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Bule, Yara Priscilla

Nagai, Yurie

Kameoka, Masanori

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Viability and acceptability of self-sampling as a primary screening method for sexually transmitted infections in female Kobe University students.

Yara Priscilla BULE[1], Yurie NAGAI[1], Masanori KAMEOKA[1]

Abstract

Objective: The objective of this study was to assess the viability and acceptability of self-sampling as a primary screening method in Kobe University and determine the prevalence of STIs within this community.

Methods: This study invited women from Kobe University to answer a questionnaire. The volunteers of the first questionnaire were then asked to participate in the self-sampling portion and perform the self-sampling procedure and answer a questionnaire related to their experience, acceptability and preference of screening procedure.

Results: For the first questionnaire 330 responses were eligible, of these 20% (66 /330) opted to participate in self-sampling. Seventy-one percent (47/66) returned the samples and 43% (29/66) completed the second questionnaire. The prevalence of HPV was 21.3% (10/47), *C. trachomatis* was 6.4% (3/47), HSV-2 was 4.3% (2/47), and *N. gonorrhoeae* was 2.1% (1/47). Factors influencing whether women were more likely to participate in self-sampling were, number of lifetime partners and number of partners in the last year.

Conclusions: A concise process is necessary to be able to collect more robust and complete data for this population. STI prevalence is elevated, particularly HPV, showing a need for stronger outreach programs.

Keywords

Sexually Transmitted Infections, Self-sampling, Under-screened Population, Women's Health Promotion, Japanese women, Screening preference

[1]Division of Global Infectious Diseases, Department of Public Health, Kobe University Graduate School of Health Sciences, Kobe 654-0142, Hyogo, Japan

Introduction

According to the World Health Organisation's (WHO) 2021 Global Progress Report, more than 1 million curable sexual transmitted infections (STIs) are acquired every day, with incidence rates of 374 million STIs per year, of which, 128 million cases are of *Chlamydia trachomatis*, 82 million cases are of *Neisseria gonorrhoeae*, 7 million cases are of *Treponema pallidum* (syphilis) and 156 million cases are of *Trichomonas vaginalis.*[1] Additionally, 291 million women are Human Papillomavirus (HPV) DNA carriers and 500 million test positive for genital herpes simplex virus (HSV-2).[2, 3]

A study by Kawado et. al. reported that the number of newly diagnosed cases in 2015 were 244 for chlamydia, 87 for genital herpes and 89 for gonorrhoea per 100,000 population.[4] Moreover, the Japanese National Institute of Infectious Diseases reported over 2,500 confirmed cases of syphilis infection by April 2022, confirming a significant rise of new cases compared to the previous years.[5] It was also reported that cervical cancer (CC) has an incidence rate of 13,277 new diagnoses per year and mortality rate of 4,088 deaths per year, in women 15 years and older.[6] Young adults and adolescents are among the group of people most vulnerable to STIs,[7] and as STI rates continue to increase in various countries around the world and in Japan, it is imperative to reduce barriers to STI screening and sexual education.[8]

Screening programs are important to help evaluate, diagnose, treat and provide education in under-screened and hard-to-reach populations. Furthermore, screening methods should be cost effective, easily transportable, stored, and accessed. To combat STIs and other gynaecological morbidities such as, HPV, *N. gonorrhoeae*, *C. trachomatis*, *T. pallidum* and *T. vaginalis*, WHO guidelines give strong to conditional recommendation to self-collected samples as an additional approach to STI testing services giving credence to the use of self-sampling as a primary screening method in multiple countries worldwide.[9-11] Aside from having characteristics of a good screening method, it also allows for patient privacy and comfort. The type of self-sampling collection tools can be very diverse. Amongst them, dry swabs have been reported to be a safe self-sampling collection tool with accurate and reliable results, even when dry stored at room temperature for several days. [12-15] Furthermore, self-collected samples coupled with DNA testing, have been shown to have the same and at times, higher sensitivity and specificity the conventional methods, with no significant differences between self-sampling tools.[16-18]

Some of the WHO’s priorities for tackling STIs globally, for the next decade, is to (1) scale up point-of-care diagnostics and self-testing, (2) Integrate sexual and reproductive health and rights, (3) Address social and structural determinants, (4) Maximise the use of differentiated and people-centred service delivery options and (5) Strengthen community engagement, community-based service delivery and community-led monitoring.[1] In this study, we aim to address the priorities, above mentioned, within the context of the Kobe University community. The project’s goal is to obtain information regarding STI prevalence and assess the viability and acceptability of the self-sampling methods.

