Editorial

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Translating artificial intelligence from code to bedside: The road towards AI-driven predictive biomarkers for immunotherapy of hepatocellular carcinoma

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Hepatocellular carcinoma (HCC) is the second most common cause of cancer-related death worldwide with growing incidence rates particularly affecting North America and Western Europe.[1,2] This increase in incidence rates is primarily the result of sequelae of hepatitis C viral infections (which are now curable), and the growing rates of non-alcoholic steatohepatitis (NASH) associated with diabetes and obesity.[3] The last decade has seen rapid growth in the therapeutic options available for HCC. As such, increasingly data-driven approaches to surgical resection and orthotopic liver transplantation, as well as modern image-guided locoregional therapies, have dramatically improved outcomes in populations with early and intermediate stage disease. These opportunities have now been incorporated into the 2022 update of the Barcelona Clinic Liver Cancer staging system which offers a truly pragmatic approach to clinical decision making in HCC.[4] However, the most remarkable changes have taken place for patients affected by advanced stage disease. The advent and rapid incorporation of systemic immunotherapy as the new first-line option in advanced stage HCC has had a truly transformational impact on our clinical practice.[5] Just 5 years ago, our choices in this cohort were limited to sorafenib or agents undergoing clinical trials. Today, the field is enriched by data from numerous phase III clinical trials that have demonstrated viable alternatives to sorafenib and promising outcomes with immunotherapy, particularly in combination with other molecular targeted therapies or locoregional therapies. While transformational in principle, immunotherapy for HCC has largely failed to replicate the breakthroughs in survival outcomes previously seen in other cancers, such as melanoma or primary lung cancer.[6] The realization that immunotherapy, alone or in combination with other systemic therapies, may not deliver durable tumor response rates greater than ~25% and only marginally improves overall survival compared to the original sorafenib data has curbed our enthusiasm and necessitates a reassessment of our expectations.[7] The issue at hand revolves around our lack of reliable data on tumor susceptibility to immunotherapy which inevitably translates into poor patient selection and suboptimal outcome. The complex interplay between the tumor microenvironment, genomic signatures and the immune system is poorly understood and will require novel immunologically based quantitative biomarkers to help us decrypt the enigma of therapeutic failure.[8] Therefore, finding predictive strategies to assess rapidly evolving tumor habitats, regarding their susceptibility to immunotherapy, represents an essential and currently unmet clinical need.

In their most recent article, Zeng *et al.* propose a novel approach to address an important aspect of the aforementioned dilemma by using artificial intelligence (AI) to predict activation of inflammatory gene signatures associated with increased sensitivity to immunotherapy (Fig. 1). The authors identified 6 key immune gene signatures and applied 3 robust and familiar machine learning models to predict the activation of these specific genes based on patterns extracted from whole-slide digital pathology images. Their training datasets included 336 samples from the Cancer Genome Atlas, a publicly available database which was utilized to identify predictive immune gene signatures and train 3 varieties of convolutional neural networks to predict genomic status. Additionally, experienced pathologists manually annotated the whole slides to obtain ground truth measurements. Upon optimization of the models, the authors used their institutional database of 139 resected HCC cases to validate model performance and investigate its reproducibility. As for the machine learning approach taken, the authors utilized 3 distinct types: a patch-based model with ShuffleNet design which was implemented in Python as well as 2 whole-slide based models; the weakly-supervised classic multiple instance learning approach and the clustering-constrained attention multiple instance learning (CLAM) model. In all 3 instances, the very familiar 10-fold Monte Carlo cross-validation strategy with a 60%/20%/20% data split was applied to train, validate and test the models, respectively. Model performance was expressed using receiver-operating characteristic curves and heatmaps were used to visualize the results of this complex and multivariate analysis more transparently. The results of the study identified the CLAM network as the best overall performing methodology to automatically extract highly predictive tumor regions on pathological slides. As such, areas on whole-tumor slides marked by CLAM as relevant predicted the presence of

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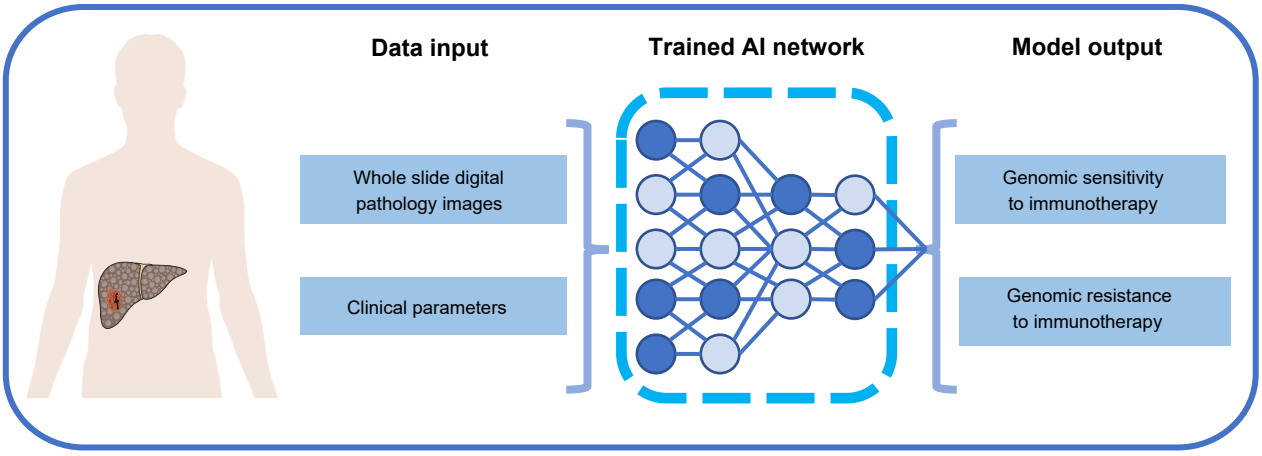

