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ORIGINAL RESEARCH

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The value of narrowband imaging using the Ni classification in the diagnosis of laryngeal cancer

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Abstract

Introduction: Narrowband imaging (NBI) is a special endoscopic optical enhancement setting allowing better visualization of mucosal microvasculature compared to white light endoscopy. This study evaluates the validity of NBI using the Ni classification in the detection and differentiation of severe dysplasia (SD) and glottic squamous cell carcinoma (SCC).

Methods: Patients with suspicious vocal cord lesions underwent conventional white light endoscopy followed by clinically indicated biopsy. At the same time, NBI images were obtained and graded independently. Lesions were graded from I to V according to the Ni classification and compared to histopathological findings.

Results: Fifty-two patients were included in this study (40 SCC and 12 SD). The sensitivity and specificity of NBI in diagnosing laryngeal cancer was 95.0% (CI, 83.9%-99.4%) and 83.3% (CI, 51.6%-97.9%), respectively. The negative likelihood ratio was 0.06. Higher Ni grades correlated very strongly with more advanced disease.

Conclusions: NBI using the Ni classification is a sensitive diagnostic tool for the detection and differentiation of early neoplastic and preneoplastic glottic lesions. As higher Ni classification correlates strongly with advanced disease, it serves as a useful adjunct to white light endoscopy in the diagnosis of laryngeal cancer.

Level of Evidence: Level IV.

KEYWORDS

glottic cancer, laryngeal cancer, narrowband imaging, NBI, Ni classification

1 | INTRODUCTION

Laryngeal squamous cell carcinoma (SCC) is one of the most common types of head and neck cancer with a global incidence of over 170 000 patients per year, resulting in almost 95 000 deaths in 2018.[1] Despite recent advances in treatment the 5-year overall survival has not changed significantly over the past 20 years.[2-5]

Early detection, histopathological diagnosis and treatment significantly improve prognosis, reducing both patient morbidity and mortality.[6]

Current workup for laryngeal cancer includes imaging such as computed tomography, magnetic resonance imaging and nasoendoscopy with white light.

However, various studies have demonstrated that white light endoscopy (WLE) lacks the sensitivity to detect early, superficial neoplastic lesions (carcinoma in situ, T1 or T2) or preneoplastic lesions such as severe dysplasia (SD).[7, 8]

Growth and progression of laryngeal SCC relies on neoangiogenesis, a process where new blood vessels are formed from the surrounding pre-existing blood vessels. This "angiogenic switch" shifts the balance in favor of proangiogenic factors, allowing for the formation of new vessels to support the metabolic requirements of the tumor.[9] These new vessels lack the histological architecture and structural anatomy of pre-existing vessels, which can be detected by nasoendoscopy using WLE in later stages.[10] Earlier detection of this change plays a critical role in the early diagnosis of laryngeal cancer leading to improved outcomes.

Narrowband imaging (NBI) is an optical imaging modality, which uses optical interference filters to spectrally narrow the bandwidth of light. The two wavelengths emitted from this filter include blue light (wavelength peak of 400-430 nm) and green light (wavelength peak of 515-555 nm) corresponding to the absorption peaks of hemoglobin.[11] This enhances and better contrasts the mucosal microvasculature also known as intraepithelial papillary capillary loops (IPCLs).[12]

By observing changes in the morphology and architecture of IPCLs, NBI can play a key part in early detection of neoplasia and its role has been established in the detection of lesions in the esophagus, pharynx, and oral mucosa.[13–16]

In 2011, Ni and colleagues[8] proposed a classification system based on the morphological changes of laryngeal IPCLs to differentiate between benign and malignant laryngeal lesions. Briefly, this system describes five patterns of change in the IPCL morphology. Types I-IV are usually associated with benign or even preneoplastic change. Type V is associated with neoplastic change and is further subdivided into Va, Vb, and Vc[8] (Table 1). Previous studies have demonstrated this classification system to be more sensitive than WLE with many authors recommending NBI to be a routine part of the assessment and workup of laryngeal lesions.[17, 18]

The aim of this study is to evaluate the sensitivity of NBI using the Ni classification in detecting neoplastic or preneoplastic laryngeal lesions. Furthermore, we aim to assess if there is a correlation between higher Ni classification and tumor stage.

