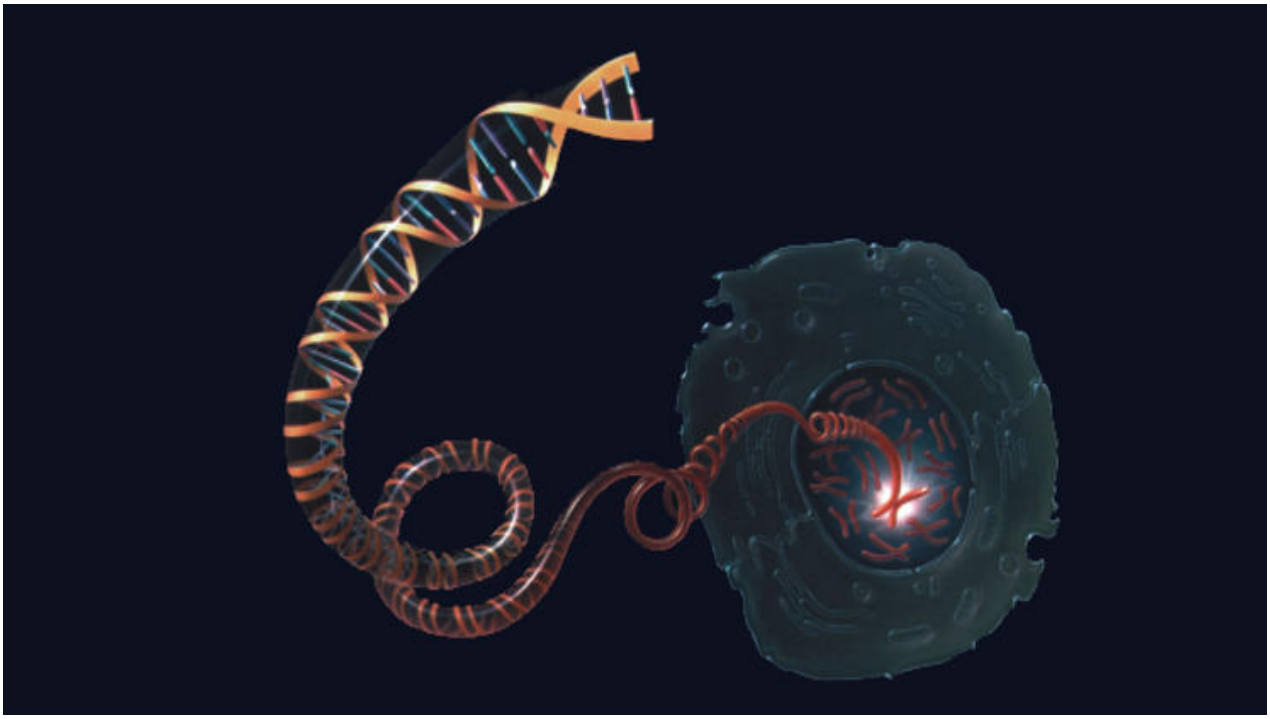
Don't judge every tumor by its tissue, scientists say



The genomes of some cancer tumors may tell doctors more about how to treat them than where they occur in the body. (National Human Genome Research Institute)

By JULIA ROSEN

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For most cancer patients and their doctors, the most important things to know about a tumor are where it arose in the body and how much it's grown. But in some cases, understanding a tumor's genomic profile is more likely to lead to an effective treatment, according to a study published online Thursday by the journal Cell.

After performing a thorough analysis of 3,527 tumor specimens representing a dozen types of cancers, scientists concluded that 10% of patients could find better therapies if they had information about their tumor's unique DNA and how it is expressed.

The genetic analysis can give doctors "clinically relevant prognostic information above and beyond tumor stage and primary tissue-of-origin," they wrote. "If used to guide therapeutic decisions, this reclassification would affect a significant number of patients to be considered for

nonstandard treatment regimens."

