Original Article

A nomogram to predict adjuvant chemotherapy recommendation in breast cancer patients with intermediate recurrence score

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Abstract

Objective: The indication of adjuvant chemotherapy recommendation (ACR) in breast cancer patients with intermediate recurrence score (RS) is controversial. This study investigated the relationship between routine clinicopathological indicators and ACR, and established a nomogram for predicting the probability of ACR in this subset of patients.

Methods: Data for a total of 504 consecutive patients with intermediate RS from January 2014 to December 2016 were retrospectively reviewed. A nomogram was constructed using a multivariate logistic regression model based on data from a training set (378 cases) and validated in an independent validation set (126 cases). A Youden-derived cut-off value was assigned to the nomogram for accuracy evaluation.

Results: The multivariate logistic regression analysis identified that age, histological grade, tumor size, lymph node (LN) status, molecular subtype, and RS were independent predictors of ACR. A nomogram based on these predictors performed well. The P value of the Hosmer-Lemeshow test for the prediction model was 0.286. The area under the curve (AUC) values were 0.905 [95% confidence interval (95% CI): 0.876–0.934] and 0.883 (95% CI: 0.824–0.942) in the training and validation sets, respectively. The accuracies of the nomogram for ACR were 84.4% in the training set and 82.1% in the validation set.

Conclusions: We developed a nomogram to predict the probability of ACR in breast cancer patients with intermediate RS. This model may aid the individual risk assessment and guide treatment decisions in clinical practice.

Keywords: Intermediate recurrence score; adjuvant chemotherapy recommendation; nomogram; receiver operating characteristic (ROC); breast cancer

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Introduction

Over the past decade, prognostic assays based on multigene expression have been used in breast cancer to estimate the residual risk of recurrence following surgery to aid appropriate decisions regarding chemotherapy. The most widely used test is the 21-gene breast recurrence score (RS) assay, which is a reverse transcriptase polymerase chain reaction (RT-PCR) assay for 5 reference genes and 16 cancer-related genes, grouped into cell proliferation, invasion, human epidermal growth factor receptor 2 (HER2) and estrogen receptor (ER) categories (1). The

assay was initially validated to predict the likelihood of a 10-year recurrence risk and chemotherapy benefit in ER-positive, HER2-negative, lymph node (LN)-negative early breast cancer (EBC) patients (2-4).

Although originally validated and recommended for LN-negative diseases, retrospective evidence accrued thereafter also demonstrated its prognostic utility among selected patients with minimal LN involvement (1–3 positive nodes) (5,6). As a consequence, the 2015 National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Breast Cancer have incorporated the RS test into a clinical routine for LN-positive patients, specifically noting that this test can be considered for selected women with 1–3 involved ipsilateral axillary nodes, to guide the addition of combination chemotherapy to standard hormone therapy (7).

Based on the RS assay results, patients are traditionally categorized into low- (RS<18), intermediate- (RS 18–30) and high-risk (RS>30) groups following the retrospective analysis of NSABP B-14 trial (1). Patients in the high-risk category benefit significantly from adjuvant chemotherapy while those in the low-risk category do not. However, the advantage of chemotherapy in patients with intermediate RS is still uncertain (2). Currently, a prospective TAILORx trial is underway to evaluate the ability of RS to optimize therapeutic decisions for this subset of patients (RS 11–25), by randomizing enrolled participants with RS≤25 to receive hormonal therapy either alone or in combination with chemotherapy (3). WSG Plan B trial was the first to evaluate the efficacy of adjuvant chemotherapy (4 cycles of epirubicin plus cyclophosphamide followed by 4 cycles of docetaxel versus 6 cycles of docetaxel plus cyclophosphamide) in genomically intermediate/high-risk HER2-negative EBC. The final analysis of the trial showed an excellent 5-year disease-free survival (DFS) in intermediate RS tumors, which suggested potential overtreatment by chemotherapy (8). At present, treatment decision for patients with intermediate RS is multifactorial, and is based on both tumor characteristics (tumor grade and size, molecular subtype and LN status) and patients' characteristics (age, menopausal status, and performance status) (9). However, the results of multivariate analysis of adjuvant chemotherapy recommendation (ACR) are usually expressed as odds ratios (OR), which make it difficult to apply and calculate the probability of ACR for a specific patient.

