Molecular tumor boards: fixture or fad?

Karen Titus

October 2014—Along with everything else the genomics revolution has wrought, there's this: Molecular testing is threatening to turn medicine into an ongoing episode of "Hoarders." So much information and so many possible uses for it—including, in some cases, none at all.

The expansion of molecular testing is also upending the role of the traditional tumor board. Early on, tumors could be covered by so-called singlet molecular testing, looking for single gene changes or microsatellite instability in a particular type of cancer, the implications of which could easily be discussed in a site-specific tumor board. "That worked really well as long as we were only testing three to five genes in lung cancer or melanoma or colon cancer or whatever," says Alexander Lazar, MD, PhD, molecular pathologist, MD Anderson Cancer Center, Houston.

Dr. Razelle Kurzrock (left) and Dr. Donna Hansel at the University of California, San Diego. The UCSD molecular tumor board has made "an enormous difference in getting people comfortable with something that's very important but very new," Dr. Kurzrock says.

Next-generation sequencing threatens to make that approach seem almost quaint. In March 2012, Dr. Lazar says, physicians at MD Anderson started using a 50-gene panel, and later a 400-gene panel. And while most institutions are working to tame the data from fairly targeted panels, the information keeps flowing, as researchers and clinicians continue their pursuit of personalized cancer treatments. "We're creating a new molecular taxonomy of cancer," he says. "We're all struggling with this, all over the country."

Traditional tumor boards aren't going away anytime soon, but clearly something else is needed as well. Enter the molecular tumor board. Or boards—there really is no one type of board yet, given that the concept is relatively new. Since the shape of these boards is in flux, it should surprise no one that there's even talk in some quarters that the molecular tumor board is simply an interesting evolutionary blip, a sabertooth salmon detour on the way back to, well, the traditional tumor board.

But the air is thick right now with talk of molecular tumor boards, including talk about what, exactly, is meant by

one. “It could mean anything in which genetic variants, of any kind, are considered,” says Jonathan Heusel, MD, PhD. That’s a lot of territory, ranging from single-gene testing for clinically actionable variants, such as BRAF or FLT3, to integrating whole-exome or whole-genome data into evaluation of a patient with a recurring cancer and in need of salvage therapy, says Dr. Heusel, chief medical officer for Genomics and Pathology Services, and associate professor in the departments of Pathology and Immunology and Genetics, Washington University School of Medicine, St. Louis. Then there are questions of whom to test, and by which technology. What can be done, versus what should be done? “Do we need to bring RNA sequencing into this?” Dr. Heusel asks. “Do we need to look at microarray data to look at copy number variation, or can we get that from the [next-gen sequencing] data in a clinically robust way?”

In some cases, institutions are using molecular tumor boards to link actionable data to clinical care as swiftly as possible. In others, the focus is on research, with an eye toward eventual clinical utility. Yet others are establishing hybrid boards; many places have multiple boards.

Dr. Heusel

“There is a lot of interest in this,” says Charles Hill, MD, PhD, director, molecular diagnostics laboratory, and program director, pathology residency, Emory University Hospital, Atlanta. Dr. Hill is also president-elect of the Association for Molecular Pathology, and he notes the organization hopes to start collecting data on molecular tumor boards. In the meantime, here’s a look at how molecular tumor boards are evolving.

Even as she discusses molecular tumor boards, Donna Hansel, MD, PhD, has her eyes on other prizes. “Next year it’s going to be called the protein tumor board,” she says, only partly hyperbolically. And after that, be on the lookout for cell-based therapy tumor boards.

Her larger point is that molecular tumor boards are a byproduct of evolving technologies in pathology, and what’s based on genomics today will almost certainly become something else in the not-too-distant future.

At UCSD, where Dr. Hansel is professor of pathology and division chief of anatomic pathology, genomic analysis and training are flourishing, she says. The institution performs high-throughput sequencing using a MiSeq and a recently acquired HiSeq 2500 (Illumina), with results available for clinical use. By early 2015, she and her colleagues will begin offering a 400-gene cancer panel and a 115-gene panel for hematologic malignancies. Further out, the institution may look to develop panels targeting constitutional diseases, such as cardiovascular disease. Little wonder clinicians have needed the guidance of a molecular tumor board.

