

Evaluation of Serum Total Immunoglobulin E, Interleukin-17 and Pentraxin-3 as Biomarkers for Chronic Rhinosinusitis With Nasal Polyposis

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Abstract

Background: Different biomarkers are detectable in cases of chronic rhinosinusitis with nasal polyposis (CRSwNP) with need for evaluation of their diagnostic and prognostic roles.

Objective: To assess the serum levels of total IgE, interleukin-17 and Pentraxin-3 in patients with CRSwNP and correlate them with the clinical evaluation using Sino-Nasal Outcome Test (SNOT-22), radiological evaluation using Lund – Mackay (LM) computed tomography scan score, and polyposis recurrence.

Methods: This cross-sectional comparative study was carried out on fifty patients with CRSwNP and twenty-five age and gender matched healthy volunteers as control group. Patients were assessed clinically by SNOT-22 and radiologically by LM score. Blood samples of patients and controls were analyzed for serum levels of total immunoglobulin E (IgE), Interleukin-17 (IL-17) and Pentraxin-3 (PTX-3). The correlation between the serum levels of every two markers of the study markers was assessed. The levels of the three biomarkers were correlated with SNOT-22 and LM scores and polyp recurrence with assessment of their sensitivity and specificity to diagnose CRSwNP.

Results: This study showed significantly higher values of the three biomarkers in patients group compared with control group ($p < 0.001$ for all). There were significant positive correlations between the levels of the three markers and SNOT 22 and LM scores ($p < 0.001$ for all) and with recurrence of polyposis ($p < 0.001$, $p = 0.005$ and $p = 0.032$ respectively). Agreement (sensitivity and specificity) for these markers to diagnose patient group was statistically significant ($p < 0.001$ for all). There was a significant positive correlation between every two markers of the study markers.

Conclusion: Serum levels of total IgE, IL-17 and PTX-3 are important biological markers for diagnosis and follow up of cases of CRSwNP with high sensitivity and specificity in detection of such cases. They should be included in the routine laboratory workup for cases of CRSwNP.

Keywords

biomarkers, chronic rhinosinusitis with nasal polyposis, immunoglobulin E, interleukin-17, Lund Mackay score, Pentraxin-3, polyposis recurrence, Sinonasal Outcome Test 22, sinusitis

Introduction

Chronic rhinosinusitis with nasal polyposis (CRSwNP) is a multifactorial disorder due to persistent irritation and inflammation of nasal and paranasal sinus mucosa with consequent oedema and prolapse in the nasal cavity. Infection, atopy, hypersensitivity or immunological disorders are diverse etiological factors for this condition.¹

Immunoglobulin E induces eosinophilia and has been used as biomarker for nasal polyposis identifying

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polyposis phenotype and line of treatment. High levels of serum and local IgE are frequently present in cases of CRSwNP with suggested etiology of sensitization to bacterial antigens.² The anti-IgE therapeutic omalizumab was also tested in patients with CRSwNP to see if it could reduce polyp burden and lead to symptomatic improvement.³ However, most of the previous studies in the literature have assessed the value of the tissue level of IgE with less emphasis on the serum level.

Recently, CRSwNP has been found to be a heterogeneous disease including different endotypes with overlapping Th cytokine expressions.⁴⁻⁶ Interleukin (IL)-17A, a cytokine generated by Th17 cells, has a highly significant role in the pathogenesis of allergic reaction, inflammation, and autoimmunity.⁷ Interleukin (IL)-17 producing Th cells (Th17 cells) are involved in respiratory epithelial damage in atopic individuals.⁸ In the airways of asthmatic patients, gene expression signatures of TH2 and TH17 pathways installed their mutual regulation action,⁹ and Brodalumab, an anti-IL-17A receptor monoclonal antibody, was presented as a magic tool for severe asthmatic patients by its marvelous bronchodilator effect.¹⁰

Most studies concerned with the immunopathological background of (CRSwNP) have focused on the humoral and cellular immune pathways and the role of innate immunity was not in focus. Pentraxin-3 (PTX-3) is the first member of the PTX family,¹¹ which produced mainly by macrophages, dendritic cells, and endothelial cells.¹² PTX-3 has a role in complement activation and acts as a chemokine in many inflammatory cells.¹³ So, it is involved in acute and chronic inflammation through its role in innate immunity.¹⁴ PTX-3 plays a great role as a guard against microbes, both fungal and bacterial.^{15,16}

Aiming to evaluate the role of serum total IgE, IL-17 and PTX-3 as prognostic factors and to understand their pathways for an appropriate endotype classification and development of therapeutic strategies for CRSwNP, this study assessed their levels in patients with CRSwNP and correlated them with clinical evaluation using Sino-Nasal Outcome Test (SNOT-22), radiological evaluation using Lund – Mackay computed tomography (LM) scan score, and polyposis recurrence.

