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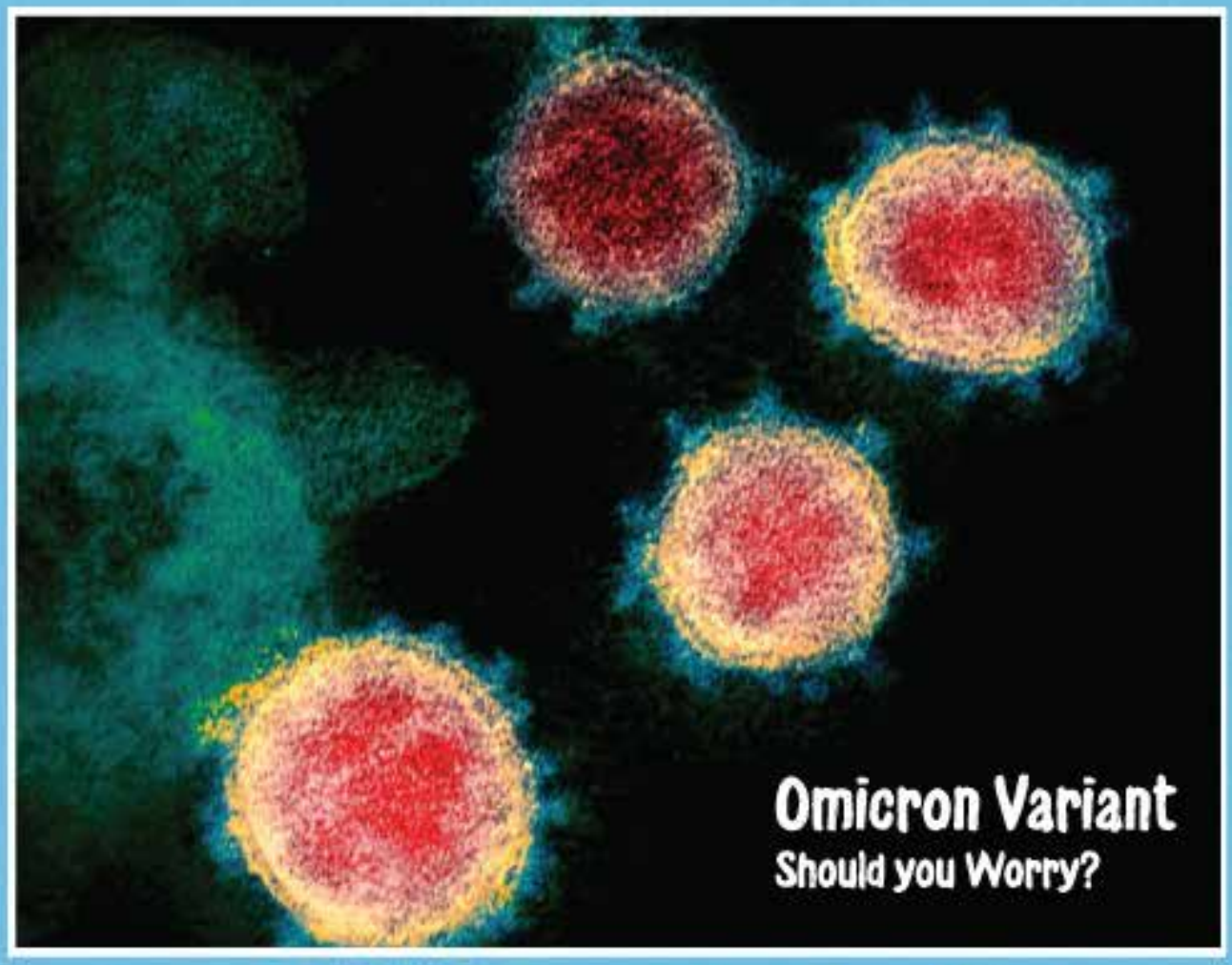


The Official Journal of the Gulf Federation For Cancer Control

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Original Article

# Assessment of Voice Outcomes Post Chemo–Radiotherapy in Non–Laryngeal Head & Neck Cancers Using Electroglottography and Voice Symptom Scale (VoiSS) Questionnaire

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## Abstract

**Background**: Laryngeal toxicity (LT) following concurrent chemo–radiotherapy (CCRT) for non–laryngeal head & neck cancers(NLHNC) has been inadequately studied. Electroglottography (EGG), a non–invasive technique for objective quantification of LT, measures the change in electrical impedance generated by glottic closure.