Materials and Methods

Female university students aged 18-30 of Japanese nationality were asked to participate in this cross-sectional study via posters and virtual flyers, circulated via email and social media. These notices were designed in order to give an explanation about the objectives of the study and how to participate.

Recruited participants were asked to answer the first questionnaire, consisting of 63 questions, that collected sociodemographic, behavioural, clinical data and requested their participation in a self-sampling project for STI detection. Participants willing to continue in the study, were asked to submit an email in order to receive instructions on the options available for how to receive and return the self-sampling kits (Table 1). Each kit contained, how-to-use instructions with a link to an instructional video, two letters of consent, a sterile dry cotton swab with round collection tube (TC2400, Eiken chemical), a sterile plastic bag, labels and a stamped return envelope. The kits were developed using previous experience and literature from various studies of similar nature performed worldwide and by commercial kits already present in the market.[9, 19, 20]

Table 1: Method of delivery and reception of self-sampling kits given to participants to choose.

About delivery of self-sampling kit			
Option	**Pick-up location**	**Sampling location**	**How to return sample**
A	Lab（B402）	Myodani Campus	Collection box
B	Lab（B402）	Home	Collection box
C	Lab（B402）	Home	Mail
D	Mail (designated address)	Home	Mail
E	Mail (designated address)	Home	Collection box

About notification of results			
Option	**Test Results**	**Notification of results**	**Notification method**
1	Positive	Always notified	Mail
2	Positive	Always notified	E-mail
3	Positive	Want to receive	Mail
4	Negative	Want to receive	E-mail
5	Negative	Don’t want to receive	-

In order to collect the sample, the women were asked to insert the swab into the vaginal canal until they reached the cervix and to rotate it for 30 seconds in the same direction and carefully insert it back into the tube. Following the sample collection, they were asked to respond to a second questionnaire consisting of 8 questions that assessed their experience.

The participants were asked to mail or drop off the sample to our facility or in the specified collection box, respectively, the day of or the day after they collected the samples. The samples received were then stored at -80°C until processing occurred. DNA was extracted using the QIAGEN DNA Blood Kit in accordance to the manufacturer's instructions and DNA concentration was confirmed using a TOMY Q5000 Micro-volume spectrophotometer.

DNA integrity was verified by polymerase chain reaction (PCR) to amplify 268 base pairs (bp) of the β-globin gene using PCO_4/GH_{20} primers.[21] Amplification mixtures contained 10X ***Ex Taq*** Buffer, 2.5mM dNTPs, 0.2mM primers, 1.25 units ***TaKaRa Ex Taq***® and 10ng of DNA. The cycling parameters were: 94°C for 1 minutes, 40 cycles of 94°C for 45 seconds, 55°C for 45 seconds,72°C for 45 seconds with a final extension step of 72°C for 5 minutes.

HPV DNA was detected by PCR using PGMY09/PGMY11 primer pools, which amplify 450bp L1 gene.[22] Amplification mixtures contained 10X ***Ex Taq*** Buffer, 2.5mM dNTPs, 0.4mM primers, 1.25 units ***TaKaRa Ex Taq***® and 10ng of DNA. The cycling parameters were: 94°C for 1 minutes, 37 cycles of 94°C at 45 seconds, 56°C at 45 seconds, 72°C at 45 seconds, with a final extension step of 72°C for 7 minutes.[23] HSV-1 primers DNAP5/DNAP3-1 and HSV-2 primers DNAP5/DNAP3-2 were used to amplify a gene at 468bp and 391bp, respectively.[24] The amplification mixtures contained 10X ***Ex Taq*** Buffer, 2.5mM dNTPs, 0.4mM primers, 1.25 units ***TaKaRa Ex Taq***® and 10ng of DNA. The cycling parameters were: 96°C for 45 seconds, 35 cycles of 96°C of 1 minute, 67°C of 2 minutes,72°C of 3 minutes, with a final extension step of 72°C for 7 minutes. For ***N. gonorrhoea*** primers HO1/HO3 which amplify 390bp gene were used.[25] Amplification mixtures contained 10X ***Ex Taq*** Buffer, 2.5mM dNTPs, 0.4mM primers, 1.25 units ***TaKaRa Ex Taq***® and 10ng of DNA. The cycling parameters were: 94°C for 45 seconds, 40 cycles of 94°C for 30 seconds, 55°C for 1 minute, 72°C for 30 seconds, with a final extension step for 72°C for 5 minutes.