Patients and Methods

This cross-sectional comparative study was carried out on fifty patients with chronic rhinosinusitis with nasal polyposis recruited from the outpatient clinic of Otorhinolaryngology Department, Menoufia University hospitals and in other private centers in Egypt, and twenty-five age and gender matched healthy volunteers as control group. Our patients were recruited in the study during the period from February 2019 to

January 2020 after their informed written consent and in agreement with the approval of the institutional review board.

Exclusion criteria for this study included patients aged less than 18 years, smokers, patients with nasal masses due to any other cause than CRSwNP as neoplastic causes, patients with concomitant nasal or paranasal sinus pathology, patients with active upper respiratory tract infections in the four weeks period preceding participation in the study or patients with coexisting debilitating major uncontrolled systemic disease or autoimmune disease. None of the subjects had used oral or nasal corticosteroids two weeks before participation in the study.

All the patients were clinically evaluated using anterior rhinoscopy and standard nasal endoscopy revealing polyps. Patients were assessed by Sino-Nasal Outcome Test (SNOT-22) for nasal symptomatology. Radiological evaluation of the patients was done by CT scan of nose and paranasal sinuses without contrast using Lund – Mackay score to assess disease severity.

Blood Samples and Biochemical Analysis

Five ml of venous blood were obtained from every participant by sterile venipuncture. Three ml of which were put in a plain tube, left for 15 min to clot at room temperature, centrifuged at 4000 r.p.m for 10 min, and the resulting sera were kept frozen at -20°C for subsequent measurement of total IgE, IL-17, and Pentraxin by ELISA technique. Assay of total IgE in serum by Total Human IgE kits (DSI Srl Milan, Italy). IL-17 was measured by Human IL-17 Picokine™ ELISA kit (Boster Biological Technology Co., Ltd., Pleasanton, CA, USA). The Human Pentraxin 3/Pentraxin 3 Picokine™ ELISA Kit (Boster Biological Technology Co., Ltd., Pleasanton, CA, USA) was used for serum Pentraxin assay.

Outcomes

The primary outcomes of the study were the assessment of the difference between cases with CRSwNP and control subjects regarding serum total IgE, IL-17 and Pentraxin-3. In addition, agreement (sensitivity, specificity) of these markers to diagnose CRSwNP were assessed. Secondary outcomes of the study included the correlation between the three markers and SNOT 22 for clinical presentation and Lund Mackay score for radiological assessment as indicators of disease load. Also, the correlations between their levels and disease recurrence were assessed. The correlation between the serum level of every two markers of the study markers was assessed.

Statistical Analysis of the Data

Data were fed to the computer and analyzed using IBM SPSS software package version 20.0. (Armonk, NY: IBM Corp). The Kolmogorov- Smirnov test was used to verify the normality of distribution of variables, Comparisons between groups for categorical variables were assessed using Chi-square test (Fisher or Monte Carlo). Student t-test was used to compare two groups for normally distributed quantitative variables while Mann Whitney test was used to compare between two groups for not normally distributed quantitative variables. Spearman coefficient was used to correlate between quantitative variables. Receiver operating characteristic curve (ROC) was used to determine the diagnostic performance of the markers. Area more than 50% gives acceptable performance and area about 100% is the best performance for the test. Significance of the obtained results was judged at the 5% level.

Results

In the current study, there was a non-significant difference between both study groups regarding age and sex ($p=0.617$ and 0.081 respectively) (Table 1). Sixteen cases (32%) of the patients group had recurrent disease. The average duration of polyposis was 18 ± 10.3 months. The average SNOT22 score was 42.4 ± 26.6 . The average Lund Mackay score was 12.9 ± 6.7 (Table 2).

