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Experts' Cognition-Driven Ensemble Deep Learning for External Validation of Predicting Pathological Complete Response to Neoadjuvant Chemotherapy from Histological Images in Breast Cancer

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Abstract: In breast cancer, neoadjuvant chemotherapy (NAC) provides a standard treatment option for patients who have locally advanced cancer and some large operable tumors. A patient will have a better prognosis when he has achieved a pathological complete response (pCR) with the treatment of NAC. There has been a trend to directly predict pCR to NAC from histological images based on deep learning (DL). However, the DL-based predictive models numerically have better performances in internal validation than in external validation. In this paper, we aim to alleviate this situation with an intrinsic approach. We propose an experts' cognition-driven ensemble deep learning (ECDEDL) approach. Taking the cognition of both pathology and artificial intelligence experts into consideration to improve the generalization of the predictive model to the external validation, ECDEDL can intrinsically approximate the working paradigm of a human being, which will refer to the various working experiences to make decisions. ECDEDL was validated with 695 whole slide images (WSIs) collected from the same center as the primary dataset to develop the predictive model and perform the internal validation, and was also validated with 340 WSIs collected from three other centers as the external dataset to perform the external validation. In external validation, ECDEDL improves the AUCs of pCR prediction from 61.52(59.80–63.26) to 67.75(66.74–68.80) and the accuracies of pCR prediction from 56.09(49.39–62.79) to 71.01(69.44–72.58). ECDEDL was quite effective for external validation of predicting pCR to NAC from histological images in breast cancer, numerically approximating the internal validation.

Keywords: ensemble deep learning, external validation, pathological complete response, neoadjuvant chemotherapy, breast cancer

1. Introduction

With the advances of deep learning (DL) [1], mostly deep neural networks [2–4] which are the state-of-the-art machine learning techniques, various studies have shown that DL-based artificial

intelligence (AI) models have significant effectiveness and potentials in medical diagnostic or prognostic prediction [5–8]. There has been an increasingly standardized paradigm of constructing DL-based AI models for medical diagnostic or prognostic prediction: Primarily, clinical data and corresponding diagnostic and prognostic results are collected as a training dataset. Subsequently, a DL architecture is selected and optimized on the collected training dataset to produce a DL-based AI model that can predict the diagnostic or prognostic results corresponding to the clinical data; Finally, the produced DL-based AI model is validated on some new data that contain clinical data and corresponding diagnostic and prognostic results unseen in the training dataset.

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Particularly, the validation procedure is an essential part in the constructing paradigm, for it can reflect the expected predictive performance and generalization of the produced DL-based AI model in practical usage. The data required by the validation procedure can be internal or external. Specifically, the internal data is assumed to have the same distribution while the external data is assumed to have a different distribution, compared with the training data collected for producing the DL-based AI model. Usually, we say that the data for the validation procedure are internal and have the same distribution compared with the training data when the data for the validation procedure and the training data are collected from the same centers, since they share common data production in the same centers. On the contrary, we say that the data for the validation procedure are external and have a different distribution compared with the training data when the data for the validation procedure and the training data are collected from different centers, since they probably have uncommon data production in different centers. The validation procedure is called internal validation when provided with internal data, or external validation when provided with external data. Both internal validation and external validation are essential [9–13], since internal validation can reflect the feasibility of constructing a DL-based AI model for a medical diagnostic or prognostic prediction task while external validation can reflect the potentials of the constructed DL-based AI model for a wider usage in practice.

In breast cancer, neoadjuvant chemotherapy (NAC) [14, 15] provides a standard treatment option for patients who have locally advanced cancer and some large operable tumors. In clinical trials, it has been shown that a patient will have a better prognosis when he has achieved a pathological complete response (pCR) with the treatment of NAC to reduce the tumor burden and promote breast-conserving surgery [16]. In breast cancer imaging, there has been a trend to directly predict pCR to NAC from histological images using DL [17]. Following the paradigm of constructing DL-based AI models for medical prediction, which has been described in the first paragraph of this section, existing studies [18–22] have provided alternative solutions for predicting pCR from histological images in breast cancer. The application of these alternative solutions can be summarized as directly building the predictive model from the histological images via DL.

However, it has been a commonly known problem that the AI models constructed for medical prediction numerically have better performances in internal validation than in external validation, which significantly affects the clinical safety of using AI models [23]. The primary reason for this situation lies in that the distribution of the external data for validation is different from the distribution of the training data for the construction of the predictive model, due to the significant variance of slide preparation and microscope scanning. This issue is also known as sample selection bias [24, 25] in statistics with small data, or out-of-distribution validation [26] and domain adaption/generalization [27–30] in machine learning with big data. According to Luo et al. [31], the out-of-distribution problem of external validation, i.e., the problem of domain generalization is the primary challenge for DL in breast cancer imaging. Therefore, it is important and necessary to investigate advanced approaches for the out-of-distribution problem of external validation in breast cancer imaging.

The usual methods for alleviating this out-of-distribution problem of external validation in breast cancer imaging can be divided into three categories [31], including data augmentation via color distortion [32, 33], domain adaption from source domain to target domain via adversarial learning [34, 35], and domain

generalization via feature alignment and domain-invariant feature learning [36–38]. Having shown promising potentials to provide alternative solutions for external validation of predicting pCR to NAC in breast cancer from histological images, these existing usual methods for as well have some limitations. Data augmentation via color distortion usually can only imitate certain aspects of variance due to the complex situation of the slide preparation and microscope scanning. Domain adaption via adversarial learning requires some image samples of the target domain in advance, which is not suitable for the situation where the target domain is unseen. Domain generalization via feature alignment and domain-invariant feature learning does not require some image samples of the target domain in advance, however, only a very few methods have been particularly proposed for tasks in medical analysis [39–42]. These approaches can be summarized as addressing the problem via making the internal data and external data less different, without targeting at the pattern that probably will not change underlying both the internal data and the external data.

In addition to these three categories of usual methods, Ogier du Terrail et al. [43] and Sarma et al. [44] have proposed to employ federated learning [45–47] to improve performance in multicenter DL without data sharing, which have shown that federated learning can help to provide alternative solutions relevant to the out-of-distribution problem of external validation in medical prediction. However, a federated learning solution requires each of the multiple centers constructs a predictive model, and it also needs a central system to manage communications between the predictive models of the multiple centers for testing in practical usage. As a result, federate learning is a technique that is more appropriate to solve the problem of data privacy among multiple centers and requires high expenses in the meantime. Thus, federated learning is theoretically less intrinsic for external validation via requiring more managing and computing resources to be implemented.

