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Individual detection of 14 high risk human papilloma virus genotypes by the PapType test for the prediction of high grade cervical lesions

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ABSTRACT

Background: HR HPV genotypes when assayed collectively, achieve high sensitivity but low specificity for the prediction of CIN2+. Knowledge of the specific genotypes in an infection may facilitate the use of HR HPV detection in routine clinical practice.

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Study design: PreservCyt samples from 1099 women referred for abnormal cervical cytology were used. CIN2+ was chosen as the primary end-point but CIN3+ was also evaluated. A hierarchy of HR HPV genotypes was created using PPV and this was used to create 3 groups of genotypes with potentially different management.

Results: The PapType assay has a specificity of 22.4% and a sensitivity of 94.6% for CIN2+ prediction. Classification into Groups A (HPV33 and HPV16, very highly predictive), B (HPV31, 18, 52, 35, 58, 51 highly predictive) and C (HPV68, 45, 39, 66, 56, 59, intermediate predictive) could double the specificity (44.5%) but only slightly reduce the sensitivity for CIN2+ (91.5%) and CIN3+ (94.0%).

Conclusions: The PapType assay is a simple, reproducible and effective test for HR HPV detection and genotyping. HPV 33 was found to have a very high PPV and should therefore be managed as for HPV16.

1. Background

Over 230 distinct papillomavirus genotypes have been identified based on nucleic acid sequence analysis and 179 are human papillomaviruses [1,2]. 12–14 HR HPV genotypes are usually assayed collectively to achieve high sensitivity for predicting high grade cervical lesions. However, this leads to a low specificity, especially in young women [3–5]. As a result, individual genotype detection (in particular HPV16 and HPV18), has been added to some commercial tests and algorithms for using these have been proposed [6]. The value of full genotyping is not clear.

Here we evaluate PapType, a new semi-automated bead-based multiplex genotyping assay from Genera Biosystems capable of identifying 16 HPV genotypes individually (HPV6, 11, 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66 and 68) in a single assay [7,8], and assess whether the identification of more HR HPV genotypes could improve the triage of HR HPV positive women.

2. Objective

To compare the rate of HR HPV detection and the accuracy of CIN2+ prediction between PapType assay and other commercially available HR HPV assays, and to examine the role of complete genotyping.

3. Study design

3.1. Study population

1099 women referred to the colposcopy clinics at the Hammersmith and St. Mary's Hospitals for an abnormal screening smear were included in this study (Predictors 2) [9]. Briefly, two 20 ml PreservCyt samples were collected at the time of colposcopy and 1 ml aliquots were stored at 4 °C [9]. DNA extraction was carried out

Abbreviations: HR HPV, high risk human papillomavirus; CIN2+ and/or CIN3+, high grade cervical intraepithelial neoplasia; PPV, positive predictive value.

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immediately before the PapType assay. No PapType results were obtained for 32 women (3 had insufficient sample volume and 29 samples yielded insufficient DNA). In the remaining 1067 women, there were 223 CIN3+ lesions (209 CIN3, 5 CGIN [high grade], 9 invasive squamous carcinomas) and 131 CIN2 lesions. CIN3+ and CIN2 lesions (total = 354) were analysed together as CIN2+.

3.2. Laboratory methods

3.2.1. PapType high risk HPV detection and genotyping (Genera)

DNA extraction and purification was carried out using the m2000 system (Abbott Molecular) and the RealTi*m*e DNA extraction reagents and protocol. Essentially, DNA was extracted from 400 μl PreservCyt samples, eluted in 100 μl water, of which 25 μl was used for PCR. Detection of 14 HR and 2 LR HPV genotypes by PapType assay uses PCR amplification using GP5+ and GP6+ consensus primers. The PCR programme used was as follows:

94 °C for 15 min; 48 cycles of 94 °C for 30 s, 44 °C for 1 min and 72 °C for 1 min; 72 °C for 5 min then hold at 10 °C. Alkali myosin light chain protein (MYL3) was used as human DNA control. Human DNA control and the test sample were amplified in the same PCR. The amplicons were labelled during PCR (48 cycles) with red fluorescent reporter dye Alexa Fluor® 647, converted to single-strands by incubation with λ-exonuclease and captured by hybridisation to HPV genotype specific sequences (16 HPV types + 1 control) individually immobilised on one of 17 PapType bead types in a BODIPY® tetramethylrhodamine (TMR, yellow fluorescence) labelled silica bead (Ampasand™) cocktail. The beads types were identified by a combination of bead diameter and discrete TMR levels and assayed for red fluorescence to detect the hybridised analyte using a flow cytometer (FACSArray, BD). This allowed all genotypes to be assayed in a single multiplex reaction.