For ***C. trachomatis*** primers CP24/CP27 were used to amplify a 207bp gene.[26] Amplification mixtures contained 10X ***Ex Taq*** Buffer, 2.5mM dNTPs, 0.4mM primers, 1.25 units ***TaKaRa Ex Taq***® and 10ng of DNA. The cycling parameters were: 95°C for 5 minutes, 29 cycles of 60°C for 1 minute, 95°C for 30 seconds,60°C for 1 minute, with a final extension step for 72°C for 7 minutes. ***T. pallidum*** primers KO3A/KO4 amplified a 260bp gene.[27] Amplification mixtures contained 10X ***Ex Taq*** Buffer, 2.5mM dNTPs, 0.4mM primers, 1.25 units ***TaKaRa Ex Taq***® and 10ng of DNA. The cycling parameters were: 94°C for 45 seconds, 45 cycles of 90°C for 1 minute, 60°C for 30 seconds,70°C for 2 minutes, with a final extension step of 70°C for 5 minutes. Finally, the ***T. vaginalis*** primers TVK3/TVK7 were used to amplify a 350/450bp gene.[28] Amplification mixtures contained 10X ***Ex Taq*** Buffer, 2.5mM dNTPs, 0.4mM

primers, 1.25 units *TaKaRa Ex Taq*® and 10ng of DNA. The cycling parameters were: 94°C for 45 seconds, 37 cycles of 94°C for 45 seconds, 56°C for 45 seconds,72°C for 45 seconds, with a final extension step of 72°C for 5 minutes.

All amplifications were carried out using a BIO RAD T100™ Thermal Cycler and included a negative control. Positive controls were also used for the β-globin and L1 genes. The amplification products for PCO4/GH20, DNAP5/DNAP3-1, DNAP5, DNAP3-1 and TVK3/TVK7 primer sets were visualised in 1,5% agarose gel. HO1/HO3 and KO3A/KO4 primer sets were visualised 2% agarose gel. Lastly, PGMY09/PGMY11 primer pools in 3% agarose gel and CP24/CP27 primer set at 4% agarose gel.

The study was conducted in accordance with the Declaration of Helsinki and was approved by the Institutional Ethics Committee of Kobe University Graduate School of Health Sciences (approval number: 965) and abided by the ethical guidelines for medical and health research involving human subjects and the act on the protection of personal information in Japan and Kobe University. All participants were volunteers and weren't compensated for their participation. Consent was obtained in both virtual and written formats, for the online questionnaires and the sample, respectively.

Data analysis was performed using SPSS version 27 (IBM, Armonk, NY, USA). Data exploring sociodemographic, behavioural and clinical characteristics were categorised and their association with willingness to participate in self-sampling and STI prevalence were explored. Descriptive statistics were used for quantitative variables. χ^2 test was used to analyse statistical difference were used for comparing categorical variables. Statistically significant values had a *P*-value were set to <0.05.

Results

A total of 357 responses were collected for the first questionnaire. After applying the exclusion criteria for the first questionnaire, 330 (92.4%) responses were included in this study (Figure 1). When asked whether they would like to proceed to self-sampling and the second questionnaire, 66 women responded positively. In total, 47 respondents returned their self-sampling kits and after applying exclusion criteria, 35 were included in the study. Of the eligible participants, 9 failed to answer the questionnaire, 5 were removed for being repeated inputs by the same participant.

