DOCUMENT Nº2.1:

DEVICE DESCRIPTION

HPV4

IRAN REGISTRATION

CONFIDENTIAL

EDICIÓN	FECHA	MODIFICACIONES
1	02.04.2018	INITIAL VERSION

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PRODUCT DESCRIPTION

CLART® HPV4 is available in two analysis formats:

- ***CLART® HPV4***, which enables to detect the 35 most clinically relevant types of Human Papillomavirus (6, 11, 16, 18, 26, 31, 33, 35, 39, 40, 42, 43, 44, 45, 51, 52, 53, 54, 56, 58, 59, 61, 62, 66, 68a and b, 70, 71, 72, 73, 81, 82, 83, 84, 85 and 89); and

- ***CLART® HPV4S***, which enables to detect the following 16 HPV types: 14 high oncogenic risk types (16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, 68) and 2 low oncogenic risk types (6 y 11).

Starting material for both formats may be both swabs as well as cell suspensions (See Section 6).

Detection is based on our CLART® technology: PCR amplification of a fragment of the viral region L1, followed by visualization in low-density microarray. The chosen sequence is highly conserved in all HPV types, while at the same time displays enough variations among HPV types so as to distinguish each type by means of specific probes.

Displayed in Figure 1 is a CLART-Strip® (CS), each well including all specific probes for testing one sample.

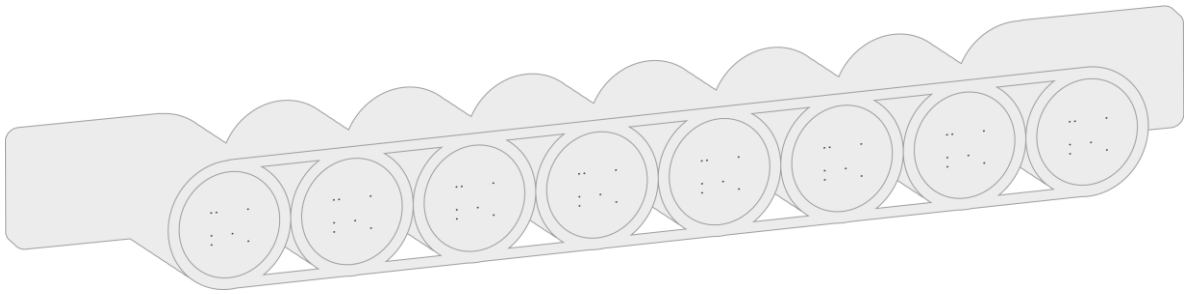
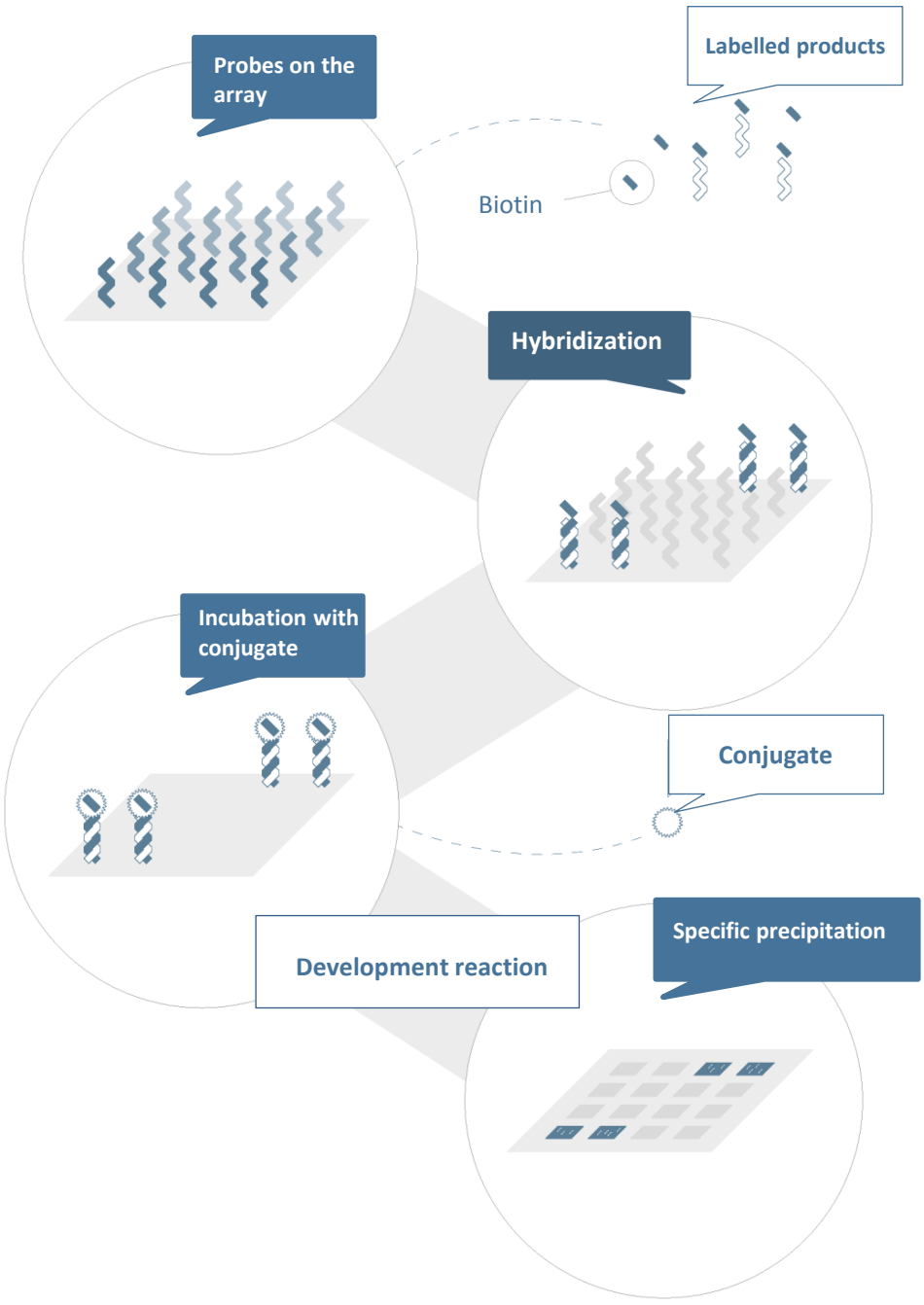


