WHO HPV LabNet

Report on HPV DNA Proficiency Panel 2008

Prepared by

Carina Eklund, Kia Sjölin, Ola Forslund &

Joakim Dillner

Table of Contents

Introduction **5**

Aims **5**

Methods **5**

Panel composition *5*
Validation of panel *7*
Distribution of panel *7*
Analysis *8*

Results **8**

Results by assays used *9*
Results analysed by assays *9*
Results achieved by participating laboratories *10*
HPV types detected *12*
Results by sample number *15*
Analysis of false positive results *16*

Discussion **17**

Conclusions **19**

Annex 1: Call for participation: WHO HPV LabNet Proficiency Study for evaluating HPV DNA Typing Methods
Annex 2: Application form
Annex 3: Participating laboratories

Tables

Table 1: Panel composition by randomised sample ID

Table 2: Assays used for typing of HPV

Table 3: Proportion of data sets with ≥90% proficient HPV typing results, by WHO region.

Table 4: Proficiency for detection of specific HPV types.

Table 5: HPV genome equivalents or IU detected per 5 μl in both single and multiple infections in commercially available assays used to test the HPV panel.

Table 6: HPV genome equivalents or IU detected per 5 μl in both single and multiple infections in-house assays used to test the HPV panel.

Table 7: Percentage of laboratories reporting correct HPV type as claimed with no false positive HPV type detected reported by sample number.

Table 8: Number of false positive HPV types detected per data set reported by assay used.

Figures

Figure 1: Global distribution of the laboratories submitting results for WHO HPV DNA proficiency panel 2008.

Figure 2: Assays in use for HPV DNA typing by WHO region

Figure 3: Proficiency for HPV DNA typing by WHO region.

Figure 4: HPV Genome Equivalents or International Units detected per 5 μl in both single and multiple infections.

.

Abbreviations

AFRO	African Regional Office
EMRO	Eastern Mediterranean Regional Office
EURO	European Regional Office
DKFZ	Deutsches Krebsforschungszentrum
CDC	Centres for Disease Control and prevention
GE	Genome Equivalent
GRL	Global Reference Laboratory
HPV	Human Papilloma Virus
HPV LabNet	HPV Laboratory Network
IU	International Unit
PAHO	Pan American Health Organisation
RRL	Regional Reference Laboratory
SEARO	South East Asian Regional Office
WHO	World Health Organization
WPRO	Western Pacific Regional Office

WHO HPV LabNet DNA proficiency panel 2008

Time for Distribution September - October 2008

Introduction

Accurate and internationally comparable HPV DNA detection and typing methodology is an essential component in the evaluation of HPV vaccines and in effective implementation and monitoring of HPV vaccination programs. The WHO Global HPV LabNet is a WHO initiative established to support the world-wide implementation of HPV vaccines through improved laboratory standardization and quality assurance of HPV testing and typing methods used for HPV surveillance and monitoring of HPV vaccination programs (*http://www.who.int/biologicals/areas/vaccines/hpv_labnet/en/index.html*). A major method for achieving progress towards this goal is development, preparation and validation of proficiency panels to qualify methods and laboratories.

Call for participation in this proficiency study was advertised on WHO website and sent to WHO Regional Offices in May 2008 for broad interest (Annex 1, 2)

Aims

The aims of this panel are to:

1. To assess the proficiency of HPV typing assays when routinely used in laboratories worldwide
2. To evaluate the sensitivity and type-specificity of HPV detection of the different HPV assays when routinely used in laboratories worldwide
3. Identify problems with any assays routinely used

Methods

Panel composition

Complete genomes of HPV cloned into plasmid vectors had been provided to the WHO HPV LabNet Global Reference Laboratory at the University Hospital in Malmö Sweden by the respective proprietors with written approval for use in this WHO proficiency panel.

All samples were purified plasmids diluted in a background of human placenta DNA.

The HPV types included were: 6, 11, 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66 and 68

Two samples, A and B, were cell lines used as controls for the DNA extraction step in the testing.

Table 1: Panel composition by randomised panel ID

WHO HPV LabNet DNA proficiency panel 2008

Randomised Panel ID	HPV types	HPV genome equivalents (IU) per 5 µl
6	16	500
17	16	50
26	16	5
11	18	500
19	18	50
1	18	5
8	6	500
15	6	50
30	11	500
37	11	50
20	31	500
29	31	50
2	33	500
9	33	50
25	35	500
14	35	50
32	39	500
39	39	50
24	45	500
36	45	50
3	51	500
18	51	50
21	52	500
10	52	50
33	56	500
41	56	50
27	58	500
38	58	50
4	59	500
13	59	50
34	66	500
40	66	50
22	68	500
31	68	50
16	16, 45, 52, 33	500
23	16, 45, 52, 33	50
5	11, 18, 31, 51	500
12	11, 18, 31, 51	50
28	35, 39, 59, 66	500
42	35, 39, 59, 66	50
35	6, 56, 58, 68	500
43	6, 56, 58, 68	50
7	None	0
A	HPV 16 Cervical cancer	2000
B	HPV-negative cells	0

Validation of panel

The panel was pre-tested at GRL Sweden using a modified GP PCR followed by Luminex-based typing for HPV types 6, 11, 16, 18, 26, 30, 31, 33, 35, 39, 40, 42, 43, 45, 51, 52, 53, 54, 56, 58, 59, 66, 67, 68a, 69, 70, 73, 74, 82, 86, 89, 90 and 91.

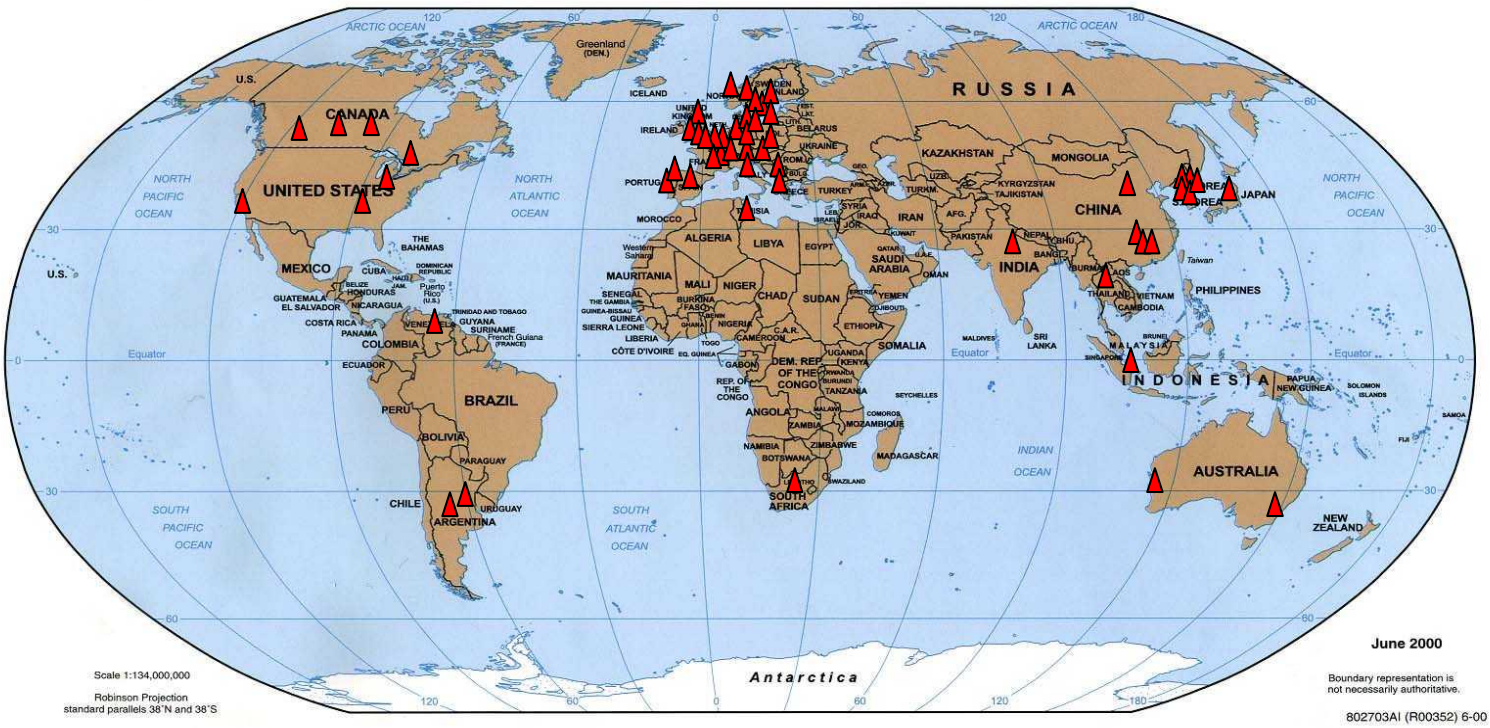
The panel was tested by two external laboratories before release:

