ORIGINAL ARTICLE

PREDICTIVE MODELLING OF VISUAL ACUITY UPON DIABETIC RETINOPATHY IN TYPE 2 DIABETES MELLITUS

Xin Wee Chen[1,2], Zaliha Ismail[2,3], Embong Zunaina[4] and Kamarul Imran Musa[1]

[1]Department of Community Medicine, School of Medical Sciences, Health Campus, Universiti Sains Malaysia, 16150 Kubang Kerian, Kelantan, Malaysia.
[2]Department of Public Health Medicine, Faculty of Medicine, Universiti Teknologi MARA, Sungai Buloh Campus, Jalan Hospital, 47000 Sungai Buloh, Selangor, Malaysia.
[3]Institute of Pathology, Laboratory and Forensic Medicine (I-PPerForM), Universiti Teknologi MARA, Sungai Buloh Campus, Jalan Hospital, 47000 Sungai Buloh, Selangor, Malaysia.
[4]Department of Ophthalmology, School of Medical Sciences, Health Campus, Universiti Sains Malaysia, 16150 Kubang Kerian, Kelantan, Malaysia.

Corresponding author: Xin Wee Chen
Email: drchenxw@salam.uitm.edu.my

ABSTRACT

The worldwide upsurge of Type 2 Diabetes Mellitus (T2DM) warrants the attention of public health, especially in complications. Diabetic Retinopathy (DR), the commonest ocular complication, contributes to the growing incidence of blindness. Recommendations that the visual acuity (VA) assessment guidelines should be used in DR screening was not routinely practiced. This study aims to model the predictive effect of VA - a simple economic clinical assessment - upon DR in patients with T2DM. A case-control study was conducted in Hospital Universiti Sains Malaysia with subjects recruited from the ophthalmology clinic. The primary variable during analysis was VA, and the outcome variable was DR. Models with eight control variables which included age, gender, and duration of DM were developed. The predictive effect measured by logistic regression showed that when unadjusted; four variables had a significant association with DR, at p-value<0.25; they were the duration of DM, systolic blood pressure, glycosylated haemoglobin and VA. From the eight different predictive models, the estimated adjusted odds ratio produced ranges from 6.09 to 11.64. Our study shows that VA has a predictive effect upon DR in T2DM patients. We suggest VA assessment, to be on par with the monitoring of blood pressure and blood glucose.

***Keywords**: Predictive, Visual acuity, Diabetic Retinopathy, Type 2 Diabetes Mellitus.*

INTRODUCTION

Diabetic Retinopathy (DR) may be defined as a retinal disorder, in which there are a presence and characteristic evolution of typical retinal microvascular lesions, leading to irreversible vision loss, in an individual with diabetes[1, 2]. More than 77% of patients having Type 2 Diabetes Mellitus (T2DM) for more than two decades will have some degree of DR[3]. Studies conducted in Malaysia reported a prevalence rate ranging from 23.7% to 51.4%[4-7].

Data from the Diabetic Eye Registry, National Eye Database 2007, showed approximately 70.9% of the patients have never undergone prior eye examination[8]. Clinical Practice Guidelines Screening of Diabetic Retinopathy was issued by the Malaysia Ministry of Health, to provide evidence-based recommendations for the screening of DR[9]. The evidence helped to clarify the role of early detection of DR and timely treatment, in preserving good functional vision and hence a better vision-related quality of life[9, 10].

A 10-year prospective case-controlled study concluded that visual acuity (VA) deteriorated more predominantly in diabetic than non-diabetic subjects; frequency and severity of DR markedly escalated in newly diagnosed Diabetes Mellitus (DM); also, diabetic status (longer duration of disease and poor glycaemic control) as the important determinants of retinopathy[11]. Findings from the Diabetic Eye Registry had shown the coherent result, in which the odds of developing DR was higher with the increasing severity of vision, where severe visual loss (worse than 6/60) would nearly triple the odds than a mild visual loss (6/9 to 6/12)[12].

