First a probe purchase, then an academic consortium

Sherrie Rice

July 2023—Bringing new technology into laboratories is important for pathology as a field and for patients—and only getting more difficult. “Each new wave of technology is more complicated than the last,” Jeremy Segal, MD, PhD, said at the USCAP meeting this spring.

The pace of technology development is picking up. “There’s a lot coming. It can’t possibly slow down; it can only speed up,” Dr. Segal said in his Nathan Kaufman Timely Topics Lecture on the molecular pathology organization he and others founded.

Dr. Segal, director of molecular and cytogenetic pathology and associate professor at the University of Chicago, told the story of the Genomics Organization for Academic Laboratories—why and how it got its start, how it grew, what its members are studying now, and how its model can work for so much more than molecular pathology.

In a nutshell, GOAL’s aim is academic cooperation and collaboration. There was already plenty of that pre-GOAL, Dr. Segal acknowledges. “But most of the time what we do is have conferences and committees. We leave our laboratories and come together as directors and talk about and decide how things should be. Or we write a position paper or set best practices.” Then it’s back to their labs for independent work.

“What’s different about GOAL is when we meet, we’re kind of bringing our laboratories with us,” he said. “And then the laboratories start to work together and integrate. Technologists in our different labs talk to each other and share protocols and troubleshooting. Bioinformaticians talk to each other, sharing software and ideas. And the labs are almost working as a single large entity.”

If how GOAL works differs from how other academic organizations work, so too is how it got off the ground—as a solution to the cost and quality problems of probes for hybrid capture sequencing.

“If the probes are good, you’re golden,” Dr. Segal said of a lab’s sequencing data. “If the probes stink, you’ve got problems.” When his lab ran into problems in the early days, it turned to IDT, a company that makes oligonucleotides and was getting into the next-generation sequencing space. “The IDT probes are made one at a time and they quality control each one. They make an oligo and check it. If it’s not right, they’ll change the conditions and make it again.”

Dr. Segal

With his lab’s original vendor, the lab was paying roughly $40,000 for every 1,000 samples tested with probes made on a batch synthesizer. To reformulate their 1,000-gene panel using IDT probes, Dr. Segal and his UChicago colleagues would have needed to purchase 50,000 individually manufactured probes, but the cost was too high to justify for their lab. Things got interesting when they realized that such a large-scale purchase would create enough reagents to test 30 million patient samples. His lab was testing about 2,000 samples yearly, “so that’s 15,000 years,” Dr. Segal noted. That’s when he turned to the notion of sharing and to his colleague and co-founder Dara Aisner, MD, PhD, professor of pathology and vice chair for genomic laboratory medicine at the University of Colorado Anschutz Medical Campus, “without whom there would be no GOAL,” he said.

Perhaps the two labs should share the cost, Dr. Segal suggested to Dr. Aisner, though even then it would still be

expensive. He and Dr. Aisner, who directs the University of Colorado's molecular correlates laboratory, set out to get a few more labs to share the cost. To their surprise, 15 labs wanted in.

"Now we had to figure out what to do," he said. They had initially thought about buying Dr. Segal's panel "or maybe carving it up a bit." But that was no longer an option with so many labs wanting to join, some of which had their own panels already. The list of requested genes began to balloon far beyond the original scope.

The only way to make this work, Drs. Segal and Aisner thought, was to buy everything. So the group purchased all 2,640 genes of interest requested by the 17 laboratories, and formulated the purchase so each gene's probes would be put into a separate tube in a removable matrix plate. "If we want to make our 1,000-gene panel," he explained, "we would pull out the 1,000 tubes we want and pipette them all together to make our capture panel." If another lab wanted to use a different set of 500 genes, they could do the same. "So it's like infinite mix and match. Anyone can make any panel they want" or a variety of panels. Each lab paid $25,000 for a vast supply of capture probes. "So everyone started working with them. They were comparable to or better than what we were doing before."

Prior to the purchase, UChicago's cost was about $40 per sample for capture. After the purchase, it's about $1 per sample and reagent (if the purchase isn't factored in), so it's a savings of about $78,000 a year. The on-target rate of the sequencing is higher and the uniformity of the sequencing coverage is better, Dr. Segal said. "That means we can put more samples onto each sequencing flow cell and save sequencing dollars." Their sequencing costs went from $270 to $193 per sample, which saves $154,000 per year, so it's a total savings of about $232,000 a year. They used a few years of that savings to buy a new NovaSeq 6000, which Dr. Segal said "sequences even more cheaply" than the HiSeq they were using, for another $200,000 in savings per year. So the yearly savings total comes to between $250,000 and $500,000—for UChicago alone. The technical assay costs for the entire process for the 1,000-gene panel can be as low as about $200 to $220 per sample.

When he and Dr. Aisner spoke at meetings about this, others would ask if they could join. In time they had another 12 labs, enough for another probe purchase.