We observe that these existing alternative methods have the paradigm that is different from the working paradigm of a medical expert. Usually, a pathological expert commonly will refer to his cognition, that has been accumulated via different working experiences, about the medical data at hand to make decisions. The out-of-distribution problem of the external data commonly will not affect a well-trained expert that much to make usual decisions, since a first-class expert is unlikely to become a third-class expert in practice because of the distribution change of data. Due to these insights, we argue that an intrinsic approach needs to be proposed for addressing the out-of-distribution problem in external validation.

In this paper, we propose an experts' cognition-driven ensemble deep learning (ECDEDL) approach for external validation of predicting pCR to NAC from histological images in breast cancer. The proposed ECDEDL, which takes the cognition of both pathology and AI experts into consideration to improve the generalization of the predictive model to the external validation, has three innovations: (1) Proposing a data preparation strategy that takes into account the cognition of pathology experts about viewing a histological image in breast cancer, which results in a Tumor dataset and a Stroma dataset respectively extracted from histological images; (2) Proposing a learning paradigm that takes into account the cognition of AI experts about exploiting complementary information among the pathologically variant contents of histological images to improve the generalization of the predictive model, which results in an ensemble DL [48] framework; (3) Constructing a new approach for the external validation of predicting pCR to NAC from histological images in

breast cancer, by integrating the proposed pathology experts' cognition-driven data preparation strategy and the proposed AI experts' cognition-driven learning paradigm. Regarding these three innovations, the proposed ECDEDL approach is different from the existing approaches [39–44] for the out-of-distribution problem of external validation in medical prediction.

Since the cognition of both pathology and AI experts have been taken to construct the predictive model, the proposed ECDEDL approach, to some extent, approximates the working paradigm of a human being which will refer to his various working experiences to make decisions. As the cognition of experts is less likely to be affected by data distribution shift in practice, the proposed ECDEDL approach for external validation is more likely to be invariant to the significant variance of slide preparation and microscope scanning of the external data.

As far as we know, this paper is the first that has proposed an experts' cognition-driven approach, which is particularly for addressing the out-of-distribution problem in external validation. On the basis of the task of predicting pCR to NAC from histological images in breast cancer, the contributions of this work include the following: (1) Proposing a novel ECDEDL approach for external validation; (2) Implementing and evaluating the proposed ECDEDL approach for improving the performance for external validation; (3) The proposed ECDEDL approach shows significant effectiveness in improving the performance for external validation.

2. Materials and Methods

This section is structured as follows: Primarily in Section 2.1, we give descriptions for the components of the proposed ECDEDL approach; Subsequently in Section 2.2, we present specific implementation details of ECDEDL. Finally, in Section 2.3, we discuss the evaluating strategy of ECDEDL for external validation.

2.1. Proposed ECDEDL

ECDEDL constitutes of a pathology experts' cognition-driven data preparation strategy, an AI experts' cognition-driven learning paradigm, and the feeding relation between them. The methodology of ECDEDL for external validation of predicting pCR to NAC from histological images in breast cancer is shown in Figure 1.

2.1.1. Pathology experts' cognition-driven data preparation strategy

We propose a data preparation strategy which respectively extracts a Tumor dataset and a Stroma dataset from the collected histological images. This data preparation strategy is established by referring to the cognition of pathology experts about viewing a histological image in breast cancer, which is that tumor and stroma are likely to be paid more attention than the whole content of the histological image and can probably possess potential predictive ability for predicting pCR to NAC from histological images in breast cancer. Moreover, Li et al. [49, 50] have shown that tumor and stroma areas of histological images in breast cancer can both be predictive for pCR to NAC. Proving that the cognition of pathology experts indeed can have effectiveness in constructing appropriate DL-based AI models for medical prediction, Li et al. [49, 50] just can explain the rationality of the proposed pathology experts' cognition-driven data preparation strategy for the external validation of predicting pCR to NAC from histological images in breast cancer.

2.1.2. AI experts' cognition-driven learning paradigm

We propose an AI experts' cognition-driven learning paradigm which is an ensemble DL framework. This learning paradigm is established by referring to the cognition of AI experts about exploiting complementary information among the pathologically variant contents of histological images to improve the generalization of the predictive model, which can be realized via ensemble learning [48, 51, 52] based on data manipulation, which is an effective basis for the realization of ensemble learning. Moreover, some researches [29, 30, 53–55] have shown that ensemble DL has the potential in addressing the out-of-distribution problem of external validation. Proving that the cognition of AI experts can also have effectiveness in constructing better DL-based AI models, these researches [29, 30, 53–55] just can explain the rationality of the proposed AI experts' cognition-driven learning paradigm for the external validation of predicting pCR to NAC from histological images in breast cancer.

2.1.3. Feeding relation for construction of ECDEDL

Based on the pathology experts' cognition-driven data preparation strategy proposed in Section 2.1.1 and the AI experts'

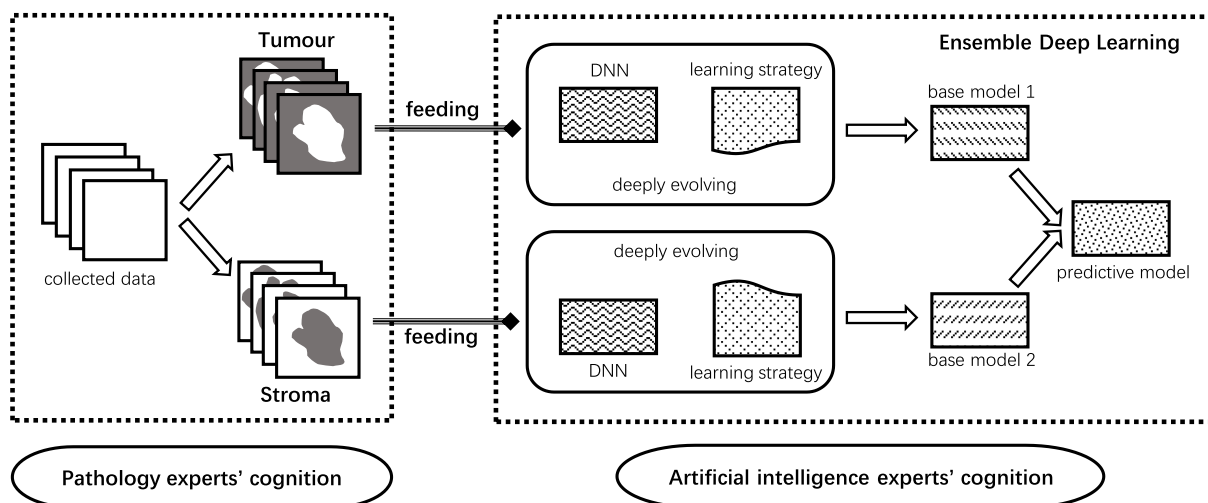


Figure 1. Outline of the proposed ECDEDL approach for external validation of predicting pCR to NAC from histological images in breast cancer

Table 1. Summarization of data basis and preprocessing.