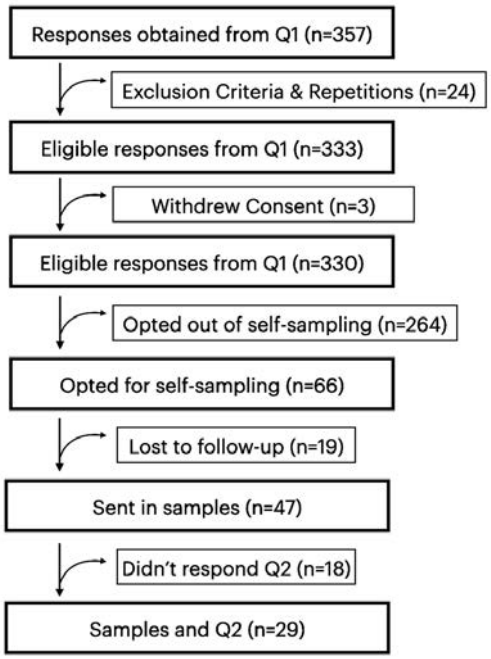

Figure 1: Recruitment and analysis flow chart.

The median age range was 19 (18-26) years. The majority of women were single (325; 98.5%), and did not consume tobacco (314; 95.2%) or alcohol (213; 64.5%). The median age of menarche was 12 (10-17) years and coitarche was 19 (13-23) years but most had not yet had their sexual debut (193; 58.5%) or had a partner in the last year (211; 63.9%) (Table 2).

A smaller percentage had experienced some form of sexual harassment (72; 21.8%) and 3 women had, at some point, engaged in sexual intercourse for favours (0.9%).

Table 2: Demographic, behavioural and clinical characteristics of study participants, collected from the first questionnaire.

Characteristic	**No. of data**	**Value[a]**
Age, y	326	19.0 (18-26)
Age group, y 18-19 20-23 24-26	326	 180 (55.2) 140 (42.9) 6 (1.8)
Marital Status Single Cohabitating	328	 325 (99.1) 3 (0.9)
Tobacco use No Yes[b]	328	 314 (95.7) 14 (4.3)
Alcohol consumption No Yes	330	 213 (64.5) 117 (35.5)
Age of menarche, y <12 >12	313	 186 (59.4) 127 (40.6)

Age of coitarche, y <19 >19	128	 88 (68.8) 40 (31.3)
Lifetime no. of sexual partners 0 1 2-5 >5	325	 193 (59.4) 73 (22.5) 43 (13.2) 16 (4.9)
No. of partner in last year 0 1 2-5 >5	322	 211 (65.5) 83 (25.8) 22 (6.8) 6 (1.9)

[a] Values given as median (range) or number (percentage).
[b] Among the 14 tobacco users, 4 were current smokers and 10 were former smokers.
[c] Among the people that reported participating in oral sex, 75.0% (90/120) reported having performed and received, 5.8% (7/120) exclusively received and 19.2% (23/120) exclusively performed.
[d] Among the people that reported not using a contraceptive, 96.5% (194/201) reported not having had their sexual debut and 3.5% (7/201) did not use any form of contraceptive.
[e] Among the people that reported not using a condom, 97.7% (173/177) reported not having had their sexual debut and 2.3% (4/177) did not use condoms.
[f] Among the people that reported using condoms, 91.5% (108/118) reported using condoms in all sexual encounters, 8.5% (10/118) reported using condoms occasionally.

Contraceptive use was present in 37.0% (122) of the cases and condom use was reported in 32.7% (108). Of the women who used contraceptives, 68.5% (61) used it primarily to prevent pregnancy, followed by menstrual cycle regulation at 24.7% (22). Majority had no history of STI infections but had also never visited an obstetrician or gynaecologist (195; 59.1%).

Most women had knowledge of STIs (215; 65.2%) and a little over half had some awareness of HPV (183; 55.5%). Additionally, a large portion of the women had not received the HPV vaccine (234; 70.9%).

Table 2: Demographic, behavioural and clinical characteristics of study participants, collected from the first questionnaire. (Continued)

Characteristic	**No. of data**	**Value[a]**
Oral sex No Yes[c]	322	 202 (62.7) 120 (37.3)
Anal sex No Yes	322	 313 (97.2) 9 (2.8)
Contraceptive use No[d] Yes	323	 201 (62.2) 122 (37.8)

Condom use No[e] Yes[f]	295	 177 (60) 118 (40)
Parity No Yes	156	 155 (99.4) 1 (0.6)
Screening pattern No Yes	133	 90 (67.7) 43 (22.8)
HPV vaccine No Yes	303	 234 (77.2) 69 (22.8)
STI History No Yes	329	 325 (98.8) 4 (1.2)

