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The Use of Artificial Intelligence to Identify People at Risk of Oral Cancer: Empirical Evidence in Malaysian University

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Abstract

The purpose of this study was to evaluate the ability of a fuzzy neural network model and fuzzy regression model to predict the likelihood of an individual in developing oral cancer based on knowledge of their risk habits and demographic profiles at Oral Cancer Research and Coordinating Centre, University of Malaya, Malaysia. Performances of the two artificial intelligent prediction models were compared with the prediction made by a group of oral cancer clinicians. The prediction performance was measured in terms of sensitivity and specificity. The mean accuracy, sensitivity and specificity of the models were 59.9, 45.5 and 85.3 for fuzzy neural network models; 63.1, 54.2 and 78.6 for oral cancer clinicians predictions and 67.5, 69.0 and 64.7 for fuzzy regression prediction models. Areas under the receiver operating characteristic curves reflect the prediction accuracy of the models. There were no significant differences in the prediction performance among the three models for single-input and two-input predictor sets. However, fuzzy regression and fuzzy neural network performed better than oral cancer clinicians when the size of input predictor set was increased to three and four. In short, this study is perhaps one of the first that address the use of artificial intelligence to identify oral cancer in Malaysia.

Keywords: Artificial Intelligent, Fuzzy Neural Network, Fuzzy Regression, Oral Cancer, Malaysian University.

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INTRODUCTION

Oral cancer often seen as a persistent ulcer is easily detected by health personnel through oral examination. However, in most cases oral cancer is detected at a late stage thus causing gross defect and reducing function. It was reported that the survival rate for oral cancer patient in Malaysia remained at 50 percent for the last 15-20 years (Zain, 2004). There is well documented risk habits associated with oral cancer worldwide which may or may not be applicable to this part of the world. Currently, an intervention program in this country is limited to the high risk group such as those associated with the usage of tobacco and betel quid chewing only. However, other factors including physical environment, genetic molecular make-up and lifestyle (occupation, dietary intake) are shown by more recent studies to be associated with oral cancer among Malaysians (Zain et al., 2006).

Even though oral cancer shows relatively low incidence compared to other types of cancers, it was found to have high mortality and morbidity due to late detection and treatment (Speight & Hammond, 1998). World wide, oral cancer is reported to have the lowest survival rate (Kujan, 2005). This has led to an increased concern over the role of cancer screening program (Kujan, 2005; Speight & Hammond, 1998).

Screening is defined to be a process by which a test is administered to detect a disease at an early stage (Miller, 1988). Case detection alone is not sufficient in a screening test but it must also be of adequate sensitivity and specificity. Ethically, a screening test must be both effective and hazard free (Miller, 1988).The whole purpose of screening is to sort out people who probably have a disease from those who probably do not (Speight & Hammond, 1998). In the case of oral cancer the aim of screening is to detect early lesion which can be cured, or precancerous lesion which can be treated before they progress.

Different strategies for oral cancer screening have been reported including mass (population) screening, opportunistic screening and targeted screening of selected high risk groups (Nagao, 2000). A Working group on Screening for Oral Cancer and Pre-cancer established in the UK in 1991 and other groups who were working on the same idea of advising on the feasibility of screening for oral cancer did not recommend population screening but instead suggested on the benefits of opportunistic screening of high risk groups (Speight & Hammond, 1998).

The first study on the potential efficacy of machine learning in oral cancer screening done by Speight and Hammond suggested the promising strategy for a cost effective screening program. A machine learning technique particularly neural network was used in that particular study. Successful applications on the use of machine learning to aid in screening for other type of cancers have also been reported for cervical cancer and also in diagnosing and predicting breast cancer and prostrate cancer (Speight & Hammond, 1998).

A machine learning prediction technique is an algorithm that estimates an unknown dependency between a set of given input variables and its response variable. When such dependency is discovered, it can be used to predict or deduce the future output associated with a different set of input values. This is done by identifying the target function that best describes the behavior governing the input-output pattern. Learning in this context refers to the process of minimizing the difference between observed data and model output (Shretha, 2006).

The current study contemplates on the use of artificial intelligent since there have been no attempts to relate all possible factors of predicting risk cancer in one single setting. To fill the gaps, this study is aimed at evaluating the ability of two artificial intelligent prediction models namely fuzzy regression and fuzzy neural network models to predict the likelihood of an individual developing oral cancer on knowledge of their risk habits and demographic profiles.

