Tumor-only genetic sequencing may misguide cancer treatment in nearly half of all patients

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DNA sequencing is becoming a key tool for determining personalized therapy for cancer patients. Credit: Sonya Parpart-Li

A study by Johns Hopkins scientists strongly suggests that sequencing tumor genomes for clues to genetic changes might misdirect treatment in nearly half of all patients unless it is compared first to a genetic readout of their noncancerous tissue.

The investigators at the Johns Hopkins Kimmel Cancer Center say their analysis of more than 800 cancer patients' sequencing data, which was generated by Personal Genome Diagnostics Inc., a company co-founded by the researchers, shows that without such comparisons, attempts to individualize cancer therapy may be inappropriate in certain cases, and patients may get the wrong targeted therapies.

A report on the work appears in the April 16 issue of *Science Translational Medicine*.

"Increasingly, hospitals and companies are beginning to sequence patients' tumors in an attempt to personalize therapy. However, many are not sequencing each person's normal tissue to filter out noncancer-related changes and to really understand what is occurring in the tumor," says Victor Velculescu, M.D., Ph.D., a professor of oncology and pathology and co-director of the Cancer Biology Program at the Johns Hopkins University School of Medicine.

Velculescu explains that personalized therapies increasingly designed to target the unique genetic changes that drive a person's tumor depend on accurate assessment of a tumor genome, but not all genetic changes in a cancer are directly related to the cancer. Some, he explains, are so-called germline changes, which are inherited changes in genes that are in normal tissues and differ from person to person.

"We all carry variations in our germline genome. They're part of what makes us individually unique," says Valsamo Anagnostou, M.D., Ph.D., a clinical fellow at the Johns Hopkins University School of Medicine and

co-author of the study. Only by comparing the genetic sequence of an individual's tumor and his or her own normal cells can clinicians know which changes are more likely to be cancer-related and which treatments are likely to work.

Treatment decisions based on faulty genetic information might affect "any patient whose genome is being sequenced right now and could amount to thousands of patients in the near future" as genetic testing of tumors becomes more common, Anagnostou says. Inaccurate genetic information can lead to serious side effects from inappropriate therapies, lack of useful targeted therapies and increased costs of patient care from misguided medicines.

For the study, Velculescu and his colleagues compared the genomes of tumor and normal tissue from 815 patients who had a variety of cancers, including breast, brain, renal, gastric, lung, pancreatic, blood cancers and melanoma.

When the researchers only looked at the genetic changes found in a patient's tumor and filtered out the most well-known germline changes, they counted 382 possible tumor-related changes. But after comparing a patient's full germline genome to his or her tumor genomes, they determined that, on average, 249 of these changes were part of the patient's normal, inherited genetic variation and were not tumor-specific.

In other words, Velculescu says, 65 percent of the genetic changes identified with tumor-only genetic sequencing were "false positives" and not related to the patient's cancer.

The researchers also looked at changes in "actionable genes," or genes for which some kind of drug or cancer therapy has already been identified. When they looked for these changes in the tumor alone, they identified on average 2.4 changes per patient. However, they found that

33 percent of those changes were also false positives when they compared the tumor genome to the patient's germline genome. These false positives affected 48 percent of the patients analyzed.

"In tumor-only analyses, we found that nearly half of patients had tumor mutations that were actually germline or false positives in actionable genes, and they could lead to inappropriate therapy," Velculescu says.

Velculescu and his team acknowledge there may be challenges in implementing tumor-normal analyses in a clinical setting. These include the additional work and costs of sequencing and analyzing a patient's normal tissue along with his or her tumor tissue but Velculescu says some efficiencies could be realized by using the patient's saliva, blood or normal tissue recovered during a biopsy or tumor removal. Costs for tumor gene sequencing begin at several thousand dollars, which would increase if sequencing was done on DNA from normal tissue as well. Velculescu also notes that health insurance may not fully cover normal-tissue genetic sequencing. Addressing concerns about patient privacy when normal genomes are sequenced, Velculescu says that comparisons of tumor and normal sequences can be designed to use germline changes as a filter without identifying what those germline changes are and what their potential health implications might be.

In addition to selecting personalized therapies for patients with cancer, sequencing the normal tissue genome can also increase the overall understanding of cancer, including finding cancer predisposition due to germline genome changes, says Velculescu. In this study, the germline analyses identified changes in cancer-related genes in 3 percent of the patients who had no known signs of genetically linked cancer. "These analyses can help us find alterations in cancer-predisposing genes in ways that weren't previously appreciated," he suggests.

More information: Personalized genomic analyses for cancer

mutation discovery and interpretation, stm.sciencemag.org/lookup/doi/ … scitranslmed.aaa7161