To Evaluate the Applicability of Parameters of Cytological Grading Systems on Aspirates of Breast Carcinoma

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Abstract

Background: Fine-needle aspiration cytology (FNAC) is still an important first line diagnostic procedure in developing countries. FNAC of breast lesions is quite specific and sensitive investigation and the results are comparable to histopathology. Aim: To evaluate applicability of parameters of different cytological grading (CG) systems, for aspirates of breast cancers, and its correlation with histopathological grading parameters. Materials and Methods: A cross-sectional observational study was carried out on 30 female patients with ductal carcinoma breast, diagnosed on FNAC and subsequently confirmed histopathologically. The cytological smears were graded using six different cytological parameters/criteria described by Robinson et al. (Robinson grading system) and modified Scarff-Bloom-Richardson (SBR) grading system considering three parameters. The results of cytological grade (CG) were compared with parameters of gold standard modified SBR histological grading (HG) system. Results: Important influential cytological parameters to predict final RBS cytological score came out to be chromatin, nucleoli, nuclear size, cell uniformity, and cell dissociation with statistically significant $P$ value (0.0001) except for mitotic count. The important influential predictor of final SBR histological score is nuclear pleomorphism. Conclusion: SBR HG has good correlation with both RBS and SBR CG systems. The cytological nuclear grade provides important prognostic information which is very sensitive and equally specific hence should be done in breast aspirates and is now replaced by Core Needle biopsy. In developing country like India FNAC of breast aspirates still holds diagnostic value in the classification of breast lesions as compared to core guided image biopsy.

Keywords: Breast cancer, parameters, robinsons grading system, scarff bloom richardson grading

Introduction

Breast cancer is by far the most frequent cancer among women, with an estimated 1.67 million new cases diagnosed in 2012 (about 25% of all cancers). It is now the most common cancer both in developed (794,000 cases) and developing regions (883,000 cases). Breast cancer ranks as the fifth cause of death from cancer, but it is still the most frequent cause of cancer death in women in developing regions.[1] It is estimated that during 2012, about 144,937 new cases of breast cancer occurred in India, which accounts for 27% of all malignant cases with a mortality of 21.5% of all cancer cases.[2]

Now a day neoadjuvant therapy has become increasingly popular as primary medical treatment of breast cancer and much focus is being given to grading of tumors on fine-needle aspiration cytology (FNAC). The evaluation of cytological features is valuable because it would allow assessment of tumor in situ and prognosis of tumor so that the most suitable treatment could be selected and the morbidity associated with overtreatment of low grade tumors can be avoided.[3]

Objective

To evaluate the aspirates of breast cancer cases by Robinson’s and Scarff-Bloom-Richardson (SBR) grading system with correlation of the cytological grading (CG) and histopathological grading (HG).

Materials and Methods

Study design: Cross-sectional observational.

Study subjects: Thirty female patients diagnosed as ductal carcinoma breast on FNAC, later confirmed by histopathology.

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following modified radical mastectomy with lymph node dissection.

Sample size: Purposive sampling.

Study period and study setting: Female patients for a period of 5 years from 2010 to 2015 in a tertiary care teaching hospital of Uttarakhand government, India.

Methodology
FNAC of breast lumps was done using 22–23G needle, fixed to a 20 mL syringe. In present study, the smeared slides were immediately placed in 95% ethyl alcohol for fixation and later on stained with hematoxylin and eosin (H and E), Papanicolaou (PAP) stains. CG of breast carcinoma was done blindly without knowing the results of other grading systems. The grading was performed together (all pathologist observers) using a multihitere microscope, but the final grade was given to the most predominant feature.

The CG of breast carcinoma was done using the criteria described by Robinson et al.[4-6] It took into account six different cytological parameters; namely cell dissociation, nuclear size, cell uniformity, nucleolus, nuclear margin, and chromatin pattern. Each of these parameters was given a score of 1-3 and scores were added to get the final score. Grade 1 was given for a score ranging from 6 to 11, scores of 12-14 were graded 2, and grade 3 was given for a score ranging from 15 to 18. CG and histological grading (HG) were performed on stained FNAC smears and formalin-fixed paraffin-embedded H and E stained sections using SBR grading system also.[7] It used three parameters namely; tubule formation, nuclear pleomorphism, and mitotic count. The mitotic count was recorded as number of mitoses per high-power field in cellular areas using 40× objective lens with a field diameter and field area of 0.65 mm and 0.372 mm² respectively. Each of these parameters was assigned a score ranging from 1 to 3. The scores of each were then added together for a final sum that ranged between 3 and 9. The scores 3-5 was graded 1, 6-7 was graded 2, and score 8-9 was graded as 3.

