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Comparison of Physician- and Self-Collected Genital Specimens for Detection of Human Papillomavirus in Men

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There is currently no consensus regarding the most appropriate methods of sampling for the detection of genital human papillomavirus (HPV) in men. We employed a recently developed collection method involving abrasion and moistened swabbing of the genital skin surface for the detection of HPV in a cohort of 136 university-affiliated males in Hawaii. Genital specimens collected by physicians using this method were compared with self-collected specimens from the same individuals obtained 24 h later. Self-collected specimens yielded a greater proportion of sufficient specimens than physician-collected specimens. HPV detection was comparable in physician- and self-collected specimens; detection was highest in the penile shaft (51.2% and 51.5%, respectively, $P = 0.96$), followed by the scrotum (41.2% and 46.2%, $P = 0.43$), the glans/coronal sulcus (31.9% and 33.1%, $P = 0.84$), and the foreskin (33.3% and 28.6%, $P = 0.74$). Site-specific agreement in HPV detection between paired physician- and self-collected samples ranged from 67.2% (kappa = 0.34) for the penile shaft to 95.0% (kappa = 0.89) for the foreskin. There was a high degree of concordance in HPV genotypes in HPV-positive pairs. The most common type was HPV type 84, which comprised approximately 15% of the specimens. The emery paper-swab method offers an efficient sampling method for genital HPV DNA detection in men that could be used both within and outside of the clinical setting.

Natural-history studies of human papillomavirus (HPV) infection among males are an emerging area of epidemiological research. The types and distributions of genital HPV are largely uncharacterized. Because this is a novel area of scientific inquiry, there is currently no consensus on the most appropriate method of sampling for the detection of genital HPV infection among men. Differences in methodology make it difficult to compare penile HPV prevalence across studies and populations (2, 3, 10, 13, 14, 17, 20). Weaver et al. (19) recently reported enhanced specimen yield and HPV detection in male genitals through abrasion with emery paper followed by swabbing with a moistened Dacron swab (19). We employed this method to compare the detection of HPV DNA in genital specimens collected by physicians to self-collected specimens from the same individuals among a cohort of men in a university population.

MATERIALS AND METHODS

Recruitment. This study was approved by the Committee on Human Studies of the University of Hawaii. Written informed consent was obtained from all study subjects. The cohort study was initiated in July 2004 among a university population in Hawaii. Self-referred volunteers were recruited through campus-based media, including flyers and newspaper advertisements. Eligible men were 18 years old and older and English speaking with no history of blood-clotting disorders. Between July 2004 and April 2005, 136 adult males were recruited and followed up at 2-month intervals. All study visits were conducted at the University Health Services of the University of Hawaii.

Genital specimen collection. A staff of seven university-based physicians were specifically trained in the collection of genital HPV specimens with the objective of standardizing the methodology prior to initiation of the study. A training video was used to ensure uniformity of specimen collection throughout the study period. During the baseline study visit, physicians collected separate cell specimens from the glans/coronal sulcus and shaft of the penis, as well as the scrotum, of each study subject. Foreskin specimens were also collected from uncircumcised study participants.

Specimens were consecutively obtained from each genital site and placed in separate collection vials. Physicians used disposable gloves which were changed after each sample collection. Sampling of any visible genital warts and lesions was avoided. (Results of the analysis of separate specimens collected from warts and lesions were not included.)

Self-collected specimens were obtained approximately 24 h following the clinic visit. Subjects were instructed to follow the same procedure used by the clinician, with the exception of the use of disposable gloves, which were not used by study participants. Written instructions and illustrations were provided with collection kits. Self-collected specimens were returned to the clinic on the same day. All specimens were transported to the laboratory and stored at minus 20°C until testing.

The method of collection has been previously described (19). Briefly, a sterilized strip of emery paper (2 by 4 cm; 600A-grit Wetordry Tri-M-ite; 3M) was used with steady pressure to repeatedly abrade the entire surface of the genital site. Next, a sterile Dacron swab moistened with sterile saline was used with steady pressure to swab the entire area. Both the emery paper and swab tip were then immersed in the specimen transport medium (Digene Corporation, Gaithersburg, MD).