The network now consists of 29 academic centers nationwide, all with the same probes in their labs and all working on assay development. Labs have reported excellent results and accelerated test development, he said, owing to the quality of the reagents and the general support of the laboratory network. Of the 29 sites, 14 were live as of June 21 with a clinical GOAL oncology panel in their labs.

At the outset, it was easy to think labs would take the probes and go back to working independently in their own labs. That didn't happen. "People started talking to each other. How are you mixing these probes? What library prep are you using? What are your informatics protocols? Can we share samples?" They started working as a joint development group. Now there is a monthly virtual meeting, the GOAL Cafe, in which anyone with a problem that needs troubleshooting or a matter to discuss can join to talk about it.

Drs. Segal and Aisner knew the collaborative group of labs could do even more together: scientific projects, provide validation support, approach regulators and payers. They decided to turn the group into a formal organization and worked with the Association of Pathology Chairs to do so. "It's an organization with the same reason for being," Dr. Segal explained. For the APC, it's to support academic pathology. For GOAL, it's to support academic molecular pathology. "We're an important part of that for them, so they took us under their wing" and provided guidance.

GOAL was incorporated in Washington, DC, in 2020, and its application for 501(c)(3) status was approved in 2022. The group assembled and ratified bylaws and established an initial board of managers.

GOAL's lab-focused mission is to help drive the advancement of genomic testing at academic and nonprofit labs by facilitating inter-institutional cooperation and leveraging group resources and expertise to lower development and implementation barriers. The patient-focused mission is to expand access to personalized biomarker testing, accelerate implementation of tests for new biomarkers nationally, and, through data mining and scientific projects, help drive future biomarker discovery. "This is how we'll decide whether we've been successful," Dr. Segal said.

Nine volunteer labs that already have live GOAL-based panels are participating now in a concordance study to demonstrate the fidelity of this approach. Twenty-five selected FFPE DNA specimens with 100 pathogenic variants were distributed to the nine labs for each lab to run through its normal processes and generate data. They also put in place a cloud-based consensus bioinformatics pipeline (DRAGEN Somatic Pipeline via Illumina Connected Analytics) to process the labs' raw data and generate a second set of results. If the two sets of results were discordant and the consensus pipeline fixes it, that could indicate a bioinformatics difference at a particular lab, he said. If it is, "we can dig in and see what contributes to it, and that's the type of thing I don't believe any other concordance study has done to date."

"Overall our study supports the hypothesis that we can attain excellent concordance using our shared probe chemistry," Dr. Segal said. Of 898 expected variant calls, only one was found to be discordant due to a wet lab issue.

To determine whether the nine labs were not only concordant but also correct, they built in external variant allele frequency confirmation using digital droplet PCR (ddPCR). "We've done 11 of them so far, and we are not only agreeing with each other but are correct."

Future analyses of the data will investigate tumor mutation burden, copy number calling, and other metrics. The group is also making extra DNA, he said, and will give it to GOAL labs to aid in validation of their tests. "A lab could join, get the probes, set up the library prep, use these samples, and, even if they wanted to run the Illumina DRAGEN pipeline off the shelf, very quickly be at 99.7 percent concordance." This is far quicker than the experience of most laboratories working independently on NGS test development, he said, while preserving the ability to customize an assay, which pre-kitted solutions cannot do.

They plan to use the study's results to push back on the premise that all laboratory-developed tests are equally risky, to approach payers about improving reimbursement, and to engage pharmaceutical companies in discussion about multisite clinical trial testing.

The next project is a shared curation platform to help labs interpret new and unknown variants. "The one question we always have that we're never able to answer is, who's seen this variant and what did they say about it? Did they grade it pathogenic or not and what did they write?" The public databases don't have that information, Dr. Segal said. "So we're siloed again in terms of our interpretation of variants."

The GOAL model could work for labs beyond molecular pathology. Specialty reference testing is one example. "What if the academic centers got together and shared an expert network nationally so that they could say, 'If your case is difficult, not only will it be reviewed by the top people at UChicago but also by 28 experts across the country who will share it digitally and come up with a consensus diagnosis.'" Approaching outreach testing in this way, Dr. Segal said, "is a more powerful marketing play that would raise all ships across all of the networks for those who wanted to try it."

Another example would be coming together for the infrastructure of digital pathology, including negotiating with data storage providers. Data storage costs associated with digital pathology are one of the things that prevent many from bringing digital pathology in, he noted.

Resident and fellow education is yet another example. "Maybe we can share the load—come up with content together, even teach our residents as a group over Zoom," which would lighten the curriculum development load and give residents and fellows a chance to meet and talk.

Another possibility: the integration of existing or novel technology. "Anything in the lab that's bothering you and is difficult" and that working with others at other academic centers can help, he said. "The elephant in the room from a technology standpoint is artificial intelligence. I don't know how we're going to manage that one, but the only way we're going to manage it is together."

"We need to make sure we're out ahead of it so we know what's under the hood, how it's working, and its benefits

and limitations, and to secure a good place in this future for pathologists.”

Sherrie Rice is editor of CAP TODAY.