Original Article

Physiologic Testicular Uptake of 18-F Fluorodeoxyglucose in the Indian Population

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Abstract

Objective: The objective of the study is to assess the physiologic uptake of testes in patients undergoing ^{18}F-fluoro-2-deoxyglucose (FDG) position emission tomography/computed tomography (PET/CT) scans for various malignancies other than testicular malignancy. **Materials and Methods:** The testicular uptake of ^{18}F-FDG expressed as the standardized uptake value (T) was measured on PET/CT images in 320 men with no known testicular pathology from July 2019 to March 2020 at Tata Main Hospital, Jamshedpur. The ratio of maximum standardized uptake value (SUVmax) of the testis (T) to SUVmax of muscle (M) T/M ratio and to SUVmax of the liver (L) T/L ratio was calculated using SUVmax of right adductor muscle and liver, respectively. Testicular volume was calculated with the measurements taken from the axial, coronal, and sagittal slices of CT images. The correlation of testicular uptake with age, blood serum glucose level, and testicular volume was also analyzed. **Results:** The mean age of 320 men was 57 ± 15 years (range: 10–94) and the mean blood glucose level was 107.7 ± 23.5 mg/dl (range: 64–175). Mean testicular SUVmax in 320 men was 2.48 ± 0.80 (range: 0.67–5.5). The mean testicular volume of 640 testes of 320 men was 18.80 ± 4.83 cm^3 (range: 3.85–33.56 cm^3). The mean values of (T/M) and (T/L) ratios in the studied population were 3.64 ± 1.21 (range: 1.08–5.58) and 0.97 ± 0.251 (range: 0.34–1.88), respectively. The laterality index (|L − R|/(L + R) ×2) in 320 men was 0.074 ± 0.050 (0.000–0.308). There was a minimal negative correlation between testicular SUVmax and age (r = −0.136, P = 0.15). Mild negative correlation was noted between T/M ratio and age (r = −0.291, P < 0.0001) and between T/L ratio and age (r = −0.182, P = 0.001) in the studied population. **Conclusion:** The physiological testicular FDG uptake (SUVmax) of testes was 2.48 ± 0.80 (0.67–5.5) among the Indian population in this study, which has a mild negative correlation with age.

Keywords: *18F-fluoro-2-deoxyglucose position emission tomography/computed tomography, testicular uptake, testicular volume*

Introduction

18F-fluoro-2-deoxyglucose (FDG) position emission tomography/computed tomography (PET/CT) is routinely used for the evaluation of patients with different malignancies.[1] Although FDG generally accumulates in malignant lesions in accordance with the Warburg effect, it can also accumulate in normal tissues.[2-5] The organs that show physiologically increased FDG uptake, include the brain, heart, and genitourinary tracts, such as kidneys and bladder. Other organs, such as the liver, spleen, and gastrointestinal tract, show mild to moderate physiologic uptake.[6-8] The testes typically show mild to moderate physiologic FDG uptake on FDG PET scans, making it challenging to distinguish between the physiological and pathological FDG uptake.[9-11] Hence, an understanding of the normal physiological variations in the distribution of FDG in testes is important for the proper interpretation of FDG-PET/CT scans.[12-14] There are few studies that have already evaluated the physiological FDG uptake in testes; however, no studies are there among the Indian population to the best of our knowledge. In this study, we have retrospectively analyzed the physiological FDG uptake in the apparently healthy testes, among the Indian population, who have undergone FDG PET/CT scans for various malignancies (excluding testicular malignancies).

Materials and Methods

A total of 340 consecutive men who underwent diagnostic FDG-PET/CT scans at Tata Main Hospital between July 2019 and March 2020 were analyzed

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in this study. Of these 340 patients, 20 with either history of testicular pathology or unilateral or bilateral orchiectomy [Figure 1] were excluded from the study. The remaining 320 men comprised the study population with no history of any testicular pathology, no abnormal findings in testis on the images of PET/CT, and in their clinical records. All the pretreated patients included in this study have a gap of at least 3 weeks postchemotherapy and 6 weeks postradiotherapy before the PET/CT study. This is our usual institutional protocol. Of the 320 men, 84 were referred for the evaluation of lymphoma, 64 for head-and-neck cancer, 57 for GI malignancy, 41 for lung cancer, 11 for renal cell carcinoma, 10 for myeloma, 10 for sarcoma, and 43 for other cancers.

