WHO HPV LabNet

Report on HPV DNA Proficiency Panel 2010

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Abbreviations

AFRO	African Regional Office
EMRO	Eastern Mediterranean Regional Office
EQUALIS	External Quality Assurance in Laboratory Medicine In Sweden
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
PP	Proficiency Panel
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 2010

Time for Distribution June - August 2010

1. 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 programmes. 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 evaluating HPV vaccines, for HPV surveillance and monitoring of HPV vaccination programmes (*http://www.who.int/biologicals/vaccines/hpv/en/index.html*). A major method for achieving progress towards this goal is development, preparation and validation of proficiency panels (PP) to qualify methods and laboratories.

Call for participation in this proficiency study was advertised on WHO website and sent to WHO Regional Offices in April 2010 for broad interest (Annex 1, 2)

2. Aims

The aims of this panel are:

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

3. Methods

3.1 Panel composition

Complete genomes of HPV cloned into plasmid vectors had been provided to the WHO HPV LabNet Global Reference Laboratory (GRL) at the University Hospital in Malmö Sweden by the respective proprietors with written approval for use in this WHO PP. All samples were purified plasmids diluted in a background of human placental DNA ((Sigma-Aldrich no 7011) at a concentration of 10 ng/µl). The HPV types included were: 6, 11, 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, 68a (HPV 68 prototype) and 68b (ME 180 isolate).

Three additional samples, A, B and C were cell lines used as controls for the DNA extraction step in the testing. The composition of the panel is shown in Table 1.

Table 1: WHO HPV PP composition by randomised sample ID

WHO HPV LabNet DNA proficiency panel 2010

Randomised Panel ID	HPV types	HPV genome equivalents (GE) or international unit (IU) (for HPV 16, 18) per 5 µl
5	16	50
23	16	5
8	18	50
29	18	5
13	6	500
33	6	50
21	11	500
37	11	50
2	31	500
41	31	50
17	33	500
25	33	50
9	35	500
28	35	50
42	39	500
18	39	50
4	45	500
34	45	50
43	51	500
12	51	50
19	52	500
39	52	50
7	56	500
24	56	50
14	58	500
30	58	50
38	59	500
1	59	50
36	66	500
15	66	50
35	68a	500
20	68a	50
10	68b	500
31	68b	50
3	6, 16, 18, 51	500
26	6, 16, 18, 51	50
22	11, 16, 31, 33, 58	500
11	11, 16, 31, 33, 58	50
16	39, 45, 52, 56, 68a	500
32	39, 45, 52, 56, 68a	50
6	35, 59, 66, 68b	500
40	35, 59, 66, 68b	50
27	None	0
C	HPV 16; SiHa Cervical cancer cells	2500
A	HPV 16; SiHa Cervical cancer cells	25
B	HPV-negative C33A cells	0

3.2 Validation of the PP

The PP was pre-tested at GRL Sweden using a modified GP5+/6+ 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, 68b, 69, 70, 73, 81, 82, 86, 89, 90 and 91.

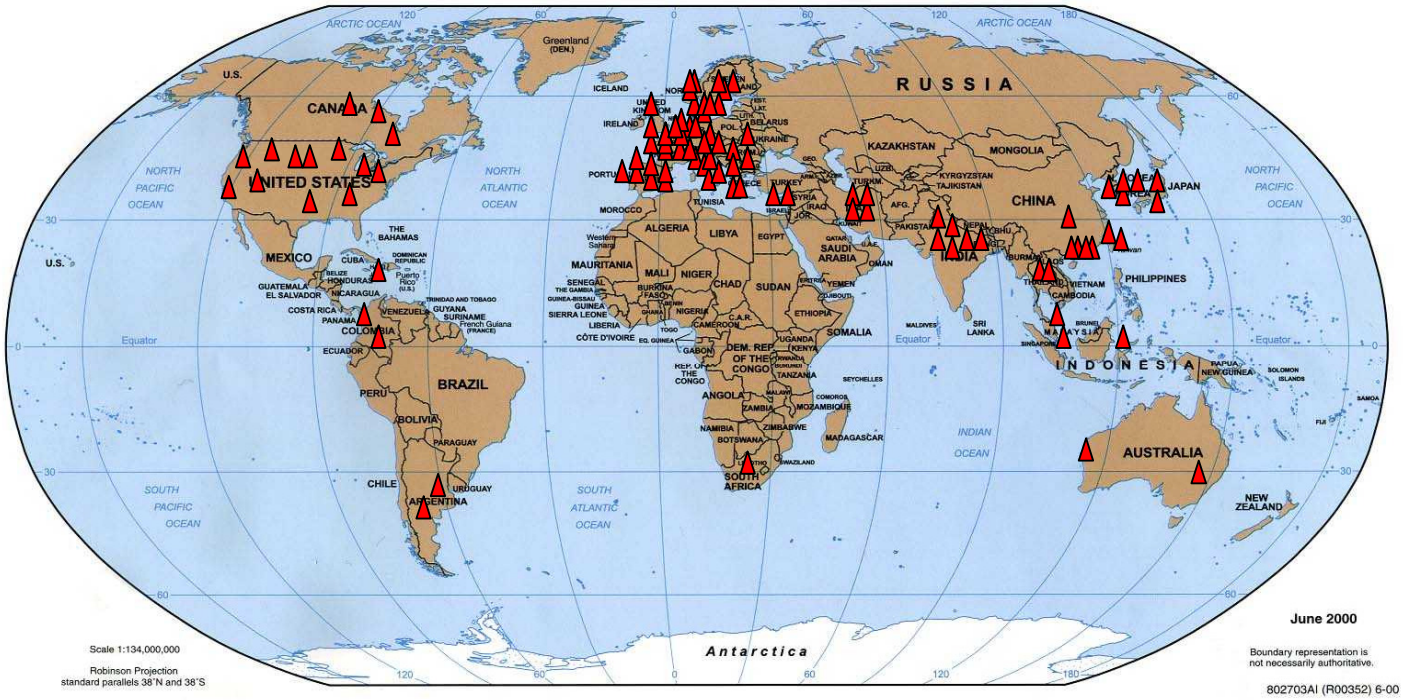
The PP was pre-tested by one external laboratory before release, namely the German Cancer Research Center (DKFZ) in Heidelberg that used the BSGP5+/6+ PCR/MPG assay (a modification of GP5+/6+-PCR followed by Luminex-based typing) for HPV types 6, 11, 16, 18, 26, 30, 31, 33, 35, 39, 42, 43, 44, 45, 51, 52, 53, 56, 58, 59, 66, 67, 68b, 68a, 69, 70, 73 and 82.

3.3 Distribution of the PP

After validation, the PP was compiled in May 2010 and distributed to 105 laboratories throughout six WHO regions in June and August 2010, following the call for participation and requests received from the laboratories. There was no charge for laboratories to participate. Shipments were also paid by the WHO HPV LabNet. The number (n) of laboratories included in the distribution per WHO Region shown in Figure 1 are: AFRO (No. of labs = 1), EMRO (n = 5), EURO (n = 49), SEARO (n = 9), WPRO (n = 18) and PAHO (n = 23). One hundred thirty two datasets with results were returned before the deadline from 98 laboratories. 73 laboratories submitted a data set from one assay only, 17 laboratories submitted data sets from 2 different assays, 7 laboratories submitted data sets from 3 assays and one laboratory submitted data sets from 4 different assays.

