Technical Report on the Global HPV LabNet DNA Genotyping Proficiency Panel 2021

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Abbreviations

AFRO	African Regional Office
EMRO	Eastern Mediterranean Regional Office
Equalis	External Quality Assessment in Laboratory Medicine in Sweden
EURO	European Regional Office
GE	Genome Equivalent
GRL	Global Reference Laboratory
HPV	Human Papilloma Virus
HPV LabNet	HPV Laboratory Network
IU	International Unit
PAHO	Pan American Health Organization
PP	Proficiency Panel
SEARO	South East Asian Regional Office
WHO	World Health Organization
WPRO	Western Pacific Regional Office

Global HPV DNA genotyping proficiency panel 2021

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1. Introduction

Accurate and internationally comparable HPV DNA detection and typing methodology is an essential component both for research and evaluation of HPV vaccines and in effective implementation and monitoring of HPV vaccination programmes. The WHO started a WHO Global HPV Laboratory Network (LabNet) in 2006 to support the world-wide development and implementation of HPV vaccines through improved laboratory standardization and quality assurance of HPV testing and typing methods used for research and evaluation of 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 was development, preparation and validation of proficiency panels (PP) to qualify methods and laboratories.

Call for participation in this proficiency study was sent to all laboratories that had participated in the HPV LabNet proficiency panels in previous years (Annex 1, 2).

2. Aims

The aims of this panel were:

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 International HPV Reference Center by the respective proprietors with written approval for use in this PP. All samples were purified plasmids diluted in TE buffer (10 mM TRIS-HCl, 0.1 mM EDTA, pH 8.0) with 10 ng/µl of human placental DNA (Sigma-Aldrich no 7011). The HPV types included were: 6, 11, 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 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: 2021 HPV PP composition by randomised sample ID

HPV types	HPV genome equivalents (GE) or international unit (IU) (for HPV 16, 18) per 5 µl	Randomised Panel ID
16	50	6
16	5	17
18	50	25
18	5	2
6	500	33
6	50	20
11	500	14
11	50	37
31	500	31
31	50	11
33	500	26
33	50	7
35	500	38
35	50	27
39	500	16
39	50	39
45	500	34
45	50	12
51	500	4
51	50	32
52	500	40
52	50	8
56	500	21
56	50	41
58	500	3
58	50	13
59	500	28
59	50	22
68a	500	29
68a	50	9
68b	500	35
68b	50	23
6, 31, 45, 52	500	18
6, 31, 45, 52	50	36
11, 33, 51, 58	500	15
11, 33, 51, 58	50	30
16, 56, 59, 68a	500	1
16, 56, 59, 68a	50	19
18, 35, 39, 68b	500	24
18, 35, 39, 68b	50	5
TE buffer with 10 ng/µl human placenta DNA	0	10
HPV 16 positive SiHa cells	2500	A
HPV 16 positive SiHa cells	25	B
HPV- negative C33A cells	0	C

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, 61, 66, 67, 68a, 68b, 69, 70, 73, 74, 81, 82, 86, 87, 89, 90 and 91.

3.3 Distribution of the PP

After pre-test validation by the International HPV Reference center in Sweden, the PP was compiled in September 2021 and distributed to laboratories throughout six WHO regions in November 2021, following the call for participation and requests received from the laboratories. The fee for participation was for commercial entities 1000 Euros, whereas academic and public health entities had a fee of 500 Euros. Participants from low and lower-middle income countries could apply for waiving of the fee. As in previous years the HPV reference laboratory in Sweden prepared the materials for the 2021 HPV DNA PP, but subcontracted the administration and distribution of the PP to Equalis (External quality assessment of laboratory medicine in Sweden; https://www.equalis.se/en/ a public, non-profit company that administrates the external quality assessment for public health care laboratories in Sweden) that handled the logistics and distribution of the panel. This model has continued to work well and is a possible mode of operation of a sustainable long-term activity with global distribution of an HPV DNA typing proficiency panel.

The number (n) of laboratories submitting results per WHO Region is shown in Figure 1. These are EMRO (n = 5), EURO (n = 49), SEARO (n = 2), WPRO (n = 59), AFRO (n = 7) and PAHO (n = 10). Two hundred eleven datasets from 132 laboratories were obtained. Ninety-six laboratories submitted a data set from one assay, thirteen laboratories submitted data sets from 2 different assays, four laboratories submitted data sets from 3 assays, eighteen laboratories submitted data sets from 4 different assays and one laboratory submitted data sets from 5 different assays.

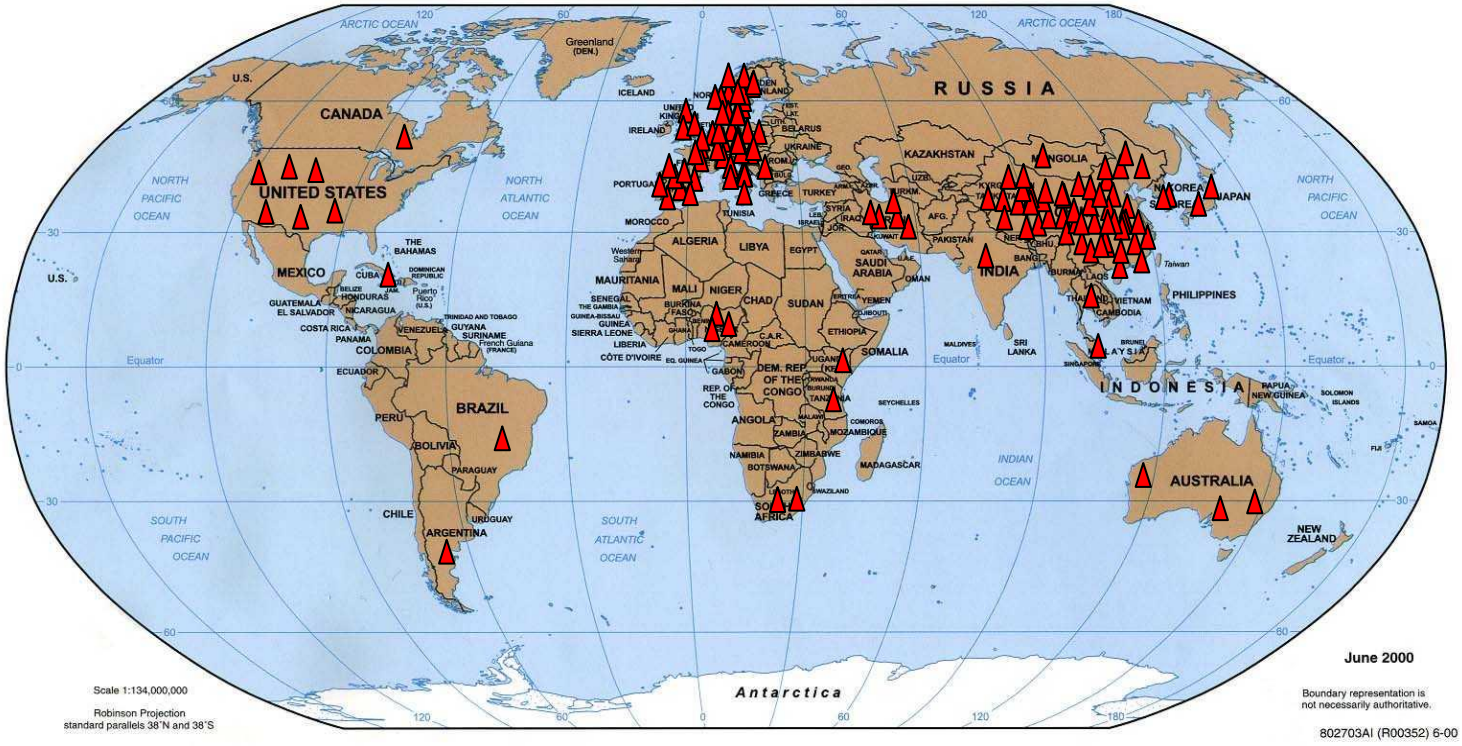

Figure 1: Global distribution of laboratories that submitted results for the 2021 HPV DNA PP.

3.4 Data analysis

Results analysed in this report include all results returned prior to the 28th of February 2021. Data was compiled by Equalis and transferred to the HPV reference laboratory in Sweden for analyses. Each data set was designated a number from 1 to 211. The data were analysed by region of the laboratory, by assay used and by HPV type.

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 5 µl and 500 genome equivalents (GE) in 5 µl of the other HPV types, in both single and multiple infection. For proficiency, it was required that no false positive type was detected.

4. Results

One hundred and thirty two of 144 participating laboratories submitted 211 data sets. Twenty eight data sets were generated using assays that either did not discriminate specific HPV types or reported

results as HPV 16, 18 and "other" High Risk HPV types (Hybribio 14 HR, Roche Cobas 4800 /6800 test, Abbot Realtime PCR, High risk HPV Screen, Harmonia HPV, and Oncopredict Screen). These data sets are only analyzed for the specific types tested for individually.