This study showed significantly higher values of serum total IgE, IL-17 and Pentraxin-3 in patients group compared with control group ($p < 0.001$ for all) (Table 3). There were significant positive correlations between the levels of the three biomarkers at one hand and SNOT 22 and Land Mackay scores at the other hand ($p < 0.001$ for all) (Table 4). There was a significant relationship between the levels of the three markers and recurrence of polyposis ($p < 0.001$, $p < 0.001$, $p = 0.005$ and $p = 0.032$ respectively) (Table 5). Agreement (sensitivity, specificity) of the three markers to diagnose patient group was statistically significant ($p < 0.001$ for

all) (Figure 1; Table 6). There were significant positive correlations between the serum levels of total IgE and PTX-3, total IgE and IL-17, PTX-3 and IL-17 ($p = 0.001$, $p < 0.001$ and $p < 0.001$ respectively) (Figures 2 to 4; Table 7).

Discussion

The current study focused on the assessment of some serum markers in cases of CRSwNP trying to include them in the routine workup for these cases for follow up and assessment of prognosis. These markers included IL-17 and Pentraxin-3 in correlation with serum total IgE, with their variable roles in the pathogenesis of nasal polyposis.

Nasal polyps are usually found in nonallergic individuals. However, when nasal polyps and atopy occur together, a special interaction exists. Total and specific immunoglobulin E (IgE) are well defined biomarkers for atopy and are found in significantly greater concentration in nasal polyp tissue than in serum. Patients with nasal polyps and allergies seem to have a greater recurrence rate after surgical polypectomy.¹⁷ Many studies assessed the tissue levels of IgE in nasal polyps of CRSwNP. In the current study, the authors aimed to assess the serum level of total IgE and compared it in these patients with healthy controls. The authors found that it was significantly higher in patients' group ($p < 0.001$) with a significant positive correlation with SNOT 22 and Lund Mackay scores and polyposis recurrence ($p < 0.001$ for both). Serum total IgE level had a significant agreement to diagnose polyposis ($p < 0.001$). The level of serum IgE in cases of CRSwNP has been previously related to staphylococcus aureus (SA) superantigen in a retrospective review on 62 patients with CRSwNP and 34 patients with chronic rhinosinusitis without nasal polyposis (CRSsNP). SA was the most prevalent bacteria in the CRSwNP group. Patients

Table 2. Distribution of the Studied Cases According to Clinical Data in Cases Group (n = 50).

	No. (%)
Recurrence	
No	34 (68%)
Yes	16 (32%)
Duration	
Mean $\pm$ SD.	18 ± 10.3
Median (Min.–Max.)	18 (6–48)
SNOT-22	
Mean $\pm$ SD.	42.4 ± 26.6
Median (Min.–Max.)	34.5 (8–98)
Lund & Mackay	
Mean $\pm$ SD.	12.9 ± 6.7
Median (Min.–Max.)	11.5 (4–24)

Table 1. Comparison Between the Two Studied Groups According to Demographic Data.

	Cases (n = 50)	Control (n = 25)	Test of Sig.	P
Sex				
Male	31 (62%)	14 (56%)	$\chi^2 = 0.250$	0.617
Female	19 (38%)	11 (44%)		
Age				
Mean $\pm$ SD.	43.4 ± 15.1	37.1 ± 13.5	$t = 1.770$	0.081
Median (Min.–Max.)	44 (18–70)	38 (18–61)		

χ^2 : Chi square test. t: Student t-test.

p: p value for comparing between the studied groups.

Table 3. Comparison Between the Two Studied Groups According to Different Parameters.

	Cases (n = 50)	Control (n = 25)	Test of Sig.	(p)
Ig-E				
Mean $\pm$ SD.	341.5 $\pm$ 241.1	59.9 $\pm$ 28.6	U = 23.0*	<0.001*
Median (Min.–Max.)	248.5 (65.7–1137.1)	55 (28.2–134.2)		
IL-17				
Mean $\pm$ SD.	25.1 $\pm$ 9.9	6.2 $\pm$ 2	t = 12.939*	<0.001*
Median (Min.–Max.)	25.8 (8.9–42.6)	6.4 (1.8–9.4)		
Pentraxin-3				
Mean $\pm$ SD.	9.1 $\pm$ 4.2	1.4 $\pm$ 1.3	U = 33.50*	<0.001*
Median (Min.–Max.)	8.4 (2–16.9)	0.9 (0.3–4.1)		

U: Mann Whitney test; t: Student t-test.

p: p value for comparing between the studied groups.