In 2008 the WHO HPV DNA PP was prepared, administrated and distributed by the GRL in Sweden. Due to resource limitation at GRL Sweden, this year the GRL Sweden prepared the materials, but subcontracted the administration and distribution of the PP to EQUALIS (*http://www.equalis.se/?strLanguage=eng*), a non-profit company active in the field of external quality assurance that handled all the logistics and distribution of the panel. The format with one scientific laboratory that sets the scientific agenda and prepares the materials and a professional company that administrates the distribution has been shown successful and practical also in other proficiency panels/external quality assurance schemes. The model used for the 2010 WHO HPV DNA proficiency panel worked well and is considered to be a possible mode of operation of a sustainable long term activity with global distribution of an HPV DNA typing proficiency panel every year.

Figure 1: Global distribution of laboratories that submitted results for HPV DNA PP.



3.3 Data analysis

Results analysed in this report include all results returned prior to the 1st of November 2010. Data was compiled by EQUALIS and transferred to GRL Sweden for analyses of the results.

Each data set submitted was designated a number from 1 to 132. The data were analysed by region of the laboratory, by assay used and by HPV type, respectively.

From the data sets submitted, it was noted that participating laboratories used a range of commercial assays as well as in-house assays (Table 2). The proportion of correct HPV typing results, reported by the laboratory, was analyzed as data sets by laboratory and according to assay used.

A data set was considered proficient when it detected 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. For proficiency, it was also required that not more than one false positive type was detected. This corresponds to a specificity of 97%.

4. Results

Ninety-eight of 105 participating laboratories submitted 132 data sets. Four data sets were generated using assays that did either did not discriminate specific HPV types or reported results as HPV 16,

18 and "other" High Risk HPV types. These data sets and 10 data sets from type-specific HPV 16 / 18 PCR were not included in the overall type-specific analyses presented in this report.

Detection of 5 IU of HPV16 and HPV18 and 50 GE of the other HPV types was not required for proficiency - these samples are intended for training and for providing information on whether the test just barely met the requirements or whether it exceeds them.

Each data set submitted by each individual laboratory was analysed and a feedback letter was sent to the participating laboratory in November 2010.

4.1 Results by assays used

4.1.1 Commercial assays

A total of 73 data sets were obtained using commercially available tests. The most commonly used assay was the Linear Array (Roche) HPV genotyping assay that was used in 17 laboratories. Other widely used assays were the clinical array test Inno-LiPA (Innogenetics) used by 12 laboratories and CLART (Genomica) used by 8 laboratories (Table 2).

4.1.2 In-house assays

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

4.2 Results analysed by assay

4.2.1 Assay Details

The different assays used for testing and typing of HPV as well as the number of submitted data sets and different part of the HPV genome targeted by each assay is shown in Table 2. The distribution of different assays in different WHO regions is shown in Figure 2.

Table 2: Assays used for testing and typing of HPV.

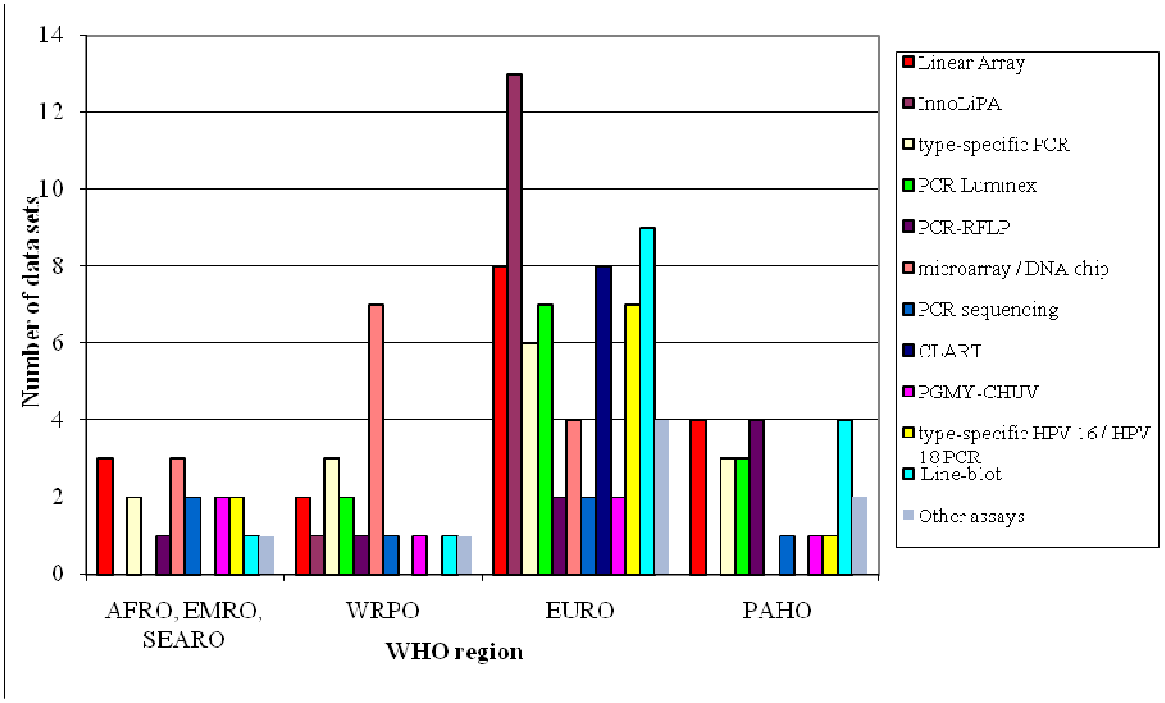
HPV assay type	Number of data sets	HPV region targeted (primers)
All assays	**132**	**L1/L2/E1/E2/E4/E6/E7**
Linear Array (Roche)	17	L1 (PGMY)
InnoLiPA (Innogenetics)	12	L1 (SPF10)
In-house Lineblot	10	L1 (GP /PGMY)
CLART HPV 2 / 3 (Genomica)	8	L1 (PGMY)
In-house realtime PCR	8	L1/E1/E4/E6/E7
In-house Type-specific PCR	7	L1/E6/E7
In-house PCR-RFLP	7	L1/E6/E7
In- house PCR Luminex	7	L1 (GP/MGP/BSGP/PGMY)
In-house PGMY-CHUV	6	L1 (PGMY)
In-house PCR sequencing	6	L1 / E6
16 /18 specific PCR (TS Lab.bio)	4	L1/E6/E7
Papillocheck Microarray	4	E1
PCR Luminex (Multimetrix)	3	L1 (GP)
In-house 16/18 specific PCR	3	E6 E7

Digene HPV genotyping LQ test (QIAGEN)	3	L1 (GP)
Digene HPV genotyping RH test (QIAGEN)	2	L1 (GP)
Hybribio microarray	2	L1
DEIA LiPA assays (Lab.Bio)	2	L1 (SPF 10)
In- house Dot-blot	2	L1
LCD array (Chipron)	2	L1 (PGMY)
EASYChip (King Car)	2	L1
Cobas 4800 (Roche)	2	L1
Other Commercial assays[a)]	10	L1
Other In-house assays [b)]	3	L1/L2/E1/E2/E6

a) Other commercial assays include one laboratory using each of; Medical Device Microarray, PnE HPV genotyping Luminex, Ampliquality reverse hybridization, Panagene microarray, PANArray TM HPV, GenoFlow HPV array kit, MolGENTIX multiplex-fluorescent PCR, Hybridcapture 2, High risk screen TM Sacace, GENOSERCH HPV 31 Luminex

b) Other In-house assays include one laboratory using each of; In-house PCR-EIA, In-house multiplex PCR gel-analysis, In-house mass-spectrometry

