

Research Article

# Evaluation of Treatment Results for Male Hypogonadism in Patients with Varicocele and Without Varicocele in Can Tho City

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## Abstract

**Introduction:** male hypogonadism is defined by the European Association of Urology 2022 as being associated with reduced testicular function, reduced androgen production, and/or impaired sperm production. Male hypogonadism has many causes and accompanying diseases such as diabetes, varicocele, etc. Male hypogonadism has symptoms of varicocele and had two treatment options: testosterone replacement therapy or surgical treatment of varicocele. Each method has different advantages and disadvantages, so we research to evaluate each treatment method's results. **Objectives:** Evaluate the results of male hypogonadism treatment of testosterone replacement therapy or varicocele surgery. **Material and methods:** conducted a cross-sectional descriptive study in 111 men with symptoms of hypogonadism from January 2022 to the end of 2023. **Result:** The average age was  $65.2 \pm 2.4$  years. The Androgen Deficiency in Aging Males (ADAM) questionnaire has the highest rate of 90.99% showing symptoms of decreased erection strength. Hypogonadism is associated with body mass index and diabetes. After treatment, the hypogonadism group with grade III varicocele had the lowest response to treatment. After treatment, total testosterone in blood levels in all treatments increased ( $p < 0.001$ ). **Conclusion:** Testosterone replacement therapy for hypogonadism without varicocele is the gold standard, and microsurgical treatment for hypogonadism with varicocele is the most effective.

## Keywords

Male Hypogonadism, Testosterone Replacement Therapy (TRT), Varicocele, Varicocelectomy

## 1. Introduction

According to the European Society of Urology 2022 guidelines, the definition of "male hypogonadism is related to reduced testicular function, reduced androgen hormone production and/or impaired sperm production" [1].

Male hypogonadism has many causes and there are risk

factors for hypogonadism, including chronic diseases (diabetes, arthritis, kidney, and HIV), obesity metabolic syndrome, etc... [2].

Currently, there are treatment methods such as non-medication (change in lifestyle, in diet), internal medi-

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cine (Androgel or Vogelxo to rub into the skin or upper arm), and surgery (Varicocele or without Varicocele surgery). For hypogonadism patients without varicocele, testosterone replacement therapy is considered standard therapy [1]. Hypogonadism men with varicocele have two treatment options: testosterone replacement therapy or varicocele treatment. Varicocele surgery significantly increases testosterone production and improves testicular Leydig cell function [3], microsurgical varicocele surgery may be preferred to bring about the best improvement for patients with hypogonadism who had varicocele [4]. Each method has different advantages and disadvantages, so we researched the results of hypogonadism treatment in 3 groups of subjects: surgical treatment of varicocele in hypogonadism patients with varicocele, testosterone replacement therapy in hypogonadism patients with and without varicocele.

## 2. Material and Methods

### 2.1. Material

The patient was diagnosed with male hypogonadism at Can Tho University of Medicine and Pharmacy Hospital and Can Tho City Obstetrics and Gynecology Hospital from 2022-2023.

*Sample selection criteria:*

1. The patient was diagnosed with clinical hypogonadism and serum total testosterone concentration < 12 mmol/l in 2 tests in the morning [1].
2. The patient agrees to participate in the study.

*Exclusion criteria:*

1. Testosterone replacement therapy treatment: patients have ever been treated or are currently receiving testosterone replacement therapy. The patient had a previous orchiectomy.
2. Varicocele Surgical treatment: We have used the treatment during the research process.

### 2.2. Methods

*Research design:* Cross-sectional study, prospective descriptive research method.

*Sample size and sampling method:* 111 men with symptoms of hypogonadism from January 2022 to the end of 2023.

*Research content:* we selected a total of 111 male hypogonadism patients who agreed to participate in the study. Record age, mass index (BMI), waist circumference, history of diabetes, dyslipidemia, androgen deficiency symptom questionnaire (ADAM), and grade of varicose veins. Clinical spermatorrhea (graded according to Dubin and Amelar at the 1970 International Conference in Dublin [5] and performed scrotal Doppler ultrasound to confirm diagnosis [6]). Measure testosterone levels twice in the morning in the blood before treatment and after 3 months of treatment. We divided into 3 treatment groups: surgical treatment of varicocele in hypogonadal patients with varicocele (33 patients), testosterone replacement therapy treatment in hypogonadism patients with varicocele (31 patients) and no varicocele (47 patients). Evaluate treatment results between 3 treatment groups and side effects of testosterone gel 1%.

