Computer algorithm used to identify bladder cancer marker

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Researchers at the Stanford University School of Medicine have used an innovative mathematical technique to find markers that effectively predict how deadly a cancer will be. The discovery, which in this case concerned bladder cancer, could lead to faster, less expensive and more accurate analysis of cancer risk and better treatment of the disease.

The findings were published online Jan. 16 in the Proceedings of the National Academy of Sciences. This is the first study in which a special Stanford-designed computer algorithm was used to identify a clinically prognostic marker from public databases, though the search tool was introduced in a paper published two years ago that established its effectiveness in identifying markers in mice.

Bladder cancer is the sixth most common malignancy and is responsible for about 15,000 deaths per year in the United States. Currently, the severity and aggressiveness of bladder cancer is gauged by a pathologist who inspects a sample of the cancer tissue in the laboratory. This approach requires time and the expertise of a pathologist with special training. "This approach is very subjective and can result in conflicting reports from expert pathologists," said Debashis Sahoo, PhD, one of three lead authors of the paper and an instructor of pathology at Stanford. The new research offers the promise of an easy, antibody-based test that can be used by someone with little training to quickly determine whether a bladder cancer is of the most dangerous type.

Allowing clinicians to evaluate the risk of individual tumors based on

their molecular characteristics will have profound impact on the health care of bladder cancer patients, the researchers said. "Currently there is no way so to predict if a patient has the less- or more-aggressive subtype of bladder cancer early on," said Jens-Peter Volkmer, MD, another first author of the paper and a postdoctoral scholar at Stanford. "This technique might be used to identify the patients with the more-aggressive subtype before the cancer becomes invasive or metastatic."

Those who already have invasive cancer of the more-aggressive subtype would be candidates for additional therapies, such as chemotherapy, even before metastasis could be detected, added Robert Chin, MD, PhD, of the University of Chicago Medical Center, the third lead author of the paper. The paper has two senior authors: Irving Weissman, MD, the Virginia and D.K. Ludwig Professor for Clinical Investigation and Cancer Research at Stanford, and Keith Syson Chan, PhD, formerly at Stanford and now an assistant professor professor at the Baylor College of Medicine in Houston.

"Patients deserve to have an accurate opinion of what will happen to them after they have had surgery for bladder cancer, and this test will give the most accurate assessment to date," Weissman said. "Its simplicity should allow surgeons and oncologists to make better decisions, and patients to understand better how they should organize their lives. The simplicity of the test should make it easily affordable, and therefore not add to the burden of medical costs."

To devise this new test, the researchers took an approach, based in developmental biology, to assess the cancer. They started with the knowledge that cancer cells that are more "primitive" (closer in appearance and function to stem cells) are more dangerous than cancer cells that are more "differentiated" (less similar to stem cells). They also knew from previous research that two molecules, keratin-5 and keratin-20, were associated with more-differentiated bladder cells (both

normal and cancerous).

The researchers used a unique tool — the computer algorithm developed at Stanford —that allows them to take two biologically related proteins and quickly sort through thousands of public databases to find other molecules that are similarly related. The validity of this "Boolean" search strategy had been demonstrated in a research paper published in *PNAS* in 2010 that looked at development of immunological cells in mice (http://www.physorg.com/news187879201.html). Using this technique, they found another molecule, keratin-14, that was associated with less-differentiated, more-primitive bladder cells.

With this information in hand, they hypothesized that bladder cancers generally come in three types corresponding to the different forms of keratin, and that the bladder cancer cells making keratin-14 would be the most malignant. The researchers then found cell surface markers unique to each of these types of cells and used antibodies to collect purified cells for further experiment.

The validity of this approach was confirmed when the scientists analyzed pathological samples from former bladder cancer patients and found that the presence of cells creating keratin-14 were indeed associated with worse prognoses. The researchers also used their antibodies to isolate different types of bladder cancer cells and showed that the "primitive" cells associated with keratin-14 could cause the most aggressive cancer when transplanted into mice.

While a bladder cancer test that uses antibody staining will not replace staging and grading by a pathologist, it offers additional information that can lead to more accurate diagnosis. "It also can provide rapid information about the cancer in rural areas or poor countries where a pathologist experienced with bladder cancer may not be immediately available," said Sahoo, the researcher who developed the Boolean search

algorithm.

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