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



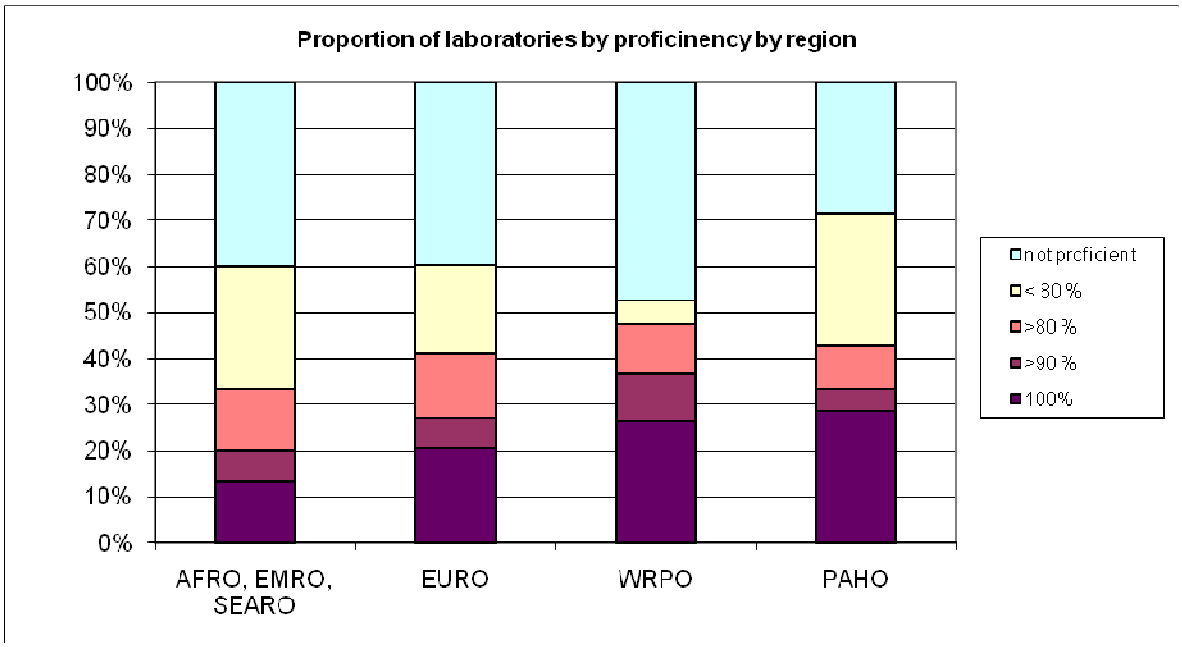
4.2.2 Results achieved by participating laboratories

According to the criteria described in 3.3, thirty-six (27 %) data sets out of the 131 data sets that typed for at least one HPV type were 100 % proficient for the types claimed to be detected by the test. Of these, 7 data sets correctly identified the content of all samples, including the samples with copy number amounts that were lower than required for proficiency. Tests that did not type for all

the types in the panel could still be 100% proficient, as the denominator was the number of types claimed to be detected by the test (not the number of types included in the panel).

The proportion of laboratory proficiency grouped by WHO region is shown in Figure 3 and in Table 3.The percent proficiency of detecting HPV types grouped by assay used for testing is shown in Table 4.

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



The figure includes only datasets that typed more than two HPV types (118 data-sets). Results from tests typing only for HPV 16 and HPV 18 are excluded in this figure.

Table 3: Proportion of data sets submitted by WHO region with ≥90% proficient HPV typing results when typing for more than two HPV types.

Region (data sets)	Proportion of laboratories with 100% correct typing	Proportion of laboratories with ≥90% correct typing
EURO (63)	21 %	27 %
AFRO, EMRO, SEARO (15)	13 %	20 %
PAHO (21)	29 %	33 %
WPRO (19)	26 %	37 %

Table 4: Proficiency of detecting HPV types 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	**118**	**26**	**8**	**15**	**23**	**46**
Linear Array (Roche)	17	8	1	1	1	6
InnoLiPA (Innogenetics)	12	0	1	1	1	9
In-house Lineblot	10	1	0	1	4	4
CLART HPV 2 / 3 (Genomica)	8	0	0	2	2	4
In-house Type-specific PCR	6	0	0	1	1	4
In-house realtime PCR	5	0	1	0	1	3
In-house PCR-RFLP	7	0	0	1	4	2
In- house PCR Luminex	7	3	0	1	1	2
In-house PGMY-CHUV	6	4	1	0	1	0
In-house PCR sequencing	6	0	0	0	5	1
Papillocheck Microarray	4	4	0	0	0	0
PCR Luminex (Multimetrix)	3	0	0	3	0	0
Digene HPV genotyping LQ test (QIAGEN)	3	0	0	0	2	1
Digene HPV genotyping RH test (QIAGEN)	2	0	1	1	0	0
Hybribio microarray	2	0	0	0	0	2
DEIA LiPA assays (Lab.Bio)	2	0	0	0	0	2
In- house Dot-Blot	2	1	0	0	0	1
LCD array (Chipron)	2	0	0	2	0	0
EASYChip (King Car)	2	2	0	0	0	0
Other Commercial assays [a)]	9	1	3	1	0	4
Other In-house assays [b)]	3	2	0	0	0	1

*Table restricted to assays testing for more than two types.

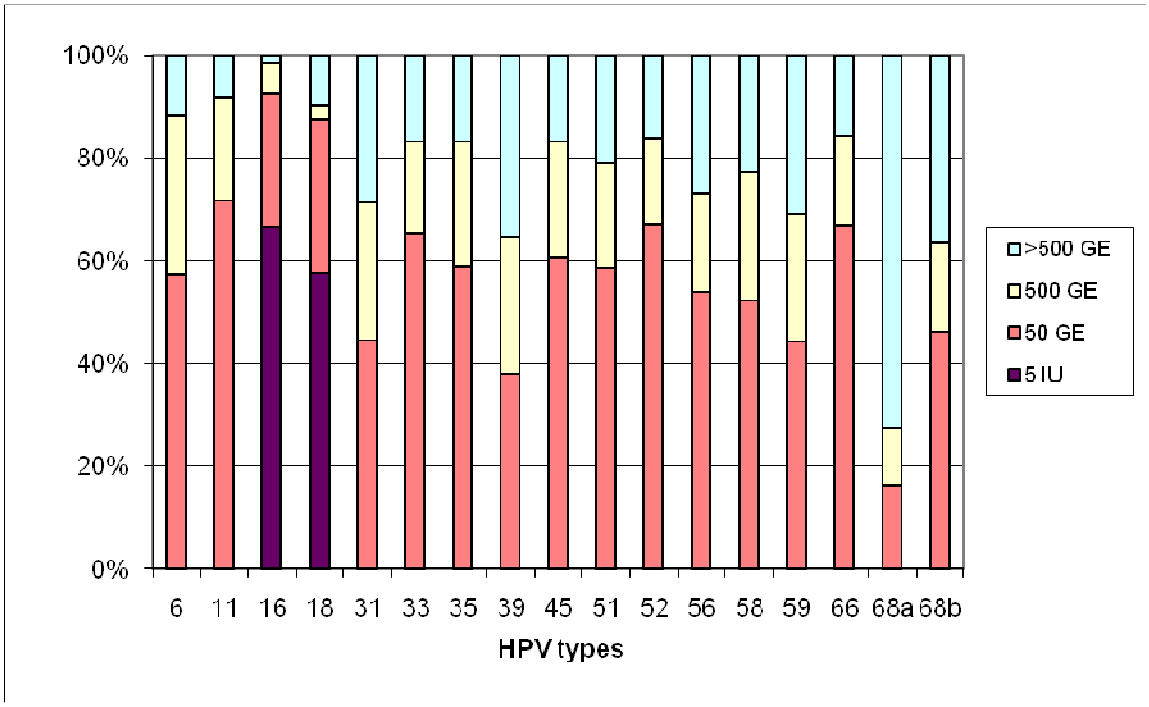
a) Other commercial assays include one laboratory using each of; Medical Device Microarray, PnE HPV genotyping Luminex, Ampliquality reverse hybridization, Panagene microarray, PANArray TM HPV, GenoFlow HPV array kit, MolGENTIX multiplex-fluorescent PCR, Hybridcapture 2, High risk screen TM Sacace, GENOSERCH HPV 31 Luminex