*Statistically significant at $p \leq 0.05$.

Table 4. Correlation Between SNOT-22 and Lund & Mackay With Different Parameters in Cases Group (n = 50).

	SNOT-22		Lund & Mackay	
	r_s	p	r_s	p
Ig-E	0.545	<0.001*	0.584	<0.001*
IL-17	0.772	<0.001*	0.716	<0.001*
Pentraxin-3	0.945	<0.001*	0.760	<0.001*

r_s : Spearman coefficient.

*Statistically significant at $p \leq 0.05$.

with elevated total serum IgE were more likely to have SA on culture in this population.¹⁸ On the other hand, the pathogenesis of nasal polyp has been studied by evaluation of the level of serum and polyp IgE in 20 cases of nasal polyps who had been subjected to polypectomy. The authors found that the levels of IgE in serum and polyps were in normal range in all cases, except 2 cases. They suggested that nasal polyp is caused by chronic inflammation rather than by allergy in most of their cases.¹⁹

Cytokine in cases of CRSwNP show different patterns depending endotype of polyposis, comorbid diseases, region, and race. T helper 2 (Th2) mediated immune response is the main contributor to pathogenesis of airway inflammatory diseases as CRSwNP. However, Th17 cells activation are evident in cases of CRSwNP with production of IL-17A, a cytokine playing critical roles in the development of allergic, inflammatory, and autoimmune reactions.²⁰ In the current study, the serum level of IL-17 was significantly higher in patient group ($p < 0.001$) with a significant positive correlation with SNOT 22 and Lund Mackay scores ($p < 0.001$ for both) and polyposis recurrence ($p = 0.005$) with a significant agreement to diagnose polyposis ($p < 0.001$). This matches the findings of previous studies including a study comparing a group of 45

patients with CRSwNP and a control group consisting of 45 healthy volunteers. The authors found that the mean serum IL-17 level in the CRSwNP group was significantly higher than the control group.²¹ On the other hand, twenty-five patients with chronic rhinosinusitis with nasal polyposis and a control group of 25 healthy subjects were assessed showing no statistically significant differences between the two groups regarding the serum levels of IL-17 or IL-23; however, a significant difference between the two groups was found in the lavage fluid levels of IL-17.²²

Some studies confirmed the role of IL-17 in chronic rhinosinusitis with nasal polyposis caused by aspergillus infection including a study showing that IL-1 β , IL-17, IL-21, and TGF- β serum levels were significantly higher in 31 patients with CRSwNP infected by *Aspergillus flavus* than in nine controls; however, IL-2, IL-4, IL-6, and IL-27 levels were lower.²³ Another case-control study involving 40 confirmed immunocompetent allergic fungal sinusitis (AFRS) patients and 20 healthy controls showed that total serum IgE level along with cytokines IL-17, IL-21, IL-1 β and TGF- β were comparatively elevated in AFRS. Nevertheless, IL-2 and IL-10 were reduced.²⁴

Pentraxins are a superfamily of pattern recognition molecules (PRMs) that detect conserved microbial agents and mobilize early defense against foreign invaders.²⁵ They are divided into short Pentraxin including C reactive protein (CRP) and long Pentraxin like Pentraxin-3 (PTX-3). They have multiple functions, including opsonization, regulation of the complement cascade, and antimicrobial resistance.²⁶ PTX-3 was recently found to have a role in the mechanism of tissue repair and remodeling during wound healing and have anti-oncogenic properties by complement activation and reduction of tumor infiltration by macrophages.¹² In the current study the serum level of Pentraxin-3 was significantly higher in patient group ($p < 0.001$) with a significant positive correlation with

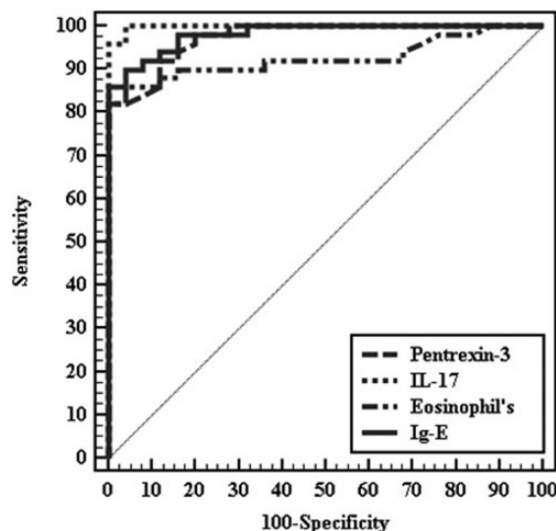
Table 5. Relation Between Recurrence and Different Parameters in Cases Group (n = 50).