18F- fluoro-2-deoxyglucose position emission tomography/computed tomography acquisition

Whole-body 18F-FDG PET/CT scanning was performed using a Siemens Biograph Horizon PET/CT scanner (Make: Siemens Medical Solutions USA Inc., Model: Biograph Horizon, Serial number: 94562). All patients had a fasting blood glucose level below 180 mg/dL and received an intravenous injection of 18F-FDG. The average injected dose was 4.3 MBq/kg body weight (range: 2.3–7.1 MBq/kg), and the average time between FDG administration and the start of the PET acquisition was 64 min (range: 43–76 min). A low-dose CT scan was performed in all patients for localization and attenuation correction purposes. Scanning parameters included 50 reference mAs and 130 kV with CARE Dose 4D (Siemens Healthcare Pvt. Ltd., USA). For PET scanning, a three-dimensional emission scan was acquired with 8–10-bedded position, using 2 min/bed position.

Parameters calculated from the position emission tomography/computed tomography images

Images were interpreted on syngo.via VJ20b equipped workstations, using the MM Oncology software package (Siemens Healthcare, Germany), which can display CT, PET, and fused PET/CT images simultaneously. In this retrospective study, following parameters for each patient were recorded in Microsoft Excel sheet: name, age, fasting blood glucose, and creatinine levels. In addition, the following parameters were noted down from the PET/CT images of each patient on the syngo.via work station: maximum standardized uptake value (SUVmax) of each testis separately [Figure 1c], SUVmax of muscle (M) from the right adductor muscle [Figure 1c], SUVmax of the liver (L) [Figure 1d], long-axis diameters of testis were obtained from axial [Figure 1a], and coronal [Figure 1b] views of the CT image. Mean testicular SUVmax (T) was calculated as the average of right and left testicular SUVmax values. The ratio between testicular uptake and muscle uptake (T/M) and the ratio between testicular uptake and liver uptake (T/L) were calculated. The volume of each testis was then calculated using Lambert's formula: width × length × height × 0.71. The bilateral testicular volumes were then averaged to provide a mean testicular volume for each patient. "Laterality Index" was by calculated using the formula ($|L - R|/(L + R) \times 2$), where L = left testicular SUVmax and R = right testicular SUVmax for each patient.

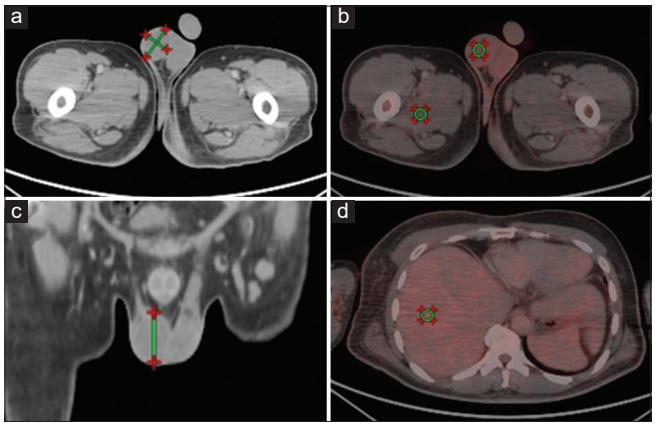

Figure 1: For testicular volume estimation length, width and height are measured (a and b) and maximum standardized uptake value is assessed of the testis, adductor magnus muscle, and liver (c and d)

Statistical analysis

All the continuous variables are represented as mean + SD correlation between age and the parameters such as testicular uptake (T), testicular to muscle uptake ratio (T/M), testicular to liver uptake ratio (T/L), plasma glucose levels, and testicular volume in all 320 men were analyzed using Pearson's correlation coefficient test that is available in the XLSTAT 2020 software of the Microsoft Excel. $P < 0.05$ was considered to be statistically significant.

Results

Mean testicular SUVmax and volume in 320 men are 2.48 ± 0.80 (range: 0.67–5.5) and 18.80 ± 4.83 cm^3 (range: 3.85–33.56 cm^3), respectively. The mean values of (T/M) and (T/L) ratios in the studied population were 3.64 ± 1.21 (range: 1.08–5.58) and 0.97 ± 0.251 (range: 0.34–1.88), respectively. The laterality index ($|L - R|/(L + R) \times 2$) in 320 men was 0.074 ± 0.050 (0.000–0.308).

