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Problem solving protocol

Biological knowledge graph-guided investigation of immune therapy response in cancer with graph neural network

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Abstract

The determination of transcriptome profiles that mediate immune therapy in cancer remains a major clinical and biological challenge. Despite responses induced by immune-check points inhibitors (ICIs) in diverse tumor types and all the big breakthroughs in cancer immunotherapy, most patients with solid tumors do not respond to ICI therapies. It still remains a big challenge to predict the ICI treatment response. Here, we propose a framework with multiple prior knowledge networks guided for immune checkpoints inhibitors prediction—DeepOmix-ICI (or ICInet for short). ICInet can predict the immune therapy response by leveraging geometric deep learning and prior biological knowledge graphs of gene–gene interactions. Here, we demonstrate more than 600 ICI-treated patients with ICI response data and gene expression profile to apply on ICInet. ICInet was used for ICI therapy responses prediciton across different cancer types—melanoma, gastric cancer and bladder cancer, which includes 7 cohorts from different data sources. ICInet is able to robustly generalize into multiple cancer types. Moreover, the performance of ICInet in those cancer types can outperform other ICI biomarkers in the clinic. Our model [area under the curve (AUC = 0.85)] generally outperformed other measures, including tumor mutational burden (AUC = 0.62) and programmed cell death ligand-1 score (AUC = 0.74). Therefore, our study presents a prior-knowledge guided deep learning method to effectively select immunotherapy-response-associated biomarkers, thereby improving the prediction of immunotherapy response for precision oncology.

Keywords: immune checkpoints inhibitors, deep learning, graph neural networks

Introduction

Over the past few years, immune checkpoint inhibitors (ICIs) or immune checkpoint blockade have greatly improved the clinical treatment level of cancer, and the use of ICIs typically produces fewer side effects and longer lasting therapeutic effects than chemotherapy. Programmed cell death-receptor 1 ligand (PD-L1) and tumor mutation burden (TMB) have been developed as biomarkers for the treatment of immune checkpoint inhibitors (ICIs). However, some patients who are TMB-high or PD-L1-high remained resistant to ICIs therapy. [1]. Recently, ICIs have been expanded to more cancer types, including non-small cell lung cancer, melanoma, bladder cancer and gastroesophageal cancer [2]. For example, the advent of ICI has revolutionized the treatment for bladder cancer. FDA has approved pembrolizumab

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for BCG-unresponsive, high-risk non-muscle invasive bladder cancer in 2020 [3]. However, despite the clinical benefits of ICI therapy, a major limitation is that only a fraction of patients responds to immunotherapy, presumably with varying proportions across cancer types. And the toxicity and side effects are very common after ICI treatment [4]. Therefore, there is a need to identify biomarkers that can detect immunotherapy response in cancer patients before or after surgery. Accurate prediction of immune therapy in different cancer patients may help to provide useful information on the clinical use of ICIs and improve survival and prognosis of cancer patient.

One of the major problems in using tumor immunotherapy approaches is the identification of markers in immunotherapy patients that can reliably predict response to immune drugs in multiple cohorts of cancer patients. For example, immunohistochemical expression of programmed cell death-1 (PD-1)/programmed death ligand-1 (PD-L1) is an FDA-approved concomitant diagnostic test for various cancer types. Therefore, many studies have reported a positive correlation between PD-L1 expression and ICI response in NSCLC [5]. However, other studies reported no significant correlation between PD-L1 expression and response to ICI treatment, and some studies even showed that ICI responders exhibited lower PD-L1 expression levels [6]. These published markers are not robust and accurate in clinical circumstances. Identification of new biomarkers for robust and accurate prediction of immunotherapy response is very important now. Traditional biomarkers explain only about 63% of ICI responses [7], suggesting that new factors remain to be discovered. However, the clinical benefit of ICIs therapy remains very limited to a subset of patients, some patients even experience severe side effects, leading to treatment discontinuation [8]. Therefore, it is urgent to develop methods to identify biomarkers from ICI-treated patients, and ultimately minimize the side effects of ICI, prolong the prognosis of patients and maximize the value of immunotherapy.

The transcription profile of patients to immune therapies reveals fundamental insights into how the drug works and how patients respond. It can describe how diverse gene regulatory machinery helps modulating or reversing disease phenotypes [9]. Knowledge of genetic perturbation outcomes can also dramatically influence the field of tumor microenvironment biology and regenerative medicine. Since complex phenotypes are known to be produced by genetic interactions between small sets of genes, these same interactions could also be leveraged to make the precise engineering of patient identity more experimentally tractable [10]. Various biological databases provide different types of prior knowledge, including protein interaction networks, gene regulatory networks and pathway databases. They provide a powerful means to identify reliable biomarkers. For example, DeepOmix [11] learned embeddings by incorporating gene functional module networks as the function module layer since genes perform functions. These methods show more interpretable and accurate than traditional deep learning or machine learning method. Patients with somatic mutations in similar network communities exhibit similar clinical outcomes. Drug efficacy can be inferred from the proximity between the drug target and the disease gene [12]. Taken together, the evidence suggests that methods such as building specific functional features or network structures based on prior knowledge provide targeted predictive and low-noise biomarkers. But how to incorporate prior knowledge from so many different data sources and fuse with drug structure information, patient data from different omics dimensions, to form robust networks has not yet been validated to predict response to ICI therapy in multiple different cancer types of patients.