The results of CG by Robinson’s Grading System and SBR system were compared with each other and with the results of gold standard modified SBR HG. The cell dissociation had been studied to evaluate its diagnostic importance.[5] The nuclear size was assessed by comparing with adjacent red blood cells (RBCs). The nuclear size was preferred to the cellular size because former is assessed more accurately in PAP and H and E stains. The nuclear pleomorphism was studied which is a subjective morphological variation of intra-sample nuclear size and shape and is different from nuclear size and shape evaluated morphometrically.[8] The presence and character of nucleoli were studied which is valuable in grading, both independently and in combination with other cytological features.[5]

The chromatin pattern was evaluated as it differentiates the nuclei of well and poorly differentiated breast carcinoma.[8] The tubule formation was identified not only by the presence of micro-acini, but also by the recognition of branching, elongated, three dimensional tubular structures and ringlet (when cross-sectioned), and if larger portions were aspirated intact, recognized as having syncytially arranged nuclei and well-defined borders. Mitotic counts: As in the SBR method, mitotic figures in metaphase, anaphase, and telophase were included excluding cells in prophase.

The mitotic count was done at the margins/periiphery of the tumor as this was the site of most active growth. Only definite mitotic figures in the invasive tumor component were counted, avoiding areas of necrosis, inflammation, in situ carcinoma, and tissue artifacts. The count was done on sufficiently large sample of cells and expressed as number of mitoses per 10 hpf.

Statistical analysis
Score was given to each of the parameters in the RBS/SBR cytology and in SBR histology. Finally, each of these scores were summed up to get the final score/grade. As the data was ordinal; therefore, the bivariate correlation analysis that is Spearman’s and Kendall tau had been used in the study to find the correlation among the three methods taking two at a time, i.e., RBS and SBR cytology, cytology and SBR histology, and SBR cytology and SBR histology.

Multiple linear regression analysis were carried out after bivariate correlation in finding out the influential predictors from among the different parameters used in the RBS and SBR cytology and SBR histology. Kappa agreement analysis was also used to find the agreement among the three methods for the different grades of breast carcinoma cases found on using the three methods. Here, the agreement analysis was not used to differentiate interobserver findings, but to differentiate the findings of grades of breast carcinoma found in three methods by the single observer only. Chi-square test was also used to find out the association of proportion of grades of breast carcinoma in each of the two cytological methods, i.e., RBS and SBR cytology and each of the cytological methods with the SBR histology, i.e., RBS and SBR histology and SBR cytology and SBR histology.

Ethical clearance: The ethical clearance for the study had been taken from the college institutional ethics committee.

Results
In the current study, the number of female patients with ductal carcinoma breast enrolled was 30 having mean age of 44 years. The minimum and maximum age of these patients was 25 years and 70 years respectively. The proportion of patients diagnosed preoperatively by the RBS cytology were—46.7% with grade 2 (N = 14/30) followed by 40% with grade 1 (N = 12/30) and 13.3% with grade 3 (N = 4/30). None of the patients had been diagnosed with grade 3 by SBR cytology as well as on gold standard SBR histology. The proportion of patients with grade 2 came out to be 63.3% (N = 19/30) and 66.7% (N = 20/30) by the SBR cytology and SBR histology respectively. The higher percentage of patients were diagnosed
with grade 2 (66.7%, N = 20/30) than with grade 1 (33.3%, N = 10/30) by the SBR histology [Table 1].

Except the statistically insignificant (P is 0.084) relationship observed with cell dissociation using Kendall’s tau correlation test, the relationship of all the cytological features taken in the RBS CG with the overall grade/score of breast carcinoma diagnosis by the RBS cytology was found to be statistically significant. The higher significant Spearman’s correlation was revealed with nucleoli (rho value is 0.672), followed by nuclear size (rho value is 0.669) and cell uniformity (rho value is 0.627).

