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Clinical use of the Onclarity test with extended HPV genotyping and phenotyping in patients with suspected squamous intraepithelial lesions

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ABSTRACT

Objectives: Human papillomavirus (HPV) is the most widespread virus with oncogenic potential that infects humans and there is a need to look for the most effective screening method among the population. Understanding the role of HPV in cervical dysplasia and viruses typing increased the usage of HPV-based cervical cancer screening tests using genotyping.

Material and methods: We aim to assess the usefulness the Onclarity Test with extended genotyping and phenotyping of HPV in detecting cervical squamous intraepithelial lesions in 695 subjects who registered for regular cervical screening or due to abnormal LBC result or positive HPV results.

Results: Incidence of positive HPV depended significantly on biopsy outcome ($p < 0.001$). It was the highest for patients with HSIL (92.5%), lower for patients with LSIL (57.9%) and with HPV outcome of biopsy (50.0%). The sensitivity of positive HPV for detecting HSIL was equal to 92.50% (95% CI: 79.61%–98.43%), and specificity equalled 55.26% (95% CI: 43.41–66.69%). Sensitivity of HPV positive for any of 16, 18, 31, 45, 51 or 52 genotypes but not belonging to the P1, P2 or P3 group for detecting HSIL equalled 62.50% (95% CI: 45.80–77.27%), specificity equalled 72.37% (95% CI: 60.91–82.01%).

Conclusions: The Onclarity test is characterised by high sensitivity and specificity in detecting CIN2+ lesions. Extended genotyping enables the identification of the most common oncogenic HPV types in the population. It can be used as a basic tool for secondary prevention or together with LBC.

Keywords: HPV; genotyping; phenotyping; SIL; Onclarity

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INTRODUCTION

Human papillomavirus (HPV) is the most widespread virus with oncogenic potential that infects humans [1]. Infection with genital genotypes of human papillomavirus affects up to 80–90% of sexually active adults during their lives. However, a healthy organism characterized by an efficiently functioning immune system within 1 to 2 years may spontaneously defeat the infection, so infections transmitted mainly through sexual routes are usually asymptomatic. The infection becomes persistent among 10–20% of patients, which allows for the overexpression of essential HPV oncoprotein-producing genes, including E6 and E7 [2, 3]. The crucial role of these proteins is cell cycle dysregulation and the promotion of uncontrolled cell survival and proliferation [4]. HPV contributes irrefutable to cancer development — cervical, anogenital, head and neck, and other locations [5, 6]. Epidemiologic studies present steadily more information concerning virus genotyping and their specific characteristics, the evolution of the infection process, and about factors responsible for the neoplastic transition [7]. Researchers compare screening modalities and consider the pros and cons of cytological methods concerning HPV testing as the primary method of population screening method for cervical cancer (cc) aims to reduce morbidity and mortality

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from the disease and detect precursor lesions that should be monitored or treated [8, 9]. According to Global Cancer Statistics, in 2020 — 604,127 new cervical cancer patients were reported, and 341,831 died. Additionally, the authors of this analysis report that death rates for cervical cancers were significantly higher in developing countries compared to developed countries (15.0 vs 12.8 per 100,000) [10]. The incidence of HPV-associated lesions is still growing. Therefore, there is a need to look for the most effective screening method among the population. Understanding the role of HPV in cervical dysplasia and viruses typing increased the usage of HPV-based cervical cancer screening tests using genotyping [11, 12].

Objectives

The study aims to assess the sensitivity and specificity of the Onclarity Test with extended genotyping and phenotyping of HPV in detecting cervical squamous intraepithelial lesions.

MATERIAL AND METHODS

Study design

To the study we enrolled 695 subjects who registered to Specialist Medical Practice between January 2022 and June 2023 for regular cervical screening or due to abnormal LBC result or positive HPV results. For verification, parallel to the Pap-smear, the women were tested for the presence of HPV, which genotypes were determined.

LBC and Onclarity HPV testing

We collected liquid-based cytology and molecular assessment samples with an endocervical Cyto-Brush preserved in SurePath ®. Then, the probes were passed to an independent, standardized laboratory.