To date, no statistical models have been reported to predict the likelihood of ACR in patients with intermediate RS. Nomograms have gained popularity in clinical practice and have been applied in individualized prognosis. They are statistical tools that provide the overall probability of a specific outcome for an individual patient. Factors associated with a defined event are incorporated in the nomogram and the calculated probability of the event occurrence is provided in graphical formats (10,11). This study aimed to identify clinicopathological predictors of ACR in breast cancer patients with intermediate RS, and to establish a nomogram for predicting the probability of ACR. This model might aid in avoiding potential overtreatment by chemotherapy in patients indicated with low ACR probability.

Materials and methods

Patients

EBC patients who underwent surgical treatment between January 2014 and December 2016 at the Shanghai Ruijin Hospital were retrospectively reviewed. The inclusion criteria were as follows: 1) female; 2) pathologically diagnosed invasive ductal carcinoma (IDC); 3) pT1b–T2; 4) pN0, N1mi or N1 [according to the MINDACT trial micrometastases measuring 0.2 to 2 mm were considered to be LN-positive in the following analysis (12)]; 5) ER and/or progesterone receptor (PR) positive tumors determined by immunohistochemistry (IHC); 6) HER2 negative; and 7) adequate formalin-fixed paraffin-embedded tissue available to perform the 21-gene assay and with an RS result of 11–30. The exclusion criteria included: 1) T1a, T3 or T4 tumor; 2) metastatic breast cancer; or 3) previous neoadjuvant treatment. The baseline data including age, tumor characteristics (tumor size, LN status, and histological grade: ER, PR, Ki67) and surgical information were retrieved.

This retrospective study was approved by the Ethical Committees of the Shanghai Ruijin Hospital. The results of this study do not affect the treatment decision of any patient enrolled. The written informed consent was obtained from the patients prior to data collection.

Pathological evaluation

Tumors were classified histologically according to the World Health Organization Classification of Tumors (13). Histological grade was evaluated according to the Elston and Ellis scoring system (14). Positive staining for ER/PR was defined as nuclear staining in ≥1% of the tumor cells (15). Negative HER2 status was considered as 0 to 1+ by

IHC or negative on fluorescence *in situ* hybridization (FISH) (16). Patients were subdivided into two different molecular phenotypes (luminal A and luminal B subtypes) according to the 2013 St. Gallen Expert Consensus (17).

Analysis of RS

The RS was analyzed from formalin-fixed, paraffin-embedded tissue as previously described (1). Briefly, micron tissue sections stained with hematoxylin and eosin (HE) were reviewed by a pathologist (XC Fei). A tumor-rich area in the tumor block was marked and manually microdissected with clean blades. RNA was extracted according to standard operating procedure for the 21-gene RS assay, and was subjected to gene-specific reverse transcription followed by quantitative RT-PCR reactions in 96 well plates using Applied Biosystems (Foster City, CA) 7500 Real-Time PCR System. Expression of each gene was measured in triplicate, and normalized relative to a set of five reference genes. Reference-normalized expression measurements range from 0 to 15, with a 1-unit increase reflecting approximately a two-fold increase in RNA. The RS, ranging from 0 to 100, was derived from the reference-normalized expression measurements for the 16 cancer-related genes (1). In order to further evaluate the effect of the cutoff point chosen in the retrospective analysis of the NSABP B-20 trial (RS results: 18–30) (2) and the ongoing prospective TAILORx trial (RS results: 11–25) (3), the enlarged intermediate category was defined as 11 to 30 in our study and was divided into three subcategories of 11 to 17, 18 to 25 and 26 to 30.

Outcomes

The outcome of nomogram was the probability of ACR in patients with intermediate RS. As the standard of care, the actual ACT decision was determined by multidisciplinary team (MDT) model, which is a critical part of the clinical practice in the management of complex malignancies. The make-up of MDT for breast cancer includes breast surgeons, medical oncologists, radiation oncologists, pathologists, and breast radiologists, as represented in the always popular "community tumor board". Breast cancer nurses (BCN) also have an important role in this model, providing information, psychological support, advocacy, and coordinating care through the pathway (18,19).

