UNC-developed tools improve accuracy of cancer DNA sequencing

The ability of researchers and physicians to use DNA sequencing to pinpoint the genetic mutations that cause cancer has led to greater understanding of the causes of the disease and development of drugs that treat tumors by targeting specific mutations. A pair of papers published by researchers at the UNC Lineberger Comprehensive Cancer Center reveal new tools that can improve the accuracy of tumor sequencing.

The first paper by UNC Lineberger member Matthew Wilkerson, PhD, published in *Nucleic Acids Research*, reveals a new tool for improving the accuracy of DNA sequencing aimed at identifying mutations in a patient's tumor that cause cancer. The tool, called UNCeqR, integrates RNA sequencing to improve the accuracy of results from DNA sequencing.

click to enlarge

UNC Lineberger members Matthew Wilkerson, PhD, and Lisle Mose

"We proved that it increases performance. The big finding is that it increases performance more than 100 percent for low purity tumors," said Wilkerson.

Personalized medicine for cancer works by identifying mutations in individual patients' DNA. Knowing which mutations caused a cancer allows physicians to choose targeted drugs that attack specific mutations. Physicians at UNC Lineberger already use DNA sequencing to assist in treatment of patients with difficult to treat cancers through the UNCseq program and to conduct basic science research on the causes and treatments of the disease.

Wilkerson's method can find mutations that would normally be missed in DNA sequenced from samples with low purity taken from tumors with a mixture of healthy and cancerous cells. While low purity samples are especially common in breast cancer, they can be found in most forms of the disease.

"It is a tumor where, when you look on a slide, there are cancer cells and also normal cells, and they are mixed in at a high proportion. In some cancer types, like breast cancer, there can be a very small proportion of cancer cells," said Wilkerson.

Since the DNA sequencing results reflect this mix of normal and cancerous cells, unique mutations can be missed. Wilkerson's RNA integrated method provides a new tool for revealing those masked mutations.

"We demonstrated that RNA often provides a greater mutational signal than DNA because cancer cells can express very high levels of mutant genes. This greater signal enables UNCeqR to make more positive mutation detections with confidence." said Wilkerson.

The second paper, written by Lisle Mose and published in *Bioinformatics,* reveals another tool developed at UNC to help researchers and physicians identify cancer-causing mutations. The Assembly Based Re-Aligner (ABRA) can identify mutations in the genome that are difficult to detect using traditional bioinformatics methods.

DNA sequencing produces “reads” that map out multiple, fragmented sequences of the genome. Researchers piece together the results by identifying overlapping areas and using a reference genome sequence to determine how to fit the results together. ABRA is able to use the context of multiple reads to generate more accurate read mappings, providing a better picture of mutations appearing in the genome.

“This improves our ability to identify more complex variants downstream, particularly insertions and deletions,” said Mose.

This improved mutation detection ability provides physicians with greater information about how to choose targeted therapies. ABRA is currently being used in identifying mutations in patients enrolled in UNCseq and has already identified patient mutations that would not otherwise have been detected.

“It enhances our ability to provide treatment for patients in that project,” said Mose.

Matthew Wilkerson, PhD and Lisle Mose are members of the UNC Lineberger Bioinformatics Core. Matthew Wilkerson is also a member of the Department of Genetics. Other UNC authors among both publications include: Joel S. Parker PhD, Christopher Cabanski PhD, Wei Sun PhD, Katherine A. Hoadley PhD, Vonn Walter PhD, Melissa A. Troester PhD, Charles M. Perou, PhD, D. Neil Hayes MD, MPh.

The research was supported by a Ruth Kirschstein National Research Service Award Individual fellowship from the National Cancer Institute (NIH F32CA142039), by the National Cancer Institute (Breast SPORE P50-CA058223) and the National Institutes of Health (U24 CA143848, U24 CA143848-02S1).