Fuzzy Neural Network Prediction Model

Fuzzy Neural Network modeling has been intensively studied since the early nineties. The learning capability of neural networks is combined with the expressiveness of fuzzy if-then rules using linguistic variables to produce a hybrid model called Fuzzy Neural Network. A neuro-fuzzy classifying system, in general, has *n* inputs (attributes or features) $x_1, x_2, x_3, \ldots, x_n$ and an output which has the form of a possibility distribution over the set $Y=\{y_1, y_2, \ldots y_H\}$ of class labels. In medical and dental field, each input x_i represents one input medical or dental attribute which could be either a 'symptom' for diagnostic purposes or a 'risk factor' for prognostic purposes (Gorzlaczany, 1999).

In this study, a fuzzy inference system called the Adaptive Neuro Fuzzy Inference System (ANFIS) introduced by Jang (1992) was used to model the relationship between the inputs and the response variable. ANFIS, posses the

main components of the fuzzy inference system namely the input fuzzification, implication and output defuzzification processes (Jang, 1992). The ANFIS system is depicted in Figure 1.

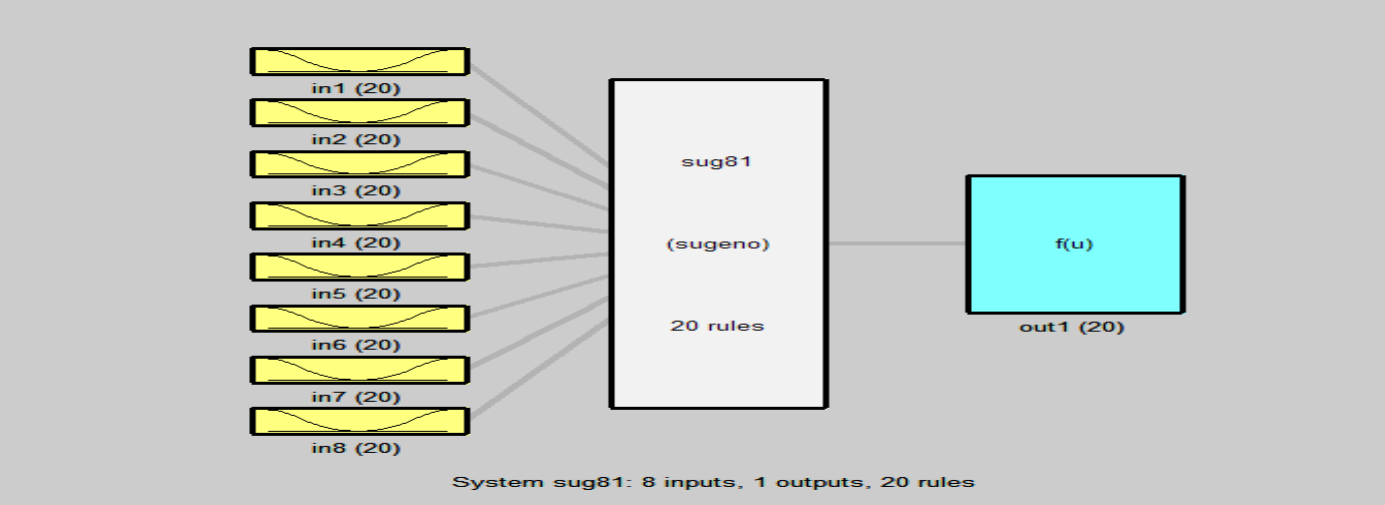

Fig.1: ANFIS inference system with 8 inputs and one output

Fuzzy Regression Prediction Model

A Fuzzy regression model is a non-parametric model that can be used to explain the variation of a dependent variable Y in terms of the variation of the independent variables X as Y=f(X) where f(X) is a linear function (Tanaka & Uejima, 1982). Fuzzy regression provides a means for handling regression problem lacking a significant amount of data and with vague relationships between the explanatory and the response variables (Shapiro, 2005, Wang, 2000). It was first introduced by Tanaka in1982. A fuzzy linear regression model expresses the regression coefficients as fuzzy numbers in an interval form (Tseng, 2005). The estimated dependent variable Y is also a fuzzy number since the regression coefficients are fuzzy numbers (Savic, 1991).