The panels were developed in collaboration with UCSD’s Moores Cancer Center, where Razelle Kurzrock, MD, is senior deputy center director, clinical science. Even for physicians with substantial expertise in oncology, says Dr. Kurzrock, “Genomics is new to them.” That’s one reason why during the weekly, 90-minute molecular tumor board she recently help set up at UCSD, 30 minutes is devoted to a formal lecture related to molecular diagnostics and related clinical trials.

It would be hard to overestimate the role of genomic testing as the basis for molecular tumor boards, says Dr. Kurzrock. “I know not everyone agrees with me,” she says, “but I think a molecular test is a diagnostic, and you always want to know the patient’s diagnosis, right from the beginning.”

Dr. Kurzrock has also been involved in setting up the Center for Personalized Cancer Therapy, which she directs. The molecular tumor board at UCSD (where Dr. Kurzrock is also chief, Division of Hematology and Oncology)

includes “classical” specialists—pathologists, medical oncologists, radiation oncologists, surgeons, and radiologists—to review cases. But it also includes basic scientists, bioinformaticians, and pathway specialists. Altogether, some 30 to 40 attendees show up—enough to fill a Chicago storefront theater. That includes pathology residents and fellows, Dr. Hansel notes. “We have them involved in the tumor boards pretty heavily.”

The first hour of each weekly meeting is devoted to discussing particular cases. “Usually it’s a difficult problem,” says Dr. Kurzrock. In that sense, the UCSD molecular tumor board resembles a traditional one, although it’s not disease-specific. Typically the molecular diagnostics launch the discussion of, What next? Anyone can bring a case, though it’s usually the medical oncologists who do so. Present at every meeting is a pathologist, who reviews the pathology and helps with the review of the molecular diagnostics. A radiologist is always present to review film. And before each meeting, a manager summarizes the cases to be presented, such as age, diagnosis, tumor site, molecular pathology test results, and prior therapy; the summaries are distributed before the meeting “so the scientists and some of the pathway specialists can have a crack at some of the data as well,” says Dr. Kurzrock.

The clinicians are comfortable ordering molecular tests, but that wasn’t always the case, Dr. Kurzrock says. Hence the second role for the molecular tumor board: education.

Not surprisingly, she said, most of the cases brought for discussion initially were confined to “last-ditch” efforts. Physicians were ordering the molecular diagnostics while patients were still stable or doing well on a prior therapy, in anticipation of a relapse—a not uncommon occurrence in patients with metastatic disease. “They would present so they would have a plan when the patient’s disease did start to progress.”

Over time, however, Dr. Kurzrock has noticed a change. As physicians have learned more about molecular testing—in no small part because of the tumor board’s educational component—they’ve become more comfortable ordering the tests, she says, and are now ordering them earlier, for expanded indications—a reflection, perhaps, of the evolving role of molecular testing in general.

That makes Dr. Kurzrock happy. She has no interest in discouraging physicians from ordering the tests. “We should want to know what’s deeper in the cell on every patient,” she says.

Viewed through that prism, the role of the pathologist on molecular tumor boards becomes indispensable, she says. “People didn’t know what to do with this data. They were really uncomfortable with it. So being able to come into a room where you have 30 colleagues and experts in a variety of fields, and discuss your patients and ask what this means and that means, it’s made an enormous difference in getting people comfortable with something that’s very important but very new.”

Dr. Hansel sees another opportunity unfolding for pathologists. “Here’s where we can take the lead—we can take these profiles and then apply them back to biomarkers on tissue, more cheaply and quickly,” as has happened with the BRAF V600E mutation antibody. If pathologists can develop a whole range of surrogate markers, she tells her lab colleagues, molecular analysis could “come back full circle to our not-so-glamorous immunohistochemistry,” she says. They’ll also help steer molecular tumor boards as pathology incorporates new testing modalities, including proteomics, cell therapy, drug sensitivity testing on patient cells, and the like, both on liquid biopsies and tissue-based biopsies.