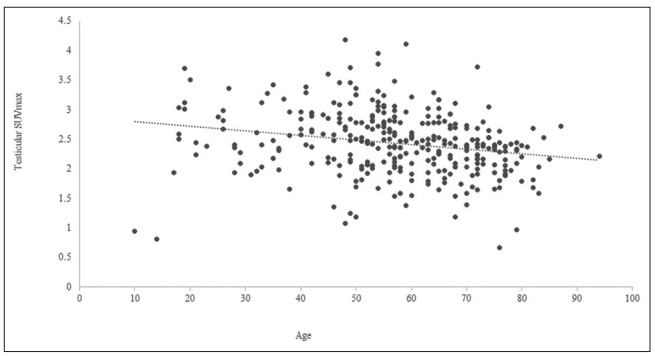

Figure 2: Correlation between age and testicular maximum standardized uptake value showing mild negative correlation with $r = -136$ and $P = 0.015$

Testicular SUVmax (T), testicular to muscular SUVmax ratio (T/M), testicular to liver SUVmax ratio (T/L), and mean testicular volume in the different age groups are shown in Table 1. Correlation of age with testicular SUVmax, T/M ratio, T/L ratio, and testicular volume is shown in Table 2.

Correlation analysis

Testicular maximum standardized uptake value (T) and age

There were no appreciable differences in the values of testicular SUVmax in the groups of patients up to the age of 70 years; however, there was a fall in SUVmax in the group of patients with age more than 70 years [Table 1]. There was a minimal negative correlation between testicular SUVmax and age ($r = -0.136$, $P = 0.15$) [Figure 2]. However, there was a positive correlation when the analysis was performed only on 23 patients with age < 30 years, which was statistically insignificant ($r = 0.293$, $P = 0.175$). There was a mild negative correlation when the analysis was done only on the remaining 227 patients with age more than 30 years, which was statistically significant ($r = -0.280$, $P \leq 0.001$).

Testicle to muscle uptake ratio (T/M) and age

T/M ratio showed an increase in value in the age group of <40 years and showed a fall in the value in the age group with age more than 40 years [Table 1]. There was a mild negative correlation between T/M ratio and age in the studied population that was statistically significant ($r = -0.291$, $P < 0.0001$) [Figure 3].

Testicle to liver uptake ratio (T/L) and age

T/L ratio also showed an increase in value in the age group of <40 years and showed fall in the value in the age group with age more than 40 years [Table 1]. There was a mild negative correlation between T/L ratio and age in the studied population, which was statistically significant ($r = -0.182$, $P = 0.001$) [Figure 4].

Testicular volume and age

Testicular volume showed an increase in value in the age group of <30 years and showed a fall in the value

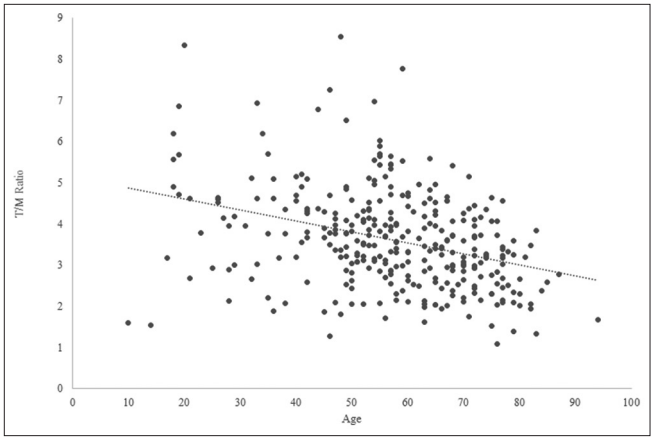

Figure 3: Correlation between age and testis to muscle SUV (T/M) ratio showing moderate negative correlation with $r = -0.291$ and $P \leq 0.0001$

Table 1: Testicular maximum standardized uptake value (T), testicle to muscle maximum standardized uptake value ratio (T/M), and testicle to liver maximum standardized uptake value ratio (T/L) and mean testicular volume in different age group