[a] Values given as median (range) or number (percentage).
[b]Among the 14 tobacco users, 4 were current smokers and 10 were former smokers.
[c] Among the people that reported participating in oral sex, 75.0% (90/120) reported having performed and received, 5.8% (7/120) exclusively received and 19.2% (23/120) exclusively performed.
[d] Among the people that reported not using a contraceptive, 96.5% (194/201) reported not having had their sexual debut and 3.5% (7/201) did not use any form of contraceptive.
[e] Among the people that reported not using a condom, 97.7% (173/177) reported not having had their sexual debut and 2.3% (4/177) did not use condoms.
[f] Among the people that reported using condoms, 91.5% (108/118) reported using condoms in all sexual encounters, 8.5% (10/118) reported using condoms occasionally.

Four (1.2%) women had a history of STIs where 100% were confirmed chlamydia cases at a physician's office. When asked if they had a custom of asking their partners about their STI status, the majority (242; 73.3%) answered no.

Self-sampling had an acceptability rate of 20.1% (66) and when asked why they opted out, the primary reason was that they had not had their sexual debut (152; 46.1%), followed by fear of not collecting the sample properly (28; 8.5%), lack of time (25; 7.6%) and finally, fear of pain (19; 5.8%).

Factors associated with the willingness to participate in self-sampling were: age, tobacco and alcohol consumption, no. of partners in their lifetime and in the last year, if they engaged in oral sex practices, contraceptive use and if they had a partner during the time the study took place (Table 3).

Table 3: Demographic, behavioural and clinical characteristics of participants willing to participate in self-sampling.

Characteristic	**Responded Yes n=66**	**Responded No n=262**	**P-value[a]**
Age group, y 18-19 20-23 24-26	 17 43 5	 161 97 1	<0.001

Tobacco use			0.004
No	58	254	
Yes[b]	7	7	
Alcohol consumption			<0.001
No	24	187	
Yes	42	75	
Lifetime no. of sexual partners			<0.001
0	13	179	
1	24	49	
2-5	16	27	
>5	13	3	
No. of partner in last year			<0.001
0	20	190	
1	29	54	
2-5	12	10	
>5	5	1	
Oral sex			<0.001
No	12	189	
Yes	53	67	
Contraceptive use			<0.001
No	2	5	
Yes	50	72	
Currently has a partner			<0.001
No	19	199	
Yes	47	58	

[a] By Pearson's χ^2 test.
[b] Among the "Yes" responses (n=14), 10 were former smokers and 4 were current smokers.

Most participants reported feeling no pain 79.3% (23/29), found the experience neutral 65.5% (19/29) but wouldn't hesitate to do use a self-sampling kit again 96.6% (28/29). Of the 29 participants, 8 (27.6%) had gone to a medical professional and received a pap-smear. They reported that self-sampling was easier 62.5% (5/8) and more comfortable 87.5% (7/8) than provider collected samples but only half 50% (4/8) preferred self-sampling over provider sampling.

The prevalence of STIs were: HPV 21.3% (10/47), *C. trachomatis* was 6.4% (3/47), HSV-2 4.3% (2/47), *N gonorrhoea* 2.1% (1/47). No positive cases were found for HSV-1 (0/47), *T. pallidum* (0/47), and *T. vaginalis* (0/47). More than one STI was found in 4.3% (2/47) samples and prevalence was highest amongst 20-23 year olds that didn't ask their partners about their STI status and currently had partners.

Discussion

This is the first study of its kind done focussing solely on a university environment using this method, that we know of. It also had the unique experience of being performed during the COVID-19 pandemic and when quarantine measures were being strictly imposed in Japan, testing communication limits as the project

required adaptation to permit us to continue to recruit participants and receive accurate data, with minimal to no face-to-face contact.