Here, we propose a deep learning framework based on prior knowledge networks that can make robust and accurate predictions on ICI therapy, and accurately identify potential biomarkers or functional modules. Specifically, we can reliably predict responders state (yes or no) using expression levels of more than 600 patient samples, including melanoma, gastric cancer and bladder cancer, who received the target ICIs treatment toward PD1/PD-L1. To identify robust biomarkers of drug responder status, we implemented a prior-knowledge-guided graph-based deep learning approach in which we identified immunotherapeutic targets located in knowledge network structures including gene regulatory networks and gene oncology networks (such as pathway database). To evaluate the performance of ICInet, we trained and tested our modeling cross-prediction studies across different cancer types and across different subtypes of the same cancer. We found that ICInet-based prediction outperformed ICI targets [including PDI, PD-L1 or cytotoxic T lymphocyte antigen 4 (CTLA4)] and tumor microenvironment-related markers [including CD8 T cells, T cell exhaustion, CAF and tumor-associated macrophage (TAM)]. These findings suggest that ICInet with prior knowledge-guided and omics-based graph convolutional neural models can help improve traditional genome-based ICI response prediction approaches. In conclusion, we here provide a method to uncover drug response mechanisms and patient immune markers from ICI-treated patients, helping to accurately predict the effect of ICI drug therapy on the basis of previously identified traditional markers.

Results

Immune therapy response prediction framework—ICInet: combines prior knowledge with graph neural network

ICInet is a deep learning-based model that predicts immune therapy response status. The gene expression profiles of cancer patients are injected into gene regulatory networks.

Biomarkers associated with anticancer drug response are located near drug targets in the gene regulatory networks. Studies have shown that biomarkers associated with treatment response can be identified from patient-derived organoid models that predict drug response in cisplatin-treated urinary bladder cancer patients [13]. Based on the understanding of biological knowledge, a gene does not function in a single role, but genes in regulatory network structures cooperate as pathways or functional modules in gene oncology networks. Our goal is to inject these biological subnetworks associated with ICI responses into gene expression profiles by selecting pathways near ICI targets (Figure 1A). We used multiple different gene regulatory networks including KEGG and String [14]. These networks are from different data sources and have different knowledge view with average 17 000 nodes and 510 000 edges. These networks are introduced with details in Supplementary Figure 1 (see Supplementary Data available online at https://academic.oup.com/bib). ICInet can drive an improved functional understanding of a detailed multi-viewed process of interest. First, we used a naïve network shrinking method for multiple networks integration. Using ICI targets (such as PD1 or PD-L1) as anchor nodes to propagate the effects of ICI targets across the network (Figure 1). Next, we selected those pathways with targeted genes related in gene oncology networks

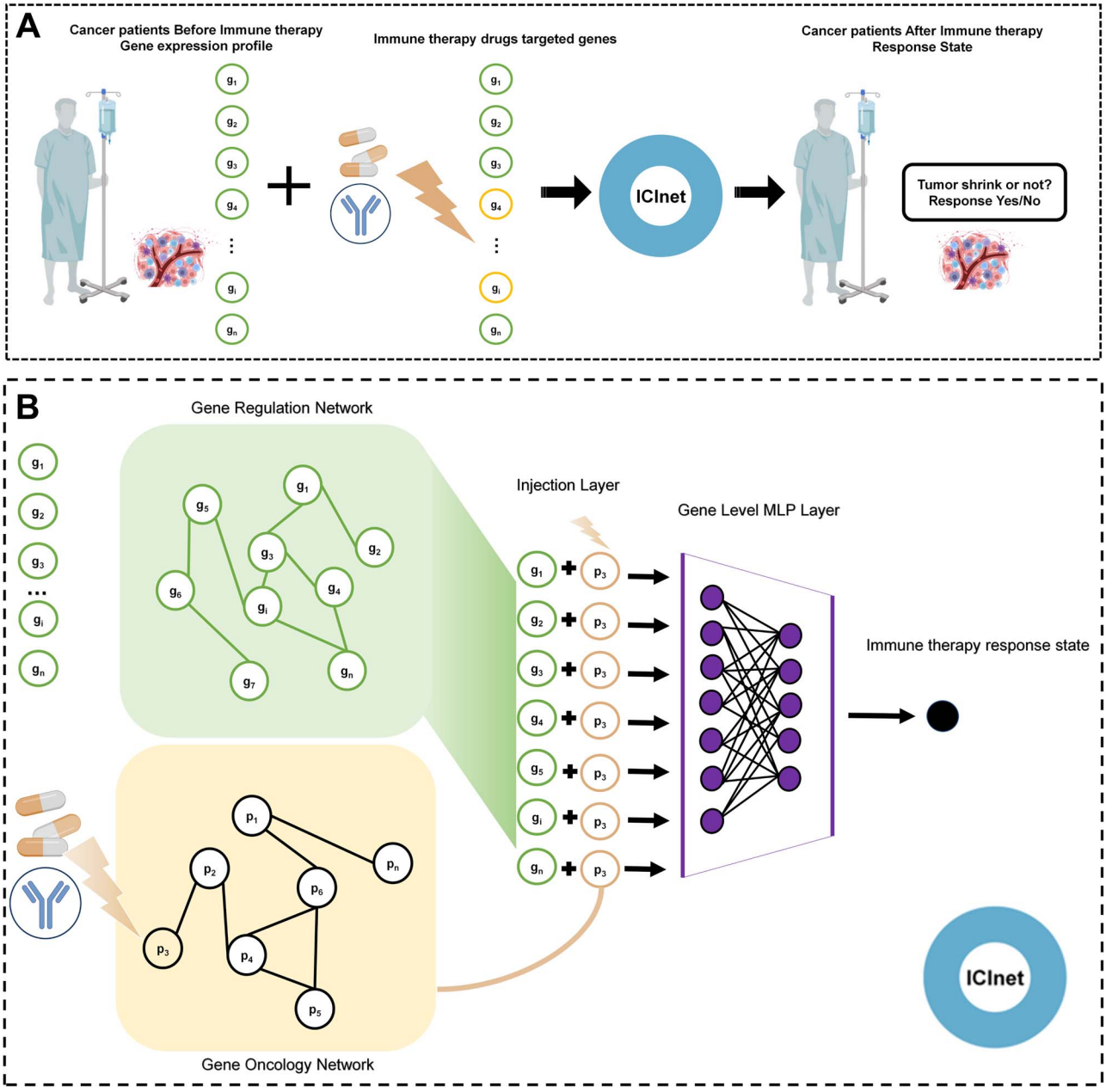

Figure 1. Overview of ICInet for immune checkpoints inhibitors prediction framework. Input gene expression profiles of cancer patients used for injected on graph with deep learning to predict immunotherapy responders or not response.

and injected these pathways on the gene sets. Then, we use the selected functional subnetworks as prior knowledge networks for graph neural network training input for immune therapy response prediction modeling.