Glans/coronal sulcus samples included the entire exterior surface of the glans of the penis extending from the tip to the coronal sulcus. Shaft samples included the entire exterior surface from the base of the penis extending the length of the penis to the area immediately below the coronal sulcus. The scrotum sample included the entire exterior surface of the scrotum.

For uncircumcised men, the foreskin sample included the entire inner surface of the retracted foreskin, the glans/coronal sulcus sample included the entire head of the penis beneath the foreskin, and the shaft included the entire exterior surface from the base of the penis extending to the tip of the unretracted outer foreskin.

Interview. A structured survey was administered by a trained interviewer at each study visit. At enrollment, a comprehensive survey queried social and demographic information and medical, sexual, and reproductive histories.

HPV DNA testing and genotyping. DNA was extracted from genital specimens with commercial reagents (QIAGEN Inc., Valencia, CA). The PCR used a modified version of the original degenerate primer system, the PGMY09 and PGMY11 primer pairs with HMB01, which together amplify a 450-bp region of the L1 HPV genome (7). Primers GH20 and PC04 were used to coamplify a

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TABLE 1. Sufficiency of male genital samples: clinically-collected versus self-collected specimens

Sample collection site	No. of human beta-globin-positive samples/total (%)		P value[a]
	Physician collected	Self-collected	
Glans/coronal sulcus	116/136 (85.3)	133/136 (97.8)	0.0002
Shaft	129/136 (94.8)	134/136 (98.5)	0.09
Scrotum	119/136 (87.5)	130/136 (95.6)	0.02
Foreskin[b]	21/22 (95.4)	21/22 (95.4)	1.00
Any genital site	385/430 (89.5)	418/430 (97.2)	<0.0001

[a] Based on the chi-square test of association with one degree of freedom.
[b] Foreskin specimens from uncircumcised men.

TABLE 2. HPV detection in male genital samples: clinically-collected versus self-collected specimens[a]

Site	No. of HPV-positive samples/total (%)		P value[b]
	Physician collected	Self-collected	
Any genital site	129/385 (41.3)	179/418 (42.8)	0.89
Glans/coronal sulcus	37/116 (31.9)	44/133 (33.1)	0.84
Shaft	66/129 (51.2)	69/134 (51.5)	0.96
Scrotum	49/119 (41.2)	60/130 (46.2)	0.43
Foreskin[c]	7/21 (33.3)	6/21 (28.6)	0.74
Glans/coronal sulcus + shaft + scrotum	29/105 (27.6)	32/127 (25.2)	0.68

[a] Beta-globin-negative specimens excluded.
[b] Based on the chi-square test of association with one degree of freedom.
[c] Foreskin specimens from uncircumcised men.

268-bp region of the human beta-globin gene as an internal control for sample sufficiency.

Each 50-μl reaction mixture consisted of 1× PCR II Buffer (Perkin-Elmer, Norwalk, CT); 6 mM $MgCl_2$ (Perkin-Elmer, Wellesley, MA); 200 μM each dATP, dTTP, dGTP, and dCTP (Perkin-Elmer); 7.5 U of Ampli*Taq* Gold (Perkin-Elmer); 50 pmol each of PGMY09 and PGMY11 (Sigma, St. Louis, MO); 10 pmol of HMB01 (Sigma); 10 pmol each of GH20 and PC04 (Midland Certified Reagent Co., Midland, TX); sterile H_2O; and 5 μl of specimen DNA. Positive controls consisted of constructed plasmid DNA containing the entire genome of cloned HPV type 16 (HPV-16) DNA. Negative controls were void of template. PCR was performed in a 96-well format on a Perkin-Elmer 9600 as follows: 95°C for 9 min; 40 cycles of 95°C for 30 s, 55°C for 1 min, and 72°C for 1 min; 72°C for 5 min; and holding at 4°C.

Amplified specimens were run on 2% precast agarose gels prestained with ethidium bromide (Invitrogen, Carlsbad, CA). Specimens that were positive for the 450- and 268-bp bands of HPV and beta-globin, respectively, were considered to be positive. Specimens found negative for beta-globin on coamplification were reamplified in a single amplification reaction. Those remaining negative for beta-globin were excluded from analysis.