- The HPV LabNet Global Reference Laboratory in the USA (CDC) used a Roche Linear array assay testing for HPV types 6, 11, 16, 18, 26, 31, 33, 35, 39, 40, 42, 45, 51, 52, 53, 54, 55, 56, 58, 59, 61, 62, 64, 66, 67, 68, 69, 70, 71, 72, 73, 81, 82, 83, 84, 89 and IS39.
- The German Cancer Research Center (DKFZ) in Heidelberg used a modification of GP PCR followed by Luminex-based typing for HPV types 6, 11, 16, 18, 26, 30, 31, 33, 35, 39, 42, 43, 44, 45, 51, 52, 53, 56, 58, 59, 66, 67, 68b (Me 180), 68a, 69, 70, 73 and 82.

Distribution of panel

After validation this panel was compiled in July 2008 and distributed throughout six WHO regions in September and October 2008. There was no charge for laboratories to participate. Shipments were also paid by the WHO HPV LabNet. The WHO Regions included in the distribution: AFRO (No. of labs = 1), EMRO (n = 1), EURO (n = 28), SEARO (n = 2), WPRO (n = 13) and PAHO (n = 16). Eighty-five datasets with results were returned before the deadline from 54 laboratories. 30 laboratories submitted a data set from one test only, 18 laboratories submitted data sets from 2 different tests, 5 laboratories submitted data sets from 3 tests and one laboratory submitted data sets from 4 tests.

Figure 1: Global distribution of laboratories submitting results for HPV DNA proficiency panel.



Analysis

Results analysed in this report include all results returned to GRL Sweden prior to December 2008. Each data set submitted was designated a number from 1 to 85. The data were analysed by laboratory, by assay used and by HPV type. Participating laboratories used a range of commercial assays as well as in-house assays. The proportion of correct HPV typing results, reported by the laboratory, was analyzed as data sets by laboratory and according to assay used.

Results

Fifty-four of 61 participating laboratories (including the three laboratories who did pre-release testing namely GRL Sweden, GRL USA, and DKFZ Germany) submitted 85 data sets within the timeline. Two laboratories responded after the deadline -these results are not included in these analyses. Four data sets were generated using assays that did not discriminate specific HPV types, and were not included in the overall type-specific analyses presented here.

A data set was considered proficient when it was detecting at least 50 international units (IU) of HPV 16 and HPV 18 in 5µl and 500 genome equivalents (GE) in 5µl of the other HPV types in both single and multiple infection, without having more than one false positive type detected this equals a specificity of 97%.

Results by assays used

Commercial assays

A total of 37 data sets results had been obtained using commercially available tests. The most commonly used assay was the Linear Array (Roche) HPV genotyping assay that was used in 15 laboratories. Other widely used assays were the clinical array test CLART (Genomica) and Inno-LiPA (Innogenetics)

In-house assays

Forty-eight of the data sets had been obtained using a variety of in-house assays (Table 2).

Results analysed by assays

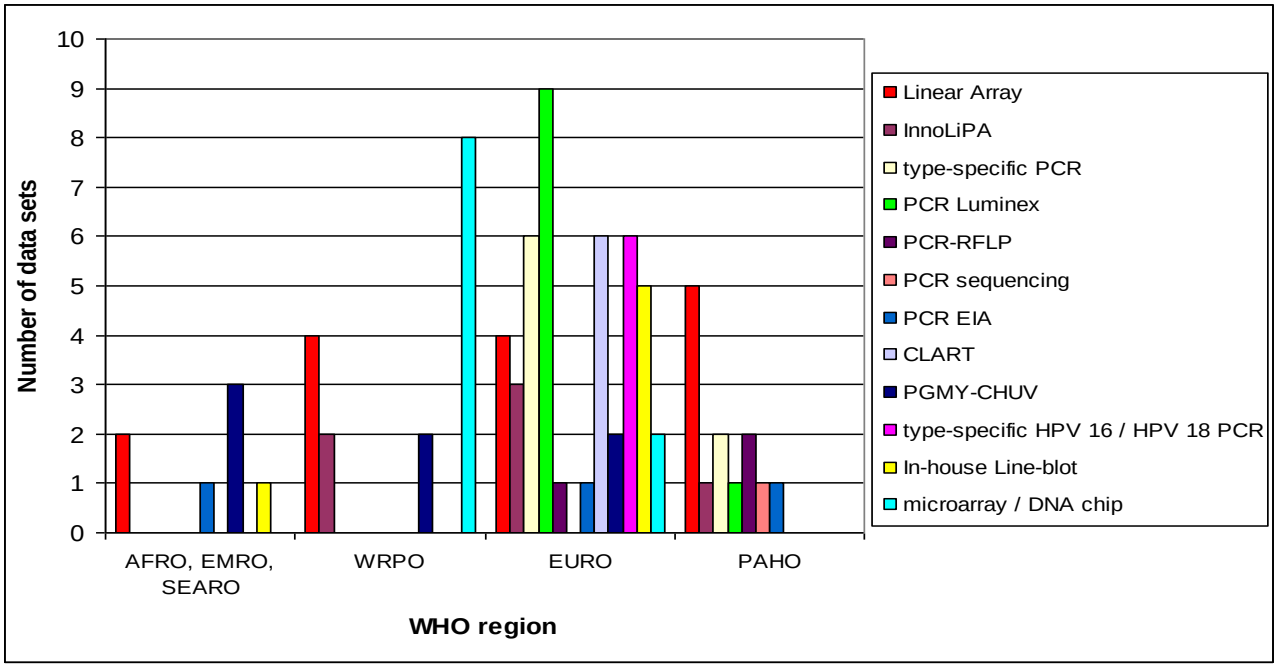
Assay Details

Table 2: Assays used for typing of HPV

HPV assay type	Number of data sets	HPV region targeted (primers)
All assays	81	L1/E1/E6/E7
Linear Array (Roche)	15	L1 (PGMY)
CLART HPV 2 (Genomica)	6	L1 (PGMY)
InnoLiPA (Innogenetics)	6	L1 (SPF10)
PGMY-CHUV	7	L1 (PGMY)
In-house Type-specific PCR	7	L1 / E6 / E7
In-house 16 /18 specific PCR	6	E6 / E7
DNA chip (Biocore)	4	L1
In-house Lineblot	4	L1 (GP)
In house PCR Luminex	4	L1 (GP or modifiedGP)
In house PCR Luminex	4	E6 / E7
In-house Microarray	3	L1 / E7
PCR-RFLP	3	L1
Microarray (Genetel)	2	L1
DEIA LiPA assays	2	L1 (SPF 10)
In house PCR EIA	2	L1
Papillocheck Microarray	1	E1
Type specific PCR (GenoID)	1	L1
In-house PCR Luminex	1	L1 (PGMY-GP)
PCR Luminex (Multimetrix)	1	L1 (GP)
PCR EIA (GenoID)	1	L1
In-house PCR sequencing	1	L1 (PGMY-GP)

Four data sets were generated using assays that did not discriminate specific HPV types and are not included in the overall type-specific analyses presented here.

Figure 2: Type of assay in use for HPV DNA typing by WHO region, data for AFRO, EMRO and SEARO region are combined.



Results achieved by participating laboratories

Nineteen (23 %) data sets were 100 % proficient.

Figure 3: Proficiency for HPV DNA typing by WHO region.