Some cross reactivity was observed between HPV33 probe with HPV35 amplimers but not vice versa. This could have arisen due to the HPV33 and the HPV35 specific probes sharing a homology involving 13 nucleotides. The manufacturer's cut-off level was set at 250–710 fluorescence units depending on the genotype (250 units for HPV11, 16, 18, 31, 33, 35, 39, 45, 51, 56, 59 and 66; 350 units for HPV52, 58 and 68; 710 units for HPV6). This gave results showing an excess of HPV33 low positives when HPV35 was also positive. To correct for this, we raised the cut-off level of HPV33 to 1750 units when and only when HPV35 was also detected while maintaining the cut-off level of HPV35 at 250 units so that the number of dual positive HPV33/35 cases was equal to the expected number under the assumption that infection with HPV 33 and HPV35 were independent events.

Fifty three samples were selected at random for repeat testing. Perfect concordance was found in 45 samples (84.9%), complete discordance in 2 samples (3.8%) and partial discordance in 6 samples (11.3%).

3.2.2. Other HPV assays

These are described in detail elsewhere [9].

3.3. Statistical methods

The main outcome measures were sensitivity, specificity and positive predictive value (PPV). Confidence intervals were based on binomial statistics. The PapType test was compared to other tests (results from Ref. [9]) using the kappa statistic and McNemar's test for discordant pairs. Added PPV for the new genotype was used to optimise the sequential addition of new genotypes from the set of 14 HR HPV genotypes to create a hierarchy of genotypes, and the results were plotted as a Receiver Operating Characteristic (ROC) curve (cumulative sensitivity versus cumulative 1-specificity). The risk of CIN2+ in relation to single versus multiple infection was assessed by logistic regression. A forest plot was used to evaluate the ability of the different HR HPV genotypes to identify CIN2+ infections, both in single and multiple infection contexts. Logistic regression models and linear discriminant analysis were used to assess the predictive ability of HR HPV genotype clusters on the probability of developing CIN2+. All statistical analyses were carried out using Stata 10.1 (StataCorp, USA) and R 2.15.0 software packages (The R Foundation for Statistical Computing).

4. Results

4.1. Diagnostic performance

With the 14 HR genotypes combined, PapType detected high grade cervical lesions (CIN2+) with a sensitivity of 94.6%, specificity

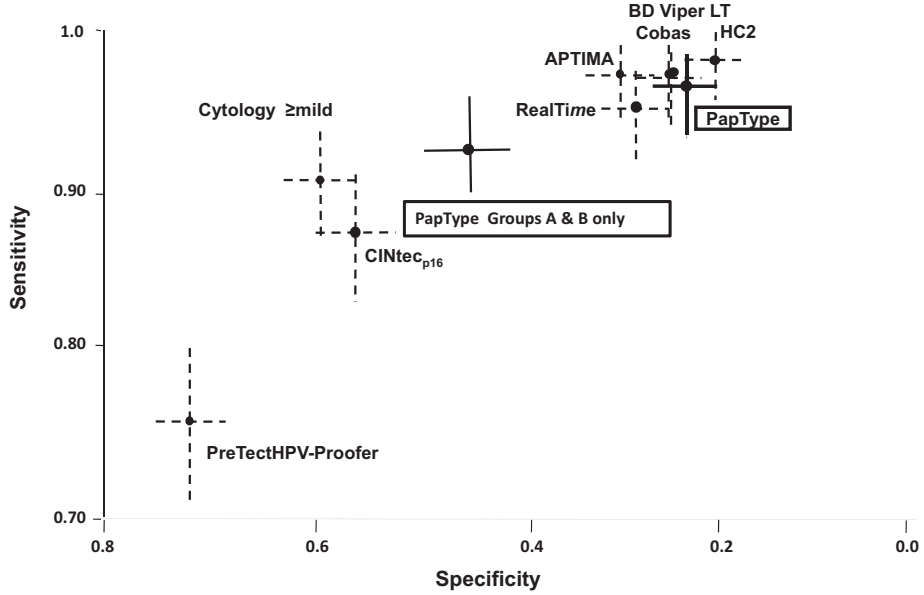

Fig. 1. Detection of CIN2+ by different HR HPV assays. Sensitivity and specificity are indicated with 95%CIs. APTIMA (Hologic/Gen-Probe), BD Viper LT (Becton Dickinson), CINtecp16 (Roche mtm), Cobas (Roche), HC2 (Qiagen), PapType (Genera), PreTectHPV-Proofer (Norchip), RealTi*m*e (Abbott).

