Growing pains put gene panels in a pinch

Karen Titus

April 2023—After years of excitement and scientific breakthroughs, the use of molecular testing to guide cancer therapeutics finally is coming into its own. Unfortunately, it appears to have landed in the wrong place at the right time.

That place is a lonely spot, surrounded by gaps in economics and coverage, as well as knowledge, guidelines, ordering patterns, turnaround times, reporting, and the like. So plentiful are the gaps that, put together, they could form a vast, inhospitable space, a veritable Colorado Plateau, with molecular testing as a majestic, enticing but remote rocky pinnacle in the middle. Think Monument Valley.

It's worth the trek. The evidence in support of genomic profiling continues to grow. Simply put, "Patients with the right markers who get the right drugs do better," says Neal Lindeman, MD, vice chair, laboratory medicine and molecular pathology, Department of Pathology and Laboratory Medicine, Weill Cornell Medicine/New York Presbyterian Hospital.

But as numerous studies are showing, the lag in testing is growing as well. "Extensive, broad biomarker testing is not happening at nearly close to what would be an appropriate target," says Samuel Caughron, MD, president, CEO, and director of the molecular pathology laboratory at MAWD Pathology Group, Lenexa, Kan. While no testing ever reaches 100 percent of patients, for those who would benefit, "We don't even get close to getting [them] all tested."

How did things end up here? What happened?

Or more to the point, what *didn't* happen?

"Reimbursement," says Dr. Lindeman.

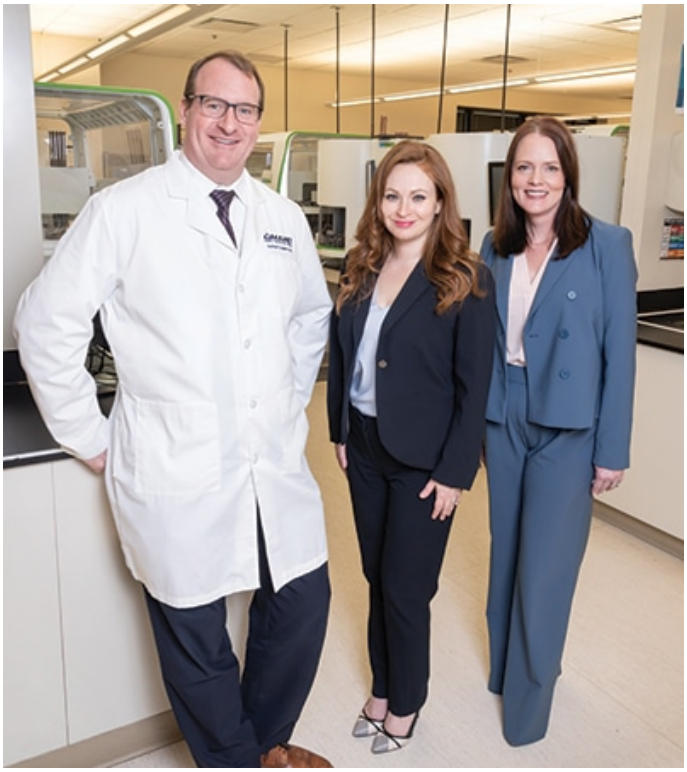
"It's a very complex issue," says Dr. Caughron. There are, of course, operational and educational challenges. But most in the molecular field, he says, see another issue underpinning it all. When he travels the country and speaks with pathology groups, "I often hear economics as one of the major barriers, if not the most important variable, that prevents more patients from getting testing."

A decade or so ago, the primary gap appeared to be the so-called town-gown split. Molecular cancer testing was expanding rapidly at academic centers and other large institutions that could afford to bring the tests (including next-generation sequencing) online, and whose faculty included experts and others heavily involved in research and clinical trials. Health care providers in community practice were the ones at risk of being left behind.

Eventually, however—or so it was hoped—testing would come down in cost. NGS platforms would make their way to smaller labs. Knowledge and biomarkers would spread like dandelion fluff in the wind. And payers would see the affordable wisdom of making sure patients received the right treatments.

In the early days of the genomic era, Dr. Lindeman recalls, costs were relatively low for single-gene tests, such as *EGFR* testing for non-small cell lung cancer.