FIGURE 1. CLART-STRIP® IN THE FORM OF AN 8-WELL STRIP.

A scheme of the detection system is displayed in Figure 2. Basically, PCR amplified products labelled with biotin, hybridize with their specific complementary probes immobilised in well-defined areas of the microarray. Subsequent incubation steps take place thereon: first, with a streptavidin-peroxidase conjugate, and second, with an o-dianisidine substrate.

A non-soluble product precipitates thereafter in regions of the microarray where specific hybridization between amplified products and their specific probes has taken place.

Thereafter, analysis and interpretation of results are automatically performed by GENOMICA's reader (CAR® or CLINICAL ARRAY READER), running tailor-made software. autoclart® plus may alternatively be used (see Section 8).



1.

Figure 2. Scheme of the detection system. Probes immobilized on the microarray surface, capture complementary biotin-labelled amplified products. Subsequent binding of biotin to the streptavidin-peroxidase conjugate takes place. Finally, incubation with the peroxidase substrate o-dianisidine, yields a precipitate in the area where hybridization has occurred.

3.

4.

5.

COMPONENTS OF THE ASSAY

CLART® HPV4 kit, in both its formats, contains enough reagents for the analysis of 16, 48 or 96 clinical samples. Components of the kit are provided at their optimal storage temperatures, and remain stable until the expiration date is reached, upon observance of recommended storage conditions.

Kit components are displayed herein:

Amplification reagents

Shipped and stored at -20ºC.

Two possible formats available:

- Amplification tubes.
- Amplification plate.

