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Deep Learning in Breast Cancer Molecular Subtyping: Recent Advances and Clinical Translation

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Abstract: Breast cancer, as the second most prevalent malignancy among women in China, necessitates molecular subtyping for precision treatment decisions. While traditional biopsies face limitations due to invasiveness and spatial heterogeneity, deep learning demonstrates significant potential in enhancing non-invasive subtype prediction through automated feature extraction and multimodal data fusion. This review comprehensively summarizes recent advances in radiomics research and DL applications across mammography, MRI, and ultrasound imaging for predicting breast cancer molecular subtypes. It critically evaluates the strengths and limitations of existing methodologies, providing a reference framework for future DL-based research and clinical implementation of non-invasive subtyping approaches.

Keywords: Breast Neoplasms; Radiomics; Deep Learning; Molecular Subtyping.

1. Introduction

Breast cancer (BC) ranks as the second most common malignancy among women in China, with approximately 357,200 newly diagnosed cases reported in 2022. According to the National Cancer Center's 2024 report, BC caused about 75,000 deaths, making it the fourth leading cause of cancer-related mortality among Chinese women, thereby posing significant impacts on their health and quality of life [1].

2. Overview of the Development of Molecular Classification in Breast Cancer

The traditional histological classification of breast cancer is based on characteristics such as tumor cell morphology, structure, and growth patterns, categorizing it into eight types, including ductal carcinoma *in situ* and invasive ductal carcinoma. However, breast cancer is highly heterogeneous; even cases with similar histological morphologies can exhibit significant differences in genetic profiles and biological behaviors among different subgroups [2].

Driven by advancements in molecular biology and the demand for precision medicine, the classification of breast cancer has shifted from traditional clinicopathological staging towards assessing intrinsic molecular subtypes. In 2000, Perou et al[3] first utilized gene expression profiling to classify breast cancer into Luminal, Human Epidermal Growth Factor Receptor 2 (HER2)-enriched, Basal-like, and Normal breast-like subtypes. In 2003, Sorlie et al [4] further refined the Luminal subtype into Luminal A and Luminal B based on the expression patterns of 85 genes. Subsequently, a subtype characterized by the absence or very low expression of three key biomarkers—Estrogen Receptor (ER), Progesterone Receptor (PR), and HER2—was defined as Triple-Negative Breast Cancer (TNBC) [5].Numerous statistical studies have revealed significant associations between these distinct molecular subtypes at the genetic level and various clinicopathological features—such as tumor size, histological grade, and lymph node metastasis status—as well as prognosis [6, 7]. Specifically, Luminal A and B subtypes generally respond well to endocrine therapy and have a more favorable prognosis. The HER2-enriched subtype is often treated with a combination of surgery, chemotherapy, and anti-HER2 targeted therapy. In contrast, the Basal-like subtype (which largely overlaps with TNBC) is typically aggressive, prone to recurrence and metastasis, and exhibits sensitivity to chemotherapy but resistance to endocrine and targeted therapies, resulting in the poorest prognosis. Therefore, predicting the molecular subtype is crucial for formulating precise and individualized treatment strategies.

3. The Predictive Value of Deep Learning for Molecular Subtyping of Breast Cancer

Deep learning, a branch of machine learning, is an advanced image analysis technique in the field of computer vision. Its core principle involves automatically learning the inherent patterns and hierarchical representations from sample data. By mimicking the connectivity of neurons in the human brain, DL constructs neural networks capable of analysis and learning. This is achieved by building multi-layer neural networks and optimizing their parameters using algorithms like backpropagation, enabling end-to-end feature learning and circumventing the limitations of manual feature design [8-10]. Prominent DL models include Multilayer Perceptrons (MLPs), Convolutional Neural Networks (CNNs), and Recurrent Neural Networks (RNNs). Since 2012, DL has rapidly expanded within the medical field. Its core value lies in automated feature extraction and multi-modal data integration [11]. Currently, the application focus in clinical oncology is significant, where DL plays an important role in areas such as disease diagnosis and prognosis prediction [12-15].

