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Gamma oscillations predict paroxetine response of patients with Obsessive Compulsive Disorder

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ABSTRACT

Background: Obsessive compulsive disorder is a distressing psychiatric illness with considerable treatment resistance rates. Prediction of treatment response leads to an increase in patient compliance and a decrease in morbidity. To decrease the treatment resistance rates, valid and useful instruments have been searched. Quantitative electroencephalography (QEEG) based markers have been objective predictors of the treatment response in psychiatric disorders.

Aim: This retrospective pilot study aims to explore QEEG as a biomarker to predict early response to paroxetine in OCD patients.

Method: Resting state QEEG and Yale-Brown Obsessive Compulsive Scale (Y-BOCS) were administered to 30 drug-free OCD patients without comorbidity. After maximum 12-week of treatment with paroxetine, patients with and without an early improvement were classified based on at least a 35% reduction in Y-BOCS scores. Pre-treatment QEEG data were compared between the two groups.

Results: Pre-treatment gamma, gamma 1 and gamma 2 oscillations were significantly higher in OCD patients who did not show an early improvement.

Conclusion: These preliminary results indicate that gamma oscillations could be acknowledged as the electrophysiological predictors of early clinical outcomes of OCD patients during paroxetine treatment.

1. Introduction

Obsessive-compulsive disorder (OCD), which is represented by intrusive thoughts, urges or images (i.e., obsessions) and repetitive ritualistic behaviors (i.e., compulsions) to avoid or suppress the anxiety induced by the obsessions (American Psychiatric Association, 2013), is an aggravating mental problem with a high prevalence. Approximately 1–3% of the population is suffering from this illness.

As the first-line treatments in OCD, Selective Serotonin Reuptake Inhibitors (SSRIs), clomipramine and/or psychotherapy are administered (APA, 2013). SSRIs and clomipramine have similar success rates (Skapinakis et al., 2016); however, SSRIs are commonly suggested due to the lower placebo response (Sugarman et al., 2017) and higher tolerability (Bandelow et al., 2008). Paroxetine is one of the SSRI compounds used in OCD pharmacotherapy with approximately 50% success rates (Saxena et al., 2002). Treatment response is similar with other SSRI compounds (Skapinakis et al., 2016).

On the other hand, prediction of treatment response to antidepressant medications has ethical and financial aspects. The ethical point is that patients have the right to be protected from ineffective and unnecessary treatment modalities. Quantitative electroencephalography (QEEG) is one of the biomarkers used for predicting the treatment response in psychiatry. It has advantages of being objective, non-invasive, affordable, and suitable for regular use in daily clinical practice. Several QEEG studies reported that SSRI treatment response of OCD patients can be differentiated by the EEG power spectral analysis of brain oscillations. An earlier study (Prichep et al., 1993) investigating pre-treatment QEEG measures found greater alpha power in responders to SSRI treatment (i.e., fluvoxamine, fluoxetine, and clomipramine) and greater theta power in the frontal and frontotemporal regions of non-responders. In a replication of this study (Hansen et al., 2003), pre-treatment EEG measures showed that there was no greater theta activity in non-responders, but higher alpha relative power of paroxetine responders was observed in frontal, frontopolar, and posterior

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temporal regions. Although the predictive ability of EEG biomarkers does not reach 100%, its specificity and sensitivity could reach 80–90% in the OCD group (Altuglu et al., 2020). Therefore, QEEG biomarkers should be taken into account for predicting the treatment response in psychiatric population.

In our present study, gamma frequencies were also searched for several reasons. Previous QEEG studies with discordant results generally have a lack of gamma search. Those studies investigated four main frequency bands, namely delta, theta, alpha, and beta waves. According to a review (Newson & Thiagarajan, 2019), EEG studies performed with psychiatric patients usually report one or two frequency bands. Evidence from these studies revealed that EEG biomarkers of OCD patients are an increase in low-frequency bands and a decrease in high-frequency bands. Nevertheless, it should be noted that reporting one or two frequency bands may create some comparison problems with respect to EEG biomarkers. According to the review, the rates of frequency bands are as follows: Gamma (18%), delta (70%), beta (80%), theta, and alpha (85/84%). One probable explanation for the scarcity of gamma reporting is its artifact like characteristics; however, new technological progress makes it possible to discriminate gamma rhythms and artifacts (Muthukumaraswamy, 2013).