The findings draw on years of work by the Cancer Genome Atlas Project, a massive collaboration between the National Institutes of Health, hospitals, universities and other research institutions across the country. Scientists working with TCGA, as the program is known, have studied various properties of each tumor in their vast collection. They have cataloged the small variations in their DNA code, which genes are turned on and off, and the assortment of proteins present in the tumor cells.

At first, they worked through each type of cancer, one by one. Then they noticed that some tumors started to seem familiar.

"As we looked at more and more tumor types, it became clear that there were some subsets of tumors that reminded us of a subset we analyzed last year," said Josh Stuart, a biomolecular engineer at UC Santa Cruz who oversaw the study. "It was obvious that we should start comparing across tumor types."

So the team came up with a mathematical technique for grouping tumors based on their genomic similarities.

Put simply, the method classifies tumors six different ways. Then it gives one "vote" to each method. The vote tally determines how the tumor is ultimately categorized, Stuart said.

Out of the multitudes of tumors, the researchers identified 11 distinct clusters. Five of these contained only cancers of a single tissue, such as endometrial cancer or renal cell carcinoma.

However, the rest were more complicated.

Two of the clusters included tumors from several different organs, revealing hidden similarities among seemingly distinct cancers. For instance, one cluster grouped colon and rectal cancers, whose resemblance has been described in previous studies.

In other cases, cancers from one part of the body wound up in multiple clusters, revealing significant differences in tumors of a single tissue. Bladder cancers, for instance, were strewn across seven different categories because of differences in their gene activity.

Breast cancers also fell into two distinct groups that distinguished between so-called luminal and basal tumors, named after the cell layers from which they arise. The researchers were surprised by the high degree of difference between them.

"They looked like different tissues," Stuart said.

The team members were particularly intrigued by a ragtag group of tumors that included specimens from head and neck cancers, bladder cancers and lung cancers. They dubbed this the group the "squamous-like" subtype, because all the specimens appeared to stem from squamous cells. These scaly cells are the main component of the skin's upper layers, but they also populate the lining of the lungs and, potentially, the bladder.

The researchers say this could be an example of the "cell of origin" idea for why cancers from different parts of the body can look similar — because they arise in the same types of cells.

An alternative possibility is that the same sequence of events leads to tumor development in different tissues, a phenomenon known as a common pathway. Or, different organs could be vulnerable to the same environmental risks. For example, Stuart said squamous cells in the throat and bladder both bathe "in the same carcinogenic 'soup' like the mutagens from tobacco smoke." In reality, he said, it's probably a combination of "what they are exposed to and what they are sensitive to."

Regardless of the cause, the researchers hope the patterns revealed in their results will eventually translate into tangible benefits for cancer patients. To accelerate this, they have made all their results available in a publicly searchable archive.

Trey Ideker, chief of medical genetics at the UC San Diego School of Medicine, said this could significantly change doctors' behavior. This work "essentially demands that alongside the normal work-up, you've got to perform these layers of profiling they talk about."

If doctors conducted any of the genomic tests used in the new study, they could use the database to classify the tumor and determine the best course of action for patients. And Ideker said the data may eventually help researchers and drug developers come up with better treatments.

"Nine out of 10 drugs fail" when they are tested in clinical trials, he said. "One of the leading hypotheses is that the subset of patients that respond have a different genetic profile. Maybe this resource has the keys to understanding that."

John Quackenbush, a computational biologist at the Dana-Farber Cancer Institute in Boston, agreed that the results have the potential to advance alternative interventions for hard-to-treat tumors. But, he added, they might gloss over important distinctions.

For instance, the analysis grouped two distinct types of breast cancer — one that feeds on

estrogen and another on an epidermal growth factor captured by a receptor called HER2 — that require very different treatments into the same category. In this case, the data "missed something big," Quackenbush said.

Stuart said he hoped the study would prompt other scientists to try to understand why some cancers show strong associations with their tissues while other do not.

"This is by no means an endpoint," Stuart said.

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