**Aim**: Objective and subjective assessment of acute LT post–CCRT in NLHNC.

**Materials and Methods**: A prospective study on 30 NLHNC patients, treated with CCRT; 66–70Gy/33–35fractions with weekly Cisplatin. Flexible laryngoscopic examination and EGG were performed at baseline, 6weeks, and 3months post–CCRT; Grades of LT and contact quotients(CQ) were documented. Patient–reported outcomes of voice–related quality of life(QoL) performed at the same intervals, using a 30–item Voice Symptom Scale (VoiSS) questionnaire.

**Statistical analysis**: Results of continuous measurements were studied by mean +/– standard deviation. Analysis of variance (ANOVA) was used for comparison of pre–treatment and post–treatment results in more than two groups. Significance was assessed at 5% level of significance. Post– hoc analysis has been done using Tukey – Krammer method for multiple comparisons. Correlation analysis was performed using Pearson correlation test.

**Results**: 26/30 patients completed CCRT; 14 were available at 6weeks; 10 at 3months post–CCRT for analysis. At 6 weeks, 3/14(21.5%) patients had Grade II LT; 11/14(78.57%) had grade III. At 3months, 2/10(20%) had Grade I, 6/10(60%) had grade II but 2/10(20%) had worsened to grade IV. Mean CQ at baseline was 50.77 $\pm$ 5.55; which decreased at 6 weeks to 48.56 $\pm$ 4.66 and further at 3months to 45.56 $\pm$ 4.66 ( $p>0.05$) suggestive of glottic hypo–adduction. VoiSS responses showed a significant impact on QoL in all three domains at six weeks and three months post–CCRT, compared to baseline ($P < 0.0001$).

**Conclusion**: Electroglottography is a potential tool to quantify acute LT post CCRT. Patient–reported outcomes may not correlate to the objective measures of laryngeal toxicity and require separate recording and reporting. A larger sample size would be required to draw further significant correlations.

**Key Words**: Electroglottography, laryngeal toxicity, head neck cancer, voice, chemo–radiotherapy

## Introduction:

Locally advanced head and neck cancers (LAHNC) are treated by concurrent chemoradiotherapy with a curative intent[(1)]. The post treatment period has several acute and late radiation toxicities. Laryngeal toxicity is one of the less studied radiation induced toxicities which can have

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lasting effects on the patients' quality of life. There is also a lack of evidence on objective quantification of impact of radiation on the quality of voice post treatment, for functional assessment of larynx sparing approaches in head neck cancers.

Electroglottograph (EGG) is a low cost, non–invasive system which registers the closure of vocal folds by measuring the transverse electrical impedance between two electrodes placed around the neck[2,3,4]. This can serve as a valuable tool for quick objective assessment of the laryngeal toxicity induced by head & neck radiotherapy[5,6].

The EGG signal represents relative vocal fold contact area[7]. This delivers physiological evidence of vocal fold vibration, contacting and de–contacting events. Contact quotient (CQ), is a useful parameter measured by EGG, which is a ratio depicting the duration of vocal fold contact during one vocal fold period[8,9]. Vocal cord pathologies leading to glottic insufficiency would cause a reduction in the mean CQ, whereas hyper–functional glottic pathologies would result in an increase in the mean CQ[5,7,8]. Very few studies have used EGG for assessment of CCRT induced changes with parameters other than contact quotient being analyzed in these studies[6,10,11]. Thus, the current study intends to analyze the acute laryngeal toxicity post CCRT in NLHNC using the CQ parameter on an EGG for an objective assessment, in conjunction with a subjective evaluation of the same using the Voice Symptom Scale (VoiSS) questionnaire.

## Methods:

A total of 30 patients with LAHNC were enrolled for the study over a period of two years, after obtaining clearance from institutional ethics committee and written informed consent from the patients. Patients between 18–70 years of age; Karnofsky Performance Score ≥ 70 and those planned for radical CCRT were included.