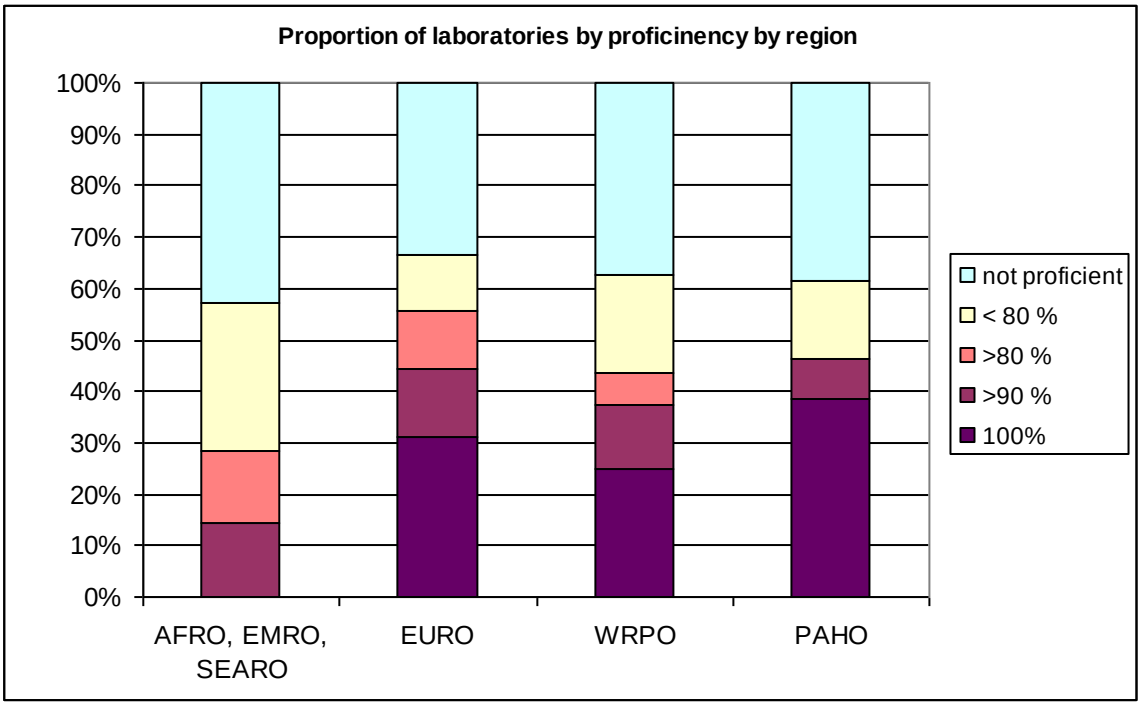


Table 3: Proportion of data sets submitted by WHO region with ≥90% proficient HPV typing results.

Region (data sets)	Proportion of laboratories with 100% correct typing	Proportion of laboratories with ≥90% correct typing
AFRO (2)	0 %	50 %
EMRO (1)	0 %	0 %
EURO (45)	31 %	44 %
SEARO (4)	0 %	0 %
PAHO (13)	38 %	46 %
WPRO (16)	25 %	37 %

Table 4: Proficiency of detecting HPV types by laboratory and by assay used*

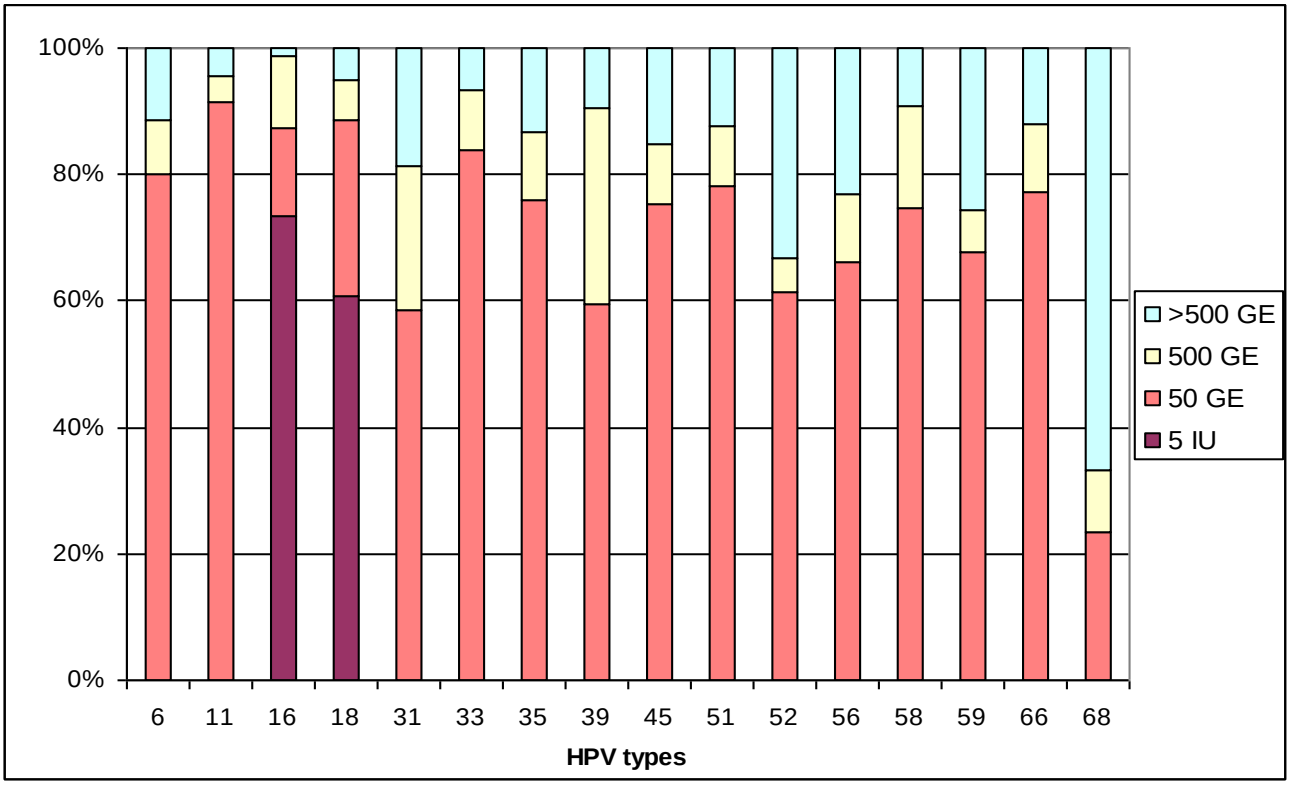
HPV assay type	Number of data sets	No. of proficient data sets				
		100% proficient	99-90 % proficient	89-80 % proficient	<80 % proficient	Not proficient
All assays	74	19	10	5	12	28
Linear Array (Roche)	15	6	5	0	0	4
CLART HPV 2 (Genomica)	6	0	0	2	0	4
InnoLiPA (Innogenetics)	6	0	1	1	0	4
PGMY-CHUV **	7	1	1	0	3	2
In-house Type-specific PCR	6	2	0	0	1	3
DNA chip (Biocore)	4	0	0	0	3	1
In-house Lineblot	4	0	1	0	2	1
In-house PCR Luminex[b]	4	3	0	0	0	1
In-house PCR Luminex[c]	4	2	0	0	0	2
In-house Microarray	3	1	0	0	0	2
PCR-RFLP	3	0	0	0	2	1
Microarray (Genetel)	2	2	0	0	0	0
DEIA LiPA assays	2	0	0	0	0	2
In-house PCR EIA	2	0	0	1	0	1
Microarray(Papillocheck)	1	1	0	0	0	0
Type specific PCR (GenoID)	1	0	1	0	0	0
In-house PCR Luminex	1	0	0	0	1	0
PCR Luminex (Multimetrix)	1	0	0	1	0	0
PCR EIA (GenoID)	1	0	1	0	0	0
In-house PCR sequencing	1	1	0	0	0	0

*Table restricted to assays testing for more than 12 types. [b]L1 region. [c]E6/E7 region

** The in-house PGMY-CHUV assay was transferred to WHO HPV LabNet members in 2008 as an effort to build up testing capacity and evaluate the assay. The use of this assay in this proficiency panel was requested by the HPV LabNet as a "validation" of the set-up.