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 exceeded them.

Each data set submitted by each laboratory was analyzed and a feedback letter was sent to all participating laboratories that had paid the fee in February 2022.

4.1 Results by assays used

4.1.1 Commercial assays

A total of 182 data sets were obtained using commercially available tests. The most commonly used assays were the Hybribio 21 array (Hybribio) that was used in 39 laboratories. Anyplex II HPV 28 (Seegene) was used in 21 laboratories. Three other Hybribio assays were used by 20 laboratories (Table 2).

4.1.2 In-house assays

Twenty-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	**211**	**L1/L2/E1/E2/E4/E5/E6/E7**
Hybribio 21 array HPV (Hybribio)	39	L1 (MY09/11)
Anyplex II HPV 28 (Seegene)	21	L1
Hybribio 37 array HPV (Hybribio)	20	L1 (MY09/11)
HPV-23 Genotyping (Hybriobio)	20	L1/L2/E1/E2/E4/E6/E7
Hybribio 14 HR (Hybribio)	19	E6 / E7
In-house PCR Luminex	11	L1 / E7
In-house realtime PCR	9	L1/E1/E4/E6/E7
MassArray MALDI-TOF(Agena)	5	E6 / E7
HPV Direct Flow-chip (Master Diagnostica)	5	L1 (GP)

InnoLiPA Extra (Fujirebio)	5	L1 (SPF10)
Anyplex HR HPV (Seegene)	5	L1
Real-time PCR MehrViru	4	E6/E7/L1/L2
In-house PGMY-CHUV	3	L1 (PGMY)
HPV SPF10-LiPA25 (Labo-bio)	3	L1 (SPF10)
Cobas 4800 / 6800 (Roche)	3	L1
Abbott m2000 / Alinity M (Abbott)	3	L1
Tellgen 27plex, 14HR	3	L1 / L2
Realquality (AB Analitica)	3	E6 / E7
In-house NGS	2	L1
Onclarity (BD)	2	E6 / E7
GenoFlow HPV array (DiagCor)	2	L1 (PGMY)
Ampliquality (AB Analitica)	2	L1
OncoPredict HPV-DNA (Hiantis)	2	E6 / E7
VisionArray HPV (ZytoVision)	2	L1
Other Commercial assays [a)]	14	L1/E1/E2/E6/E7
Other In-house assays [b)]	4	L1 / E6 / E7

a) Other commercial assays include one laboratory using each of: Venus HPV, Harmonia HPV, Molgentix, Papilloplex, AmpFire, OncoPredict Screen, GeneProof, HPV Operon, HPV screen, SACACE HPV screen, yd-diagnostics, aid-diagnostika, Cephid GeneXpert, CLART 4 Genomica

b) Other In-house assays include one laboratory using each of: In-house RFLP, In-house Blot, In-house gel-elfores, In-house Mass-array

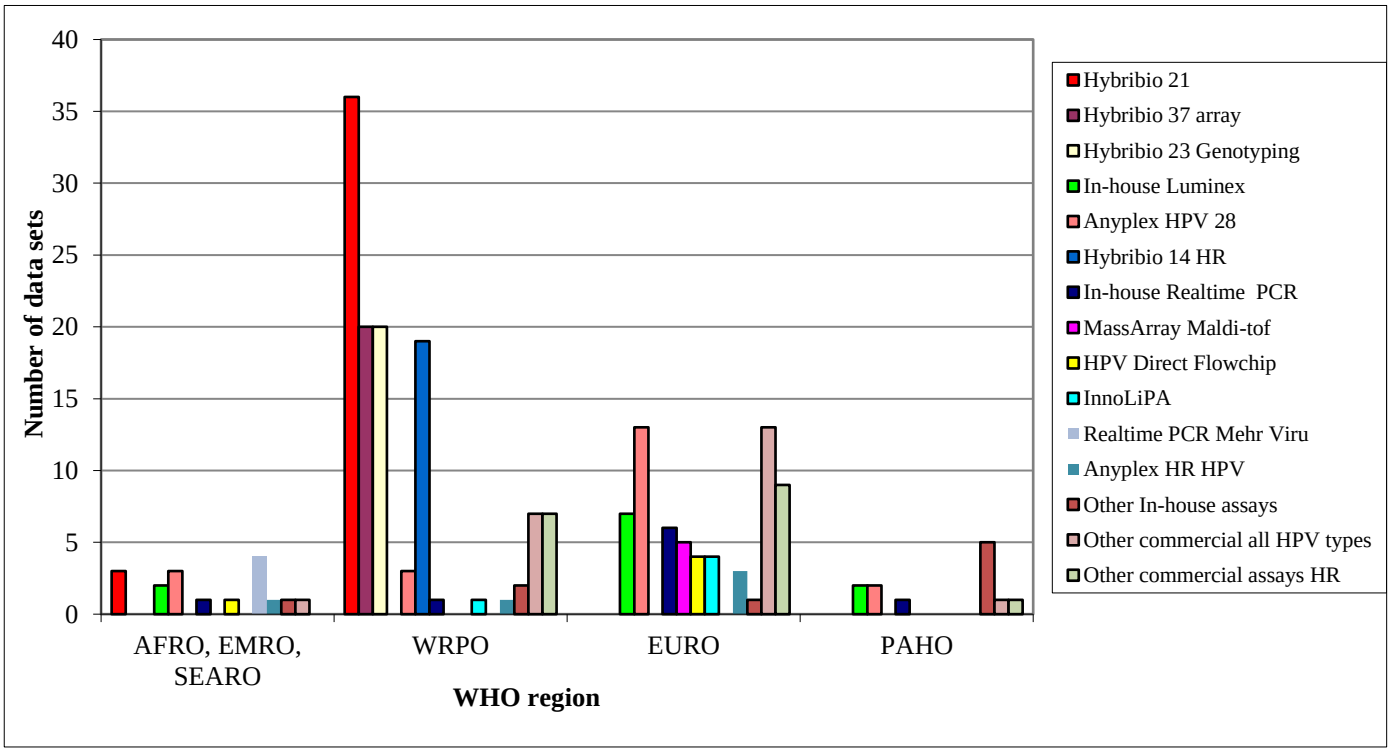

Figure 2: Type of assay in use for HPV DNA typing by WHO region, data for AFRO, EMRO and SEARO region are combined.

4.2.2 Results achieved by participating laboratories

The criteria for proficiency was since the panel issued 2019 no false positive results allowed (in previous years, a maximum of one false positive had been allowed for proficiency). According to the criteria described in 3.4, 158 (75 %) data set out of the 211 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, 119 data set 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 including all datasets grouped by WHO region is shown in Figure 3 and Table 3. The percent proficiency of detecting HPV types grouped by assay used for testing is shown in Table 4.

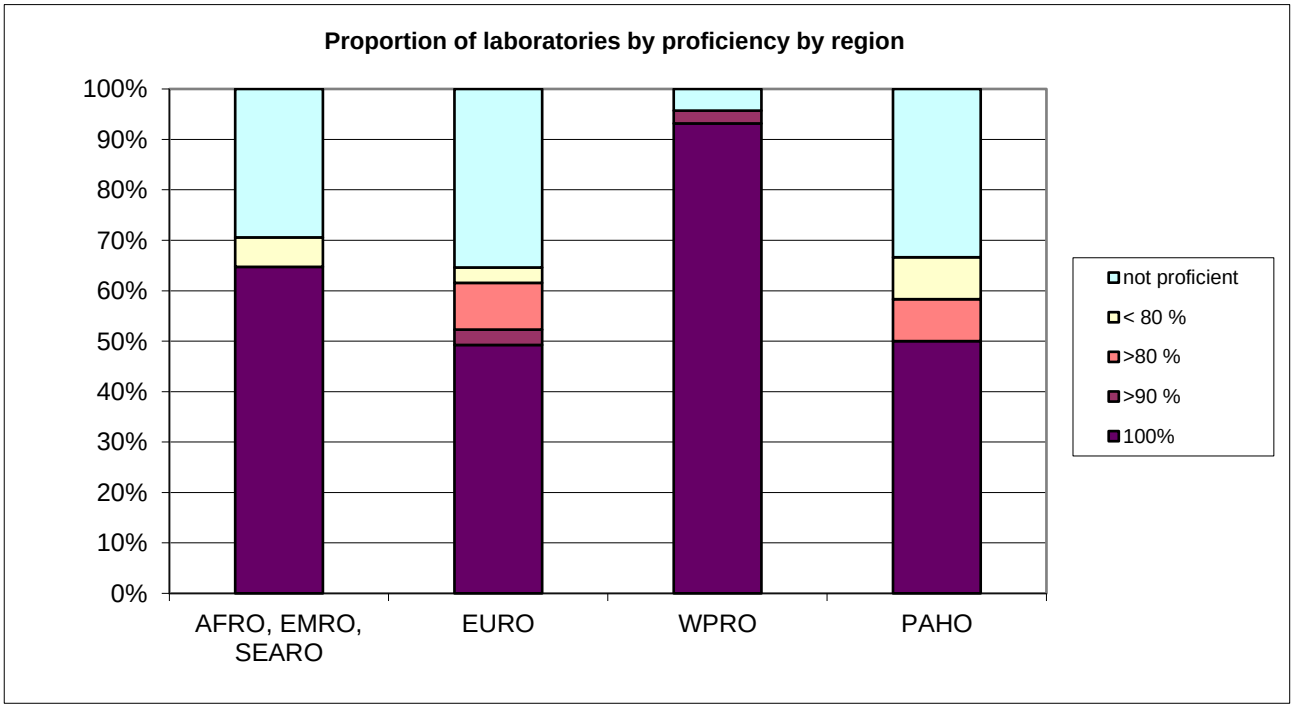

Figure 3: Proficiency for HPV DNA typing by WHO region. The figure includes 211 data set.