Fig. 1. This figure demonstrates a simplified workflow of the model proposed by Zeng Q. *et al.* A patient diagnosed with HCC undergoes tissue sampling and clinical assessment. The obtained data is used as input for a neural network. This pre-trained model predicts genomic marker expression status as a surrogate for tumor sensitivity to immunotherapy. HCC, hepatocellular carcinoma.

pertinent immune gene signatures with relatively high accuracy (AUC values of 0.74 to 0.87). More importantly, these results were reproducible in the validation dataset with AUCs as high as 0.81 to 0.91. At the same time, the authors demonstrated the added value of manual annotations across all techniques, which in their opinion underscored the importance of human-machine interactions. Although the vast majority of data were based on tissue obtained from surgically resected whole-tumor samples, the authors also included a very small subset of cases with tissue originating from pre-operative biopsies. Despite the limited sample size of just 7 cases, the previously trained and validated CLAM model accurately depicted 38 out of 42 predictive tumor immune clusters. The authors therefore concluded that AI-based pathology could in fact add value in the clinical environment and potentially deliver predictive biomarkers that will allow us to improve patient allocation to immunotherapy.

The findings of Zeng *et al.* represent a valuable contribution to the current evidence base in the rapidly evolving field of immunotherapy biomarker development and the authors should be commended for their rigorous experimental design and approach to patient data.[9] The team of investigators introduces clinically impactful knowledge that may be relatively straightforward to translate into practice in the near future. An important take-home message of this research relates to the combination of utilized methodologies. From a technical standpoint, a critical reader might argue that none of the utilized techniques introduce significant technical breakthroughs when considered in isolation. However, the authors must be given significant credit for combining numerous highly advanced but already established technologies to make a very strong case in favor of their clinical application to liver cancer management. All of the applied machine learning techniques are “off-the-shelf” and have been previously introduced and validated by the computer science community. Similarly, all of the applied methodologies of RNA sequencing and pathological image analysis are widely established. Yet, the key strength of this study lies in the combination and rigorous implementation of these tools applied in a highly complex cohort of patients with focus on a very practical outcome. The authors should be further commended for adding an unparalleled level of transparency to their study by making code and even aspects of their institutional data available on publicly accessible platforms. An additional important strength of this study is the fact that the authors used a combination of publicly available data for algorithm training and institutional data for validation. This approach represents good machine learning practice and highlights the landmark character of this study in setting a new standard in the field of liver cancer-related AI research. The authors clearly acknowledge limitations of their own study including its proof-of-concept character. One such issue is the utilization of surgically extracted whole-tumor samples rather than biopsies for the predictive process. While certainly valuable in a scenario where immunotherapy is used as adjuvant therapy after surgical resection, the application to tissue originating from biopsy samples in advanced stage disease is not yet sufficiently established. The authors also highlight the growing need for tissue sampling in HCC for the purpose of tumor characterization, suggesting that rigorous application of the Liver Imaging Reporting and Data Systems (LI-RADS) algorithm might be enough for diagnostic purposes but insufficient for personalized allocation of therapy. Ultimately, the translation of such high impact research from code to bedside demands time, effort and the understanding that broad success of immunotherapy in HCC will rely on our ability to predict therapeutic outcomes prior to allocating patients to specific drugs or their combinations. Machine learning-based methodologies are here to stay, and they are undoubtedly helpful when facing complex data samples. Yet, we should also acknowledge that such algorithms are not a panacea for biomarker development as long as we are limited by the quality and quantity of data we use as inputs. Therefore, collecting and curating high-quality datasets in our community remains critical to translating exciting research into daily practice. In conclusion, the authors deliver an impressive and thought-provoking proof-of-principle study which expands our knowledge base and motivates us to continue pursuing the translation of science from code to bedside as a promising direction to improve the management of HCC.

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Conflict of interest

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Please refer to the accompanying ICMJE disclosure form for further details.

Supplementary data

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References

[1] Siegel RL, Miller KD, Fuchs HE, Jemal A. Cancer statistics, 2022. CA Cancer J Clin 2022;72:7–33.

[2] Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, et al. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 2021;71:209–249.

[3] Karlsen TH, Sheron N, Zelber-Sagi S, Carrieri P, Dusheiko G, Bugianesi E, et al. The EASL-Lancet Liver Commission: protecting the next generation of Europeans against liver disease complications and premature mortality. Lancet 2022;399:61–116.

[4] Reig M, Forner A, Rimola J, Ferrer-Fabrega J, Burrel M, Garcia-Criado A, et al. BCLC strategy for prognosis prediction and treatment recommendation: the 2022 update. J Hepatol 2022;76:681–693.

[5] Llovet JM, Castet F, Heikenwalder M, Maini MK, Mazzaferro V, Pinato DJ, et al. Immunotherapies for hepatocellular carcinoma. Nat Rev Clin Oncol 2022;19:151–172.

[6] Huang AC, Zappasodi R. A decade of checkpoint blockade immunotherapy in melanoma: understanding the molecular basis for immune sensitivity and resistance. Nat Immunol 2022.

[7] Ruf B, Heinrich B, Greten TF. Immunobiology and immunotherapy of HCC: spotlight on innate and innate-like immune cells. Cell Mol Immunol 2021;18:112–127.

[8] Rebouissou S, Nault JC. Advances in molecular classification and precision oncology in hepatocellular carcinoma. J Hepatol 2020;72:215–229.

[9] Zeng Q, Klein C, Caruso S, Maille P, Laleh NG, Sommacale D, et al. Artificial intelligence predicts immune and inflammatory gene signatures directly from hepatocellular carcinoma histology. J Hepatol 2022;77:116–127.