HPV types detected

Figure 4: HPV Genome Equivalents or International Units detected per 5 µl in both single and multiple infection. Please note that only HPV16 and 18 were diluted all the way to 5 IU (not all data sets analyze for all HPV types).



This data includes the laboratories with multiple false positives. Detection with input volume 50 µl classified as data for the next 10-fold dilution compared to input with 5 µl. Input with 10 or 15 µl classified as same dilution compared to input with 5 µl. 8 laboratories used 50 µl input volume in Linear Array.

Table 5: HPV genome equivalents or IU detected per 5 µl in both single and multiple infections in commercially available assays used to test the HPV panel.

HPV type	HPV IU /GE	All Assays (%)	Linear Array*	CLART (HPV 2)	InnoLiPA	DNA chip (biocore)	Microarray (Genetel)	Papillocheck Microarray	Luminex (Multimetrix)	PCR-EIA (GenoID)	Type specific PCR (GenoID)
16	5	50 / 79 (63)	7 / 15	4/6	2 / 6	4 / 4	2 / 2				1 / 1
16	50	69 / 79 (87)	15 / 15	5/6	3 / 6			1 / 1	1 / 1		
16	500	78 / 79 (99)			6 / 6					1 / 1	
18	5	41 / 78 (53)	4 / 15	1/6	5 / 6	4 / 4	2 / 2		1 / 1		1 / 1
18	50	69 / 78 (88)	14 / 15	6/6						1 / 1	
18	500	75 / 78 (96)	15 / 15					nt			
6	50	48 / 70 (69)	6 / 15	6 / 6	6 / 6	4 / 4	2 / 2	1 / 1			1 / 1
6	500	62 / 70 (88)	15 / 15							1 / 1	
11	50	56 / 70 (80)	6 / 15	6 / 6	5 / 6	4 / 4	2 / 2	1 / 1	1 / 1	1 / 1	1 / 1
11	500	67 / 70 (96)	14 / 15								
31	50	36 / 75 (48)	6 / 15	3 / 6	5 / 6		2 / 2	1 / 1		1 / 1	1 / 1
31	500	61 / 75 (81)	15 / 15	4 / 6							
33	50	55 / 75 (73)	7 / 15	5 / 6	6 / 6	4 / 4	2 / 2		1 / 1	1 / 1	1 / 1
33	500	70 / 75 (93)	15 / 15					1 / 1			
35	50	50 / 75 (67)	7 / 15	4 / 6	5 / 6	4 / 4	1 / 2		1 / 1	1 / 1	1 / 1
35	500	65 / 75 (87)	14 / 15		6 / 6		2 / 2	1 / 1			
39	50	25 / 42 (60)			5 / 6	1 / 4	1 / 2	1 / 1	1 / 1		1 / 1
39	500	38 / 42 (90)	nt	nt	6 / 6	3 / 4	2 / 2			1 / 1	
45	50	48 / 74 (65)	7 / 15	1 / 6	2 / 6	4 / 4		1 / 1	1 / 1	1 / 1	1 / 1
45	500	63 / 74 (85)	15 / 15	2 / 6	5 / 6		2 / 2				
51	50	49 / 73 (67)	7 / 15	6 / 6	5 / 6	2 / 4	2 / 2	1 / 1	1 / 1	1 / 1	1 / 1
51	500	64 / 73 (88)	15 / 15								
52	50	40 / 75 (53)	3 / 15	4 / 6	1 / 6	2 / 4	2 / 2		1 / 1		1 / 1
52	500	50 / 75 (67)	9 / 15			3 / 4		1 / 1		1 / 1	
56	50	41 / 74 (55)	4 / 15	1 / 6	6 / 6		2 / 2	1 / 1	1 / 1	1 / 1	1 / 1
56	500	56 / 74 (76)	14 / 15	2 / 6							
58	50	48 / 75 (64)	7 / 15	5 / 6	1 / 6	3 / 4	2 / 2			1 / 1	1 / 1
58	500	68 / 75 (91)	15 / 15	6 / 6	4 / 6	4 / 4		1 / 1	1 / 1		
59	50	42 / 74 (57)	7 / 15	4 / 6	1 / 6		2 / 2	1 / 1		1 / 1	1 / 1
59	500	55 / 74 (74)	15 / 15						1 / 1		
66	50	44 / 66 (67)	6 / 15	6 / 6	6 / 6		1 / 2	1 / 1	1 / 1	1 / 1	1 / 1
66	500	58 / 66 (88)	14 / 15				2 / 2				
68	50	7 / 29 (24)					1 / 2				
68	500	10 / 29 (34)	nt	nt	1 / 5		2 / 2	nt			

Table 6: HPV genome equivalents or IU detected per 5 µl in both single and multiple infections in in-house assays used to test the HPV panel.

HPV type	HPV IU /GE	PGMY - CHUV	Type specific PCR	Lineblot	Luminex (GP)	Luminex (E6/E7)	Microarray	PCR-RFLP	DEIA LIPA	PCR-EIA	Luminex (PGMY-GP)	PCR sequencing
16	5	4 / 7	6 / 7	2 / 4	3 / 4	3 / 4	2 / 3	1 / 3	2 / 2	1 / 2	1 / 1	1 / 1
16	50	6 / 7		3 / 4	4 / 4		3 / 3	2 / 3		2 / 2		
16	500	7 / 7	7 / 7	4 / 4		4 / 4		3 / 3				
18	5	2 / 7	5 / 7	1 / 4	4 / 4	2 / 4	2 / 3		2 / 2		1 / 1	1 / 1
18	50	6 / 7		4 / 4		4 / 4	3 / 3			1 / 2		
18	500		7 / 7					2 / 3		2 / 2		
6	50	4 / 7	3 / 5	1 / 4	4 / 4	1 / 2	1 / 2	3 / 3	2 / 2	1 / 2	1 / 1	1 / 1
6	500	5 / 7	5 / 5			2 / 2						
11	50	5 / 7	4 / 5	4 / 4	4 / 4	1 / 2	2 / 2	3 / 3	2 / 2	2 / 2	1 / 1	1 / 1
11	500	7 / 7	5 / 5									
31	50		5 / 7	2 / 4	1 / 4	2 / 4	1 / 3	1 / 3	2 / 2	2 / 2		1 / 1
31	500	5 / 7	6 / 7	4 / 4	4 / 4	3 / 4	3 / 3	2 / 3				
33	50	2 / 7	7 / 7	3 / 4	4 / 4	3 / 4	2 / 3	2 / 3	2 / 2	2 / 2		1 / 1
33	500	5 / 7		4 / 4			3 / 3	3 / 3				
35	50	2 / 7	6 / 7	4 / 4	4 / 4	2 / 4	2 / 3		2 / 2	2 / 2	1 / 1	1 / 1
35	500	5 / 7				4 / 4						
39	50		4 / 6		4 / 4	3 / 4	2 / 3		2 / 2			
39	500	nt	6 / 6	3 / 4		4 / 4				1 / 1	nt	nt
45	50	6 / 7	5 / 7	4 / 4	4 / 4	4 / 4	2 / 3		2 / 2	1 / 1	1 / 1	1 / 1
45	500						3 / 3					
51	50	5 / 7	5 / 6	1 / 4	4 / 4	2 / 4	1 / 3	1 / 3	2 / 2		1 / 1	1 / 1
51	500	7 / 7	6 / 6	3 / 4		3 / 4				1 / 1		
52	50	5 / 7	7 / 7		4 / 4	4 / 4	3 / 3		2 / 2			1 / 1
52	500			1 / 4								
56	50	1 / 7	5 / 6	4 / 4	4 / 4	4 / 4	1 / 3		2 / 2	1 / 2	1 / 1	1 / 1
56	500	4 / 7								2 / 2		
58	50	5 / 7	7 / 7	3 / 4	3 / 4	2 / 4	2 / 3	2 / 3	2 / 2		1 / 1	1 / 1
58	500			4 / 4	4 / 4	3 / 4				2 / 2		
59	50	6 / 7	5 / 7	3 / 4	3 / 4	2 / 4	2 / 3		1 / 2	1 / 1	1 / 1	1 / 1
59	500	7 / 7			4 / 4	3 / 4			2 / 2			
66	50	5 / 7		2 / 4	4 / 4	2 / 3	2 / 3	1 / 3	2 / 2	1 / 1	1 / 1	1 / 1
66	500	6 / 7	nt	4 / 4		3 / 3	3 / 3					
68	50				4 / 4		1 / 2		1 / 2			
68	500					nt		nt	2 / 2		nt	nt

Results by sample number

Table 7: Percentage of laboratories reporting correct HPV type as claimed and with no false positive HPV type detected, categorised by sample number.