*Statistical processing of data:* data processing using SPSS 22.0 statistical software.  $p \leq 0.05$  is considered statistically significant.

*Ethics in research:* This study was approved by the Ethics Council in Biomedical Research of Can Tho University of Medicine and Pharmacy (number: 23.012.NCS/PCT-HĐĐĐ).

## 3. Result

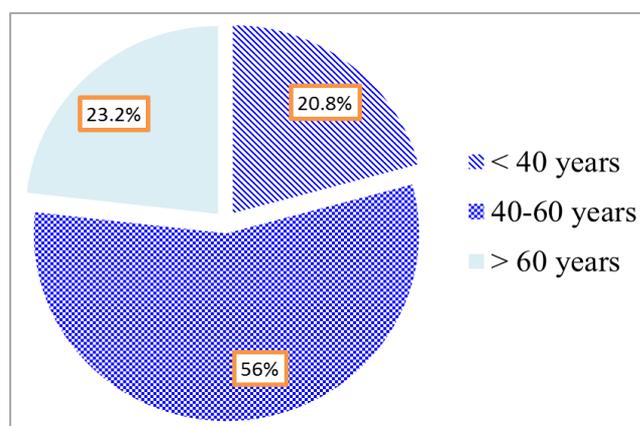


Figure 1. Distribution by age group.

Comment: average age is  $65.2 \pm 2.4$  years old. The age group from 40-60 years old accounts for the most, 56%.

Table 1. Comorbid underlying diseases.

Accompanying disorders	Frequency (n)	Ratio (%)	
Waist circumference (cm)	> 90	35	31.53
	$\leq 90$	76	65.47
Body mass index ( $\text{Kg/m}^2$ )	< 30	67	60.36

Accompanying disorders		Frequency (n)	Ratio (%)
	≥ 30	44	39.64
Diabetes	Yes	36	32.43
	No	75	67.57
Blood lipid disorders	Yes	48	43.24
	No	63	56.76

Comment: waist circumference > 90 cm accounts for 31.53%, and mass index ≥ 30 Kg/m<sup>2</sup> accounts for 39.64%. Diabetes accounts for 32.43%. Lipid disorders account for 43.24%.

**Table 2.** Symptoms of androgen deficiency according to the ADAM questionnaire.

Symptoms of androgen deficiency	Frequency (n)	Ratio (%)
Reduced vitality	24	21.62
Recently there has been a decline in physical and sports activities	36	32.43
Reduce height	46	41.44
Bored and/or grumpy	58	52.25
Reduced strength and/or endurance	64	57.65
Reduced interest in life	62	55.85
Feeling sleepy after dinner	71	63.96
Reduced sexual desire	88	79.27
Reduce labour productivity	89	80.18
Reduce erection	101	90.99

Comment: The symptoms of male hormone deficiency according to the ADAM questionnaire account for the highest rate of 90.99%, which is the symptom of decreased erection strength, and the second place is decreased labor productivity, accounting for 80.18%.

**Table 3.** Total testosterone of the study group.

Total Testosterone	Frequency (n)	Ratio (%)
8-12 nmol/L	48	43.25
<8 nmol/L	63	56.75
Total	111	100