The BD Onclarity HPV Assay is a method for detecting 14 different HPV genotypes while incorporating a β-globin internal control (IC) as a processing control. The HPV genotypes are detected using specific primers designed to target a region of 79 to 137 bases in the E6/E7 genome, while the IC primers am. In contrast, a 75-base region in the human β-globin gene. To perform the assay, three polymerase chain reaction (PCR) assay tubes, namely G1, G2, and G3, are utilized, along with four optical channels for the detection process. The HPV genotypes that can be detected individually are HPV 16, 18, 31, 45, 51, and 52. The remaining genotypes are grouped as follows: HPV 33/58, 56/59/66, and 35/39/68. The IC serves as a control to ensure the accuracy and validity of the assay.

Colposcopy and punch biopsy

Further validation of abnormal screening results was performed on all patients with an abnormal smear as follows: ASC- US, ASC-H, LSIL, HSIL, AGC, cervical cancer), a positive HPV test for types 16, 18, 31, and a clinically suspicious cervical image. A specialist in gynecologic oncology with 10 years' experience examined colposcopy with SmartOPTIC colposcope. Trial with a 3–5% aqueous solution of acetic acid and Schiller's test with Lugol's iodine were performed in all cases. The colposcopic images were evaluated according to Reid's Colposcopic Index, which assesses the colour, lesion boundaries and surface, blood vessels, and iodine test. The Polish Society of Colposcopy and Cervical Pathophysiology recommended the International Federation of Cervical Pathology and Colposcopy classification.

Statistical methods

Analysis was conducted with statistical software R, version R4.1.2. All calculations assumed a significance level of $\alpha = 0.05$. Nominal variables were presented as n and %, and age was summarised with mean and standard deviation. Dependencies between categorical variables were analyzed with Pearson chi-square test. Diagnostic abilities of HPV genotypes for HSIL or LSIL biopsy outcome were assessed with sensitivity, specificity, PPV (positive predictive value), NPV (negative predictive value) and accuracy with a 95% confidence interval (CI).

RESULTS

The study group includes 695 patients aged 18-76, with an average of 37 years. The characteristics of the study group are presented in Table 1.

Dependency between age and: cytology, biopsy, HPV +/-, HPV genotype

A significant difference in Pap-smear outcome across age groups was confirmed, $p = 0.044$. The proportion of specific results connected with an age are shown in Table 2.

The significant difference in biopsy outcome across age groups was not confirmed, as presented in Table 3.

The incidence of positive HPV differed significantly across age groups ($p = 0.002$). Incidence of specific HPV genotypes connected with an age are presented in Table 4.

Dependency between biopsy outcome and HPV

Incidence of positive HPV depended significantly on biopsy outcome, $p < 0.001$. It was the highest within patients with HSIL (92.5%), lower for patients with LSIL (57.9%) and with HPV outcome of biopsy (50.0%, n = 4) and the lowest within patients with NILM (27.6%, n = 8). One patient with a condyloma biopsy outcome had a negative HPV outcome. Incidence of HPV genotype 16 depended significantly on biopsy outcome, $p < 0.001$. It was the highest within patients with HSIL (72.5%) and lower with patients with HPV

Table 1. Group characteristics

Characteristics	Values
n	695 (100.0)
Age [years], mean ± SD	37.45 ± 9.94
Age [years], n (%)	
< 25	56 (8.1)
25–34	255 (36.7)
35–44	244 (35.1)
45–54	109 (15.7)
≥ 55	31 (4.5)
LBC result, n (%)	
NILM	514 (74.0)
ASC-US	68 (9.8)
LSIL	57 (8.2)
ASC-H	28 (4.0)
HSIL	25 (3.6)
AGC	3 (0.4)
HPV, n (%)	
Positive	159 (22.9)
Negative	536 (77.1)
HPV genotype, n (%)*	
16	68 (9.8)
18	9 (1.3)
31	30 (4.3)
45	9 (1.3)
51	14 (2.0)
52	15 (2.2)
P1	18 (2.6)
P2	29 (4.2)
P3	30 (4.3)
Biopsy, n (%)	
HSIL	40 (5.8)
LSIL	38 (5.5)
NILM	29 (4.2)
HPV	8 (1.2)
Condyloma	1 (0.1)
None	579 (83.3)