Total 1035 WSIs				
Primary dataset (695 WSIs from the same center)		External dataset (340 WSIs from other 3 centers)		
Training dataset (555 WSIs)		Internal dataset (140 WSIs)		
Total (32556 tiles)		Total (6981 tiles)		
Training (26045 tiles)	Validation (6511 tiles)			
Per WSI (59 tiles on average)		Per WSI (50 tiles on average)	Per WSI (54 tiles on average)	
Model development		Internal validation	External validation	

cognition-driven learning paradigm proposed in Section 2.1.2, we constructed ECDEDL by feeding the Tumor and Stroma datasets of the data preparation strategy to ensemble DL framework of the learning paradigm as the data manipulation basis, as the Tumor and Stroma datasets of the data preparation strategy naturally fit the data manipulation basis for the ensemble DL framework of the learning paradigm.

2.2. Implementation details of ECDEDL

2.2.1. Data basis and preprocessing

The histological images used in this study to evaluate ECDEDL for external validation are the same as Li et al. [50], in which more details are provided. The used histological images were 1035 whole slide images (WSIs) collected from four centers. Among the 1035 WSIs, 695 WSIs collected from the same center are used as the primary dataset to develop the predictive model and perform the internal validation, and the rest 340 WSIs collected from other three centers are used as the external dataset to perform the external validation. More details are available at Li et al. [50] in 2022. Among the primary dataset, 555 WSIs are used as the training dataset to develop the predictive model, and the rest 140 WSIs are used as the internal dataset to perform the internal validation.

As a WSI usually contains many repetitive and less informative regions, pathological experts were invited to annotate representative regions containing tumor and stroma on each of the collected WSIs. The annotated representative region is called region of interest (ROI), which ensures that the stroma inside the ROI was near the tumor and surrounded by tumor cells. Small images from the ROIs annotated on each of the collected WSIs were cropped at $233 \times 233 \mu\text{m}$ squares (256×256 pixels at $10 \times$ magnification), which are called “tiles”. More details about how the ROIs were annotated, readers can refer to Li et al. [50] in 2022.

The data basis and preprocessing can be summarized as Table 1.

2.2.2. Technical details

For the preparation of the Tumor and Stroma datasets, we used a previously developed image segmentation tool to extract the Tumor and the Stroma contents from the collected histological images tiles. Readers can refer to Yang et al. [56] in 2024, for the technical details of the used image segmentation tool. Some examples of the Tumor and Stroma datasets extracted from the original histological image tiles are shown in Figure 2.

For the implementation of the ensemble DL framework, two key points need to be considered: (1) the settings of deep convolutional neural network (DNN) architecture and learning

strategy for generating base models and (2) the ensembling criterion for forming the final predictive model. For point (1), we employ existing state-of-the-art DNNs [57] and corresponding learning strategy to generate base models. More specifically, we respectively employed MobileNetV2 [58], ResNet101V2 [59], and NASNetLarge [60] as the DNN architecture from light weight to complex, which will be further discussed in the next section of evaluating ECDEDL for external validation.

The details of the learning strategy include, optimizer: SGD [61] with learning rate = 0.001, momentum = 0.9; batch size: 16; epochs: 256; online augmentation: horizontal flip = True, vertical flip = True, rotation range = 10, zoom range = [0.8, 1.2], width shift range = 0.2, height shift range = 0.2, brightness range = [0.7, 1.3]; and weighted cross-entropy loss. For point (2) we employ weighted average strategy to integrate the predictions of the base models for forming the final predictive model. More specifically, we weighted the base models according to their individual predictive performance (default is fifty-fifty).

For the evolvement of ECDEDL, we firstly used the corresponding learning strategy to optimize the DNN architecture to produce two base models, respectively feeding the prepared Tumor and Stroma datasets to the DNN architecture. Then, based on the produced two base models, we weighted and averaged their predictions to form the final prediction.

2.3. Evaluating strategy of ECDEDL for external validation

We respectively trained four series of predictive models for predicting pCR to NAC from histological images in breast cancer. The trained four series of predictive models include the following: (1) the predictive model produced by training the given DNN architecture based on the original prepared data, examples of which are shown in Figure 2(A); (2) the predictive model produced by training the same DNN architecture based on the Tumor dataset, examples of which are shown in Figure 2(B); (3) the predictive model produced by training the same DNN architecture based on the Stroma dataset, examples of which are shown in Figure 2(C); (4) the ensemble model of the predictive models respectively produced based on the Tumor and Stroma dataset, which represents the ECDEDL approach.

The four series of predictive models were trained with the same learning strategy described in Section 2.2.2. We respectively denote the four series of predictive model as Direct model, Tumor model, Stroma model, and TS-Ensemble model. We validate and compare their performances using different metrics, to show the effectiveness of the ECDEDL approach for external validation.