As panel testing became more common, "the costs went up an order of magnitude, and it became a financial issue. It was certainly a town-gown issue then," says Dr. Lindeman, who until recently was affiliated with Dana-Farber/Harvard Cancer Center and Brigham and Women's Hospital. There, he says, "We were a relatively early adopter of the panel testing approach, because the only places that could afford it were the tertiary care cancer centers and academic institutions that saw this as the future and were willing to take a loss on it."



Dr. Samuel Caughron with Natasha Villanueva (center), VP of clinical laboratory, and Kathleen Little, VP of pathology operations, MAWD Pathology Group. “There is a significant lack of alignment,” Dr. Caughron says, between reimbursement and the pathologist’s role in molecular testing workups to guide cancer treatment. [Photo by: Don Ipock]

That has changed. It’s becoming less common for academic medical centers to willingly take a loss on the testing, Dr. Lindeman says. Even though it’s standard of care, and National Comprehensive Cancer Network and other guidelines recommend this testing, payers balk at paying, impose restrictions, or pay for only one company’s test.

This goes beyond the usual suspects that affect molecular access. “Now there are market forces weighing in on this,” Dr. Lindeman says.

For example, “When we propose to do it now, the answer is, ‘Who’s going to pay for it?’ We didn’t have those conversations a decade ago. The institutions were willing to invest in it because they perceived it would be an interesting future development. Now that it’s a present development, the sense is the insurance companies should be paying for it—and they’re not.”

Dr. Lindeman also says he’s seen examples of Medicare paying for molecular cancer testing that private insurers won’t cover. “Which I find interesting.”

Delving deeper into the present, Dr. Lindeman describes a landscape in which some private companies offer deeply discounted testing in exchange for patient data, which can then be sold to pharmaceutical companies. “They are getting secondary value from resale and re-presentation of the data so that they don’t need to cover their costs with clinical billing.”

And for physicians who don’t believe that their patients’ data should be repurposed in this way? Says Dr. Lindeman: “You’re stuck. That’s the deal you make with these companies.” Otherwise, “You have to figure out the

cost of doing the work."

Dr. Lindeman

Not many laboratories have. Major cancer centers, such as MD Anderson, Dana-Farber, and Memorial Sloan Kettering, have their own extensive testing programs, Dr. Lindeman says. Major academic centers continue to offer testing as well, but within smaller programs.

Some insurers are reimbursing for FDA-approved tests, but not laboratory-developed tests, which benefits a select number of commercial laboratories with ample resources and processes, Dr. Lindeman says. Many academic hospitals are essentially frozen out. This is the new town-gown paradigm, perhaps. "That has created—I'm not sure what to call the commercial labs—it's sort of a business-gown conflict."

Regulatory issues have further marooned testing, Dr. Lindeman suggests.

"We're stuck in this model where the regulatory agencies are requiring a specific test for each drug," he says. "And it's a model that doesn't scale or work terribly well." Instead of an approach where test certification, clearance, or approval is predicated on detecting a specific analyte, with specific performance characteristics—sensitivity, specificity, precision, etc.—pathologists are limited to individual, branded assays that worked in the clinical drug trials. "That's unsustainable for pathology organizations. It makes it harder for labs to offer tests," Dr. Lindeman says. "And in the end, it denies access to patients.

"It's an inhibitor of a molecule," he continues. "Why not just get a test for that molecule to get any class of inhibitor, within a reasonable safety profile? I don't want to tell the FDA how to manage drugs." But the current model "has a chilling effect on access to testing and then, by extension, access to therapeutics."

These wide gaps are starkly clear to Pranil Chandra, DO, as well. "Over the past decade or so, the field of molecular pathology has seen some pretty severe reimbursement as well as regulatory pressure," says Dr. Chandra, senior vice president and chief genomics officer, PathGroup, Nashville, Tenn.

He uses elephants to illustrate the problem—not the familiar trope of vision-impaired folks sussing out the mammal from different points; rather, it's more of a pachyderm cocktail party. When it comes to addressing the gaps in molecular testing, "there are a lot of elephants in the room," says Dr. Chandra.

One of the larger elephants, he says, is inconsistent, highly variable coverage by payers, which has an impact on equitable access to care. "Ultimately, in our experience, most of the time the testing gets done," Dr. Chandra says. "But it's with a lot of difficulty."

Dr. Chandra says he's seen improvements in payer coverage policies by certain payers, but that noncovered status with many payers affects significant populations in the United States.

In his experience, private payers may be informed by their own medical directors who are unfamiliar with molecular pathology and cancer genomics testing. Medical policy decisions may be outsourced, Dr. Chandra continues, stoking requirements for prior authorization.