In the field of diagnosis, imaging modalities such as mammography, ultrasonography, and MRI are widely used as auxiliary tools [16, 17]. Traditional radiomics involves extracting high-throughput imaging features from medical images to create high-dimensional datasets. By analyzing and

mining the information within images of regions of interest, it quantifies image heterogeneity indiscernible to the human eye, thereby extracting clinically significant features that indirectly characterize tumor biology and treatment response. This supports disease diagnosis, staging, and prognosis assessment. However, this method has a triple limitation: reliance on manual processes leading to omission of deep biological information, low workflow efficiency, and susceptibility to errors. In contrast, deep learning models, through their end-to-end architecture, enable direct mapping from raw images to predictive outcomes. They can automatically learn multi-scale features and, within multi-task learning frameworks, simultaneously integrate multi-modal imaging, genomic, and clinical data [18-21]. This advances the transformation of imaging diagnostic systems into tools for precision treatment decision-making. However, current research methods suffer from non-standardized aspects such as single-center design, multi-modal data confounding, algorithm variability, and sample heterogeneity, which limit the reproducibility of results. This systematic review summarizes the methodologies and conclusions of radiomics-based studies, aiming to provide a theoretical framework for future standardized research.

4. Application of Deep Learning in Molecular Subtyping of Breast Cancer

4.1. Mammography

Owing to its prominent advantage in accurately identifying early-stage microcalcifications, mammography has become a fundamental tool for breast cancer screening in women over 40. Consequently, it is currently a major platform for applying artificial intelligence (AI) technologies aimed at improving the precision of calcification detection [22, 23]. To date, the primary mammographic technologies in use include Full-Field Digital Mammography (FFDM), Digital Breast Tomosynthesis (DBT), and Contrast-Enhanced Spectral Mammography (CESM).

With the integration of multi-modal imaging and AI, researchers are exploring more accurate predictive models for molecular subtyping, thereby establishing a link between imaging features and molecular characteristics. Mota et al [24] proposed a deep learning prediction model based on mammography. Utilizing an improved ResNet-101 architecture, they analyzed 1,397 mammographic images from patients. By employing transfer learning and data augmentation to optimize the model's generalizability, it achieved an accuracy of 89.79% (AUC 73.31%) in the binary task of distinguishing HER2-positive from HER2-negative subtypes, significantly outperforming its classification of other subtypes (e.g., TNBC accuracy was only 65.25%). However, this study did not incorporate clinical parameters such as age, family history, and hormone levels, which are independent predictive factors, thereby limiting further improvement in predictive performance. Liu Siteng et al [25] developed a CNN model based on DL features extracted from preoperative mammograms. They also established a combined model integrating these DL features with independent clinical predictive factors. The results demonstrated that the combined model achieved good consistency between predictions and actual outcomes, with higher AUC (0.97) and clinical net benefit in the training set compared to the DL model alone. Gong Yue et al [26] integrated features from both FFDM and DBT to construct DL models based on three pre-trained CNNs: ResNet50, DenseNet121, and ResNet101. The results confirmed that among the three DL models, the ResNet50 model performed best (AUC=0.894). Furthermore, the integrated DL model combining 2D and 3D features, as well as the comprehensive model combining imaging and clinical data, showed AUC values ranging from 0.920 to 0.878 and 0.922 to 0.883, respectively. These findings collectively demonstrate that models combining clinical and imaging data can effectively distinguish between HER2-expressing and non-HER2-overexpressing patients. The aforementioned studies indicate a positive predictive role for mammography-based models in breast cancer molecular subtyping to a certain extent. However, previous research has predominantly focused on analyzing intratumoral features, lacking in-depth investigation of the peritumoral region. Therefore, Zhang Yongxia et al [27] developed a radiomics-deep learning fusion model based on CESM to predict TNBC. This model combined an optimal radiomics model based on both intratumoral and a 9mm peritumoral region with an optimal DL model utilizing a transfer learning strategy based on a pre-trained ResNet34. The fused model achieved an AUC of 0.91. This study explored the value of features extracted from different views, phases, and particularly the peritumoral area. Existing research confirms that combined models integrating clinical and imaging features can significantly enhance predictive performance. It preliminarily validates that multi-modal techniques like DBT and CESM can reflect tumor angiogenesis through enhancement patterns, thereby establishing associations with molecular characteristics like HER2 overexpression. Nevertheless, current X-ray-based deep learning approaches show insufficient systematic recognition of subtypes such as TNBC and Luminal A/B. Additionally, neglecting peritumoral tissue information may lead to the loss of critical data regarding tumor aggressiveness and microenvironment changes. Future work could leverage mammography's precise identification of calcifications and structural distortions – features often associated with Luminal subtypes – to develop more discriminative morphological analyses. Furthermore, efforts should focus on developing deep learning models capable of simultaneously capturing both intratumoral and peritumoral features.