b) Other In-house assays include one laboratory using each of; In-house PCR EIA, In-house multiplex PCR gel-analysis, In-house mass-spectrometry

4.2.3 HPV types detected

The sensitivity to detect each HPV type included in the panel, as percent of laboratories detecting the different copy number (IU / GE) of the HPV types is shown in Figure 4. This data includes the laboratories with multiple false positives. In table 5 and 6 the lowest detected GE / IU grouped by assay used are shown.

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



Assays with input volume of 50 µl were classified as testing sample with 10-fold higher IU/GE content compared to that of 5 µl in put. Input with 10 or 15 µl was classified as same IU/GE content as compared to input with 5 µl. Thirteen laboratories used 50 µl input volume in Linear Array.

Table 5: HPV GE or IU detected per 5 µl in both single and multiple infections in commercially available assays used to test the HPV PP, lowest detected GE / IU indicated.

HPV type	HPV IU /GE	Linear Array	InnoLiPA	CLART (HPV 2)	Digene genotyping LQ	Papillocheck Microarray	Luminex (Multimetrix)	Digene genotyping RH	Hybribio Microarray	DEIA-LiPA (Lab.Bio)	EASY chip (King Car)	LCD array (chipron)	Other Commercial [a]
16	5	3 / 17	10 / 12	8 / 8	2 / 3	4 / 4	3 / 3	2 / 2		2 / 2	2 / 2	2 / 2	7 / 9
16	50	16 / 17	12 / 12		3 / 3								7 / 9
16	500	17 / 17							1 / 2				9 / 9
18	5	3 / 17	9 / 12	5 / 8	3 / 3	nt[b]	3 / 3	2 / 2		2 / 2	2 / 2	2 / 2	6 / 9
18	50	17 / 17	12 / 12	5 / 8									6 / 9
18	500			8 / 8					1 / 2				9 / 9
6	50	4 / 17	11 / 12	6 / 8		4 / 4	2 / 3		1 / 2	2 / 2	2 / 2	2 / 2	8 / 8
6	500	17 / 17	12 / 12	8 / 8	nt		3 / 3	nt	2 / 2				
11	50	4 / 17	12 / 12	8 / 8		4 / 4	3 / 3		2 / 2	2 / 2	2 / 2	2 / 2	6 / 8
11	500	16 / 17			nt			nt					8 / 8
31	50	4 / 17	12 / 12	8 / 8	1 / 3	1 / 4		2 / 2		2 / 2	2 / 2		4 / 9
31	500	15 / 17			3 / 3	4 / 4			1 / 2				
33	50	4 / 17	10 / 12	8 / 8	3 / 3	4 / 4	3 / 3	2 / 2	2 / 2	2 / 2	2 / 2	2 / 2	7 / 8
33	500	16 / 17											8 / 8
35	50	4 / 17	12 / 12	8 / 8	3 / 3		3 / 3	2 / 2		2 / 2	2 / 2	2 / 2	6 / 9
35	500	14 / 17				4 / 4							9 / 9
39	50	4 / 17	9 / 12			4 / 4	3 / 3	1 / 2		2 / 2	2 / 2	2 / 2	5 / 9
39	500	15 / 17	11 / 12	1 / 8									7 / 9
45	50	4 / 17	7 / 12	1 / 8	3 / 3	3 / 4	3 / 3	2 / 2		2 / 2	2 / 2	2 / 2	9 / 9
45	500	17 / 17	12 / 12	4 / 8		4 / 4			1 / 2				
51	50	4 / 17	11 / 12	8 / 8	1 / 3	4 / 4	3 / 3	1 / 2		2 / 2	2 / 2	2 / 2	8 / 9
51	500	15 / 17	12 / 12		3 / 3			2 / 2					
52	50	4 / 17	11 / 12	8 / 8		4 / 4	3 / 3		2 / 2	2 / 2	2 / 2	2 / 2	9 / 9
52	500	17 / 17	12 / 12		1 / 3			2 / 2					
56	50	4 / 17	10 / 12		3 / 3	4 / 4	3 / 3	2 / 2		2 / 2	2 / 2		7 / 9
56	500	15 / 17	12 / 12	3 / 8									
58	50	4 / 17	1 / 12	8 / 8	1 / 3	3 / 4	1 / 3	2 / 2		2 / 2	2 / 2	2 / 2	7 / 9
58	500	17 / 17	5 / 12		3 / 3		2 / 3		1 / 2				9 / 9
59	50	3 / 17	1 / 12	7 / 8	1 / 3	4 / 4	3 / 3	1 / 2		2 / 2	2 / 2	2 / 2	7 / 9
59	500	16 / 17	2 / 12		2 / 3			2 / 2	2 / 2				8 / 9
66	50	4 / 17	11 / 12	8 / 8	3 / 3	3 / 4	3 / 3	2 / 2		2 / 2	2 / 2	2 / 2	6 / 7
66	500	14 / 17				4 / 4			2 / 2				7 / 7
68a	50		1 / 12							2 / 2			2 / 6
68a	500	nt	4 / 12	nt		nt			nt		nt	nt	

68b	50	4 / 17	11 / 12	4 / 4	3 / 3	1 / 2	2 / 2	2 / 2	2 / 2	2 / 2	7 / 9	
68b	500	14 / 17	11 / 12									

a) Other commercial assays include one laboratory using each of; Medical Device Microarray, PnE HPV genotyping Luminex, Ampliquality reverse hybridization, Panagene microarray, PANArray TM HPV, GenoFlow HPV array kit, MolGENTIX multiplex-fluorescent PCR, High risk screen TM Sacace, GENOSERCH HPV 31 Luminex

b) Nt: Not tested

Table 6: HPV GE or IU detected per 5 µl in both single and multiple infections in in-house assays used to test the HPV PP, lowest detected GE / IU indicated.