The original DNA samples from HPV-positive specimens were subsequently genotyped by a reverse line blot detection method for 37 different HPV types including 6, 11, 16, 18, 26, 31, 33, 35, 39, 40, 42, 45, 51, 52, 53, 54, 55, 56, 58, 59, 61, 62, 64, 66, 67, 68, 69, 70, 71, 72, 73, 81, 82, 83, 84, CP6108, and IS39 (8, 15). Genotyping reagents were kindly supplied by Roche Molecular Systems (Pleasanton, CA). HPV PCR was performed under reaction conditions identical to those described above, with the exception of the use of dUTP (instead of dTTP) and 5′-biotinylated primers. PCR products were denatured and hybridized to a nylon membrane containing the immobilized HPV probes. This genotyping assay also included probes for high and low levels of the human beta-globin gene. Amplicons hybridized to probes were detected by streptavidin-horseradish peroxidase-mediated color precipitation. HPV-positive specimens that were subsequently found to be negative in the genotyping assay were considered to be unclassified HPV-positive specimens.

Statistical analyses. All analyses were conducted with SAS (version 8). The detection of beta-globin and HPV DNAs was compared in physician-collected and self-collected specimens by using the chi-square statistic with one degree of freedom.

Physician- and self-collected specimens from the same individual were paired to estimate agreement. For each individual, results from the self-collected specimen from a particular genital site were compared against results from the physician-collected specimen from that site. Detection at any site was also compared for each individual. The detection of HPV DNA in paired specimens was evaluated by using the percent agreement and the kappa statistic to determine the agreement beyond that expected by chance (6).

RESULTS

The present analysis included baseline results for 136 men enrolled in the cohort study. Foreskin samples were available from 22 uncircumcised participants for whom both physician-collected and self-collected specimens were obtained. Visible genital warts were observed in 5.2% (7/136) of the study participants, and lesions were observed in 3.7% (5/136) of the study participants.

Study subjects ranged in age from 18 to 63 years, but the majority of the men were less than 30 (mean, 28.5; standard deviation, 10.6) years old. Whites composed the majority of the participants (60.3%), followed by Asians and Pacific Islanders (including Hawaiians) (18.4%) and individuals of mixed race or ethnicity (21.3%). Most of the men were born on the U.S. mainland (61.0%) and were single or never married (78.7%), and all except one had at least some postsecondary education. The majority of the men were circumcised (82.4%) and heterosexual (77.8%), and approximately half of the participants reported a total of seven or more female sexual partners during their lifetimes (51.5%). Self-reported history of sexually transmitted infections included genital warts (11.8%), genital herpes (9.6%), chlamydia (7.4%), gonorrhea (3.7%), and human immunodeficiency virus (HIV) (3.7%). Exchanging drugs and/or money for sex with a female was reported by 12.6% of the men.

Sample sufficiency (beta-globin positivity) was significantly higher among self-collected genital specimens (97.2%) than among physician-collected specimens (89.5%; $P < 0.0001$) (Table 1). The difference in sample sufficiency between the two sampling procedures was greatest for the glans/coronal sulcus, followed by the scrotum. Among physician-collected specimens, specimen sufficiency varied by genital site, ranging from a low of 85.3% in glans/coronal sulcus specimens to more than 94% in shaft and foreskin samples. Only three beta-globin-negative specimens collected by physicians were HPV positive. No self-collected specimens were negative for beta globin and positive for HPV.

Site-specific detection of HPV in genital specimens was comparable in physician- and self-collected specimens (Table 2). Excluding beta-globin-negative specimens from analysis, the overall prevalence of genital HPV DNA was 41.3% in physician-collected specimens and 42.8% in self-collected samples ($P = 0.89$). HPV prevalence varied by site but was comparable in physician- and self-collected specimens: HPV prevalence was highest in the penile shaft, followed by the scrotum, the glans/coronal sulcus, and the foreskin. More than one-fourth of the individuals had concurrent HPV infection of the glans/coronal sulcus, shaft, and scrotum in both physician- and self-collected samples.