Testing vision is important as a cheap and simple screening for DR detection. Vision acuity is a conveniently performed measure of visual function, in part because of the greater availability compared to digital fundus camera in Malaysia and the familiarity among health care providers without requiring special training[13, 14]. Based on our experience and observation, the measurement and record of VA are not practiced as a baseline screening despite a recommendation for the first step in the screening of DR in patients with diabetes, especially for health care facilities with fundus camera[9]. To our knowledge, research that explores the relationship between VA and DR is limited, particularly the information pertaining to the population in Peninsula Malaysia. Even with the currently limited studies, there is inconclusive

evidence reporting on the independent role of VA in predicting DR. Therefore, this study aims to model the independent predictive effect of VA upon DR in patients with T2DM in Kelantan, Malaysia.

METHODOLOGY

A single hospital-based case control study was conducted in Hospital Universiti Sains Malaysia (HUSM), a north eastern teaching hospital in Malaysia. It is one of the major referral ophthalmology centres in Kelantan. The source population was T2DM patients attending HUSM ophthalmology clinic, between June and December 2015, whereby those fulfilling the subject criteria were recruited in this study. The inclusion criteria were they needed to be T2DM patients, aged over 18 years, with active follow-up (at least one visit) at Hospital USM ophthalmology clinic from June to December 2015. The exclusion criteria were patients suffering from juvenile diabetes, gestational diabetes, and other concurrent ophthalmology pathology (cataract, glaucoma, age-related macular degeneration and any causes of maculopathy besides diabetic maculopathy).

The sample size was calculcated using PS software with the following parameters: significance level $\alpha = 0.05$ (two-tailed); power, $1-\beta = 0.8$; proportion of abnormal vision among T2DM patients without DR, $P_0 = 0.57$; true probability among DR, $P_1 = 0.77$; ratio, $m = 2$. An estimated 187 samples were required to adequately rejecting the null hypothesis. The cases were defined as patients with T2DM, based on the most recent documentation of the diagnosis of DR by physicians. Controls were defined as patients with T2DM without being diagnosed as suffering from DR, in this case normal fundus documented from retinal photographs. No sampling method was applied for this study. Consecutive case and control selection were established based on the attendance list provided by the Hospital USM ophthalmology clinic. Patients' case notes were retrieved from the Hospital USM's Medical Record Unit and reviewed by a single researcher to complete the pro forma checklist.

The variables in the current study comprised of the outcome or response variable, primary variable and covariates[15]. The outcome variable was the diagnosis of DR (yes versus no), in which the common tools used for examination of the fundus at the ophthalmology clinic in most of the centres in Malaysia, including Hospital USM were binocular indirect ophthalmoscope and slit lamp biomicroscope, with the sensitivity of 87.4% and specificity of 94.9%[9]. Control variables were obtained from literatures, in which several risk factors have been reported to be associated with DR, older age[16-19], male gender[10], race[12, 16], longer duration of DM[5, 6, 10-12, 16-22], concomitant hypertension[4, 6, 18, 19, 21], blood pressure control [1], glycaemic control in terms of glycosylated haemoglobin (HbA1c) level[11, 16, 18, 19, 23], elevated serum creatinine level[5, 12, 19, 24], and insulin usage[16, 19, 20, 22, 24].

The primary variable was the VA, coded as normal (6/6) or impaired (worse than 6/6). The eye examination, on the other hand, was made up of VA testing, followed by fundus photography or ophthalmoscopy in the DR assessment[9]. The grading of DR was based on the eye with the more severe VA was taken into analysis[19]. The Reichert Clear Chart Digital Acuity System with Snellen configuration was performed by trained medical personnel in Hospital USM ophthalmology clinic for VA testing[25]. The setting of the refraction room was properly set up for the measurement of VA. VA was measured with and without pinhole. The result of VA with a pinhole was taken into analysis.

Data analysis was conducted using SPSS Version 22[26]. Descriptive analysis was performed to summarise the characteristic of the T2DM populations. Logistic regression model was used for predictive modelling. There were eight covariates or control variables simultaneously modelled with VA: age, gender, duration of DM, concomitant hypertension, systolic blood pressure (SBP) and diastolic blood pressure (DBP), HbA1c, and fasting blood glucose (FBS). We used a manual purposeful variable selection throughout to develop the predictive models[27, 28]. The decisions to include the control variable were based on both the previous literature and statistical importance[27]. Confounding variables that were associated with both the test result and the outcome parameters need to be measured and included in the analysis while evaluating the test accuracy[29].

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and Local Regulations and Standards in Ethical Review.