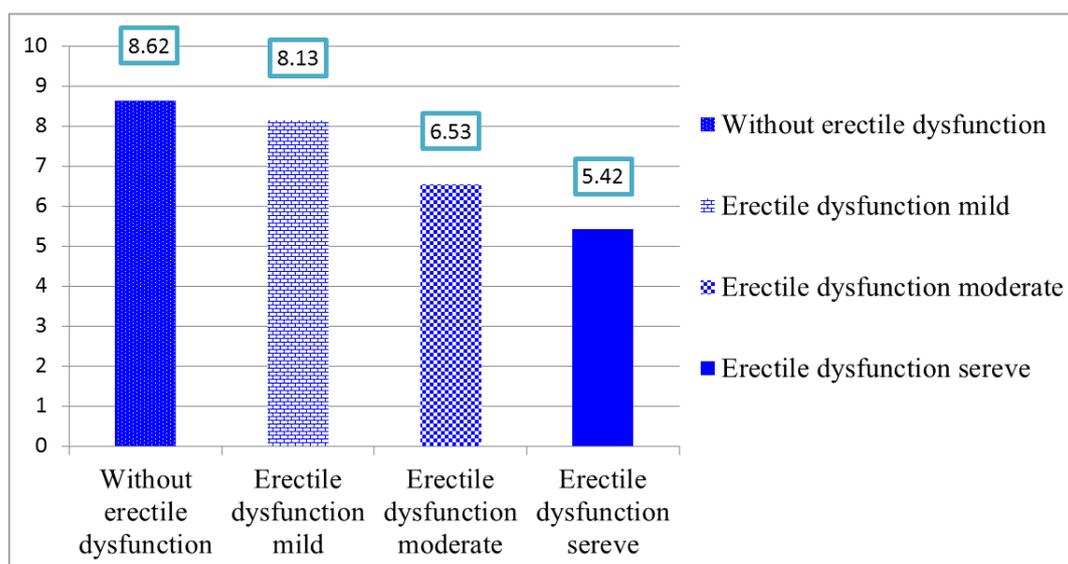
Comment: 56.75% had a total testosterone concentration <8 nmol/L.

**Table 4.** Total testosterone concentration according to varicocele grading.

Grade	Total Testosterone concentration (nmol/L)	Frequency (n)	Ratio (%)
I	8.22	29	26.12
II	6.78	23	20.72

Grade	Total Testosterone concentration (nmol/L)	Frequency (n)	Ratio (%)
III	5.56	12	10.81
Without varicocele	8.32	47	42.34

Comment: 47 patients without varicocele reduction had the highest average testosterone concentration of 8.32 nmol/L, the clinical grade III varicocele group had the least incidence and the lowest average concentration of 5.56 nmol/L.



**Figure 2.** Testosterone concentration according to level of erectile dysfunction.

Comment: The more severe the level of erectile dysfunction (ED), the lower the testosterone concentration, the difference between groups is statistically significant ( $p < 0.05$ , Kruskal-Wallis H-test).

**Table 5.** Relationship between the degree of hypogonadism and the underlying disease.

Characteristic		Testosterone concentration		Total	p
		8-12 nmol/L	<8 nmol/L		
Body mass index (Kg/m <sup>2</sup> )	≥30	13	31	44	0.04*
	<30	35	32	67	
Diabetes	Yes	8	28	36	0.03*
	No	40	35	75	
Total		48	63	111	

\* Chi-square test

Comment: hypogonadism with body mass index and history of diabetes have a statistically significant difference ( $p < 0.05$ ).

**Table 6.** Relationship between testosterone concentration and degree of varicocele.

Degree of varicocele	Quantity	Testosterone concentration before treatment (nmol/L)		Testosterone concentration after treatment (nmol/L)		P
I	29	8.22		16.52		
II	23	6.78	7.20	12.75	13.17	
III	12	5.56		5.91		0.02**
Without varicocele	47	8.32	8.32	15.31	15.31	
Total	111	7.67		14.07		
P		0.04*		0.01*		

\* Kruskal–Wallis test

\*\* Wilcoxon-test

Comment: before and after treatment, the more the degree of varicocele increases, the more testosterone levels decrease, with a statistically significant difference ( $p < 0.05$ ). All groups responded to treatment, grade III varicocele had the lowest response ( $p < 0.05$ ).

**Table 7.** Treatment outcomes between treatments.

Hypogonadism	Testosterone replacement therapy		Surgery	Total
	Without varicocele	Varicocele	Varicocele	
Sample size	47	31	33	111
Testosterone concentration before treatment (nmol/L)	8.32	8.37	6.08	7.67
Testosterone concentration after treatment (nmol/L)	15.31	12.31	13.95	14.07
P	0.02*			

\* Friedman test

Comment: After treatment, total blood testosterone levels in all treatments increased ( $p < 0.001$ ). Among them, the hypogonadism group without varicocele had the best response, while testosterone replacement therapy in hypogonadism subjects with varicocele had the lowest response.