"Things are getting better," he says, "but the fact of the matter remains: There is a lack of standardization amongst third-party commercial payers, and many of them are kind of doing their own thing."

Some elephants are especially unruly. "With certain carriers, we've noticed they do not pay for testing, even for

tests that are recommended in medical guidelines," Dr. Chandra says. "That's starting to become an issue. We have to ensure that people have equitable access to care."

A potential solution could occur on the state legislative level, Dr. Chandra says. In some states, lawmakers are requiring insurers to pay for biomarker testing that is recommended by medical guidelines. Such an approach is especially appealing, he says, because it democratizes access to testing as well as to therapies.

These larger forces exert specific pressures on pathologists and laboratories. "There is a significant lack of alignment," Dr. Caughron says, between reimbursement and the pathologist's role in molecular workups.

He, too, digs into historical roots to explain current problems. The professional component of biomarker testing has never been on par with other anatomic pathology work. "With genomics, because it's done in a test tube, instead of through the microscope, we limit it," he says.

With the reimbursement for professional work minimal or nonexistent, he says, "any time the pathologist spends on this is unpaid time."

"When that problem is solved, and pathologists can justify the time they spend on the issue, then they can give that time," he says, noting that ER, PR, and HER2 testing became commonplace when testing was compensated appropriately.

That may not happen as easily with other cancer biomarkers, he concedes, given that molecular biomarkers straddle both clinical laboratory tests and anatomic pathology tests. ("Though I disagree a little bit with the use of those terms," he adds.) When the CMS put molecular tests onto the clinical lab fee schedule, that removed a separately valued professional service. "What we need to be successful is for them to be more like pathology tests," he says.

Teasing out that analogy a bit more, he says there's every reason to test most tumors, especially advanced ones, with extensive molecular workups to guide treatment. "Why wouldn't we use our tools to gain that information?" Dr. Caughron asks. "We don't look through a microscope and just say, *OK, we found the part that has invasion, so we're not going to look anywhere else.*"

At one point, it looked like NGS would be the one-size-fits-most solution, allowing for identification of multiple rare markers. It could still happen, says Dr. Caughron. "But it's still a volume game—you need to have a certain volume to make it not economically catastrophic. And there's still the problem of the time the pathologist has to spend on this. Nowhere in the system is that time appropriately counted for and reimbursed."

It can work for large reference labs, Dr. Caughron says. But in smaller settings, even when it's possible to show overall cost savings to the institution, "How do you move some of that to the pathologist, who makes it all possible? Without a direct payment model, it can be very difficult for that to happen," given that with most hospitals, there remains a direct correlation between the professional services provided and how physicians are paid. In this view, the molecular gap is actually the gap in the professional reimbursement. When the system figures out how to close that gap, he says, "I think you'd find many pathologists who suddenly become interested in bringing this into their laboratory and spending time on it."

Ideally, practice guidelines that call for molecular testing would light a way through the wilderness. But again, there's no easy path, says Dr. Lindeman. While the NCCN guidelines, for example, have no shortage of molecular tests, "they're often miscellaneous recommendations—category 2A. They're not always baked into the algorithm per se," he says. Moreover, guidelines for working up a case from a diagnostic perspective are a bit more rudimentary compared with treatment guidelines, he observes.

In a tidy world, testing could easily be divided into diagnostic, prognostic, and therapeutic columns. But biomarkers fail to heed the divisions craved by the medical profession and insurers. "It's becoming very hard to distinguish" what a biomarker's utility is, Dr. Chandra says. "Those three uses overlap," to the consternation of payers who are laser-focused on so-called actionable biomarkers.

Says Dr. Lindeman, “I’ve had payers tell me they’re not interested in paying for things that are in the WHO diagnostic guideline if it doesn’t lead to a change in treatment.”

Dr. Lindeman also sees a gap between how pathologists and treating physicians interact with guidelines. He would like to see the NCCN expand its scope to include a set of algorithms and guidelines for diagnostic workups, done in parallel with, or anticipation of, what needs to be done for management. It would be helpful, he adds, if more pathologists were involved in creating the NCCN guidelines. “There’s usually a few. I don’t want to complain that there’s no voice. But it’s usually a minority.”