Giving the crystal ball another spin, Dr. Kurzrock offers a prediction of her own. For now, UCSD has one molecular board, “mainly because it’s quite new.” That’s likely to change in the future, she says, both at UCSD and elsewhere, given the emerging expertise at most centers. “You can’t have all the specialties do their own molecular tumor board because the training and expertise are not there yet.” Eventually, she says, “Regular tumor boards are all going to become molecular tumor boards.”

Jan Nowak, MD, PhD, couldn’t agree more. Or less.

“I’d say it differently: All tumor boards will eventually have molecular input,” says Dr. Nowak. The discussion is

partly a matter of semantics—do you want ice in your drink, or your drink over ice?—but the struggle is real: How can medicine incorporate an unending flow of information?

While molecular tumor boards "are a necessary exercise for us to go through in the next few years, they're educational exercises," Dr. Nowak says. He applauds those boards that explain molecular testing to oncologists, clinicians, and, yes, even pathologists. But he cautions against tumor boards where the focus veers away from patients.

At Evanston (Ill.) Hospital, NorthShore University HealthSystem, where Dr. Nowak is the medical director of the molecular diagnostics laboratory, there is no formal molecular tumor board. Nor has he been approached about setting up one, in large part, he says, because he regularly discusses molecular results at the traditional tumor boards. He attends the individual disease-specific tumor boards (GI, endocrine, breast, GYN, head and neck, etc.) that meet throughout the week, bringing with him molecular test results. "This isn't about the test; it's about the patient," he says. "But there are some unusual molecular results, and that's an opportunity for me to talk about those, and to teach, as appropriate. It's also an opportunity for me to learn from the oncologists how they're going to use that information." The format also allows Dr. Nowak to learn what tests they're interested in adding.

Just as critical, from Dr. Nowak's point of view, is that the traditional-board-with-molecular, versus a strictly molecular board, allows him to remind colleagues of some critical, pathology-specific aspects of molecular testing. Molecular-only boards, he fears, run the risk of overlooking a basic but critical fact: "We do this testing on real bits of tissue. So we need to be able to say to the interventional radiologist who is doing the needle biopsies, 'Look, this piece of tissue you gave us for biomarker testing is not adequate,'" Dr. Nowak says.

Tom Hensing, MD, codirector of the thoracic oncology program at NorthShore, says the traditional-with-molecular approach "works wonderfully." He shares Dr. Nowak's concern about tissue-related issues. With the limited samples typically available to him and to his colleagues, "We have to be selective about what we're going to order." In some cases, he adds, such as when the clinical diagnosis is fairly clear, it makes sense to tell the diagnostic pathologist to limit IHC stains. The best approach, he says, is to review the patient and clinical situation, understand the clinical questions being asked, and apply clinical profiling to those questions, all in the context of a tumor board. "The nice thing is our molecular pathologist [Dr. Nowak] is sitting right there and understands what we're looking for in terms of what would change patient management. That's the best way to do it—have everyone in the room and discuss what you need from the sample. Because pathologists can't run every test under the sun."

The choices will only become harder in the future. How will laboratories put together the various "-omes" that are starting to bloom—transcriptome, genome, methylome, and potentially even the proteome—in a way that makes sense for patients and physicians, asks Dr. Heusel. It's not as if learning about a few more genes and molecular tests, as they become mainstream, will reduce the need for molecular tumor boards. Like biographies about Abraham Lincoln, there will always be something new.

Dr. Heusel and his colleagues at Washington University are doing the heavy lifting through a number of molecular tumor boards. It's important, he says, to clarify the boundary between clinical use and clinical research. There's too much to learn right now about which methods and analyses work best to do otherwise, he says, though he adds that the goal for most molecular tumor boards should eventually be patient management.