2 | METHODS

This study was approved by the institutional human research ethics committee (Ethics number 5424). From December 2017 to June 2019, patients presenting to the Department of Otolaryngology Head and Neck Surgery at Westmead Hospital (Sydney, Australia) were recruited if they had a clinically suspicious laryngeal lesion. These patients were referred to the tertiary head and neck clinic from either general practitioners or general otolaryngology clinics.

TABLE 1 Ni classification and corresponding description of IPCL morphology

Classification	Description
Type I	Thin, oblique and arborescent vessels are interconnected and intraepithelial papillary capillary loops are almost invisible
Type II	Diameter of oblique and arborescent vessels is enlarged, and intraepithelial papillary capillary loops are almost invisible
Type III	Intraepithelial papillary capillary loops are obscured by white mucosa
Type IV	Intraepithelial papillary capillary loops can be recognized as small dots
Type Va	Intraepithelial papillary capillary loops appear as solid or hollow, with a brownish, speckled pattern and various shapes
Type Vb	Intraepithelial papillary capillary loops appear as irregular, tortuous, line-like shapes
Type Vc	Intraepithelial papillary capillary loops appear as brownish speckles or tortuous, line-like shapes with irregular distribution, scattered on the tumor surface

[a]*Source:* Adapted from Ni et al.[8]
Abbreviation: IPCL, intraepithelial papillary capillary loops.

The reasons for referral were patients with chronic hoarseness or voice change with a lesion on the vocal cord identified by either imaging (computed tomography or magnetic resonance imaging) or nasoendoscopy.

During the consultation, an in-office nasoendoscopy was performed. The nasal cavity was anesthetized topically with cophenylcaine (lignocaine hydrochloride 5%/phenylephrine 0.5%) spray. Nasoendoscopy was performed with an ENF-VQ transnasal flexible fiberscope connected to an Evis Exera III CV 190 light source (Olympus Medical Systems, Tokyo, Japan) while patients were awake and seated. Any suspicious lesions of the vocal cords on WLE including leuko-erythroplakia, polypoid lesions, ulcerated lesions, exophytic, and endophytic lesions were captured.

The light was then switched to NBI mode where the lesions were assessed in real time and captured.

A clinically indicated biopsy was performed under general anesthesia in the operating theater. The biopsy specimens were fixed in formalin, embedded in paraffin and sent for histopathological examination. Slides were examined with hematoxylin and eosin staining by an experienced head and neck pathologist.

Lesions with a histopathological diagnosis of SCC were graded based on tumor size as carcinoma in situ (Cis), T1, T2, T3, and T4 according to the American Joint Committee on Cancer grading of glottic cancer.[19] Lesions with SD on histopathology were also included. Following the histopathology results, the respective NBI images captured during in-office nasoendoscopy were independently graded according to the Ni classification.[8] Any lesions considered being neoplastic on NBI were graded V (including Va, Vb, or Vc). SD received a grade of I-IV[8] (see Figure 1A-D).