For deep learning-based immunotherapy-response prediction with graph convolutional neural networks, we used ICInet, and as a comparison group, we selected gene-based method (i.e. immunotherapy target genes) and tumor microenvironment-based method. We used the expression level of the input features to train with a deep learning GNN model with prior knowledge subnetworks integrated. To test the predictive performance of the input features, the model needs to be tested to predict drug response (measured by shrinking tumor size) after immunotherapy.

To fully train and generalize ICInet model, we broadly measured prediction performance using different combined training and testing datasets. Specifically, we performed intra-cohort prediction, where the training and test datasets were from a single cohort; cross-cohort prediction, where two independent datasets were used as training and test datasets. Furthermore, we alternately used a large or small number of training samples to measure the consistency of prediction performance across different training conditions.

Experiment results show that different subtypes of the same tumor can accurately predict ICI treatment response. We first performed leave-one-out cross-validation using ICInet and immunotherapy-related biomarkers to measure performance. Here, ICInet was applied to three cancer immunotherapy research datasets (one gastric cancer cohort [15] and two melanoma cohorts (Gide [16], Liu [17]) with training on all datasets. Accurate predictions were consistently maintained (Figure 2). In contrast, predictions made using drug target expression levels were less

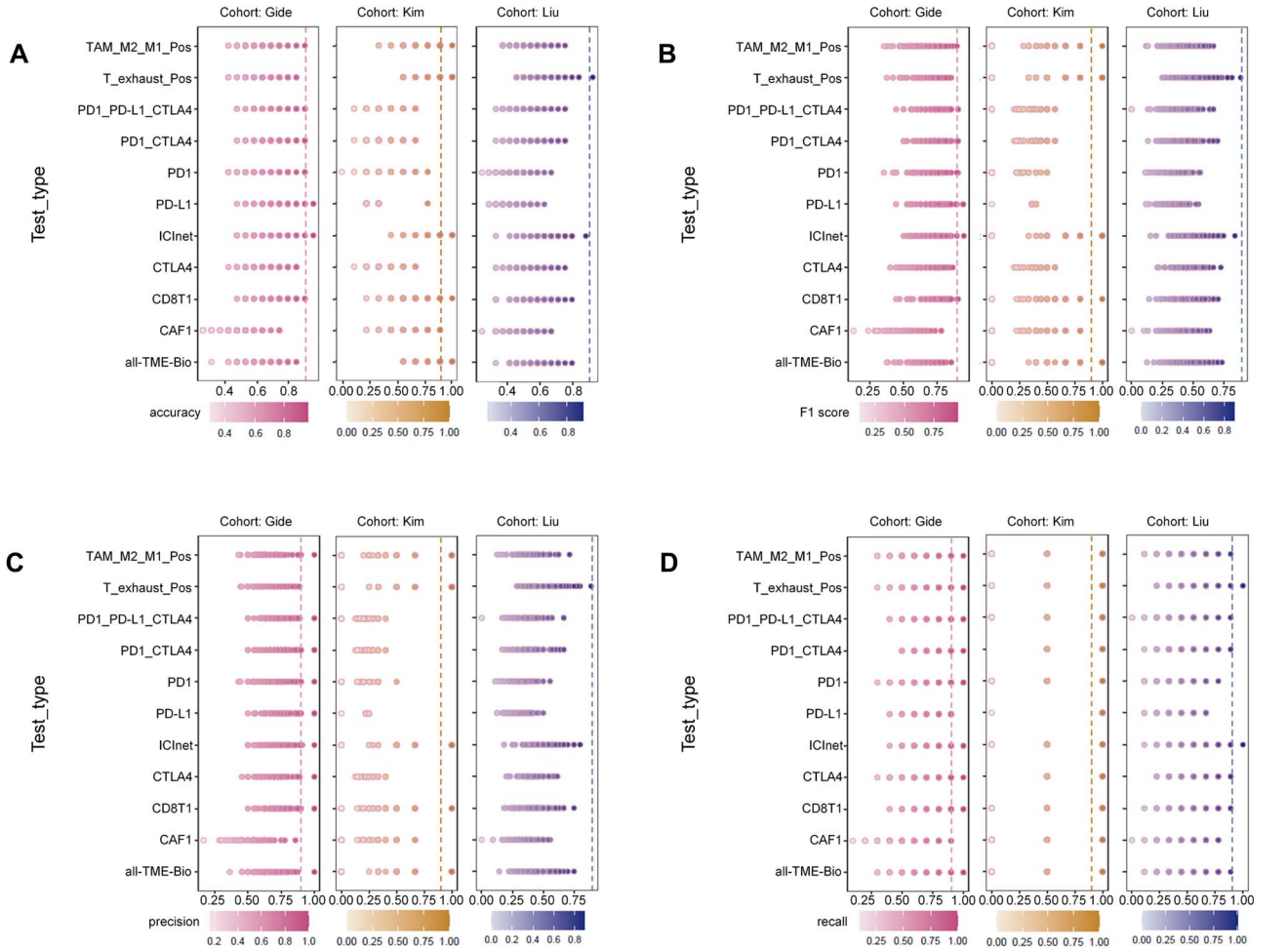

Figure 2. Modeling of response from different cancer types. (**A**) In the three different cohorts, we applied ICInet with other types of prediction biomarkers. The performance of each prediction test types is shown, including accuracy, F1 score, precision and recall.

consistent, and drug targets were only accurately predicted in the melanoma cohort (Figure 2), but not in the other 2 cancer cohorts (Figure 2).