Multiple regressions were carried out using stepwise method excluding the nuclear margin as cytological parameters. The important influential cytological parameters to predict the final RBS cytological score came out to be chromatin, nucleoli, nuclear size, cell uniformity, and cell dissociation with statistically significant P value (0.0001) obtained for all these parameters. The constant obtained in the regression analysis was used to form prediction equation using B coefficient of each of the parameters of RBS method [Table 2].

The relationship of mitotic count with the SBR cytological grade (CG)/score and the SBR histological grade/score was found to be statistically insignificant on applying both correlation tests (Spearman’s rank correlation and Kendall’s tau test) as compared to the significant relationship observed with the remaining two parameters of tubule formation and nuclear pleomorphism. The higher significant correlation value obtained was 0.729 for nuclear pleomorphism in both SBR cytology and SBR histology score followed by 0.667 for tubule formation in case of SBR cytology and 0.644 in SBR histology. In the multivariable model for finding the predictors of final SBR cytology score/histology, the mitotic count parameter had been excluded. The important influential predictor of final SBR cytological score was nuclear-pleomorphism (B value is 1.092) followed by tubule formation (B value is 0.715) with statistically significant P values. The important influential predictor of final SBR histology score was nuclear-pleomorphism (B value is 1.083) followed by tubule formation (B value is 0.700) with statistically significant P values. The constant obtained in the regression analysis was used to form prediction equation using B coefficient of each of the parameters of SBR cytology and SBR histology method [Table 3].

The absolute agreement, seen between the RBS cytology and SBR cytology grading, was 19/30 × 100 = 63.33% and between the RBS cytology/SBR cytology and SBR histology grading was 18/30 × 100 = 60.0% [Table 4]. The unweighted kappa value obtained was 0.455—signify that there is fair agreement between the RBS cytology and SBR cytology, 0.373-signify that there is less than fair agreement between the RBS cytology and SBR histology, 0.920-signify better agreement between the SBR cytology and SBR histology. The concordance rate for grade 1 and grade 2 breast carcinoma of each of the RBS and SBR cytology with the SBR histology was 58.3% and 78.5% respectively with overall concordance rate of 60%, while concordance rate for grade 1 and grade 2 breast carcinoma of the RBS with the SBR cytology was 66.7% and 78.5% respectively with overall concordance rate of 63.3%. The association between the proportion of grades in RBS cytology and SBR cytology, between RBS cytology and SBR histology, and between SBR cytology and SBR histology was significant statistically using chi square test of association [Table 4].

Moderate correlation was observed in the scores obtained by the RBS cytology and SBR cytology and the RBS cytology and SBR histology in grading the breast carcinoma as the rho value was between 0.40 and 0.70. The highest correlation was observed in the scores obtained by the SBR cytology and SBR histology in grading the breast carcinoma as the rho value was >0.7 [Table 5].

**Discussion**

Breast cancer is a malignant disease with a heterogeneous prognosis; evaluation of possible prognostic parameters is of growing interest. These include HG/type, lymph node status, lymphatic and vascular invasion, TNM (tumor, node, and metastasis) stage, cell proliferation index (proliferation markers: ki67, mib-1, and p53), hormone

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**Table 1: Distribution of breast carcinoma cases by the RBS cytology and SBR cytology grading and gold standard SBR histology**

| Grading of breast carcinoma aspirates | RBS cytology | SBR cytology | SBR histology |
|--------------------------------------|-------------|-------------|--------------|
|                                      | Number | %    | Number | %    | Number | %    |
| Grade 1 (Well-differentiated)        | 12      | 40.0 | 11     | 36.7 | 10     | 33.3 |
| Grade 2 (Moderately differentiated)  | 14      | 46.7 | 19     | 63.3 | 20     | 66.7 |
| Grade 3 (Poorly differentiated)      | 4       | 13.3 | 0      | 0    | 0      | 0    |
| Total                                | 30      | 100.0| 30     | 100  | 30     | 100  |

