The outlook for in-house next-generation sequencing

May 2023—*Bringing next-generation sequencing in-house was at the center of a March 27 roundtable led by* CAP TODAY *publisher Bob McGonnagle, with costs, reimbursement, equity, and the electronic health record part of the conversation.*

Jeremy Segal, MD, PhD, of the University of Chicago, explains why the Genomics Organization for Academic Laboratories was formed. "By lowering barriers and encouraging cooperation," he said, "we've seen our labs increase the pace of development and the quality of the assays they're bringing on."

CAP TODAY*'s interactive guide to next-generation sequencing systems begins here.*

There's increasing interest in bringing next-generation sequencing in-house as opposed to sending it to a reference laboratory. While there are costs associated with bringing it in-house, if you look at total cost of the test and turnaround time, it's an even horse race or slightly preferable to bring it in-house. Luca Quagliata, would you agree with that?
Luca Quagliata, BCMAS, PhD, VP and global head of medical affairs, Thermo Fisher Scientific: I do agree. Cost is an important component of being able to bring these tests in-house. We often think cost is driven only by reagents, but it's not the component that most impacts overall expenditure. Cost of personnel to perform the analysis is equally important. With solutions that are going toward fully automated or semiautomated systems, you can free hands, better utilize the lab workforce, and effectively maximize budget.

The other part of the equation is the cost of treatment. A long turnaround time to results usually means placing the patient on any available treatment, which is not necessarily the best option. If a suboptimal treatment decision is made and subsequently a treatment change needs to be forced, the patient will pay for it in terms of outcomes. The health care system will probably also bear additional costs because those patients usually experience more side effects, which means rehospitalization costs and a prolonged process.

Fiona Nohilly, can you comment on the movement to in-house and how you look at the total cost of performing the test for the benefit of patients?

Nohilly

Fiona Nohilly, senior manager, product marketing, Americas regional marketing, Illumina: We are thinking about the total cost of ownership from sample and library preparation through sequencing and analysis. Since we last met for this roundtable, we have launched three new platforms. The NovaSeq X Series, which has our DRAGEN [Dynamic Read Analysis for GENomics] secondary analysis pipeline built into the instruments, allows for the cost of the secondary analysis to be included in the sequencer. With the NovaSeq X Series, you can get through a variant call and a VCF [variant call format] file on the instrument, and that can kick off immediately after the sequencing run is done.

We also launched our NovaSeq 6000Dx, which is paired with the DRAGEN server. We are continuing to invest on the informatics side and thinking about the analysis piece, as it is a costly and time-consuming resource for our lab customers and partners.

Today we launched our latest tertiary analysis platform, Illumina Connected Insights, for oncology testing.

Jeremy Segal, do you have initial thoughts on this topic or would you like to make an opening

statement?

Dr. Segal

Jeremy Segal, MD, PhD, director, genomic and molecular pathology, and associate professor, University of Chicago: These cost issues have gotten a bit better over the past years. Our local MAC [Medicare administrative contractor] has decided to cover comprehensive testing for a large group of patients—600 different ICD-10 codes covering at a reasonable cost for the large panel code, which is surprising and nice. That changes our outlook a little. It gives us the possibility of running a profit, which, if you're in an academic center and bringing in positive dollars, makes it a lot easier to talk to the hospital about what we can do to arrange to get every patient tested here rather than sending it out. The whole conversation is different.

I've been involved in setting up a consortium of academic centers called GOAL [Genomics Organization for Academic Laboratories]. We have 29 academic centers collaborating on NGS development around a core set of shared chemistry reagents. As a result of that and bringing on a new, larger sequencer, our per-sample costs, the raw cost, are down to around $200. That doesn't include my salary or those of the bioinformaticians. What Fiona said about DRAGEN-based informatics is something to consider long term—how do we make that more efficient? The combination of maybe improved reimbursement and ways to reduce some of the cost overhead of NGS is helping to make the conversation a better one at an academic center or community hospital about whether it makes sense to invest and bring it in-house.