There are two approaches to fuzzy regression. The first approach also known as the possiblistic regression is based on minimizing fuzziness as an optimal criterion. The second approach uses least squares of errors as a fitting criterion (Shapiro, 2005, Savic, 1991). In fuzzy regression, deviations between observed values and estimated values are assumed to be due to system fuzziness or fuzziness of regression coefficients (Tanaka & Uejima, 1982). In this study the fuzzy regression model used is based on Tanaka's possibilistic regression in which

$$Y=A_0x_0 + A_1x_1 + A_2x_2 +\ldots..+ A_jx_j +\ldots+ A_kx_k$$

where Y is the fuzzy output, $x = [x1, x2, \ldots, xk]^T$ is the real-valued input vector of independent variables and each regression coefficient Aj, j=0, . . ., k, was assumed to be a symmetric triangular fuzzy number with center αj and half-width cj, $Cj \geq 0$.

The fuzzy linear regression model can now be rewritten as:

$$y = (\alpha_0, c_0)+ (\alpha_1, c_1)x_1 + (\alpha_2, c_2)x_2 + \ldots.+ (\alpha_k, c_k)x_k.$$

The following linear programming formulation was employed to estimate $A_j = (\alpha_j, c_j)$:

Minimize $J = \sum_{j=0}^{k}(c_j \sum_{i=1}^{n} x_{ij})$

Subject to $\sum_{j=0}^{k}\alpha_j x_{ij} + (1-h)\sum_{j=0}^{k} c_{jx}x_{ij} \geq y_i$

and

$$\sum_{j=0}^{k} \alpha_j x_{ij} - (1-h)\sum_{j=0}^{k} c_{jx} x_{ij} \le y_i$$

$a_j \varepsilon R$, $c_j \geq 0$ j= 0,1,2,…..,k

$x_{i0} = 1$, i=1, 2,….., n $0 < h < 1$

Where *J* is the total fuzziness of the fuzzy regression model. The *h* value is the threshold level that determines the degree of fitness of the fuzzy linear model to its data (Wang 2000).

MATERIALS AND METHODS

The two artificial intelligent prediction models used in this study were described above. An unmatched case-control study was conducted using 84 newly diagnosed oral cancer patients and 87 non-cancer subjects selected from the same locations as cases. Sociodemographic data was obtained from the Malaysian Oral Cancer Database and Tumour Bank System (MOCDTBS) provided by the Oral Cancer Research and Coordinating Center (OCRCC), University of Malaya, Malaysia. Cancer patients and control group demographic profiles (age, gender) and oral cancer risk habits (cigarette smoking, alcohol drinking, tobacco chewing) were used as input variables and the outcome refers to health condition of 'cancer' or 'healthy'. Through the MOCDTBS, peripheral blood was obtained from consented individuals, genomic DNA extracted and the GSTM1 and GSTT1 genotypes were determined using Polymerase Chain Reaction (PCR) and restriction enzyme digestion at the CARIF laboratory.

Demographic and disease variables of patients that were reported to be associated risk factors to oral cancer were used as the predictor variables in developing the fuzzy regression and fuzzy neural network prediction models. The full dataset were split randomly into a modeling dataset (65 percent of the total) and testing dataset (the remaining 35 percent).The dichotomous output refers to the health state of either "cancer" (1) or "healthy" (0). In this study a validation exercise was carried out involving twenty seven (27) oral cancer clinicians from the Faculty of Dentistry at the University of Malaya. The group of clinicians ranges from junior clinicians to professors. The validation exercise was pen and paper based where the oral cancer clinicians were asked to make predictions whether an individual will develop oral cancer based on several risk habit factors such as betel quid and tobacco chewing, cigarette smoking, alcohol drinking as well as patients' demographic profiles including age group and gender.

The objectives of this validation exercise were;

- To measure the prediction accuracy of human expert prediction
- To measure the prediction consistency of human predictions.

The two artificial intelligent prediction models were similarly tested by presenting them with the same 12 different input variable sets as used by the oral cancer clinicians in the validation exercise. The 12 input variable sets were made up of either single-input, two-input, three-input or four-input predictor sets based on the variables shown in Table 1.