But if the underlying problem is economic, even the best guidelines will only go so far, Dr. Caughron says. Not only is it hard for guidelines to keep up with the published literature, but, more concerning, he says, “is there seems to be a reluctance on the part of payers to look to guidelines as a definitive answer to their questions. I have heard payers speak with cynicism about guidelines, which I find disappointing and a little disturbing.” Guidelines can help physicians deliver the right care, but they might not push the payment needle.

Why the cynicism? “Not all guidelines are created equal, if I can put it that way,” says Dr. Caughron. Some are better researched and written than others. “It only takes one less than perfect example for someone who’s writing the checks and paying the bills to believe that these can be dismissed.”

There’s another problem: Payers aren’t steeped in practice patterns and realities, patient care trends, and technologies the way health care providers are. Guidelines don’t map directly onto what happens in practice, and thus can’t fully answer the questions payers may have when deciding what to pay for.

“A great example of that is prior authorization,” Dr. Caughron says. While guidelines make it clear that certain testing should occur with NSCLC, for example, payers may say, “‘We agree, but we want to review these charts, these patients, and make sure they meet the criteria,’” rather than trusting the system.

No one talks about taking economics off the table when pondering these problems—clearly, economics *is* the table on which other laboratory challenges are set.

But there is room around that table to work out some answers, Dr. Chandra says. “Medicine is practiced at the local level,” he says.

PathGroup has its own high-volume, high-throughput molecular laboratory, providing services to more than 200 hospitals belonging to integrated regional health care systems spanning multiple states. “We have different testing protocols that are institution-specific.” Those most involved with genomic profiling—pathologists, medical oncologists, interventional pulmonologists, interventional radiologists, genetic counselors, hospital administrators—identify standards of care and appropriate testing protocols at each hospital.

Equally important, Dr. Chandra says, is they agree on who will order the testing.

In some cases, that might be pathology-driven reflex testing. This can be a standing order that’s arrived at through a consensus, multidisciplinary conversation. It could also be an institution-specific order, Dr. Chandra says. “In one of our institutions, every stage three and stage four lung cancer gets molecular testing based on medical and NCCN guidelines.” In other institutions, oncologists and pathologists can simply order molecular testing ad hoc.

Dr. Chandra

However, the ad hoc approach appears to be less successful, Dr. Chandra says. “In our experience, either testing

doesn't get ordered or it doesn't get ordered quickly enough. And oftentimes the pathologist will wait for the oncologist, and the oncologist will wait for the pathologist—and the test never gets ordered." The literature also backs up the efficacy of multidisciplinary approaches and developing local protocols, he says.

"I've always been a proponent of pathology-driven reflex testing," Dr. Chandra says, adding that a growing literature suggests it leads to more improved identification of actionable biomarkers, shorter time to treatment, and better outcomes.

"What can't be done is nothing," Dr. Chandra says. "That is just unacceptable."

Dr. Caughron is also a fan of pathologists initiating the testing at the time they identify a malignant tumor, though he notes some can be reluctant to take that step. "In many environments the pathologist says, *I don't feel comfortable doing that because I'm only doing the analysis to guide this specific treatment. And since I'm not the one treating the patient, I'll wait for the oncologist to order the testing.*" In some cases, he says, the pathologist might not know, at the time of diagnosis, who the treating oncologist will be, adding to delays.

Pathologists might also pause knowing that the testing is expensive and may not be covered. "We're going to wait and only do it in certain environments, or for certain conditions." They may also encounter delays with the uptick in prior authorization requirements.

MAWD Pathology Group has more than 50 pathologists spread over three states. "In each environment it plays out a little differently in terms of how the local care team best sees biomarker testing implemented," Dr. Caughron says.

Echoing Dr. Chandra as well as the literature, Dr. Caughron suggests the most successful approach uses pathologist-initiated testing. At some MAWD sites, however, oncologists have stated a clear preference for ordering the tests themselves; at others, the pathologist orders it at the time of diagnosis.

There are times when everyone agrees (at, say, a tumor conference) that biomarker testing should be done. In those situations it's often a send-out test, and the pathologist might not be compensated for pulling the block, reviewing the slide, and sending it out. And when the results do come back, the pathologist may be left out of the loop.

If the past was characterized by the town-gown divide, these days nearly everyone, pathologists and oncologists alike, has shed their gowns and entered the town, given the rapid advances in molecular pathology.

Simply put, it's hard to keep up. "It's hard for *me* to keep up," says Dr. Chandra. "And I'm specifically trained and boarded in molecular pathology."