What do you think most influenced the MAC on the coverage decision?
Dr. Segal (University of Chicago): I don't know. It wasn't us. I would guess it was some of the corporate laboratories.

Luca, do you have insight into what would influence these MAC decisions?
Dr. Quagliata (Thermo Fisher): This is not something a single company has achieved alone. The entire industry has had a lot of conversations with the payers. One critical point that changed the conversation is that now, especially for certain tumor types, there is enough clinical evidence that genomic testing, especially with a fast turnaround time, is making a substantial difference for the patient, and that is reflected also in the costs. Payers understand now that the cost of sequencing is an investment, one that has a return in terms of clinical outcomes and costs, because the cost of testing is a fraction of the cost of the treatment. A good investment in the right testing has a very good ROI in terms of spent dollars and clinical outcomes.

Dr. Segal (University of Chicago): NGS testing used to be more experimental. But at this point, it's just standard of care and it's more difficult for payers to say, "No, we're not going to pay for this" when they're already paying for the drugs. These are standard-of-care algorithms that everybody is using for their patients. That helps a lot, too.

Karla Bellett, what are your views on this?
Karla Bellett, MT(ASCP), CLS, segment marketing manager, clinical oncology, Americas regional marketing, Illumina: Illumina is a founding member of the Access to Comprehensive Genomic Profiling coalition, which is a coalition of 13 members, including large reference laboratories, specialty laboratory providers, manufacturers, and pharmaceutical companies. Its mission is to increase commercial payer coverage of comprehensive genomic profiling by engaging directly with U.S. payers and educating on the value the assay brings to the health care system. While we've seen great progress in coverage in recent months, there is more work to be done for more equitable access. Insurance companies historically cover single-gene testing. If you add up several FISH tests in a row, they will end up paying more than $2,000 for a typical FISH panel for leukemia, for example. The tipping point

comes when you get enough different biomarkers that are medically necessary in each advanced cancer. It becomes obvious when you're doing five or more single-gene assays that it's likely above the cost of a CGP, yet the information you're getting is more limited than a CGP, maybe doesn't provide all treatment options, and is surely not comprehensive of potential clinical trial enrollment opportunities, which remain recommended care per medical guidelines. If you're doing two, maybe single-gene testing works, but doing four or five or up to 12, as with non-small cell lung cancer, the tipping point is to pay for the comprehensive testing.

Jeremy, I'm assuming part of the increasing interest in adopting this more widely, including with a Medicare administrative contractor, for example, is a greater recognition by clinical colleagues that this is the desirable route based on their understanding of the diseases.
Dr. Segal (University of Chicago): Yes. It's also easier. From a workflow standpoint it's easier to have every patient go through the same process than it is to figure out which individual tests you're going to order on different groups of patients, and how you organize that. Also, running multiple tests on a single patient may not be possible. If you're talking about single-gene testing and you have to do four different tests—we often have small biopsies, and that doesn't work. With minimal tissue, you want to get the most out of a single DNA extraction, and running a comprehensive test is far better for that. It wouldn't be possible to run many of our tests in that divided fashion. Even if the individual tests existed, some of the genes are tumor specific and there is no single-gene test. Developing all those tests would be an enormous challenge.

Jeremy, you were invited to give the Nathan Kaufman Timely Topics Lecture at the USCAP annual meeting. Give us a few takeout points you wanted to get across when you gave that lecture.
Dr. Segal (University of Chicago): The basic purpose of the lecture was to go over the history of our multi-institutional consortium. The early pattern in next-gen development and academic centers was that everybody was working independently and competing with one another—who can bring on the first panel, who can do it quicker, whose panel is bigger. It's a lot of redundant effort and it slowed us down. Since starting to build the GOAL consortium, we've seen a change in the way people work—more cooperation between centers and co-development, and communal work on bioinformatics and software development, et cetera. By lowering barriers and encouraging cooperation, we've seen our labs increase the pace of development and the quality of the assays they're bringing on. So the intention was to show what we've been doing, what we're working on, and to encourage people in other areas of pathology to think the same way—as academics, we're all on the same team and it's worthwhile for us to figure out how we can work together. We'll be better off for it.