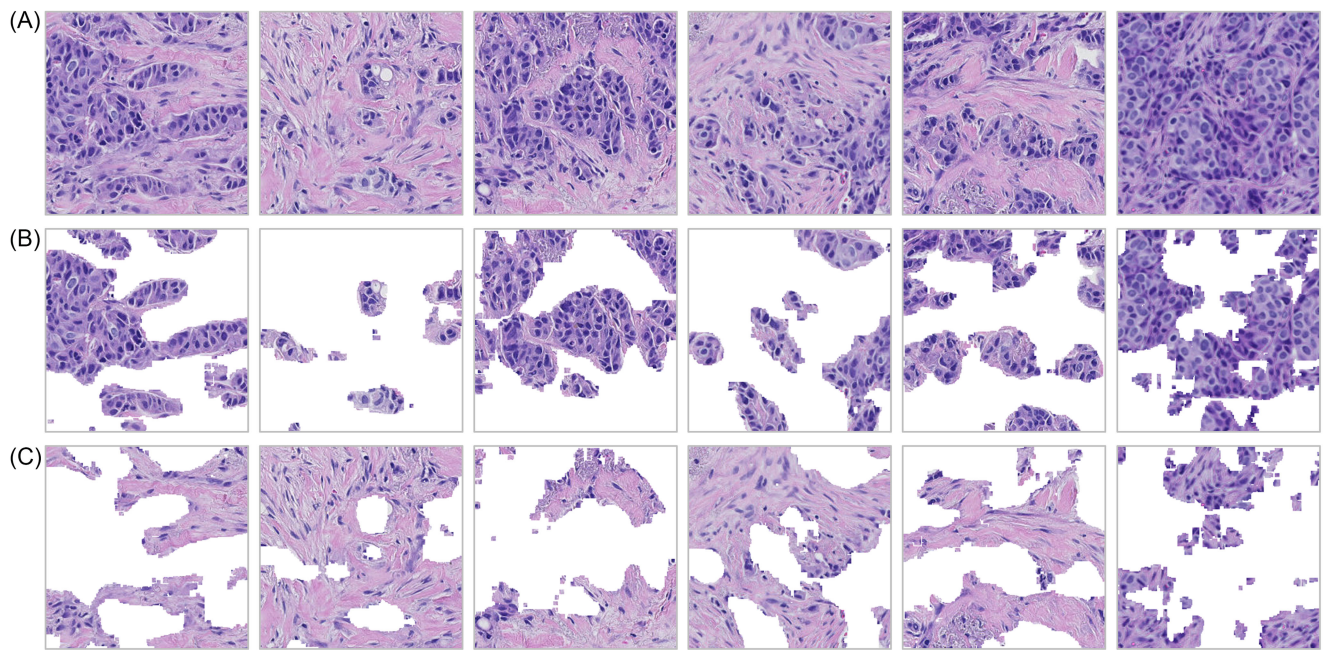


Figure 2. Examples of original histological image tiles and extracted Tumor and Stroma tiles. (A) Original histological image tiles; (B) extracted Tumor tiles; (C) extracted Stroma tiles

More specifically, we first compare the Tumor and Stroma models with the Direct model to show the effectiveness of the pathology experts' cognition in ECDEDL. Second, we compare TS-Ensemble model respectively with Tumor model and Stroma model to assess the effectiveness of the AI experts' cognition in ECDEDL. Then, we compare TS-Ensemble model with the Direct model to show the effectiveness of the ECDEDL approach for external validation, since the Direct model can be regarded as the usual model constructed without experts' cognition. To avoid the effects of possible experimental bias errors, we repeated the training and validation of the four series of predictive models five times and summarize corresponding evaluation metrics for a fair comparison.

We respectively employed MobileNetV2 [58], ResNet101V2 [59] and NASNetLarge [60] (from light weight to complex) as the DNN architecture in the procedures of the training and validation of the two series of predictive models, to show the stability of the effectiveness of the ECDEDL approach for external validation with different DNN architectures. Particularly, from light weight to complex DNN architectures is chosen for experiments, in order to simulate the situation of real-world applications regarding the consideration of computing resource and efficiency. We employed ROC and PR curves to evaluate the overall performances of predictive models, and metrics of Precision, Recall, $F1$, and Accuracy calculated at the threshold of probability 0.5 evaluate the practical performances of predictive models, as well as different probabilities from 0 to 1 to evaluate the ablation performances of predictive models.

3. Results and Discussion

In this section, we show the effectiveness of the proposed ECDEDL referring to the evaluating strategy in Section 2.3. The

results and discussion are enclosed in the experiments regarding the training dataset, the internal dataset, and the external dataset in Table 1. Primarily, different predictive models were produced based on the training dataset. Subsequently, the predictive models were respectively evaluated on the internal dataset and the external dataset. Finally, the evaluated results were discussed to show the effectiveness of the proposed ECDEDL for external validation.

Basically, it is reasonable to assume the internal dataset is independent and identically distributed (i.i.d) with the training dataset, since they are from the same primary dataset. However, we assume the external dataset is independent and non-identically distributed with the primary dataset (both the training dataset and the internal dataset), since it is independently and differently collected regarding the primary dataset. Thus, a predictive model produced based on the training dataset will have better performance on the internal dataset than the external dataset. And, the performance of a predictive model on the external dataset closer to the performance on the internal dataset is better.

Notably, as the external dataset was collected with limited number (340) of WSIs, the distribution of the external dataset can inevitably be not able to fully represent the distribution of the real-world external dataset beyond the primary dataset.

3.1. Effectiveness of experts' cognition in ECDEDL

The ROC and PR curves of the Tumor model, the Stroma model, and the Direct model on external data are shown in Figure 3(A). In Figure 3(A), the curves were drawn with different DNN architectures and repeated experiments. From Figure 3(A), we can summarize that the Tumor model and the Stroma model perform better than both the Direct model on external data, which