RESULTS

Data were analysed for 186 eligible T2DM patients fulfilling the mentioned criteria, 62 (33.3%) and 124 (66.7%) of them are from the control group (T2DM patients with non-DR) and case group (T2DM patients with DR), respectively. Both groups have comparable socio-demographic characteristics in terms of age, sex and ethnicity, as can be seen in Table 1.

Table 1: The baseline demographic characteristics, clinical factors and laboratory parameters of controls (T2DM with non-DR) and cases (T2DM with DR).

Variables	Controls (n = 62)		Cases (n = 124)	
	Mean (SD)	n (%)	Mean (SD)	n (%)
Demographics				
Age (years)	56.23 (13.455)		57.22 (9.377)	
Sex				
Male		27 (43.5)		62 (50.0)
Female		35 (56.5)		62 (50.0)
Ethnicity				
Malay		57 (91.9)		117 (94.4)
Chinese		5 (8.1)		6 (4.8)
Siamese		0		1 (0.8)
Clinical factors				
Duration of DM (years)	10.48 (6.708)		14.86 (7.530)	
Treatment				
OHA		38 (61.3)		43 (34.7)
OHA + Insulin		10 (16.1)		20 (16.1)
Insulin		13 (21.0)		59 (47.6)
Not documented		1 (1.6)		2 (1.6)
Concomitant Hypertension				
No		13 (21.0)		21 (16.9)
Yes		49 (79.0)		103 (83.1)
Clinical examination				
Systolic BP (mmHg)	134.38 (14.722)		142.46 (20.151)	
Diastolic BP (mmHg)	76.39 (7.705)		75.39 (10.622)	
VA of the worst eye				
Normal (6/6)		14 (22.6)		4 (3.2)
Impaired (worse than 6/6)		48 (77.4)		120 (96.8)
Laboratory parameters				
HbA1c (%)	8.60 (2.292)		9.60 (2.159)	
FBS (mmol/L)	8.96 (4.432)		8.91 (3.697)	

OHA: oral hypoglycaemic agents, HbA1c: glycosylated haemoglobin, FBS: fasting blood sugar, SD: standard deviation, VA: visual acuity, DM: diabetes mellitus, BP: blood pressure

We found a total of 168 T2DM patients in our study with impaired VA, with 48/168 (28.6%) have no DR. While among those who have been tested to have impaired VA and subsequently diagnosed to have DR, the largest proportion 57/168 (33.9%) fall in the stage of proliferative diabetic retinopathy (PDR), followed by moderate non-proliferative diabetic retinopathy (NPDR), 29/168 (17.37%), mild NPDR, 17/168 (10.1%), severe NPDR 11/168 (6.5%) and lastly advanced diabetic eye disease (ADED) 6/168 (3.6%).

Our crude (unadjusted) logistic regression analysis in the present study publicises that four variables are significantly associated with DR, at p-value < 0.25 [27, 28]. They are 1) the VA (as the primary variable), 2) duration of DM, 3) SBP and 4) HbA1c, as illustrated in Table 2.

Table 2: Crude Logistic Regression analysis showing estimated regression coefficients (b), crude odds ratio (OR), 95% Confidence Interval (CI) and corresponding p-value for each of the variables associated with diabetic retinopathy among T2DM patients (n=186).

Variables	b	Crude OR	95% CI	p-value*
Age (years)	0.008	1.008	0.981, 1.037	0.557
Sex (male versus female)	0.260	1.296	0.702, 2.393	0.407
Duration of DM (years)	0.088	1.092	1.040, 1.146	< 0.001
Concomitant Hypertension (yes versus no)	0.263	1.201	0.602, 2.813	0.503
SBP (mmHg)	0.025	1.025	1.006, 1.045	0.011
DBP (mmHg)	-0.011	0.989	0.956, 1.023	0.533
HbA1c (%)	0.214	1.238	1.042, 1.472	0.015
FBS (mmol/L)	-0.003	0.997	0.917, 1.084	0.941
VA (normal versus impaired)	2.169	8.750	2.742, 27.926	<0.001

OR=exp (B), 95% CI = exp (B-1.96SE(B)), exp (B+1.96SE(B))
**Level of significance p < 0.25*
DM: diabetes mellitus, SBP: systolic blood pressure, DBP: diastolic blood pressure, HbA1c: glycosylated haemoglobin, FBS: fasting blood sugar, VA: visual acuity

Next, we used Multiple Logistic Regression models containing three control variables, to generate a total of eight (8) models (Table 3). From our evaluation, VA consistently (in all eight models) predicts DR, with no evidence of an additive influence on the adjustment of the other risk factors. The estimated adjusted odds ratio for eight different models ranges from 6.09 to 11.64, as presented in Table 4 suggesting that the odds of developing DR when VA is impaired (worse than 6/6), increase from 6.1 times to 11.6 times in all of the eight models.