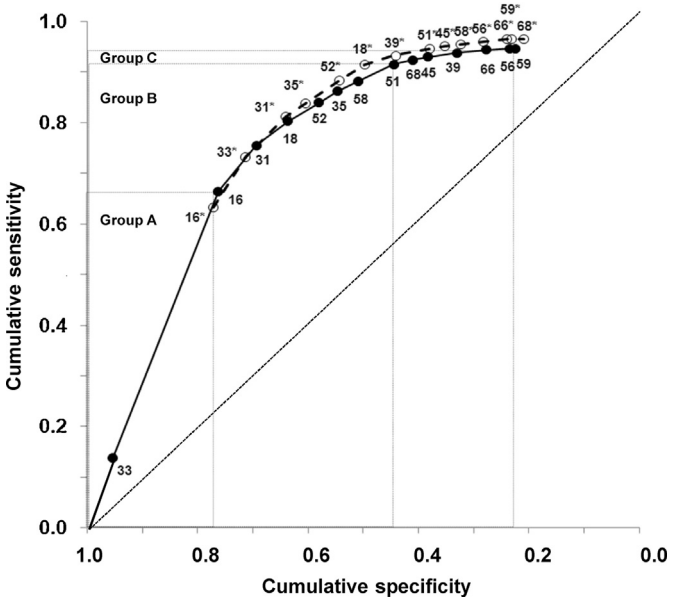

Fig. 2. ROC curve of cumulative sensitivity and specificity for CIN2+ (•—•) or CIN3+ (o--o) when genotypes are ordered according to positive predictive value in women not already deemed positive by prior genotypes.

of 22.4% and PPV of 37.7%. Its performance was similar to that of other DNA-based assays (Fig. 1 and Table 1, Ref. [5]).

4.2. Genotype specific performance

PapType showed good agreement with other sensitive assays for overall HR HPV genotype detection, PPV for CIN2+ (Table 1) and detection of HPV16 or HPV18 (Table 2).

Genotypes were selected to maximise the PPV among remaining women not having a genotype already selected (Fig. 2). The resulting order was HPV 33, 16, 31, 18, 52, 35, 58, 51, 68, 45, 39, 66, 56 and 59. HR HPV genotypes were clustered into 3 hierarchical groups (Table 3). Group A (HPV33 and 16; PPV ~ 60%), group B (HPV31, 18, 52, 35, 58 and 51; PPV 20–40%) and group C (HPV68, 45, 39, 66, 56 and 59; PPV ≤ 11%). HPV31 (PPV = 39.5%) was intermediate between groups A and B but was included in group B because clustering based on linear discriminant analysis gave a better fit for this assignment.

Inclusion of genotypes from groups A and B only resulted in sensitivity for CIN2+ detection of 91.5% and a specificity of 44.5% (Fig. 1 and Table 3). This sensitivity was higher than for p16 or for mild or worse repeat cytology taken at colposcopy, but the specificity was not as high (Fig. 1). If the genotypes are ranked according to PPV using CIN3+ as the endpoint, HPV16 and HPV33 remain in Group A but are reversed in ranking. The exact order within Group B would change slightly and the rank order would be HPV31, 35, 52, 18, 39 (added) and 51 with HPV58 now reclassified as Group C. The sensitivity of Groups A and B combined for CIN3+ is 94% based on the CIN2+ ranking and 95% based on the CIN3+ ranking (Fig. 2).

4.3. CIN2+ risk associated with single or with multiple infections other than HPV16

When HPV16 was present, co-infection with other genotypes did not confer additional risk (Fig. 3). The same was true for HPV33 when HPV16 was not present. The odds ratio for CIN2+ for multiple rather than single infection with any HR HPV genotype in women without HPV16 was 1.61 (95%CI = 1.07–2.41) (Fig. 3). In

Table 1
Positivity rate and PPV for CIN2+ by HR HPV genotype for different assays.