HPV type	HPV IU /GE	All Assays (%)	Lineblot	PCR -RFLP	Luminex	PGMY-CHUV	Type-specific PCR	Realtime PCR	PCR sequencing	Dot-Blot	Other In-house[a)]
16	5	85 / 127 (67)	3 / 10	2 / 7	7 / 7	4 / 6	4 / 6	4 / 5	3 / 5	1 / 2	3 / 3
16	50	118 / 127 (93)	9 / 10	5 / 7		5 / 6		5 / 5	4 / 6	2 / 2	
16	500	125 / 127 (98)	10 / 10	7 / 7		6 / 6	5 / 6		5 / 6		
18	5	72 / 119 (60)	2 / 10	1 / 7	5 / 7	4 / 6	3 / 6	3 / 5	3 / 5	2 / 2	2 / 3
18	50	106 / 119 (89)	7 / 10	3 / 7	7 / 7	5 / 6	4 / 6	4 / 5	4 / 6		
18	500	108 / 119 (91)	8 / 10			6 / 6	5 / 6	5 / 5			
6	50	64 / 110 (58)	2 / 10	3 / 7	2 / 6	5 / 6	4 / 5	2 / 4	2 / 6		1 / 3
6	500	97 / 110 (88)	8 / 10	6 / 7	4 / 6	6 / 6	4 / 5	3 / 4	3 / 6	1 / 2	3 / 3
11	50	79 / 109 (72)	6 / 10	4 / 7	6 / 6	5 / 6	4 / 5	2 / 4	1 / 6	2 / 2	3 / 3
11	500	100 / 109 (92)	8 / 10	7 / 7		6 / 6	4 / 5	3 / 4	2 / 6		
31	50	52 / 118 (44)	3 / 10		3 / 7	3 / 6	2 / 6	4 / 5			2 / 3
31	500	84 / 118 (71)	5 / 10	3 / 7	5 / 7	5 / 6	4 / 6		1 / 6	1 / 2	3 / 3
33	50	76 / 117 (65)	4 / 10	2 / 7	4 / 7	5 / 6	3 / 6	5 / 5		2 / 2	3 / 3
33	500	97 / 117 (83)	7 / 10	3 / 7	5 / 7		4 / 6		2 / 6		
35	50	70 / 118 (59)	5 / 10	1 / 7	5 / 7	5 / 6	3 / 6	2 / 5	1 / 6	1 / 2	3 / 3
35	500	98 / 118 (83)	8 / 10	2 / 7	7 / 7		4 / 6	4 / 5	3 / 6	2 / 2	
39	50	45 / 118 (38)	3 / 10		3 / 7	3 / 6	1 / 6	4 / 5		1 / 2	2 / 3
39	500	77 / 118 (65)	6 / 10		5 / 7	6 / 6	3 / 6	5 / 5			3 / 3
45	50	71 / 118 (60)	7 / 10	2 / 7	6 / 7	5 / 6	3 / 6	5 / 5	2 / 6	2 / 2	2 / 3
45	500	98 / 118 (83)	9 / 10	2 / 7	7 / 7				3 / 6		
51	50	69 / 117 (59)	3 / 9	1 / 7	5 / 7	5 / 6	3 / 6	4 / 5			2 / 3
51	500	92 / 117 (79)	5 / 9	2 / 7	6 / 7	6 / 6	4 / 6	5 / 5		1 / 2	3 / 3
52	50	79 / 117 (67)	4 / 9	3 / 7	7 / 7	5 / 6	3 / 6	5 / 5	1 / 6	1 / 2	3 / 3
52	500	98 / 117 (84)	7 /9	3 / 7							
56	50	63 / 118 (53)	5 / 10	1 / 7	6 / 7	3 / 6	3 / 6	4 / 5		2 / 2	3 / 3
56	500	86 / 118 (73)	8 / 10		7 / 7	4 / 6					
58	50	62 / 118 (52)	4 / 10	4 / 7	6 / 7	5 / 6	3 / 6	3 / 5		1 / 2	2 / 3

58	500	91 / 118 (77)	7 / 10	5 / 7	7 / 7			4 / 5			3 / 3
59	50	52 / 117 (44)	3 / 9	1 / 7	5 / 7	4 / 6	2 / 6	1 / 5		1 / 2	1 / 3
59	500	80 / 117 (68)	6 / 9	2 / 7	6 / 7	5 / 6	3 / 6	3 / 5			2 / 3
66	50	75 / 113 (66)	4 / 9	3 / 7	6 / 7	5 / 6	3 / 5		3 / 6	1 / 2	3 / 3
66	500	95 / 113 (84)	7 / 9	6 / 7	7 / 7		3 / 5		4 / 6		
68a	50	10 / 61 (16)		1 / 5	3 / 6					1 / 1	
68a	500	17 / 61 (28)	2 / 8		4 / 6	nt[b)]	nt	nt			1 / 1
68b	50	53 / 114 (46)	3 / 10	1 / 7	3 / 7	5 / 6	2 / 5	1 / 3			1 / 3
68b	500	73 / 114 (64)	5 / 10	2 / 7	6 / 7					1 / 2	3 / 3

a) Other In-house assays include one laboratory using each of; In-house PCR EIA, In-house multiplex PCR gel-analysis, In-house Mass-spectrometry
b) Nt: Not tested

4.3 Results by sample number

The numbers of laboratories testing for and reporting correct HPV type, with no false positive HPV type detected are shown in table 7. The number of dataset without false positive results differs for each sample.

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

Randomised Panel ID	HPV types	HPV genome equivalents per 5 µl	Percent correct data sets (N)
5	16	50	**95.0 (114 / 120)**
23	16	5	77.5 (93 / 120)
8	18	50	**87.0 (94 / 108)**
29	18	5	71.9 (82 / 114)
13	6	500	**96.1 (99 / 103)**
33	6	50	69.5 (73 / 105)
21	11	500	**98.1 (102 / 104)**
37	11	50	77.1 (81 / 105)
2	31	500	**87.4 (97 / 111)**
41	31	50	59.3 (67 / 113)
17	33	500	**97.2 (104 / 107)**
25	33	50	74.5 (82 / 110)
9	35	500	**89.1 (98 / 110)**
28	35	50	67.2 (76 / 113)
42	39	500	**76.2 (80 / 105)**
18	39	50	53.7 (58 / 108)
4	45	500	**85.4 (94 / 110)**
34	45	50	67.6 (75 / 111)
43	51	500	**85.7 (96 / 112)**
12	51	50	66.7 (74 / 111)
19	52	500	**87.4 (97 / 111)**
39	52	50	73.4 (83 / 113)
7	56	500	**87.2 (95 / 109)**
24	56	50	61.8 (68 / 110)
14	58	500	**95.4 (105 / 110)**
30	58	50	66.7 (70 / 105)
38	59	500	**85.7 (96 / 112)**
1	59	50	56.5 (61 / 108)
36	66	500	**95.3 (102 / 107)**

15	66	50	78.1 (82 / 105)
35	68a	500	**36.8 (21 / 57)**
20	68a	50	21.8 (12 / 55)
10	68b	500	**75.0 (78 / 104)**
31	68b	50	57.1 (64 / 112)
3	6, 16, 18, 51	500	**78.3 (101 / 129)** [a]
26	6, 16, 18, 51	50	69.0 (89 / 129) [a]
22	11, 16, 31, 33, 58	500	**57.9 (73 / 126)** [a]
11	11, 16, 31, 33, 58	50	46.1 (59 / 128) [a]
16	39, 45, 52, 56, 68a	500	**44.5 (53 / 119)** [b]
32	39, 45, 52, 56, 68a	50	35.0 (41 / 117) [b]
6	35, 59, 66, 68b	500	**50.0 (59 / 118)**
40	35, 59, 66, 68b	50	32.2 (38 / 118)
27	None	0	**97.0 (128 / 132)**
A	HPV 16 Cervical cancer	25	61.1 (77 / 126) (5 false positive)
B	HPV-negative cells	0	83.3 (105 /126) (12 false positive)
C	HPV 16 Cervical cancer	2500	83.3 (105 / 126) (4 false positive)

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

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

4.4 Analysis of false positive results

To be considered as proficient for HPV testing in this study only one false positive result was accepted. The number of false positive samples by assay used is shown in Table 8.