Next, we compared the predictive performance of ICInet with other previously identified ICI-related biomarkers and found that ICInet was better on all three cancer datasets in most cases (Figure 3). For single gene markers, expression levels of immunotherapy targets (PD1, PD-L1 or CTLA4) were considered. For markers associated with the tumor microenvironment, we considered gene sets associated with CD8 T-cell ratio, T-cell exhaustion, CAFs and TAMs. We also considered the use of all single gene markers (gene-based) or all tumor microenvironment-related markers (TME-based) for prediction. We used AUC and F1 scores to measure the predictive performance, and ICInet predictions generally outperformed experimental predictions using all other biomarkers. In addition, we perform 5-fold cross validation. With 80% of the samples randomly selected as the training set and the remaining 20% as the test set (Figure 3), ICInet showed significantly better or equal performance compared with all other biomarkers.

Cross-cancer types prediction analysis based on ICInet

ICInet showed that consistent predictions can be made in other independent melanoma datasets. Key aspects of an accurate robust generalizable deep learning model include: (i) its ability to generalize to new datasets and (ii) its consistent performance with few training samples.

First, experimental results show that a graph convolutional neural network trained with ICInet can make accurate predictions when using an independent dataset, but poor prediction performance when using other biomarkers (Figure 3). To test the generalizability of the model, we trained the ML (machine learning) model using the melanoma dataset of Gide *et al.* To measure the performance of our model, we choose AUC as the performance metric. ICInet showed high-accuracy index in different data cohorts including the Aus, Prat and other datasets.

Predictions using other biomarkers showed highly variable predictive performance compared with ICInet-based graph convolutional neural networks (Figure 4). For example, the optimal performance of PD-1 expression is lower, and the maximum AUC is only 0.66. Furthermore, when AUPRC was used as a performance metric, ICInet-based predictions outperformed those based on drug targets or tumor microenvironment markers (Figure 4). When three independent training datasets were merged into a single dataset (Figure 4), ICInet-based predictions outperformed other methods.

Furthermore, when the training data and test data come from different cohorts, the ICInet prediction performance outperforms other methods. When we trained a machine learning model using Liu data [17] and then tested prediction performance in three

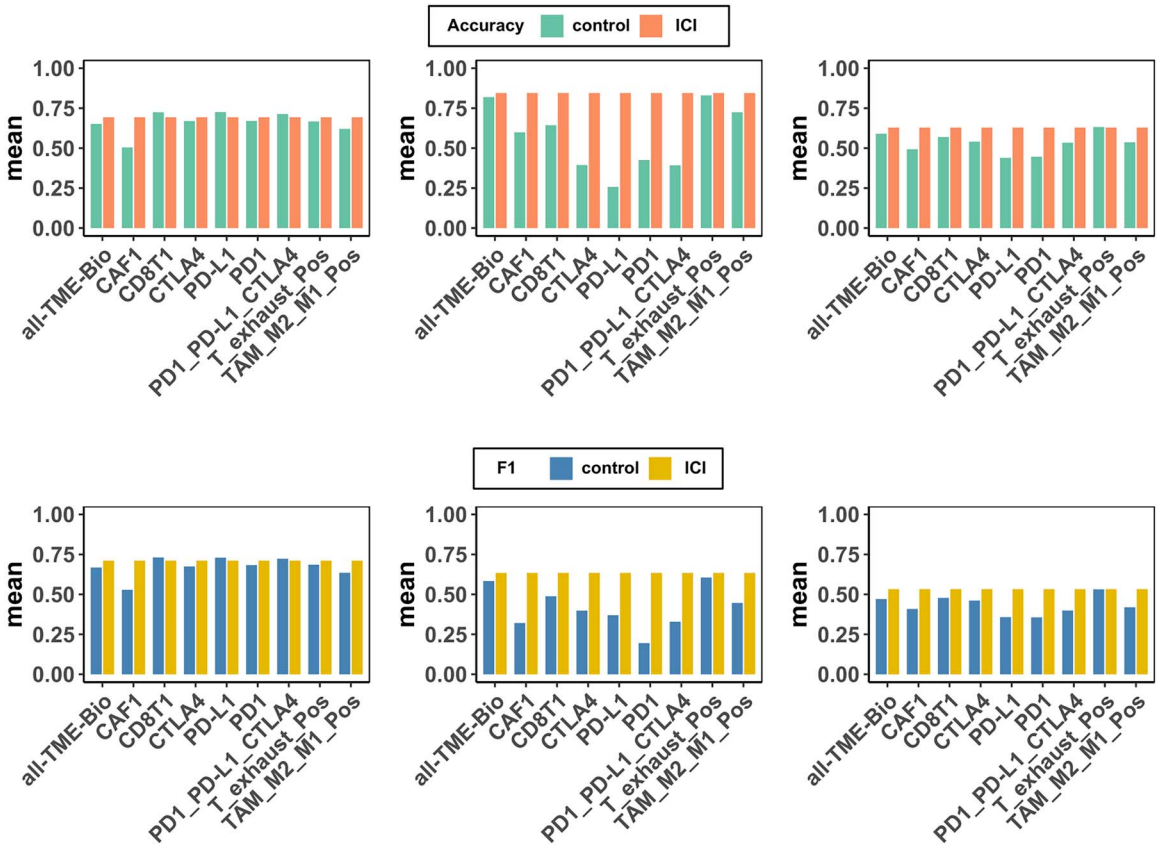

Figure 3. Performance evaluation of ICInet with other biomarkers for immune therapy prediction methods applied within the same cancer type. Immunotherapy-response prediction using the expression information of drug targets (PD-1, PD-L1 or CTLA4, or ICInet). Leave-one-out cross-validation predictions for the (**A**) Gide, (**B**) Liu and (**C**) Kim datasets are plotted.

different cohorts, ICInet-based predictions outperformed predictions based on other ICI-related biomarkers in 88.6% of comparisons. These results suggest that regardless of the dataset used to train the machine learning model, ICInet is better compared with drug target-based or tumor microenvironment-based biomarkers.