**Table 8.** Complications when using testosterone gel 1%.

Side effects	Quantity (n)	Ratio (%)	Side effects	Quantity (n)	Ratio (%)
Diabetes	3	2.70	Skin reactions	7	6.30
Hypertension	6	5.40	Increased red blood cells	18	16.21
Headache	8	7.20	Total	42	37.83

Comment: all are mild side effects. The highest rate is erythrocytosis accounting for 16.21% (18 cases), the second place is headache accounting for 7.2% (8 cases), skin reactions accounting for 6.3% (7 cases), hypertension accounting for 5.4% (6 cases), diabetes accounts for 2.7% (3 cases).

## 4. Discussion

### 4.1. General Features

We recorded an average age of  $65.2 \pm 2.4$  years. The age group from 40–60 years old accounts for the most, 56%. The Wei Chen study recorded  $59.4 \pm 7.4$  years old [7]. Author Jorge Panach-Navarrete et al. recorded an average age of  $56.72 \pm 10.83$  years [8]. Our general research is quite similar in terms of research results when male hypogonadism is common in older people because as age increases, the rate of male hypogonadism increases [1]. About 50% of circulating testosterone is bound to sex hormone-binding globulin and 50% is bound to albumin. Only about 0.5 – 3.0% is free, which is the biologically active form. Sex hormone-binding globulin levels increase with age, meaning testosterone levels decrease. Therefore, although mean testosterone concentrations remain within normal limits in most men, free testosterone concentrations decrease by approximately 2 - 3% per year [9]. 20% of men over 60 years old and 50% of men over 80 years old have testosterone levels lower than normal testosterone levels for their age group.

### 4.2. Clinical

We recorded waist circumference > 90 cm accounting for 31.53%, and mass index  $\geq 30$  Kg/m<sup>2</sup> accounting for 39.64%. Diabetes accounts for 32.43%. Lipid disorders account for 43.24%. The degree of hypogonadism with body mass index and history of diabetes was statistically significantly different ( $p < 0.05$ ). Author Panach-Navarrete J noted a history of hypertension accounting for 45.55%, dyslipidemia 36.66%, and diabetes accounting for 27.77%. BMI  $\geq 30$  Kg/m<sup>2</sup> is associated with low total testosterone concentration ( $p < 0.001$ ) and patients with BMI  $\geq 30$  Kg/m<sup>2</sup> are 2.94 times more likely to have I hypogonadism than those with BMI < 30 Kg/m<sup>2</sup> ( $p < 0.001$ ) [8]. The mechanism of varicocele causing male hypogonadism is related to different mechanisms such as oxidative stress, local hormonal imbalance, blood stasis, reduced cell perfusion, and heat stress [10]. However, author Jorge Panach-Navarrete et al had the opposite result when they noted that hypogonadism did not correlate with decreased testosterone levels and varicocele [8].

Symptoms of hypogonadism account for the highest rate of 90.99%, decreased erection strength, and second place is decreased labor productivity, accounting for 80.18%. The first study in 1975 reported that 10 of 33 (30%) men with varicocele who had reduced testosterone levels had erectile dysfunction, and symptoms improved in these men after surgery to remove varicocele [11]. Wei Chen's study found that 83.65% of patients responded with symptoms when asked about the ADAM score, with the highest score being reduced erection [7]. It can be seen that the ADAM score plays a great role in screening male hypogonadal patients in the community because it is easy to perform.

Erectile dysfunction according to the IIEF scale is 83.3%,

of which mild level accounts for the highest rate of 45.8% (average testosterone concentration 8.13 nmol/L), moderate level 23.6% (average testosterone concentration 6.53 nmol/L), severe level accounts for 13.8% (average testosterone concentration 5.42 nmol/L), and no erectile dysfunction accounts for a low rate of 16.7%. Our study is similar to the study of Giuseppe Lisco (2023) in a cross-sectional study on a group of functional hypogonadism (165 patients), the level of mild erectile dysfunction was 44.8%, and the average erectile dysfunction was 38.8%. % and severe erectile dysfunction is 16.4% [12]. In a study by author Dachille G and colleagues, among 124 male patients, 25 (20.1%) had severe erectile dysfunction (IIEF score <10), 11 (8.8%) had moderate erectile dysfunction (score from 11 to 16) and 20 people (16.12%) had mild erectile dysfunction [13]. Ji B et al. noted that varicocele causes decreased blood testosterone levels and decreased erectile function corresponding to a decrease in total testosterone levels in the blood [14]. The degree of hypogonadism is associated with erectile dysfunction [15-17]. It has been shown that erectile dysfunction symptoms often appear in patients with reduced testosterone levels and are often mild and can respond to treatment.