Fiona, do you also see greater unity in the field now?
Fiona Nohilly (Illumina): Yes. It's necessary for us to help bring those folks together who are within an academic medical center, as an example, because there's power in being able to consolidate across one platform, whether that's within oncology or working across different areas. We see a benefit for our instruments to have utility for multiple types of assays and within different departments.

Sohaib Qureshi, where do we stand now on the bioinformatics component of NGS? It's one of the bigger fears some labs have as they consider this, thinking, We know how to run a machine, we can buy reagents, validate runs of almost any process, but the bioinformatics intimidates us.


Dr. Qureshi

Sohaib Qureshi, PhD, senior director of product management, instrumentation clinical NGS division, Thermo Fisher Scientific: Jeremy hit the nail on the head. The cost of sequencing is just one component; it doesn't include the salaries of bioinformaticians. Having said that, when you look at the cost of that investment, it's negligible

compared with the cost of treatment and therapy. But we need to make it easier. Bioinformatics is intimidating, especially as you move down market toward smaller hospitals where it becomes a major issue.
At Thermo Fisher, we do tertiary analysis in-house. Oncologists can look at annotated variants and get to a targeted therapy. We're constantly trying to improve that. We'll continue to invest in providing the soup to nuts so all the back-end work is taken away.

Can you tell us where NGS is in terms of being integrated with the electronic health record?
Dr. Qureshi (Thermo Fisher): There's a gap in integrating NGS to the point where it's as easy to order a test up front with an electronic health record as it is on the back end to see a result. There's an aspect of working with middleware companies, in addition to EHR companies, to advance or evolve EHRs. This is a pain point NGS can help support and move forward, but the NGS community can't do it alone. This is a much larger problem. We need to help contribute but it's another area of investment for us. Upgrading and evolving EHRs will benefit everyone, not just the NGS community.

Some of the consensus on more in-house sequencing reflects a recognition that we need to get on a more level playing field for all patients, regardless of where they first get care. Does that resonate with you, Jeremy, as you look at it?
Dr. Segal (University of Chicago): I think that's fair. I don't have a lot of visibility into what happens in the community, but the numbers I hear are that many patients are not being tested, or oncologists are jumping to immunotherapy rather than testing their lung patients for targetable markers. That may be happening because it's easier to do.


Dr. Quagliata

Dr. Quagliata (Thermo Fisher): There's a movement to go in-house for NGS, which is good; we all want that. But this cannot happen all at once because there must be additional investment made not just from the corporate side but also the health care side, from university and academic centers, to educate more people who are ready to make the change happen. We need more trained professional laboratory staff. As much as we want to automate the system, link it to the electronic health record, we still need people to do that. That's why the send-out model will be there for some time, because there's a need. It still captures a large proportion of patients today because the system is not yet ready for a full switch to in-house.

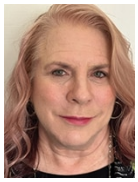
Jeremy, it would seem there's a great need for algorithm-based testing even in the NGS space. Do you agree?
Dr. Segal (University of Chicago): Yes, I do. We haven't gotten into methylation-based testing and I assume spatial transcriptomics is coming. It will all take algorithmic and AI-based processing to look at. There are a lot of questions there. How will we manage this so it's more like a black box algorithm? How do you prove it's working? How do you know what's under the hood? If it's an AI-based system, how do you demonstrate clinical validity of those tests? How do labs bring on a test that's comparable to a black box test and validate against that and show it's working well? How do you proficiency test it? There are a lot of questions with no answers yet, but we'll figure it out. It's daunting. But it's going to happen.