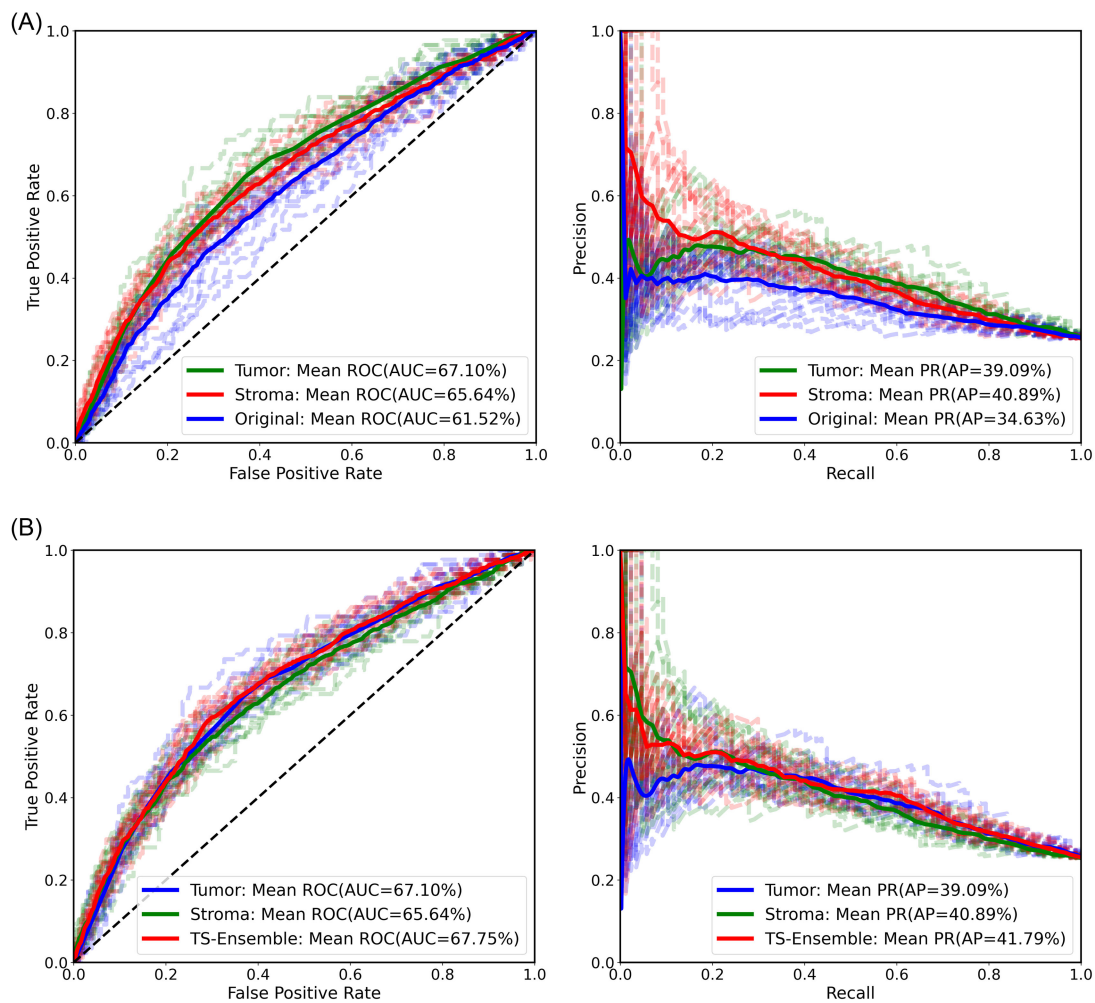


Figure 3. ROC and PR curves of various models on external data. (A) The ROC and PR curves of the Tumor model, the Stroma model, and the Direct (original) model on external data. (B) The ROC and PR curves of the TS-Ensemble model (ensemble of the Tumor and Stroma models), the single Tumor model, and the single Stroma model on external data

reflects that pathology experts' cognition in ECDEDL is significantly effective, leading to better performances for external validation.

The ROC and PR curves of the TS-Ensemble model (ensemble of the Tumor and Stroma models), the single Tumor model, and the single Stroma model on external data are shown in Figure 3(B). In Figure 3(B) the curves were drawn with different DNN architectures and repeated experiments. From Figure 3(B), we can summarize that the TS-Ensemble model performs better than both the Tumor model and the Stroma model on external data, which reflects that AI experts' cognition in ECDEDL is comparatively effective, leading to even better performances for external validation.

3.2. Overall performance of ECDEDL

The ROC curves of the TS-Ensemble model on external data and the Direct model respectively on Internal data and external are shown in Figure 4(A). In Figure 4(A), the curves were drawn regarding different DNN architectures with repeated experiments and their union results. The corresponding PR curves are shown in Figure 4(B). The 95% confidence intervals (CI) of the AUCs

for ROC curves corresponding to Figure 4(A) and the APs for PR curves corresponding to Figure 4(B) are shown in Table 2. From Figure 4 and Table 2, we can summarize that the TS-Ensemble model performs much better than the Direct model on external data, and the performances of the TS-Ensemble model on external data are close to the performances of the Direct model on internal data. These results indicate that the overall performances of the ECDEDL approach for external validation are quite effective, approximating the internal validation.

3.3. Practical performance of ECDEDL

The 95% CI for the metrics of Precision, Recall, $F1$, and Accuracy at the threshold of probability 0.5 for the TS-Ensemble model on external data and the Direct model respectively on internal data and external data are shown in Table 3.

From Table 3, we can summarize that the TS-Ensemble model performs much better than the Direct model on external data, and the performances of the TS-Ensemble model on external data are close to the performances of the Direct model on internal data, regarding the metrics of Precision, Recall, $F1$, and Accuracy. These results indicate