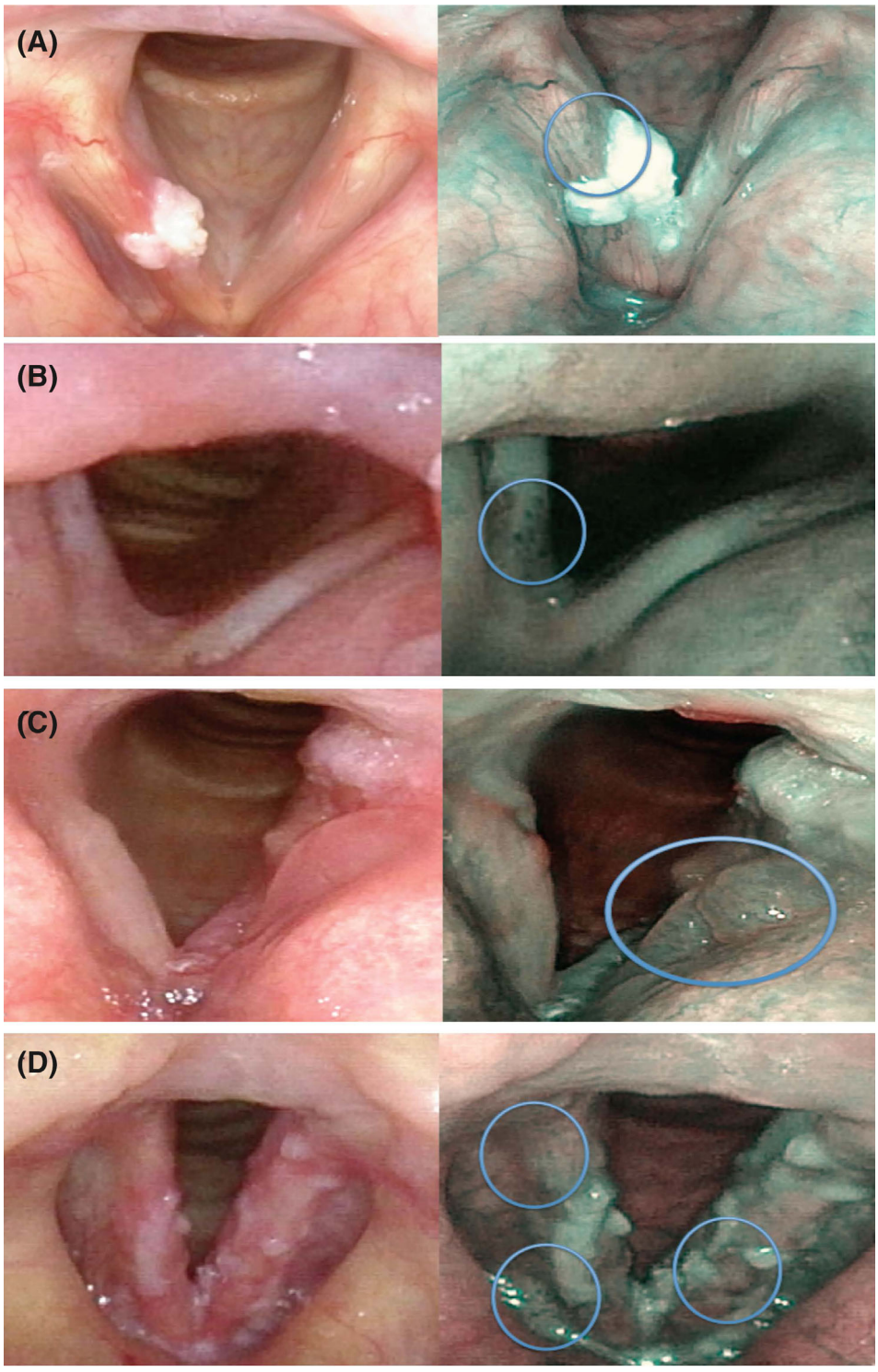

FIGURE 1 Comparison of WLE and NBI images with Ni classification IV-Vc. A, Type IV pattern; IPCLs recognized as small dots as marked. Histopathology demonstrated SD. B, Type Va pattern; IPCLs appear as solid brownish dots scattered on right vocal cord as marked. Histopathology demonstrated carcinoma in situ. C, Type Vb pattern; IPCLs appear as irregular, line-like shapes as marked. Histopathology demonstrated T1a. D, Type Vc pattern; IPCLs appear as scattered brownish speckles on multiple sites. Histopathology demonstrated T1b. IPCLs, intraepithelial papillary capillary loops; NBI, narrowband imaging; SD, severe dysplasia; WLE, white light endoscopy

Histopathological grades were then compared to their respective Ni classification.

Based on this, sensitivity and specificity of NBI using the Ni classification in detecting glottic cancers were calculated. Correlations between the Ni classification and grade of tumor were also measured.

Patients were excluded if they had an adverse reaction/allergy to co-phenylcaine, had previous laryngeal cancer, or were unable to tolerate nasoendoscopy. Patients with benign disease, mild or moderate dysplasia were also excluded.