QEEG gamma activity is one of the promising investigation subjects in the electrophysiological research area. As one of the high-frequency brain waves, gamma oscillations are associated with the integration of sensory-cognitive related events in cortical and subcortical regions. According to the evidence from a large body of research (Başar, 2013; Ward, 2003), gamma oscillations play a role in binding of sensory features in the sensory cortex, processing ambiguous visual features, facial recognition, attention in frontal and central regions, and memory.

The primary aim of this study is to explore QEEG measures, including the gamma oscillations, as biomarkers to predict early paroxetine treatment response in OCD patients.

2. Method

2.1. Sample and data collection procedures

Participants consisted of OCD patients consulted Kemal Arıkan Psychiatry Clinic (a private psychiatric practice), Istanbul, Turkey. A consent form was provided from each patient. Local ethics committee approved the study. The diagnosis of participants was made by the same psychiatrist based on the psychiatric interview (First et al., 2016). Totally, 30 patients with OCD (10 female and 20 male), aged at 19–57 (mean ± SD: Age = 33 ± 8.6 years) providing the following criteria were examined:

1. Medication free for ≥3 weeks,
2. A 10-item Yale-Brown Obsessive-Compulsive Scale (Y-BOCS) score before and after paroxetine monotherapy.
3. A QEEG before the paroxetine treatment.

None of the participants were acknowledged to have treatment-refractory OCD before the paroxetine therapy. They did not have any neurological or organic diseases (e.g., epilepsy). Yale-Brown Obsessive-Compulsive Scale (Y-BOCS) was administered to assess OCD symptomatology. Scores in the Y-BOCS were categorized by the subsequent clusters: mild symptoms (0–13), moderate symptoms (14–25), moderate-severe symptoms (26–34), and severe symptoms (35–40) (Storch et al., 2015). The mean pre-treatment Y-BOCS score was 27.1 ± 10.5 (range: 9–40). Although some patients have Y-BOCS scores below 13 points, medication was prescribed on the basis of clinical interview. All patients were prescribed paroxetine as monotherapy. At least a 35% reduction in post-treatment Y-BOCS scores was determined as an early improvement (da Conceição Costa et al., 2013).

2.1.1. EEG recording

All subjects underwent QEEG recording before paroxetine treatment. Resting state QEEG recordings were taped in a silent, dim room with well air-conditioning. A 19-channel (FP1, F7, T3, T5, F3, C3, P3, O1, FZ, CZ, PZ, F4, C4, P4, O2, FP2, F8, T4, and T6) electro-cap was positioned onto the head of the participants according to the 10–20 international system. A transparent electro-gel was injected into the scalp to increase conductivity. The ground electrode was placed in the FPz position. Mastoid electrodes were positioned to both earlobes as reference electrodes. The impedance of electrodes was controlled whether they were <5000 Ω for each electrode. A Neuron-Spectrum-4/P device was utilized to record resting-state QEEG activity while patients were in a comfortable sitting-positioned, closed-eye state. The total duration of records was approximately 7 min, consisted of 3- minute background recording, 30-sec open eyes condition, and 3.30-min closed-eyed condition. Data were sampled at 500 Hz rate; signals were bandpass filtered at 0.15–70 Hz and notch filtered at 50 Hz. Muscle artifacts were eliminated from the raw QEEG recordings. Artifacts were cleared by an experienced EEG reader manually. Finally, 3-min edited data were obtained. Each patients' data were averaged across the recording epochs for each electrode, and the absolute power was computed for five frequency bands; namely, gamma (>35 Hz), beta (12–35 Hz), alpha (8–12 Hz), theta (4–8 Hz), delta (0–4 Hz) including their sub-groups, i.e., alpha 1 (8–10 Hz), alpha 2 (10–12 Hz), beta 1 (12–15 Hz), beta 2 (15–18 Hz), beta 3 (18–25), gamma 1 (30–35 Hz) and gamma 2 (35–40 Hz).