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
EURO (65)	49 %	52 %
AFRO, EMRO, SEARO (17)	65 %	65 %

PAHO (12)	50 %	50 %
WPRO (117)	93 %	96 %

Table 4: Proficiency for detection of specific 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	**211**	**158**	**5**	**7**	**4**	**37**
Hybribio 21 array HPV (Hybribio)	39	38	0	0	0	1
Anyplex II HPV 28 (Seegene)	21	15	1	0	0	5
Hybribio 37 array HPV (Hybribio)	20	20	0	0	0	0
HPV-23 Genotyping (Hybriobio)	20	20	0	0	0	0
Hybribio 14 HR (Hybribio)	19	19	0	0	0	0
In-house PCR Luminex	11	7	0	0	0	4
In-house realtime PCR	9	4	0	0	0	5
MassArray MALDI-TOF(Agena)	5	2	0	3	0	0
HPV Direct Flow-chip (Master Diagnostica)	5	4	0	0	0	1
InnoLiPA Extra (Fujirebio)	5	2	0	0	0	3
Anyplex HR HPV (Seegene)	5	3	1	0	0	1
Real-time PCR MehrViru	4	4	0	0	0	0
In-house PGMY-CHUV	3	2	0	0	0	1
HPV SPF10-LiPA25 (Labo-bio)	3	0	0	0	0	3
Cobas 4800 / 6800 (Roche)	3	2	0	0	0	1
Abbott m2000 / Alinity M (Abbott)	3	0	2	1	0	0
Tellgen 27plex, 14HR	3	3	0	0	0	0
Realquality (AB Analitica)	3	1	0	0	0	2
In-house NGS	2	1	0	0	0	1
Onclarity (BD)	2	1	0	0	1	0
GenoFlow HPV array (DiagCor)	2	2	0	0	0	0
Ampliquality (AB Analitica)	2	0	1	0	0	1
OncoPredict HPV-DNA (Hiantis)	2	2	0	0	0	0
VisionArray HPV (ZytoVision)	2	0	0	1	1	0
Other Commercial assays [a)]	14	5	0	2	1	6
Other In-house assays [b)]	4	1	0	0	1	2

a) Other commercial assays include one laboratory using each of; Venus HPV, Harmonia HPV, Molgentix, Papilloplex, AmpFire, OncoPredict Screen, GeneProof, HPV Operon, HPV screen, SACACE HPV screen, yd-diagnostics, aid-diagnostika, Cephid GeneXpert, CLART 4 Genomica

b) Other In-house assays include one laboratory using each of; In-house RFLP, In-house blot, In-house gel-elfores, In-house Mass-array

4.2.3 HPV types detected

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

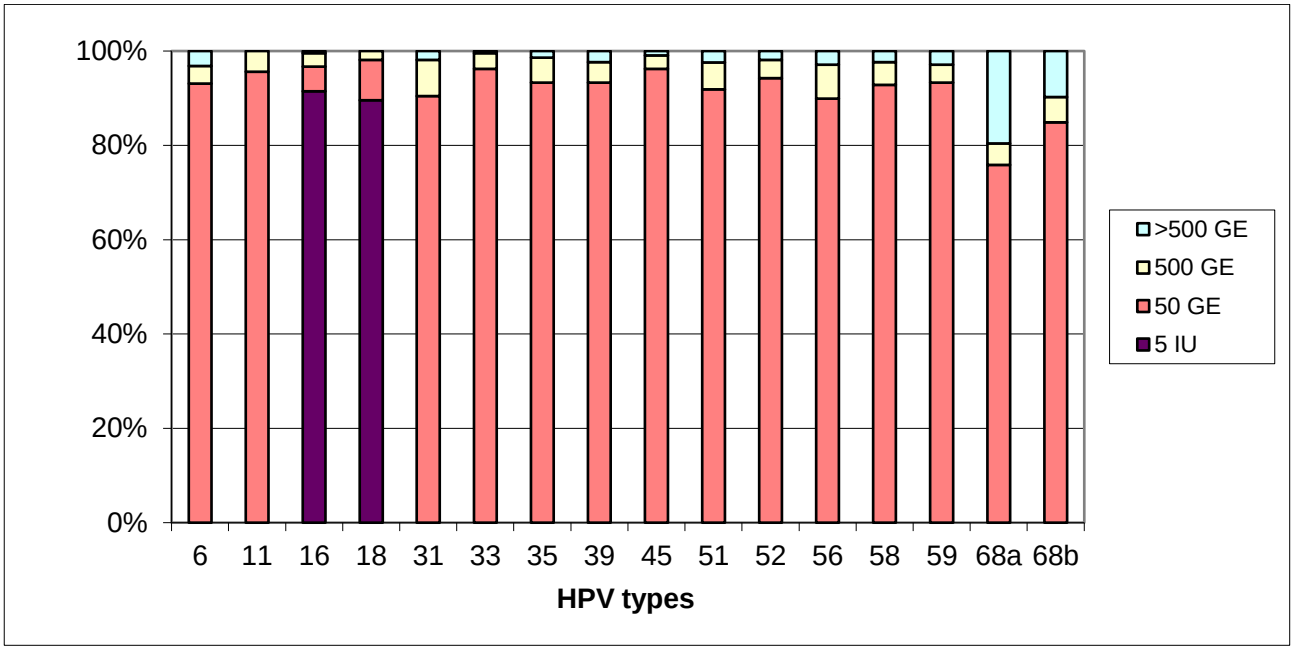

Figure 4: HPV Genome Equivalents (GE) or International Units (IU) detected per 5 µl in both single and multiple infections. Please note that only HPV16 and 18 were diluted to 5 IU (not all data sets analyze all HPV types).

Table 5: HPV GE or IU detected and typed per 5 µl in samples in both single and multiple HPV infections among the most commonly used commercial assays. Lowest detected GE / IU are indicated.