4.2. Breast MRI

Owing to its advantages of being free from ionizing radiation damage and providing multi-planar imaging capabilities, Magnetic Resonance Imaging (MRI) has become a highly sensitive imaging modality for diagnosing, guiding treatment planning, and evaluating treatment response in breast cancer (BC) patients [28]. The imaging mechanism of Dynamic Contrast-Enhanced MRI (DCE-MRI) primarily stems from the biological characteristic of BC where microcirculation alterations occur early. By tracking hemodynamic changes, DCE-MRI quantifies parameters such as time-signal intensity curve types and the volume transfer constant, revealing microvascular permeability and perfusion function in the lesion area [29]. Compared to conventional contrast-enhanced MRI, DCE-MRI not only clearly depicts tumor morphology but also provides an objective quantification of metabolic functional differences between the lesion and normal glandular tissue. This offers a new imaging basis for tumor segmentation, mass detection, benign-malignant discrimination, and molecular subtyping

[29]. Furthermore, in Diffusion-Weighted Imaging (DWI), the high cellular density of tumor cells significantly restricts water molecule diffusion, leading to a lower Apparent Diffusion Coefficient (ADC) in malignant lesions compared to normal tissue and a correspondingly increased DWI signal. This imaging technique indirectly reflects tumor aggressiveness by measuring and assessing the microscopic changes in water molecule diffusion [30, 31]. Currently, multi-parametric MRI analysis, which integrates functional imaging techniques like DCE-MRI and DWI, has become an important research direction for exploring breast cancer heterogeneity and molecular subtyping [31].

Ha et al [32] collected pre-treatment DCE-MRI images from 216 breast cancer patients to develop a CNN model for predicting all four major molecular subtypes, achieving an AUC of 0.871. However, the study was limited by a small and imbalanced sample size for subtypes like HER2+/Basal-like, which affected the model's generalizability. Furthermore, using only a single post-contrast time point meant key hemodynamic and microvascular functional information was overlooked. To address the underutilization of temporal information, Zhang et al [33] developed a Convolutional Long Short-Term Memory (CLSTM) model based on DCE-MRI data from five time points (pre- and post-contrast). Their results demonstrated that the CLSTM model achieved a training accuracy of 0.91, outperforming traditional CNN models. Additionally, they proposed a cross-center transfer learning strategy to tackle data heterogeneity from multiple institutions, which substantially improved the model's classification accuracy from 0.4–0.5 to 0.78–0.91, thereby enhancing its generalizability. This experiment confirmed the high precision of CLSTM in handling long-sequence imaging like DCE-MRI and validated the adaptability of deep learning models in clinical diagnostic scenarios. Information from a single MRI sequence is limited, and traditional radiomics models often ignore the complementary nature of multi-sequence data. Consequently, Ba et al [34] constructed a multi-sequence fusion Deep Neural Network (DNN) using pre-operative DCE-MRI and non-monoexponential model DWI (NME-DWI) for the non-invasive prediction of breast cancer molecular subtypes. Their model employed a dual-channel feature extraction architecture, using convolutional layers to learn morphological and hemodynamic features from DCE-MRI, and cellular structure and diffusion heterogeneity features from NME-DWI, respectively. A channel attention mechanism was also incorporated to adaptively weight and fuse the multi-sequence information. Experiments showed that the dual-sequence fusion model effectively discriminated between the five major subtypes, demonstrating particularly high discriminatory power for the HER2-enriched (AUC > 0.85) and triple-negative (AUC = 0.85) subtypes. However, distinguishing morphologically similar Luminal subtypes still required optimization by incorporating clinical parameters like Ki-67. This study pioneered the fusion of DCE-MRI and NME-DWI, overcoming the limitations of conventional monoexponential DWI models and enabling precise quantification of multidimensional features in the tumor microenvironment. A limitation was the uneven distribution of samples across different molecular subtypes, potentially reducing the model's generalizability for minority subtypes, and all data came from a single institution, lacking external multi-center validation. Addressing the challenge of misclassifying morphologically similar subtypes in benign vs. malignant discrimination, Yu et al [35] conducted a multi-center study. They developed a bimodal model that fused intratumoral and peritumoral radiomic features with deep transfer learning features. The study found that the fusion model achieved an AUC of 0.950 on the internal test set and 0.921 on an external independent test set, significantly outperforming models using only intratumoral or peritumoral features. Peritumoral features were particularly sensitive to microenvironmental changes in non-luminal tumors, achieving a specificity of 88.9% in distinguishing Luminal B HER2-negative subtype, effectively mitigating classification disputes caused by ambiguous Ki-67 expression levels.