ASC-US — atypical squamous cells of undetermined significance; AGC — atypical glandular cells; ASC-H — atypical squamous cells, cannot exclude a high-grade squamous intraepithelial lesion; LSIL — low-grade squamous intraepithelial lesion; HSIL — high-grade squamous intraepithelial lesion; HPV — human papillomavirus; NILM — negative for intraepithelial lesion or malignancy; LBC — liquid-based cytology; SD — standard deviation; *Various genotypes could be observed for one patient

outcome of biopsy (25.0%, n = 2), LSIL outcome (15.8%, n = 6) and NILM outcome (13.8%, n = 4). One patient with Condyloma biopsy outcome had a negative outcome for HPV genotype 16. Incidence of other HPV genotypes did not significantly differ across biopsy outcomes ($p > 0.05$), as presented in Table 5.

Diagnostic abilities of HPV genotypes for HSIL

The sensitivity of positive HPV for detecting HSIL was equal to 92.50% (95% CI: 79.61–98.43%), and specificity equalled 55.26% (95% CI: 43.41–66.69%). Sensitivity of HPV positive for any of 16, 18, 31, 45, 51 or 52 genotypes but not belongin to the P1, P2 or P3 group for detecting HSIL equalled 62.50% (95% CI: 45.80–77.27%), specificity equalled 72.37% (95% CI: 60.91–82.01%). Among particular HPV genotypes, sensitivity for detecting HSIL was the highest in the case of HPV genotype 16 and equalled 72.50% (95% CI: 56.11–85.40%), specificity equalled 84.00% (95% CI: 73.72––91.45%). The sensitivity of other HPV genotypes for detecting HSIL ranged from 0.00% (95% CI: 0.00–8.81%) for HPV genotype 51 to 15.00% (95% CI: 5.71–29.84%) the in case the of P1 group genotype. Specificity of HPV genotyped other than 16 ranged from 86.67% (95% CI: 76.84–93.42%) for HPV genotype 31 to 98.67% (95% CI: 92.79–99.97%) for HPV genotype 18. Further details on PPV, NPV and accuracy by HPV genotype were given in Table 6.

DISCUSSION

This paper aimed to analyze the clinical usefulness of the Onclarity test with extended genotyping and HPV phenotyping in the screening and diagnosis of precancerous conditions of the cervix. In the study group, we also detected that the most frequent HPV genotypes in CIN 2+ lesions were HPV 16, HPV 31, HPV 51, HPV 52, and P2 and P3. Iacobone et al. [13] point out that the most common genotypes in precancerous lesions, particularly CIN 2+, are: 16, 31 and 58. They had a statistically significant impact on the higher advancement of lesions in cervical biopsies. In addition, they emphasize that these are the genotypes present in the nonavalent vaccine and therefore recommend population vaccination, which we strongly agree with [13]. Similar data were obtained by researchers checking the effectiveness of the quadriwalent vaccine on a large population. They also correlated a significantly higher risk of advanced precancerous lesions in unvaccinated patients with current persistent HPV 16 and 18 infections [14].

A study by Bonde et al. [15], which assessed the prevalence of highly oncogenic HPV genotypes in a large cohort in the European population, contributes a lot to the current knowledge. The most common HPV genotypes that were observed in the CIN 2+ population were: HPV 16 (69.1%), HPV 31 (63.3%), HPV 33/58 (52.7%), HPV 18 (46.6%) and HPV 52 (40.8%). Regarding CIN3+ lesions, the frequencies were as follows: HPV 16 (44.3%), HPV 31 (38.5%), HPV 18 (36.8%),

Table 2. Dependency between age and cytology outcome

LBC	Age [years], n (%)					p value
	< 25, n = 56	25–34, n = 255	35–44, n = 244	45–54, n = 109	≥ 55, n = 31	
NILM	37 (66.1)	181 (71.0)	187 (76.6)	84 (77.1)	25 (80.6)	0.044
ASC-US	7 (12.5)	27 (10.6)	16 (6.6)	12 (11.0)	6 (19.4)	
LSIL	10 (17.9)	27 (10.6)	13 (5.3)	7 (6.4)	0 (0.0)	
ASC-H	1 (1.8)	9 (3.5)	16 (6.6)	2 (1.8)	0 (0.0)	
HSIL	1 (1.8)	10 (3.9)	11 (4.5)	3 (2.8)	0 (0.0)	
ACG	0 (0.0)	1 (0.4)	1 (0.4)	1 (0.9)	0 (0.0)	