RBS: Robinson grading system, SBR: Scarff-Bloom-Richardson
receptor status.\textsuperscript{[5]} However, a seemingly constant criticism of histological tumor grading is that, it is a subjective evaluation and therefore inherently lacks consistency and reproducibility.\textsuperscript{[9]} Among other prognostic factors more reliance is given to overexpression of ER\textsubscript{α}- a well-established prognostic factor in breast cancer patients. Generally, ER\textsubscript{α}-positive breast cancers are associated with slow tumor growth, lower histology grade, DNA diploidy, and thus a better overall prognosis. Overexpression of the progesterone receptor (PR) indicates that the estrogen receptor (ER) pathway is intact, even if the tumor is reported as ER-negative.\textsuperscript{[10]} Amplification and/or overexpression of human epidermal growth factor-2 (HER2) oncogene are/is associated with higher tumor grade, a poor prognosis, and with axillary node-positive breast cancer.\textsuperscript{[11]} For node-negative patients, tumor size (>1–2 cm) is the most powerful prognostic factor and is routinely used to make adjuvant treatment decisions.

The acceptance of FNAC report reliability both by surgeons and pathologists allows for radical surgery on the basis of an FNAC diagnosis. Regrettably, instead of signing a more precise “surgical pathology” type diagnosis on FNAC, its widest application is limited to just categorizing the breast lesion as benign or malignant.\textsuperscript{[12,13]} Since treatment plans are frequently made preoperatively on the basis of FNAC diagnosis and neoadjuvant therapy has become increasingly popular as primary medical treatment of breast cancer. This necessitates as much prognostic information should be gleaned from cytology specimen as possible by perform grading on aspirates.\textsuperscript{[14]} Such grading would allow assessment of tumor in situ, so the most suitable treatment could be selected before the primary surgery, and the morbidity associated with overtreatment of low-grade tumors can be avoided.\textsuperscript{[5]}

The most reliable method for CG that closely reflects the most widely used HG system is yet to be determined. There are differing conclusions regarding different cytological parameters of CG. The nuclear size is assessed by comparing with adjacent RBCs.\textsuperscript{[13–15]} Use of morphometry for nuclear size though accurate, but time consuming hence not widely used.\textsuperscript{[16]}

The presence and character of nucleoli are valuable in grading both independently and in combination with other cytological features. An increase in the size and the number of nucleoli is a well-known characteristic of cells engaged in growth and synthesis.\textsuperscript{[13]}

The chromatin pattern differentiates the nuclei of well and poorly differentiated breast carcinoma. This might be related

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**Table 2: Bivariate correlation and multiple linear regression analysis for different cytological parameters of RBS score/grading**

| Cytological parameters | Spearman’s rho value | P   | Kendall’s tau value | P   |
|------------------------|----------------------|-----|---------------------|-----|
| Cell dissociation      | 0.437                | 0.016 | 0.300              | 0.084 |
| Nuclear size           | 0.669                | 0.001 | 0.582              | 0.001 |
| Cell uniformity        | 0.627                | 0.001 | 0.526              | 0.003 |
| Nucleoli               | 0.672                | 0.001 | 0.617              | 0.001 |
| Nuclear margin         | 0.430                | 0.018 | 0.515              | 0.004 |
| Chromatin              | 0.456                | 0.011 | 0.442              | 0.012 |

**Multiple Linear Regression**

| Predictors | Unstandardized B coefficient | t     | P   |
|------------|------------------------------|-------|-----|
| Cell dissociation | 0.798 | 6.757 | 0.001 |
| Nuclear size           | 1.052 | 6.890 | 0.001 |
| Cell uniformity        | 0.948 | 4.985 | 0.001 |
| Nucleoli               | 1.231 | 9.824 | 0.001 |
| Nuclear margin         | 1.188 | 6.316 | 0.001 |
| Chromatin              | 1.575 | 3.505 | 0.006 |

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**Table 3: Bivariate correlation and multiple linear regression for different parameters of SBR cytology and SBR histology**

| Parameters in SBR cytological grading | Spearman’s rho value | P   | Kendall’s tau value | P   |
|---------------------------------------|----------------------|-----|---------------------|-----|
| Tubule formation                      | 0.667                | 0.001 | 0.623              | 0.001 |
| Nucleopleomorphism                    | 0.729                | 0.001 | 0.420              | 0.024 |
| Mitotic count                         | 0.221                | 0.241 | 0.298              | 0.108 |