HER2-low expression represents a novel category of targetable breast cancer, characterized by low HER2 protein expression without gene amplification, rendering it resistant to traditional anti-HER2 therapies but potentially responsive to antibody-drug conjugates (ADC) [36]. Addressing the pressing need for precise HER2-low grading to guide targeted therapy, Li et al [37] innovatively proposed a multimodal prediction framework integrating a DCE-MRI 3D habitat model with deep learning. They segmented lesions from 340 patients into three biological subregions based on perfusion levels (high, medium, low), extracted heterogeneity features such as spatial distribution entropy and the proportional volume of each perfusion subregion, and combined these with deep learning features from ResNet50 and independent clinical predictors to build a composite model. Results demonstrated that this composite model achieved an AUC of 0.912 on the validation set for distinguishing HER2-positive from HER2-negative cases. More importantly, in the more challenging task of grading HER2-low versus HER2-negative, its AUC increased to 0.917, significantly outperforming any single-modality model. A key finding was that a medium-perfusion habitat volume exceeding 40% strongly correlated with the patchy enhancement pattern typical of HER2-low expression, suggesting its potential as a non-invasive imaging biomarker. This approach could potentially avoid targeted therapy omission in 86% of patients caused by spatial sampling heterogeneity in biopsy. This study is the first to achieve synergistic integration of 3D tumor heterogeneity mapping with deep learning, providing an interpretable decision-making tool for the precise selection of candidates for ADC therapy. However, it remains limited by its retrospective design and potential missing multimodal data. Future prospective multi-center trials and biological validation of HER2 expression spatial heterogeneity are warranted to further enhance the model's efficacy.

In summary, multi-parametric MRI provides multidimensional information on tumor microvascular formation, perfusion heterogeneity, and cellular density. Preliminary studies have begun exploring single-sequence 3D habitat models to identify, define, and quantify biological subregions, offering a critical foundation for enhancing the predictive accuracy of deep learning models.

However, these models commonly suffer from issues such as class imbalance and insufficient external validation. Furthermore, most studies have not adequately integrated key pathological indicators and independent clinical predictors, which limits their discriminative capability.

Future efforts should focus on integrating temporal features from dynamic contrast-enhanced imaging across multi-center, large-sample cohorts, with a dedicated emphasis on incorporating habitat characteristics derived from multi-parametric analysis.

4.3. Breast Ultrasonography

Ultrasonography is a form of real-time examination. Due to differences in sound wave transmission and reflection properties between normal breast tissue and lesions, it can clearly depict the internal morphological structures of the breast, providing auxiliary information for assessing the size, shape, location, and vascularity of breast masses [38]. Current techniques include conventional 2D ultrasonography, color Doppler ultrasonography, contrast-enhanced ultrasound (CEUS), elastography, and 3D ultrasonography. These modalities have their own emphases and are often used in combination in clinical practice to improve the early detection rate and diagnostic accuracy of breast cancer. Ultrasonography, characterized by its low cost, ease of implementation in primary care settings, and facilitation of large-scale data accumulation, aligns well with the requirement of radiomics for large sample sizes. It is also suitable for high-frequency dynamic monitoring, facilitating the construction of longitudinal models. Furthermore, being radiation-free and not requiring routine contrast agents, it can cover sensitive populations such as pregnant women and patients with renal insufficiency, giving it a broader range of application [39, 40].