There was limited agreement in HPV detection between

TABLE 3. Agreement in HPV detection between paired physician-collected and self-collected male genital specimens[a]

Site and result for physician collected samples	No. of self-collected samples		Agreement	
	HPV$^+$	HPV$^-$	Overall (%)	Kappa (95% CI)[c]
Glans/coronal sulcus				
HPV$^+$	23	12	79.0	0.51 (0.33–0.68)
HPV$^-$	12	67		
Shaft				
HPV$^+$	43	22	67.2	0.34 (0.18–0.51)
HPV$^-$	20	43		
Scrotum				
HPV$^+$	31	15	69.0	0.36 (0.19–0.53)
HPV$^-$	21	48		
Foreskin[b]				
HPV$^+$	6	1	95.0	0.89 (0.67–1)
HPV$^-$	0	13		

[a] Beta-globin-negative specimens excluded.
[b] Foreskin specimens from uncircumcised men.
[c] CI, confidence interval.

paired physician- and self-collected specimens for all sites. Agreement between physician-collected and self-collected specimen pairs ranged from 67.2% in penile shaft specimens to 95.0% in foreskin specimens (Table 3).

A total of 28 different genotypes were detected in physician-collected genital specimens, compared to 33 types detected in self-collected specimens. The distribution of types was generally similar in physician-collected and self-collected specimens (Fig. 1).

In the 159 HPV-positive specimens collected by physicians, a total of 286 individual HPV types were detected, or an average of 1.8 genotypes per specimen. In the 179 HPV-positive specimens collected by study subjects, a total of 340 individual HPV types (average of 1.9 genotypes per specimen) were detected.

A greater proportion of infections detected in self-collected specimens were composed of multiple HPV genotypes compared to physician-collected specimens. Overall, 60.8% (79/130) of the infections in self-collected specimens were composed of two or more genotypes, compared to 49.6% (56/113) of the infections in physician-collected specimens.

The most common genotype in both physician- and self-collected specimens was nononcogenic HPV-84, which comprised 14.7% (42/286) of the individual types detected in HPV-positive physician-collected specimens and 15.3% (52/340) of individual types detected in HPV-positive self-collected specimens. HPV-84 was also the most common genotype found in