Patient with comorbidities (Diabetes Mellitus); primary tumors with laryngeal invasion; Laryngeal cancers and post–operative cases were excluded.

**Electroglottography** (EGG): This procedure was used to assess the Contact Quotient (CQ) of vocal cords. The gold–plated electrodes of the EGG Model 6103, Kay Labs (Figure. 1) were placed on the anterior surface of the neck of the patient, with the circular surface of the electrodes contacting the ala of the thyroid cartilage. The voice signal for sustained phonation of 'ıaı'was recorded which appeared as a waveform (Figure. 2). The CQ was derived from this signal.

**CQ = Time duration of glottis closure/ ( time duration of glottis closure + glottis opening)**


**Figure 1:** The Electroglottography apparatus (EGG Model 6103, Kay Labs)

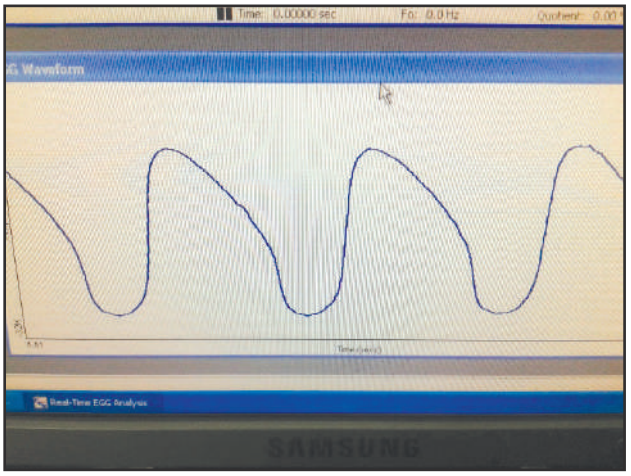


**Figure 2:** The voice signal for sustained phonation of 'ıaı' recorded appearing as a waveform from which CQ is derived

### Radiotherapy protocol

All patients received wide–field external beam radiation therapy by the 2 dimensional shrinking field technique on Cobalt–60 tele–therapy unit. A total dose of 66 to 70 Gy at 2 Gy / fraction over 6.5 to 7 weeks was delivered along with concurrent single agent weekly Cisplatin.

Follow up was done at 6 weeks and 3 months after the completion of the treatment. During the follow up, the tumor response was assessed by local examination and endoscopic examination. Laryngeal toxicity pattern was assessed by Indirect Laryngoscopy (IDL). Voice outcomes were assessed by EGG at the same time periods. Deaths and loss to follow ups which occurred during the course of treatment and during follow up were recorded as well.

**VoiSS questionnaire**[12] (Annexure I): comprises of three components i.e., the physical symptoms (7 items), emotional reaction (8 items) and voice impairment scales (15 items). It was administered to the patients in the language that they understood and the responses were recorded.

## Statistical Methods

Results of continuous measurements were studied by mean ±SD. Analysis of variance (ANOVA) was used for comparison of pre and post treatment results in more than two groups. Significance was assessed at 5% level of significance. Post– hoc analysis has been done using Tukey – Krammer method for multiple comparisons. Correlation analysis was performed using Pearson correlation test.

# Results:

The mean age of the cohort was 53 ± 8.6 years. The sex ratio of the study cohort was 19 males and 11 females. Most patients presented with primary tumors in oral cavity and oropharynx. 23% of the patients presented with T2 tumors, 40 % with T3 tumors and 37% with T4 tumors. The flow chart of the patients is shown in Figure 3.

## Baseline pretreatment evaluation:

All 30 patients underwent baseline pre–treatment evaluation. Clinical examination included IDL and flexible endoscopy which revealed mobile vocal cords with no detectable pathology. EGG done at baseline for all 30 patients were within normal limits. The mean and standard deviation (SD) values at baseline CQ on EGG was 50.19 ± 5.09. VoiSS questionnaire was administered and responses were recorded.