The SPSS 26.0 statistical software package (SPSS, Inc, Chicago, Illinois) was used for statistical analysis. Data were found to be non-parametric by Shapiro-Wilk test and histogram analysis. Sensitivity, specificity, positive predictive value, and negative predictive values were calculated using a two-by-two cross tabulation table. Correlation between the Ni classification and tumor grade was calculated using

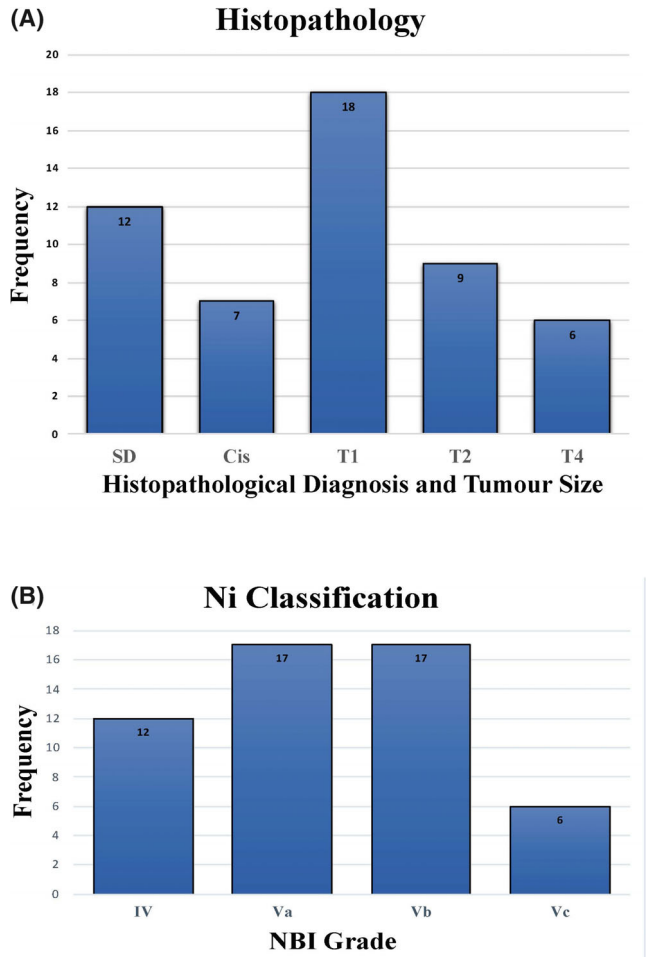

FIGURE 2 Distribution of lesions based on A, Tumor size following histopathological diagnosis; B, NBI grade using the Ni classification.[8] Cis, carcinoma in situ; NBI, narrowband imaging; SD, severe dysplasia

the Spearman's rank-order correlation test. A *P*-value <.05 was considered statistically significant.

3 | RESULTS

From December 2017 to June 2019, 52 patients were included in this study with a male to female ratio of 3.5:1. The mean age was 67 (42-86).

All patients were able to tolerate an in-office nasoendoscopy for WLE and NBI assessment.

On histopathological examination 23.1% (n = 12), 13.5% (n = 7), 34.6% (n = 18), and 17.3% (n = 9) of patients were diagnosed with SD, Cis, T1, and T2, respectively (Figure 2A). Six patients who were biopsy proven SCC were staged T4 after CT examination demonstrated thyroid cartilage invasion.

Based on the Ni classification, 23.0% (n = 12) of lesions were graded type IV while 77.0% (n = 40) of patients were graded type V. Of the type V lesions, 32.7% (n = 17) were graded Va, 32.7% (n = 17) were graded Vb, and 11.6% (n = 6) were graded Vc (Figure 2B).

TABLE 2 Diagnostic accuracy of narrowband imaging using the Ni classification[8]

	Value	95% confidence interval
Sensitivity	95.0%	83.1% to 99.4%
Specificity	83.33%	51.6% to 98.0%
PLR	5.70	1.61 to 20.24
NLR	0.06	0.02 to 0.24

Abbreviations: NBI, narrow band imaging; NLR, negative likelihood ratio; PLR, positive likelihood ratio.

