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# New diagnostic tool for complex cancer cases

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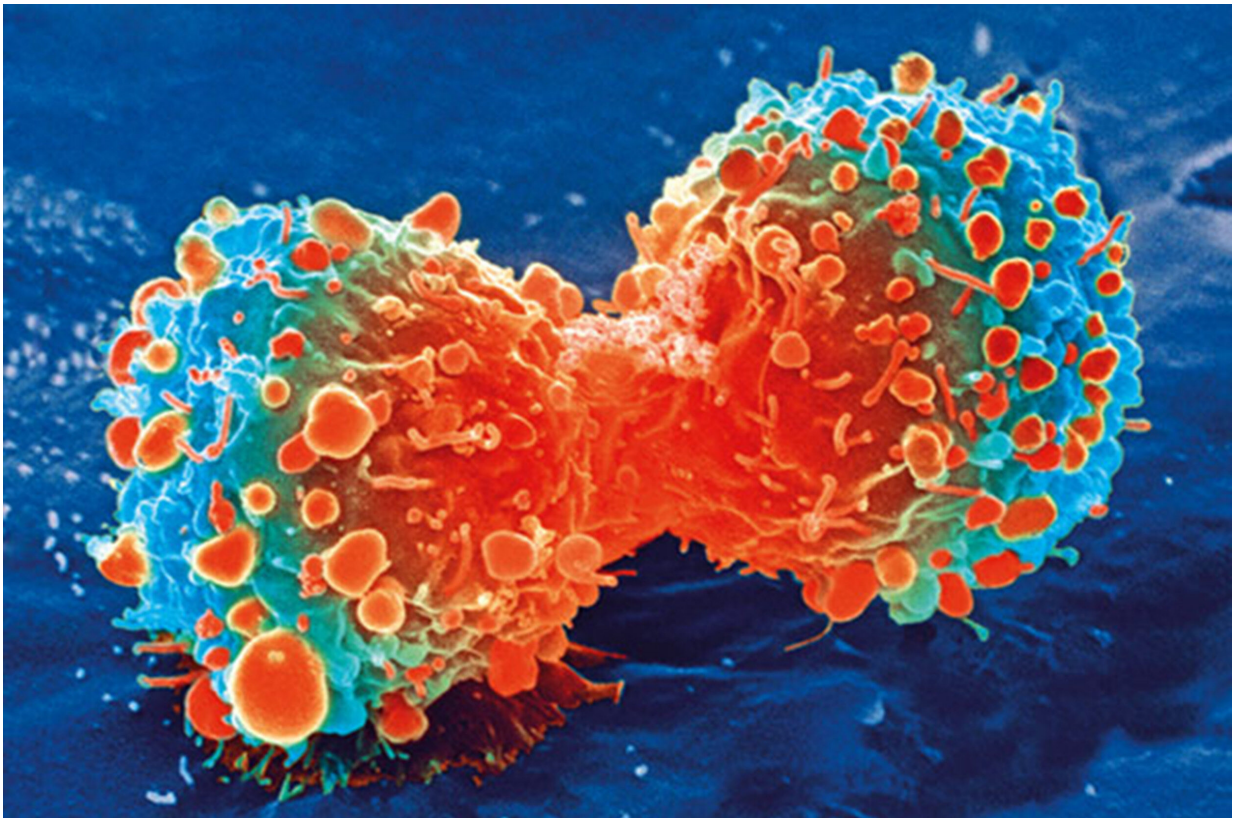

Cancer cell during cell division. Credit: National Institutes of Health

A new diagnostic tool is expected to result in better treatment of cancer that is difficult to diagnose. The tool was developed by cancer researchers at Sahlgrenska Academy and doctors at Sahlgrenska University Hospital, Sweden. Their study, which has been published in *JCO Precision Oncology*, started with a single cancer patient.

"We believe that the analytical methods described have rather direct implications that can help patients who lack a correct diagnosis of cancer," says Jonas Nilsson, professor of experimental cancer surgery and director of the Sahlgrenska Cancer Center.

The patient came to Sahlgrenska University Hospital with lung cancer that had recurred several times, despite various treatments in the hospital. The disease proved fatal, but the patient contributed several biopsies for research before dying. The key to a correct diagnosis in this case turned out to be ascertaining and defining the tumor's character and origin in detail, which did not correlate with the clinical picture. This required a large number of analyses before and after the patient's death.

The extensive analytical work presented many surprises. One was a rapid growth of the tumor under the skin of mice when a biopsy was introduced. Another analysis showed that this did not involve a traditional type of lung cancer, but rather a neuroendocrine (hormone-producing) cancer. The tumor also proved to have an unexpected mutation in a specific cancer gene called BRAF.

"What is most remarkable about this finding was that it meant the patient could be treated with what are called BRAF inhibitors, which were effective and also led to a shrinkage of the patient's tumor," Jonas Nilsson says. "The patient's tumor in the mouse also grew more slowly when the mouse was treated with BRAF inhibitors. But unfortunately, the tumor recurred after half a year, and the patient died."

A novel method called mutation signature analysis showed that the tumor most likely originated in the patient's skin. Joakim Karlsson, a doctoral student in bioinformatics and one of three lead authors explains: "When ultraviolet rays from the sun strike skin cells, a very characteristic mutational pattern occurs with the repair of ultraviolet-induced DNA damage. All biopsies from the patient we analyzed had this pattern," he

says.

A comparison with the RNA sequencing data from 9,000 tumors in the Cancer Genome Atlas (TCGA) database showed that biopsies from the lung cancer had a correlation to malignant melanoma of more than 90 percent. Therefore, this tumor was not a lung cancer but a metastasis of melanoma residing in the lung. The value of applying multiple advanced analyses to more complicated tumors to provide proper treatment is underscored by Joakim and the other two lead authors, Roger Olofsson Bagge, a surgeon, and Akif Demir, a pathologist, at Sahlgrenska University Hospital.

Many treatments are approved by the Medical Products Agency Sweden for a certain diagnosis, but not for other. Correction of a diagnosis can therefore result in a different and more appropriate treatment for the patient with complex cancer.

**More information:** Roger Olofsson Bagge et al. Mutational Signature and Transcriptomic Classification Analyses as the Decisive Diagnostic Tools for a Cancer of Unknown Primary, *JCO Precision Oncology* (2018). DOI: 10.1200/PO.18.00002

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