Finally, we tested whether ICInet could make robust predictions with fewer training samples. Likewise, ICInet with a smaller sample size made consistent predictions compared with Gene-based or TME-based models. For training model, cross validation with 80–20% randomly sampled patients from Gide dataset [16], the melanoma datasets were used as test data for performance evaluation (Figure 4). ICInet showed statistically significantly better or equal performance in 48 of 56 comparisons (Figure 4). Only PD-L1 was expressed in the Auslander dataset, only CTLA4 was expressed in the Riaz dataset and only the CD8 T-cell exhaustion marker was present in the Riaz dataset.

ICInet prediction outperforms purely without prior knowledge baseline methods

A major limitation of using a data-driven model in clinical applications is that it does not perform consistently well on new datasets, although the model may perform well on training datasets. Therefore, we tested whether incorporating prior biological knowledge representing PPI networks in this study could improve feature selection compared with purely data-driven feature selection methods without prior-knowledge information. Compared with purely data-driven method predictions, the ICInet-based model is able to consistently improve the prediction performance (Figure 4). Specifically, for the data-driven model, we selected K numerical features (where K equals the number of ICInet) that best distinguishes responders and non-responders in the training dataset, and used the selected features to train the model (Figure 4A; method). Across 11 different tasks, we found that ICInet-based predictions performed significantly better than plain data-driven feature selection, suggesting that network-guided feature selection can provide robust features compared with purely without prior-knowledge guided feature selection methods.

Interpretation of the ICInet modeling

Our AI model employs an attention module, which scores each interval of data according to its contribution to making an immune response therapy prediction (model details in Methods). We can analyze the whole genes set and with the targeted pathways drug targeted-genes with high attention scores, and the corresponding response status. Such analysis allows interpretation and interpretation of the model's results.

Methods

Data preprocessing and collection

We collected data from the following different cohorts of patients treated with PD-1/PD-LI-targeting ICIs: (i) Gide *et al.* (nivolumab, pembrolizumab or ipilimumab-treated melanoma; $n = 91$); (ii) Liu *et al.* (nivolumab or pembrolizumab-treated melanoma); (iii) Kim *et al.* (pembrolizumab in metastatic gastric cancer; $n = 45$) [15]; (iv) Aus *et al.* $n = 37$; (v) Prat *et al.* melanoma; $n = 25$; (vi) Riaz *et al.* (nivolumab-treated melanoma; $n = 49$) and (vii) Huang *et al.*