Age group	*n*	Testicular uptake (SUV_{max}) (T)		Mean testicular volume (cm^3)		Ratio testicular uptake/ muscle uptake (T/M)		Ratio testicular uptake/ liver uptake (T/L)	
		Mean±SD	Range	Mean±SD	Range	Mean±SD	Range	Mean±SD	Range
10-20	10	2.52±0.67	0.82-3.70	14.52±6.08	3.55-21.91	4.86±1.13	1.55-6.15	1.02±0.41	0.58-1.34
21-30	13	2.53±0.40	1.94-3.36	16.59±4.82	11.10-25.24	3.70±0.86	2.13-4.36	1.13±0.25	0.71-1.52
31-40	21	2.54±0.49	1.67-3.43	18.62±4.32	12.09-7.02	4.13±1.36	1.89-6.94	1.04±0.29	0.65-1.75
41-50	50	2.62±067	1.08-4.19	18.74±3.25	12.39-25.04	3.89±1.36	1.29-5.71	1.01±0.22	0.56-1.53
51-60	90	2.52±0.52	1.38-4.12	18.93±4.07	9.72-28.87	3.90±1.13	1.72-6.02	0.97±0.24	0.54-1.80
61-70	68	2.52±1.34	1.19-4.09	19.47±4.65	11.71-1.02	3.51±1.74	1.62-5.59	0.99±0.47	0.40-2.83
71-80	58	2.20±0.44	0.67-3.73	19.02±4.57	10.45-2.99	3.04±0.88	1.08-5.15	0.87±0.19	0.34-1.44
81-94	10	2.18±0.40	1.59-2.73	19.67±5.62	14.13-1.94	2.53±0.81	1.34-3.85	0.89±0.21	0.64-1.26
Total	320	2.48±0.80	0.67-4.19	18.80±4.83	3.85-33.56	3.64±1.21	1.08-6.15	0.97±0.25	0.34-1.80

SD: Standard deviation, SUV_{max}: Maximum standardized uptake value

Table 2: Correlation of age between mean testicular maximum standardized uptake value, T/M ratio, T/L ratio, mean testicular volume, and fasting blood glucose

Correlation between		Correlation co-efficient (*r*)	*P*
Testicular uptake (SUV_{max}) (T)	Age	−0.136	0.015
Ratio testicular uptake/muscle uptake (T/M)	Age	−0.291	<0.0001
Ratio testicular uptake/liver uptake (T/L)	Age	−0.182	0.001
Mean testicular volume (cm^3)	Age	+0.124	<0.0001
Testicular uptake (SUV_{max}) (T)	Blood glucose	−0.049	0.387
Testicular uptake (SUV_{max}) (T)	Mean testicular volume	+0.086	0.124

SUV_{max}: Maximum standardized uptake value

in the age group with age more than 30 years [Table 1]. There was a moderate positive correlation when the analysis was done only on the patients with age <30 years (r = 0.448, P = 0.0004). However, there was no significant correlation found when the analysis was done on the patients with age more than 30 years (r = −0.039 $P \leq 0.0001$).

Testicular standardized uptake value and blood glucose level

The mean blood glucose level before FDG injection in the 320 men was 107.7 + 23.5 mg/dl (64–175). None of these patients received an insulin injection before the scan. There was a statistically insignificant weak negative correlation between blood glucose level and testicular SUVmax (r = −0.049, P = 0.387).

Testicular standardized uptake value and testicular volume

There was a weak positive correlation between the mean testicular SUVmax and volume of bilateral testes in the studied population (r = −0.094, $P \leq 0.0001$) that was statistically significant.