HPV type	HPV IU /GE	All Assays (%)	Hybribio 21	Anyplex II HPV 28	Hybribio 37	HPV 23 Genotyping Hybribio	Hybribio 14	InnoLiPA	HPV Direct Flow-chip	Anyplex HR HPV	Mass-Array (Agena)
16	5	193/211 (91)	39 / 39	21 / 21	20 / 20	20 / 20	19 / 19	5 / 5	4 / 5	5 / 5	5 / 5
16	50	204/211 (97)							5 / 5		
16	500	211/211 (100)									
18	5	189/211 (90)	39 / 39	20 / 21	20 / 20	20 / 20	19 / 19	5 / 5	5 / 5	4 / 5	2 / 5
18	50	207/211 (98)		21 / 21						5 / 5	5 / 5
18	500	211/211 (100)									
6	50	148 / 159 (93)	39 / 39	21 / 21	20 / 20	20 / 20	nt [a)]	5 / 5	5 / 5	nt [a)]	4 / 5
6	500	155 / 159 (97)									5 / 5
11	50	152 / 159 (98)	39 / 39	21 / 21	20 / 20	20 / 20	nt [a)]	5 / 5	5 / 5	nt [a)]	4 / 5
11	500	159 / 159 (100)									5 / 5
31	50	190 / 210 (90)	39 / 39	21 / 21	20 / 20	20 / 20	19 / 19	3 / 5	5 / 5	4 / 5	5 / 5
31	500	206 / 210 (98)						5 / 5		5 / 5	
33	50	202 / 210 (96)	39 / 39	21 / 21	20 / 20	20 / 20	19 / 19	5 / 5	5 / 5	5 / 5	5 / 5
33	500	209 / 210 (99)									
35	50	196 / 210 (93)	36 / 39	21 / 21	20 / 20	20 / 20	19 / 19	5 / 5	5 / 5	5 / 5	5 / 5
35	500	207 / 210 (99)	39 / 39								
39	50	196 / 210 (93)	39 / 39	21 / 21	20 / 20	20 / 20	19 / 19	5 / 5	5 / 5	5 / 5	5 / 5
39	500	204 / 210 (97)									
45	50	205 / 211 (97)	39 / 39	21 / 21	20 / 20	20 / 20	19 / 19	5 / 5	5 / 5	5 / 5	5 / 5
45	500	209 / 211 (99)									
51	50	192 / 209 (92)	39 / 39	21 / 21	20 / 20	20 / 20	19 / 19	5 / 5	5 / 5	5 / 5	5 / 5
51	500	204 / 209 (98)									
52	50	198 / 210 (94)	39 / 39	21 / 21	20 / 20	20 / 20	19 / 19	5 / 5	5 / 5	5 / 5	5 / 5
52	500	206 / 210 (98)									
56	50	187 / 208 (90)	39 / 39	18 / 21	20 / 20	20 / 20	19 / 19	5 / 5	5 / 5	5 / 5	1 / 5
56	500	202 / 208 (97)		21 / 21							4 / 5
58	50	197 / 210 (94)	39 / 39	21 / 21	20 / 20	20 / 20	19 / 19	5 / 5	5 / 5	5 / 5	5 / 5
58	500	205 / 210 (98)									
59	50	195 / 209 (93)	36 / 39	21 / 21	20 / 20	20 / 20	20 / 20	4 / 5	5 / 5	5 / 5	5 / 5
59	500	203 / 209 (97)	38 / 39					5 / 5			
68a	50	151 / 199 (76)	36 / 39	20 / 21	20 / 20	20 / 20	19 / 19	5 / 5	5 / 5	5 / 5	nt [a)]
68a	500	159 / 199 (80)	38 / 39	21 / 21							
68b	50	174 / 205 (85)	36 / 39	18 / 21	20 / 20	20 / 20	19 / 19	5 / 5	5 / 5	4 / 5	0 / 5
68b	500	185 / 205 (90)	39 / 39	20 / 21							2 / 5

a) Nt: Not tested

Table 6: HPV GE or IU detected and typed per 5 µl in samples with in both single and multiple HPV infections among in-house assays and commercial assays used by 3 laboratories and less. Lowest detected GE / IU are indicated.

HPV type	HPV IU /GE	In-house Luminex	In-house Realtime PCR	In-house PGMY-CHUV	MehrViru Realtime PCR	HPV SPF10-LiPA25	Cobas 4800 / 6800	Alinity M (Abbott)	Tellgene 27 plex 14 HR	Realquality (AB Analitica)	Other In-house[a)]	Other Commercial[b)]	Other Commercial[c)]
16	5	10/11	5 / 9	3 / 3	4 / 4	2 / 3	2 / 3	2 / 3	3 / 3	3 / 3	4 / 6	7 / 10	10 / 14
16	50	11/11	7 / 9			3 / 3	3 / 3	3 / 3			5 / 6	9 / 10	12 / 14
16	500		9 / 9								6 / 6	10 / 10	14 / 14
18	5	9/11	5 / 9	1 / 3	4 / 4	2 / 3	2 / 3	2 / 3	3 / 3	3 / 3	5 / 6	7 / 10	12 / 14
18	50	11/11	9 / 9	3 / 3		3 / 3	3 / 3	3 / 3				9 / 10	
18	500										6 / 6	10 / 10	14 / 14
6	50	9/10	3 / 4	3 / 3	4 / 4	2 / 3	nt[a)]	nt[a)]	1 / 1	2 / 3	3 / 6	4 / 6	3 / 5
6	500	10/10				3 / 3					5 / 6		5 / 5
11	50	10/10	4 / 4	3 / 3	4 / 4	2 / 3	nt[a)]	nt[a)]	1 / 1	2 / 3	4 / 6	4 / 6	4 / 5
11	500					3 / 3					6 / 6	6 / 6	5 / 5
31	50	9/11	6 / 8	2 / 3	4 / 4	3 / 3	3 / 3		3 / 3	3 / 3	4 / 6	7 / 10	9 / 14
31	500	10/11	8 / 8	3 / 3				3 / 3				10 / 10	13 / 14
33	50	10/11	7 / 8	3 / 3	4 / 4	3 / 3	3 / 3	1 / 3	3 / 3	3 / 3	5 / 6	7 / 10	14 / 14
33	500	11/11	8 / 8					3 / 3				10 / 10	
35	50	10/11	6 / 8	3 / 3	4 / 4	3 / 3	3 / 3	2 / 3	3 / 3	3 / 3	4 / 6	7 / 10	12 / 14
35	500	11/11	8 / 8					3 / 3			5 / 6	10 / 10	
39	50	10/11	6 / 8	3 / 3	4 / 4	3 / 3	3 / 3	2 / 3	3 / 3	3 / 3	4 / 6	7 /10	9 / 14
39	500		8 / 8					3 / 3				10 / 10	12 / 14
45	50	11/11	8 / 9	3 / 3	4 / 4	3 / 3	3 / 3	3 / 3	3 / 3	3 / 3	3 / 6	7 / 10	13 / 14
45	500		9 / 9								4 / 6	10 / 10	14 / 14
51	50	9/11	5 / 7	3 / 3	4 / 4	3 / 3	3 / 3		3 / 3	3 / 3	3 / 6	7 / 10	10 / 14
51	500	11/11	7 / 7					2 / 3			5 / 6	9 / 10	12 / 14
52	50	10/11	7 / 8	3 / 3	4 / 4	3 / 3	3 / 3		3 / 3	3 / 3	4 / 6	7 / 10	12 / 14
52	500		8 / 8					1 / 3			6 / 6	10 / 10	13 / 14
56	50	11/11	5 / 7	3 / 3	4 / 4	3 / 3	1 / 3	2 / 3	1 / 1	3 / 3	5 / 6	8 / 10	9 / 14
56	500		7 / 7				3 / 3	3 / 3					12 / 14
58	50	11/11	6 / 8	3 / 3	4 / 4	1 / 3	3 / 3	1 / 3	3 / 3	3 / 3	4 / 6	6 / 10	11 / 14
58	500		8 / 8			2 / 3		3 / 3			6 / 6	8 / 10	12 / 14
59	50	10/11	6 / 7	3 / 3	4 / 4	2 / 3	2 / 3	3 / 3	3 / 3	3 / 3	4 / 6	8 / 10	12 / 14
59	500	11/11	7 / 7				3 / 3					10 / 10	12 / 14
68a	50	6 / 8		3 / 3		1 / 3	nt[a)]	2 / 3	1 / 1		2 / 6	2 / 8	4 / 14
68a	500		1 / 6			2 / 3		3 / 3				4 / 8	5 / 14
68b	50	9/10	3 / 6	3 / 3	4 / 4	3 / 3	2 / 3		3 / 3	3 / 3	3 / 6	5 / 8	9 / 14
68b	500		4 / 6				3 / 3	2 / 3				7 / 8	

a) Other In-house assays include one laboratory using each of; In-house NGS x 2,In-house RFLP, In-house blot, In-house gel-elfores, In-house Mass-array
b) Other commercial assays include two laboratories using each of; GenoFlow HPV array, VisionArray HPV, OncoPredict, Ampliquality, Onclarity (BD)

c) Other commercial assays include one laboratory using each of; Venus HPV, Harmonia HPV, Molgentix, Papilloplex, AmpFire, OncoPredict Screen, GeneProof, HPV Operon, HPV screen, SACACE HPV screen, yd-diagnostics, aid-diagnostika, Cephid GeneXpert, CLART 4 Genomica

d) Nt: Not tested

4.3 Results by sample number

The numbers of laboratories typing for and reporting correct HPV type, with **no false positive** HPV type detected are shown in table 7. The number of datasets 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, including test that type HPV 16 and HPV 18 and other HR, reported by sample number.