Randomised Panel ID	HPV types	HPV genome equivalents per 5 µl	Percent correct data sets (N)
6	16	500	**94,9 (75 / 79)**
17	16	50	88,6 (70 / 79)
26	16	5	68,3 (54 / 79)
11	18	500	**92,3 (72 / 78)**
19	18	50	92,3 (72 / 78)
1	18	5	59,7 (46 / 78)
8	6	500	**91,4 (64 / 70)**
15	6	50	80,0 (56 / 70)
30	11	500	**88,6 (62 / 70)**
37	11	50	94,3 (66 / 70)
20	31	500	**85,3 (64 / 75)**
29	31	50	66,6 (50 / 75)
2	33	500	**89,3 (67 / 75)**
9	33	50	85,3 (64 / 75)
25	35	500	**86,6 (65 / 75)**
14	35	50	77,3 (58 / 75)
32	39	500	**90,5 (38 / 42)**
39	39	50	69,0 (29 / 42)
24	45	500	**89,2 (66 / 74)**
36	45	50	81,1 (60 / 74)
3	51	500	**89,0 (65 / 73)**
18	51	50	75,3 (55 / 73)
21	52	500	**85,3 (64 / 75)**
10	52	50	78,7 (59 / 75)
33	56	500	**75,7 (56 / 74)**
41	56	50	67,6 (50 / 74)
27	58	500	**90,7 (68 / 75)**
38	58	50	76,0 (57 / 75)
4	59	500	**73,0 (54 / 74)**
13	59	50	66,2 (49 / 74)
34	66	500	**84,8 (56 / 66)**
40	66	50	78,8 (52 / 66)
22	68	500	**37,9 (11 / 29)**
31	68	50	34,4 (10 / 29)
16	16, 45, 52, 33	500	**58,2 (46 / 79)** [a]
23	16, 45, 52, 33	50	46,8 (37 / 79) [a]
5	11, 18, 31, 51	500	**71,8 (56 / 78)** [a]
12	11, 18, 31, 51	50	59,0 (46 / 78) [a]
28	35, 39, 59, 66	500	**58,7 (44 / 75)** [b]
42	35, 39, 59, 66	50	49,3 (37 / 75) [b]
35	6, 56, 58, 68	500	**49,3 (37 / 75)** [b]
43	6, 56, 58, 68	50	41,3 (31 / 75) [b]
7	None	0	**92,6 (75 / 81)**
A	HPV 16 Cervical cancer	2000 cells	34,3 (23 / 67) (3 false positive)
B	HPV-negative cells	0	65,7 (44 /67) (6 false positive, 17 invalid)

[a] Including data set generated by type specific HPV 16 / HPV 18 PCR.

[b] Data sets known not to detect the HPV 39 or HPV 68 plasmids in this panel are considered as correct when the other HPV types in the sample are detected.

Analysis of false positive results

Table 8: Number of false positive HPV types detected per data set reported by assay used

HPV assay type	Number of data sets	No. of false positive samples per data set				
		0 samples	1 sample	2 samples	3 samples	> 3 samples
All assays	81	35	16	9	9	12
Linear Array (Roche)	15	6	5	2	2	0
CLART (Genomica)	6	1	1	1	0	3
InnoLiPA (Innogenetics)	6	1	1	0	2	2
PGMY-CHUV	7	4	0	0	3	0
In-house Type-specific PCR	7	1	3	1	0	2
In-house 16 /18 specific PCR	6	5	0	1	0	0
DNA chip (Biocore)	4	1	2	0	1	0
In-house Lineblot	4	2	1	0	0	1
In house PCR Luminex[a]	4	3	0	0	0	1
In house PCR Luminex[b]	4	2	0	1	0	1
In-house Microarray	3	0	1	1	0	1
PCR-RFLP	3	1	1	1	0	0
Microarray (Genetel)	2	2	0	0	0	0
DEIA LiPA assays	2	0	0	1	1	0
In house PCR EIA	2	0	1	0	0	1
Papillocheck Microarray	1	1	0	0	0	0
Type specific PCR (GenoID)	1	1	0	0	0	0
In-house PCR Luminex[c]	1	1	0	0	0	0
PCR Luminex (Multimetrix)	1	1	0	0	0	0
PCR EIA (GenoID)	1	1	0	0	0	0
In-house PCR sequencing	1	1	0	0	0	0

[a] L1 region (GP or modified GP) [b] E6/E7 region [c]L1 region PGMY-GP

Discussion

The panel was distributed to 61 laboratories worldwide and 85 datasets were returned for analysis from 54 laboratories. Participating laboratories were public health laboratories, research laboratories, diagnostic test manufacturers and vaccine companies. The annual number of samples analysed for HPV type per laboratory varied from 100 to 100 000 per year with approximately 40 % of the laboratories performing less than 2000 HPV typing tests per year and around 40 % between 2000 and 10 000 assays per year.

In a total of 37 data sets results had been obtained using commercially available tests. The most commonly used assay was Liner Array (Roche) that was used to generate 15 data sets. Other widely used assays were CLART (Genomica) and Inno-LiPA (Innogenetics). Forty-eight of the data sets had been obtained using a variety of in-house assays.

A proficiency of 100% detecting at least 50 IU of HPV 16 and HPV 18 in 5µl and 500 GE in 5µl of the other HPV types tested for without having more than one false positive type detected was achieved by 19 laboratories. The Linear Array assay was the commercial test with the highest number of proficient results, 6 out of 15 laboratories reported 100 % proficient data sets. Two commercially available micro-array assays (Genetel and Papillocheck) used by only two laboratories as well as several data sets generated by in-house assays based on type-specific PCR or by PCR with Luminex-based typing were 100 % proficient. The 28 data sets classified as not proficient all detected more than one false positive HPV type.

The HPV 39 plasmid used in the panel was cloned into the vector at the binding site of one of the most commonly used PCR primers (PGMY). All assays using the PGMY primer system including Liner Array and CLART could not detect the HPV 39 plasmid in the panel. As this was because of the way the plasmid was constructed all these data sets were considered as not having been evaluated for HPV39 in this study.

The plasmid used to test for HPV 68a was not full-length, but contained only the L1 gene. It was noted that Linear Array and all other PGMY-based assays that are indeed directed against L1 could not detect the HPV68a plasmid. Comparison of the sequences of HPV68a and HPV68b (ME180 isolate) showed significant difference in the sequence corresponding to the PGMY primer site. As the sequence of HPV68b (ME180 isolate) was published before the sequence of HPV68a, it appears that these systems are designed to only detect HPV68b. All data sets reporting usage of primers directed to genes other than L1 or that used the PGMY primers were considered as not testing for HPV 68 in this proficiency panel study. Accordingly only 29 data sets could be analysed for

detection of HPV 68a. Only 11 of the 29 laboratories (38 %) could detect 500 GE of HPV 68a. This was the lowest number of correct data sets among all HPV types tested.
The HPV 18 plasmid used in the panel was cloned into the vector in the E1 region. The Microarray kit Papillocheck used primers directed to the E1 region which meant that this test could not detect HPV 18 in this panel.

The Linear Array can not exclude HPV 52 when the sample is positive for HPV 33, HPV 35 or HPV 58. Some laboratories have developed a type-specific PCR for HPV 52 to test HPV33, 35 and 58-positive samples, whereas some laboratories (4/15) scored all sample with multiple infections containing HPV 52 as negative for HPV 52. This resulted in that they are regarded as not proficient for HPV 52 in this study. Four data sets generated using Linear Array was considered as not proficient since they reported 2 or even 3 false positive results. HPV 66 was detected as false positive in 7 of in total 15 false positive results submitted in the 15 data sets using Linear Array, 6 of these samples contained 500 GE of HPV 56 that was correctly identified. The detection of HPV 66 in these samples was not reported by any other assay, indicating that the false detection of HPV66 in HPV56-positive samples is a problem that is commonly seen with the Linear Array assay.

