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Editorial

Capturing hallmarks of cancer through the lens of artificial intelligence

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The conceptual framework for the hallmarks of cancer, which was first proposed by Hanahan and Weinberg in 2000[1] and updated in 2011[2] and 2022,[3] with a more recent version published in the spring of 2026, is the foundational blueprint of modern cancer research. This latest review moves beyond a simple list of tumor traits to organize the immense complexity of cancer into four interconnected dimensions.[4] The first dimension concerns acquired capabilities, which are the core functional capabilities cancer cells need to survive and spread. The original six hallmarks have grown to nine and now formally include unlocking phenotypic plasticity—the ability of cancer cells to change their identity to fuel growth, metastasis, and therapy resistance. The second dimension concerns enabling phenotypic characteristics, which is a new dimension that explains how cells acquire hallmarks. It includes long-recognized factors, such as genomic instability and tumor-promoting inflammation, alongside newer concepts, including non-mutational epigenetic reprogramming, the influence of polymorphic microbiomes, and innervation. The third dimension is the hallmark of conveying cells. As tumors are composed of many cell types, this dimension formally recognizes the critical roles of non-cancer cells, such as cancer-associated fibroblasts, immune cells, and endothelial cells, which are actively recruited and reprogrammed to enable every hallmark capability. Lastly, the fourth dimension involves systemic interactions. As cancer's influence extends beyond the tumor, this dimension covers cancer's impact on the entire body, including inducing cachexia, systemic immunosuppression, and the disruption of overall homeostasis. In essence, the current multidimensional model offers a powerful framework for understanding the full complexity of cancer and for guiding therapeutic strategies by co-targeting these interrelated parameters.

This expanded conceptual framework arrives at a pivotal moment. The same decades that saw the hallmarks framework mature have witnessed an explosion of genomic, transcriptomic, proteomic, spatial, and clinical data that threatens to overwhelm traditional analytical approaches. Into this breach steps artificial intelligence (AI). AI is not merely another tool in the cancer researcher's arsenal; it is becoming an indispensable lens capable of integrating the hallmarks framework's multiple dimensions, quantifying the previously unquantifiable, and revealing new biological insights that guide intelligent oncology. How AI is transforming each dimension of the hallmarks framework has accelerated our understanding and treatment of cancer. Collectively, AI technologies are helping crack each of these hallmarks in several ways.

Within Dimension 1, AI facilitates the quantitative characterization of the nine core hallmarks of cancer. Neural network architectures specifically designed for modeling biological complexity can now quantify hallmark activity directly by analyzing tumor gene-expression data. OncoMark,[5] a neural multi-task learning framework, has been found to achieve an average accuracy of over 99% in predicting the activity of the cancer hallmarks from a single tumor biopsy sample based on transcriptomic data. The datasets it used cover the nine classic hallmarks and refined enabling characteristics. The model has been trained on a total of 3.1 million single cells from 14 distinct cancer types, providing a comprehensive molecular profile that elucidates the active hallmarks in each patient's cancer. It moves diagnosis far beyond traditional staging, which often misses the molecular story behind why two patients with seemingly identical tumors can have dramatically different outcomes.[6] Similarly, HallmarkGraph[7] employs graph neural networks to integrate transcriptomic profiles with gene regulatory interactions. The use of the hallmarks framework as a biological guide achieves 85%–99% accuracy in classifying tumor subtypes across 11,476 samples from 26 cancers. These tools demonstrate that the hallmarks are not merely descriptive but can serve as quantitative biomarkers with prognostic and therapeutic significance.

AI can be used to decode the characteristics of the cellular ecosystem, thereby helping address Dimensions 2 and 3. Phenotypic characteristics, such as tumor-promoting inflammation, polymorphic microbiomes, and innervation, are shaped by both intrinsic tumor cells and interactions with non-cancerous cells in the tumor microenvironment. Deep learning's unique ability to decipher intricacies makes it a particularly suitable solution for problems involving cellular ecosystem characteristics. Single-cell RNA sequencing and spatial transcriptomics generate datasets of enormous dimensionality, capturing the transcriptional states of thousands of individual cells within a tumor.[8]

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Machine learning algorithms can deconvolve these data to map the heterogeneous populations of cancer-associated fibroblasts, tumor-associated macrophages, neutrophils, endothelial cells, and pericytes that collectively enable hallmark acquisition.[9,10] In the context of tumor-promoting inflammation, algorithms can now infer the activation states of innate immune cells from bulk transcriptomic data, revealing whether a tumor is dominated by inflammatory subsets that support cancer progression or by those that might respond to immunotherapy.[11] Similar approaches have increasingly been applied to investigate how the polymorphic microbiome, which is comprised of diverse bacterial and fungal communities within host tissues, modulates cancer phenotypes.[12] Furthermore, AI-driven analyses are advancing the emerging field of cancer neuroscience, which explores how neural signals, acting in concert with immune and microbial components, influence pro-tumor inflammation, anti-tumor immunity, and additional cancer hallmarks. Moreover, single-cell and spatial transcriptomics demonstrate intricate interactions between neurons and cancer cells.[13] Machine learning approaches applied to these high-dimensional datasets can identify receptor-ligand interactions mediating this crosstalk,[14] thereby uncovering novel therapeutic opportunities.