**Multiple linear regression for parameters of SBR cytology**

| Predictors | Unstandardized B regression coefficient | t     | P   |
|------------|----------------------------------------|-------|-----|
| Tubule formation | 0.715 | 5.814 | 0.001 |
| Nucleopleomorphism   | 1.092 | 7.513 | 0.001 |
| Constant          | 1.640 | 4.150 | 0.001 |

| Parameters in SBR histological grading | Spearman’s rho value | P   | Kendall’s tau value | P   |
|---------------------------------------|----------------------|-----|---------------------|-----|
| Tubule formation                      | 0.644                | 0.001 | 0.614              | 0.001 |
| Nucleopleomorphism                    | 0.729                | 0.001 | 0.420              | 0.024 |
| Mitotic count                         | 0.221                | 0.241 | 0.298              | 0.108 |

**Multiple linear regression for parameters of SBR histology**

| Predictors | Unstandardized B regression coefficient | t     | P   |
|------------|----------------------------------------|-------|-----|
| Tubule formation | 0.700 | 5.799 | 0.001 |
| Nucleopleomorphism   | 1.083 | 7.605 | 0.001 |
| Constant          | 1.707 | 4.277 | 0.001 |
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Table 4: Association of proportion of grades in the different cytological and histological classification and the concordance rate and the agreement analysis

| RBS cytology grading | SBR cytological grading | Total | Agreement analysis | Condonce rate |
|----------------------|-------------------------|-------|--------------------|---------------|
|                      | Grade 1 | Grade 2 | Grade 3 |               |               |
| Grade 1              | 8       | 4       | 0       | 12             | Kappa value P |
| Grade 2              | 3       | 11      | 0       | 14             | 0.455 0.020 8/12 × 100=66.7% |
| Grade 3              | 0       | 4       | 0       | 4              |               |
| Total                | 11      | 19      | 0       | 30             | -19/30 × 100=63.3% |

The Chi-square likelihood ratio value χ is 9.605, df=2, P is 0.008

Table 5: Correlation observed in scores obtained by the RBS cytology and SBR cytology

| Criteria             | RBS cytology | SBR cytology |
|----------------------|--------------|--------------|
| Minimum score        | 9.00         | 5.00         |
| Maximum score        | 15.00        | 7.00         |
| Mean score           | 12.63        | 5.87         |
| Standard deviation   | 1.69         | 0.73         |
| Standard error of mean | 0.308   | 0.133        |

Spearman’s rho value is 0.629, P=0.001

| Criteria             | RBS histology | SBR histology |
|----------------------|--------------|--------------|
| Minimum score        | 9.00         | 5.00         |
| Maximum score        | 15.00        | 7.00         |
| Mean score           | 12.63        | 5.90         |
| Standard deviation   | 1.69         | 0.71         |
| Standard error of mean | 0.308   | 0.12         |

Spearman’s rho value is 0.597, P=0.001

| Criteria             | SBR histology | SBR histology |
|----------------------|--------------|--------------|
| Minimum score        | 5.00         | 5.00         |
| Maximum score        | 7.00         | 7.00         |
| Mean score           | 5.87         | 5.90         |
| Standard deviation   | 0.73         | 0.71         |
| Standard error of mean | 0.13        | 0.12         |

Spearman’s rho value is 0.964, P=0.001, SBR: Scarff-Bloom-Richardson

to subjectivity in assessment of this characteristic as well as limitation of our eye resolution in detection of subtle grades of nuclear chromasia and granularity with the light microscope.[14]

Threshold for number of mitosis for each point in the scoring system was arbitrarily lowered in cytological application of the SBR grading system, because, mitosis are seen less frequently in aspirates than in surgical biopsy material. The relative absence of mitosis may be because these cells are more fragile and less likely to survive smear preparation or because fewer cells are examined by FNA than with biopsy, so mitosis is less likely to be detected.[7] For convenience mitosis has been arbitrarily divided into four phases—prophase, metaphase, anaphase, and telophase. In the SBR method, mitotic figures in metaphase, anaphase, and telophase are included, excluding cells which are in prophase would avoid possible confusion with apoptotic cells and intratumoral lymphocytes.[17]

