At the Colorado Molecular Correlates Laboratory: Bioinformatician and Instructor Carolyn Lawrence, PhD; Director Dara L. Aisner, MD, PhD; and Assistant Professor and Lead Assay Development Scientist Kurtis Davies, PhD. Photo by Stephen Cardinale

Pursuing precision oncology with world-class custom bioinformatic pipelines

How the Colorado Molecular Correlates Laboratory advances molecular diagnostics with the help of Illumina technology—and the knowledge and buying power of an academic consortium

LOCATED IN AURORA, the Colorado Molecular Correlates Laboratory (CMOCO)[1] at the University of Colorado (UC) Department of Pathology is a primary in-house molecular diagnostic facility that supports the UC Health hospital system. CMOCO offers a broad menu of tests for solid tumor analysis, running several dozen next-generation sequencing (NGS) assessments of clinical samples every week. The lab also performs testing for hematologic malignancies, infectious disease, and constitutional (germline) disorders.

As a university lab routinely running complex and costly assays, CMOCO looks to reduce costs wherever and however possible. In 2018, CMOCO Director Dara L. Aisner, MD, PhD, cofounded the Genomics Organization for Academic Laboratories, or GOAL,[2] to enable academic labs to make large group purchases of next-generation-sequencing reagents.

Through forming the GOAL consortium and meeting regularly, the member labs began to realize myriad benefits in addition to purchasing power, including the ability to collaborate on studies, create educational opportunities, and share technical knowledge. Through GOAL, members have a single line of communication they can use to ask others about data analysis or find out who might have samples to share for a specific assay validation. Six years after its founding, GOAL is now a growing international consortium with nearly 40 member sites.

In addition to performing clinical testing for the hospital system, CMOCO operates as a shared resource for the University of Colorado Cancer Center,[3] offering their clinical assays to the research community. “About 10% of the testing we perform is for research purposes,” says Kurtis Davies, PhD, assistant professor in the Department of Pathology and CMOCO’s lead assay development scientist. “We are well suited to efficiently provide genomic variant information for researchers looking to characterize their preclinical and clinical samples.”

The team recently completed a several-hundred-sample research project that looked at the mutational spectrum in low-grade endometrial cancer samples.

1. medschool.cuanschutz.edu/pathology/department-of-pathology-our-services/cmoco
2. goalabs.org
3. medschool.cuanschutz.edu/colorado-cancer-center

Other recent inquiries include a residual disease assessment via droplet digital PCR to support an investigator-initiated clinical trial in pancreatic cancer, and gene fusion and mutation analysis of samples from a rare, aggressive case of inflammatory myofibroblastic tumor.

The CMOCO researchers are enjoying taking on bigger projects and having more flexibility ever since they transitioned in June 2023 from an Illumina NextSeq 500 System to two NextSeq 2000 Systems. They also calculate that the purchase will save them money in the long term, on top of giving them significantly higher sequencing bandwidth.

Revamping the workflow

CMOCO's large NGS assay, called GOAL – Solid Tumor , interrogates 498 cancer-related genes and uses Illumina DRAGEN (version 4.2.4) on Illumina Connected Analytics for data analysis.

The assay employs hybrid-capture chemistry to generate enriched libraries that are sequenced on the NextSeq 2000s. DRAGEN on Connected Analytics then processes the raw NGS data into variant calls. The output from DRAGEN is populated in another program—an interface for viewing variant calls—that bioinformatician and instructor Carolyn Lawrence, PhD, helped develop. The program is based on the open-source System for Informatics in the Molecular Pathology Laboratory (SIMPL),[4] originally developed at the University of Chicago. A team of attending pathologists, board-certified PhDs, and medical residents and fellows interprets all the variant calls and generates a report for each case.

Initially the team used a custom-designed bioinformatic pipeline run on a cloud-based platform, but they decided to move to a commercial option that was well vetted and managed in a commercial setting. The former bioinformatic workflow could take up to 24 hours or more to complete a run, whereas analysis on Connected Analytics is often completed in a few hours. "So, it basically can shave a day off our turnaround time, and getting the reports out a day earlier can be very valuable," Davies says.

In addition to speed improvements, they've noticed pipeline performance improvements with DRAGEN. Using their former pipeline, they would occasionally see insertion-deletion events in the DNA at lower variant allele frequencies (VAF) than expected. With DRAGEN, the calling of these types of alterations has been more consistent with the expected VAF.

Lawrence says it was significantly faster to develop and validate their assay without having to build a custom pipeline. She also adds that "it went very smoothly versus other times when we've developed custom pipelines. In the past there's been a lot of back-and-forth troubleshooting, debugging, rerunning sample cohorts and things like that, and we avoided most of that."

Doing more with data

Because CMOCO is an academic pathology lab, Davies and his team enjoy a close and mutually beneficial relationship with the oncologists on campus. Davies says he can solicit expert feedback from oncologists on whether they would have use for a specific test, and the oncologists can directly influence what genes Davies might add to a test. Because CMOCO can flex its research and testing based on what is happening in the clinic or what questions naturally form in the course of practicing medicine, the lab collaborates quite easily with the physicians on studies, clinical trials, and publications.

"We can adapt our testing, following a full assay validation process, to fit the needs of the clinical mission at our hospital system," Davies says, "whereas an outside reference laboratory would not be that nimble or be able to customize their offerings just to support a smaller group of oncologists."

In the future, CMOCO plans to launch an NGS assay for hematological malignancies based on reagents they purchased through the GOAL consortium. They're also interested in testing for homologous recombination deficiency (HRD) and other mutational signatures that can guide clinical management.

"The long view is that we'd like to do more complex, cutting-edge assessments of the data that we are already generating," Davies says. "That's next on the horizon." ◆

4. doi.org/10.1016/j.jmoldx.2018.03.008