is the AutoGenomics INFINITI® Analyzer or the INFINITI® PLUS Analyzer with the Qmatic® Operating Software.

The **BioFilmChip Microarray** consists of a polyester film coated with proprietary multi-layer components designed for DNA analysis. The layers have been designed to provide a versatile surface to enhance test performance. The INFINITI® HPV-HR QUAD uses a microarray chip (S-Chip) which has capture probes spotted on the surface of the film. Four (4) samples can be run on one microarray. Twelve (12) microarrays are housed in a magazine.

The **Intellipac Reagent Module** which acts as a communication link contains four reservoirs that house the test reagents and has an integrated memory chip. Reagent information such as lot number, expiration date, and volume usage are stored in the memory chip. The Intellipac Reagent Module communicates with the Analyzer and provides the reagent information which appears on the assay report and printout. The Intellipac Reagent Management Module provides test reagent for 96 samples.

The **PCR Amplification Mix** consists of the reagents needed for the PCR amplification step of the assay. Each box of the PCR Amplification Mix provides 4 x 500µl vials of PCR Amplification.

The **INFINITI® Analyzer or INFINITI® PLUS Analyzers** automates the INFINITI® HPV-HR QUAD and integrates all the discrete processes of sample (PCR reaction product) handling, reagent management, hybridization, detection, and results analysis. The assays are processed automatically and read by the built-in confocal microscope. Results are analyzed and presented as positive or negative for each of the HPV types.

The Analyzers are provided with the Operator's Manuals. The Operator's Manual provides detailed description and operating principle of the Analyzer and instruction for use.

The INFINITI® Analyzer and the INFINITI® PLUS Analyzer are CE-marked.

WARNINGS AND PRECAUTIONS

Handling Requirements

- **For *in vitro* diagnostic use. To be used by qualified laboratory personnel.**
- This test is to be used only with cervical specimens collected in Cytyc ThinPrep® Pap Test™ PreserveCyt® Solution.
- To minimize the risk of cross contamination, sample preparation, PCR reaction set up and PCR product analysis should be performed according to approved guidelines such as CLSI (Molecular Diagnostic Methods for Genetic Diseases: Approved Guideline).
- All patient specimens are potentially hazardous and care should be taken when handling materials of human origin. No test method can offer complete assurance that HCV, HIV or other infectious agents are absent.
  Follow the CLSI Guidelines (Molecular Diagnostics Methods for Infectious Diseases; Approved Guidelines; MM3-A).
- Do not pool/mix reagents from different lots.
- Do not use a kit or reagent past its expiration date.
- Store kits and reagents according to the product label.

Laboratory Procedures

- Follow normal precautions for handling laboratory reagents. Do not mix reagents from different containers or from different lots.
- Follow safe laboratory procedures: do not pipette by mouth; wear protective clothing (e.g., disposable gloves laboratory coats) and eye protection; do not eat, drink or smoke in the laboratory work areas; wash hands thoroughly after handling samples and reagents.

Waste Handling

- Dispose of unused reagents, specimens and waste according to applicable country, federal, state and local regulations.
- Safety data Sheets (SDS) are available upon request from AutoGenomics Customer Service.

Sample Preparation

- Refer to the instructions provided with INFINITI® Sample Processing Kit.
- The PCR product cannot be stored prior to loading it onto the microarray. Use immediately**.**

INFINITI® Analyzer or INFINITI® PLUS Analyzer

- **Read the Operator's Manuals before operating the instruments.** Pay particular attention to "Notes".
- Follow the Caution and Safety Warning in the Operator's Manual.
- Refer to the Installation Requirements Section when installing the instrument.
- Refer to the Errors Section when errors are encountered while operating the instrument.
- Refer to the Help Section when problems are encountered.

STORAGE / STABILITY

BioFilmChip Microarray: 24 months Refrigerated (2°C to 8°C)
Intellipac Reagent: 18 months Refrigerated (2°C to 8°C)
Note: Remove the Intellipac from the Analyzer and store refrigerated as soon as possible. Do not use after Intellipac has been opened for four weeks.
Amplification Mix: 18 months Frozen (-30°C to -15°C)

Note*:* Specific product expiration date is printed on the product label.

SPECIMEN COLLECTION AND STABILITY

ThinPrep® cervical specimens are recommended for use in the INFINITI® HPV-HR QUAD. Specimens taken with other sampling devices or transported in other transport media have not been qualified for use with this assay. The performance characteristics of the INFINITI® HPV-HR QUAD with other specimen types and collection devices have not been documented. Specimens for use in making ThinPrep Pap Test slides should be collected using a broom-type collection device and then placed in PreservCyt Fluid. PreservCyt Solution specimens may be held for up to three weeks at temperatures between 4°C and 37°C, following collection and prior to processing for the INFINITI® HPV-HR QUADs. PreservCyt Solution specimens cannot be frozen.