2.1.2. Statistical analyses

QEEG data were analyzed by Neuroguide Deluxe v.2.5.1 program (Applied Neuroscience, Largo, FL). The absolute power of each frequency band was calculated for all electrodes and the logarithmic transformation was applied for each one. Statistical analyses were computed in SPSS version 24. Each QEEG measurement was counted as a dependent variable. The condition of improvement, determined by a minimum 35% decrease in post-treatment Y-BOCS scores, was taken as an independent variable. Normality was checked via the Kolmogorov-Smirnov test. The normality assumption was rejected, and Mann-Whitney U test was selected for the following analyses. To protect the integrity of science and reduce false-positive findings, there may be a case to set the bar higher, such as at $p < .005$ (Andrade, 2019). Therefore, the significance level was decided to set at $p < .005$ level for the following analyses. Outliers were checked via Tukey's outlier definition and no outliers were found (Solberg & Lahti, 2005). Patients who exhibited an early improvement and who did not were compared for the absolute powers of the QEEG frequency bands.

3. Results

The study investigated 30 patients (10 females and 20 males) diagnosed with OCD who received paroxetine treatment. All the patients were drug-free for at least 3-weeks. The 3-weeks of wash-out period is found sufficient in several early studies (Caley & Weber, 1993; Hansen et al., 2003; Knott et al., 2002). The duration of paroxetine treatment was maximum 12-weeks when the second Y-BOCS was measured. The number of patients who exhibited an early improvement was 10 (%33.3) while the patients who did not manifested an early improvement constitute 66.7% of the sample (n = 20). Other demographic and clinical information were provided in Table 1. Patients were also compared for gender, age, age at OCD onset, duration of OCD before treatment, paroxetine dosage, paroxetine duration, pre-treatment severity symptoms of depression measured by Hamilton Depression Rating Scale (HDRS), pre-treatment and post-treatment severity of OCD symptoms measured by Y-BOCS scores (Table 2). As expected, they were homogenous except for the severity of OCD symptoms after paroxetine treatment ($p < .001$).

Table 1
Demographic and clinical characteristics of OCD patients.

Patient Profile		*N*	Min	Max	*M*	*SD*
Gender	**Female**	10	N/a	N/a	N/a	N/a
	Male	20	N/a	N/a	N/a	N/a
Age		30	19	57	33.03	8.71
Age at OCD onset		23	13	38.50	24.23	7.32
OCD duration (year)		23	0.50	23	9.67	7.17
Paroxetine dose		28	40	80	43.57	9.51
Paroxetine duration (week)		30	4	12	9.37	2.57
Pre-HDRS		30	0	40	9.83	10.59
Pre- YBOCS		30	9	40	27.03	10.51
Post- YBOCS		30	0	40	16.90	13.75

Note: OCD = Obsessive Compulsive Disorder, Pre = Pre-treatment, Post- = Post-treatment, YBOCS = Yale Brown Obsessive Compulsive Scale, HDRS = Hamilton Depression Rating Scale.

3.1. QEEG band powers

Non-parametric independent sample Mann-Whitney U test revealed that there was a significant ($p < .005$) difference between OCD patients who exhibited an early improvement and who did not after paroxetine treatment in terms of gamma, gamma 1, and gamma 2 absolute powers in F3, C3, Cz, P3, O1, and T5 regions (see Table 3 and Fig. 1). Pre-treatment QEEG recordings demonstrate that OCD patients who did not exhibit an early improvement had greater gamma activity in the left parietal-temporal area, suggesting that elevated gamma, particularly gamma 2 absolute power predicts early clinical improvement during paroxetine treatment.

3.2. Y-BOCS correlations

Descriptive statistics of pre-treatment and post-treatment Y-BOCS scores were provided in Table 1. Groups based on early clinical improvement did not differ concerning pre-treatment Y-BOCS scores ($p = .442$). Non-parametric correlation analysis was applied to the statistically significant QEEG bands (in F3, C3, Cz, P3, T5 regions) and pre-treatment Y-BOCS scores. No significant correlation was found (Table 4). Correlations between pre-post Y-BOCS percentage change and significant gamma bands were also searched. Although some correlations tended to be significant, i.e. gamma 2 at P3 and O3 for the non-improvement group, there was no significant correlation (Table 5).

4. Discussion

Statistical analysis executed on QEEG data revealed an elevated gamma activity, particularly in the gamma 2 band in OCD patients who did not demonstrate an early improvement after paroxetine treatment, exclusively at the left parieto-temporal regions. To the best of our knowledge, this is the first study in which gamma and gamma 2 activities were predominantly observed as the electrophysiological indices of antidepressant treatment outcomes within OCD samples.