The clefts induced by shrinkage artifact should not be mistaken for tubular structures.[8] The majority of discordance between CG and HG was observed in grade 3 tumors (0/4). Of the four cases grades as grade 3 by CG, none were graded as grade 3 by HG and all were graded as grade 2 it is clear that a total of 12 cases (40.0%) showed discordant grading and in the majority of cases there is one grade difference. Similar results were obtained by Das et al.[9]

Robinson’s grading system, in our study too grade 2 46.6% being the most common followed by grade 1 (40%) and grade 3 (13.3%). The important influential cytological parameters to predict the final RBS cytological score came out to be chromatin, nucleoli, nuclear size, cell uniformity, and cell dissociation with statistically significant P value obtained for all these parameters.

According to SBR HG systems in our study 66.6% of cases were graded as grade 2 (66.6%) followed by grade 1 (33.3%) and no case was found to be in grade 3. In most of the studies, a large number of patients have been placed in grade 2. This is
one of the limitations of SBR grading in which there is unequal distribution of patients among the three grades with over 50% of patients in grade 2. Furthermore, even though there is a relatively clear prognostic separation between grade 1 and grade 3, grade 2 patients often overlap with grade 1 or grade 3. Dousal et al. documented that duct differentiation was the lowest predictor whereas nuclear pleomorphism and mitotic index are the highest predictors of survival.[29]

Regarding concordance of Robinson’s CG with HG, the present study showed 58.3% concordance in grade 1, and 78.5% concordance in grade 2. The overall concordance of CG with HG is 60% which is comparable with other published data. The original study by Robinson et al.[20] found only 57% concordance, while Das et al.[19] [Table 6], Sinha[21] and Lingegowda et al.[22] found 71.2%, 73.0%, and 64.0% concordance between CG and HG respectively. However, Kaushik Sha et al. in 2013 compared six CG system and concluded that absolute concordance or percent agreement between CG and HG was maximum (77.19%) in both Robinson’s and Mouriquand’s system but the kappa value (0.62) of agreement was more favorable in case of the former because of more objective set of criteria and easy reproducibility.[23]

In our study, all cases were under graded by one grade while no case was two grades over graded. The lower absolute concordance percentage of RBS cytology and SBR histology may be due to the subjective nature of the investigators doing cytological and histological evaluation of the breast carcinoma specimens and less number of cases studied. In CG, much importance have been given to multiple nuclear features like nuclear size, nucleoli, nuclear membrane, and chromatin pattern in contrast to histological grade, in which nuclear feature is only one component. By applying strict criteria of different parameters more consistent grading can be obtained, giving good prognostic information.

In our study better agreement is there between the SBR cytology and SBR histology since the unweighted kappa value obtained is 0.920. Correlation between SBR cytological and histological score is 96.4% and the disparities in the cytological grade and histological grade in some cases were chiefly due to difficulties in detecting mitosis or tubules in fine needle aspiration (FNA) smears. Tubule formation was difficult to assess in FNA smears; this might be responsible for over grading on FNA smears. The difficulty in identification of mitosis in the aspirated material could be the cause of under grading on cytology.

**CONCLUSION**

The important influential cytological parameters to predict the final RBS cytological score came out to be chromatin, nucleoli, nuclear size, cell uniformity, and cell dissociation with statistically significant P value obtained for all these parameters. The important influential predictor of final SBR histological score is nuclear pleomorphism followed by tubule formation with statistically significant P values. The highest correlation is seen between SBR cytological and histological score with less significant correlation observed between RBS cytological and SBR histological score.

**Limitations**

Despite the FNAC of breast aspirates as diagnostic and prognostic importance, the current study fails to show the prognostic value of FNAC as none of the grade 3 ductal carcinoma revealed who can be considered for the administration of neoadjuvant therapy.

Also, the number of female breast ductal carcinoma cases was only 30 enrolled in 5 years period and hence the study findings recommends the future research in this direction with more number of patients so as to reveal both the diagnostic and prognostic value of FNAC.

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**Conflicts of interest**

There are no conflicts of interest.

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