Table 3: Regression-based model showing the constant, estimated regression coefficient (b) and corresponding standard error for eight different models. Each of the models analysed the predictive effect of visual acuity upon Diabetic Retinopathy in patients with T2DM, with adjusted confounders (n = 186). Model 1 is the crude model with only the primary variable (VA) as the covariate.

		Covariates							
		Visual acuity		DM duration (years)		SBP (mmHg)		HbA1c (%)	
Model	Constant	b	SE	b	SE	b	SE	b	SE
1	-1.253	2.169	0.592						
2	-1.777	1.807	0.609	0.069	0.025				
3	-5.088	2.454	0.687			0.025	0.010		
4	-3.248	2.171	0.682					0.201	0.093
5	-5.176	2.174	0.705	0.058	0.027	0.022	0.010		
6	-3.393	1.814	0.707	0.062	0.029			0.159	0.093
7	-5.933	2.211	0.700			0.020	0.011	0.189	0.095
8	-5.709	1.916	0.725	0.050	0.029	0.017	0.011	0.155	0.095

$g(x) = ln[\pi(x)/1-\pi(x)] = \beta_0 + \beta_1 x_i + \beta_2 x_i + \beta_p x_i$

From our study, the area under the Receiver Operating Characteristic (ROC) curve remained relatively constant across all adjusted models (Model 2 to Model 8), with areas ranging from 0.60 to 0.70 and corresponding p-value of less than 0.05, indicating that all the models have adequate discriminatory ability. We also ascertained the discriminating ability of VA testing for detecting DR improved, by adding additional covariates into the model (in comparison to unadjusted Model 1), supported by a larger area under ROC curve (Table 4).

The accuracy of the VA assessment is determined from the data collected and derived based on the crude and adjusted predictive effect of VA. The summary of the eight models show positive predictive values (PPV) ranging from 87.8% to 96.8%, negative predictive values (NPV) ranging from 22.6% to 38.9%, sensitivity values ranging from 31.4% to 73.8% and specificity values ranging from 50.0% to 82.4%.

DISCUSSION

The study developed eight different predictive models for VA upon DR based on the T2DM patients in Kelantan, Malaysia. They demonstrated that VA (a simple economic and easily accessible clinical assessment) was able to consistently predict DR, with and without the adjustment of other variables. This proves that VA is a useful tool to predict the likelihood of T2DM patients to develop DR, prioritise the population at highest risk for further investigation and referral to ophthalmologists.

Table 4: Regression-based model showing adjusted odds ratio, 95% confidence interval, corresponding p-value and area under Receive Operating Characteristic (ROC) curve for eight different models. Each of the model analysed predictive effect of visual acuity upon diabetic retinopathy among T2DM patients, with adjusted cofounders (n = 186). Model 1 is the crude model with only the primary variable (visual acuity) as the covariate.

Models	Variables								Area under ROC curve
	Visual Acuity		Duration of DM (years)		SBP (mmHg)		HbA1c (%)		
	Adj OR (95% CI)	p-value*	Adj OR (95% CI)	p-value*	Adj OR (95% CI)	p-value*	Adj OR (95% CI)	p-value*	
1	8.75 (2.74, 27.93)	<0.001							0.597
2	6.09 (1.85, 20.12)	0.003	1.07 (1.02, 1.13)	0.007					0.700^
3	11.64 (3.03, 44.73)	<0.001			1.03 (1.01, 1.05)	0.013			0.684^
4	8.77 (2.30, 33.38)	0.001					1.22 (1.02, 1.47)	0.031	0.702^
5	8.80 (2.21, 35.01)	0.002	1.06 (1.01, 1.12)	0.031	1.02 (1.00, 1.04)	0.030			0.728^
6	6.14 (1.54, 24.52)	0.010	1.06 (1.01, 1.13)	0.030			1.17 (0.98, 1.41)	0.087	0.734^
7	9.12 (2.31, 36.00)	0.002			1.02 (1.00, 1.04)	0.075	1.21 (1.00, 1.46)	0.047	0.703^
8	6.80 (1.64, 28.14)	0.008	1.05 (0.99, 1.11)	0.088	1.02 (1.00, 1.04)	0.128	1.17 (0.97, 1.41)	0.103	0.725^