All patient care testing is done through the clinical NGS-based testing service, Genomics and Pathology Services, or GPS, which was started about four years ago and which provides NGS-based testing in both oncology and constitutional disease detection, complementing traditional services such as cytogenetics, single-gene testing, traditional anatomic pathology, and immunohistochemistry. For oncology, the lab uses a comprehensive panel of clinically actionable genes; the third version of the test is being validated this fall.

With clinical action in mind, it's important for molecular tumor boards to figure out what and how to report. (Dr. Heusel isn't alone in this concern. "The revised CAP checklists are very much focused on how evidence is being used in clinical decision-making," he says.) "It really boils down to what is determined to be actionable. For somatic

variants in oncology, actionability refers to whether the variant provides diagnostic, prognostic, or predictive [drug efficacy] information."

The GPS oncology test reports variants in five categories, or levels. A level one variant is one that has been previously identified in the disease of interest and is known to be actionable—BRAF V600E in melanoma, for example. A level two variant is similar in that it's known to be actionable, but in a different disease type. A level three variant has been described previously in the setting of cancer but is one that does not have a well-defined association for actionability. And, skipping level four for a moment, a level five variant would be a common polymorphism.

The remaining category is trickier. "A level four variant may look and smell pathologic," Dr. Heusel jokes, "but there's no compelling evidence about its clinical effect. It's important enough to report, and we can cite some interesting scholarship associated with it." Putting it in the level four classification, however, "is an indication to the ordering physician that you need to be really careful and use it conservatively."

In the oncology setting, these variants of uncertain clinical significance, or VUS, could also be called grist for the molecular mill. Their ultimate disposition as pathologic may be dependent on the specific disease and the constitutional genetic background. In this regard, Dr. Heusel says, a potentially deleterious change in the amino acid sequence does not always mean the variant will be contributing to disease. In a very practical sense, the real function of molecular tumor boards is to figure out what to do with such variants. Are they drivers of the disease, or are they modifiers of the disease? Or are they just passenger mutations that can be safely ignored?

To answer those questions, "every institution will need to rely on local expertise," Dr. Heusel says, echoing Dr. Kurzrock. Molecular tumor boards need to include clinical pathologists, who know how to run the tests, evaluate their performance, spot and avoid errors, and report variants; bioinformaticians, who assemble data analysis pipelines and filters to help sort through the data; so-called content experts, who are well-versed in oncology, human molecular genetics, or other subspecialties that manage patients with cancer and other diseases with a strong genetic component; and cytogeneticists, since FISH and chromosomal microarrays aren't in imminent danger of being replaced by whole-genome sequencing. Looking at the lineup, Dr. Heusel says, "One of the great things about this is that it's forcing us to bring together fairly diverse fields."

While such groups aren't filled with fierce opponents, there are challenges for its members. Much of it's linguistic. Dr. Heusel says he had to learn the language of bioinformatics; bioinformaticians, on the other hand, had to learn a new language of human genetics or oncology. And nearly everyone has to learn the language of testing. "It's a challenge at every institution," he says. "There's a very basic communication and education that has to occur between the folks who offer the test and the folks who are ordering it. But once they come to grips with that, they fall in love with the quality of data."

The molecular tumor board has served to inspire Dr. Heusel as well. "I'm surprised at how often, even in routine testing, we come across interesting and unexpected things that are sobering—and also very exciting." These are early days, and molecular tumor boards face the humbling fact that it's hard to know if what they're seeing is important or merely noise. The literature is filled with exciting variants that eventually turn out to have no significance and, like Amelia Earhart, simply disappear.

In that sense, the tumor board has another important role to play: making sure the data are handled cautiously. The boards can even bring to the surface discrepancies between how treating physicians and pathologists respond to limited or even weak data. A new mutation in a well-studied gene might be a green light to those who've long had few or no treatment options. Pathologists might then need to decide if they're comfortable hoisting a red flag instead. As one pathologist notes: "I'm not used to that. I never thought I was conservative, but apparently I am." But as pathologists can find ways to validate their observations and link genes and pathways in clinically useful ways, Dr. Heusel says, "it will be truly powerful."