REAGENTS REQUIRED AND PROVIDED BY AUTOGENOMICS

ASSAY REAGENTS (SUFFICIENT FOR 192 TESTS)

- AutoGenomics Product Number 02-1100-02 HPV-HR QUAD Magazine – BioFilmChip® Microarray
  AutoGenomics Product Number 02-2100-02 HPV-HR QUAD Intellipac® Reagent Management Module (96 tests per Module, 2 modules per box), which contains:
  dNTPs
  Labeled -dCTP
  Analyte Specific Primers
  Extension Reaction Buffer
- AutoGenomics Product Number 02-3100-02 HPV-HR QUAD Amp Mix: 4 x 500µl vials of PCR reaction master mix containing:
  dNTPs
  Multiplex Primer Mix
  $MgCl_2$
  PCR Reaction Buffer

REAGENTS REQUIRED BUT NOT PROVIDED WITH THE ASSAY REAGENTS

- AutoGenomics Catalog Number 12-0470-02 INFINITI Sample processing Kit
- Internal Control 4 Catalog Number 12-0930-02
- AutoGenomics Product Number 12-0030-02 Solution Hybridization Buffer 2 : 6 x 30ml bottles. The hybridization buffer consists of:
  SSC
  Sodium Azide Preservative 0.08%
  EDTA
  10X Blocking Buffer

- AutoGenomics Product Number 12-0040-02 HPV Type 16 DNA Template Control
- AutoGenomics Product Number 12-0050-02 HPV Type 18 DNA Template Control
- AutoGenomics Product Number 12-0060-02 HPV Type 31 DNA Template Control
- AutoGenomics Product Number 12-0070-02 HPV Type 33 DNA Template Control
- AutoGenomics Product Number 12-0080-02 HPV Type 45 DNA Template Control
  Also available:
- AutoGenomics Product Number 12-0090-02 HPV Combo pack (Type 16, 18, 31, 33, 45) DNA Template Control

REAGENTS REQUIRED BUT NOT PROVIDED BY AUTOGENOMICS

- Molecular Grade Water (DNAse and RNAse free)
- Platinum Taq DNA Polymerase (Invitrogen, Catalog No.: 10966-018)

EQUIPMENT

The following equipment is required but not provided with the assay reagents

- Pipettors
- Mini Centrifuge
- Pipette tips
- Microfuge tube Racks
- Thermocycler
- Vortex
- 0.2 ml thin wall tubes for PCR
- 1.5 ml microcentrifuge tubes
- 8-well Flat Strip Caps (Genesee Scientific, Catalog No. 22-623)
- AutoGenomics Product Number 11-0060-00: INFINITI® Waste tray Stir Bars
- AutoGenomics Product Number 11-0020-00: INFINITI® Waste Tray Liners
- AutoGenomics Product Number 11-0080-00: INFINITI® Pipette Tips

- **FOR INFINITI® Analyzer***:*
  - AutoGenomics Product Number 10-0010-99: INFINITI® Analyzer
  - AutoGenomics Product Number 11-0030-00: 24-Well Plates with Lids
  - AutoGenomics Product Number 11-0050-00: INFINITI® Temp Cycle Plate

- **FOR INFINITI® PLUS Analyzer***:*
  - AutoGenomics Product Number 10-0020-99: INFINITI® PLUS Analyzer
  - AutoGenomics Product Number 11-0100-00: 48-Well Plates
  - AutoGenomics Product Number 11-0110-00: 48 Well Plate Lid (reusable)

ASSAY PROCEDURE

DNA Extraction

The INFINITI® Sample Processing Kit (AutoGenomics Catalog Number 12-0470-00) has been developed for use with the INFINITI® HPV-HR QUAD. Follow the instructions provided with the processing kit.

DNA Controls
It is required to run a known Positive control and a negative control should be included in each test run..

The following positive controls from AutoGenomics are recommended for use with the HPV-HR QUAD (refer to section on REAGENTS REQUIRED for Product Number):

(a) HPV Type 16 DNA Template Control
(b) HPV Type 18 DNA Template Control
(c) HPV Type 31 DNA Template Control
(d) HPV Type 33 DNA Template Control
(e) HPV Type 45 DNA Template Control
or
(f) HPV Combo pack (Type 16, 18, 31, 33, 45) DNA Template Control

Note: Please use proper PCR technique to prevent contamination of reagents with HPV controls.
It is recommended to seal the wells containing sample HPV DNA and "no template control" samples with cap before adding the HPV controls, to prevent cross contamination.