The operation flow of MDT in this study is as below: Following surgery and pathology assessment, upon receipt of the RS results, BCN coordinate a meeting of the MDT team members at a given time to discuss the given patients recently operated. After briefly introducing the patient's clinicopathological information by interns, the members vote for adjuvant therapies. The staff then discusses mainly the controversies or inconsistencies in treatment strategies based on the results of the primary vote. Finally, a secondary vote is completed, and the treating doctor informs the patients of the final decision.

Nomogram construction and validation

Univariate and multivariate logistic regression analyses were used to screen the predictors (20). Variables that were statistically significant ($P<0.05$) in the univariate logistic analysis of the training set were included in the multivariate logistic regression analysis, which was performed to screen independent predictors for ACR. Independent predictors ($P<0.05$ in the multivariate logistic regression analysis) were included in the nomogram construction. Hosmer and Lemeshow test was applied to assess the goodness of fit of the model, and $P>0.05$ indicated a good fit (21). The OR and 95% confidence interval (95% CI) were also calculated.

Evaluation of nomogram performance

The nomogram was validated internally in the training set and externally in the validation set. The internal validation was performed by a calibration method and receiver-operating characteristic (ROC) curves. The area under the curve (AUC) was calculated. The external validation was performed by calculating the AUC. The calibration plot with bootstrapping was used to illustrate the association between the actual probability and the predicted probability (22). Statistical differences between different AUCs were investigated by the DeLong method (23). All the statistical analyses and graphics were performed with the IBM SPSS Statistics (Version 20.2; IBM Corp., New York, USA) and R software (Version 2.11.1; R Foundation for Statistical Computing, Vienna, Austria). $P<0.05$ was considered statistically significant.

Results

Patient characteristics and predictors for ACR

The overall data from 504 breast cancer patients with intermediate RS were retrospectively analyzed. The mean age of the patients enrolled was 57 (range, 29–88) years. The patients enrolled were randomized 3:1 and divided

into a training set (n=378) and a validation set (n=126). Of the 504 patients, 255 (50.6%) were recommended for chemotherapy following the MDT discussion. The clinicopathological characteristics and the univariate logistic regression analysis of the total population, the training set and the validation set are shown in *Table 1*. Patients with younger age (≤50 years), larger tumor size, higher histological grade, LN involvement, luminal B subtype or higher RS were more likely to have ACR than the other patients (P<0.05). No significant difference in the ACR rate was observed among patients with different types of breast surgery (P=0.092). Univariate analysis of the training set and the validation set showed similar results compared with patients in the total population.

Associations between candidate predictive indicators and ACR were evaluated using multivariate logistic regression analysis. Predictors that were statistically significant (P<0.05) in the univariate logistic analysis were included in the multivariate logistic regression analysis. The results of the analysis indicate that age, histological grade, tumor size, LN status, molecular subtype and RS are independent predictors associated with ACR (*Table 2*).

Construction and validation of nomogram

Independent predictors identified in the multivariate logistic regression analysis (P<0.05), including age, tumor size, histological grade, LN status, molecular subtype and

Table 1 Clinicopathological characteristics and univariate logistic regression analysis of different variables predicting ACR of the total population, the training set and the validation set

Variables	Overall population				Training set				Validation set			
	Overall (N)	ACR (n)	ACR rate (%)	P	Overall (N)	ACR (n)	ACR rate (%)	P	Overall (N)	ACR (n)	ACR rate (%)	P
Total	504	255	50.6		378	184	48.7		126	71	56.3	
Age (year)				0.002				0.027				0.026
≤50	223	130	58.3		163	90	55.2		60	40	66.7	
>50	281	125	44.5		215	94	43.7		66	31	47.0	
Breast surgery				0.092				0.279				0.719
Lumpectomy	220	113	51.4		165	83	50.3		55	30	54.5	
Mastectomy	284	142	50.0		213	101	47.4		71	41	57.7	
Histological grade				<0.001				<0.001				<0.001
Low	65	16	24.6		53	13	24.5		12	3	25.0	
Intermediate	346	161	46.5		257	115	44.7		89	46	51.7	
High	93	78	83.9		68	56	82.4		25	22	88.0	
Tumor size				<0.001				<0.001				<0.001
pT1b	91	23	25.3		64	14	21.9		27	9	33.3	
pT1c	267	138	51.7		203	100	49.3		64	38	59.4	
pT2	146	94	64.4		111	70	63.1		35	24	68.6	
Node status				<0.001				<0.001				<0.001
pN0	398	169	42.5		296	119	40.2		102	50	49.0	
pN1mi–1	106	86	81.1		82	65	79.3		24	21	87.5	
Molecular subtype				<0.001				<0.001				<0.001
Luminal A	171	40	23.4		136	31	22.8		35	9	25.7	
Luminal B (HER2-neg)	333	215	64.6		242	153	63.2		91	62	68.1	
RS subcategory				<0.001				<0.001				<0.001
11–17	118	23	19.5		89	15	16.9		29	8	27.6	
18–25	256	122	47.7		191	87	45.5		65	35	53.8	
26–30	130	110	84.6		98	82	83.7		32	28	87.5	

