Cancer Fight Enters the Next Generation

By Tyler Smith

We all know the needle-in-a-haystack metaphor. In cancer care, the needle-finding challenge is to isolate cells with altered genetic codes floating in a sea of healthy tissue. It is these mutant strains that trigger the ruinous cell division that is cancer’s hallmark.

Data dig. The process at CMOCO uses sophisticated equipment to burrow through enormous haystacks of genetic data in search of a mutation in any one of a panel of 26 cancer-associated genes known to respond to targeted therapy or predict the outcome of therapies. If the sequencing identifies one of the cancer culprits—such as EGFR, which is associated with non-small cell lung cancer—clinicians can turn to a drug that targets it.

“We have a better chance of using the right therapy based on the information,” said Dara Aisner, MD, PhD, co-director of CMOCO and assistant professor of pathology at CU. “When we find the specific mutation, we can say a patient should get therapy ‘x’ or not therapy ‘y,’” she said.

The process also helps to identify mutations that make a tumor behave more or less aggressively, another important variable in devising a treatment plan, Aisner said.

In recent years, scientists have broken the codes of an increasing number of genes linked to cancer and developed therapies that target the mutations. But it’s a task that requires analyzing millions of nucleotide sequences that make up the DNA of normal and cancer-causing genes. As the number of targeted therapies has increased, so has the burden of lab work required to find the “needles” so vital to planning treatment.

A new technology known as next-generation sequencing, or NGS, addresses that burden. It processes exponentially larger amounts of DNA thanks to mass automated throughput of genetic material. The Colorado Molecular Correlates Laboratory (CMOCO) at the University of Colorado School of Medicine is among a relatively small group of institutions offering it.

Knowing there is no targeted therapy for a mutation identified by NGS is equally important information, noted Dan Theodorescu.
MD, PhD, director of the University of Colorado Cancer Center. For example, he said, the mutant protein KRAS is an important driver of cancers of the colon, lung, and pancreas, but targeted therapies have thus far failed to quell it.

“If we identify KRAS as the mutation, we won’t waste time and money and cause side effects in our patients treating it with drugs we know won’t work,” Theodorescu said.

Theodorescu said NGS will transform the practice of cancer care to what he calls “precision oncology.” On the research side, scientists will use it to identify more cancer-causing mutations, he said. As oncologists develop more therapies that target those mutations, NGS will be needed to sift through the growing mountain of genetic data to match a tumor’s genetics with a drug, he said.

“It’s inevitable, and we’d better catch up quickly,” Theodorescu said.

Trust, but verify. But NGS is not for every hospital or laboratory. The testing requires laborious attention to detail to validate each step of the process, powerful bioinformatics systems to digest terabytes of data from DNA samples, a pathologist’s finely discerning eye and steady hand, and the clinical expertise to interpret the findings.

CMOCO follows an exacting set of standards established by the federal government’s Clinical Laboratory Improvement Amendments (CLIA). These require the lab to check every step of the NGS process to ensure its accuracy.

“It’s technologically complicated and expensive,” Aisner said. “Every test has its limitations, and no test is perfect. But this is the closest thing to certainty that we have.”

The tests take from one to two-and-a-half weeks, depending on when CMOCO receives a sample of biopsied tumor tissue, Aisner said. That’s when the proverbial search for the needle begins.

Stain and sift. The lab first sections and stains the tissue on slides for microscopic examination, then microdissects it. Any piece of tissue on a slide is a mix of normal and healthy cells, said Gregory Bocsi, DO, director of the Core Laboratory at University of Colorado Hospital. The trick, he said, is to identify and isolate the tumor cells in the specimen so they can be teased out with a finely pointed scalpel. Take too much normal tissue, he said, and the test can return a false negative.

The lab extracts the DNA from the tumor cells, then sends it through its MiSeq gene sequencer, which uses powerful computing equipment to process the data, returning a report that reveals the genetic secrets of the tumor sample. But the final report relies on the work that went before, Bocsi said.

“The results are only as good as the pathologic evaluation, the chemistry and the computing,” he said.

Since going live with NGS about two months ago, CMOCO has run tests for more than 40 cases covering eight types of cancer, Aisner said. She expects the number to increase as the march of medical discovery accelerates.

The slide shows sections of tumor cells (top, circled in black) before they have been isolated from the specimen. The bottom slide shows the same specimen after the tumor cells have been isolated (white circles).

“This is our first test of NGS to start the process,” she said. Several leading institutions have already launched large-scale NGS testing to identify alterations of tumor cells, she added.

Theodorescu said he believes building a robust NGS program will help to raise the profile of UCH, University of Colorado Health, the Cancer Center and the School of Medicine.

“It’s good 21st-century medicine,” he said, “and it’s clearly the right thing to do for our patients across UCHealth, the state and the region.”