Amplification Reaction
Note:

- Keep Taq DNA polymerase on ice.
- Completely thaw reagents at room temperature then immediately place on ice.
- Vortex the amplification mix tube for 2 to 5 seconds then centrifuge briefly to bring the contents to the bottom of the tube.
- To avoid contamination, a separate area is recommended for assembly of the PCR reaction. Decontaminate pipettes and all work surfaces with freshly prepared 10% bleach.
- Filter tips and gloves must be used when handling specimens and controls.
- Ensure that tubes are properly sealed to avoid evaporation or spillage.
- Make sure there is no abnormal evaporation of the PCR product. After PCR is complete, visually inspect for any volume change. All amplification reaction volumes should be about 15 µl. Otherwise, do not proceed with the assay.

Note:

- For the INFINTI Analyzer use the 24WP.
- For the INFINTI PLUS Analyzer use the 48WP.

1. Prepare the PCR master mix.

Amplification mix	9.75 µl
Platinum Taq polymerase	0.25 µl
Internal Control 4	1.00 µl
Total volume of PCR Master mix	11.00 µl

Note: Calculate the amount of each reagent needed based on the number of reactions.

2. Gently vortex the PCR master mix then dispense 11.0 µl of master mix into wells of the well plate.

3. Add 4 µl of sample or control DNA to each well.

PCR master mix	11.0 µl
Sample or control DNA	4.0 µl
Total volume of amplification reaction	15.0 µl

Note: **This is a QUAD assay**. When loading samples, always load the samples in multiples of four and in consecutive order. For example, if loading 8 samples, load wells A1 to A8. **Do not** load the B wells**.**

4. Place the well plate, sealed with 8-well flat strip caps, in a thermocycler and immediately commence the amplification reaction using the following program.

Step No.	Temperature °C	Time (sec)	No. of Cycles
1	94	120	1
2a 2b 2c	94 58 - 50 (-0.8/cycle) 72	5 60 40	10x
3a 3b 3c	94 50 72	5 60 40	30x
4	4	hold	1

Note: After each cycle in step 2 the temperature is decreased by 0.8°C. When an Eppendorf Mastercycler EP was used with the ramp rate set at 75%, the total cycling time was 1 hour and 53 minutes (± 5 min). If using other thermocycler models we recommend adjusting the ramp rate in order to obtain an equivalent total cycling time.

Sample Loading

1) Carefully remove the 8-well flat strip caps to avoid splashing.
2) Load the well plate in the appropriate orientation (with well A1 in the back left corner) into the Analyzer
   - **INFINITI® Analyzer:** Load the assembled 24WP with the associated lid (Catalog # 11-0030-00).
   - **INFINITI® PLUS Analyzer:** Load the assembled 48WP with a clean 48WP lid (see instructions in the INFINITI PLUS Analyzer Operator's Manual) (Catalog # 11-0110-00, reusable).
3) Load the following: assay specific magazines, Intellipac, INFINITI Static Free Pipette tips, and buffer.
   - **FOR INFINITI® Analyzer***:*
     Wash buffer and hybridization buffer should be placed in the INFINITI® bottle holders. Wash buffer goes in the left holder (near the magazine) and the Hybridization buffer 2 in the right holder (near the Intellipac).
   - **FOR INFINITI® PLUS Analyzer***:*
     Hybridization buffer should be placed in the right INFINITI® bottle holder (near the Intellipac).

Operation of the Analyzers

Follow the instructions in the Operator's Manuals

INFINITI® Analyzer Operator's Manual (Part Number EM-34000)
INFINITI® PLUS Analyzer Operator's Manual (Part Number EM-34041)

QUALITY CONTROL

- Maintain calibration of thermocycler according to manufacturer's specifications.
- Maintain calibration of INFINITI® or INFINITI® PLUS Analyzer according to AutoGenomics' specifications.
- Maintain calibration of pipettes according to manufacturer's specifications.

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LIMITATIONS
The results obtained from the INFINITI® HPV-HR QUAD should be used and interpreted only in the context of the overall clinical diagnosis. AutoGenomics is not responsible for any clinical decisions that are made.

INTERPRETATION OF RESULTS
Results from the INFINITI® HPV-HR QUAD are reported to the user as "Positive" or "Negative" for each of the HPV DNA types detected.