ACR, adjuvant chemotherapy recommendation; HER2, human epidermal growth factor receptor 2; RS, recurrence score.

Table 2 Multivariate logistic regression analysis of variables

Variables	OR (95% CI)	P
Age (year)		
≤50	4.45 (2.25–8.79)	<0.001
>50	1	
Histological grade		<0.001
Low	1	
Intermediate	5.53 (2.27–13.51)	<0.001
High	11.85 (3.38–41.59)	<0.001
Tumor size		0.029
pT1b	1	
pT1c	1.18 (0.60–2.32)	0.627
pT2	3.56 (1.33–9.53)	0.012
Node status		
pN0	1	
pN1mi–1	12.03 (5.25–27.56)	<0.001
Molecular subtype		
Luminal A	1	
Luminal B (HER2-neg)	5.94 (2.98–11.85)	<0.001
RS*	1.30 (1.23–1.38)	<0.001

Variables with P<0.05 from the univariate logistic regression analysis predicting ACR were used. ACR, adjuvant chemotherapy recommendation; HER2, human epidermal growth factor receptor 2; RS, recurrence score; OR, odds ratio; 95% CI, 95% confidence interval; *, RS considered as a continuous variable, with the OR and 95% CI relative to an increment of 1 unit.

RS were utilized to construct the nomogram. The total points were calculated by summing up the points for each variable (top plotting scale). The ACR probability was subject to the total points (bottom plotting scale). The P-value for the Hosmer and Lemeshow test was 0.286, indicating that the model had a good fit. The final nomogram is shown in *Figure 1*. The calibration of the nomogram was performed internally by a calibration plot with bootstrap sampling (n=1,000) (*Figure 2*). The calibration plot of an accurate model may fall along the 45-degree line. Our bias-corrected curve was close to the ideal curve, which indicated that the nomogram was well calibrated. Next, the ROC was calculated to validate the nomogram internally in the training set (*Figure 3A*) and externally in the validation set (*Figure 3B*). The AUC was 0.905 (95% CI: 0.876–0.934) in the training set and 0.883 (95% CI: 0.824–0.942) in the validation set. The difference between the two AUCs was not statistically significant (P=0.132), illustrating that the predicted and observed ACR probabilities were in good concordance, and the goodness of fit of the nomogram was favorable.

The optimal cutoff values for the training and validation sets were 0.61 (sensitivity: 85.5%; specificity: 83.3%; positive predictive value: 83.7%; negative predictive value: 85.2%; accuracy: 84.4%) and 0.67 (sensitivity: 89.1%; specificity: 75.0%; positive predictive value: 78.1%; negative predictive value: 87.3%; accuracy: 82.1%), respectively.