Both the Amplification tubes as well as the wells of the Amplification plate are provided ready-to-use. Each of them contains 45 µL of master mix. Only the exact number of required tubes should be thawed on ice. Remaining ones should be kept at -20ºC.

Note: Boxes containing amplification tubes include a self-adhesive and irreversible temperature indicator; Red color displayed on the visualization window of the indicator means that the package has exceeded at some time the storage temperature of –20ºC and reagents should be discarded.

Visualization components

Visualization components are divided into two groups, according to optimal shipping and storage temperatures:

- Shipped at 4ºC and stored at Room Temperature:

- **CLART-Strip® (CS)**, each well including all specific probes for detection of all HPV types to be detected.

Note: Required **CS** units are shipped in a sealed pouch. Each unit should be kept until use, in the unopened pouch, at room temperature (i.e. 25ºC maximum) and protected from direct light and high temperatures.

- Shipped and stored at 4ºC:

- **DC** (Conjugate Diluent).
- **SH** (Hybridization Solution).
- **CJ** (Conjugate Solution).
- **RE** (Development Solution). Keep away from light.
- **TL** (Wash Buffer).
- **Microtiter plate adaptor and plastic lid.**

Other components

- GENOMICA's **CAR®** or CLINICAL ARRAY READER (Figure 3).

CAR® grants automatic reading, analysis and interpretation of up to 12 **CS** units (i.e., to a maximum of 96 samples) *per* run. It displays a user-friendly and intuitive graphical interface (CLEIS), and includes updates of GENOMICA's proprietary image processing software SAICLART® as well as kit-specific Software.

Note: CAR® is to be used exclusively with GENOMICA's diagnostic kits.

FIGURE 3. CAR® (CLINICAL ARRAY READER)

- GENOMICA's **autoclart®**.
  autoclart® allows automatic processing of up to 12 CSs strips (96 samples) during the visualization step.

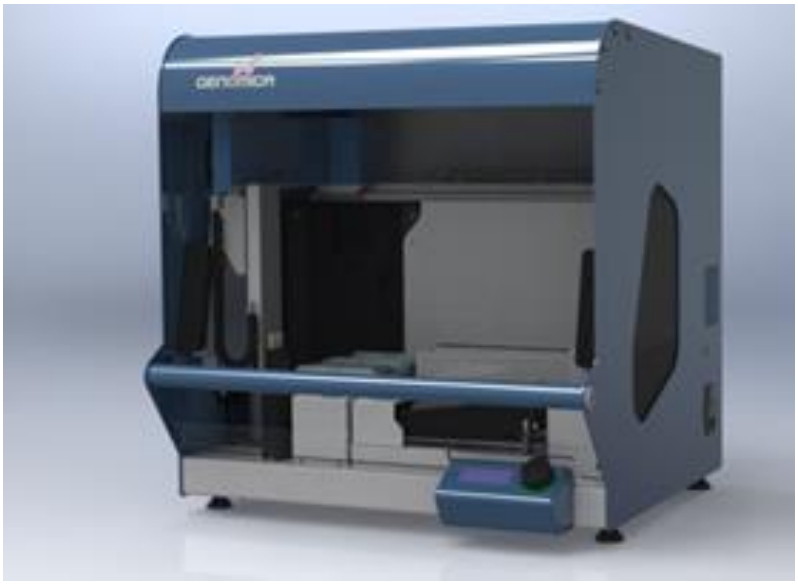


FIGURE 4. AUTOCLART®

- GENOMICA's **autoclart® plus**.

autoclart® plus is a fully automated electromedical device capable of processing up to 96 samples per run, starting from the denatured amplification product, and ending with issuance of the corresponding diagnostic report.