HPV types	HPV genome equivalents per 5 µl	Percent correct data sets (N)
16	50	**96.7 (204 / 211)**
16	5	90.5 (191 / 211)
18	50	**98.1 (207 / 211)**
18	5	89.1 (188 / 211)
6	500	**95.6 (152 / 159)**
6	50	93.7 (149 / 159)
11	500	**98.7 (157 / 159)**
11	50	93.7 (149/ 159)
31	500	**99.0 (208 / 210)**
31	50	91.4 (192 / 210)
33	500	**97.6 (205 / 210)**
33	50	94.8 (199 / 210)
35	500	**97.6 (205 / 210)**
35	50	95.7 (201 / 210)
39	500	**97.6 (205 / 210)**
39	50	93.3 (196 / 210)
45	500	**98.1 (207 / 211)**
45	50	96.7 (204 / 211)
51	500	**98.6 (206 / 209)**
51	50	91.4 (191 / 209)
52	500	**96.7 (203 / 210)**
52	50	94.8 (199/ 210)
56	500	**95.2 (198/ 208)**
56	50	89.4 (186 / 208)
58	500	**97.1 (204 / 210)**
58	50	93.3 (196 / 210)
59	500	**98.6 (206 / 209)**
59	50	96.2 (201 / 209)

68a	500	**78.9 (157 / 199)**
68a	50	75.9 (151 / 199)
68b	500	**92.7 (190 / 205)**
68b	50	87.3 (179 / 205)
6, 31, 45, 52	500	**95.3 (201 / 211)**
6, 31, 45, 52	50	88.6 (187 / 211)
11, 33, 51, 58	500	**91.9 (194 / 211)**
11, 33, 51, 58	50	91.5 (193 / 211)
16, 56, 59, 68a	500	**93.4 (197 / 211)**
16, 56, 59, 68a	50	89.1 (188 / 211)
18, 35, 39, 68b	500	**93.4 (197 / 211)**
18, 35, 39, 68b	50	89.1 (188 / 211)
TE buffer with 10 ng/µl human placenta DNA	0	**97.2 (205/ 211)**
HPV 16 positive SiHa cells	2500	97.6 (204 / 209) (3 false positive)
HPV 16 positive SiHa cells	25	94.7 (198 / 209) (5 false positive)
. HPV-negative C33A cells	0	97.1 (203 / 209) (6 false positive)

[a] Data sets known not to detect the HPV 68a 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 no false positive result was accepted. The number of false positive samples by assay 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	**211**	**174**	**19**	**7**	**1**	**10**
Hybribio 21 array HPV (Hybribio)	39	38	1	0	0	0
Anyplex II HPV 28 (Seegene)	21	16	3	1	0	1
Hybribio 37 array HPV (Hybribio)	20	20	0	0	0	0
HPV-23 Genotyping (Hybriobio)	20	20	0	0	0	0
Hybribio 14 HR (Hybribio)	19	19	0	0	0	0
In-house PCR Luminex	11	7	3	1	0	0
In-house realtime PCR	9	4	3	1	0	1
MassArray MALDI-TOF(Agena)	5	5	0	0	0	0
HPV Direct Flow-chip (Master Diagnostica)	5	4	0	1	0	0
InnoLiPA Extra (Fujirebio)	5	2	2	1	0	0
Real-time PCR MehrViru	4	4	0	0	0	0
Anyplex HR HPV (Seegene)	5	4	1	0	0	0
In-house PGMY-CHUV	3	2	0	0	0	1

HPV SPF10-LiPA25 (Labo-bio)	3	0	0	2	1	0
Cobas 4800 / 6800 (Roche)	3	2	1	0	0	0
Abbott m2000 / Alinity M (Abbott)	3	3	0	0	0	0
Tellgen 27plex, 14HR	3	3	0	0	0	0
Realquality (AB Analitica)	3	1	2	0	0	0
In-house NGS	2	1	1	0	0	0
Onclarity (BD)	2	2	0	0	0	0
GenoFlow HPV array (DiagCor)	2	2	0	0	0	0
Ampliquality (AB Analitica)	2	1	0	0	0	1
OncoPredict HPV-DNA (Hiantis)	2	2	0	0	0	0
VisionArray HPV (ZytoVision)	2	2	0	0	0	0
Other Commercial assays [a)]	14	8	3	0	0	3
Other In-house assays [b)]	4	2	0	0	0	2

a) Other commercial assays include one laboratory using each of; Venus HPV, Harmonia HPV, Molgentix, Papilloplex, AmpFire, OncoPredict Screen, GeneProof, HPV Operon, HPV screen, SACACE HPV screen, yd-diagnostics, aid-diagnostika, Cephid GeneXpert, CLART 4 Genomica

b) Other In-house assays include one laboratory using each of; In-house RFLP, In-house blot, In-house elfores, In-house MassArray

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). Five laboratories detected HPV 31 in the sample that contained only human DNA. The assays used was Anyplex HPV 28 (used by in total 20 laboratories - 18 tested this sample as correctly negative), Onclarity and in-house Luminex.

4.5 Comparison of results for laboratories that participated 2021 and in the years 2008, 2010, 2011, 2013, 2014, 2017 and 2019

In total 65 laboratories that participated in 2021 had also participated in the HPV LabNet PPs from at least one previous year. Fifteen laboratories that submitted results in 2021 participated from the start 2008 of these 10 laboratories participated in all 8 PPs (2008, 2010, 2011, 2013, 2014, 2017, 2019 and 2021). Four laboratories analysed the PP in 7 years, 6 laboratories in 6 years, 7 laboratories in 5 years, 8 laboratories in 4 years, 13 laboratories in 3 years and 17 laboratories analysed the panel in 2019 and 2021. Comparisons of these results were made for each laboratory. Some of the laboratories used the same tests during all years, whereas some laboratories had

changed at least one of the tests used. Percent proficiency, for each year and compared with the results from all data sets submitted 2021 is shown in Table 9a and 9b, the sensitivity for individual HPV types in Table 10 and the specificity with number of false positive samples in Table 11a and 11b.

Table 9a: Proficiency of detecting HPV types by laboratories that participated in 2021 PP, using identical assays in 2008, 2010, 2011, 2013, 2014, 2017 and 2019 in comparison with all data sets submitted in 2021.

Not proficient = One or more false positive results

Proficiency	Laboratories that participated in 2008, 2010, 2011, 2013, 2014, 2017, 2019 and 2021 using identical assays								All datasets 2021 (%)
	2008 (%)	2010 (%)	2011 (%)	2013 (%)	2014 (%)	2017 (%)	2019 (%)	2021 (%)	
100 % proficient	1 / 6 (17)	2 / 11 (18)	9 / 19 (47)	11 / 21 (52)	19 / 29 (66)	27 / 49 (55)	16 / 61 (26)	45 / 79 (57)	158 / 211 (75)
99-90 % proficient	1 / 6 (17)	1 / 11 (9.1)	0 / 19 (0)	0 / 21 (0)	2 / 29 (6.9)	3 / 49 (6.1)	16 / 61 (26)	5 / 79 (6.3)	5 / 211 (2.4)
89-80 % proficient	0 / 6 (0)	1 / 11 (9.1)	3 / 19 (16)	3 / 21 (14)	1 / 29 (3.4)	5 / 49 (10)	3 / 61 (4.9)	2 / 79 (2.5)	7 / 211 (3.3)
<80 % proficient	2 / 6 (33)	1 / 11 (9.1)	1 / 19 (5.3)	0 / 21 (0)	0 / 29 (0)	2 / 49 (4.1)	2 / 61 (3.3)	2 / 79 (2.5)	4 / 211 (0.9)
Not proficient	2 / 6 (33)	6 / 11 (54)	6 / 19 (32)	7 / 21 (33)	7 / 29 (24)	12 / 49 (24)	24 / 61 (39)	25 / 79 (32)	37 / 211 (17)

Table 9b: Proficiency of detecting HPV types by laboratories that participated in 2021 PP, with data from 2008, 2010, 2011, 2013, 2014, 2017 and 2109 in comparison with all data sets submitted 2021.

Not proficient = false positive result

Proficiency	All test by laboratories that participated in 2008, 2010, 2011, 2013, 2014, 2017, 2019 and 2021								All datasets 2021 (%)
	2008 (%)	2010 (%)	2011 (%)	2013 (%)	2014 (%)	2017 (%)	2019 (%)	2021 (%)	
100 % proficient	5 / 17 (29)	5 / 27 (19)	16 / 33 (48)	15 / 38 (39)	26 / 43 (60)	35 / 65 (54)	19 / 77 (25)	56 / 94 (60)	158 / 211 (75)
99-90 % proficient	1 / 17 (5.9)	1 / 27 (3.7)	2 / 33 (6.1)	3 / 38 (7.9)	2 / 43 (4.7)	5 / 65 (7.7)	17 / 77 (22)	5 /94 (5.3)	5 / 211 (2.4)
89-80 % proficient	1 / 17 (5.9)	3 / 27 (11)	3 / 33 (9.1)	4 / 38 (11)	3 / 43 (7.0)	6 / 65 (9.2)	6 / 77 (7.8)	2 / 94 (2.1)	7 / 211 (3.3)
<80 % proficient	3 / 17 (18)	3 / 27 (11)	2 / 33 (6.1)	0 / 38 (0)	1 / 43 (2.3)	2 / 65 (3.1)	2 / 77 (2.6)	2 / 94 (2.1)	4 / 211 (0.9)
Not proficient	7 / 17 (41)	15 / 27 (56)	10 / 33 (30)	16 / 38 (42)	11 / 43 (26)	17 / 65 (26)	33 / 77 (43)	29 / 94 (31)	37 / 211 (17)

Table 10: HPV GE or IU detected and typed per 5 µl in both single and multiple infections by laboratories participating in 2010, 2011, 2013, 2014, 2017, 2019 and 2021. Table includes samples with detection of false positive HPV types. Lowest detected GE/IU is indicated.