## Results at 6 weeks post CCRT:

EGG revealed a reduced mean contact quotient of 48.80 ±5.73. However, the difference was not statistically significant. (Table 1)

VoiSS showed a significant increase in the total score and sub scores in all three domains (Table 2.) However, statistically significant correlation could not be established between the total VoiSS score and the grade of laryngeal edema or the Contact Quotient ($p > 0.05$).

## Results at 3 months post CCRT:

Only 10 patients were available for follow up. Endoscopic evaluation revealed that 2 patients (20%) had residual grade I; 6 patients (60%) grade II and 2 patients grade IV toxicity. The 2 patients with grade IV laryngeal edema developed stridor and did not respond to conservative management, hence underwent emergency tracheostomy. A decrease in CQ was recorded, however, not significant. (Table 1.)

VoiSS questionnaire was administered to these 8 patients. The total score and sub scores ( Table 2.) showed a significant relative improvement in all three domains compared to 6 weeks post CCRT scores ($p< 0.001$). A significant difference between the scores at 3 months post CCRT and baseline could not, however, be established.

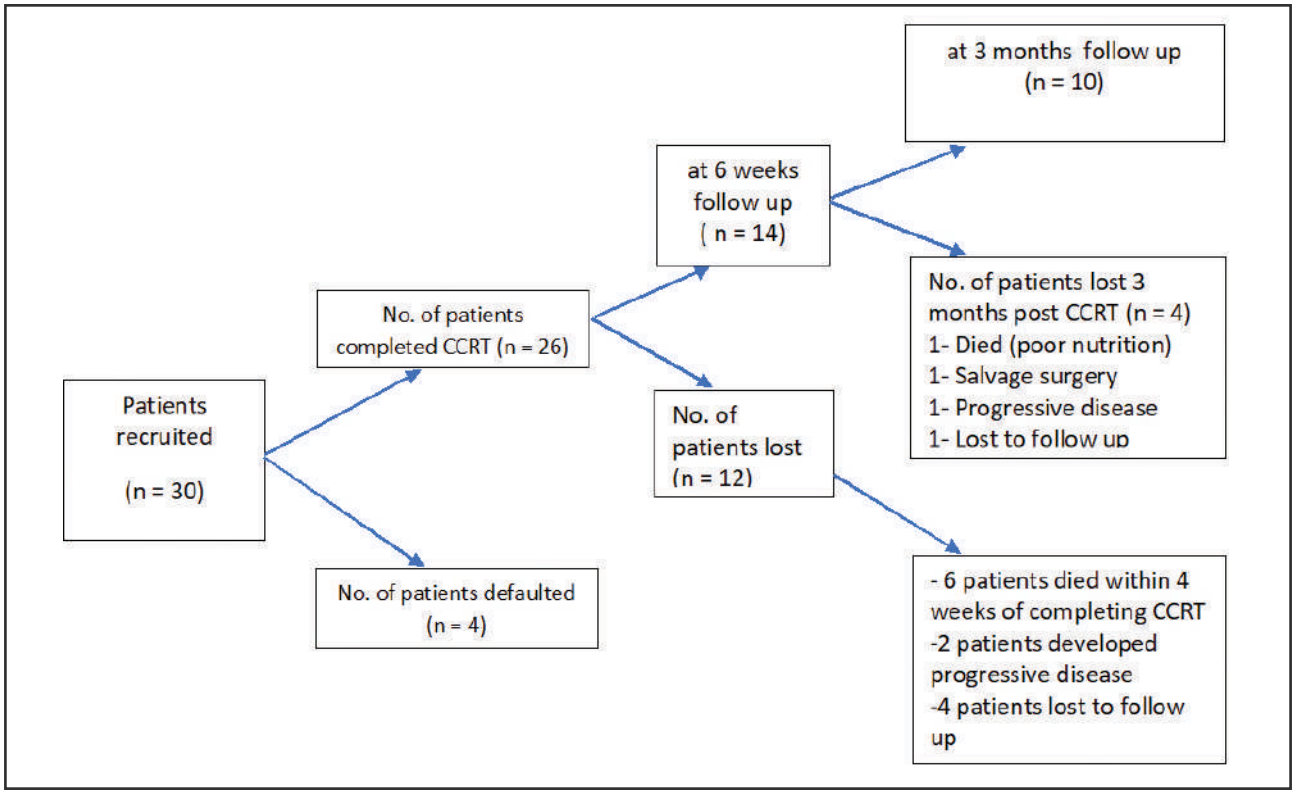


**Figure 3:** Flowchart depicting the patient recruitment details

Statistically significant correlation could not be established between the grade of laryngeal edema and the total VoiSS score ($p > 0.05$), possibly owing to the small sample size. No statistically significant co–relation could be established between CQ and VoiSS total scores and sub–scores.