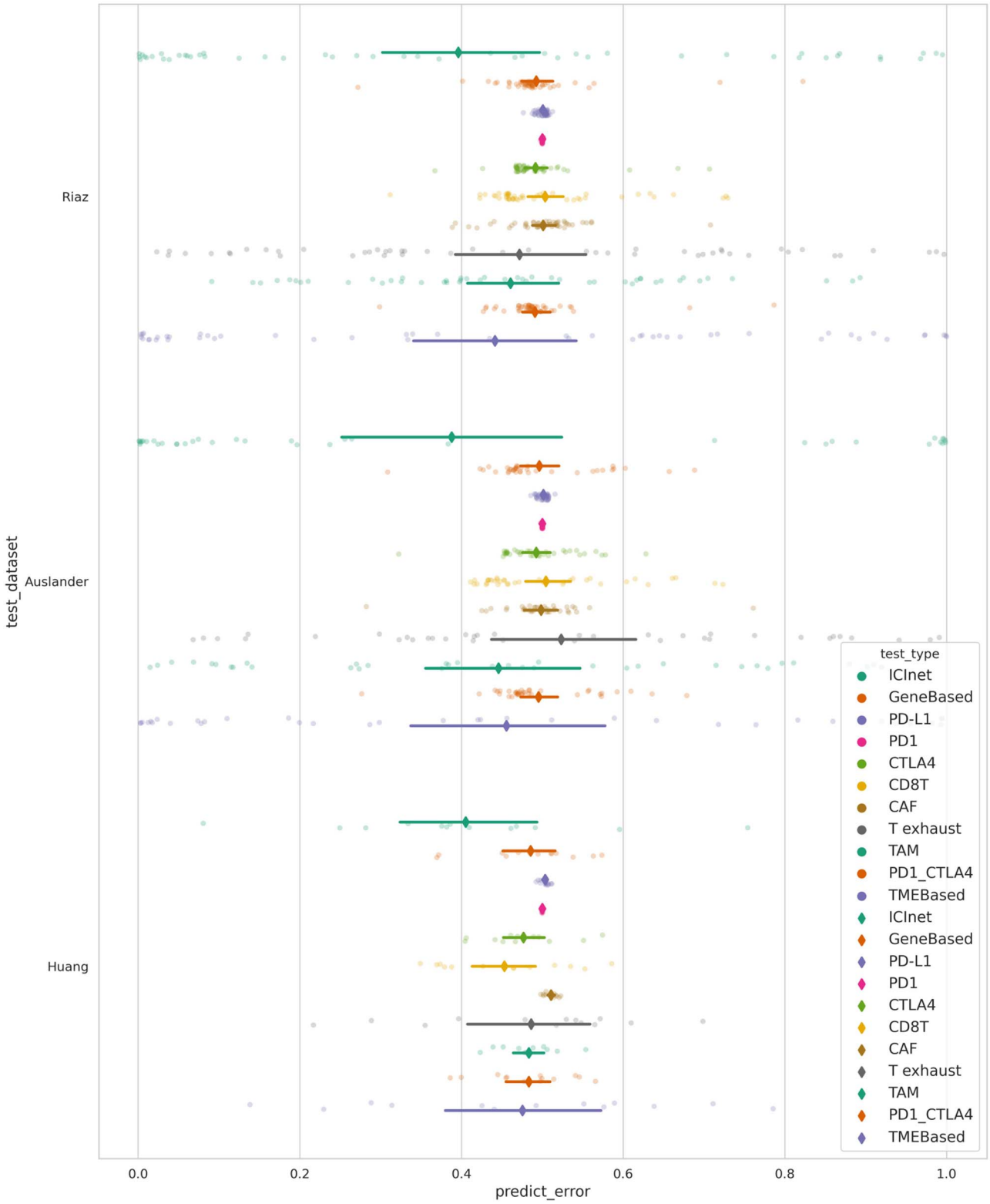

Figure 4. Across studies for ICInet evaluation of generalization.

(pembrolizumab-treated melanoma; $n = 13$). Among them, for the Prat *et al.* dataset, we only considered melanoma samples. Complete responses and partial responses were classified into responders based on (RECIST) [18]. Stable disease and progressive transmitted diseases (PD) were classified as non-responders, the same as in the previous study. For datasets that did not provide or use the RECIST criteria [19], we used the responder and non-responder classifications from the original paper. Details of the drug response labels used in this study are provided in Supplementary Figure 2 (see Supplementary Data available online at https://academic.oup.com/bib), and data on clinical responses are provided in Supplementary Figure 3 (see

Supplementary Data available online at https://academic.oup.com/bib).

The framework building of ICInet

The detection of ICInet pathway consists of two steps: (i) detect the anchor-networks of ICI target genes in the integrated PPI network; (ii) construct graph input of transcript expression profile based on graph convolutional neural network and (iii) train the prediction model.

First, we used the page-ranking algorithm in NetworkX to identify ICI target-proximal genes through network propagation. In the page-ranking algorithm, we use 1 as the ICI target and 0 as the input for the personalization parameters of all other genes in the network. The other parameters of the page rank algorithm use default Settings. After network propagation, we set a hyperparameter to test that the top 3000 genes with the highest impact score are ICI target-proximal genes.

Next, we used ICI target proximal gene subnetwork and transcriptional expression profile for chimerism. Each graph node represented a gene, and the transcriptional expression profile of each gene was used as feature input G = (V, E). Each node has feature vector formed with 10 000 genes normalized expression vector $V = (g_1, g_2, \cdots, g_N)$, $N = 10000$.

Finally, the number of ICInet nodes selected by Gide, Liu and Kim queues is 4720, 3230 and 2920, respectively. We trained neural networks using input graph structure-dominated transcriptional expression profiles constructed from all different prior networks.

Injecting transcript profile with prior-knowledge graph GNN

ICInet predicts the outcome of perturbing genes never seen perturbed before through leveraging a key intuition that perturbation responses are extremely similar for genes that are involved in the same pathways. This observation suggests that we could build a representation of novel gene perturbations by learning from a composition of previously seen gene perturbations that share the same pathways as recorded in the Integrated Gene graph IGG. ICInet leverages this prior knowledge and injects it into the model through a GNN encoder.

Here notably, we first construct a gene regulatory integration graph IGG based on the Gene Ontology graph and other 13 different prior knowledge information databases. The final integrated graph is a bipartite graph where an edge links a gene to a pathway term. We denote Nu as the set of pathways for a gene u. We compute Jaccard index between a pair of gene u, v as Ju,v = |Nu\Nv| |Nu[Nv|. It measures the fraction of shared pathways between the two genes. For each gene u, we then select the top Hpert gene v with the highest Ju,v to construct the graph embeddings. Next, we initialize all possible gene expression profile (P1, ···, PK) with learnable embeddings (xpert 1, ···, xpert K). We then feed them into a GNN parameterized by p to augment every perturbation v's embedding by integrating information from gene expression embeddings that share similar pathways.

Hyperparameters

We use HyperBand [20] on the validation set of 5-fold split dataset to find the best hyperparameters. The same set of hyperparameters is then used across all datasets and multiple splits. The set of ranges for the hyperparameters includes: GNN architecture; GNN layer size – {1, 2, 3, 4}; hidden size d – {32, 64, 128, 256}; learning rate – {1e−2, 1e−3, 1e−4, 1e−5} and batch size – {32, 64, 128,256}. Since we have a large set of hyperparameters, for a more efficient selection, we apply HyperBand [20] on different groups of hyperparameters where each group has a small set of hyperparameters while fixing the rest.

Using a graph to represent prior knowledge

ICInet requires a specific representation of prior knowledge about gene–gene relationships. For gene perturbation embeddings, we used the multiple integrated graph which was generated by adding weighted edges between genes that shared a significant number of link terms. The generation procedures for both graphs were described previously. We also experimented with 14 different networks to use in place of the single gene regulatory network including a protein–protein interaction network, a gene coessentiality network or the gene co-expression network described above. We decided to proceed with the integration graph which has the best coverage over the gene setof interest, yielded very good predictive performance and was the most general-purpose for application to future tasks.

Measuring the performances of different methods predictions

For LeaveOneOut evaluation part, we considered three cohorts from Gide *et al.*, Liu *et al.* and Kim *et al.* We used the LeaveOneOut evaluation from the Scikit-learn module to split the training and test datasets. For predictions based on genes (Gene-Based) and the tumor microenvironment (TME-Based), we used gene expression levels to train/test the ML model. PD-1, PD-L1 and CTLA4 were used as comparation for gene-based methods. CD8 T cells, T-cell exhaustion, CAFs and TAMs were used as the evaluation transcriptomic profiles in TME-based method.