The primary strength of the present study originates in the OCD patient profile: all patients were drug-free without any comorbid disorder before receiving paroxetine as monotherapy. Furthermore, the groups were homogenous for demographic and clinical characteristics except for post-Y-BOCS scores. Finally, all the patients were examined by the same physician. On the other hand, this is a retrospective pilot study, and one of the limitations of the study is the small sample size. Thus, we failed to perform control(s) for age and/or gender. Even though some statistical precautions were exercised, i.e., non-parametric tests for analyses and small significant values ($p < .005$), the findings should be regarded as preliminary which needs to be confirmed by studies with larger sample sizes.

As for the monotherapy, paroxetine was selected for several reasons. Since it has higher tolerability and lower placebo response (Bandelow et al., 2008; Sugarman et al., 2017), it is one of the commonly prescribed psychotropic drugs in the treatment of mood disorders and anxiety-related disorders (Food and Drug Administration, 2015). Another reason is its efficacy in the psychiatric comorbidities of OCD; namely, major depressive disorder (MDD), general anxiety disorder (GAD), panic disorder (PD), and posttraumatic stress disorder (PTSD) (Food and Drug Administration, 2008; Brakoulias et al., 2017; Subramaniam et al., 2020; Ruscio et al., 2010; Wahl et al., 2019).

To date, electrophysiological predictors of response to antidepressant treatments have been extensively researched within various psychiatric samples, including OCD and MDD patients. A QEEG study (Arikan et al., 2018) investigating electrophysiological predictors of response to paroxetine treatment in MDD patients found that patients with higher pre-treatment gamma power in the fronto-central regions exhibited less decrease in depressive symptoms after paroxetine therapy.

Table 2
Descriptive statistics and mean difference for clinical characteristics between OCD patients with and without an early improvement during paroxetine treatment.

Characteristics		n	Min	Max	*M*	*SD*	Group difference (*p*)	Groups
Gender	Female	8	N/a	N/a	N/a	N/a	**.419**[a]	Non-improv.
		2						Improvement
	Male	12	N/a	N/a	N/a	N/a		Non-improv.
		8						Improvement
Age		20	20	57	32.0	8.25	**.367**	Non-improv.
		10	19	47	35.2	9.69		Improvement
Age at OCD onset		17	13	38.5	24.56	8.18	**.733**	Non-improv.
		6	16	28	23.33	4.54		Improvement
OCD duration (Year)		17	0.5	23	8.44	6.52	**.170**	Non-improv.
		6	3	23	13.16	8.40		Improvement
Paroxetine dose		18	40	80	45.55	11.49	**.056**	Non-improv.
		10	40	40	40.00	0.00		Improvement
Paroxetine duration (week)		20	4	12	9.00	2.20	**.278**	Non-improv.
		10	5	12	10.10	3.21		Improvement
Pre-HDRS		20	0	40	10.45	11.45	**.660**	Non-improv.
		10	0	23	8.60	9.04		Improvement
Pre- YBOCS		20	9	40	28.10	10.76	**.442**	Non-improv.
		10	10	40	24.90	10.21		Improvement
Post- YBOCS		20	8	40	24.50	10.09	**.000**[b]	Non-improv.
		10	0	10	1.70	3.05		Improvement

Note: OCD = Obsessive Compulsive Disorder, Non-Improv. = Patients who did not show an early improvement, Pre = Pre-treatment, Post- = Post-treatment, YBOCS = Yale Brown Obsessive Compulsive Scale, HDRS = Hamilton Depression Rating Scale.

[a] Fisher's exact test result.

[b] $p < .001$.

Table 3
Pre-treatment Gamma, Gamma1, Gamma2 absolute power difference between OCD patients with and without an early improvement at F3, C3, Cz, P3, O1 and T5 regions.