The commercial tests InnoLiPA and CLART did not generate any 100 % proficient data sets and for both assays 4 of 6 data sets were non-proficient because of too many false positives. InnoLiPa could not identify HPV 52 in 5 of 6 data sets. On the other hand HPV 52 was reported in 9 samples where it was not present. The number of false positive samples reported by InnoLiPA was between 3 and 5 for the 4 laboratories that were not proficient. Three laboratories using CLART reported 7, 17 and 21 false positive results - some with more than 3 false positives in each sample. Four laboratories using CLART could not detect HPV 56 and 45 in samples with multiple types.
There was no consistent false positivity for any specific sample for these two assays. The false positivities for these assays appeared to be essentially randomly distributed among the samples, indicating that the problem is not related to the assay kit itself.

Experience in performing assays is also critical in generating qualified results in addition to the assay per se. The in-house PGMY-CHUV assay was transferred to all WHO HPV LabNet members in 2008 as an effort to build up testing capacity and evaluate the assay. The use of this assay in this proficiency panel was requested by the HPV LabNet as a "validation" of the set-up. In this proficiency study, the PGMY-CHUV assay was used by 7 members in WHO LabNet among them

the data was 100 % proficient in one laboratory, >90% proficient in one laboratory, 3 laboratories generated data sets that were < 80 % proficient whereas 2 laboratories reported not proficient data sets (all with 3 false positive results). Only one laboratory (the originator) has been routinely using this assay before and 6 laboratories had just set up the assay according to instruction, for use in this proficiency panel test. The 2 labs that had reported false positive results had written remarks on "questionable positivity" and it appears that a more critical review of the same blots would have resulted in proficient datasets for these 2 labs. Three laboratories had problems with too low sensitivity and a more thorough training and improvement would have been required for proficiency.

The majority of data sets submitted were generated using assays that were used by 4 or fewer laboratories. This makes it difficult to draw conclusions regarding the generalisability of the performance of the assays.

Conclusions

This was the first WHO HPV DNA proficiency study that was open for participation to all laboratories worldwide, following advertisement at the WHO website. Previous HPV DNA panels have mostly focused on HPV 16 and HPV 18. This panel gave the possibility to analyse the specificity and sensitivity for different HPV typing assays to correctly identify 14 high risk HPV types and 2 low risk HPV types which are the most important in HPV surveillance and monitoring. All WHO regions were represented in testing this panel, with the majority of laboratories from the EURO, WPRO and PAHO regions.

Overall, it can be said that a majority of laboratory had a good performance of their HPV DNA typing tests. HPV 16 and HPV 18 were the types detected at lowest IU in most data sets. Only 1 and 3 datasets, respectively, could not detect 500 IU / 5 μl. In contrast, HPV 52, HPV 59 and HPV 56 could not be detected in the 500 GE / 5 μl amount by 25, 19 and 18 data sets respectively, suggesting that many surveys of circulating HPV types may underestimate the importance of these 3 types.

The 2 samples that evaluated the DNA extraction step before the HPV testing and typing had a surprisingly low amount of correct results. The sample containing 2000 cells of the cervical cancer cell line SiHa with about 1 copy of HPV16 per cell (i.e. total 2000 IU of HPV16/5ul) was detected only in about 1 third of datasets. Also, a large number of datasets (six) reported false positive results in the sample containing an HPV-negative human cell lines. This indicates that low yield in the

DNA extraction step as well as contamination in the DNA extraction step may be significant problems in HPV DNA testing and would need to be evaluated further in future proficiency panels.

The WHO HPV DNA proficiency panel 2008 shows that it is possible to perform a study comparing the sensitivity and specificity of different HPV typing assays, as well as the performance of participating laboratories. The use of such panels validating different HPV DNA tests allows standardisation and quality improvement of HPV DNA typing results worldwide which promote the comparability of data generated from different labs worldwide.

Annex 1

Call for participation:

WHO HPV LabNet Proficiency Study for evaluating HPV DNA Typing Methods

Accurate and internationally comparable HPV DNA detection and typing methodology is an essential component in the evaluation of HPV vaccines and in effective implementation and monitoring of HPV vaccination programs. The WHO Global HPV LabNet is a WHO initiative established to support the world-wide implementation of HPV vaccines through improved laboratory standardization and quality assurance of HPV testing and typing methods to promote international comparability of results. The major methods for achieving progress towards this goal are developing international biological standards, preparing and validating proficiency panels to qualify methods.

The WHO is now seeking international participation in an international WHO HPV DNA testing and typing proficiency study. Laboratories that are or will be involved in HPV surveillance and/or vaccine development are particularly welcome.
Participant laboratories will be asked to perform HPV typing using one or more of their usual assays on the 43 challenges in this first panel. This challenge is intended to evaluate assays that type HPV and is not appropriate for assays that detect HPV in general or grouped as high risk/low risk.

The challenge material will be composed of purified whole genomic plasmids of sixteen HPV types (HPV6, 11, 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, 68) in a background of human cellular DNA. The samples will be prepared to include single types and mixtures at varying copy numbers to evaluate the sensitivity and type-specificity of detection. Two samples with cell suspensions will also be provided to allow evaluation of DNA extraction methods. Laboratories that have more than one assay are encouraged to provide results on each assay they commonly use. The challenge samples will be shipped with directions for how to store the specimens, volume to test and coded forms to return results and assay description.

Participation in the proficiency study is voluntary and free of charge. The WHO HPV Global Reference Laboratory in Malmö, Sweden is organizing this study on behalf of WHO and the WHO HPV LabNet. Laboratories will be expected to return the results within **4 weeks** of specimen receipt. Data submitted will become the property of WHO, and may be analyzed for publication by the HPV LabNet either as an internal document or peer reviewed manuscript. All results will be handled in a coded anonymous fashion, with summaries grouped by method. WHO will ensure that the code linking data to originating laboratories will be kept confidential. Laboratories that provide data within the required time-frame will receive a copy of their own results and the summary data.

Any laboratory interested in participation should fill in the **Application Form** (downloadable). Requests should be sent to the address below and must be received no later than the **15th of June 2008**. Laboratories will be notified of their enrolment, the date and mode of shipment of the panel.

Contact:
Dr Joakim Dillner
WHO HPV LabNet Global Reference Laboratory
Dept. of Clinical Microbiology
University Hospital
Se-20502 Malmö
Sweden
Tel: +46 40 338126
Fax: +46 40 337312
E-mail: helena.e.persson@skane.se

Annex 2

Application for participating in
WHO HPV LabNet Proficiency Study for evaluating
HPV DNA Typing Methods

Laboratory details (Name, postal address, telephone & fax, E-mail address, etc)	
Shipping address of samples (if different from the above)	
Principal Investigator (Title and name)	
Experience of your laboratory in HPV DNA typing	
Methodology used (may be more than one)	
Annual volume of HPV typing tests	
Brief description of involvement in HPV surveillance or HPV vaccine development	

Annex 3

List of participants for WHO HPV LabNet Proficiency Study for Evaluating HPV DNA Typing methods

AMRO – Regional Office for the Americas (16 labs)