DM: diabetes mellitus, SBP: systolic blood pressure, HbA1c: glycosylated haemoglobin
Interactions were unlikely.
*Level of significance $p < 0.05$
^p-value for the area under ROC curve <0.001

Several studies have documented the fact that a separate analysis of SBP and HbA1c is significantly associated with the development of DR[1, 16, 18, 19, 23]. Nonetheless, once we recruited the primary variable of VA in our adjusted models, this was no longer the case.

Our results are coherent with earlier analyses; however, our models advocate that the odds of having DR (adjusted OR for eight different models ranges from 6.09 to 11.64) for those with impaired VA (worse than 6/6) may be greater than previously described elsewhere, for example:

i) One study conducted in a primary care setting in Kuching, with the normal VA as reference, produced the adjusted OR 1.0 (95% CI: 0.7, 1.5) for mild visual loss, adjusted OR 2.1 (95% CI: 1.3, 3.5) for moderate visual loss and no subjects in the severe visual loss group. This single model contained the covariates of the duration of DM, body mass index (BMI) and hypertension control (in terms of both SBP and DBP)[4].
ii) Another study analysing data from the National Diabetic Eye Registry, pertaining to Sarawak, also used normal VA as reference yield the adjusted OR 1.49 (95% CI: 1.10, 2.02) for mild visual loss, adjusted OR 2.21 (95% CI: 1.62, 3.04) for moderate visual loss and adjusted OR 3.10 (95% CI: 2.04, 4.70) for severe visual loss. The variables that were adjusted in this particular model included ethnicity, duration of DM, the presence of ischemic heart disease and renal impairment[12].

In agreement with the above-mentioned studies conducted in East Malaysia, the similar third variable selected was the duration of DM, in which we also found that our Model 2 (VA + Duration of DM) had the smallest adjusted OR of 6.09 and the narrowest 95% CI interval range of 18.27 among the eight models. Our results reinforced the evidence of the predictive effect of VA upon DR, irrespective of the primary or secondary care populations.

Visual acuity is a standard DR screening assessment for all patients with diabetes in Malaysia. Hence, the accuracy (overall value of a test) of VA assessment needs to be addressed[9]. In a population with a high prevalence of T2DM and a surge of DR as a consequence of diabetes, it is crucial to have a valid screening programme for DR. Such test must have high sensitivity and specificity[30]. A single DR screening method with high sensitivity and specificity, at a cost-effective price, is not yet available, but a double screening involving the assessment of vision and retinal examination has been recommended with evidence supporting the combination of the two modalities of screening[13].

The above mentioned retinal examination such as fundus photography or ophthalmoscopy requires a proper setting of the dark room facilities and pupillary dilatation in the peripheral clinic or district hospitals[9]. The benefits of using digital retinal imaging are evident to replace direct ophthalmoscopy in large-scale DR screening programmes. However, the validity of retinal photography is unclear[31]. Even so, taking into consideration cost-effectiveness and training time, digital fundus camera (non-mydriatic fundus camera) is superior to direct ophthalmoscope[9, 13, 14]. Barriers to effective implementation of digital fundus camera in screening for DR, include the scarcity of the machine (only 50 fundus cameras available in Malaysia primary health clinics), manpower (high turnover of trained screeners and graders) and money (approximately RM 120,000 per unit)[13, 14].

Contrary to the high-tech screening tools, Snellen charts, a cheap and convenient facility, is easily available in most of the health care facilities in Malaysia (114 Ministry of Health hospitals and 772 health clinics)[13] for DR screening. For that reason, we recommend VA examination be inculcated as the parallel test in DR screening. Hence, all T2DM patients must be checked for VA as one of the "vital signs" at each visit to their health care providers. At the same time, the retinal examination should still be conducted as per current guideline. As such, the consideration to provide training to all potential examiners who have the chance to manage T2DM patients, including general practitioners, physicians, registrars, clinical assistants, nurses, cardiologists, endocrinologists, optometrists, and opticians, in performing an assessment of vision must be highlighted.

