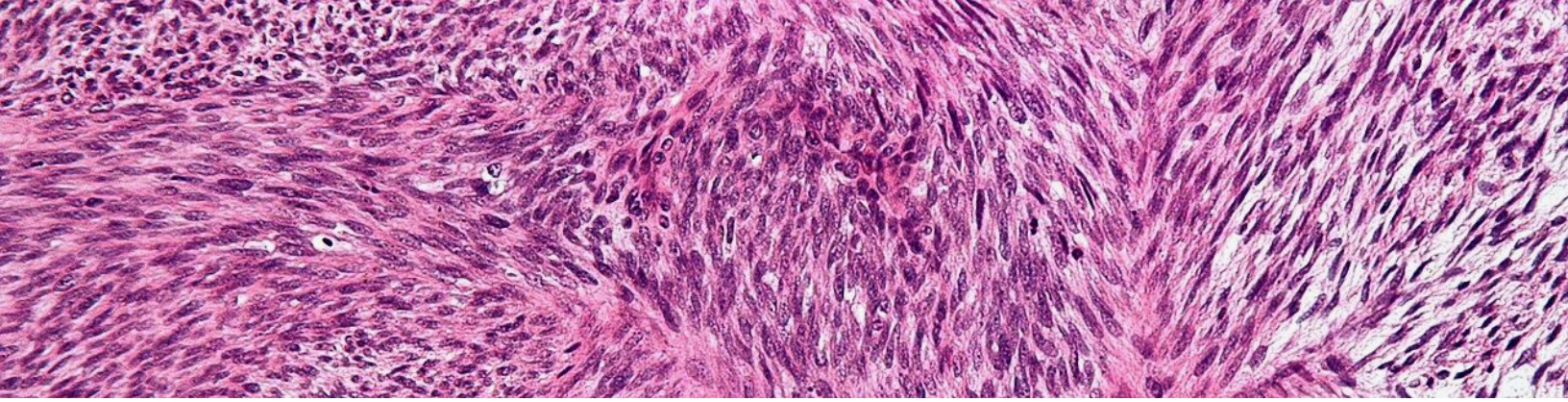

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Profiling cancer with SEQUOIA

Deep-learning model estimates gene expression from images of pathology slides

Cancer can look monolithic, a diagnosis that touches many of us across our lifetimes. But to think of cancer as a single disease misses its complexity: tumors — and the cells within them — are constantly evolving, locked in an arms race with the body's defenses.

Knowing which genes are expressed within a tumor, from the cells in its center to those rapidly growing and dividing at its invasive edges, can tell clinicians a lot: how fast the tumor is growing, what therapies it may be resistant to, and how to best treat it. But current technologies, like RNA sequencing (RNA-seq), remain too expensive and time-consuming for routine use in clinical diagnostics, where every minute and every dollar counts.

In a recent article in *Nature Communications*, Marija Pizurica and colleagues introduce SEQUOIA, an AI tool that uses routine clinical pathology slides to predict gene-expression patterns in tumors with remarkable accuracy.

Approach

SEQUOIA is a deep-learning model that builds on recent AI advances with two innovations: a new image encoder ("UNI") optimized for the unique visual characteristics of pathology slides, and a "linearized attention" mechanism that allows its transformer model to process gigapixel-sized pathology images more efficiently.

SEQUOIA at a glance

- **What it is:** AI model that predicts tumor gene expression directly from standard pathology slides, aiding cancer research and diagnosis.
- **How it works:** Analyzes digital images of H&E-stained slides to estimate whole-slide and regional gene-expression patterns.
- **Tested on:** 7,584 tumor samples representing 16 cancer types from The Cancer Genome Atlas.
- **Results:** Predicted several-fold more genes with significant accuracy than earlier image-based approaches.
- **Why it matters:** Provides a faster, potentially lower-cost way to molecularly profile tumors using routine clinical samples.

To train and evaluate SEQUOIA, the authors used 7,584 tumor samples from The Cancer Genome Atlas, representing whole-image slides matched to bulk RNA-seq gene expression data from 16 cancer types.

Benchmarking
SEQUOIA was benchmarked against earlier deep-learning approaches for predicting gene expression from histology, including architectures inspired by HE2RNA (which aggregates image features with simple MLP neural networks) and tRNAsformer (which uses transformer aggregation).

Across cancer types, SEQUOIA consistently outperformed earlier approaches, accurately predicting several-fold more genes. Replacing the traditional ResNet image encoder with UNI increased the number of well-predicted genes by 155% to 830%, depending on the dataset and aggregation method. The genes SEQUOIA predicted reflect those involved in processes implicated in cancer, like inflammation, metabolism, and cell-cycle regulation.

SEQUOIA also generalizes well to unseen data, maintaining its predictive accuracy on two independent datasets (CPTAC and Tempus) representing 1,368 tumor samples. And even though SEQUOIA was trained on images of whole slides, it accurately reconstructed localized gene expression patterns within slides when tested on two spatial transcriptomic datasets, outperforming HE2RNA.

Implications
SEQUOIA offers a more computationally efficient alternative to state-of-the-art approaches, with the added benefit of accurately estimating gene-expression profiles of different cellular regions on a slide.

While the tool is promising for cancer research, it has prognostic value in the clinic too: the risk scores it generated from images of breast cancer tissue matched closely with both RNA-seq data and patient survival — demonstrating the potential to use histology-only prognostic screening.

As digital pathology and AI continue to evolve, tools like SEQUOIA could make molecular profiling a routine part of cancer diagnosis, bringing genomic insights directly to the microscope.

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