Jiang et al [41] integrated preoperative ultrasound images from multi-center patients and constructed a deep learning model using the ResNet-50 architecture. Results showed the model achieved an accuracy of 0.98 in identifying Luminal A subtype in the test set. Furthermore, the study used Grad-CAM heatmaps for visual interpretation, confirming that the model focused on pathologically relevant areas such as tumor margins and microcalcifications. This work first validated the feasibility of predicting molecular features from conventional B-mode ultrasound images using deep learning.

The Boulenger team [42] built a lightweight convolutional neural network based on transfer learning and a channel attention mechanism to achieve non-invasive prediction of TNBC using conventional ultrasound images. The model employed a two-stage optimization strategy, first pre-training a general feature extractor on a large natural image dataset, and similarly incorporated Grad-CAM heatmap visualization to enhance clinical interpretability. Validation showed the system achieved an AUC of 0.86, significantly outperforming traditional CAD (Computer-Aided Diagnosis) systems. It was also found that morphological features of TNBC, such as oval shape and posterior acoustic enhancement, could be effectively captured by the DL model, while CDFI hemodynamic parameters provided more discriminatory value for the HER2-overexpressing subtype. However, a limitation was the single-center data source and insufficient sample size, necessitating future multi-center prospective trials to address performance degradation due to data heterogeneity. Zhou et al [43] developed an Assembled Convolutional Neural Network (ACNN) model to predict the status of key molecular biomarkers in breast cancer. This model was a combined framework integrating three CNNs: DenseNet121, ResNet50, and SENet50. The study compared the predictive performance of a unimodal model using only grayscale ultrasound images, a bimodal model combining grayscale and color Doppler images, and a multimodal model incorporating grayscale ultrasound, color Doppler, and shear-wave elastography information. Results indicated that the ACNN model with multimodal input demonstrated excellent discriminative ability in differentiating the four molecular subtypes, achieving AUC values between 0.89 and 0.99 in the validation and test sets, outperforming preoperative core needle biopsy. This ensemble strategy effectively combined the characteristics of different base networks, enabling the extraction and fusion of complementary feature information from diverse imaging modalities. However, the study did not explore the application of the Transformer architecture, transfer learning techniques, or other high-performance CNN models. Qian et al [44] constructed a multimodal deep learning model named BMU-Net. By integrating mammography, trimodal ultrasound, and clinical data, they established a tree-like hierarchical risk assessment system, achieving refined stratification from basic benign/malignant discrimination down to molecular subtyping. The model utilized CNNs to extract local lesion features and employed Transformer's cross-modal attention mechanism to fuse multi-source data. To address the common clinical issue of missing data, an innovative random masking training strategy was introduced. The model achieved an overall accuracy of 90.1% for molecular subtype risk stratification, approaching the 92.7% accuracy of histopathology. Particularly for BI-RADS 4a cases (the diagnostic "gray zone"), it significantly reduced unnecessary biopsies by 20%.Huang et al [45] developed a Deep Learning Radiopathology (DLRP) multimodal framework by fusing preoperative ultrasound images and whole-slide histopathological images. This model demonstrated significant advantages in the early differentiation between Luminal and non-Luminal breast cancer subtypes, achieving a test set AUC of 0.90. Its diagnostic performance was markedly superior to any single-modality model. The experiments showed that a deep learning architecture integrating macroscopic ultrasound features and microscopic pathological information possesses superior discriminatory capability.

In recent years, ultrasound-based deep learning models have proven capable of effectively extracting information relevant to molecular subtyping from morphological, hemodynamic, and elastographic features, demonstrating high discriminatory performance. However, most current methods still rely on static images and fail to fully leverage the potential of real-time, dynamic ultrasound imaging containing temporal information. Future efforts should prioritize the development of deep learning models capable of analyzing temporal features, such as time-intensity curves from Contrast-Enhanced Ultrasound (CEUS) and dynamic imaging sequences, to more comprehensively capture tumor biological characteristics and enhance the accuracy and clinical utility of molecular subtyping predictions.

5. Black-Box Decision-Making

Black-box prediction refers to the non-interpretable decision-making process between input data and output results in machine learning or deep learning models. It is characterized by non-transparent internal processes such as feature extraction, weight assignment, and decision logic, making the basis for predictions untraceable and the results difficult to understand or verify. In breast cancer radiomics, this problem manifests as models potentially relying on non-causal features like equipment artifacts or background noise for diagnosis, rather than genuine pathological markers. This can trigger a clinical trust crisis and misdiagnosis risks. Consequently, Explainable AI (XAI) techniques are required to decipher these models and establish transparent decision chains aligned with medical logic. Currently, the primary model interpretation methods are SHAP (SHapley Additive

exPlanations) and LIME (Local Interpretable Model-agnostic Explanations) [46-48].