Assay	Samples tested (100%)	Positivity rate (%) and PPV (%) for CIN2+													
		HPV16	HPV18	HPV45	HPV31	HPV33	HPV58	HPV56	HPV66	HPV35	HPV39	HPV68	HPV51	HPV52	HPV59	All HR
PapType	1067	31.21 (58.26)	8.81 (40.43)	5.34 (31.58)	10.68 (49.12)	7.69 (59.76)	5.53 (33.90)	6.56 (14.29)	6.84 (17.81)	4.78 (31.37)	7.31 (25.64)	4.40 (29.79)	10.78 (35.65)	9.84 (40.95)	3.19 (32.35)	83.22 (37.73)
BD Viper LT[a]	1067	31.40 (59.70)	9.65 (38.83)	5.15 (41.82)	12.65 (49.63)		28.21 (33.22)				20.15 (29.30)		11.25 (34.17)	11.15 (45.38)	4.59 (34.69)	83.97 (37.72)
RealTime[a]	1065	31.36 (58.68)	8.73 (40.86)						59.53 (33.44)							81.31 (38.12)
Cobas[a]	1065	32.77 (58.74)	10.33 (38.18)						65.73 (34.00)							84.41 (37.60)
APTIMA[a]	955	30.89 (60.34)	12.04 (40.00)		12.67 (51.59)	7.12 (66.18)										52.46 (39.35)
PreTectHPV-Proofer[a]	1026	27.00 (66.43)	7.99 (42.68)	5.56 (42.11)	2.44 (32.00)	7.89 (58.02)										45.03 (55.19)

[a] Data from Ref. [9]. PapType (Genera), BD Viper LT (Becton Dickinson), RealTime (Abbott), Cobas (Roche), APTIMA (Hologic/Gen-Probe) and PreTectHPV-Proofer (Norchip).

Table 2
Comparison of PapType (Genera) with other HR HPV assays for the detection of HPV16, HPV18 or any HR HPV in <CIN2 and ≥CIN2 lesions. The *P* value was calculated with McNemar's test with the continuity correction.

Lesion grade	HPV genotype	Assay[a]	Assay type	Kappa index	McNemar's test for discordant pairs		
					PapType = +/− vs. −/+	OR (95%CI)	*P* (2-tailed)
<CIN2	HPV16	RealTime	DNA	0.93	8, 7	0.88 (0.27, 2.76)	1.0
		BD Viper LT	DNA	0.89	14, 10	0.71 (0.28, 1.73)	0.5
		Cobas	DNA	0.92	7, 12	1.71 (0.62, 5.14)	0.4
		PreTectHPV-Proofer	RNA	0.76	44, 2	0.05 (0.01, 0.17)	<0.0001
		APTIMA	RNA	0.88	15, 8	0.53 (0.20, 1.34)	0.2
	HPV18	RealTime	DNA	0.95	3, 2	0.67 (0.06, 5.82)	1.0
		BD Viper LT	DNA	0.90	2, 9	4.50 (0.93, 42.80)	0.1
		Cobas	DNA	0.89	0, 12	∞	0.002
		PreTectHPV-Proofer	RNA	0.85	11, 3	0.27 (0.05, 1.03)	0.06
	HPV18 or 45	APTIMA	RNA	0.82	19, 5	0.26(0.08, 0.73)	0.008
	AnyHR	RealTime	DNA	0.86	26, 9	0.35 (0.14, 0.76)	0.006
		BD Viper LT	DNA	0.86	15, 20	1.33 (0.65, 2.80)	0.5
		Cobas	DNA	0.83	17, 25	1.47 (0.76, 2.90)	0.3
		PreTectHPV-Proofer	RNA	na	na	na	na
		APTIMA	RNA	0.72	51, 22	0.43 (0.25, 0.72)	0.0009
CIN2+	HPV16	RealTime	DNA	0.97	1, 4	4.00 (0.40, 196.99)	0.37
		BD Viper LT	DNA	0.95	1, 7	7.00 (0.90, 315.48	0.08
		Cobas	DNA	0.94	0, 11	∞	0.003
		PreTectHPV-Proofer	RNA	0.91	10, 5	0.50 (0.13, 1.61)	0.3
		APTIMA	RNA	0.96	1, 6	6.00 (0.73, 275.99)	0.1
	HPV18	RealTime	DNA	0.97	1, 1	1.00 (0.01, 78.50)	0.5
		BD Viper LT	DNA	0.94	1, 3	3.00 (0.24, 157.49)	0.6
		Cobas	DNA	0.94	0, 4	∞	0.1
		PreTectHPV-Proofer	RNA	0.91	4, 2	0.50 (0.05, 3.49)	0.7
	HPV18 or 45	APTIMA	RNA	0.82	7, 7	1.00 (0.30, 3.34)	0.8
	AnyHR	RealTime	DNA	0.82	5, 2	0.40 (0.04, 2.44)	0.5
		BD Viper LT	DNA	0.79	2, 5	2.50 (0.41, 26.25)	0.5
		Cobas	DNA	0.80	1, 5	5.00 (0.56, 236.49)	0.2
		PreTectHPV-Proofer	RNA	na	na	na	na
		APTIMA	RNA	0.71	2, 7	3.50 (0.67, 34.53)	0.2