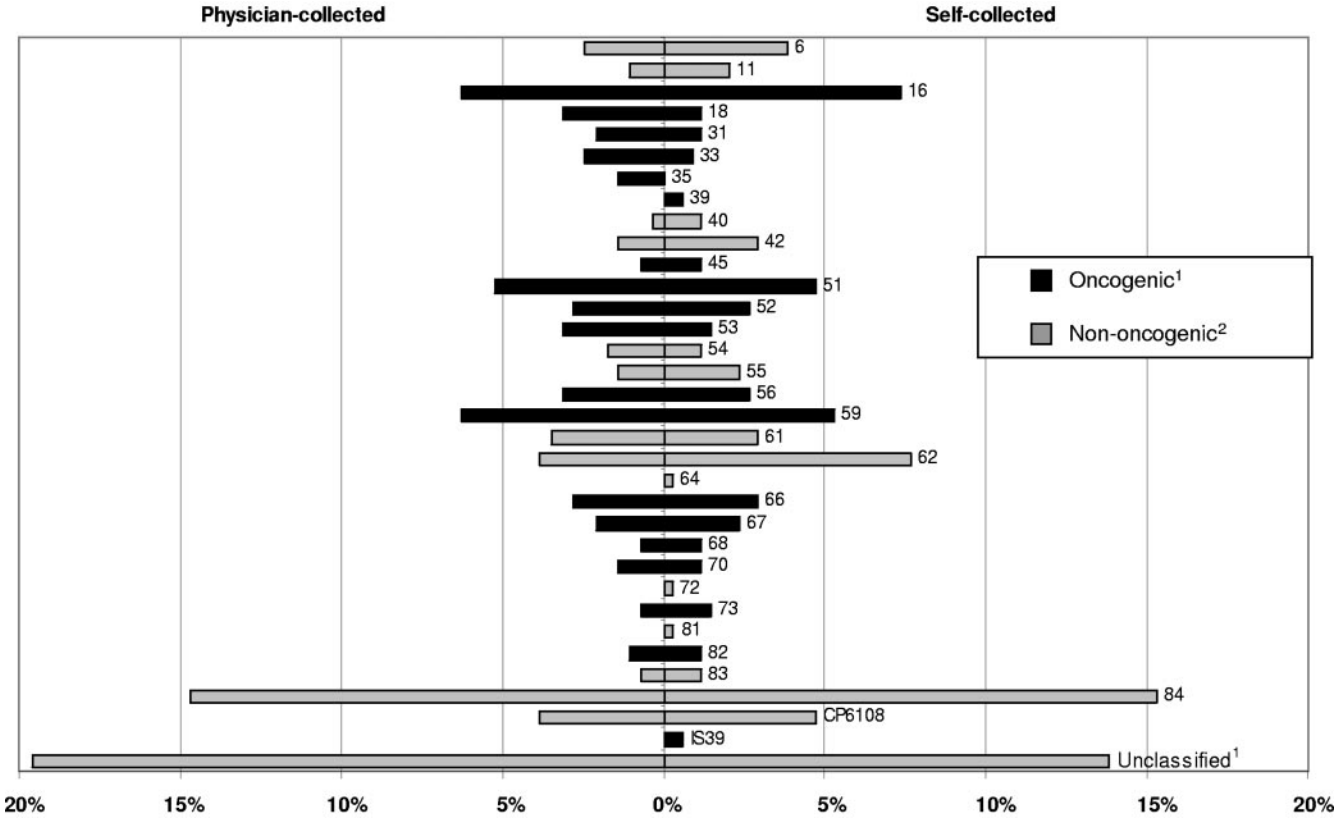

FIG. 1. Distribution of genotypes in physician- and self-collected, HPV-positive specimens. Superscript numbers: 1, ocogenic types include those classified as possibly carcinogenic, including HPV-26, -53, and -66; 2, ononcogenic types include those whose carcinogenic potential is undetermined, such as HPV-83; 3, unclassified specimens are HPV-positive specimens that were not positive for any of the 37 genotypes detected by the Roche assay.

TABLE 4. Genotype-specific HPV detection between paired physician-collected and self-collected male genital specimens

Agreement	No. (%) of samples			
	Glans/coronal sulcus	Shaft	Scrotum	Foreskin
All identical genotype(s)	10 (43.5)	19 (44.2)	10 (32.2)	3 (50)
Some identical genotypes	8 (34.8)	14 (32.6)	10 (32.3)	3 (50)
Different genotype(s)	0 (0)	0 (0)	1 (3.2)	0 (0)
Unclassified genotypes				
One of the pair	1 (4.3)	2 (4.6)	1 (3.2)	0 (0)
Both of the pair	4 (17.4)	8 (18.6)	9 (29.0)	0 (0)
Total HPV-positive pairs	23 (100)	43 (100)	31 (100)	6 (100)

each of the four individual genital sites in both physician- and self-collected specimens. Nononcogenic HPV-62 and -CP6108 and oncogenic HPV-16, -51, and -59 were other predominant types. Unclassified HPV types composed a substantially greater proportion of the HPV-positive specimens collected by physicians (19.6%; 56/286) compared to HPV-positive self-collected specimens (13.8%; 47/340).

When HPV-positive specimen pairs were compared, we observed a high degree of genotype-specific agreement between HPV-positive physician- and self-collected specimen pairs (Table 4). For each genital site, when both clinician- and self-collected specimens were HPV positive, the majority of the specimen pairs had genotypes that were completely concordant or partially concordant. Only one HPV-positive pair had completely different HPV genotypes. The remainder of the HPV-positive pairs had undetermined genotypes in either one of the pair or both specimens. Undetermined genotypes in both paired specimens may likely indicate concordant genotypes other than the 37 types detected by the assay.

DISCUSSION

Genital HPV is presumed to be transmitted between males and females through direct physical contact during sexual intercourse. Cervical infection likely occurs when virus from the infected male's penis enters the basal layer of the squamous epithelium (1, 18). Although genital contact during sexual intercourse is probably the dominant form of HPV transmission, there is evidence that genital infection can be acquired through fomites or other nonsexual means (4). Uncertainties about the sexual transmission of HPV are complicated by evidence that condoms may not protect against HPV infection (12).

Our results affirm that asymptomatic genital HPV infection is common in men and often appears to be multifocal, with concurrent infection of multiple genital sites. The ability to detect HPV in genital specimens over a consecutive 2-day period combined with genotype-specific concordance suggests that genital infection in men does not reflect surface contamination but rather represents actual infection of the epithelium by the virus. These results affirm that men are important sources of HPV infection such that strategies to control viral transmission should ideally target both sexes.