Discussion

In addition to the accumulation of FDG in malignant lesions, physiological FDG uptake has also been seen in some normal tissues on PET scan. It is therefore of utmost importance to differentiate the normal physiological variant from the pathological FDG uptake. Among other organs that show physiological FDG uptake, the testis is not much studied. The physiologic testicular uptake of FDG has been analyzed in a few studies. The mean testicular SUV observed in our study done on the Indian population was 2.48 ± 0.80 [Table 1], which is comparable with the values reported in a study by Kitajima *et al*.[15] that showed a mean testicular SUV of 2.44 ± 0.45 done on 203 patients. Varying levels of testicular uptake have been reported in various age groups in different studies.[9,15-19] Our study showed a testicular SUV of 2.52 ± 0.67 in the age group of 10–20 years [Table 1]. Goethals *et al*. reported a mean testicular SUV of 0.6 ± 0.3 in a study done on 22 patients in the age group of 9–17 years,[17] which is much lower than the SUV observed in our study. This might be due to a high number of prepubertal boys in the study population of Goethals *et al*. However, there was only one patient with the age of 10 years who showed a mean testicular SUV of 0.82 in our study. Testicular SUV observed in our study on 13 patients in the age group of 21–30 years was 2.53 ± 0.40 [Table 1]. Meij-de Vries *et al*. reported SUV of 3.42 ± 0.61 in a study done on 20 patients the age group of 18–32 years,[16] that is slightly higher than the SUV observed in our study, probably due to geographical variation. Testicular SUV values observed on 208 patients in the age groups of 41–50, 51–60, and 61–70 years in our study were 2.62 ± 0.0.67, 2.52 ± 0.0.67, and 2.52 ± 1.34, respectively [Table 1]. Moon *et al*. reported a mean testicular SUV of 1.85 ± 0.33 in a study done on 66 patients in the age group of 37–72 years.[18] Our study has shown slightly higher testicular SUV in this age group of 41–70 years. The variation in testicular SUV among different studies could be due to different instrumentation also, as with time more and more advanced technologies are being used for SUV calculation. However, there is a gradual decrease in the uptake values with increasing age as shown in Table 1. Few hypotheses have been put forth to explain this reduction in FDG uptake with increasing age. Some researchers documented that with increasing age, factors such as testicular perfusion and metabolism reduce.[15] As age increases, the germ cell begins to degenerate, and the number and function of the Sertoli and Leydig cells decrease, causing an overall decrease in testicular volume.[20,21] Thus, our finding that testicular FDG uptake decreased mildly with age after the age of 30 years can also be explained by these physiologic phenomena.

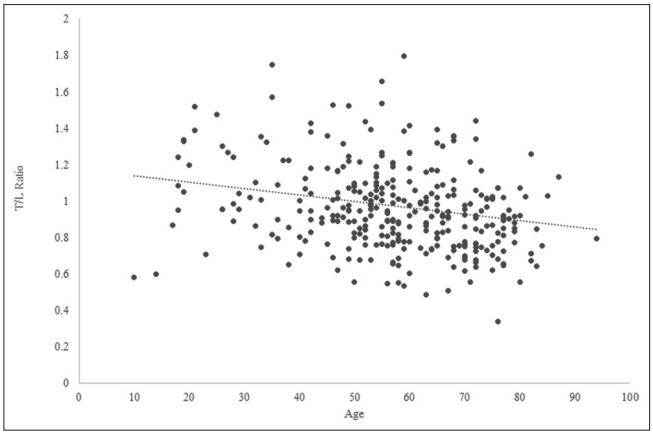

Figure 4: Correlation between age and testis to liver SUV (T/L) ratio showing mild negative correlation with r = −0.182 and P = 0.001

Various formulae have been used to calculate the testicular volume measured from ultrasonography. The formula introduced by Lambert ($L \times W \times H \times 0.71$) in 1951 has been used in many studies including the one done on the Indian population and is found to be more accurate than other methods.[22-25] Therefore, we have also used this formula [Figure 2a and b]. The mean testicular volume observed from CT images in our study was 18.80 ± 4.83 cm^3 (3.85–33.56). The mean testicular volume reported by Kitajima *et al*. was 22.1 ± 6.4 cm^3 (3.8–41.5)[15] and by Meij-de Vries was 23.0 ± 6.4 cm^3 (10.2–42.8).[16] Mean testicular volume reported by Gupta *et al*., Huang *et al*., Fui MNT *et al*., and Anafa *et al*. was 16.73 cm^3,[23] 16.57 cm^3,[25] 18.0 cm^3,[26] and 18.57 cm^3,[14] respectively. These values observed in studies done in Asia and Australia are similar to the values observed in the Indian population of our study. Higher values observed in other studies may be due to factors such as the regional variation in size of the testes, measurement method, and formula used.