HPV type	HPV IU /GE	All test by laboratories participating both in 2010, 2011, 2013, 2014, 2017, 2019 and 2021						
		2010 (%)	2011 (%)	2013 (%)	2014 (%)	2017 (%)	2019 (%)	2021 (%)
16	5	25 / 27 (93)	21 / 31 (68)	30 / 38 (79)	31 / 43 (72)	46 / 64 (72)	69 / 77 (90)	84 / 94 (89)
16	50		30 / 31 (97)	31 / 38 (82)	39 / 43 (91)	57 / 64 (89)	75 / 77 (97)	91 / 94 (97)
16	500		31 / 31 (100)	37 / 38 (97)	43 / 43 (100)	63 / 64 (98)	77 / 77 (100)	94 / 94 (100)
18	5	21 / 25 (84)	19 / 31 (61)	30 / 38 (79)	28 / 42 (67)	44 / 65 (68)	66 / 77 (86)	81 / 94 (86)
18	50	23 / 25 (92)	27 / 31 (87)	32 / 38 (84)	35 / 42 (83)	55 / 65 (85)	75 / 77 (97)	93 / 94 (99)
18	500		30 / 31 (97)	38 / 38 (100)	42 / 42 (100)	60 / 65 (92)		94 / 94 (100)
6	50	16 / 25 (64)	20 / 27 (74)	21 / 33 (64)	26 / 36 (72)	38 / 48 (79)	54 / 60 (90)	61 / 68 (90)
6	500	20 / 25 (80)	25 / 27 (93)	29 / 33 (88)	34 / 36 (94)	46 / 48 (96)	60 / 60 (100)	64 / 68 (94)
11	50	21 / 25 (84)	22 / 27 (81)	26 / 33 (79)	30 / 36 (83)	41 / 48 (85)	58 / 60 (97)	64 / 68 (94)
11	500		26 / 27 (96)	32 / 33 (97)	35 / 36 (97)	47 / 48 (98)	60 / 60 (100)	68 / 68 (100)
31	50	17 / 26 (65)	18 / 31 (58)	25 / 38 (66)	31 / 43 (72)	44 / 65 (68)	66 / 77 (86)	80 / 94 (85)
31	500	20 / 26 (77)	29 / 31 (93)	33 / 38 (87)	40 / 43 (93)	59 / 65 (91)	74 / 77 (96)	91 / 94 (97)
33	50	22 / 26 (85)	24 / 31 (77)	33 / 38 (87)	36 / 43 (84)	56 / 65 (86)	72 / 77 (94)	90 / 94 (96)
33	500		29 / 31 (93)	38 / 38 (100)	43 / 43 (100)	64 / 65 (98)	77 / 77 (100)	94 / 94 (100)

35	50	23 / 26 (88)	24 / 31 (77)	30 / 36 (83)	36 / 42 (86)	56 / 64 (86)	70 / 77 (91)	87 / 94 (93)
35	500	25 / 26 (96)	30 / 31 (97)	36 / 36 (100)	41 / 42 (98)	62 / 64 (97)	76 / 77 (99)	92 / 94 (98)
39	50	15 / 26 (58)	20 / 31 (64)	29 / 37 (78)	31 / 42 (74)	55 / 64 (86)	74 / 77 (96)	85 / 94 (90)
39	500	20 / 26 (77)	28 / 31 (90)	36 / 37 (97)	40 / 42 (95)	63 / 64 (98)	77 / 77 (100)	90 / 94 (96)
45	50	23 / 26 (88)	25 / 31 (80)	31 / 38 (81)	36 / 43 (84)	58 / 65 (89)	75 / 77 (97)	91 / 94 (97)
45	500	24 / 26 (92)	30 / 31 (97)	36 / 38 (95)	42 / 43 (98)	64 / 65 (98)	76 / 77 (99)	93 / 94 (99)
51	50	21 / 26 (81)	25 / 31 (81)	30 / 38 (79)	36 / 43 (84)	53 / 65 (81)	73 / 76 (96)	82 / 93 (88)
51	500	22 / 26 (85)	30 / 31 (97)	36 / 38 (95)	41 / 43 (95)	60 / 65 (92)	74 / 76 (97)	90 / 93 (97)
52	50	23 / 26 (88)	22 / 32 (69)	30 / 38 (79)	36 / 43 (84)	58 / 65 (89)	76 / 77 (99)	82 / 94 (87)
52	500	24 / 26 (92)	31 / 32 (97)	36 / 38 (95)	42 / 43 (98)	65 / 65 (100)		91 / 94 (97)
56	50	17 / 26 (65)	24 / 31 (77)	29 / 37 (78)	36 / 42 (86)	46 / 64 (72)	68 / 76 (89)	78 / 92 (85)
56	500	20 / 26 (77)	30 / 31 (97)	35 / 37 (95)	40 / 42 (95)	58 / 64 (91)	72 / 76 (95)	88 / 92 (96)
58	50	19 / 26 (73)	22 / 31 (71)	26 / 37 (70)	36 / 42 (86)	49 / 64 (77)	72 / 77 (94)	85 / 94 (90)
58	500	22 / 26 (85)	29 / 31 (93)	35 / 37 (95)	41 / 42 (98)	62 / 64 (97)	76 / 77 (99)	89 / 94 (95)
59	50	16 / 26 (62)	23 / 31 (74)	27 / 37 (73)	33 / 42 (79)	51 / 64 (80)	67 / 76 (88)	83 / 93 (89)
59	500	18 / 26 (69)	27 / 31 (87)	36 / 37 (97)	41 / 42 (98)	63 / 64 (98)	74 / 76 (97)	89 / 93 (96)
68a	50	1 / 10[a)] (10)	8 / 19 (42)	11 / 25 (44)	17 / 28 (61)	33 / 53 (62)	46 / 71 (65)	54 / 82 (66)
68a	500	4 / 10 (40)	11 / 19 (58)	15 / 25 (60)	21 / 28 (75)	34 / 53 (64)	51 / 71 (72)	57 / 82 (70)
68b	50	16 / 24 (67)	19 / 30 (63)	24 / 35 (69)	28 / 41 (68)	49 / 63 (78)	6 / 74 (8.1)	72 / 89 (81)
68b	500	18 / 24 (75)	27 / 30 (90)	34 / 35 (97)	38 / 41 (93)	57 / 63 (90)	22 / 74 (30)	79 / 89 (89)

a) 68a cannot be detected by PGMY based primers except version 2 of PGMY-CHUV, the plasmid used contains the L1 fragment only.

Table 11a: Number of false positive HPV types detected per data set reported by laboratories using identical assays in 2008, 2010, 2011, 2013, 2014, 2017 and 2019 years proficiency studies in comparison with all data sets submitted 2019.

No of false positive samples	Laboratories that participated in 2008, 2010, 2011, 2013, 2014, 2017, 2019 and 2021 using identical assays								All datasets 2021 (%)
	2008 (%)	2010 (%)	2011 (%)	2013 (%)	2014 (%)	2017 (%)	2019 (%)	2021 (%)	
0 samples	4 / 6 (67)	5 / 11 (45)	13 / 19 (68)	14 / 21 (67)	22 / 29 (76)	37 / 49 (76)	37 / 61 (61)	54 / 79 (68)	174 / 211 (82)
1 sample	0 / 6 (0)	0 / 11 (0)	1 / 19 (5.3)	3 / 21 (14)	1 / 29 (3.4)	6 / 49 (12)	13 / 61 (21)	15 / 79 (19)	19 / 211 (9.0)
2 samples	1 / 6 (17)	3 / 11 (27)	3 / 19 (16)	0 / 21 (0)	1 / 29 (3.4)	2 / 49 (4.1)	3 / 61 (4.9)	4 / 79 (5.1)	7 / 211 (3.3)
3 samples	0 / 6 (0)	0 / 11 (0)	0 / 19 (0)	2 / 21 (9.5)	1 / 29 (3.4)	1 / 49 (2.0)	4 / 61 (8.1)	1 / 79 (1.3)	1 / 211 (0.5)
>3 samples	1 / 6 (17)	3 / 11 (27)	2 / 19 (10)	2 / 21 (9.5)	4 / 29 (14)	3 / 49 (6.1)	4 / 61 (8.1)	5 / 79 (6.3)	10 / 211 (4.7)

Table 11b: Number of false positive HPV types detected per data set reported by laboratories participating in 2008, 2010, 2011, 2013, 2014, 2017, 2019 and 2021 years proficiency studies in comparison with all data sets submitted 2021.