Table 1: Input Variable Descriptions

Variable	Description
Smoke (S)	No=0
	Yes=1
Drink (D)	No=0
	Yes=1
Chew (C)	No=0
	Yes=1
Age group (A)	> 40 years : 0
	< 40 years : 1
Gender (G)	Female=0
	Male=1

RESULTS AND DISCUSSION

A Chi-squared concordance test was carried out to measure the consistency among oral cancer clinicians' predictions. The consistency or the concordance evaluation of the clinicians' prediction was done based on the Phi-value of the test. High Phi value together with p-value of less than 0.05 indicates high concordance or high consistency between the clinicians' predictions and vice versa.

Table 2 lists the Phi values when consistency in predictions based on 1-input variable sets and 4-input variable sets for clinician R1 was compared with the other 26 clinicians. For 1-input variable sets, clinician R1 was completely consistent with clinicians R11 and R22 only (7.69 percent). Consistency of clinician R1 with the other clinicians varies with 16 out of the 26 clinicians (61.5 percent) having high consistency with R1, while the remaining 8 (30.8 percent) showing low consistency relationship.

When the number of input predictor was increased to 4, none of the clinicians was found to have complete consistency with other clinicians involved in the validation exercise. The concordance test also shows that for predictions based on 4-input predictor variables the percentage of high consistency among clinicians also dropped from 61.5 percent to 50 percent (13 out of 26 clinicians found to have high Phi value when tested against clinician R1) and that leaves the remaining 50 percent having low consistency relationship to clinician R1.

Table 2: Measured prediction consistency between R1 and the other 26 oral cancer clinicians' predictions

Clinicians	Phi Value for 1-input variable sets	High Consistency	Phi Value for 4-input variable sets	High Consistency
R1&R2	.802	Yes	.818	Yes
R1&R3	.535	No	.522	No
R1&R4	.429	No	.499	No
R1&R5	.089	No	.351	No
R1&R6	.429	No	.533	No
R1&R7	.655	Yes	.732	Yes
R1&R8	.764	Yes	.605	No
R1&R9	.802	Yes	.614	No
R1&R10	.429	No	.454	No
R1&R11	1.000	Yes	1.000	Yes
R1&R12	.655	Yes	.529	No
R1&R13	.802	Yes	.790	Yes
R1&R14	.802	Yes	.706	Yes
R1&R15	.764	Yes	.680	Yes
R1&R16	.535	No	.248	No
R1&R17	.655	Yes	.522	No
R1&R18	1.000	Yes	.965	Yes
R1&R19	.218	No	.457	No

R1&R20	.655	Yes	.719	Yes
R1&R21	.802	Yes	.964	Yes
R1&R22	1.000	Yes	.965	Yes
R1&R23	.655	Yes	.889	Yes
R1&R24	.764	Yes	.402	No
R1&R25	.655	Yes	.732	Yes
R1&R26	.655	Yes	.523	No
R1&R27	.535	No	.719	Yes

Oral cancer experts' predictions and the two artificial intelligent models predictions on oral cancer susceptibility based on twelve (12) different input sets were measured. The accuracy, sensitivity and specificity of the models are summarized in Table 3. Definitions of accuracy, sensitivity and specificity are summarized in Table 4 and Table 5. Different predictor set was found to exhibit different prediction abilities. Comparison of the mean values of the accuracy, sensitivity and specificity for the models showed that fuzzy neural network prediction model has the lowest mean accuracy and mean sensitivity but the highest in mean specificity. Fuzzy regression prediction model has higher mean accuracy and mean sensitivity but lower mean specificity compared to oral cancer clinicians predictions.

Table 3: Prediction measurements based on accuracy, sensitivity and specificity for fuzzy regression (FuReA), fuzzy neural network (Fnn) and oral cancer clinicians (Occ).