	Recurrence		Test of Sig.	p
	No (n = 34)	Yes (n = 16)		
Ig-E				
Mean $\pm$ SD.	209.8 $\pm$ 90.5	621.4 $\pm$ 221.3	U=7.00*	<0.001*
Median (Min.–Max.)	199.1 (65.7–480.0)	587.2 (360.9–1137.1)		
IL-17				
Mean $\pm$ SD.	22.4 $\pm$ 9.3	30.7 $\pm$ 9.1	t = 2.944*	0.005*
Median (Min.–Max.)	20.3 (8.9–42.3)	30.6 (12.2–42.6)		
Pentraxin-3				
Mean $\pm$ SD.	8.1 $\pm$ 3.9	11.0 $\pm$ 4.5	U = 169.0*	0.032*
Median (Min.–Max.)	7.8 (2.0–16.2)	10.5 (3.1–16.9)		

t: Student t-test; U: Mann Whitney test.

p: p value for association between different categories.

*Statistically significant at $p \leq 0.05$.

**Figure 1.** ROC curve for Pentrexin-3, IL-17, Eosinophil's and Ig-E to diagnose patient group (n = 50) from control group (n = 25).

SNOT 22 and Lund Mackay scores ($p < 0.001$ for both) and polyposis recurrence ($p = 0.032$), with a significant agreement to diagnose polyposis ($p < 0.001$). No previous studies have assessed the serum level of Pentraxin-3 in CRSwNP. However, in a study comparing PTX-3 in nasal polyp tissue, normal nasal mucosa, and serum of CRSwNP patients and healthy subjects, normal nasal mucosa was found to have 100-fold higher levels of PTX-3 compared with serum. No measurable local increase of PTX-3 was observed in polyps compared with normal mucosa. Immunohistochemistry revealed PTX-3 expression in the lining of blood vessels both within normal mucosa and nasal polyps. The authors attributed the role of PTX3 in nasal polyposis to its role in innate immunity against Aspergillosis infection with its etiological role in nasal polyposis pathogenesis

especially in allergic fungal sinusitis, an endotype of chronic rhinosinusitis with nasal polyposis.²⁷

In the current study, significant positive correlation existed between every two markers of the study markers. The positive correlation between PTX-3 and serum total IgE has been previously reported in a study showing that serum total IgE levels were positively correlated with sputum PTX-3 concentrations ($r = 0.16$, $P = 0.015$) in cases with childhood asthma.²⁸ Regarding the correlation between PTX-3 and IL-17, a study assessed the role of exogenous Pentraxin-3 in airway inflammation in experimental asthma. The authors found that in both eosinophilic and neutrophilic asthma models, PTX-3 treatment provoked airway hyperresponsiveness, with increased inflammatory cytokines IL-4, IL-17, eotaxin, and transforming growth factor (TGF)- $\beta 1$.²⁹ However, the relationship between Pentraxin 3 deletion and allergic inflammation was assessed in a study that showed that PTX-3 deficiency resulted in augmented airway hyperresponsiveness, mucus production, and IL-17A-dominant pulmonary inflammation, suggesting a regulatory role of PTX-3 in the development of allergic inflammation.³⁰ Such relationships between PTX-3 and both serum total IgE and IL-17 express the link existing link between innate and adaptive immunity. Regarding the correlation between serum total IgE and IL-17, several studies assessed such relationship in different diseases. A significant elevation of serum IL-17 levels has been found to be associated with an increase in serum IgE in the patients with allergic rhinitis compared with controls.³¹ Another study reported a positive correlation between the IL-17 level and the serum levels of IL-23 and IgE among allergic rhinitis patients.³²