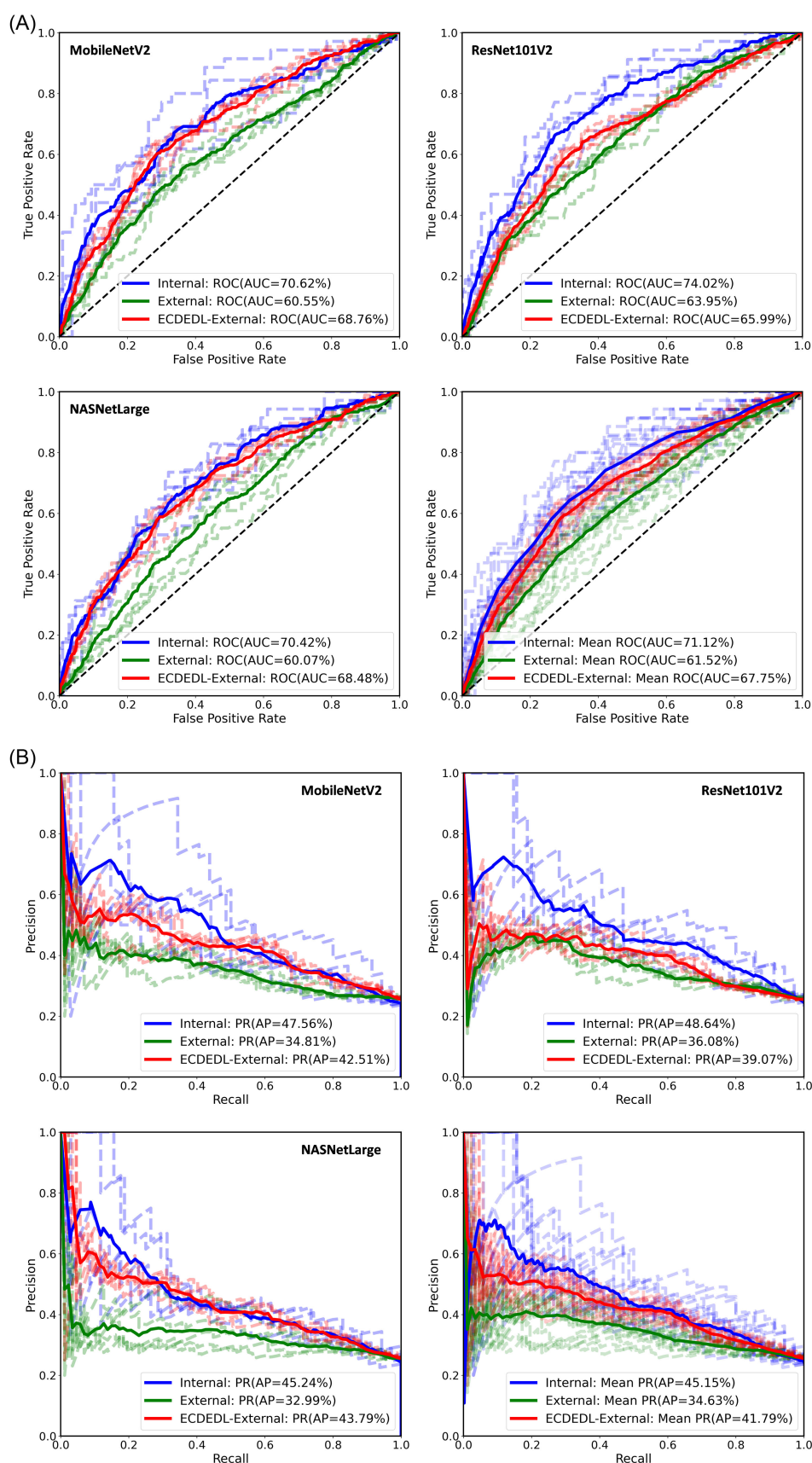


Figure 4. ROC curves of various models on internal dataset and external dataset. (A) ROC curves. (B) PR curves

Note: Internal: direct model on internal data; External: direct model on external data; ECDEDL-External: TS-Ensemble model on external data

Table 2. The 95% confidence intervals (CI) of the AUCs for ROC curves and the Aps for PR curves corresponding to Figure 4

Metrics-Architecture		Internal(CI)	External(CI)	ECDEDL-External(CI)
AUC	MobileNetV2	70.62(66.12–75.07)	60.55(58.57–62.53)	68.76(66.90–70.67)
	ResNet101V2	74.02(70.87–77.11)	63.95(62.30–65.59)	65.99(65.15–66.88)
	NASNetLarge	70.42(68.69–72.16)	60.07(56.06–64.12)	68.48(66.97–70.07)
	Union	71.12(69.71–73.64)	61.52(59.80–63.26)	67.75(66.74–68.80)
AP	MobileNetV2	47.56(38.95–53.76)	34.81(32.71–36.13)	42.51(40.31–43.72)
	ResNet101V2	48.63(42.00–52.39)	36.08(34.14–37.23)	39.07(37.39–39.96)
	NASNetLarge	45.24(40.70–48.12)	32.99(28.73–36.22)	43.79(41.94–44.55)
	Union	45.15(42.95–49.21)	34.63(32.67–35.72)	41.79(40.04–42.58)

Table 3. The 95% confidence intervals (CI) for the metrics of precision, recall, $F1$, and accuracy of the TS-Ensemble model on external data and the Direct model, respectively, on internal data and external data.

Metrics-Architecture		Internal(CI)	External(CI)	ECDEDL-External(CI)
Precision	MobileNetV2	61.07(46.28–75.87)	40.32(37.59–43.05)	45.98(41.18–50.78)
	ResNet101V2	47.24(43.24–51.25)	32.40(29.18–35.62)	40.87(37.66–44.08)
	NASNetLarge	41.88(40.64–43.12)	29.05(26.60–31.50)	45.14(42.11–48.18)
	Union	50.07(43.70–56.43)	33.92(31.03–36.82)	44.00(41.67–46.33)
Recall	MobileNetV2	30.74(26.41–35.07)	29.43(16.18–42.67)	33.10(20.06–46.15)
	ResNet101V2	45.48(34.13–56.82)	70.80(56.69–84.92)	51.72(42.25–61.20)
	NASNetLarge	50.82(44.02–57.62)	78.62(65.47–91.77)	42.30(34.75–49.85)
	Union	42.34(36.16–48.53)	59.62(46.20–73.03)	42.38(35.59–49.16)
$F1$	MobileNetV2	40.36(35.34–45.38)	31.55(20.96–42.14)	37.04(28.82–45.25)
	ResNet101V2	45.77(38.03–53.50)	43.40(41.99–44.82)	45.10(41.51–48.70)
	NASNetLarge	45.64(43.29–47.99)	41.92(40.35–43.49)	43.12(39.50–46.74)
	Union	43.92(40.70–47.14)	38.96(34.63–43.29)	41.75(38.27–45.24)
Accuracy	MobileNetV2	77.85(75.10–80.60)	70.44(67.97–72.91)	72.84(70.99–74.70)
	ResNet101V2	74.55(72.55–76.54)	53.37(45.96–60.78)	68.27(65.47–71.07)
	NASNetLarge	70.79(69.35–72.24)	44.46(35.74–53.18)	71.91(70.08–73.74)
	Union	74.40(72.51–76.29)	56.09(49.39–62.79)	71.01(69.44–72.58)

Note: Internal: direct model on internal data; External: direct model on external data; ECDEDL-External: TS-Ensemble model on external data

that the practical use of the ECDEDL approach for external validation is also quite effective to be able to approximate the internal validation.

3.4. Ablation performance of ECDEDL

The visualized metrics of Precision, Recall, $F1$, and Accuracy at the threshold of different probabilities from 0 to 1 for the TS-Ensemble model on external data and the Direct model respectively on internal data and external data are respectively shown as Figures 5 and 6.

From Figures 5 and 6, we can observe that the change in the probability threshold will change the performances of different predictive models. Specifically, the overall performances of Accuracy and $F1$ will generally increase as the threshold of probability value increases, when the threshold of certain probability value is not exceeded. Meanwhile, the overall performances of Accuracy and $F1$ will generally decrease as the threshold of probability value increases, when the threshold of certain probability value is exceeded.

