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# Machine learning tool could help oncologists make better treatment decisions

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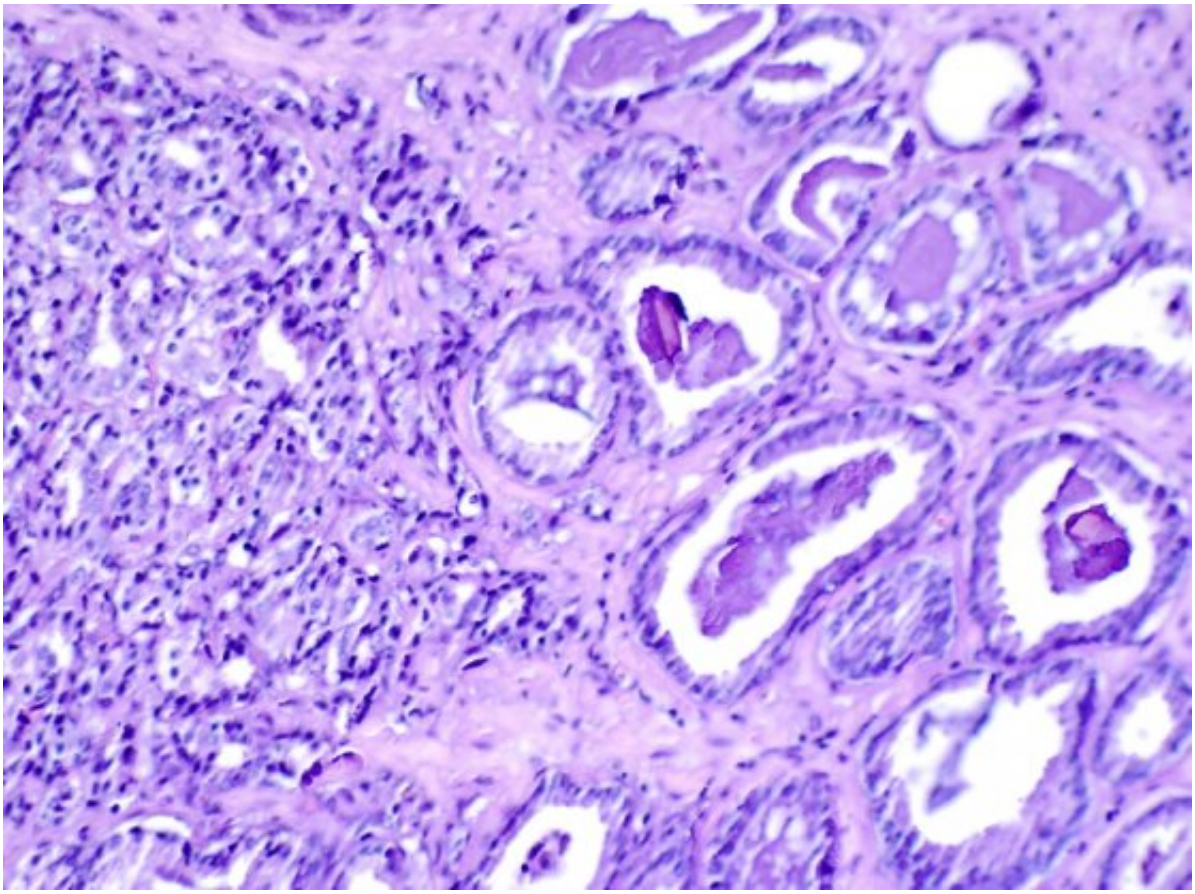

A histological slide showing prostate cancer. Credit: Otis Brawley

When treating a cancer patient, oncologists aim to predict the course of the patient's disease to make critical treatment decisions. Knowing a tumor's unique molecular signature can help guide these decisions by

providing clues on whether a cancer is slow-growing or aggressive and deadly, or one that will resist treatment. New molecular profiling technologies have generated a wealth of information on tumors, but physicians have struggled to turn all that data into meaningful prognoses.

Researchers at the Broad Institute of MIT and Harvard and the Dana-Farber Cancer Institute have developed a new model that can differentiate between the genomic profiles of prostate cancers that are lethal and those that are unlikely to cause symptoms or death. It may also help clinicians predict whether a prostate cancer patient's tumor will spread to other parts of the body or become more resistant to treatment over time. The model, called P-NET, can also identify molecular features, genes, and biological pathways that may be linked to disease progression. P-NET uses machine-learning based algorithms to analyze a tumor's known molecular characteristics and indicate whether the tumor has or will likely spread to a different part of the body—a sign of an aggressive and potentially lethal cancer. Published in *Nature*, the model could also help cancer researchers learn more about the biology of drug-resistant disease, and it may be generalizable to other cancers.

P-NET offers more than just a prognosis for patients, said Eliezer (Eli) Van Allen, associate member at the Broad, associate professor at Dana-Farber Cancer Institute and Harvard Medical School, and senior author of the study. "Not only do we improve our ability to predict if a cancer will be metastatic, and which genes might be associated with that state, but as cancer researchers, we can use the interpretability of this model to learn about the biology of these disease states," he said.

## Building a better model

To build a model that could distinguish between early and advanced prostate cancer tumors, the researchers developed a specialized deep learning model with custom architecture and improved interpretability

compared to other algorithms. In deep learning models, multilayered neural networks "learn" from large datasets to recognize patterns as a human brain might.

Using this approach, the team—led by Haitham Elmarakeby, instructor at the Dana-Farber Cancer Institute, affiliate researcher at Broad, and first author of the study—encoded biological information, such as known relationships between genes and metabolic or signaling pathways, directly into their model. They then trained P-NET to predict whether a tumor was aggressive using data such as genomic sequences and somatic, or uninherited, mutations from more than 1,000 prostate cancer patients. When the team tested their model on data from other prostate cancer patients, they found that it correctly distinguished 80 percent of metastatic tumors from primary, less advanced tumors. This shows that the trained model is able to perform the same function on new data.

By examining P-NET and weighting genes and pathways based on their importance, the team also identified the gene MDM4 as potentially involved in prostate cancer progression and drug resistance. Scientists had previously implicated the gene in other cancers, but not prostate cancer. In collaboration with the lab of William Hahn, institute member at Broad, the team found that MDM4 overexpression in prostate tumor cells was associated with drug resistance. When they turned off the gene using gene editing, cell proliferation decreased, showing that the cancer cells could be more sensitive to treatment. These results suggest that scientists could repurpose drugs that inhibit MDM4—some of which are currently being studied for other cancers—to treat prostate tumors.

The researchers say that with modifications, P-NET could help oncologists predict disease progression and treatment response in other cancers, too. "This kind of architecture is not limited to prostate cancer," said Elmarakeby. "Our model has a lot of potential to be expanded in different ways."

Van Allen adds that P-NET will continue to improve as he and his team integrate other kinds of data—including more genetic and imaging data—into the model. "This is just the beginning for how we can enable a convergence between cancer biology and machine learning," he said. "That convergence is where we believe we can really deliver more discoveries to cancer patients."

**More information:** Haitham A. Elmarakeby et al, Biologically informed deep neural network for prostate cancer classification and discovery. *Nature* (2021). doi.org/10.1038/s41586-021-03922-4

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