The Internal Control 1 is intended to identify specimens that contain polymerase inhibitors. For a valid run, specimen results are interpreted as follows:

HPV Result	Internal Control (IC) Result	INTERPRETATION
ALL HPV Types Negative	Positive	HPV Negative
ALL HPV Types Negative	Negative	Invalid Test Result
ANY HPV Type Positive	Positive or Negative	Valid Test Result

If the analyzer detects a problem or an error (e.g., assay parameters not met), no results will be reported. Instead, a description of the problem or error code will be displayed. The Trouble Shooting section of the INFINITI® Analyzer Operator's Manual provides an explanation of the errors. The assay needs to be repeated.

DISPOSAL
Waste materials for the INFINITI® HPV-HR QUAD are common waste materials generated in clinical laboratories, and should be handled/disposed of in accordance with the policies/procedures in place in the clinical laboratory.

PERFORMANCE CHARACTERISTICS
Analytical Specificity
Studies related to specificity were conducted during assay development. PCR primer specificity was determined by amplicon size on a gel and sequencing the amplicon. ASP primer specificity was determined by the correct calls made by the assay using known genomic samples. Capture probe specificity was determined by hybridizing different oligos and demonstrating that correct oligo hybridizes to the known spot.

Analytical Sensitivity (Level of Detection)

Plasmids containing HPV genomic DNA for Types 16, 18, 31, 33, 45 and 66 were used as samples to establish the level of detection for the INFINITI® HPV-HR QUAD.

HPV Type	Lowest detectable copy number of plasmid DNA	Highest detectable copy number of plasmid DNA
Type - 16	2,000	2,000,000
Type - 18	2,000	2,000,000
Type - 31	2,000	2,000,000
Type - 33	2,000	2,000,000
Type - 45	2,000	2,000,000
Type - 66	50	1,000*

* Levels higher than 1,000 copies were not tested.

Note: In clinical specimens, HPV 16 is present in the highest copy number. Over 55% of HPV 16 positive clinical specimens contain more than 10^8 copies/µg of extracted DNA. Normal cytology for Type 16 is 2.2 x 10^7 copies/µg. Median DNA copy number varies by >10^4 among the viral types. [15]

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Sample Carry-over
There is no sample carry-over with the INFINITI® HPV-HR QUAD.

Potential Interference from Blood and other Substances
Interference from potential interfering substances such as whole blood, douche, anti-fungal cream and contraceptive jelly (agents that may commonly be found in cervical specimens) is not expected for the INFINITI® HPV-HR QUAD.

Assay Interference
Interference from other assays run on the Analyzer is not expected for the INFINITI® HPV-HR QUAD.

INFINITI® HPV-HR QUAD vs. CE Marked INFINITI® HPV-QUAD
Like the INFINITI® HPV-QUAD, the INFINITI® HPV-HR QUAD is a qualitative assay for use in clinical laboratories upon prescription by the attending physician. The INFINITI® HPV-HR QUAD utilizes the same AutoGenomics proprietary film-based microarray technology combined with process automation, reagent management and software technology for multiplex detection of the presence of HPV genotypes in deoxyribonucleic acid (DNA) obtained from cervical specimens.

A comparison study was performed to compare the results of the INFINITI® HPV-HR QUAD to the INFINITI® HPV-QUAD using 106 clinical samples. The results of the comparison demonstrated a 94% concordance between the INFINITI® HPV-HR QUAD and the INFINITI® HPV-QUAD. These results were obtained without repeating discordant samples. During the comparison study, five of 106 samples (4.7%) had invalid assays or no results and were repeated. Repeat results are reflected in the concordance analysis.

CLINICAL VALIDATION
The INFINITI® HPV-HR QUAD Assay was validated using the Roche COBAS® HPV Test as the comparator method. The COBAS® HPV Test provides pooled HPV DNA testing of 12 high-risk types and individually genotypes HPV 16 and 18 to help clinicians follow cervical cancer screening. The INFINITI® HPV-HR-QUAD detects and individually identifies all the 14 high-risk HPV types simultaneously.

- 50 samples were tested.
- 90% (45/50) of samples had consistent results between the COBAS® and INFINITI® HPV-HR QUAD
- 97% (95/150) of the genotype calls were consistent between the COBAS® and the INFINITI® HPV-HR QUAD
- INFINITI® HPV-HR QUAD provided specific genotyping information for samples identified by COBAS® as "Other HR HPV positive"
    - 4 Type 66
    - 2 Type 31
    - 1 Type 39
    - 1 Type 56
    - 1 Type 59

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