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	**132**	**70**	**12**	**19**	**4**	**27**
Linear Array (Roche)	17	10	1	2	1	3
InnoLiPA (Innogenetics)	12	2	1	5	0	4
In-house Lineblot	10	4	2	1	1	2
CLART (Genomica)	8	3	1	2	1	1
In-house RFLP	7	4	1	0	1	1
In house PCR Luminex	7	5	0	1	0	1
In-house realtime PCR	6	2	1	1	0	2
PGMY-CHUV	6	6	0	0	0	0
In-house type-specific PCR	6	2	0	2	0	2
In-house PCR sequencing	6	3	2	0	0	1
In-house 16 /18 specific PCR	6	4	1	1	0	0
16 /18 specific PCR (TS Lab.Bio)	4	4	0	0	0	0
Papillocheck Microarray	4	4	0	0	0	0
PCR Luminex (Multimetrix)	3	3	0	0	0	0

Digene HPV genotyping LQ test (QIAGEN)	3	2	0	1	0	0
Digene HPV genotyping RH test (QIAGEN)	2	2	0	0	0	0
Hybribio Microarray	2	0	0	1	0	1
DEIA LiPA assays (Lab.Bio)	2	0	0	0	0	2
In house Dot-blot	2	0	1	0	0	1
LCD array (Chipron)	2	2	0	0	0	0
EASYChip (King Car)	2	2	0	0	0	0
Cobas 4800 (Roche)	2	0	0	1	0	1
Other Commercial assays [a)]	10	5	1	1	0	3
Other In-house assays [b)]	3	2	0	0	0	1

a) Other commercial assays include one laboratory using each of; Medical Device Microarray, PnE HPV genotyping Luminex, Ampliquality reverse hybridization, Panagene microarray, PANArray TM HPV, GenoFlow HPV array kit, MolGENTIX multiplex-fluorescent PCR, Hybridcapture 2, High risk screen TM Sacace, GENOSERCH HPV 31 Luminex

b) Other In-house assays include one laboratory using each of; In-house PCR-EIA, In-house multiplex PCR gel-analysis, In-house mass-spectrometry

We searched the data sets for patterns of consistent false positivity for any specific sample in the panel. The false positivities appeared to be essentially randomly distributed among the samples, indicating that the problem with false positives is usually not related to a property of the assays itself (e.g. cross-reactivity), but rather with the laboratory conditions of use (e.g. contamination). A systematic false positivity was found in the samples that contain the HPV 58 plasmid, where 15 data sets also detected HPV 52 in at least one of the HPV58-containing samples. This could be related to the fact that both the Linear Array and InnoLipa assays state that these tests cannot exclude HPV 52 in samples that contain HPV 58. Most of the HPV52 detection in the HPV58-positive samples were generated using the SPF10 primers used in InnoLipa, but there were also other assays, including HPV 52 type-specific PCRs (Table 9). As HPV52 and HPV58 are closely related viruses, it is conceivable that several assays could have problems to distinguish these HPV types. However, it should also be considered whether the PP panel itself could have been contaminated in these samples. There were no less than 94 data sets from laboratories proficient to detect HPV52 in the lowest dilution that did not report this false HPV52 positivity in these samples - several of them using the same assays as those reporting the false HPV52 positivity (Table 9) suggesting that a general PP panel contamination is unlikely as explanation. Feedback from one of the participants suggested that there might be a small batch variation in InnoLiPA that can be interpreted as false positive results for HPV 52. Interestingly in the 2008 PP, 5 out of 6 data sets using InnoLiPa could not identify HPV 52.

Table 9: Detection of HPV 52 in samples containing plasmid HPV 58
Includes datasets that correctly detected 50 copies / 5µl of HPV 52 and that did not have more than 3 false positive results (in addition to HPV 52 in HPV 58 samples).

	HPV 52 detected (N=datasets)	**HPV 52 not detected** (N=datasets)*
HPV 58, 500 copies in mix	**7** (5 InnoLipa/SPF10, two of these confirmed type specific) (1 Linear array, confirmed type specific) (1 Genoserch Luminex)	**78** (12 Linear array) (8 CLART) (8 InnoLipa/SPF10) (4 Papillocheck) (5 PGMY-CHUV) (6 In-house Luminex) (6 type-specific PCR) (4 In-house Line-blot) (3 Multimetrix)
HPV 58, 50 copies in mix	**1** (inhouse dotblot) (this assay also detects HPV 52 in two samples containing HPV 33)	**84** (14 Linear array) (8 CLART) (11 InnoLipa /SPF10) (4 Papillocheck) (5 PGMY-CHUV) (6 In-house Luminex) (6 type-specific PCR) (4 In-house Line-blot) (3 Multimetrix)
HPV 58, 500 copies	**5** (4 InnoLipa, one of these confirmed type specific) (1 type-specific PCR E6/E7)	**80** (13 Linear array) (8 CLART) (9 InnoLipa /SPF10) (4 Papillocheck) (5 PGMY-CHUV) (6 In-house Luminex) (5 type-specific PCR) (3 sequencing) (4 In-house Line-blot) (3 Multimetrix)
HPV 58, 50 copies	**11** (6 InnoLipa, one of these confirmed type specific) (1 Linear array confirmed type specific) (2 type-specific PCR E6/E7) (1 Genoserch Luminex) (1 CLART)	**74** (13 Linear array) (7 CLART) (6 InnoLipa /SPF10) (4 Papillocheck) (5 PGMY-CHUV) (6 In-house Luminex) (4 type-specific PCR) (4 In-house Line-blot) (3 Multimetrix)

* Assays used in less than 2 laboratories not specified.

4.5 Comparison of results for laboratories that participated in both 2008 and 2010 PP

Forty-one laboratories analysed the PP in both 2008 and 2010. Comparisons of the results from the two years were made for each laboratory. Some of the laboratories used the same tests in both years whereas some laboratories had changed at least one of the tests used. Percent proficiency, for both years and compared with the results from all data sets submitted 2010 is shown in Table 10, the sensitivity for individual HPV types in Table 11 and the specificity with number of false positive samples in Table 12.

Table 10: Proficiency of detecting HPV types by laboratories that participated in both 2008 and 2010 PP in comparison with all data sets submitted 2010*.

Proficiency	**Identical assays used**		**All test by laboratories that participated in both 2008 and 2010**		**All datasets 2010**
	2008 (%)	**2010 (%)**	**2008 (%)**	**2010 (%)**	**2010 (%)**
100 % proficient	10 / 37 (27)	11 / 37 (30)	13 / 60 (22)	13 / 52 (25)	26 / 118 (22)
99-90 % proficient	2 / 37 (5.4)	2 / 37 (5.4)	9 / 60 (15)	4 / 52 (7.7)	8 / 118 (6.8)
89-80 % proficient	6 / 37 (16)	4 / 37 (11)	7 / 60 (12)	7 / 52 (13)	15 / 118 (13)
<80 % proficient	5 / 37 (14)	6 / 37 (16)	11 / 60 (18)	7 / 52 (13)	23 / 118 (19)
Not proficient	14 / 37 (38)	14 / 37 (38)	20 / 60 (33)	21 / 52 (40)	46 / 118 (39)

*Table restricted to assays testing for more than two HPV types.