WHO Lab nr	Laboratory details
1	Institute of Tropical Medicine ¨Pedro Kourí¨. Laboratory of Molecular Biology. Department of Virology. WHO/PAHO Collaborating Center for viral diseases. WHO/PAHO Collaborating Center for Dengue study and its vector Autopista Novia del Mediodía Km 6, e/ Autopista Nacional y Carretera Central N-251, La Lisa, Ciudad de la Habana, Cuba. Telef. 2020450, Telex: CUIPK 511902, 512341, Fax: 537 215957, E mail. yudira@ipk.sld.cu
2	Laboratorio de Genetica Molecular . Instituto de Oncología y Hematología Av. Minerva . Universidad Central de Venezuela . Los Chaguaramos . 1040, Venezuela 58-212-9874230/ fax 58-212-5527910 Dra. María Correnti , PhD mcorrentip@yahoo.com
3	Laboratorio de Micorbiología Molecular Insituto de Biomedicina . San Nicolas a Providencia . Al Lado del Hospital Vargas . Caracas . 1010, Venezuela 58-212-5500133/ fax 58-212-5527910 Dra. María Eugenia Cavazza , PhD
4	Merck Research Laboratories 770 Sumneytown Pike, PO Box 4 West Point, PA, 19486 USA Tel: 215-652-3157; FAX: 215-993-3095 E-mail: frank_taddeo@merck.com
5	Dr Anu Rebbapragada Ontario Ministry of Health and Long-Term Care Ontario Public Health Laboratory Branch, Central Reference Lab Molecular Diagnostics Division 81A Resources road, Room 241 Toronto, ON, M9P 3T1, Canada Anu.rebbapragada@ontario.ca
6	Isabelle Gòrska-Flipot, PhD Laboratoire d'oncopathologie moléculaire CHUM-Hôtel-Dieu, 3840 rue St-Urbain, Montreal, QC, H2W 1T8, CANADA Tel.: 01-514-890-8000, local 14172 e-mail: Isabelle.Gorska.CHUM@ssss.gouv.qc.ca
7	National Microbiology Laboratory Public Health Agency of Canada 1015 Arlington Street Winnipeg, Manitoba, Canada R3E 3R2 Tel. 1-204-789-6022; Fax 1-204-789-2140 Email: Alberto_Severini@phac-aspc.gc.ca
8	Institution Name: Weinmann Laboratório Postal Adress: Rua Ramiro Barcelos, 910/ 5 andar, Porto Alegre, RS, Brazil Zip Code: 90035-001 Telephone: 55-51-33143850 Fax: 55-51-33117813 E-mail : vcantarelli@weinmann.com.br / dpilger@weinmann.com.br Vlademir Vicente Cantarelli, PhD

9*	Oncogenic Viruses Service National Reference Laboratory for Papillomavirus National Institute of Infectious Diseases- ANLIS "Dr. Malbran" Av. Velez Sarsfield 563 C1282AFF- Buenos Aires ARGENTINA Phone: +5411-43017428; Fax: +5411- 4302 5064/ 303 2210 mapicconi@anlis.gov.ar; mapicconi@gmail.com Dr. Maria Alejandra PICCONI
10	Roche Molecular Systems Inc. 4300 Hacienda Drive Pleasanton, California 94588, USA Carrie L. Aldrich carrie.aldrich@roche.com
11	Diagnósticos da América S/A – MOLECULAR BIOLOGY - Avenida Juruá, 434, Alphaville, Barueri. BRAZIL - CEP: 06455-010. Telephone: 55-11 4197-5345 or FAX: 55-11 4197-5341 lscarpelli@danet.com.br, aalfieri@danet.com.br, ngaburo@danet.com.br Dr: Nelson Gaburo Junior
12	Virology Area Institute of Molecular and Cell Biology of Rosario – CONICET School of Biochemistry – Rosario National University Suipacha 531 2000 Rosario, Argentina agiri@fbioyf.unr.edu.ar giri@ibr.gov.ar Adriana A Giri
13	Dr. Qinghua Feng 815 Mercer St. Department of Pathology, School of Medicine, Box 358050 Seattle, WA 98109 206-897-1583 (Tel), 206-897-1334 (Fax), qf@u.washington.edu
14*	David Swan/ Juanita Onyekwuluje Centers for Disease Control and Prevention 1600 Clifton Road MS-G41 Atlanta, GA 30333 404-639-0409, 404-639-1300 Fax:404-6393540, jjo8@cdc.gov Elizabeth R. Unger PhD, MD
15	Francois Coutlee Laboratoire De Microbiologie Hopital Notre-Dame Du Chum 1560 Sherbrooke E Montreal, Que Canada H2L 4MI Fax : 514-412-7512 labo.coutlee.chum@ssss.gouv.qc.ca
16	Dr Francisco Romero Pastrana FRP Genetica Priv Astronomia 1711 Col. Universidades Puebla Mexico Phone: + 52-222-233-2035 Email ; biologopaco@yahoo.com.mx

	EMRO–Eastern Mediterranean Region (1 lab)
17*	Institut Pasteur Tunis. Laboratoire d'Anatomie Pathologique. 13 Place Pasteur. BP 74. 1002 le Belvédère Tunis. Tel : 00 216 71 843 755 Fax : 00 216 71 791 833 Pr Ag Emna Ennaifer-Jerbi emna.jerbi@pasteur.rns.tn
	EURO –European Region (28 labs)
18	Akershus University Hospital, Center for Laboratory Medicine Section for Molecular Diagnostics 1478 Lørenskog Norway Telephone: +47 02900111 E-mail (direct): cjon@ahus.no Dr.scient Christine Monceyron Jonassen
19	Department of Cytopathology University General Hospital "ATTIKON" Rimini 1, 12462, Chaidari, Athens, Greece 00302105831452, fax-secretary 00302105831942, e-mail cytopedt@attikonhospital.gr, pkaraki@med.uoa.gr Petros Karakitsos, MD, PhD
20	Pantelis V. Constantoulakis Locus Medicus S.A Sofias Sliman 4 Athens 11526 Greece Tel : 011-3210-6981332 Fax: 011-3210-6996870 Email; locus@otenet.gr
21	Institute of Hematology and Blood Transfusion National Reference Laboratory U Nemocnice 1 CZ-128 20 Prague 2, Czech Republic Ruth.Tachezy@uhkt.cz
22	DDL Diagnostic Laboratory Fonteijnenburghlaan 7 2275 CX Voorburg The Netherlands Dr WGV Quint Linda.struijk@ddl.nl
23	Laboratory for Molecular Pathology c/o Sintef Box 124 Blindern N-0314 Oslo, Norway A Kathrine Lie Kjersti.Brenne@rikshospitalet.no

24	Multimetrix GmbH Maass-Str. 30 D-69123 Heidelberg Phone: +49-6221-752060 Fax: +49-6221-7520628 Email: dove@multimetrix.com Dr. Britta Haberpursch Scientific Director
25	GENOID Ltd. Röppentyű str. 48. Budapest, Hungary -1139 Tel:+36 1 465 0124, Fax:+36 1 465 01 27 E-mai: gybernath@genoid.hu
26*	Dr Roland Sahli Institute of Microbiology Bugnon 48 1011 Lausanne Switzerland +41-21-314 40 82 roland.sahli@chuv.ch
27	QIAGEN Hamburg GmbH Thomas Grewing, Director Koenigstr. 4a 22767 Hamburg Germany Phone +49-(0)40-41364 700 Fax +49-(0)40-41364 710 thomas.grewing@qiagen.com
28	dr. DAM. Heideman, prof.dr. PJF Snijders, prof.dr.CJLM Meijer Department of Pathology Unit of Molecular Pathology VU University Medical Center PO Box 7057 1007 MB Amsterdam, The Netherlands Telephone +31 20 444 4023 Fax +31 20 444 2964 dam.heideman@vumc.nl pjf.snijders@vumc.nl cjlm.meijer@vumc.nl
29	Department of Genetics and Pathology, Rudbeck Laboratory S-751 85 Uppsala, Sweden Phone: 46-18-4714909 (0708-993413) Fax: 46-18-4714931 Email: ulf.gyllensten@genpat.uu.se Inger Gustavsson
30	Dr Simon Beddows HPV R&D Section, Virus Reference Department Centre for Infections, Health Protection Agency 61 Colindale Avenue, London NW9 5EQ, UK simon.beddows@hpa.org.uk Tel: +44 (0) 208 327 6169 / Fax: +44 (0) 208 200 1569
31	Karolinska Universitetssjukhuset Huddinge Clinical Microbiology, Virology, F68 141 86 Stockholm phone: 0858581304 fax: 0858581305