AP Gamma, Gamma1 and Gamma 2	Groups	*n*	*M*	*SD*	*SE*	*p*
AP F3 Gamma 2	Non-improv.	20	0.123	.084	.019	**.005**
	Improvement	10	0.056	.027	.008	
AP C3 Gamma 2	Non-improv.	20	0.136	.121	.027	**.003**
	Improvement	10	0.053	.021	.006	
AP Cz Gamma 2	Non-improv.	20	0.103	.055	.012	**.002**
	Improvement	10	0.049	.014	.004	
AP P3 Gamma	Non-improv.	20	0.488	.239	.053	**.002**
	Improvement	10	0.263	.066	.020	
AP P3 Gamma 1	Non-improv.	20	0.426	.216	.048	**.002**
	Improvement	10	0.229	.059	.018	
AP P3 Gamma 2	Non-improv.	20	0.102	.067	.014	**.000**
	Improvement	10	0.044	.011	.003	
AP O1 Gamma 2	Non-improv.	20	0.125	.101	.023	**.003**
	Improvement	10	0.057	.024	.007	
AP T5 Gamma	Non-improv.	20	0.513	.247	.055	**.002**
	Improvement	10	0.261	.090	.028	
AP T5 Gamma1	Non-improv.	20	0.443	.217	.049	**.003**
	Improvement	10	0.226	.080	.025	
AP T5 Gamma 2	Non-improv.	20	0.116	.077	.017	**.000**
	Improvement	10	0.045	.016	.005	

Note: AP = Absolute Power, Non-Improv. = Patients who did not show an early improvement.

In parallel with this study, the results of our present investigation demonstrated that OCD patients who did not exhibit an early improvement during paroxetine treatment had higher pre-treatment gamma activity in the parieto-temporal regions. On the basis of these studies, it can be concluded that gamma oscillations may be the significant electrophysiological indices of OCD and MDD patients who did not adequately benefit from paroxetine treatment. Nevertheless, it should be noted that the main restriction of these studies is the small sample size. A better deduction can be made after a follow-up study in which the EEG predictors of paroxetine response are investigated in three groups of patients (MDD, OCD, and MDD + OCD).

5. Conclusion

OCD is a mental problem hard to treat completely despite promising treatment modalities. SSRI medications are one of the initially applied treatments due to a considerable success rate, approximately 50%, and high tolerability. However, predicting treatment outcomes after these medications is important for both clinicians and patients since: (1) it eliminates unnecessary side effects of ineffective medications, (2) it prevents withdrawal symptoms after the ineffective medication ceased

Table 4
Correlations between baseline Gamma, Gamma1 and Gamma2 absolute powers and pre-treatment Y-BOCS scores.

	Correlation Coefficient	*p*[a]	*n*
AP F3 Gamma 2	-.106	.577	30
AP C3 Gamma 2	-.124	.514	30
AP Cz Gamma 2	-.103	.587	30
AP P3 Gamma	-.201	.287	30
AP P3 Gamma 1	-.208	.271	30
AP P3 Gamma 2	-.191	.313	30
AP O1 Gamma 2	-.207	.273	30
AP T5 Gamma	-.205	.278	30
AP T5 Gamma 1	-.208	.270	30
AP T5 Gamma 2	-.221	.241	30

Note: AP = Absolute Power.
[a] Significance (2-tailed).