### 4.3. Subclinical

Total testosterone concentration < 8 nmol/L accounts for 56.75%. 43.25% had total testosterone levels of 8-12 nmol/L. 42.34% did not have varicocele, 26.12% had grade I varicocele, 20.72% grade II and 10.81% grade III. Author Panach-Navarrete J recorded a total of 248 cases (70.8%) without varicocele, 46 patients (13.1%) with grade I varicocele, 36 patients (10.3%) with grade II and 20 patients (5.7%) grade III [8]. The higher the degree of varicocele in hypogonadal patients, the lower the incidence. We classify varicocele clinically because this is a common classification in the world, but the use of grading on ultrasound is still controversial and inconsistent [6].

Varicocele is also a common disease accounting for 15% of the general population in men, 35% of primary infertility, and 80% of secondary infertility [18]. In our study, varicocele accounted for 57.66% of the hypogonadal group, the reason may be that the study site took samples at the infertility department of Can Tho City Obstetrics and Gynecology Hospital and the patients had symptoms of hypogonadism when examined at the male urology clinic at Can Tho University of Medicine and Pharmacy Hospital, so there is such a big difference. It will be difficult for the patient to know that he has a varicocele when it is still grade I or II, but the patient can know the symptoms of hypogonadism, so going to the doctor for simple symptoms of hypogonadism is the most common.

We noted that as the degree of varicocele increases, testosterone levels decrease. Specifically, total testosterone concentration in hypogonadal patients without varicocele is 8.32 nmol/L, grade I varicocele is 8.22 nmol/L, and grade II

varicocele is 6.78 nmol/L. L, grade III varicocele is 5.56 nmol/L. Varicocele causes impaired Leydig cell function and this is a risk factor for hypogonadism, patients with hypogonadism accompanied by varicocele have a greater decrease in testosterone levels than the hypogonadism without varicocele [1]. Tanrikut et al. demonstrated that men with varicocele had lower serum total testosterone concentrations than controls [19]. Authors Ji B and Jin XB noted that patients with grade II or III varicocele have a higher risk of hypogonadism [14]. Author Jorge Panach-Navarrete and colleagues had different results from ours as they could not establish a relationship between the presence of varicocele and reduced serum testosterone levels [8]. Author Al-Ali BM had opposite results to ours when hypogonadal patients with grade III varicocele ( $5.7 \pm 0.2$  nmol/L) were higher than grade II ( $5.0 \pm 0.1$  nmol/L) and grade II was higher than grade I ( $4.9 \pm 0.2$  nmol/L) [20].

#### 4.4. Treatment Results

*Effective:* All 3 groups of hypogonadal patients increased testosterone after treatment, with a statistically significant difference ( $p=0.02$ ). The hypogonadism group without varicocele increased from 8.32 to 15.31 nmol/L. The hypogonadism group with varicocele increased from 7.2 to 13.17 nmol/L, in which grade I varicocele from 8.22 to 16.52 nmol/L, grade II from 6.78 to 12.75 nmol/L, grade III from 5.56 up to 5.91 nmol/L. The more the varicose veins increase, the lower the response to treatment.

The treatment method of testosterone replacement therapy in the group of patients without varicocele had the highest treatment response from 8.32 before treatment to 15.31 nmol/L after treatment (an increase of 6.99 nmol/L), ranking 2nd in varicocele surgery method increased from 6.08 before treatment to 13.95 nmol/L after treatment (an increase of 7.87 nmol/L), ranked last is testosterone replacement therapy in the group of varicocele patients increased from 8.37 to 12.31 nmol/L after treatment (an increase of 3.94 nmol/L). The treatment response of the 3 methods is different but all methods respond to treatment, it can be said that testosterone replacement therapy for hypogonadism without varicocele is the gold standard [1], and surgical treatment of hypogonadism with varicocele is the most effective [4]. However, we still do not have enough data to compare the combined method of varicocele surgery and testosterone replacement therapy after surgery. According to research compiled around the world, although there are many methods of varicocele surgery, microsurgery is the most effective until now [4].