	Accuracy			**Sensitivity**			**Specificity**		
	Occ	**Fnn**	**FuReA**	**Occ**	**Fnn**	**FuReA**	**Occ**	**Fnn**	**FuReA**
A	80	35	80	94.9	0	94.9	52.4	100	52.4
C	61.7	61.7	61.7	51.3	51.3	51.3	81	81	81
D	63.3	63.3	63.37	46.2	46.2	46.2	95.2	95.2	95.2
G	35	35	48.37	0	0	59	100	100	28.6
S	48.3	35	51.7	30.8	0	69.3	81	100	19.0
CS	71.7	61.7	61. 7	76.9	51.3	51.3	61.9	81	81
CD	75	75	75	74.4	74.4	74.3	76.12	76.2	76.2
CA	61.7	61.7	61. 7	51.3	51.3	51.3	81	81	81
CDS	71.7	70	75	76.9	66.7	74.4	61.9	76.2	76.2

CDA	75	75	75	74.4	71.8	74.4	76.2	71.8	76.2
ADCG	59.6	71.7	76. 7	37.5	66.7	89.74	95	81	52.4
ADCS	53.70	73.37	80	36.4	69.27	92.34	81	81	57.1
Mean Value	**63.1**	**59.9**	**67.5**	**54.2**	**45.5**	**69.0**	**78.6**	**85.3**	**64.7**

Table4: Measures of prediction performance

Measure	Description	Calculation
Accuracy	Probability to correctly classify outcome	$\frac{a+d}{a+b+c+d}$
Sensitivity	Probability to predict positive outcome when true state is positive	$\frac{d}{c+d}$
Specificity	Probability to predict negative outcome when true state is negative	$\frac{a}{a+b}$

Table 5: Conditions of terms used in the measurement of prediction performance

		Predicted Output	
		Negative	Positive
Observed Output	Negative	*a* (True Negative)	*b* (False Positive)
	Positive	*c* (False Negative)	*d* (True Positive)

Next, comparisons were made based on area under the receiver operating characteristic curves by grouping the single-input and two-input predictor set in one group and three-input and four-input predictor set in another as shown in Table 6 and Table 7. Common measures of discrimination are sensitivity, specificity and percent accuracy (Dreiseitl 2002). The area under the Receiver-Operating-Characteristics Curve (ROC) is normally used to depict the graphical representation of discrimination.

The receiver operating characteristics (ROC) was originally used for signal detection during the Second World War before it was used in medical diagnostic and prognostic tests (Hopley, 2001). The receiver operating characteristics (ROC) is used to determine the accuracy of predicted values and can be used across different classification tools (Abdul Kareem, 2002; Speight et al., 1995). The plot of an ROC curve shows the false positive rate on the x-axis and the 1 minus the false negative rate on the y-axis. It is normally termed as the sensitivity versus one minus specificity.

A good diagnostic test is one that has small false positive and false negative rates across a reasonable range of cut off values. A bad diagnostic test is one where the only cut offs that make the false positive rate low have a high false negative rate and vice versa. The larger the area, the better the diagnostic test is. An ideal test will have an AUC of 1 because it achieves both 100 percent sensitivity and 100 percent specificity (Lasko, 2005).

Table 6: Prediction measurements based on area under the receiver operating characteristic curves for fuzzy regression, fuzzy neural network and oral cancer clinicians on single-input and two-input predictor sets

Input Predictor	AUC for Occ	AUC for FuReA	AUC for Fnn
A	0.644	0.634	0.634
C	0.648	0.684	0.684
D	0.724	0.713	0.713
G	0.43	0.455	0.456
S	0.5	0.452	0.456
CS	0.6	0.672	0.675
CD	0.78	0.766	0.767
CA	0.724	0.782	0.782
Mean Value	**0.631**	**0.645**	**0.646**

Table 7: Prediction measurements based on area under the receiver operating characteristic curves for fuzzy regression, fuzzy neural network and oral cancer clinicians on three-input and four-input predictor sets

Input Predictor	AUC for Occ	AUC for FuReA	AUC for Fnn
CDS	0.619	0.81	0.785
CDA	0.779	0.826	0.816
ADCG	0.661	0.737	0.785
ADCS	0.465	0.824	0.828
Mean Value	**0.631**	**0.799**	**0.804**

Two different statistical measurements were employed in the comparison procedure namely the Analysis of Variance (ANOVA) for the 1-input and 2-input predictor sets and the Non-Parametric Mann-Whitney U test for the 3-input and 4-input variable sets. The ANOVA (An analysis of Variance) One-Way Between-Groups test was run by taking the areas under the receiver operating characteristic curves (AUC) values as the "dependent variable" and the three prediction models as the "factor". In the comparison carried out in this study the ANOVA test is appropriately used for comparing the differences in the areas under the receiver operating characteristic curves (AUC) values associated with the 1-input and 2-input variable sets since the normality assumption is satisfied as reflected by the p-values bigger than 0.05 for both the Kolmogorov-Smirnov and Shapiro-Wilk tests and by the skewness statistic values lying in the range of [-1,1] which indicate normality in distribution shown in Table 8.