LBC — liquid-based cytology; NILM — negative for intraepithelial lesion or malignancy; ASC-US — atypical squamous cells of undetermined significance; LSIL — low-grade squamous intraepithelial lesion; ASC-H — atypical squamous cells, cannot exclude a high-grade squamous intraepithelial lesion; HSIL — high-grade squamous intraepithelial lesion; AGC — atypical glandular cells; Comparison produced with Pearson chi-square test

Table 3. Dependency between age and biopsy outcome

Biopsy	Age [years], n (%)					p value
	< 25, n = 56	25–34, n = 255	35–44, n = 244	45–54, n = 109	≥ 55, n = 31	
HSIL	1 (1.8)	20 (7.8)	17 (7.0)	2 (1.8)	0 (0.0)	0.678
LSIL	4 (7.1)	19 (7.5)	12 (4.9)	3 (2.8)	0 (0.0)	
NILM	1 (1.8)	13 (5.1)	10 (4.1)	4 (3.7)	1 (3.2)	
HPV	0 (0.0)	2 (0.8)	4 (1.6)	2 (1.8)	0 (0.0)	
Condyloma	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	
None	50 (89.3)	200 (78.4)	201 (82.4)	98 (89.9)	30 (96.8)	

HPV — human papillomavirus; NILM — negative for intraepithelial lesion or malignancy; LSIL — low-grade squamous intraepithelial lesion; HSIL — high-grade squamous intraepithelial lesion; Comparison produced with Pearson chi-square test.

Table 4. Dependency between age and human papillomavirus (HPV) outcome

HPV	Age [years], n (%)					p value
	< 25, n = 56	25–34, n = 255	35–44, n = 244	45–54, n = 109	≥ 55, n = 31	
Positive	18 (32.1)	71 (27.8)	53 (21.7)	16 (14.7)	1 (3.2)	0.002
Negative	38 (67.9)	184 (72.2)	191 (78.3)	93 (85.3)	30 (96.8)	
Genotype						
16	5 (8.9)	36 (14.1)	24 (9.8)	2 (1.8)	1 (3.2)	0.005
18	2 (3.6)	3 (1.2)	3 (1.2)	1 (0.9)	0 (0.0)	0.586
31	1 (1.8)	17 (6.7)	9 (3.7)	2 (1.8)	1 (3.2)	0.183
45	0 (0.0)	4 (1.6)	4 (1.6)	1 (0.9)	0 (0.0)	0.802
51	3 (5.4)	5 (2.0)	1 (0.4)	5 (4.6)	0 (0.0)	0.031
52	3 (5.4)	5 (2.0)	5 (2.0)	2 (1.8)	0 (0.0)	0.476
P1	2 (3.6)	5 (2.0)	11 (4.5)	0 (0.0)	0 (0.0)	0.095
P2	7 (12.5)	11 (4.3)	7 (2.9)	4 (3.7)	0 (0.0)	0.016
P3	4 (7.1)	11 (4.3)	10 (4.1)	5 (4.6)	0 (0.0)	0.639

Comparisons produced with Pearson chi-square test

HPV33/58 (30.9%) and HPV 52 (16.8%). The percentages do not differ much from those observed in our population, however, the genotypes of HPV viruses present in the lead overlap [15]. Onclarity studies show mostly promising results and show high sensitivity and specificity. Observations of researchers from Milan showed the superiority of the Onclarity test over Hybrid Capture 2 (HC2) and linear array. They revealed that evaluating the HPV genotype persistence may

Table 5. Dependency between biopsy outcome and human papillomavirus (HPV) outcome