TABLE 3 Narrowband Imaging lesion grades and histopathological diagnosis and tumor size

	Histopathological diagnosis and tumor size				
NBI grade	SD	CIS	T1	T2	T4
IV	10	1	0	1	0
Va	2	6	8	1	0
Vb	0	0	10	7	0
Vc	0	0	0	0	6

Abbreviation: NBI, narrowband imaging.

The sensitivity and specificity of NBI in diagnosing laryngeal cancer was 95.0% (CI, 83.9%-99.4%) and 83.3% (CI, 51.6%-97.9%), respectively. The negative likelihood ratio and the positive likelihood ratio was 0.06 and 5.76, respectively (Table 2). Higher Ni grades correlated very strongly with more advanced disease as demonstrated by the Spearman's rank-order correlation value of 0.83.

There were two false negative results in this study where both patients were graded as type IV on NBI but were diagnosed as CiS and T2 on histopathology (Table 3). Both patients had previous SD in that site. In the two false positive results, both patients were graded as type Va but histopathology demonstrated SD.

4 | DISCUSSION

This study demonstrates NBI to be a sensitive diagnostic tool in the work up and management of glottic cancer. The high sensitivity of 95.0% is comparable to sensitivities reported in many previous studies.[8,10,20]

In 2017, Sun and colleagues[18] published a systematic review and meta-analysis assessing the diagnostic value of NBI in laryngeal cancer demonstrating a pooled sensitivity of 94%. Furthermore, they demonstrated a high negative likelihood ratio of 0.08 using a likelihood ratio scattergram analysis, similar to the negative likelihood ratio of 0.06 demonstrated in this study. A limitation of their systematic review and meta-analysis however, was the low number of included studies.

Several other studies that did not meet their inclusion criteria have reported a much lower sensitivity of NBI in detecting laryngeal

cancer. Piazza and colleagues,[21] assessed 279 patients with laryngeal cancer and reported a sensitivity of only 61% using flexible NBI alone. Although the sensitivity increased substantially to 98% when NBI was coupled with HDTV, most office based flexible video endoscopes do not have the capability of HDTV integration at the time of this writing. In a separate study, Shoffel-Havakuk and colleagues[22] compared NBI with WLE in diagnosing laryngeal cancer and reported a sensitivity of 58.62% using NBI. However, it is important to note that the sensitivities reported in this study were based on three expert assessments of still NBI and WLE images, not histopathological diagnosis. Recently, Hosono and colleagues[23] further reported a sensitivity of 84.4% using NBI even with high definition magnifying endoscopy. Although this is a higher sensitivity relative to Piazza et al[21] and Shoffel-Havakuk et al,[22] it is much lower than the pooled sensitivity reported by Sun et al.[18]

The reasons for the low sensitivities remain unclear but may be due to regional or institutional differences in patient referral or presentation, quality of image processing and/or method of assessment.

More recent studies, however, have demonstrated higher sensitivities of >90% when using NBI in laryngeal cancer. Yang and colleagues[24] reported a sensitivity of 91.2% in 23 malignant lesions. Sakthivel and colleagues[25] reported a sensitivity of 100% when using NBI with WLE. Rzepakowska and colleagues[26] demonstrated a sensitivity of 98.8% when using NBI in diagnosing premalignant and malignant laryngeal lesions.

The high sensitivities and low negative likelihood ratio in this study suggests that NBI is a reliable tool in differentiating between benign and malignant laryngeal lesions. By contrasting and enhancing the mucosal microvasculature, early changes in IPCL morphology can be detected, particularly when integrated with HDTV. This is evident in this study as 46/52 lesions were either preneoplastic change or early stage cancer. This can significantly affect patient outcomes especially since the local control with transoral laser microsurgery for early stage laryngeal cancer can be up to 85%-100%.[27] Furthermore, the use of intraoperative NBI allows for greater precision of resection margins greatly reducing second looks and their associated complications and costs.

Another finding in this study was the very strong correlation between Ni classification and primary size of tumor as suggested by a Spearman's rank-order correlation value of 0.83. Types Va and Vb accounted for almost all of the Cis-T2 lesions while all of the lesions that were T4 were graded Vc. Most SD were graded as type IV and no lesions received a grade of I-III.

