

## A Roadmap to Transcriptomic Deconvolution in Cancer

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### **Abstract:**

Cancer is characterized by vast transcriptional variations in genes and pathways. Cancer tissues are complex heterogeneous mixtures of epithelial, stromal and immune cells, with each group comprising multiple distinct cell types and states. This heterogeneity has likely led to numerous contradictory findings in the literature over the past 30 years of high-throughput transcriptomic profiling of tumor tissues, thereby impeding a better understanding of cancer biology. Two approaches to address this issue are single-cell RNA-seq profiling and bulk RNA-seq deconvolution. Due to the higher cost and sample quality requirements of single-cell profiling, bulk RNA sequencing remains widely used for a vast amount of patient tissues. An important analytical challenge is how to integrate information from the two technologies to fully uncover the tumor-microenvironment (TME) landscape of cancer. I will provide a guide to more than 50 published deconvolution methods and introduce our work on DeMixT/TmS, DeMixSC and DeMixNB to demonstrate methodological unmet needs and outstanding opportunities for cancer biomarker discoveries to improve clinical decision-making through deconvolution.

### **Reading list:**

- A guide to transcriptomic deconvolution. [Dai, Yaoyi, et al. "A Guide to Transcriptomic Deconvolution in Cancer." Nature Reviews Cancer, 2025, pp. 1–20, <https://doi.org/10.1038/s41568-025-00886-9>.](https://doi.org/10.1038/s41568-025-00886-9)
- DeMixNB. [Montierth, M. D., Yan, H., Xie, L., Nemeth, K., Pan, X., Li, R., Ercan, C., Yang, P., Sinjab, A., Zhou, T., Peng, F., Singh, M., Wang, L., Kopetz, S., Kadara, H., Yuan, Y., Calin, G. A., & Wang, W. \(2025\). Deconvolution of Sparse-Count RNA Sequencing Data for Tumor Cells Using Embedded Negative Binomial Distributions. <https://doi.org/10.1101/2025.11.21.689822>](https://doi.org/10.1101/2025.11.21.689822)
- DeMixSC. [A deconvolution framework that uses single-cell sequencing plus a small benchmark data set for accurate analysis of cell type ratios in complex tissue samples](#)
- TmS. [Cao, S., Wang, J.R., Ji, S. et al. Estimation of tumor cell total mRNA expression in 15 cancer types predicts disease progression. Nat Biotechnol 40, 1624–1633 \(2022\). <https://doi.org/10.1038/s41587-022-01342-x>](https://doi.org/10.1038/s41587-022-01342-x)