[a] Data from Ref. [9]. na, Norchip is not included since it assayed for 5 genotypes only.PapType (Genera), BD Viper LT (Becton Dickinson), RealTime (Abbott), Cobas (Roche), APTIMA (Hologic/Gen-Probe) and PreTectHPV-Proofer (Norchip).

general having a multiple infection conveyed no additional risk for those HPV genotypes in Group B in the absence of HPV16 (OR = 1.44, 95%CI = 0.90–2.30) but it did increase risk for those HPV genotypes in Group C (OR = 4.85, 95%CI = 2.29–10.26). It would appear that in multiple infections the genotype with the highest PPV largely determines the risk and the impact of the additional genotypes is small.

5. Discussion

The PapType assay described here detects 14 individual HR HPV genotypes in a single assay and provides a simple, reproducible and relatively high throughput semi-automated genotyping test which takes approximately 9 h of hands-on time for each run of 91 DNA samples. PapType has the potential for full automation

Table 3
The classification of HR HPV genotypes according to PPV for CIN2+.

Subgroup	Genotype	For the new type			Cumulative			
		N at risk	CIN2+/HPV+	PPV	CIN2+/HPV+	PPV	Sensitivity	Specificity
A	HPV 33	1067	49/82	59.76	49/82	59.76	13.84	95.37
	HPV 16	985	186/322	57.76	235/404	58.17	66.38	76.30
	Subtotal		235/404	58.17				
B	HPV 31	663	32/81	39.51	267/485	55.05	75.42	69.42
	HPV 18	582	17/58	29.31	284/543	52.30	80.23	63.67
	HPV 52	524	13/53	24.53	297/596	49.83	83.90	58.06
	HPV 35	471	8/32	25.00	305/628	48.57	86.16	54.70
	HPV 58	439	7/34	20.59	312/662	47.13	88.14	50.91
	HPV 51	405	12/58	20.69	324/720	45.00	91.53	44.46
	Subtotal		89/316	28.16				
C	HPV 68	347	3/27	11.11	327/747	43.78	92.37	41.09
	HPV 45	320	2/22	9.09	329/769	42.78	92.94	38.29
	HPV 39	298	3/40	7.50	332/809	41.04	93.79	33.10
	HPV 66	258	2/40	5.00	334/849	39.34	94.35	27.77
	HPV 56	218	1/32	3.13	335/881	38.02	94.63	23.42
	HPV 59	186	0/7	0.00	335/888	37.73	94.63	22.44
	Subtotal		11/168	6.55				
	Total		335/888	37.73				

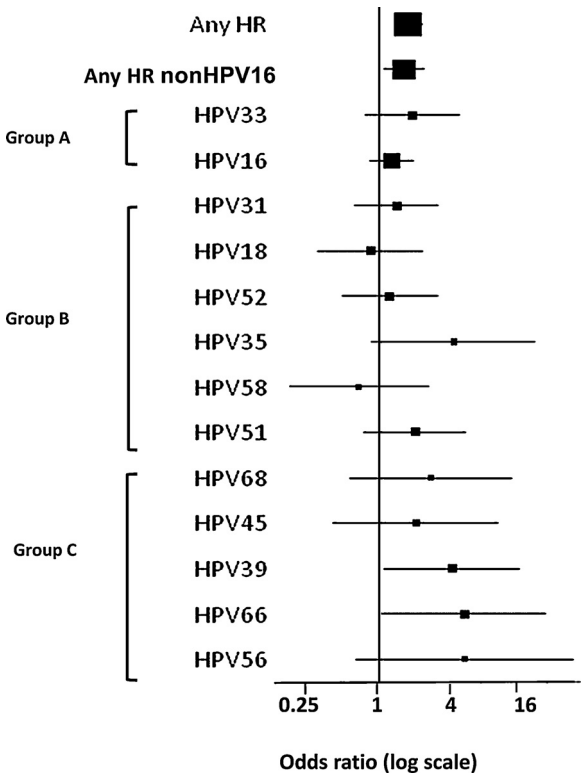

Fig. 3. Odds ratio for CIN2+ for multiple versus single type infection. For all individual genotypes except HPV16, the multiple infections considered are those which do not include HPV16. There were no CIN2+ lesions with single HPV59 infection.

in a convenient microtitre format with full objective quantitative readout.