HPV	Biopsy, n (%)					p value
	HSIL, n = 40	LSIL, n = 38	NILM, n = 29	HPV, n = 8	Condyloma, n = 1	
Positive	37 (92.5)	22 (57.9)	8 (27.6)	4 (50.0)	0 (0.0)	< 0.001
Negative	3 (7.5)	16 (42.1)	21 (72.4)	4 (50.0)	1 (100.0)	
Genotype						
16	29 (72.5)	6 (15.8)	4 (13.8)	2 (25.0)	0 (0.0)	< 0.001
18	3 (7.5)	0 (0.0)	1 (3.4)	0 (0.0)	0 (0.0)	0.455
31	5 (12.5)	7 (18.4)	3 (10.3)	0 (0.0)	0 (0.0)	0.639
45	4 (10.0)	4 (10.5)	0 (0.0)	0 (0.0)	0 (0.0)	0.380
51	0 (0.0)	2 (5.3)	0 (0.0)	1 (12.5)	0 (0.0)	0.195
52	2 (5.0)	6 (15.8)	1 (3.4)	0 (0.0)	0 (0.0)	0.252
P1	6 (15.0)	2 (5.3)	0 (0.0)	1 (12.5)	0 (0.0)	0.196
P2	2 (5.0)	4 (10.5)	0 (0.0)	1 (12.5)	0 (0.0)	0.414
P3	4 (10.0)	5 (13.2)	1 (3.4)	0 (0.0)	0 (0.0)	0.571

NILM — negative for intraepithelial lesion or malignancy; LSIL — low-grade squamous intraepithelial lesion; HSIL — high-grade squamous intraepithelial lesion; Comparisons produced with Pearson chi-square test

Table 6. Sensitivity and specificity of different human papillomavirus (HPV) genotypes in high-grade squamous intraepithelial lesion (HSIL)

HPV genotype		HSIL, n = 40	Non–HSIL, n = 75	Total, n = 115	Sensitivity [%]	Specificity [%]	PPV [%]	NPV [%]	Accuracy [%]
Any	+	37	34	71	92.50 (79.61–98.43)	55.26 (43.41–66.69)	52.11 (45.50–58.65)	93.33 (82.23–97.69)	68.10 (59.62–76.59)
	–	3	42	45					
Any*	+	25	21	46	62.50 (45.80–77.27)	72.37 (60.91–82.01)	54.35 (43.50–64.80)	78.57 (70.59–84.85)	68.97 (60.55–77.38)
	–	15	55	70					
16	+	29	12	41	72.50 (56.11–85.40)	84.00 (73.72–91.45)	70.73 (58.17–80.77)	85.14 (77.42–90.53)	80.00 (72.69–87.31)
	–	11	63	74					
18	+	3	1	4	7.50 (1.57–20.39)	98.67 (92.79–99.97)	75.00 (24.38–96.54)	66.67 (64.59–68.68)	66.96 (58.36–75.55)
	–	37	74	111					
31	+	5	10	15	12.50 (4.19–26.80)	86.67 (76.84–93.42)	33.33 (15.50–57.67)	65.00 (61.59–68.27)	60.87 (51.95–69.79)
	–	35	65	100					
45	+	4	4	8	10.00 (2.79–23.66)	94.67 (86.90–98.53)	50.00 (20.89–79.11)	66.36 (63.71–68.90)	65.22 (56.51–73.92)
	–	36	71	107					
51	+	0	3	3	0.00 (0.00–8.81)	96.00 (88.75–99.17)	0.00 (6.86–65.56)	64.29 (62.80–66.69)	62.61 (53.77–71.45)
	–	40	72	112					
52	+	2	7	9	5.00 (0.61–16.92)	90.67 (81.71–96.16)	22.22 (5.86–56.74)	64.15 (61.78–66.45)	60.87 (51.95–69.79)
	–	38	68	106					
P1	+	6	3	9	15.00 (5.71–29.84)	96.00 (88.75–99.17)	66.67 (34.56–88.34)	67.92 (64.84–70.86)	67.83 (59.29–76.36)
	–	34	72	106					
P2	+	2	5	7	5.00 (0.61–16.92)	93.33 (85.12–97.80)	28.57 (7.51–66.33)	64.81 (62.66–66.91)	62.61 (53.77–71.45)
	–	38	70	108					
P3	+	4	6	10	10.00 (2.79–23.66)	92.00 (83.40–97.01)	40.00 (16.64–69.00)	65.71 (62.89–68.43)	63.48 (54.68–72.28)
	–	36	69	105					

PPV — positive predictive value; NPV — negative predictive value; *Any HPV genotype of 16, 18, 31, 45, 51, 52 and not belonging to P1, P2 or P3 genotypes

represent a valid option to monitor patients treated for CIN 2+ lesions, because relapses were detected [16]. However, a similar study conducted in Japan on 144 women showed similar sensitivity and specificity of the Onclarity and HC2 tests (93.8% and 94.4%, respectively) [17].