Lack of awareness among both patients and healthcare professionals is one of the hurdles of implementing effective DR screening[9, 13]. Employing VA assessment as a "vital sign" for all T2DM patients at each follow-up provides an important opportunity to increase awareness through an advanced understanding of DR as the complication of diabetes. Studies publicised low retinopathy awareness to be the risk factor associated with poor glucose control. Nevertheless, the paradoxical finding of high awareness and low ophthalmological assessment proportion among Malaysian diabetic patients, can be explained by the unwillingness or lack of motivation to undergo eye examination[8, 14, 20]. Perhaps, when the policy makers give adequate attention to and emphasis on VA assessment in daily practice, it helps to educate patients and improve their awareness.

Apart from the patient factor, health care professionals impede the execution of DR screening by having limited knowledge and/or poor attitude, lack of utilization of the screening

tools and lack of optimal usage of the fundus camera[9]. To a certain extent, the goal of secondary prevention for DR might not be optimized as a result of this. Again, our emphasis to incorporate VA test by means of vital signs for all T2DM patients during their follow-up visits offer apparent advantages by nurturing awareness among patients and healthcare providers. This, in turns, places significant weight on the role of healthcare professionals in educating the patients about the timely detection of DR. **S**ubsequently such move will assist the patients to be informed about the importance of receiving the expert care, regardless of their glycemic control.

The case-control study design allowed us to have a better estimation of the predictive effect upon DR when comparing to the usual comparative cross-sectional study. We designed the current research to distinguish T2DM patients who are clearly diseased (case group) from those who are clearly not diseased (control group), such as perfectly healthy people (non-diabetic subjects or medical student volunteers), for us to obtain a more valid estimates of diagnostic accuracy via the odds ratios in clinical practice[11, 32]. Other than that, a retrospective study minimizes the selection bias by decreasing the likelihood having an inaccurate diagnosis because of a clinical impression, as the fundus examination is subjectively interpreted[29, 30].

Using retrospective clinical information (data abstracted from medical record) have certain limitations in terms of the variables collected. It is difficult to disentangle factors like poor access to medical services and late diagnosis in dealing with the true duration of T2DM. Besides, the risk factors indicated as the protective effect of DR in patients with diabetes, such as smoking, being overweight and obese were examined in other studies[4, 19], but not available in our medical records.

The other limitation is the issue of limited generalizability. This hospital clinic-based survey is from a single ophthalmology referral centre, potentially reduces the representation of the Kelantan T2DM population, especially those receiving care in primary settings. It also reduces the generalizability of T2DM patients coming from resource-poor-health facilities in rural areas. Apart from that, patients with diet-controlled diabetes may be under-represented.

In future studies, bigger sample size from multicentre recruiting patients with a wider spectrum of DM and DR (severity), different socio-demographic characteristics, clinical and metabolic factors could be considered, when manpower resources and time are more permissible. It is also recommended that this study be extended in a more relevant health care setting, for example taking the reliable source for clinical data from the National Diabetes Registry that includes 64 government health clinics throughout Malaysia. This is useful for further evaluation in relation to feasible reproducibility in clinical practice of the T2DM patients from different spectrum of characteristics[19, 29, 33].

Another suggestion will be the variable selection. A preliminary analysis revealed that the fasting plasma glucose variability, irrespective of mean HbA1c, could self-determine the onset of DR in T2DM patients, evidenced by an average annual incidence rate of 7 per 100 patients[34]. As such, this independent risk factor and other factors with a protective effect (smoking and BMI status) would need to be considered for adjustment in future studies.

CONCLUSIONS

Our results verify the predictive effect of VA upon DR among T2DM patients in Kelantan. We propose that the VA assessment be conducted as “vital sign” for every visit of the T2DM patients to the health care facilities. The small benefit of an adjustment coming from other predictors (risk factors) suggests that VA can be predictive on its own. We strongly urge that policymakers use VA in routine follow-up for T2DM patients, at par with the monitoring of blood pressure and blood glucose level; with the aim to halt the rise of blindness as a complication of DR.

CONFLICT OF INTEREST

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