Notably, from Figure 6(A), we can observe that the $F1$ curves of ECDEDL-External are generally over the $F1$ curves of External

and are close to the $F1$ curves of Internal, when the threshold of certain probability value is not exceeded. This indicates that the ECDEDL approach for external validation is quite effective to be able to approximate the internal validation in terms of $F1$, when the threshold of certain probability value is not exceeded. However, as shown in the dashed bounding boxes in Figure 6(A), the $F1$ curves of ECDEDL-External are surpassed by the $F1$ curves of External results, when the threshold of certain probability value is exceeded. This indicates that the proposed ECDEDL approach will be ineffective for external validation in terms of $F1$, when the threshold of certain probability value is exceeded.

Particularly, from Figure 6(B), we can observe that the Accuracy curves of ECDEDL-External are roughly over the Accuracy curves of External and are close to the Accuracy curves of Internal. This indicates that the ECDEDL approach for external validation is quite effective to be able to approximate the internal validation in terms of Accuracy at most thresholds of probability values, which reflects the stableness of the ECDEDL approach in improving the external validation.

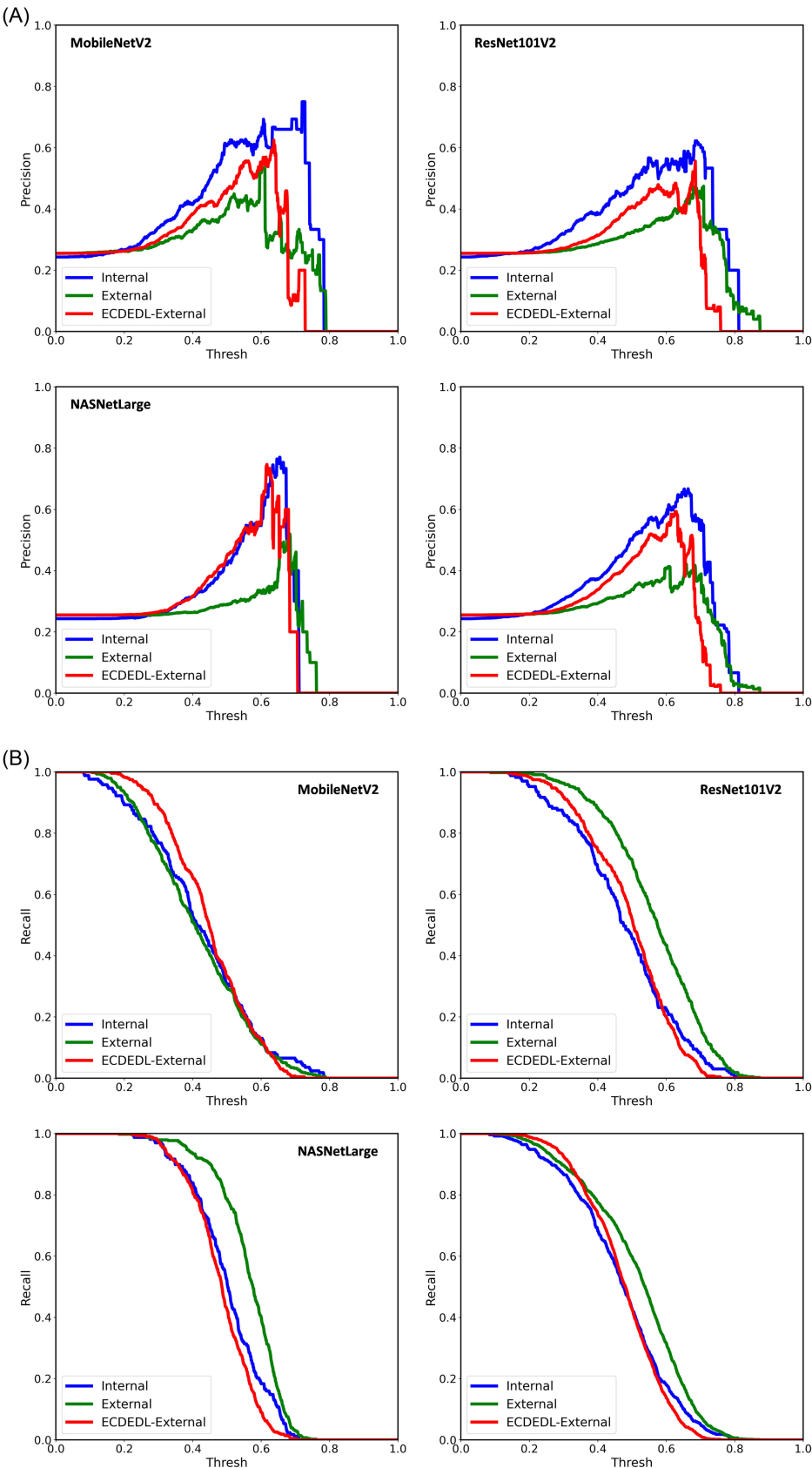


Figure 5. Precision and recall curves of various models on internal dataset and external dataset regarding thresholds of probabilities from 0 to 1. (A) Precision curves. (B) Recall curves