To test the performance of other traditional machine learning methods predictions [21], we conducted feature selection from Scikit-learn [22]. To train and test the other machine learning model, feature selection was conducted with 5-fold cross-validation in training datasets.

Comparation with other state-of-the-art methods

We use EASIERscores [23] provided by the original author. We calculated IMPRES scores by pairwise comparisons of 15 gene pairs [19], as in the original text. TIDE scores were calculated using the TIDEpy Python package [24]. For the TMEsubtypes score [25], we used the microenvironment subtype of melanoma patients. We use a graph convolutional neural network to examine the performance of four state-of-the-art prediction methods. For the GCN-based method, 10 groups of hyperparameters were randomly selected from the hyperparameter grid and 5-fold cross-validation was performed to screen out the best hyperparameters. For the activation function, we use hyperbolic tangent (TANH) for all hidden layers, except for the final output layer, where we use the sigmoid function.

Statistical analysis and software

Fisher's exact test, Mann–Whitney U test and two-sided Student t test were used for data analysis and generation of P-values. For correlation analysis, we used Pearson correlation. All analyses were done in python 3.7. Python packages used are pandas, numpy, scipy, matplotlib, sklearn, lifelines, networkx, statsmodels and pytorch.

Discussion

Broadly, ICInet leveraged a biologically knowledge guided, rather that purely data-driven over-parameterized architecture to predict the immune therapy response. ICInet markedly reduced the

number of parameters for learning, which led to enhanced interpretability to the drug-target of immune therapies. Applications of ICInet to three cohorts of cancer patients with immune therapy responses were demonstrated.

Furthermore, in this study, we tested whether a network-based biomarker discovery pipeline could make robust predictions for immunotherapy. ICInet-based GCNs show consistent prediction performance, while Gene-based, TME-based predictions or features identified by purely data-driven methods show poor optimization performance. For example, reference [26] used network modules to identify cancer-type-specific and pan-cancer driver genes. Furthermore, disease-associated germline mutations that alter protein–protein interactions are highly associated with cancer patient survival and response to anticancer drugs, a finding that disease-associated variants frequently reside at protein-interaction interfaces [27]. Taken together, our findings provide a prior knowledge-based neural network model that can relatively accurately predict immunotherapy response in cancer patients.

We hope that our work will provide interesting new research opportunities for precision medicine using ICI therapy. We developed a method that can be trained directly from ICI-processed samples, while most state-of-the-art models learn from non-ICI-processed samples to predict ICI processed response [28]. Since supervised and unsupervised learning use different cancer patients to train the model, the two learning methods can complement each other and can improve prediction performance when used together (such as semi-supervised methods). Because the biological outcomes of immunotherapy are very complex, approaches that rely on a single omics signature have limitations in predicting patient response to immunotherapy. Combining a network-based machine learning model with different omics layers can achieve better clinical results. As more and more tumor sample sequencing datasets become available for ICI-treated and non-ICI-treated cancer patients, we hope that our work here, and other previous and future approaches, will lead to major improvements in precision oncology.

Key Points

- The availability of integrating biological knowledge graphs with patients' molecular profiles can help illustrate the immune therapy response and reduce side effects.
- In this article, we propose a graph-based framework with multiple prior knowledge networks guided for immune checkpoints inhibitors prediction—DeepOmix-ICI (or ICInet for short).
- The results showed that the guided deep learning method can help effectively select immunotherapy-response-associated biomarkers, improving the prediction of immunotherapy response for precision oncology.

Data availability

For the Gide *et al.* [16], Kim *et al.* [15] and Liu *et al.* [17] datasets, we used normalized expression values and drug responses provided by Lee *et al.* [29]. The data sets are available with the access in Zenodo (https://zenodo.org/record/4661265). The Aulander dataset [19] and Riaz dataset [30] were downloaded from GSE115821 and GSE91061, respectively. The Prat dataset [31] was downloaded from the Supplementary Material of the original paper. The human PPI network was downloaded from the Nichenet [14]. All data used in this study are publicly available. Source data are provided with this paper.

Supplementary data

Supplementary data are available online at https://academic.oup.com/bib.

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Authors' Contributions

Lianhe Zhao: Data Curation, Methodology, Writing-Original Draft, Writing- Review & Editing.
Xiaoning Qi: Methodology, Writing - Original Draft, Writing-Review & Editing.
Yang Chen: Investigation, Writing - Original Draft.
Yixuan Qiao: Investigation, Writing.
Dechao Bu: Investigation.
Yang Wu: Investigation.
Yufan Luo: Investigation.
Sheng Wang: Investigation.
Rui Zhang: Writing.
Yi Zhao: Conceptualization, Methodology, Supervision, Project administration.

Code availability

The source codes for reproduction of the results were developed in python 3.7.1 and are available at repository https://github.com/CancerProfiling/ICInet.