Crombé et al [49] integrated quantitative radiomics from multiparametric MRI with the SHAP explainable framework to analyze the decision logic for all molecular subtypes. Their approach revealed that the HER2+ subtype relied heavily on malignant calcifications (highest SHAP value), while the triple-negative subtype was associated with homogeneous enhancement patterns. This effectively addressed the black-box limitations of traditional machine learning models. Furthermore, Zhou et al [50] built an explainable XGBoost model based on multiparametric MRI from 1,024 breast cancer patients across multiple centers. Using SHAP, they quantified the decision contributions of the peritumoral edema zone (SHAP +0.43) and necrotic area (SHAP +0.41), achieving efficient discrimination between Luminal and non-Luminal subtypes (AUC=0.88). However, the study overlooked key indicators like the Ki-67 index and PR expression, resulting in low discriminative power within the Luminal subtypes themselves. Future work could integrate such data to enhance the model's ability to identify the Luminal B HER2- subtype.

Technologies like SHAP and LIME have significantly enhanced the transparency and clinical acceptability of black-box models, providing a crucial foundation for understanding model logic and establishing trustworthy diagnostic pathways. However, they are still limited to post-hoc explanations and require further validation in complex, highly heterogeneous multi-center clinical scenarios. Future efforts should focus on developing modeling frameworks with greater intrinsic interpretability, advancing XAI towards a priori design to enhance its reliability in real-world healthcare environments.

6. Summary and Outlook

Current advancements in radiomics and deep learning technologies have progressed beyond single-parameter or single-sequence studies, increasingly favoring multi-modal and multi-temporal fusion analyses, as well as subgroup analyses within the same pathological type. Deep learning is transitioning from a passive diagnostic tool to an active decision-making aid in predicting breast cancer molecular subtypes. A core breakthrough lies in its ability to quantify tumor heterogeneity through multi-modal image fusion, offering the potential for non-invasive tools that could replace traditional biopsies. However, a significant gap remains between existing technologies and the goal of effectively assisting clinical diagnosis and enabling precise personalized treatment. This can be summarized into three major challenges(1) Generalization Ability Hampered by Data Heterogeneity: The sample distribution across different molecular subtypes is often imbalanced. Existing DL models heavily depend on retrospective datasets and lack validation from prospective, multi-center studies. This makes it difficult to verify their dynamic performance in real-world clinical workflows and to demonstrate their value in optimizing clinical decision-making pathways. Furthermore, variations in equipment hardware and operator techniques lead to heterogeneity in image resolution and information fidelity. When models are applied to data from new institutions or different scanners, the stability of their identification of key features decreases, posing a severe challenge to generalization. (2) Limitations of Single Imaging Modalities: While research on subtyping based on various breast imaging techniques is advancing, the principles and formats of different imaging technologies vary. A single imaging modality is often insufficient to fully characterize the morphological and functional features of breast tissue.

(3) Insufficient Algorithm Interpretability Hindering Clinical Adoption: The decision-making process of deep neural networks lacks transparency. Further research is needed on how to enable clinicians and patients to understand and trust the model's predictions.

Looking ahead, efforts should focus on establishing high-quality databases with standardized image acquisition and annotation protocols to address data heterogeneity and provide a foundation for algorithm optimization. Deep integration of multi-modal data with genomics, proteomics, immunomics, and other multi-omics data is essential to overcome the limitations of single imaging modalities. Simultaneously, priority should be given to solving the "black box" problem of DL models by enhancing their interpretability and visualization, thereby increasing their reliability and acceptability in clinical practice. Driven by innovations in artificial intelligence algorithms and interdisciplinary convergence, the technology for non-invasively assessing breast cancer molecular subtypes based on imaging features and deep learning will ultimately achieve deep clinical integration. This promises not only to replace some invasive diagnostic procedures but also to provide crucial decision support for formulating individualized treatment plans.

Conflicts of Interest Statement

All authors declare that they have no conflicts of interest.

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