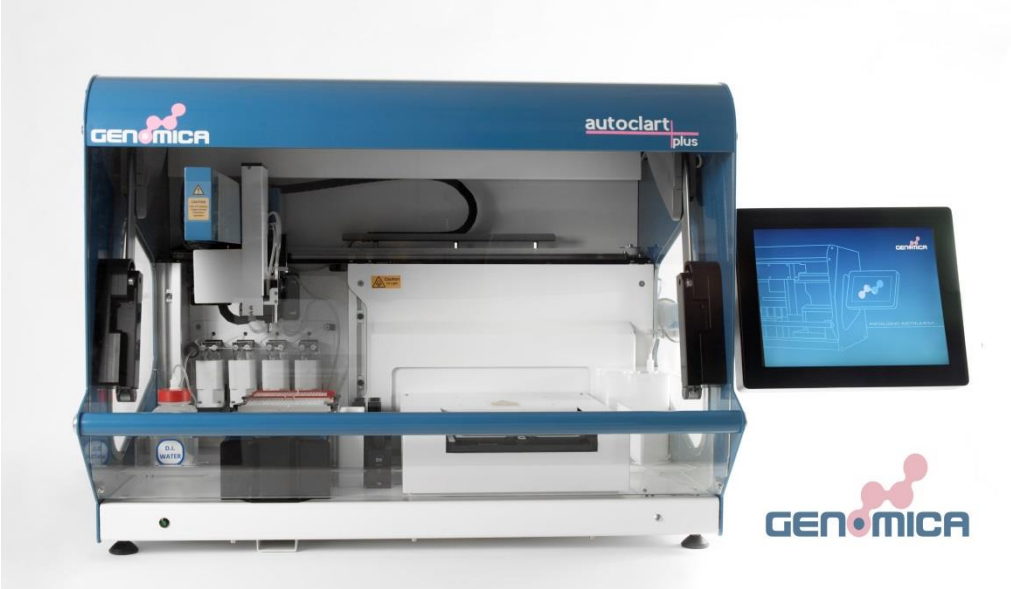


FIGURE 5. AUTOCLART® PLUS

PAKAGING

SECUNDARY PACKAGING:

The kit package is made of cardboard.

The secondary labeling is fixed on the packaging. This packaging has imprinted the name and the address of the manufacturer.

Front of the packaging	***Back of the packaging***
	
In this packaging is printed the name and the adress of the manufacturer	
	

Please note: The amplification reagent package includes a self-adhesive and irreversible temperature indicator; the appearance of a reddish color on the visualization window indicates that, at a certain moment, products have exceeded storage temperature of -20 ^{o}C and they should not be used.

STORAGE

Reagents included in the kit have been grouped into various packages, depending on the temperature at which they should be stored.

Amplification reagents : They should be stored at -20ºC.

Visualization reagents :. This visualization kit should be stored at 2ºC to 8ºC

Components	Storage Temperature
Hybridization Solution (SH)	**STORE AT 2ºC TO 8ºC**
Conjugate (CJ)	**STORE AT 2ºC TO 8ºC**
Conjugate Diluent (DC)	**STORE AT 2ºC TO 8ºC**
Development Solution (RE)	**STORE AT 2ºC TO 8ºC**
Wash Buffer (TL)	**STORE AT 2ºC TO 8ºC**
CS Strips (Arrays)	**STORE AT 20ºC TO 22Cº (ROOM TEMPERATURE)**

EXPIRATION DATE

Stability experiments are intended confirm that functionality of the reagents was not affected by their shelf-life, always within the expiration date limits recommended by the manufacturer.

The stability of the extraction and Amplification part is determined by the stability of the amplification tubes. This stability has been assessed and is for one year.

The stability of the Visualization part is determined by the stability of its most critical component: the Develoment Solution. This stability has been assessed and is for 15 months

INTENTED USE

FUNTION

CLART® HPV4 is intended for following use: genotyping of human papillomavirus via genomic identification for *IN VITRO* DIAGNOSIS.

USER

CLART® HPV4 is intended to be used by professional people with adequate qualification because it requires the interpretation of the results obtained from the assay.

RISK CLASS OF THE PRODUCT: CLASSIFICATION

CLASSIFICATION IN EUROPE

The Classification of an IVD Medical Device is based on the following criteria:

- The intended use and indications for use as specified by the manufacturer (specific disorder, condition or risk factor for which the test is intended)
- The technical/scientific/medical expertise of the intended user (lay person or professional)
- The importance of the information to the diagnosis (sole determinant or one of several), taking into consideration the natural history of the disease or disorder including presenting signs and symptoms which may guide a physician
- The impact of the result (true or false) to the individual and/or to public health

The device is subject to special national rules that apply within a particular jurisdiction.