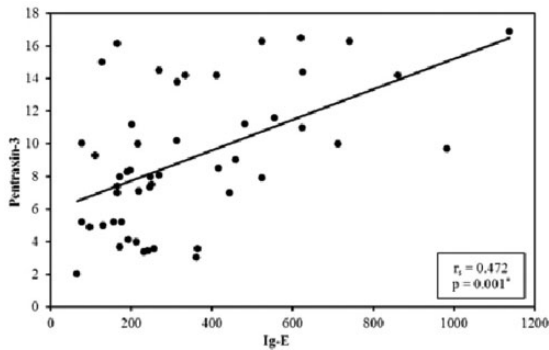
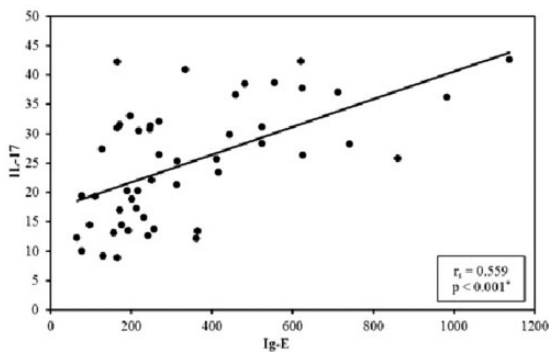
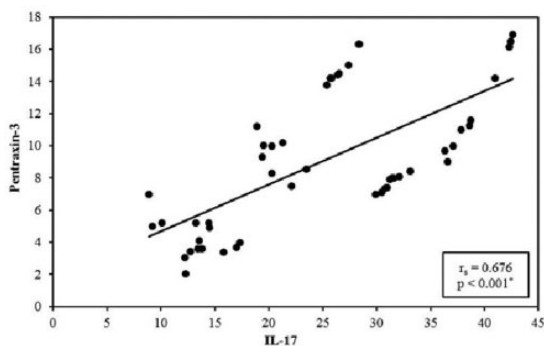
The limitations of this study include lack of assessment of the study biomarkers in nasal polyp tissues with comparison with their serum levels. Another limitation is the need for assessment of these biomarkers in different

Table 6. Agreement (Sensitivity, Specificity) for Pentraxin-3, IL-17, Eosinophil's and Ig-E to Diagnose Patient Group (n = 50) From Control Group (n = 25).

	AUC	p	95% C.I		Cut off value	Sensitivity	Specificity	PPV	NPV
			LL	UL					
Pentraxin-3	0.973	<0.001*	0.944	1.002	>4.12	82.0	96.0	97.6	72.7
IL-17	0.998	<0.001*	0.994	1.003	>9.2	96.0	96.0	98.0	92.3
Ig-E	0.982	<0.001*	0.959	1.004	>125	90.0	96.0	97.8	82.8

AUC: Area Under a Curve; p value: Probability value; CI: Confidence Intervals; NPV: Negative predictive value; PPV: Positive predictive value.

*Statistically significant at $p \leq 0.05$.

**Figure 2.** Correlation between serum Pentraxin-3 and total Ig-E in cases group (n = 50).**Figure 3.** Correlation between serum IL-17 and total Ig-E in cases group (n = 50).**Figure 4.** Correlation between serum IL-17 and Pentraxin-3 in cases group (n = 50).**Table 7.** Correlation Between Every Two Markers of the Study Markers in Cases Group (n = 50).

	r_s	P
Pentraxin-3 vs. Ig-E	0.472	0.001*
Pentraxin-3 vs. IL-17	0.676	<0.001*
IL-17 vs. Ig-E	0.559	<0.001*

r_s : Spearman coefficient.

*Statistically significant at $p \leq 0.05$.

endotypes of nasal polyposis including nasal polyposis caused by Aspergillosis. Further studies are needed to evaluate the effect of treatment either medical or surgical on the levels of these markers.

Conclusion

Serum levels of total IgE, IL-17 and PTX-3 are important biological markers for diagnosis and follow up of cases of CRSwNP. They should be included in the routine laboratory workup for cases of CRS with nasal polyposis having the advantage of being minimally invasive. Further studies evaluating their levels in different endotypes of nasal polyposis with correlation between serum and tissue levels of this biological markers are recommended.

Declaration of Conflicting Interests

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