Table 8: Test values for normality check for 1-input and 2-input variable sets

Model	Skewness		
		Kolmogorov-Smirnov	Shapiro-Wilk
Oral cancer clinicians	-.633	.168	.630
Fuzzy regression	-.848	.216	.117
Fuzzy neural network	-.845	.216	.109

The Tukey HSD ANOVA test results are tabulated in Table 9. A p-value of greater than 0.05 implies that the Null hypothesis H_0 is true and therefore H_0 is accepted. Accepting H_0 in this case implies that the means of the AUC values for the models are significantly similar ($\mu = 0$). Thus the prediction performance of fuzzy regression, fuzzy neural network and oral cancer clinicians' prediction models are found to be significantly the same for single-input and two-input predictor sets (p-values =1.0).

Table 9: The Tukey HSD ANOVA calculated p-values and comparison implication between fuzzy regression, fuzzy neural network and oral cancer clinicians' prediction for single-input and two-input predictor sets

Pair	p-value	Implication on comparison of Prediction performance
FuReA & Fnn	1.0	No Significant Difference
FuReA & Occ	1.0	No Significant Difference
Fnn & Occ	1.0	No Significant Difference

The Mann-Whitney U test results for the 3-input and 4-input variable sets are given in Table 10. Mann-Whitney U test is the non-parametric alternative to the *t*-test for independent sample commonly used for comparing the mean value for some variable of interest between two samples. A p-value of greater than 0.05 implies that the Null hypothesis H_0 is true and vice-versa. Thus the prediction performance of fuzzy regression prediction model is significantly the same as the prediction performance of fuzzy neural network model for 3-input and 4-input predictor sets. However, the prediction performance of both fuzzy regression and fuzzy neural network models are found to be significantly different from the prediction performance of oral cancer clinicians for 3-input and 4-input predictor sets (p-value=0.043 and p-value=0.02). Looking back at the mean AUC values (Table 5) we conclude that fuzzy regression and fuzzy neural network perform better in predicting oral cancer susceptibility in the given sample.

Table 10: Mann-Whitney U test calculated p-values and comparison implication between fuzzy regression, fuzzy neural network and oral cancer clinicians' prediction for three-input and four-input predictor sets

Pair	p-value	Implication on comparison of Prediction performance
FuReA & Fnn	1.0	No Significant Difference
FuReA & Occ	0.043	Significant Difference
Fnn & Occ	0.02	Significant Difference

CONCLUSION

Human experts' valuable knowledge and abilities in making predictions can never be replaced. This is a fact that cannot be mistaken especially in the medical and dental field. However, in many professional fields including medicine and dental, expertise is a scarcity and the documentation of knowledge is limited in practice. Furthermore, the ability of individual expert varies according to their previous knowledge and working experience. These are among the reasons why there have been an increased interest in implementing computer aids to decision making in areas such as dental prediction understudy. The argument is not whether the computer-based systems have the potential to exceed the performance of experts. This paper argues that the best system may yield results from the integration of specific domain expert knowledge with the machine learning approaches.

Good performance is one of the desired features in an artificial intelligent prediction tool for it to be useful for medical and dental diagnostic applications (Kononenko 2000). Good prediction performance of the fuzzy regression and fuzzy neural network prediction models measured in terms of the model calibration and discrimination ability were recorded in this study as compared to the human expert prediction performance. These results may set the foundation for future use of artificial intelligent prediction in oral cancer susceptibility in this country.

In conclusion, the findings of this study suggest that both fuzzy regression and fuzzy neural network models provide good alternative to human expert prediction in predicting oral cancer susceptibility. Hence the use of artificial intelligent prediction models is proposed as a suitable filtering system in identifying people at risk of oral cancer based on their risk habits and demographic profiles.

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