In Europe, the In Vitro Diagnostic Medical Devices Directive 98/79/CE describes, for the purposes of the conformity assessment procedures, the groups IVDs into four categories:

• General IVDs, i.e. all IVDs other than those covered by Annex II and IVDs for self-testing;

• IVDs for self-testing (a device intended by the manufacturer to be able to be used by lay persons in a home environment) excluding self-test devices covered in Annex II;

• IVDs in Annex II List B of the Directive: Which, amongst others, includes reagents products for rubella, toxoplasmosis and phenylketonuria, cytomegalovirus, Chlamydia as well as devices for self testing for blood sugar.

• IVDs in Annex II List A of the Directive: Which includes reagents and products for HIV I and II, Hepatitis B, C and D, and reagent products for determining ABO systems and anti-kell.

The device concerned is intended to be used to detect the presence of, or exposure to, a transmissible agent that causes a life-threatening often incurable disease with a high risk of propagation.

CLART® HPV4 meets the provisions of the EC Council Directive 98/79/EC on in vitro diagnostic medical devices, transposed to the Spanish legislation by the Royal Decree 1662/2000 of 29th September 2000. MDD 98/79/EC.

It is intended to be used by professional people with adequate qualification but it is not included in Annex II of 98/79/CE Directive. This kit only requires Declaration of Conformity from GENOMICA (Annex III, 98/79/CE Directive).

TECHNICAL STANDARDS USED

For further details see DECLARATION OF CONFORMITY

BACKGROUND

Verdasca, N., A. Coelho, F. Ribeira, A. Pista.: *"Detection of VPH ADN from cervical samples in a group of portuguese women: comparison of two VPH genotyping assays*". 23rd International papillomavirus conference and clinical workshop. September 2006. Praga.

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Bonde J., Rebolj M., Ejegod DM., Preisler S., Lynge E., Rygaard C.: "*HPV prevalence and genotype distribution in a population-based split-sample study of well-screened women using CLART® HPV2 2 Human Papillomavirus genotype microarray system*". BMC Infectious Diseases 2014, 14:413.

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Ejegod DM., Rebolj M., Bonde J.: "*Comparison of analytical and clinical performance of CLART HPV2 genotyping assay to Linear Array and Hybrid Capture 2: a split-sample study*". DOI 10.1186/s12885-015-1223-z

ONCOGENIC RISK OF THE HPV TYPES DETECTABLE WITH CLART® HPV

TYPE	ONCOGENIC RISK *
PVH 6	Low Risk
PVH 11	Low Risk
PVH 16	High Risk
PVH 18	High Risk
PVH 26	Problable High Risk
PVH 31	High Risk
PVH 33	High Risk
PVH 35	High Risk
PVH 39	High Risk
PVH 40	Low Risk
PVH 42	Low Risk
PVH 43	Low Risk
PVH 44	Low Risk
PVH 45	High Risk
PVH 51	High Risk
PVH 52	High Risk
PVH 53	Probable High Risk
PVH 54	Low Risk

TYPE	ONCOGENIC RISK *
PVH 56	High Risk
PVH 58	High Risk
PVH 59	High Risk
PVH 61	Low Risk
PVH 62	Low Risk
PVH 66	High Risk
PVH 68	High Risk
PVH 70	Low Risk
PVH 71	Low Risk
PVH 72	Low Risk
PVH 73	Probable High Risk
PVH 81	Low Risk
PVH 82	Probable High Risk
PVH 83	Low Risk
PVH 84	Low Risk
PVH 85	Low Risk
PVH 89	Low Risk

*According to: *Bouvar d V, Baan R, Straif K, Grosse Y, Secretan B, El Ghissassi F et al.*

A review of human carcinogens -Part B: biological agents. Lancet Oncol