The laterality index calculated with testicular SUV in our study showed a mean value of 0.074 ± 0.050 (0–0.308) with 99% values below 0.204. Laterality index above this range could be a pathological process; however, it will require further evaluation. Laterality index observed in our study was comparable with the values quoted in two other studies with 0.066 ± 0.067 by Kitajima *et al*.[15] and with 0.077 ± 0.066 by Meij-de Vries *et al*.[16]

In the correlation analysis between the age and testicular SUV, our study showed a mild negative correlation ($r = -0.136$, $P = 0.015$). This is comparable with the correlation values reported by Kitajima *et al*. ($r = -0.284$, $P < 0.001$)[15] and by Moon *et al*. ($r = -0.509$, $P \leq 0.001$).[18] However, we have also observed a positive correlation ($r = 0.293$, $P = 0.1575$) on 23 patients with age <30 years that was not statistically significant and a negative correlation ($r = -0.280$, $P = 0.001$) on 297 patients with age >31 years. This is comparable to the values observed by Moon *et al*. with a positive correlation ($r = +0.718$ and $P = 0.005$) in the patients below 25 years of age[18] and a negative correlation ($r = -0.240$, $P \leq 0.05$) in patient above 25 years of age.[9] Meij-de Vries *et al*. reported a positive correlation (r = 0.349, $P < 0.0001$) in a study done 20 males with mean of 26.5 ± 3.9 years.[16] Our study shows a mild positive correlation up to the age of 30 years and a mild negative correlation after the age of 31 years while comparing the age and testicular FDG uptake.

When correlating the age with mean testicular volume, we have observed a positive correlation ($r = +0.448$, $P = 0.0004$) on 23 patients with age <30 years and a weak negative correlation that is statistically significant ($r = -0.039$, $P \leq 0.0001$) on 297 patients on with age >31 years. Kitajima *et al*. reported a negative correlation ($r = -0.269$, $P = 0.0001$) in the study done on 203 patients with age more than 30 years.[15] Goethals *et al*.[17] reported a positive correlation ($r = +0.670$, $P \leq 0.001$) in the study done on 22 patients in the age group of 9–17 years. This shows that testicular volume grows for up to approximately 30 years of age, after which no significant change occurs.

Correlation between testicular SUVmax and testicular volume in our study showed a weak positive correlation ($r = +0.094$, $P \leq 0.001$) that was statistically insignificant. Kitajima *et al*. reported a positive correlation ($r = +0.368$ and $P \leq 0.001$) that was statistically significant.[15]

Correlation between testicular SUV and fasting blood glucose in our study showed a negative correlation ($r = -0.049$, $P = 0.387$) that was statically insignificant. Kitajima *et al*. also reported a negative correlation ($r = -0.065$ and $P = 0.358$).[15]

Correlation between age and (T/M) ratio in our study showed a mild negative correlation ($r = -0.291$, $P \leq 0.0001$). This is comparable with the results in a study by Han *et al*.[19]

We also tried to find if any correlation between age and (T/L) ratio in our study, which showed a mild negative correlation ($r = -0.182$, $P = 0.001$).

With such physiological FDG uptake in the testes and variation with age, the nuclear medicine physician needs to rule out physiological uptake before reporting any uptake as pathological. It could also be possible to have a cutoff value for these ratios if done on patients with testicular pathology, which may be useful in differentiating the various types of testicular pathologies. Testicular FDG uptake in various malignant and nonmalignant tumors has been reported in various studies.[27-34] More studies and clinical trials are required and would help formulate uniform guidelines for the management of various testicular diseases.

The following are the limitations of the present study: (i) it is a retrospective study, (ii) the age distribution of the participants was uneven, (iii) most participants were in the age groups between 41 and 80 years, and the number of participants in other age groups was relatively small. Around one-fourth of the study patients were having lymphoma. Although we have excluded patients with any apparent testicular abnormality, this could be another limitation of this study.

Conclusion

In healthy Indian males, the mean SUVmax of the testis was 2.48 ± 0.80 on FDG PET/CT scan. The degree of testicular FDG uptake, testicular to muscle SUV (T/M) ratio, and testicular to liver SUV (T/L) ratio decreases with the increase in age with a mild negative correlation suggesting their limited significance in PET/CT reporting.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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