No of false positive samples	All test by laboratories that participated in 2008, 2010, 2011, 2013, 2014, 2017, 2019 and 2021								All datasets 2021 (%)
	2008 (%)	2010 (%)	2011 (%)	2013 (%)	2014 (%)	2017 (%)	2019 (%)	2021 (%)	
0 samples	9 / 17 (53)	12 / 27 (44)	23 / 33 (70)	22 / 38 (58)	32 / 43 (74)	48 / 65 (74)	44 / 77 (57)	65 / 94 (69)	174 / 211 (82)
1 sample	1 / 17 (5.9)	2 / 27 (7.4)	5 / 33 (15)	7 / 38 (18)	2 / 43 (4.7)	8 / 65 (12)	16 / 77 (26)	17 /94 (18)	19 / 211 (9.0)
2 samples	4 / 17 (24)	5 / 27 (18)	3 / 33 (9.1)	1 / 38 (2.6)	2 / 43 (4.7)	2 / 65 (3.1)	5 / 77 (6.5)	6 / 94 (6.4)	7 / 211 (3.3)
3 samples	1 / 17 (5.9)	5 / 27 (18)	0 / 33 (0)	3 / 38 7.9)	3 / 43 (2.3)	1 / 65 (1.5)	6 / 77 (7.8)	1 / 94 (1.1)	1 / 211 (0.5)
>3 samples	2 / 17 (12)	3 / 27 (11)	2 / 33 (6.1)	5 / 38 (13)	4 / 43 (9.3)	6 / 65 (9.2)	6 / 77 (7.8)	5 / 94 (5.3)	10 / 211 (4.7)

5. Discussion

A total of 144 laboratories applied for participation in the 2021 proficiency study, requiring up to 165 proficiency panels. The 2021 proficiency panels were distributed to all solicitants and a total of 211 datasets from 132 laboratories were returned before the deadline (February 2022). There is a record of participant laboratories and submitted datasets since the beginning of the proficiency studies in 2008. The highest number of participant laboratories and submitted datasets considering all 7 previous proficiency studies was seen in 2014, including 121 laboratories and 148 datasets.

Gladly, the global deterioration in HPV typing proficiency that was seen and reported in the 2019 PP has significantly reversed, with a total of 75% (158/211) datasets showing 100% proficiency. Again, this is the highest percentage of 100% proficient datasets seen in all proficiency studies. The highest percentage was seen in 2017 with 73% (114/141) datasets being 100% proficient.

Proficiency criteria was defined as: i) detection at least 50 international units (IU) per 5 ul of HPV 16 and HPV 18, in both single and multiple HPV infections, ii) detection of at least 500 genome equivalents (GE) in 5 ul of the other HPV types (not HPV 16 nor HPV 18) in both single and multiple HPV infections and iii) no false positivity detection. The criteria for proficiency since the 2019 PP includes no false positivity (in previous years, a maximum of one false positive had been allowed for proficiency). Not all assays tested for every HPV type included in the panel. Twenty-eight datasets were generated using assays that either did not discriminate specific HPV types or reported results as HPV 16, 18 and “other” High Risk HPV types (Hybribio 14 HR, Roche Cobas 4800 /6800 test, Abbot Realtime PCR, High risk HPV Screen, Harmonia HPV, and Oncopredict Screen). In the analyses for proficiency only the HPV types tested for were included. E.g., if an assay did not include HPV 68, laboratories using such an assay were considered as not testing for HPV 68. According to these criteria, 158/211 (75%) datasets that typed for at least one HPV type were 100 % proficient for the types claimed to be detected by the test. Of these, 119/158 datasets correctly identified the content of all samples, including the samples with copy number amounts that were lower than required for proficiency. HPV 16, 18, 45 and 35 (most prevalent ones in cervical cancer) were detected in more than 96% datasets.

Most datasets were provided using commercially available assays (182/211), being Hybribio 21 array (Hybribio, 39 laboratories), Anyplex II HPV 28 (Seegene, 21 laboratories) and 3 other Hybribio assays (20 laboratories) the most commonly assays used. Twenty-nine datasets were obtained using a variety of in-house assays. The proportion of commercial assays used in the proficiency studies has exponentially increased over time, from 57% in 2011, 80% in 2019, and now 86% in 2021 (182/211 datasets using commercial assays in 2021). Surprisingly, only 13/211 datasets had used any one of the assays that in systematic reviews of the literature had been found to have had published, adequate

validation studies (Abbott RealTime High Risk HPV, n=3; Anyplex II HPV HR Detection, n=5; BD Onclarity HPV Assay, n=2; Cobas 4800 HPV Test, n=3).

There were several assays from which all the datasets provided showed 100% proficiency (Hybribio 37 array HPV (Hybribio), HPV-23 Genotyping (Hybriobio), Hybribio 14 HR (Hybribio), Real-time PCR MehrViru, Tellgen 27plex 14HR, GenoFlow HPV array (DiagCor) and OncoPredict HPV-DNA (Hiantis)), followed by Hybribio 21 array HPV (Hybribio) with 97.44% of datasets being 100% proficient. On the contrary, none of the datasets obtained with HPV SPF10-LiPA25 (Labo-bio), Abbott m2000 / Alinity M (Abbott), Ampliquality (AB Analitica) and VisionArray HPV (ZytoVision) were 100% proficient.

Overall, 82.46% (174/211) of datasets showed no false positivity. Up to 11 assays (all commercial) showed no false positivity including Abbott m2000 / Alinity M (Abbott), VisionArray HPV (ZytoVision), MassArray MALDITOF (Agena), Onclarity (BD) and Hybribio 37 array HPV (Hybribio) besides the assays being 100% proficient and described above. The assay HPV SPF10-LiPA25 (Labo-bio) was used in 3 datasets and all of them were non-proficient due to false positivity. Regarding the 4 validated assays used in the proficiency study, both Anyplex II HPV HR Detection and Cobas 4800 showed false positivity in one dataset, and none of the 4 other validated assays were fully proficiency in more than 2/3ds of datasets.

We aimed to investigate if there was any specific sample or assay where false positivity was consistently detected. Results from false positivity investigation revealed that false positivity appeared to be essentially randomly distributed among the samples, indicating that the problem with false positivity was not related to a specific sample nor an assay itself (e.g. cross-reactivity), but rather due to laboratory conditions of use (e.g. cross-contamination).

A common finding, seen also in previous studies, is that the laboratory performing the test has a big impact on the performance of the test itself in particular for certain assays. While several of the datasets submitted in 2021 were generated using assays that were used by 4 or fewer laboratories and thus, it was difficult to draw conclusions regarding the generalisability of the performance of these assays, some assays were used for generating quite several datasets. As an example, Anyplex II HPV 28 which was used to generate 21 data sets, provided 15/21 datasets which were fully proficient and 5/21 datasets which were not proficient with 1 to 3 false positive results. This is an example of the impact of the laboratory.

A major finding with robustness was detected with the assays by Hybribio. Datasets generated with these assays were fully proficiency in nearly all cases (97/98 datasets) from different laboratories, translating into being 45.97% from the overall proficiency (74.88%) achieved by the 2021 proficiency study. The widespread use of these assays in laboratories in the WPRO region appears to be a major

reason why the proficiency was highest in this region. Hybribio was used in 59/132 laboratories, with most of them (44/47) belonging to the WPRO region.

All plasmids in the panel were detected at the required concentration for proficiency (at least 50 international units (IU) per 5 ul for HPV 16 and HPV 18, and at least 500 genome equivalents (GE) in 5 ul of the other HPV types) in minimum 91.9% datasets, except for HPV 68a (78.9% of datasets generated with assays targeting this HPV type were 100 proficient for its detection). Plasmids in the panel contained full-length genomes, except HPV 68a that only contained L1. All datasets generated using assays targeting other parts of HPV 68a or that used the PGMY primers were considered as not testing for HPV 68a in this study. It is well reported in literature that all PGMY-based assays (directed against L1) cannot detect HPV68a, except version 2 of PGMY-CHUV assay, and therefore, we also added HPV 68b in the panel. HPV68b can be detected by PGMY-based primers and other common primer systems.

Three additional samples (A, B, C) in the PP were used to evaluate the DNA extraction step prior to HPV testing and typing. Two of the samples contained different amounts of the cervical cancer cell line SiHa mixed with the HPV negative cancer cell line C33A and one sample with only C33A cells served as negative control. There were at least 25 different extraction procedures used among the laboratories. The most commonly used was organic solvent extraction in 35 dataset, followed by different extraction kits from Qiagen used to generate 22 data sets. Other utilised methods were MagNa Pure LC (Roche), Hybribio extraction kit, STARMag from Seegene and Maxwell from Promega. The HPV Direct flow-chip from Master Diagnostica is performed without DNA extraction, the cell suspensions are added directly to the PCR mix. Two laboratories reported false positive results in all three sample A, B, C. We did not observe any obvious difference in performance between different extraction methods.