Author Thanaboonyawat noted a significant increase in testosterone ratio ( $p = 0.008$ ) after applying the gel for 3 consecutive months [21]. Author Ramasamy R noted that the testosterone rate increased significantly after applying the gel for 3 consecutive months ( $p<0.05$ ) [22]. Li et al noted an increase in mean plasma testosterone level of 97.48 ng/dL after varicocele repair, suggesting improvement in

Leydig cell function [3]. Hsiao et al included 78 patients with varicocele who underwent microsurgical varicocele repair and compared serum testosterone levels from pretreatment to posttreatment based on the degree of varicocele. They found that 83% of patients showed increased testosterone after surgery and that varicocele treatment increased serum testosterone levels, regardless of the grading of the varicocele [23]. Zohdy et al noted that 75.5% of patients had normal testosterone levels after varicocele treatment [24]. Tanrikut et al similarly concluded that varicocele may cause androgen deficiency and that varicocele treatment may increase testosterone levels in hypogonadal men with varicocele [19]. A meta-analysis of 28 studies by author Whelan P et al noted that: 15 studies concluded that there was a significant increase in total serum testosterone hormone levels after surgery and high serum hormone levels peak was achieved at 6-9 months after varicose vein surgery, however, 13 concluded that there was no association [25]. Although all methods respond to treatment, the increase in hormone levels after varicocele surgery is not certain (currently, research around the world is still debated.), because a large number of studies did not show that and because most studies were retrospective, with small samples and short follow-up periods of several months, in addition to the criteria for diagnosing hypogonadism in the past is unclear because the diagnosis of hypogonadism is based on total or free testosterone in the blood and what is the threshold for diagnosing hypogonadism.

*Side effects of testosterone replacement therapy:* all are mild side effects. The highest rate is erythrocytosis accounting for 16.21% (18 cases), the second place is headache accounting for 7.2% (8 cases), skin reactions accounting for 6.3% (7 cases), hypertension accounting for 5.4% (6 cases), diabetes accounts for 2.7% (3 cases). Author Wittert GA et al noted that side effects of testosterone gel 1% applied during 2 months of treatment monitoring include: headache (Headache) accounting for 25%, fatigue (Fatigue) accounting for 25%, pain in the limbs (Pain in extremities) accounts for 6%, coma (Lethargy) accounts for 6%, rash (Rash) accounts for 6%, Application site rash accounts for 6% [26].

In contrast to us, authors Vinarov AZ et al did not have any clinically significant side effects observed during follow-up after 3 months of applying testosterone gel 1% [26]. his difference may depend on treatment compliance, site of use, product type, product formulation, and differences in each skin type. During the development of the T-patch, it was determined that the decreased absorption of testosterone in the back > thigh > upper arm > abdomen > chest > shin and application to the trunk may not absorb testosterone as well as the shoulders, upper arms, and abdomen.

The most important side effect associated with the use of testosterone gel is the potential for testosterone medication to be transferred to others when it comes into contact with skin surfaces. Approximately 10% of patients discontinued the use of the patch due to skin irritation and 50% experienced transient skin irritation within 12 months. These reactions can be

reduced by using corticosteroids (triamcinolone cream 0.05%) To limit irritation due to testosterone adhesion, new medications with higher concentrations of testosterone will help overcome this situation (high concentrations require less medication).

However, transdermal androgens are prepared in the form of 1% testosterone gel (T gel) most commonly used worldwide because T gel has proven pharmacokinetic properties, safety, and clinical effectiveness demonstrated [26].

## 5. Conclusion

The average age was  $65.2 \pm 2.4$  years. The ADAM questionnaire has the highest rate of 90.99% showing symptoms of decreased erection strength. The more severe the level of ED, the lower the testosterone concentration. Hypogonadism is associated with body mass index and diabetes. The more the degree of varicocele increases, the more testosterone levels decrease.

After treatment, the hypogonadal group with grade III varicocele had the lowest treatment response and total blood testosterone levels increased in all treatments ( $p < 0.001$ ). Testosterone replacement therapy for hypogonadism without varicocele is the gold standard, and microsurgical treatment for hypogonadism with varicocele is the most effective.

## Conflicts of Interest

The authors declare no conflicts of interest.

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