## Discussion:

The current study demonstrates the EGG recordings which register the closure of vocal folds by measuring the electrical impedance between two electrodes placed around the neck. The resultant wave reflects variations of the vocal fold contact area (VFCA).

Post radiation, the mobility of the cords may be affected due to the tumor related and treatment related causes. Tumors directly involving the glottis distort voice quality by causing an obstruction of the airflow through the glottis[6]. Such tumors impair of the movement of the cords by a direct invasive effect or by the neuromuscular weakness of the vocal fold, which is further accentuated by the edema induced by radiation[11]. Radiation induces mucositis of the larynx in the acute phase, often progresses to vocal fold fibrosis and atrophic changes during the later phase. Most studies like Kazi et al[6], Orlikoff et al[9] and Melecca et al[10] have evaluated voice outcomes in laryngeal and non–laryngeal malignancies together. We have selected only non–laryngeal cases in our study to analyze the true impact of radiation alone upon the voice outcomes.

Late changes commonly observed post radiation are xerostomia, loss of mucus secreting glands, fibrosis, telangectasia and delayed edema due to an alteration in the lymphatic drainage and microcirculatory pattern. Such factors which affect the rheological properties of the vocal folds have also been postulated to have a pervasive effect on the vibrational properties of the cords[13].

Perceptual evaluation using GRABS scale by Hamdan et al[14] has alluded to the worsening of voice post radiotherapy in non–laryngeal head –neck tumors. In patients with hypofunctional voices (breathy, paretic, paralyzed) vocal fold closure may occur less quickly or possibly, not at all. Furthermore, the relative duration of closure tends to decrease (thereby increasing the duration of the open portion of the glottal cycle) in hypofunctional voices. The longer open phase has the effect of dampening the resonance tract that results in decreased vocal intensity associated with breathy voices. At 6 weeks post CCRT, the present study showed a decrease in the contact quotient and the same trend was maintained at 3 months post CCRT also. This may be attributable to the hypo adduction of the vocal cords.

| Timeline | Mean Contact quotient |
|---|---|
| Baseline N = 14 | 50.77 (SD = ± 5.55) |
| 6 weeks post CCRT N = 14 | 48.80 (SD = ± 5.73) |
| 3 months post CCRT N = 8 | 45.56 (SD = ± 4.66) |
| P value | > 0.05 |

**Table 1:** Results of Electroglottography

| Timeline | VoiSS total score | Impairment | Emotion | Physical |
|---|---|---|---|---|
| Baseline N = 14 | 11.92 | 6.00 | 2.14 | 3.78 |
| 6 weeks post CCRT N = 14 | 81.86 | 46.64 | 15.64 | 19.57 |
| 3 months post CCRT N = 10 | 39.12 | 17.50 | 8.62 | 6.90 |
| P value | <0.0001 | <0.0001 | <0.0001 | <0.0001 |
| Post hoc contrast | Baseline< 6weeks P<0.001,<br>6 weeks > 3 months P<0.0001<br>3months > baseline P>0.05 | Baseline< 6weeks P<0.001,<br>6 weeks > 3 months P<0.0001<br>3months > baseline P>0.05 | Baseline< 6weeks P<0.001,<br>6 weeks > 3 months P<0.0001<br>3months > baseline P>0.05 | Baseline< 6weeks P<0.001,<br>6 weeks > 3months P<0.0001<br>3months > baseline P>0.05 |