Luca, can you comment on the need for the validation of certain black box tests?
Dr. Quagliata (Thermo Fisher): That's going to be a focus for the entire community in the next year. People don't like black boxes anymore. We are now in a situation in which if you test in-house, you have full control over what you're doing, you know which informatic pipeline you're using. If you're making an update, you know what you're looking for. You can open the box and understand which parameters are used, which is not always the case when

you do a send-out. In-house offers an opportunity for more transparency about how the data are analyzed.

But I don't think we will soon see one solution that fits all patients, meaning we do epigenomics and methylation and exon, et cetera, for all patients. The vast majority of patients are not going to the University of Chicago or Memorial Sloan Kettering or MD Anderson; they are getting the first diagnosis and even the first treatment in the community setting. We should make sure they—about 85 percent of all patients in the United States—get an NGS test, because they're not getting it today. We can't think we're going to jump straight ahead to having methylation for all patients. That's why we are focused on making sure, with the solutions we are developing, that as many patients as possible may get an opportunity to be tested for what is necessary and what is in the guidelines.

Dr. Segal (University of Chicago): There's a risk that the disparities will worsen. There are things laboratories can do—as community centers bring in their own testing, I think we'll find it opens the eyes of the oncologists. Even if there's a profit motive to be had at the community practice by doing the testing, normally that's a conflict-of-interest issue, but in this case you're encouraging the center to think about it and make sure everybody gets tested, so maybe it's worth spending a little money to do that. If we can get this democratization moving forward even more, then we will have more success trying to push back against those disparities. Other than that, it's an education issue for the oncologists to know they need to be doing this and testing everybody. Having more infrastructure on the ground in more community centers will be helpful.



Bellett

Many of what we now call community places of practice are subsumed under large health systems. These large systems geographically and in terms of locations over time may refine their own test algorithms to have samples going to the right place immediately. Do you get that feeling, Karla, as you look at the consolidation of testing, which has been pretty dramatic in the last few years?

Karla Bellett (Illumina): Absolutely. I live in the Pacific Northwest, and we have Providence, Swedish, plus our big academic centers, but all the small places got bought up, even the small regional reference labs. In the past 20 years most regional health systems have moved to integrated delivery networks. Sometimes that's part of what we need to maneuver through.

Providence St. Joseph's Hospital in Chewelah is a community-based hospital in eastern Washington. It is part of the Providence health system, so going there for NGS testing done locally is probably not going to work because Providence in Portland, Oregon, centralized its high-level molecular testing and NGS. So it puts a finer point on when you say community-based hospital. Are patients being seen in Chewelah? Absolutely. Is the testing performed there? Probably not. It's going to the centralized Providence molecular genomics laboratory in Portland.

Rural IDNs aspire to bring academic-level testing and accessibility to their patients. Often these systems use send-outs to accomplish this goal. They are making a point of saying, Our patients will get this access, even if we're not bringing it in-house. They could bring it in eventually, but it starts with them saying, Our patients deserve precision health care and will get the access. When they reach the volume of testing where it makes sense and costs decline, it will be the perfect storm to bring the testing in-house.

NGS has many applications beyond tumor genomic testing. Sohaib, tell us from Thermo Fisher's perspective what is new and exciting in the other areas.

Dr. Qureshi (Thermo Fisher): The two areas in which we'll likely invest more is reproductive health, using NGS for preimplantation genetic screening or testing. It's still highly centralized but we see it expanding to become more

decentralized. Carrier screening has been around as well to do germline testing.

SARS-CoV-2 changed the landscape for infectious disease testing. At some level, the infectious disease community will have interest in making a pan-bacterial, pan-infectious–disease type test. Today there are tests, not NGS, that can distinguish between different types of diseases and microbiomes and viruses.