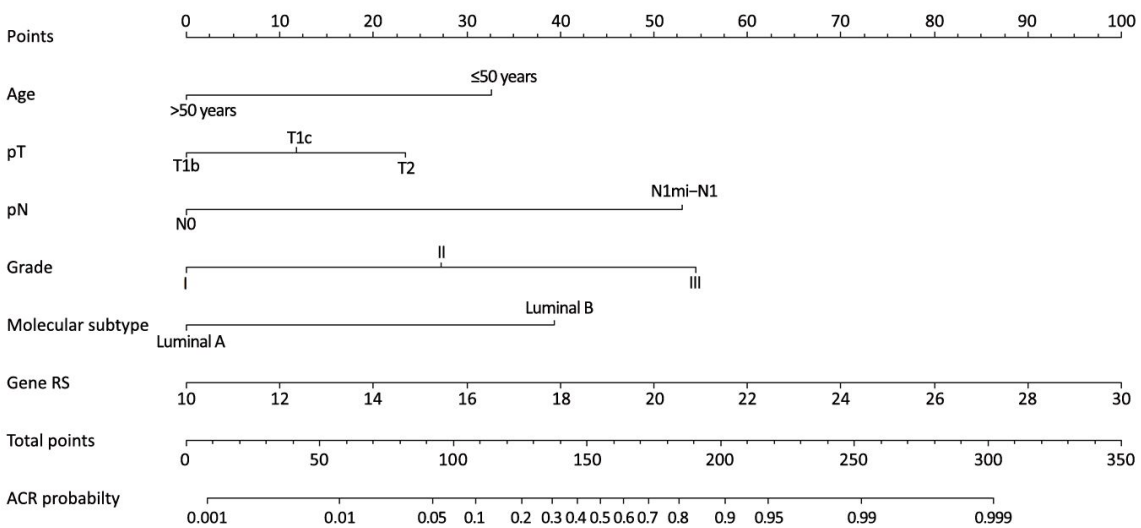

Figure 1 The nomogram predicting the probability of adjuvant chemotherapy recommendation (ACR) for patients with intermediate recurrence score (RS).

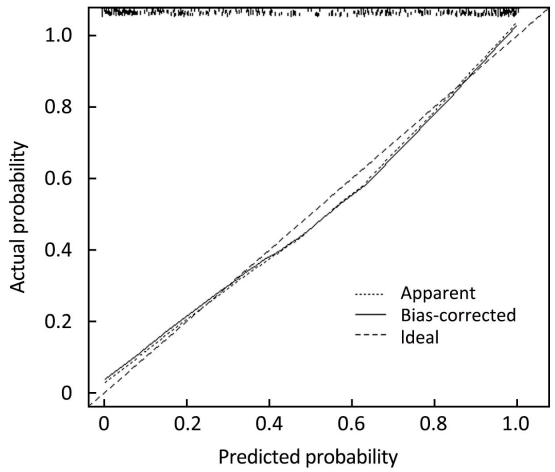

Figure 2 Calibration plot of the nomogram. The nomogram was calibrated for the probability of adjuvant chemotherapy recommendation (ACR) in patients with intermediate recurrence score (RS) (bootstrap 1,000 repetitions).

Discussion

Our results demonstrate that younger age, larger tumor size, higher histological grade, LN involvement, luminal B subtype and higher RS are associated with high ACR rates in patients with intermediate RS. The predictive value of each of the above-mentioned indicators was relatively poor, and we, therefore, combined the significant predictive indicators based on multivariate logistic regression analysis of the training set and developed a nomogram for evaluating the probability of ACR in this subset of patients. Furthermore, we validated the effectiveness of the nomogram using the second data set. The AUC values for the training and validation sets suggested that the nomogram performed well. We also proposed a cut-off value for ACR to help avoid potential overtreatment by chemotherapy. We believe that this user-friendly nomogram will be useful for risk assessment and could be the basis for individualized risk-adaptive therapy.

To date, few predictive models have been reported for breast cancer patients with intermediate RS. In 2011, Tang *et al*. (24) developed an online Recurrence Score Pathology-Clinical (RSPC) calculator, which is used in node-negative patients and combines RS with clinico-pathological variables including age, tumor size, grade, and planned adjuvant hormonal therapy. RSPC calculator is likely to have the greatest clinical utility in patients with intermediate RS by refining assessments of recurrence risk where RS and traditional measures are discordant and by reducing the number of patients classified as intermediate risk. In this study, the gene signature (GS) was combined into a nomogram on the basis of five important clinicopathological factors for better discrimination power (AUC=0.860 without RS). These results indicated that integration of clinicopathological factors with molecular features could enhance the prognostic power of risk assessments.