AI can be used to explore Dimension 4 by providing the capability to quantitatively model systemic interactions. The acknowledgment that cancer exerts effects beyond the primary tumor to influence the organism at the whole-body level is a particularly significant extension of the hallmark's framework. Systemic effects are not mere epiphenomena but integral components of the disease.[15] Thus, the modeling of these systemic interactions necessitates sophisticated AI approaches capable of integrating data across various scales, from molecular pathways to organ systems and whole-organism physiology. AI virtual cells[16] constitute a prime example of such methods, as it simulates interactions between tumors and the human body by integrating multimodal data. Although these approaches are still in early development, they embody a systemic view of cancer as a whole-organism disease rather than a localized abnormality.

The ultimate measure of any conceptual framework is its impact on patient care. The convergence of AI and the cancer hallmarks framework offers transformative potential in this regard. By providing a quantitative hallmark activity profile for tumors, AI can guide rational therapy selection.[17] As these tools mature, they will enable a new generation of clinical trials designed around hallmark-guided therapeutic strategies.

Cancer is a multidimensional, systems-level disease whose complexity the 2026 hallmarks framework seeks to capture. Intelligent oncology approaches, including AI-driven analyses of large-scale multimodal data, can operationalize this framework into a quantitative, clinically actionable guide for both oncologists and cancer researchers. Looking forward, as AI is used to help uncover previously unrecognized biological dimensions, the hallmarks framework can evolve to incorporate these new insights.

CRediT authorship contribution statement

Mengjiao Wei: Writing – original draft, Conceptualization. **Bo Xu:** Writing – review & editing, Supervision, Conceptualization.

Declaration of Competing Interest

Bo Xu is the Editor-in-Chief of Intelligent Oncology and the authors declare no conflicts of interest.

References

1. Hanahan D, Weinberg RA. The hallmarks of cancer. *Cell.* 2000;100(1):57–70.
2. Hanahan D, Weinberg RA. Hallmarks of cancer: the next generation. *Cell.* 2011;144(5):646–674.
3. Hanahan D. Hallmarks of cancer: new dimensions. *Cancer Discov.* 2022;12(1):31–46.
4. Hanahan D. Hallmarks of cancer-then and now, and beyond. *Cell.* 2026;189(8):2254–2277.
5. Priyadarshi S, Mazumder C, Neekhra B, et al. OncoMark: a high-throughput neural multi-task learning framework for comprehensive cancer hallmark quantification. *Commun Biol.* 2025;8(1):1434.
6. Parker JS, Mullins M, Cheang MCU, et al. Supervised risk predictor of breast cancer based on intrinsic subtypes. *J Clin Oncol.* 2009;27(8):1160–1167.
7. Zhang Q, Liu F, Lai X. HallmarkGraph: a cancer hallmark informed graph neural network for classifying hierarchical tumor subtypes. *Bioinformatics.* 2025;41(9):btaf444.
8. Ma C, Yang C, Peng A, et al. Pan-cancer spatially resolved single-cell analysis reveals the crosstalk between cancer-associated fibroblasts and tumor microenvironment. *Mol Cancer.* 2023;22(1):170.
9. Xue Y, Friedl V, Ding H, Wong CK, Stuart JM. Single-cell signatures identify microenvironment factors in tumors associated with patient outcomes. *Cell Rep Methods.* 2024;4(6):100799.
10. Huynh KLA, Tyc KM, Matuck BF, et al. Deconvolution of cell types and states in spatial multiomics utilizing TACIT. *Nat Commun.* 2025;16(1):3747.
11. Mayoh C, Gifford AJ, Terry R, et al. A novel transcriptional signature identifies T-cell infiltration in high-risk paediatric cancer. *Genome Med.* 2023;15(1):20.
12. Hernández Medina R, Kutuzova S, Nielsen KN, et al. Machine learning and deep learning applications in microbiome research. *ISME Commun.* 2022;2(1):98.
13. Winkler F, Venkatesh HS, Amit M, et al. Cancer neuroscience: state of the field, emerging directions. *Cell.* 2023;186(8):1689–1707.
14. Chen B, Zhou X, Yang L, et al. A cuproptosis activation scoring model predicts neoplasm-immunity interactions and personalized treatments in glioma. *Comput Biol Med.* 2022;148:105924.
15. Swanton C, Bernard E, Abbosh C, et al. Embracing cancer complexity: hallmarks of systemic disease. *Cell.* 2024;187(7):1589–1616.
16. Bunne C, Roohani Y, Rosen Y, et al. How to build the virtual cell with artificial intelligence: priorities and opportunities. *Cell.* 2024;187(25):7045–7063.
17. Chang TG, Park S, Schäffer AA, et al. Hallmarks of artificial intelligence contributions to precision oncology. *Nat Cancer.* 2025;6(3):417–431.