Dr. Quagliata (Thermo Fisher): COVID opened the box when it comes to molecular testing. All the vendors have benefited from expanding their installation bases to places not on top of their list for NGS testing, and now the instruments are there and being used. For example, water and sewage testing was done before but not by NGS. Now we have a better understanding of what is happening, if there's a new bug in the community. Microbiome testing is also coming on strong and will continue to grow, not just in the context of cancer because it has an impact on drug metabolism, but because of its overall impact on human health.

Fiona, what can you tell us about these areas outside of cancer?
Fiona Nohilly (Illumina): We have seen many system placements in our public health labs for COVID-19 surveillance efforts. We've seen a lot of work by our customers on wastewater surveillance. We have a partnership on the use of NGS for tuberculosis screening. We've done a lot in the infectious disease space with COVID along with a pan-viral panel that launched. We've seen the ability to use that same instrument for reproductive health, for cancer, whether that's somatic profiling or germline testing or for research-based applications like NGS as a readout for spatial technologies. It can cover all the clinical applications as well as research.

Karla, would you like to make a final comment?
Karla Bellett (Illumina): Our Illumina instrument platforms have multiple testing modalities and options for combining genomics solutions for NGS and arrays on a single platform, as is possible on the NextSeq 550. For example, in addition to infectious disease, there are epilepsy and Alzheimer's biomarker panel capabilities. Last year I was at the American Association of Neuropathologists meeting, which has two tracks: neuroscience and oncology. NGS can be used for both because in addition to being able to do an epilepsy panel, you can do biomarker panels for CNS tumors.

For CNS tumor classification, it is becoming standard of care to perform epigenetic testing using DNA methylation array. A lab could utilize one instrument to perform testing across the neuropathology spectrum. When you talk to groups that have developed these early classifiers using AI, they see tumor profiling using DNA methylation becoming part of the standard. The chief of the laboratory of pathology at the National Cancer Institute presented at AMP last year on CNS tumor classification plus the vision of all cancers being worked up by methylation profiling. Also reviewed were new classifiers for hematolymphoid neoplasms and kidney cancers, including a look at a pan-cancer classifier with 43,000 cases collected. The tumor classifier approach compares a sample's methylation pattern against a reference set, then provides a report with a score that says if it's above 0.9, then you have confidence to integrate the DNA methylation result with the rest of your pathology testing. Methylation array also provides a whole genome CNV analysis for a comprehensive tumor profiling report. Now you have a definitive diagnosis that you can use before looking at the biomarker testing for therapy selection. They all go hand in hand.

Jeremy, hearing about these applications reminds me of the PCR problem. In the early days it was a question of where the PCR machine belonged. Is there a PCR department or do we develop PCR assays? We put some in microbiology with its own dedicated analyzer, some in anatomic pathology with a dedicated analyzer. Tell us what you and your colleagues are looking at beyond somatic cancers.
Dr. Segal (University of Chicago): Whether you have one unit or distributed sequencing is a tricky question. It's a little different from PCR, where the PCR machines were all the same. Here we have different sequencers of different types and scales, with different sequencing profiles they can generate and different specs. All of our next-gen sequencing is now within our unit. Our germline genetics lab, cancer lab, and HLA lab use our sequencers. But you could imagine, depending on turnaround time or other issues, having one, focally, at a certain lab. We haven't started doing a lot with microbiology yet, but it's an area where we should be expanding over the next couple of years. Whether we'll be doing it on our machines or using nanopore sequencing or whatever is best for that

application, we'll have to see. If it's an operation where you need a lot of sequencing reads, then you're better off pooling everything onto one big sequencer in a core location. If you need fast turnaround times and smaller batches and you're running it every day, then maybe you're better off having a small sequencer. It's tricky. Also there's a sequencing core facility at every university, and they're running many types of tests, including microbiome and genomes. As some of that becomes more clinical, maybe it moves toward us. There's a lot to think about when making decisions on how to set it up. Currently, we have one clinical group and we do everything. Ask me next year, maybe things will be different.