This is similar to previous studies suggesting type V on the Ni classification is strongly suggestive of neoplasia. In 2018, Mehlum and colleagues[17] reported that Ni type IV and V had a high diagnostic accuracy for detecting laryngeal cancer with a sensitivity of 89% and specificity of 82%. Rzepakowska and colleagues[26] compared laryngovideostroboscopy (LVS) and NBI in malignant laryngeal pathologies and demonstrated that LVS was sensitive (97.6%) in detecting malignant laryngeal pathologies. The LVS findings correlated strongly with NBI findings using the Ni classification with a spearman correlation value of 0.54.

In type IV and V of the Ni classification, the IPCLs begin to lose the oblique and longitudinal vascular pattern seen in types I-III and appear as "brown dots."[8] These brown dots change morphology and become progressively fainter as the IPCLs are destroyed suggesting progression of the neoplasm. Many authors have also reported the appearance of "brown dots or spots" using NBI as a sign of neoplasia and could reflect perpendicular branching of new vessels seen in growing tumors.[28,29]

Recently the European Laryngological Society proposed nomenclature dividing superficial vascular changes into longitudinal and perpendicular lesions. While longitudinal vessels may be benign, perpendicular changes of IPCLs (including enlarged vessel loops, dot like vessels and worm like vessels) represent precancerous and cancerous lesions.[30,31]

Given the ability of NBI to detect early change in IPCL morphology using the Ni classification, many authors have suggested using NBI not only as an adjunct for workup or laryngeal cancer but also for surveillance of disease, as an "optical biopsy" to prevent unnecessary biopsies requiring general anesthesia and intraoperatively to assist in resection margins.[32, 33] The findings of this study suggest NBI is a useful visualization adjunct to WLE and clinical examination in monitoring known disease. However, it would need further validation, experience and greater sensitivity before it is used an "optical biopsy."

This study is limited be the relatively small number of patients who were included. Although patients were recruited from a major tertiary head and neck clinic, the small number is reflective of a single institution study.

Although all patients tolerated nasoendoscopy well, a thorough assessment is needed for complete visualization of the lesion for a reliable assessment. This becomes difficult if the lesion is obscured by mucus, blood or excessive saliva. Furthermore lesions with leukoplakia can become difficult to assess owing the "umbrella effect" obscuring adequate assessment of underlying IPCL changes.[34]

Although some authors have mentioned the extra costs associated with purchasing the NBI filter, most video-endoscopy machines are fitted with NBI filters since 2017.

Many authors have also suggested a learning curve exists before reliable assessment can be made when using NBI.[35,36] Vilaseca and colleagues[37] suggested a learning curve of 200 examinations using NBI based on analysis of 480 patients. In this study, they analyzed 480 biopsy proven cancers in the head and neck region with WLE and NBI and subdivided the sample in groups of 100 patients according to the experience of the examiner. They demonstrated that accuracy of detecting malignant lesions using NBI increases with experience and, plateaus after approximately 200 cases.[37]

During this learning curve, there may be an increased rate of false positive findings on NBI particularly in areas with active inflammation, mucositis, recurrent respiratory papillomatosis, or previous radiotherapy.[31,38] However, NBI has been shown to differentiate between post radiotherapy changes and neoplasm and is even recommended as a routine part of surveillance for cancer.[39]

Further prospective studies are required to validate the role of NBI in surveillance for laryngeal cancer and its intraoperative use to

assess suspicious lesions. Although the Ni classification has been demonstrated to be reliable in detecting laryngeal cancer, it is still operator dependent. More studies addressing the role of inter and intraobserver reliability in the detection of laryngeal cancer are needed to validate its role in both surveillance and use as an "optical biopsy" technique.

5 | CONCLUSION

This study demonstrates NBI using the Ni classification to be a sensitive diagnostic tool in the detection of early neoplastic and preneoplastic glottic lesions. Given its high sensitivity and low negative likelihood ratio, it is recommended to be a routine part of work up for laryngeal cancer as an adjunct to white light imaging.

CONFLICT OF INTEREST

None to report.

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