Table 11: HPV GE or IU detected per 5 µl in both single and multiple infections by laboratories participating both 2008 and 2010. Including samples with detection of additional false positive HPV types.

HPV type	HPV IU /GE	Identical assays used		All test by laboratories participating both 2008 and 2010		All datasets 2010
		2008 (%)	2010 (%)	2008 (%)	2010 (%)	2010 (%)
16	5	27 / 37 (73)	33 / 37 (89)	47 / 65 (72)	49 / 56 (88)	85 / 127 (67)
16	50	32 / 37 (86)	37 / 37 (100)	55 / 65 (85)	55 / 56 (98)	118 / 127 (93)
16	500	37 / 37 (100)		62 / 65 (95)		125 / 127 (98)
18	5	25 / 36 (69)	29 / 36 (81)	38 / 64 (59)	44 / 55 (80)	71 / 119 (60)
18	50	35 / 36 (97)	33 / 36 (92)	56 / 64 (88)	51 / 55 (93)	105 / 119 (88)
18	500	36 / 36 (100)	35 / 36 (97)	59 / 64 (92)	52 / 55 (95)	108 / 119 (91)
6	50	32 / 37 (86)	26 / 37 (70)	43 / 60 (72)	35 / 52 (67)	63 / 110 (57)
6	500	34 / 37 (92)	34 / 37 (92)	47 / 60 (78)	45 / 52 (86)	97 / 110 (88)
11	50	35 / 37 (95)	35 / 37 (95)	52 / 60 (87)	47 / 52 (90)	78 / 109 (72)
11	500	37 / 37 (100)	36 / 37 (97)	55 / 60 (92)	48 / 52 (92)	100 / 109 (92)
31	50	23 / 37 (62)	27 / 37 (73)	34 / 61 (56)	33 / 52 (63)	52 / 118 (44)
31	500	33 / 37 (89)	32 / 37 (86)	48 / 61 (79)	40 / 52 (77)	84 / 118 (71)
33	50	32 / 37 (86)	32 / 37 (86)	47 / 61 (77)	43 / 52 (83)	76 / 117 (65)
33	500	36 / 37 (97)	35 / 37 (95)	54 / 61 (88)	46 / 52 (88)	97 / 117 (83)
35	50	30 / 37 (81)	31 / 37 (84)	47 / 61(77)	43 / 52 (83)	69 / 118 (58)
35	500	34 / 37 (92)	37 / 37 (100)	51 / 61 (84)	50 / 52 (96)	98 / 118 (83)
39	50	15 / 21[a)] (71)	25 / 37 (68)	18 / 37[a)] (49)	32 / 52 (61)	45 /118 (38)
39	500	17 / 21 (81)	30 / 37 (81)	25 /37 (68)	41 / 52 (79)	77 /118 (65)
45	50	28 / 37 (76)	29 / 37 (78)	43 / 60 (72)	41 / 52 (79)	71 /118 (60)
45	500	31 / 37 (84)	34 / 37 (92)	47 / 60 (78)	47 / 52 (90)	98 /118 (83)
51	50	32 / 37 (86)	31 / 37 (84)	43 / 60 (72)	42 / 52 (81)	69 /117 (59)
51	500	35 / 37(95)	35 / 37 (95)	49 / 60 (82)	46 / 52 (88)	92 /117 (79)
52	50	26 / 37 (70)	36 / 37 (97)	34 / 60 (57)	46 / 52 (88)	79 / 117 (67)
52	500	28 / 37 (76)		37 / 60 (62)	47 / 52 (90)	98 /117 (84)
56	50	28 / 37 (76)	27 / 37 (73)	33 / 60 (55)	36 / 52 (69)	63 /118 (53)
56	500	30 / 37 (81)	31 / 37 (84)	40 / 60 (67)	43 / 52 (83)	86 /118 (73)
58	50	28 / 37 (76)	27 / 37 (73)	45 / 60 (75)	36 / 52 (69)	61 / 118 (52)
58	500	35 / 37 (95)	35 / 37 (95)	54 / 60 (90)	44 / 52 (85)	91 / 118 (77)
59	50	26 / 37 (70)	25 / 37 (68)	40 / 60 (67)	34 / 52 (65)	51 /117 (44)
59	500	27 / 37(73)	30 / 37 (81)	44 / 60 (73)	40 / 52 (77)	80 / 117 (68)
66	50	28 / 35 (80)	29 / 35 (83)	42 / 59 (71)	41 / 49 (84)	75 /113 (66)
66	500	31 / 35 (88)	30 / 35 (86)	49 / 59 (83)	43 / 49 (88)	95 /113 (84)
68a	50	5 / 15[b)] (33)	5 / 15 (33)	6 / 35[b)] (17)	6 / 28 (21)	10 / 61 (16)

68a	500	7 / 15 (47)	8 / 15 (53)		9 / 28 (32)	17 /61 (28)
68b	50		22 / 35 (63)		30 / 49 (61)	53 /114 (46)
68b	500	nt[c)]	27 / 35 (77)	nt	37 / 49 (76)	73 /114 (64)

a) 2008 years panel used a HPV 39 plasmid where HPV 39 was cloned into the vector in L1, this plasmid could not be detected by PGMY based primers.
b) 68a cannot be detected by PGMY based primers, the plasmid used contains the L1 fragment only.
c) Nt: not tested

Table 12: Number of false positive HPV types detected per data set reported by laboratories participating in both 2008 and 2010 years proficiency studies in comparison with all data sets submitted 2010.

No of false positive samples	**Identical assays used**		**All test by laboratories participating both 2008 and 2010**		**All datasets 2010**
	2008 (%)	**2010 (%)**	**2008 (%)**	**2010 (%)**	**2010 (%)**
0 samples	18 / 37 (49)	20 / 37 (54)	34 / 67 (51)	34 / 59 (58)	69 / 132 (52)
1 sample	5 / 37 (14)	3 / 37 (8.1)	13 / 67 (19)	4 / 59 (6.8)	12 / 132 (9.2)
2 samples	4 / 37 (11)	6 / 37 (16)	7 / 67 (10)	8 / 59 (14)	19 / 132 (14)
3 samples	4 / 37 (11)	3 / 37 (8.1)	5 / 67 (7.5)	3 / 59 (5.1)	4 / 132 (3.0)
>3 samples	6 / 37 (16)	5 / 37 (14)	8 / 67 (12)	10 / 59 (17)	27 / 132 (21)

5. Discussion

The 2010 PP was distributed to 105 laboratories worldwide and 132 datasets were returned for analysis from 98 laboratories. Participating laboratories involved public health laboratories, research laboratories, diagnostic test manufacturers and vaccine companies. According to the survey, the annual number of samples analysed for HPV type per laboratory varied from 60 to 100,000 per year with approximately 52 % of the laboratories performing less than 2,000 HPV typing tests per year and around 35 % between 2,000 and 10,000 assays per year, 12 % of the laboratories performed more than 10,000 assays yearly.