	email: bo.johansson@karolinska.se
32	Department of Epidemiology, Mathematics & Statistics, Wolfson Institute of Preventive Medicine, Charterhouse Square, London EC1M 6BQ UK tel. +44(0)20 7014 0259 email. linda.ho@cancer.org.uk Professor Jack Cuzick
33	GENOMICA S.A.U. C/Alcarria Nº 7, Polígono Industrial de Coslada Coslada, 28823, Madrid (SPAIN) Phone & FAX: 34-916748990 & 34-916748991 E-mail: mlvillahermosa@genomica.es María Luisa Villahermosa Jaén
34	GlaxoSmithKline Biologicals Rue de l'institut 89 B-1330 Rixensart BELGIUM For : Nathalie Houard (Clinical Manager) Clinlabs / molecular biology Tel : +32 26569539 Fax : +32 26569144 e-mail : nathalie.houard@gskbio.com
35	International Agency for Research on Cancer Infections and Cancer Biology Group 150 cours Albert-Thomas – 69008 Lyon – France Tel. +33 4 72.73.81.91 – Fax +33 4 72.73.84.42 – tommasino@iarc.fr Dr Massimo TOMMASINO
36	National Institute of Health Department of Infectious Disease 1649-016 Lisboa, Portugal Angela Pista Angela.Pista@insa.min-saude.pt
37	CSPO- Scientific Institute of Tuscany Region Operative Unit: Analytical and biomolecular cytology Villa delle Rose, via Cosimo il Vecchio, 2 50139 Firenze +39-05532697852 fax +39-05532697879 f.carozzi@ispo.toscana.it Francesca Maria Carozzi, PhD
38	Statens Serum Institut Artillerivej 5 2300 Copenhagen Denmark Phone: +45 3268 8310, Fax: +45 3268 3906 Manager of Virology Laboratory Jesper Bonde HAZ@ssi.dk
39	Pr. Christine CLAVEL & Dr. Véronique DALSTEIN Laboratoire Pol Bouin, UF Biologie Cellulaire CHU Reims, Hôpital Maison Blanche, 45 rue Cognacq-Jay 51092 REIMS, France Tel : +33 326 78 82 76 (desk) / 75 52 (secretariat) cclavel@chu-reims.fr veronique.dalstein@univ-reims.fr

40	Laboratory of clinical Virology, Sahlgrenska University Hospital Guldhedsgatan 10B SE-413 46 Göteborg Sweden Elin.andersson@microbio.gu.se
41	Portuguese Institute of Oncology, Lisbon Francisco Gentil, EPE Clinical Pathology Laboratory Virology Rua Prof. Lima Basto, 1099-023 Lisbon Tel: +351 21 722 98 66 Fax: +351 21 720 04 95 Email: labvirologia@ipolisboa.min-saude.pt
42*	Joakim Dillner Department of Medical Microbiology Lund University UMAS entrance 78 205 02 Malmö, Sweden Tel: +46 40 338126 Email: Joakim.Dillner@med.lu.se
43	Ola Forslund Clinical Microbiology Malmö University hospital entrance 78 205 02 Malmö, Sweden Email: Ola.Forslund@med.lu.se
44	Scottish HPV Reference Laboratory (SHPVRL) Specialist Virology Centre Dept of Laboratory medicine Royal Infirmary of Edinburgh 51 Little France Crescent Edinburgh EH16 4SA, UK E-mail: Kate.Cuschieri@luht.scot.nhs.uk
45	Michael Pawlita Genome Changes and Carcinogenesis (F020) Im Neuenheimer Feld 242 D-691 20 Heidelberg, Germany M.Pawlita@dkfz.de
	SEARO –South-East Asia Region (2 labs)
46*	National Cancer Institute 268/1 Rama 6 Rd. Ratchatavee Bangkok 10400 THAILAND Tel: 66 2354 7025 Fax: 66 2354 7037 Ms.Sukhon Sukvirach sukvira@health.moph.go.th
47*	Dr Alok Chandra Bharti Division of Molecular Oncology Institute of Cytology and Preventive Oncology (ICMR) I-7, Sector 39 NoIDA, Ditt Gautam Buddha Nagar, UP 201 301, India Phone: +91-120-2579471 Fax: +91-120-2579473 Email: bhartiac@icmr.org.in
	WPRO –Western Pacific Region (13 labs)

48	DNA Laboratories Sdn Bhd B1-4 Blok Plasma UKM-MTDC Technology Centre, 43650 Bangi, Selangor, Malaysia Tel: +603-8925-2700, Fax: : +603-8925-4700, yw.wong@dna-laboratories.com WONG Yong Wee
49	Kyung Ryul Lee Seoul Clinical Laboratories & Seoul Medical Science Institute 714 Dongbinggo-Dong Youngsan-Gu Seoul 140-809 South Korea dkrlee@scllab.co.kr
50	Diagnostics Division, LG Life Sciences, Ltd. 104-1 Munji-dong, Yuseong-gu, Daejeon, 305-380, Korea TEL: 82-42-866-5903, FEX: 82-42-866-2496 E-mail: yspark@lgls.com Park, Young Suk
51	Genetel Pharmaceuticals (Shenzhen) Co., Ltd. 2-310 Bio-Incubator, Gao Xin C., 1st Avenue, Hi-Tech Industrial Park, Shenzhen, Guangdong, 518057, China E-mail: grbai@genetel.com.cn Dr. Bai GR
52	Division of AIDS, Korea CDC 94 Tongillo, Eunpyung, Seoul, 122-701, Republic of Korea Tel; 82-2-380-2151, Fax; 82-2-359-1397 E-mail; sungskim@nih.go.kr, sungskimkiss@empal.co.kr Sung-Soon Kim, Director Division of AIDS
53	PathWest Laboratory Medicine QE II Medical Centre Hospital Ave, Nedlands, Western Australia, 6009 Tracy.perris@health.wa.gov.au
54	Department of Microbiology, 1/F Clinical Science Building, Prince of Wales Hospital, Shatin, New Territories, Hong Kong SAR, China Fax: (852) 2647 3227 Tel: (852) 2632 3333 E-mail: paulkschan@cuhk.edu.hk Prof. Paul KS Chan
55*	Center for Pathogen Genomics, National Institute of Infectious Diseases, 4-7-1 Gakuen, Musashi-Murayama, Tokyo 208-0011, Japan Phone: [81]-42-561-0771 ext 371 Fax: [81]-42-567-5632 e-mail: ikuki@nih.go.jp Iwao Kukimoto, Ph.D., Lab Head
56	Applied Research Centre of Genomic Technology (ACGT) Department of Biology and Chemistry, City University of Hong Kong, 83 Tat Chee Avenue, Kowloon Tong, Hong Kong SAR, PRC China Tel: (852) 2788 7797; Fax: (852) 2788 7406; E-mail: bhmyang@cityu.edu.hk Prof. Mengsu Yang, Michael
57	Name: BioCore Institute Address: #605 ACE Technotower V, 197-22, Guro 3-dong, Guro-gu, Seoul, Korea

	Tel: +82-2-839-9815 Fax: +82-2-863-1489 Email: dnachip@bio-core.com Dr. Jong-Man Kim
58	HPV Laboratory Dept of Cancer Epidemiology, CICAMS 17 South Panjiayuan Lane, Chaoyang District Beijing 100021 China Prof You-lin Qiao qiaoy@cicams.ac.cn Tel 86-10-8778 8489 Fax 86-10-6771 3648
59*	The Royal Woman's Hospital Department of Molecular Microbiology, level 6 132 Grattan Stret Carlton Victoria 3052 Australia Sepher Tabrizi Phone: +613-9344-2050 Fax: +613-9344-2713 Email: sepehr.tabrizi@rch.org.au
60	Neodin medical institute Korea Food and Drug Administration 2-3, Yongdap-dong ,Seongdong-gu, Seoul, Korea 133-847 Telephone No : 82-2-2244-6500(300) Fax No : 82-2-2212-1307 E-mail : lshkim@neodin.com Keum.choi@kdfa.go.kr
	AFRO- African Region (1 lab)
61*	Professor Anna-Lise Williamson, Bruce Allan Room S3.01 Institute of Infectious Disease and Molecular Medicine Faculty of Health Sciences University of Cape Town, Anzio Road Observatory, Cape Town, South Africa Phone: +21-4066124 Bruce.Allan@uct.ac.za Anna-Lise.Williamson@uct.ac.za

* : WHO HPV LabNet members