PathGroup has expanded its efforts to centralize the educational information that goes out to its enterprise network of 240 pathologists, with a team of locally based physicians and scientists developing evidence-based recommendations, to help standardize testing protocols across institutions.

Other challenges are also evergreen, including collecting sufficient tissue or plasma, deciding whether to initiate treatment while waiting for testing, and reviewing test results.

In the latter case, Dr. Chandra says, "Many next-generation sequencing providers give you a 15-page report with all the alterations detected." The message, if not the actual wording, he says, is, *Here you go—you all figure out what to do with it. Good luck!*

PathGroup tries to get a handle on that via its molecular tumor boards across its enterprise network, which meet virtually twice a month. Dr. Chandra and his colleague Michelle Shiller, DO, lead the sessions—she's PathGroup's medical director of genomics and molecular pathology services, based at Baylor University Medical Center in Dallas—which are now being offered for CME credit.

"It's a somewhat decent solution," says Dr. Chandra, "but how do we scale that effort? It needs to be driven by a

champion on the oncology side and a champion on the pathology side."

As for the lengthy reports themselves, PathGroup spent several years gathering input from its community oncologists about what they liked and disliked in NGS reports, then designed a report that was implemented when PathGroup launched its FDA-cleared Endeavor assay in May 2020, Dr. Chandra says. "All the relevant information that an oncologist will need is condensed to one page."

The most actionable alterations are placed prominently on the front page, where the biomarker result is listed along with potential therapies, organized according to the strength of medical evidence. The report lists clinical trials that might be appropriate for the patient. Also included are sections for tumor mutational burden, microsatellite instability, and pertinent negatives.

Dr. Chandra also points to another feature of the reports: two or three paragraphs written by a team of molecular professionals including board-certified PhD directors and physicians, then reviewed, edited, and signed out by a molecular pathologist. The text provides a summary of the diagnostic, prognostic, and/or therapeutic significance of the results. It's particularly helpful, he says, when two results suggest opposing information—for example, finding an *EGFR* exon 19 deletion that would indicate treating with an EGFR inhibitor, as well as high PD-L1 expression, which would suggest using immunotherapy.

"The NCCN guidelines will tell you to prioritize the *EGFR* mutation over the immunotherapy in those contexts," Dr. Chandra says. "So we take that effort out and reconcile those differences, speaking to the clinical utility in our report. We made a lot of effort to design it in a way that is most meaningful and optimal to the oncologists," enabling them to quickly understand the therapeutic strategy for their patients.

Is Dr. Lindeman surprised by how the field has played out? Not particularly, he says, before adding, "It's disappointing, to be sure."

Yet he and others sound more optimistic than resigned when they contemplate the work that lies ahead. "It sounds kind of 'apple pie,' but everything comes back to communication," Dr. Lindeman says. "Pathology shouldn't be making decisions or formulating opinions without input from our [oncologist] colleagues. And vice versa."

He says that worked well at his former institutions in Boston. He met every couple of weeks with the clinical and academic research leaders to discuss what was emerging in their work. "I knew what was coming, and they knew our issues in the lab, and we worked together."

Like so many others, Dr. Lindeman notes the pandemic took its toll on some of those routines. "A lot of that communication suffered, to be perfectly honest. But we still tried to be partners with our oncologists, as opposed to contractors for them."

Molecular testing for cancer slowed down considerably at the height of the pandemic, he says, because the laboratory had to divert resources to viral testing.

With the crisis-mode portion of the pandemic now receding, it might be easy to settle into a lower intensity routine. Sometimes, he concedes, "it's easier to be a contractor. We might just want to do our work and get paid and move on, and maybe they just want to pay us and not interact on a different level.

"But one of the problems for pathology in general," Dr. Lindeman continues, "is that our specialty has become a little transactional in that regard with our colleagues. It's important for us to be active consultants and contribute to patient care decisions at all of our institutions, and to demonstrate our value beyond just the testing and the microscopy. But we also need to be advocates for overall care, and for ourselves in the process."

He pauses, then says: "I gave a speech; I didn't mean to. But for me, that's what works."

He continues: "Many people are doing this, so I don't want to make it sound like I'm the only person who's thought of it—far from it." But his emphasis is clear: "This is an important part of our career and our role in medicine that

we shouldn’t give up.”

Karen Titus is CAP TODAY *contributing editor and co-managing editor.*