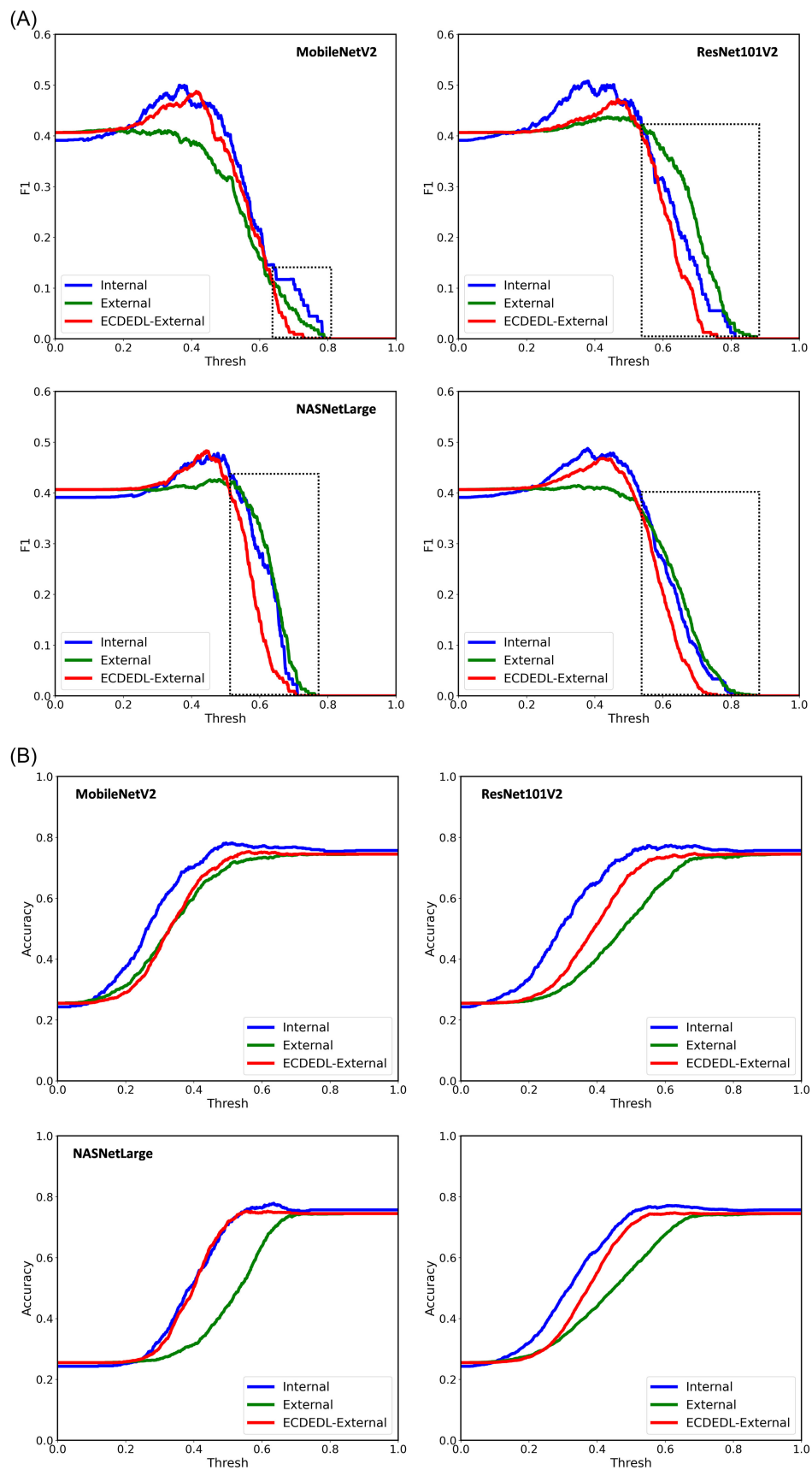


Figure 6. *F1* and accuracy curves of various models on internal dataset and external dataset regarding thresholds of probabilities from 0 to 1. (A) *F1* curves. (B) Accuracy curves

5. Conclusion

Directly predicting pCR to NAC in breast cancer from histological images using DL has been shown to be a new trend recently [17]. However, it has been a commonly known problem that the AI models constructed for medical prediction have better performances in internal validation than in external validation, which significantly affects the clinical safety of using AI models [23]. Moreover, Luo et al. [31] indicate that the poor performance in external validation is the primary challenge for DL applied to breast cancer imaging. Therefore, it is very meaningful and necessary to investigate advanced approaches for the out-of-distribution problem of external validation in predicting pCR to NAC in breast cancer from histological images.

In this paper, we propose the ECDEDL approach for external validation and show its effectiveness in predicting pCR to NAC from histological images in breast cancer. Since the cognition of both pathology and AI experts have been taken to construct the predictive model, the proposed ECDEDL approach, to some extent, approximates the working paradigm of a human being which will refer to his various working experiences to make decisions. The proposed ECDEDL approach is more intrinsic than the existing alternative solutions and federated learning for external validation of predicting pCR to NAC in breast cancer from histological images. This property of the proposed ECDEDL approach makes it can fundamentally be combined with existing solutions and federated learning for addressing the problem.

Extensive experimental results and corresponding analysis in this paper primarily indicate the following: (1) The experts' cognition in the proposed ECDEDL approach is effective with external validation; (2) The overall and practical performances of the proposed ECDEDL approach for external validation are quite effective, numerically approximating the internal validation. These two indications reflect that the proposed ECDEDL approach is closer to the working paradigm of an expert than some existing alternatives solutions which simply ignored the experts' cognition in constructing predictive models for addressing problem.

The proposed ECDEDL approach still has limitations. The selected experts' cognition ought to have been widely acknowledged because it is used to construct the predictive model in the application of the ECDEDL-based solution for addressing problem. In fact, the cognition of individual experts that has not been generally accepted can bring personal bias to the final predictive model, leading to biased predictions that can be noxious. Thus, we should try to avoid introducing any expert's cognition that has not been generally accepted in constructing the predictive model of the proposed ECDEDL approach. In addition, although DNN architectures from light weight to complex have been leveraged as the foundation models for investigating the effectiveness of the proposed ECDEDL approach, only three types of architectures were chosen for experiments. This might also lead to biased results regarding the change of the DNN architecture in implementing the proposed ECDEDL approach. Besides, the number of WSIs collected for external validation was also limited, and there might be fluctuations in the experimental results when a larger number of WSIs are available for external validation.

This paper has demonstrated the promising potential of ECDEDL for addressing the out-of-distribution problem of external validation in predicting pCR to NAC in breast cancer from histological images. In future works, it is interesting to explore additional experiments to test the generalizability of the ECDEDL approach across different cancer types or imaging modalities. As the concept behind the proposed ECDEDL

approach is fundamentally a new paradigm for AI alignment [62], which can be widely leveraged in building predictive models, we particularly look forward to widely testing this paradigm in many other types of cancer-related prediction problems or alternative data preparation strategies [63, 64].

Recommendations

The proposed ECDEL approach has the potential to be effective to improve the performance of predictive models for external validation, numerically approximating the internal validation.

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Ethical Statement

This study does not contain any studies with human or animal subjects performed by any of the authors.

Conflicts of Interest

The authors declare that they have no conflicts of interest to this work.

Data Availability Statement

The data that support this work are available upon reasonable request to the corresponding author.

Author Contribution Statement

Yongquan Yang: Conceptualization, Methodology, Software, Validation, Formal analysis, Investigation, Resources, Data curation, Writing – original draft, Visualization, Supervision, Project administration. **Fengling Li:** Conceptualization, Validation, Resources, Data curation, Writing – review & editing. **Yani Wei:** Resources, Writing – review & editing. **Yuanyuan Zhao:** Resources, Writing – review & editing. **Jing Fu:** Resources, Writing – review & editing. **Xiuli Xiao:** Resources, Writing – review & editing. **Hong Bu:** Resources, Writing – review & editing, Supervision, Funding acquisition.

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