In sample A containing 2500 cells / 5 ul of the cervical cancer cell line SiHa, HPV 16 was correctly identified by 98 % of the datasets. Three data sets reported false positive HPV types in this sample. In sample B containing 25 SiHa cells / 5ul, HPV 16 was detected in 95 % of the data sets with five false positive result reported. The negative control containing only C33A cells was correctly reported as negative by 97 % of the laboratories.

Participating laboratories involved public health laboratories, research laboratories and diagnostic test manufacturers. There was a charge for laboratories to participate, although participants from low and lower middle-income countries could have their fees waived. It cannot be ruled out that some laboratories from low-income countries may have chosen not to participate because of the fee. It is thus possible that the improved performance observed in the 2021 proficiency study may reflect a bias with a preferential participation of laboratories who can afford the fee and who may preferentially come from high income countries and/or have HPV genotyping as a central priority for their activities.

However, the analysis that was restricted to laboratories that have participated multiple times did also find the improvement in performance in 2021 (from 19/77 being 100% proficient in 2019 to 59/94 in 2021, from 25% to 60%), indicating that there has indeed occurred a global improvement in the performance of HPV genotyping.

The PP is designed for the genotyping needs in HPV vaccine research and the proficiency criteria are not intended for clinical HPV screening purposes, where the requirements for analytical sensitivity may be different. Starting in 2022, we will also be issuing HPV screening panels (with screening-relevant concentrations of the HPV genotypes important for screening) to promote proficiency in HPV screening services as well.

6. Conclusions and recommendations

This technical report summarizes the results obtained from the 8th HPV LabNet HPV DNA proficiency study that was open for participation to all laboratories across the globe. The proficiency panel provided the possibility to evaluate the specificity and sensitivity for different HPV typing assays to correctly identify 13 high risk HPV types and 2 low risk HPV types, the HPV types that are the most important for HPV vaccine research as well as for HPV surveillance and monitoring.

We report that the global proficiency in HPV genotyping services had increased in the 2021 proficiency study. The increased proficiency is seen both in laboratories that had participated in previous studies as well as in laboratories participating for the first time. Laboratories from all WHO regions participated in testing the 2021 PP. An increase in submitted datasets from the WPRO (117 datasets) was seen, surpassing the EURO region (65 datasets) which usually was the region with more laboratories participating in the previous proficiency studies.

The 2021 Global HPV LabNet HPV DNA proficiency panel further supports 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. Comparing the results from 2008, 2010, 2011, 2013, 2014, 2017, 2019 and 2021 Global HPV DNA PPs, we can see overall improvements. Contrary to what was seen in 2019, the 2021 PP revealed an increase in 100% proficiency from 25% to 60% of submitted datasets, and a decrease in <80% proficiency from 45.1% to 33.1% submitted datasets when compared to 2019 results.

Moreover, the highest overall proficiency (75% of datasets) was achieved in this proficienty study, 2021 – higher than in any previous proficiency study. We suggest that recommendations for HPV laboratory testing should continue to include a strong emphasis on the use of negative controls in the assays.

It is possible to achieve a global improvement in proficiency of HPV genotyping services. The improvement in proficiency seen in the 2021 proficiency study suggests that continuing proficiency testing is helpful to sustain and improve accuracy and to avoid a deterioration in proficiency, as seen in the last proficiency study in 2019. In the efforts to eliminate cervical cancer, the International HPV Reference Center will continue to issue PP yearly to promote proficiency in HPV testing services. Starting in 2022, we will also be issuing HPV screening panels (with screening-relevant

concentrations of the HPV genotypes important for screening) to promote proficiency in HPV screening services as well.

Annex 1:

Call for participation:
The 2021 Global HPV LabNet Proficiency Study for HPV DNA Typing

Accurate and internationally comparable HPV DNA detection and typing methodology is an essential component in research on HPV vaccines and in effective implementation and monitoring. A WHO initiative established a Global HPV LabNet to support the worldwide 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.We are now seeking international participation in an international 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 44 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.

Composition of sample material

- 41 tubes containing purified whole genomic plasmids of **HPV 6, 11, 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68a** and **68b** in a background of human cellular DNA. Each sample may contain either single types or a mixture of HPV types at varying concentrations.
- 3 samples containing cell suspensions to allow evaluation of DNA extraction methods.

Participation fee

Participation in the proficiency study is subject to a participation fee per panel consisting of 44 samples: 1000 Euros for commercial entities and 500 Euros for academic entities. Laboratories that have outstanding payments from past Global HPV LabNet proficiency studies will need to clear their debts before their registration is accepted.

Data submission

The International HPV Reference Laboratory in Sweden is organizing this study in collaboration with the Swedish external quality assurance provider Equalis AB, who is responsible for management and distribution. Laboratories that have more than one assay are encouraged to provide results on each assay they commonly use. Data submitted will become the property of the organizers and may be analyzed for publication by the Global 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. 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.

Scientific issues

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Registration

Application forms for the 2021 study can be found at:
http://www.equalis.se/en/products-and-services/project/hpv-typing-proficiency-study/

Preliminary dates

18th of June 2021:	Registration for participation opens.
30th of August 2021:	Registration for participation closes.
October 2021:	Dispatch of panels begins.

Participation, management and practical issues

Equalis AB, Sweden www.equalis.se
E-mail: HPV@equalis.se

Annex 2: Application for participating in The 2021 Global HPV LabNet DNA Typing Proficiency Study

Fee for commercial entities: 1000 Euros, Fee for academic entities: 500 Euros. Participants from low and lower middle-income countries (World Bank classification with GNI (gross national income) per capita: <3 975 USD) can apply for waiving of fee.	
Delivery address:	
Lab ID (from previous participation):	
Department /Laboratory	
Address	
City	Postal code
Province /State	Country
E-mail	Fax
Phone	
Invoice address (if different from above):	
VAT number:	
Department /Laboratory	
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City	Postal code
Province /State	Country
Mode of payment (please check the preferred choice):	
By Credit Card/PayPal:	
By Invoice:	
Principal Investigator:	
First Name	
Surname (Title)	
HPV DNA typing experience in your laboratory	
Methodology used (may be more than one)	
Annual number of HPV typing tests performed	
Brief description of involvement in HPV surveillance or HPV vaccine development	

Return registration form by email or fax to: info@equalis.se. **Fax: +46 18 69 31 46**

Annex 3:

Source of panel material.

Complete genomes of HPV cloned into plasmid vectors had been provided to the Lund University by the respective proprietors with a written approval to be used in this proficiency panel: Dr Ethel-Michele de Villiers (HPV types 6, 11, 16, 18 and 45), Dr Gérard Orth (HPV types 33, 39 and 68a prototype), Dr Elisabeth Schwarz (HPV 68b), Dr Saul Silverstein (HPV type 51), Dr Attila Lörincz (HPV types 31, 35 and 56), Dr Wayne Lancaster (HPV type 52) and Dr Toshihiko Matsukura (HPV types 58 and 59).

The HPV genomes are cloned into different cloning vectors: HPV 6 in pBR322 at position 4724 in the HPV genome, HPV 11 in pGEM4Z at position 4781, HPV 16 in pBR322 at position 6152, HPV 18 in pGEM-5Zf vector in the L2 region, HPV 31 in pT713 at position 3362, HPV 33 in pBR322 at position 2797, HPV 35 are cloned in two fragments 5012-956 and 956-5012 in pT713, HPV 39 in pGEM4z at position 1714, HPV 45 in pGEM4Z at position 75, HPV 51 in pGEM4z at position 4511, HPV 52 in pUC19 at position 7559, HPV 56 in pT713 at position 5521, HPV 58 in pGEM4Z at position 1158, HPV 59 in pUC9 at position 69, HPV 68a prototype in a bluescript vector, and HPV68b (ME180) of about 7 kb containing L1, L2, E1, E2, E4, E5, E6, E7 with an incomplete E2 gene in pCR4-TOPO.

The nucleic acid sequences for each of these HPV genomes have been reported previously and are available in Gene Bank with the following accession numbers; HPV 6 nr X00203; HPV 11 nr M14119; HPV 16 nr K02718; HPV 18 nr X05015; HPV 31 nr J04353; HPV 33 nr M12732; HPV 35 nr M74117; HPV 39 nr M62849; HPV 45 nr X74479; HPV 51 nr M62877; HPV 52 nr X74481; HPV 56 nr X74483; HPV 58 nr D90400; HPV 59 nr X77858; HPV 68a nr X67161 and HPV 68b nr FR751039.

Annex 4:

List of participants in the HPV LabNet Proficiency Study of HPV DNA Typing, 2021

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