The diagnostic performance and genotyping accuracy of the PapType assay were found to be comparable to other assays using well documented routine clinical samples (Fig. 1, Tables 1 and 2). Two type specific findings were of particular interest. First, HPV18 ranked 4th and HPV45 ranked only 10th in risk for CIN2+. HPV18 consistently ranks 2nd for cancer risk but much lower for high grade CIN [10]. The lower ranking of HPV45 is similar to the ranking order of 9th for CIN3+ in the ATHENA trial for CIN3+ based on the Linear Array assay [11], but is in contrast to in 3rd place ranking in risk for cervical cancer worldwide [12]. In our study population, the number of HPV45 positive lesions was too small ($n = 22$) to have sufficient statistical power to fully evaluate this, but its position in the risk hierarchy needs further evaluation. HPV18 and 45 have been consistently related to adenocarcinoma and low PPV for CIN2+. Persistent positivity of these 2 genotypes may indicate a lesion not easily visible by colposcopy and suggests further investigations higher in the endocervical canal. This may be a reasonable justification for genotyping them despite their low PPV. Secondly, HPV33 was associated with a PPV for CIN2+ and CIN3+ as high as HPV16 and substantially more predictive than HPV18 and other genotypes. This has been reported previously [13–18], but its significance has not been fully recognised. Our results suggest that the oncogenic status of HPV33 should be elevated and it should be assayed for in addition to HPV16 and HPV18 as in current practice. Similarly, HPV33 should also be targeted by future HPV vaccines. PapType detected 7 samples positive for both HPV33 (at the raised cut-off value of 1750 units) and HPV35. The median HPV33 signal was 3237, well above the raised cut-off value. The manufacturer estimates that the HPV33 probe signal due to cross-reactivity with HPV35 amplimer is of the order of 30% of the HPV35 probe signal. If this is the case, 5 of the 7 samples had an HPV33 signal far in excess of what could be attributable to HPV35 and are therefore considered true positives for HPV33. In this group, there are 2 high grade lesions. In the remaining 2 samples, the HPV33 signal might have been attributable to the presence of HPV35. Neither of these lesions were high grade. A full exploration of this cross reactivity would require a dilution experiment with clones of HPV 33 and 35 which we have not yet done.

As far as we are aware, this is the first report which demonstrates a diagnostic classification of HR HPV genotypes by sequential maximising of PPV which could facilitate the triage of women at risk of CIN2+. Our results suggest that Group A (HPV16 and HPV33) has the highest risk of being associated with high grade CIN and require the most aggressive management [19–21]. Group B includes 6 further genotypes (HPV31, 18, 52, 35, 58, 51) and also has a high PPV for disease, but referral would probably also depend on the degree of cytologic abnormality, or the existence of other risk factors such as p16 positivity. The remaining 6 'high risk' genotypes (68, 45, 39, 66, 56, 59) clearly carry a lower risk of disease with a PPV of only 6.5%, although they are still responsible for an additional 3.1% of CIN2+ in this study and 6% of all cancers in Europe [10]. Here colposcopic referral probably needs to be based on additional evidence of persistence, high grade cytological abnormality or other risk factor (e.g. p16).

Our genotype grouping also provided additional insight into multiple infections with HR HPV, which are common in women referred with abnormal cytology. Previously, two models have been proposed to attribute disease risk [22]. The "proportional model" accords equal risk to individual genotypes in each multiple infection. The "hierarchical model" attributes the risk to the genotype most frequently found in multiple infections. Neither of these models takes the varying oncogenic potential of individual HPV genotypes into account. In this study, we found that risk of high grade disease in women with multiple infections can be assessed by the single genotype present with the highest PPV (Table 3). This is consistent with the observation that multiple infection with HR HPV genotypes per se does not add to the risk of high grade CIN beyond the risk associated with the highest risk single infection [3].

The results obtained here are from a referral population with abnormal cytology. We believe our conclusions regarding the genotype hierarchy are likely to also hold for a screening population, but this remains to be established and validated in such a population. Our collection and aliquotting procedures were also different from those which would be used in routine practice, but this is unlikely to affect our findings.

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Competing interests

None.

Ethics approval

All women provided written consent and the project was approved by the Local Research Ethics Committee.

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