References

1. Johnson DB, Nebhan CA, Moslehi JJ, *et al.* Immune-checkpoint inhibitors: long-term implications of toxicity. *Nat Rev Clin Oncol* 2022;**19**(4):254–67.
2. Argemi J, Ponz-Sarvise M, Sangro B. Immunotherapies for hepatocellular carcinoma and intrahepatic cholangiocarcinoma: current and developing strategies. *Adv Cancer Res* 2022;**156**: 367–413.
3. Li R, Zhang J, Gilbert SM, *et al.* Using oncolytic viruses to ignite the tumour immune microenvironment in bladder cancer. *Nat Rev Urol* 2021;**18**(9):543–55.
4. Zhang D, Shi Y, Liu X, *et al.* Safety and efficacy of immune checkpoint inhibitors in non-small cell lung cancer patients with preexisting antinuclear antibodies: a retrospective cohort study. *Transl Lung Cancer Res* 2022;**11**(7):1420–33.
5. Vega DM, Nishimura KK, Zariffa N, *et al.* Changes in circulating tumor DNA reflect clinical benefit across multiple studies of patients with non-small-cell lung cancer treated

with immune checkpoint inhibitors. *JCO Precis Oncol* 2022;**6**: e2100372.
6. Labriola MK, Zhu J, Gupta R, *et al.* Characterization of tumor mutation burden, PD-L1 and DNA repair genes to assess relationship to immune checkpoint inhibitors response in metastatic renal cell carcinoma. *J Immunother Cancer* 2020;**8**(1): e000319.
7. Litchfield K, Reading JL, Puttick C, *et al.* Meta-analysis of tumor- and T cell-intrinsic mechanisms of sensitization to checkpoint inhibition. *Cell* 2021;**184**(3):596–614.e14.
8. Fernandez-Torras A, Duran-Frigola M, Aloy P. Encircling the regions of the pharmacogenomic landscape that determine drug response. *Genome Med* 2019;**11**(1):17.
9. Kitano H. Systems biology: a brief overview. *Science* 2002;**295**(5560):1662–4.
10. Low LA, Mummery C, Berridge BR, *et al.* Organs-on-chips: into the next decade. *Nat Rev Drug Discov* 2021;**20**(5):345–61.
11. Zhao L, Dong Q, Luo C, *et al.* DeepOmix: a scalable and interpretable multi-omics deep learning framework and application in cancer survival analysis. *Comput Struct Biotechnol J* 2021;**19**: 2719–25.
12. Guney E, Menche J, Vidal M, *et al.* Network-based in silico drug efficacy screening. *Nat Commun* 2016;**7**:10331.
13. Ecke TH. Biomarker in cisplatin-based chemotherapy for urinary bladder cancer. *Adv Exp Med Biol* 2015;**867**:293–316.
14. Browaeys R, Saelens W, Saeys Y. NicheNet: modeling intercellular communication by linking ligands to target genes. *Nat Methods* 2020;**17**(2):159–62.
15. Kim ST, Cristescu R, Bass AJ, *et al.* Comprehensive molecular characterization of clinical responses to PD-1 inhibition in metastatic gastric cancer. *Nat Med* 2018;**24**(9):1449–58.
16. Gide TN, Quek C, Menzies AM, *et al.* Distinct immune cell populations define response to anti-PD-1 monotherapy and anti-PD-1/anti-CTLA-4 combined therapy. *Cancer Cell* 2019;**35**(2):238–255.e6.
17. Liu D, Schilling B, Liu D, *et al.* Integrative molecular and clinical modeling of clinical outcomes to PD1 blockade in patients with metastatic melanoma. *Nat Med* 2019;**25**(12): 1916–27.
18. Padhani AR, Ollivier L. The RECIST (response evaluation criteria in solid Tumors) criteria: implications for diagnostic radiologists. *Br J Radiol* 2001;**74**(887):983–6.
19. Auslander N, Zhang G, Lee JS, *et al.* Robust prediction of response to immune checkpoint blockade therapy in metastatic melanoma. *Nat Med* 2018;**24**(10):1545–9.
20. Li L, Jamieson K, DeSalvo G, *et al.* Hyperband: a novel bandit-based approach to Hyperparameter optimization. *The Journal of Machine Learning Research* 2017;**18**:185.1–185.52.
21. Kong J, Ha D, Lee J, *et al.* Network-based machine learning approach to predict immunotherapy response in cancer patients. *Nat Commun* 2022;**13**(1):3703.
22. Pedregosa F, Varoquaux G, Gramfort A, *et al.* Scikit-learn: machine learning in python. *The Journal of Machine Learning Research* 2011;**12**:2825–30.
23. Lapuente-Santana O, van Genderen M, Hilbers PAJ, *et al.* Interpretable systems biomarkers predict response to immune-checkpoint inhibitors. *Patterns (N Y)* 2021;**2**(8): 100293.
24. Jiang P, Gu S, Pan D, *et al.* Signatures of T cell dysfunction and exclusion predict cancer immunotherapy response. *Nat Med* 2018;**24**(10):1550–8.
25. Zeng D, Li M, Zhou R, *et al.* Tumor microenvironment characterization in gastric cancer identifies prognostic and immunotherapeutically relevant gene signatures. *Cancer Immunol Res* 2019;**7**(5):737–50.
26. Mathews JC, Nadeem S, Pouryahya M, *et al.* Functional network analysis reveals an immune tolerance mechanism in cancer. *Proc Natl Acad Sci U S A* 2020;**117**(28):16339–45.
27. Gajic ZZ, Deshpande A, Legut M, *et al.* Recurrent somatic mutations as predictors of immunotherapy response. *Nat Commun* 2022;**13**(1):3938.
28. Bagaev A, Kotlov N, Nomie K, *et al.* Conserved pan-cancer microenvironment subtypes predict response to immunotherapy. *Cancer Cell* 2021;**39**(6):845–865.e7.
29. Lee JS, Nair NU, Dinstag G, *et al.* Synthetic lethality-mediated precision oncology via the tumor transcriptome. *Cell* 2021;**184**(9):2487–2502.e13.
30. Riaz N, Havel JJ, Makarov V, *et al.* Tumor and microenvironment evolution during immunotherapy with Nivolumab. *Cell* 2017;**171**(4):934–949.e16.
31. Prat A, Navarro A, Paré L, *et al.* Immune-related gene expression profiling after PD-1 blockade in non-small cell lung carcinoma, head and neck squamous cell carcinoma, and melanoma. *Cancer Res* 2017;**77**(13):3540–50.