In this study, we show that young Japanese women are curious when it comes to sexual education but apprehensive about the self-sampling procedure. From the 330 volunteers, the HPV self-sampling uptake was only 20%, which is low but was within the project's expectations for this particular population. Similar percentages was also observed in previous Japanese studies, which stated that the national cervical cancer screening rates, in Japan, fall between 20-40% and in women in their early 20s, this rate falls below 10%.[29-31] The high adhesion to the first questionnaire is encouraging as it could be a solution to overcome a communication barrier that may exist between this population and healthcare providers.[32] STI knowledge and prevention studies, carried out in the Japanese population, have reported that even though university students have some knowledge of STIs, they continue to engage in high-risk sexual behaviour.[33, 34] Comprehensive sexual education can lead to participants that are more comfortable about their sexual education knowledge and thus, increase adherence to self-sampling as an alternative primary screening method, improving the coverage of STI screening.[8, 35]

Age, tobacco and alcohol consumption, number of lifetime partners and partners in the last year, oral sex performance, contraceptive use and presence of a partner were all statistically significant when relate to willingness to use a self-sampling kit for STI screening.[20] These results are according to literature present in multiple studies of similar kind around the world.[36] With the exception of oral sex performance, which has limited research and literature available on its connection to self-sampling as a screening process. These results provide information on what should possibly be targeted in order to increase adherence to screening programs in this population.

To assess self-sampling acceptability, we focused initially on whether the volunteer felt pain, their perception of the procedure and ease of use of the kits. Overall, the results go according to the literature available, in which majority of the participants did not experience pain and would opt to use a self-sampling kit if it were available to them.[37] However, a little over half classified their perception of the procedure as neutral. This perception may be due lack of self-confidence or confidence in the screening method. [38]

In order to compare user experience with provider collected samples, we focussed on evaluating whether the volunteers felt self-sampling was easier, less painful and more comfortable than provider collected samples. The questions were solely posed to women who had previous experience of having undergone a pap smear or other similar types of procedures at a physician's office.[20, 39] The responses to said questions were congruent with previous studies. Nevertheless, even though majority had a positive experience with the self-sampling process, the preference for self-sampling over provider collected samples was the same, showing a need for a self-sampling process that best fits the needs of this population.

STI prevalence was 29.8% (14/47) which is higher than was expected for the sample size. HPV infections were the most common, which is in agreement with the literature available. High HPV incidence in this study, could be due to fact that Japan was reported to have one of the highest rates of vaccine hesitancy in the world, increasing mortality rates by CC, poor screening attendance and poor sexual education. [40] The elevated incidence rates are observed mostly in vulnerable populations, particularly young female adults, where sexually active students have been shown to have low consistent condom usage.[33] Additionally, as dating applications become a popular means of having casual sexual interactions, special attention must be given in order to promote healthier choices when engaging in sexual intercourse.

The prevalence of HSV-2, *N. gonorrhoeae* and *C. trachomatis*, even if low, are of importance and their presence within this population goes according to literature.[26, 41] This is also true, in regard to, the absence of HSV-1 and *T. vaginalis* infections.[28] Based on the literature available, *T. vaginalis* infection prevalence is very low within the Japanese population.[42] However, the absence of *T. pallidum* infections did not go according to the literature that states that the Japanese population has seen a rapid increase in novel infections of STIs, particularly, syphilis and chlamydia.[5] According to literature, in 2021, Japanese women in their 20s formed the largest group of patients reported positive for syphilis.[5] The observed null infections, may be due to our sample size being less robust leading to an erroneous idea that our study population is not at risk of acquiring these STIs. Additionally, even thought these women are more educated and of higher social financial status, they may still experience social and cultural norms that heighten their vulnerability in acquiring STIs.[43]

Of importance is the elevated drop-out rate we observed. For future studies of this kind, this possibility should be taken into account when elaborating the methodology and questionnaires. Having a fragmented process, devoid of face-to-face contact, in its entirety, may alienate patients from participating in studies of this kind. Additionally, a hybrid, virtual and face-to-face, process may aid in the self-confidence some women may need in order to collect their samples.

This study is not without its limitations. We did not use positive controls to verify the accuracy of the positive results we obtained and relied on negative controls and previous literature that validated the protocols, this could lead to data that is not entirely reliable. We also had sample size limitations which inhibited our ability to extrapolate the data to a larger population, determine accurate statistical significance and validate our findings

In conclusion, even if small, there is an interest in self-sampling as a screening tool within this population and the prevalence of STIs is elevated but needs further studies to further validate the results we obtained in our study.

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Conflict of Interests

The authors report no conflicts of interest.

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