**Table 2:** Results of subjective analysis by VoiSS questionnaire (Mean Scores)

The rapid variation in the electrical conductance is caused mainly by the movement of the vocal folds. As they are abducted, the transversal electrical impedance is high as air impedance is much higher than tissue impedance. As they adduct and the contact between them increases, the impedance decreases, which results in a relatively higher current flow through the larynx structures. CCRT alters the vibrational characteristics of the cord, thus, in turn impacting the conductance[15,16]. Fung et al have observed that structural integrity of the vocal folds are affected by the soft tissue edema at the mucosal and muscular level[15]. This in turn alters the aerodynamic responses of the larynx, which has been demonstrated by the changes in the amplitude–based parameters of Shimmer and Noise to Harmonics ratio in acoustic analysis[15,16]. Vocal fold edema ranging from grade 2–3 was documented by IDL and flexible endoscopy post radiotherapy in the current study, which increases the mass of the cords. The key effects of this on the vocal quality[9] are (i) Aperiodicity in the vocal fold vibration associated with perceived roughness and elevated perturbation (ii) Inability of the vocal folds to approximate adequately during phonation, resulting in excessive airflow, perceived breathiness and increased perturbations.

EGG has been used for assessment of CCRT induced changes by Kazi et al[6], Orlikoff et al [10] and Meleca et al[11]. Parameters other than contact quotient, such as Normalized noise energy (NNE), Maximum phonation time (MPT) have been analyzed in these studies which showed that phonation remained abnormal until 1–2 months post treatment, and showed gradual improvement towards 12 months post treatment. Contact quotient alone was considered in this study as the study period was limited. A comparative account cannot be given as the parameters between the aforementioned studies and current study were different.

VoiSS questionnaire[12] and Vocal Handicap Index (VHI) [17] are two commonly used instruments for subjective assessment of vocal function. In the present study, VoiSS questionnaire administered at 6 weeks post treatment revealed significantly increased scores in all three domains in comparison to baseline. The scores at 3 months post treatment were lower than the scores at 6 weeks, reflecting a subjective improvement in the voice with time. The impairment domain of this instrument reflects the day to day use of voice. Hoarseness of voice was the most commonly reported symptom in the impairment domain, owing to which they were not being adequately heard by others on telephone and were unable to compete against background noise. They also perceived a strain during phonation, associated with voice breaks which increased when they attempted to shout/ raise their voice. Verdolini et al[18] have elucidated the negative impact of local dryness upon voice outcomes.

In the physical domain, the most essential symptom reported was the repeated throat clearing due to a sensation of phlegm in the throat, which reflects the altered sero–mucus secretions post CCRT compromising the voice related QoL. These findings concur with the VoiSS scores recorded by Paleri et al[19], who have shown a significant increase in impairment scores. Stroboscopic examination of larynx post wide field RT by Roh et al[20] has demonstrated the vocal fold dryness and altered viscosity with increasingly sticky laryngeal secretions. Campos et al[21] and Fung et al[14] have assessed the voice related QoL by Vocal Handicap Index (VHI) which has also shown similar results, with deterioration of scores in the immediate pre–treatment period , followed by a partial improvement in the late post treatment phase.

The correlation between objective evaluation parameters and patient reported outcomes using the subjective evaluation questionnaires have not been consistent in several studies.

The worsened VoiSS scores corresponded to the acute post RT laryngeal edema and the fall in CQ of EGG at 6 weeks post CCRT and 3 months post CCRT. This highlights the disproportion between voice outcomes perceived by the patients and the objective scorings in the clinic. This emphasizes the need for use of both objective reporting as well as patient–reported outcomes to comprehensively assess the impact of organ preserving treatment modalities on QoL. Such a multidimensional assessment will enable us to design strategies for voice therapy and rehabilitation post CCRT[22].

The limitations of the present study include the small sample size and lack of stroboscopic examination for detailed analysis of vocal fold vibration. Further long–term assessment with larger number of patients is warranted.

## Conclusion:

Electroglottography has the potential to quantify laryngeal toxicity post radiotherapy with contact quotient as the assessment parameter at baseline and on follow up. Larger sample size will enable us to draw further significant correlations. The VoiSS questionnaire is an effective tool for subjective assessment of the patient reported outcomes of voice post treatment. Patient reported outcomes may not correlate to the objective measures of laryngeal toxicity and requires separate recording and reporting.

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## Conflicts of interest

There are no conflicts of interest.

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