As expected, in our study, higher odds of recommending

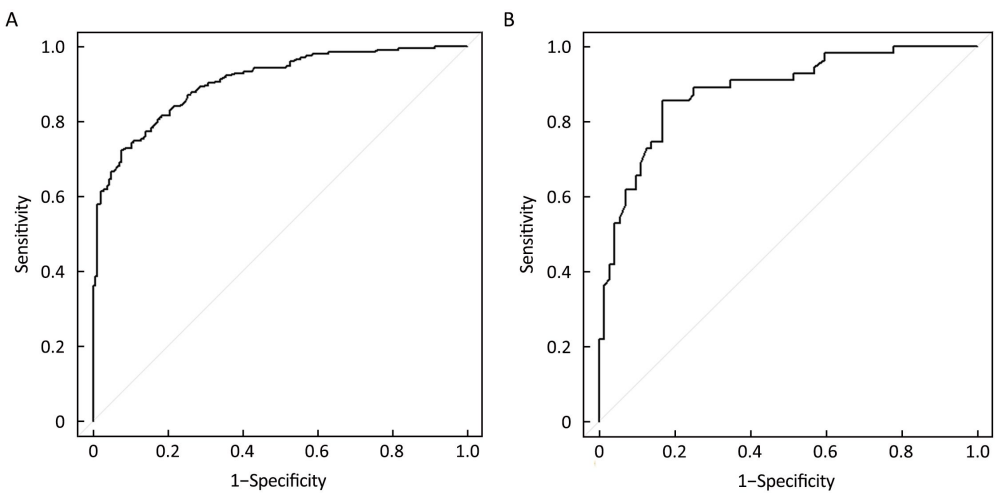

Figure 3 Validation of the nomogram. (A) Internal validation using the receiver operating characteristic (ROC) curve. The area under the ROC curve (AUC) is 0.905 [95% confidence interval (95% CI): 0.876–0.934]; (B) External validation using the ROC curve. The AUC is 0.883 (95% CI: 0.824–0.942).

chemotherapy were associated with younger age, larger tumor size, higher tumor grade, more nodes involvement and luminal B subtype. It is noteworthy that the RS result is an independent predictor of ACR in our study. Moreover, when the intermediate group was further subdivided, those with scores of 26 to 30 had a significant chance of receiving a chemotherapy recommendation than those with scores of below 25 (P<0.05). Our findings were concordant with those of Jasem *et al*., who evaluated the effect of RS cutoff point on chemotherapy decision. It was indicated that, when divided based on the cutoff point of 25 adopted by the TAILORx trial, those with an RS of 18 to 25 had significantly lower odds of chemotherapy recommendation compared with those with an RS of 26 to 30 (OR=0.32; 95% CI: 0.26–0.40) (25). These results suggested that clinicians evaluate the RS as a continuous parameter and do not consider all intermediate RS patients as having the same risk of recurrence.

Of note, in our study 20% of the enrolled patients are node-positive, of whom 18.9% were not recommended for chemotherapy. This finding supported the evidence that not all patients with the LN-positive disease have aggressive characteristics. In this context, the prospective RxPONDER trial was designed to test whether the difference of chemotherapy compared with no chemotherapy depends directly on RS score in patients with one to three positive axillary nodes, thus determining the optional cut point for recommending chemotherapy (26). Accrual is currently underway and outcomes are not yet available. However, in clinical practice, routine administration of adjuvant chemotherapy is still strongly proposed for women with node-positive breast cancer regardless of their tumor biology (27).

One strength of our study is that this nomogram can be used for predicting ACR with the combined TAILORx-trial (using a cutoff of 11 and 25) and the original cut-off score model (using a cutoff of 18 and 30). This nomogram, therefore, accommodates for the differences in the intermediate risk scoring results currently in use. We believe that this option gives our study an advantage over other studies which did not use the combination of original and TAILORx-trial cut-off values.

Lastly, our model is imperfect. This study was limited by the relatively small number of cases associated with the retrospective nature of the study. The data were collected from a single institution, and selection bias existed even though consecutive patients were included and eligibility criteria were performed to minimize the bias. Further prospective studies are therefore warranted to validate the suitability of this model for clinical practice.

Conclusions

The present study constructed a nomogram based on routine clinicopathological parameters and a GS (21-gene RS). This tool might help in predicting the probability of ACR in patients with intermediate RS and thus can assist clinicians in making adjuvant chemotherapy decisions.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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