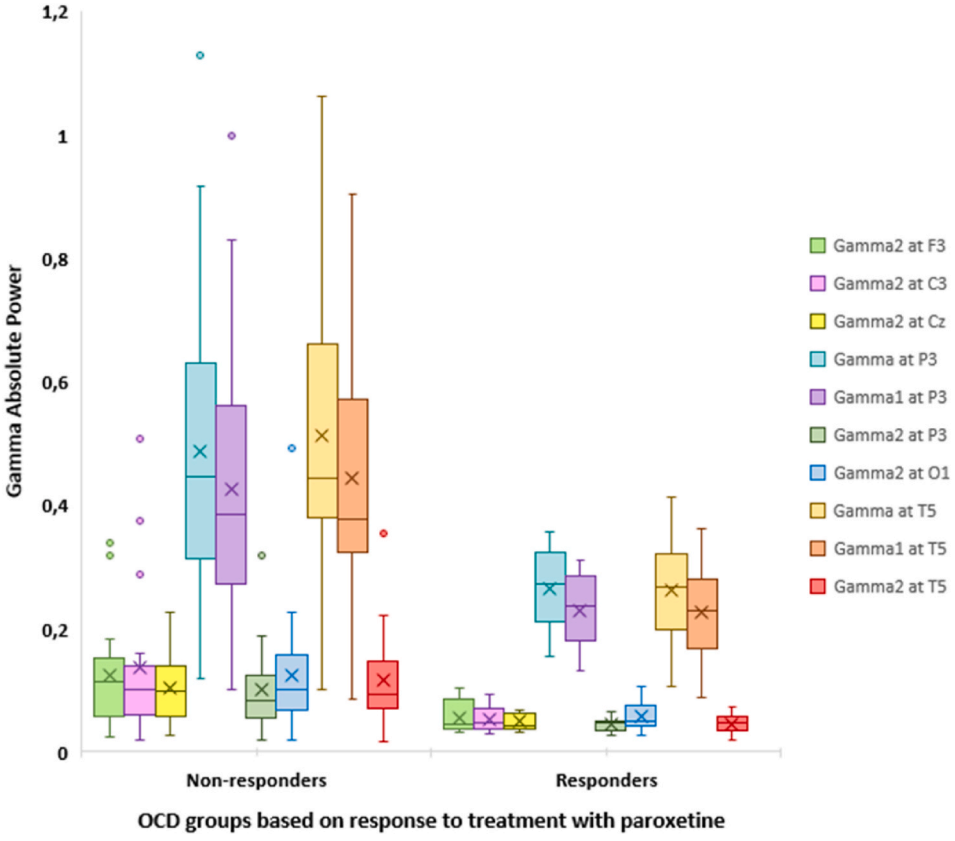

Fig. 1. Pre-treatment QEEG Gamma, Gamma1 and Gamma2 absolute power between OCD patients who showed an early response and non-response to paroxetine treatment.

Table 5
Correlations between significant QEEG bands and Y-BOCS pre-post percentage change.

	Change in Y-BOCS (in percent)			
	Correlation Coefficient	p^a	*n*	Groups
Change in Y-BOCS (in percent)	1.000	.000	20	**Non-improv.**
	1.000	.000	10	**Improvement**
AP F3 Gamma 2	-.282	.229	20	**Non-improv.**
	.097	.789	10	**Improvement**
AP C3 Gamma 2	-,367	.111	20	**Non-improv.**
	.006	,986	10	**Improvement**
AP P3 Gamma	-.403	.078	20	**Non-improv.**
	.149	.681	10	**Improvement**
AP P3 Gamma 1	-.426	.061	20	**Non-improv.**
	.149	.681	10	**Improvement**
AP P3 Gamma 2	-.434	.056	20	**Non-improv.**
	.078	.831	10	**Improvement**
AP O1 Gamma 2	-.457	.051	20	**Non-improv.**
	.441	.202	10	**Improvement**
AP T5 Gamma	-.295	.207	20	**Non-improv.**
	.461	.180	10	**Improvement**
AP T5 Gamma 1	-.274	.242	20	**Non-improv.**
	.461	.180	10	**Improvement**
AP T5 Gamma 2	-.346	.135	20	**Non-improv.**
	.480	.160	10	**Improvement**

Note: AP = Absolute Power, Y-BOCS = Yale Brown Obsessive Compulsive Scale, Non-Improv. = Patients who did not show an early improvement.
[a] Significance (2-tailed).

and (3) it helps to save time and money by removing unsuccessful medical choices. In the present study, our results displayed the predictive value of QEEG in the medical treatment outcomes in OCD patients. Given that QEEG is a non-invasive, cheap, and easy to use method; we propose that it should be applied to daily psychiatric practice in general.

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The study did not receive any funding.

Contributors

Author 1 designed the research and wrote the protocol. Author 2 and author 3 conducted literature searches and provided summaries of previous research studies. Author 2 conducted the statistical analysis. Author 3 wrote the first draft of the manuscript and all authors contributed to and have approved the final manuscript.

Declaration of competing interest

The authors whose names are listed immediately below certify that they have NO affiliations with or involvement in any organization or entity with any financial interest (such as honoraria; educational grants; participation in speakers' bureaus; membership, employment, consultancies, stock ownership, or other equity interest; and expert testimony or patent-licensing arrangements), or non-financial interest (such as personal or professional relationships, affiliations, knowledge or beliefs) in the subject matter or materials discussed in this manuscript.

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