The authors of the paper from 2022 compared HPV testing via the Hybrid Capture 2 assay in the Canadian Cervical Cancer Screening Trial (CCCaST). They assessed hrHPV genotype concordance between BD Onclarity HPV Assay and Roche's Linear Array, overall and stratified by hrHPV viral load. Among 734 hrHPV samples tested, there was near perfect concordance regardless of viral load between the Onclarity and Linear Array assays for the individual genotypes (HPV 16, 18, 31, 45, 51, 52. The highest value was for testing for HPV16 and/or 31 (Sensitivity: 65.2%, Specificity: 76.9%) and HPV16 and/or 18 (Sensitivity: 58.7%, Specificity: 81.6%) This is another study highlighting the importance of HPV 31 for the triage of HPV-positive patients [18]. Wong et al. [19] tested 605 stratified random archived samples of LBC samples with both assays. The sensitivities (Onclarity, 96.32%; Cobas, 95.71%) and specificities (Onclarity, 46.38%; Cobas, 45.25%) of the high-risk HPV (hrHPV) components of the two tests were not significantly different. When HPV16 and HPV18 were used to further interpret hrHPV-positive cases, Onclarity displayed significantly higher specificity (Onclarity, 87.10%; Cobas, 80.77%). Both hrHPV tests achieved the same sensitivities (Onclarity, 90.91%; Cobas, 90.91%) and similar specificities (Onclarity, 48.46%; Cobas, 51.98%) when used for triaging atypical squamous cells of undetermined significance. Positivity in both HPV16 and HPV33/58 of the Onclarity channels entails the highest probability of developing CIN2+ lesions. Incorporating other hrHPVs into the outcome classifiers improved the specificity of identifying CIN2/3 to up to 94.32%. The extended genotyping of Onclarity, therefore can help to highlight patients having the highest risk of developing CIN2/3, with the potential to reduce unnecessary colposcopy and negative psychosocial impact on women receiving the reports [19].

A long-term follow-up led by Elfgren et al. [20] showed that all patients with persistent hrHPV infection developed precancerous lesions of the cervix CIN 2 or more advanced. However, none of the women who had HPV remission developed CIN ($p < 0.001$). Among women with human papillomavirus persistence but did not continue with repeated HPV tests (unknown persistence status), 56% (15 of 27 women) developed cervical intraepithelial neoplasia grade 2 or worse. Almost all cases occurred within six years [20]. Additionally, being aware that persistent infection with highly oncogenic HPV genotypes leads to the development of precancerous changes, we should take advantage of the benefits of science — the most modern and highly sensitive diagnostic methods and vaccines against HPV infection.

CONCLUSIONS

The Onclarity test is characterised by high sensitivity and specificity in detecting a high-grade squamous intraepithelial lesions. Extended genotyping enables the identification of the most common oncogenic HPV types in the population, such as 16, 31, 51, 52 and P2 and P3. It can be used as a basic tool for secondary prevention or together with LBC. The most frequent high-risk oncogenic HPV types in HSIL are 16, 31, 45 and P1 and P3.

Article information and declarations

Data availability statement

The data presented in this study are available on request from the first author. The data are not publicly available due to sensitive information regarding both the health and epidemiological status of the study group.

Ethics statement

The study was conducted according to the guidelines of the Declaration of Helsinki and approved by the Bioethics Committee of the Medical Chamber of Wielkopolska (protocol code 95/2021, date of approval: 17.03.2021).

Author contributions

Dominik Pruski: concept, assumptions, study design, acquisition of data, analysis and interpretation of data, article draft, corresponding author.
Sonja Millert-Kalińska: concept, assumptions, study design, acquisition of data, analysis and interpretation of data.
Paula Klemenska: article draf. Robert Jach: revised article critically. Marcin Przybylski: revised article critically.

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Conflict of interest

All authors declare no conflict of interest.

Supplementary material

None

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