Previous estimates of genital HPV prevalence in men have ranged widely, from 10% to 70% (2, 3, 10, 13, 14, 17, 19, 20). Although this variation may be real, comparisons of genital HPV prevalence between studies are hampered by differences in the genital sites sampled, sampling techniques, and HPV testing methods. The HPV prevalence of 41 to 43% overall is higher than the 33% prevalence found in a university population in Washington State by using the same specimen collection method and the same PCR-based HPV DNA assay (19). This difference may reflect our comparatively high-risk population with respect to sexual behavior.

Our cohort was older compared to the Washington State population (mean, 20.5 years; range, 18 to 25 years) and had a greater number of female sexual partners in their lifetimes (median, four partners in the Washington State population). Five study subjects reported being HIV positive compared to no men testing positive for HIV type 1 in the Washington population.

HPV-84, a nononcogenic genotype, appears to be the predominant type in men at all genital sites, and this is consistent with a previous study of HPV in men, which used the same genotyping assay (2). This finding contrasts with the consensus that oncogenic HPV-16 is the most common genotype associated with cervical HPV infection (16). Furthermore, the distribution of other HPV genotypes observed in this cohort is very different from that observed in female populations, including our own (9), in which HPV-16 was the most common genotype and HPV-84 composed less than 3% of the types found in the cervix. Interestingly, HPV-84 was the most common type detected in the anus among women in Hawaii who were also HPV negative in the cervix (9).

The apparent inconsistency of HPV genotype distribution observed in men and women is evidence that different HPV types are selectively transmitted between the sexes due to differential tropism of types. HPV-84, a cutaneous type, is likely to be more trophic to the male genitals compared to HPV-16, which is trophic to the mucosa of the cervix. Genotype differences between males and females also raise the possibility of other modes of transmission of HPV to the genitals, including self-inoculation. In the same male cohort, HPV-84 was one of the most common types observed in swabs of the hands (unpublished data), raising the prospect of hand-to-genital transmission in men.

Physician collection generally provided less sufficient samples than that yielded though self-collection. The poorer sufficiency of clinical specimens may have resulted from the amount of pressure applied to abrade the skin surface. Physicians may have been hesitant to apply firm pressure with the emery paper out of concern for the participant's comfort. Furthermore, the application of uniform, firm pressure to sites such as the scrotum may be particularly difficult because of the large surface area and the presence of hair.

The overall and site-specific prevalence of HPV was similar in physician- and self-collected specimens with sufficient material for analysis. However, agreement in HPV detection varied by the surface area of the genital site, with the best agreement observed for the foreskin, which has the smallest surface area, and the poorest agreement for the shaft and scrotum. The limited agreement in HPV detection between paired samples may reflect the variation in the sample yield between the

two methods, with generally more cells obtained through self-collection.

Although there was a high degree of genotypic concordance between HPV-positive specimens, a greater proportion of multiple genotypes and a greater number of total genotypes were observed in the self-collected specimens than in the physician-collected specimens.

The possibility must be considered that self-collected samples, which did not involve the use of gloves and which were obtained outside the clinic, were more susceptible to contamination in the collection process. This could explain the higher detection rates of beta-globin, as well as the detection of a greater proportion of multiple types and more total genotypes identified in self-collected samples. An alternative explanation is that abrading the skin surface during clinical collection may have resulted in a greater cell yield during self-collection 24 h later when the skin was abraded a second time.

The development of effective strategies to prevent and control HPV, including the implementation of vaccination programs, requires knowledge of the natural history of HPV infection in men, as well as women. The paucity of knowledge of HPV infection in men requires the development of simple and reliable sampling methods for the detection of HPV. Given the general transience of HPV infection in women (5, 11), an ideal sampling method would facilitate repeated measurements of HPV in men over time.

Based on the comparable rates of site-specific HPV detection and the high degree of genotypic concordance between HPV-positive specimen pairs, the emery paper-swab method appears to be a reliable method of sampling that could be used within and outside of a clinical setting. Nevertheless, the variation in sample sufficiency, combined with the limited agreement in HPV detection between physician- and self-collected specimens, underscores the importance of deliberate, thorough, and consistent sampling to maximize specimen yield while taking care to limit the possibility of extraneous contamination.

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