In a total of 72 data sets, results had been obtained using commercially available tests. The most commonly used assay was Liner Array (Roche) that was used to generate 17 data sets. Other widely used assays were Inno-LiPA (Innogenetics) and CLART (Genomica). Fifty-nine 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 35 laboratories.

The PP is designed for the genotyping needs in HPV vaccinology and the proficiency criteria are not intended for clinical HPV screening purposes, where the requirements for analytical sensitivity are different. Not all assays test for all HPV types included in the panel. In the analyses for proficiency only the HPV types tested for are included. E.g., if an assay does not include HPV 66, laboratories using that assay are considered as not testing for HPV 66.

The micro-array based Papillocheck was the commercial test with the highest proportion of proficient results. Four laboratories, all from different countries in Europe that used the test reported 100 % proficient data sets. Also, the commercially available micro-array assay EASYChip used by only 2 laboratories from one country in the western pacific region were 100 % proficient. Among the laboratories that used the Linear Array assay, only 47% (8 out of 17) had reported results being 100% proficient. Several data sets generated by in-house assays based on type-specific PCR, the PGMY-CHUV assay or by PCR followed by Luminex-based typing were 100 % proficient. The 48 data sets classified as not proficient all detected more than one false positive HPV type.

All plasmids were full-length, except the plasmid used to test for HPV 68a that contained only the L1 gene. In the proficiency study 2008 it was noted that Linear Array and all other PGMY-based assays that are indeed directed against L1 could not detect the HPV68a plasmid. This year we

included a plasmid for HPV 68b in the panel. HPV68b can be detected by PGMY-based primers and other common primer systems. 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 68a in this proficiency panel study. Accordingly only 61 data sets could be analysed for detection of HPV 68a. Only 17 of the 61 (28 %) 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 and was considered as not having been tested.

Six data sets generated using Linear Array was considered as not proficient since they reported between 2 and up to 10 false positive results. HPV 66 was detected as false positive in 10 of in total 31 false positive results submitted in the 17 data sets using Linear Array. Seven of these samples were detected in samples containing HPV 56 that was correctly identified in all the samples.
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 microarray based assay CLART was used by 8 laboratories of which 4 were not proficient reporting 2 to 4 false positive results. Only one of the data-sets could detect HPV 39; while HPV 68 could not be detected at all. When comparison is made with the results from 2008 PP, two participants using CLART in both PPs that reported 17 and 21 false positive results in 2008 PP – some with multiple positives in each sample - have had a major improvements with now only 1 and 2 false positive results reported in the 2010 PP.

The commercial tests InnoLiPA and CLART did not generate any 100 % proficient data sets. For InnoLiPA, 9 out of 12 data sets were not proficient because of 2 to 6 false positive results. Two laboratories using InnoLiPA reported no false positives, showing that it is possible to perform InnoLipa with no false positive results. However, it seems that stringent conditions with attention to prevention of contamination and negative controls are required. HPV 59 could only be detected in 2 out of 12 data sets using InnoLiPA.

Experience in performing assays is 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. In 2008 HPV DNA PP only

one laboratory out of 7 was 100 % proficient using the assay. This year 4 of 6 laboratories are 100 % proficient, one is >90% proficient and one <80%. None of the laboratories reported any false positive results. There is now only one laboratory that has substantial problems with this assay.

The majority of data sets submitted 2010 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.

Three additional samples (A, B, C) in the PP were used to evaluate the DNA extraction step before the HPV testing and typing. Two of the samples contained cells from the cervical cancer cell line SiHa mixed with the HPV negative cancer cell line C33A in different amounts and one sample with only C33A cells was negative control.
Most laboratories did not give any information on which extraction method that was used. For 27 data sets this information is available. Among these laboratories, 3 used MagnaPure LC (Roche), 5 laboratories used different extraction kits from Qiagen, other methods used were from Flexi Gene, Genomica, MagAttract and Nuclisens from BioMerieux. One laboratory used an in-house method with proteinase K extraction. We did not observe any obvious difference in performance between different extraction methods.
In sample C containing 2500 cells / 5 ul of the cervical cancer cell line SiHa, HPV 16 was correctly identified by 83% of the data sets. Four data sets reported false positive HPV types in this sample. In sample A containing 25 SiHa cells / 5ul, HPV 16 was detected in 61% of the data sets with five false positive results reported. The negative control containing only C33A cells was correctly reported as negative by only 83% of the laboratories.
This suggests that a minority of laboratories has problems with low yield in the DNA extraction step. The problem with false positivity in the negative control suggests that, at least for a minority of laboratories, contamination can occur also in the DNA extraction step.

6. Conclusions and recommendations

This was the second WHO HPV DNA proficiency study that was open for participation to all laboratories worldwide, following advertisement at the WHO website. The 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- the HPV types that are the most important for HPV vaccine characterization as well as for HPV surveillance and monitoring.

All WHO regions were represented in this 2010 PP, with the majority of participating laboratories from the EURO, WPRO and PAHO regions.

The 2010 WHO HPV DNA proficiency panel has shown that it is possible to perform global studies comparing the sensitivity and specificity of different HPV typing assays, as well as the performance of participating laboratories, in a consistent manner that allows comparison of results generated by different laboratories worldwide and over time.

Compared to the results of the 2008 WHO HPV DNA PP, we observe only marginal overall improvements. Looking at laboratories that used the same assay both years 27 % were proficient in 2008, as compared to 30 % in 2010. However, there are several noteworthy examples of laboratories that have achieved major improvements.

We see a definite trend towards increased sensitivity of assays. E.g., among the laboratories using the same assay in 2008 and 2010, 50 IU of HPV 16 could be detected by all (100%) laboratories this year compared to 86% in 2008. However, for several laboratories the increased sensitivity is accompanied by an increased amount of false positive results, resulting in non-proficiency.
We suggest that recommendations for HPV laboratory testing should include an increased emphasis on the use of negative controls in the assays. Furthermore, we suggest that the requirements for proficiency in future WHO HPV DNA Proficiency Panels should at the outset announce that proficiency will require that there are no false positives at all.

As also detected in previous studies, HPV 16 and HPV 18 were the types detected at lowest IU in most data sets. Only 2 and 11 datasets, respectively, could not detect 500 IU / 5 µl. In contrast, HPV 39, HPV 59 and HPV 56 could not be detected in 500 GE / 5 µl by 41, 37 and 32 data sets respectively. The continued presence of a differential analytic sensitivity for different HPV types suggests that many surveys of circulating HPV types may give biased results.

In summary, we find that the use of global HPV DNA typing proficiency panels for validating different HPV DNA tests and laboratories promotes the comparability of data generated from different laboratories worldwide. Regularly issued global HPV DNA typing proficiency panels that allow comparison of global results over time will be required for the continuing work towards international standardisation and quality improvement of HPV DNA typing results worldwide.

Annex 1:

Call for participation:

The 2010 WHO HPV LabNet Proficiency Study of HPV DNA Typing

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 as well as 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 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 **HPV 6, 11, 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, 68a and 68b** in a background of human cellular DNA. The samples will be prepared to include single types and mixtures at varying concentrations that are traceable to established or candidate International Standards to evaluate the sensitivity and type-specificity of detection. Three 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 instructions 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 2010**. Laboratories will be notified of their enrolment, the date and mode of shipment of the panel.

Contact:
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Annex 2:

Application for participating in The 2010 WHO HPV LabNet Proficiency Study of HPV DNA Typing

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, 2010

Laboratory details
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