If pathologists sometimes use molecular tumor boards to hit the brakes, clinicians can, and do, use the

same forum to shift to a higher gear.

At a recent molecular tumor board meeting at Emory, says Dr. Hill, “We were discussing an unusual mutation, and our clinical trials director looked up and said, ‘Oh, there is a clinical trial for this particular tumor type and this particular mutation underway.’ None of us had ever heard of it, but the medical oncologist quickly went about trying to enroll the patient.”

The board was launched in the spring, shortly after the institution began offering a multigene sequencing panel, primarily for lung cancer and melanoma. With the new testing came more questions, Dr. Hill recalls. “We realized we could all benefit from having a bigger group discussion, rather than multiple people having similar discussions” in isolation. The board was a logical next step, and has, says Dr. Hill, “been a great learning opportunity not just for the trainees but for the faculty as well.”

Dr. Hill

“It’s really nice, from the laboratory side, to hear when there are new options for patients based on the data we’re providing,” Dr. Hill continues. Case in point: Dr. Hill recalls the surprise he felt at a recent molecular tumor board when a medical oncologist colleague responded to a report that a patient had tested positive for a lung cancer resistance mutation. To Dr. Hill, the news seemed bad: The patient was failing therapy, and here was the proof. “But my colleague was very happy.” Not only had his suspicions been confirmed, but the patient now qualified for a new drug specifically tailored to this situation: patients with the mutation who were failing therapy. “Now we are very careful to communicate that kind of information as rapidly as we can, because we’ve seen how they may use it to qualify patients for a different therapy.”

He’s also noticed that while presenters at the molecular tumor board come bearing similar research, the face-to-face discussions yield slightly different responses. “Everybody’s looking at the literature, but with a slightly different point of view. It’s actually a bias, but we’ll call it a point of view,” he says with a laugh. “So the board gives us a well-rounded picture of the new information.”

Dr. Hill says the molecular tumor board, which meets monthly (that may change to weekly at some point) to discuss three or four cases, on average, has been “incredibly valuable. It gives me an opportunity to be more up-to-date on how information coming out of my laboratory is being used.” Like many of the tumor boards, the format presents clinical findings (in this case, from a hematology-oncology fellow) followed by pathology and molecular reports.

Dr. Hill doesn’t see either traditional or molecular tumor boards disappearing. Like many others, he expects more molecular findings to wind up in traditional discussions. “But unless we start significantly reducing the number of patients who present in late-stage disease, I don’t think we’ll see the molecular tumor board go away.” Even as the board continues to cope with the high-tech challenge of molecular testing, one low-tech challenge persists, he says. Doctors are busy; time is fleeting. “But we find it valuable enough that we make time to do this.”

So important is the molecular tumor board at MD Anderson that even the institution’s president, Ronald DePinho, MD, finds time to periodically attend, says Dr. Alexander Lazar. “This is something that he’s particularly interested in and supportive of.”

Some 150 clinical cases are sequenced each week using multiple next-gen panels of approximately 30 to 400

genes; the board meets monthly for 90 minutes. There's no need here for even a quick calculation. "Clearly all of those aren't going to be discussed at this conference," Dr. Lazar says. Instead, he and his colleagues try to pick several particularly thought-provoking cases—a novel mutation, intriguing mutation patterns, comparisons between a primary and metastatic tumor. The conference also is a place to discuss changes to the panels. Some 25 to 50 people attend the tumor board. In the near future, these discussions will likely expand to sister institutions within the MD Anderson network through videoconferencing.

In a typical discussion, a clinician presents the clinical features of a case, followed by someone else presenting a literature review of the tumor's genetic features. A pathologist might fill in with additional details about allele frequency or pitfalls in interpretation, for example. Then comes discussion and an attempt to synthesize the information, all with an eye toward dealing with similar cases in the future.

Dr. Lazar uses the example of BRAF to describe this trickle-down approach. It's commonly mutated in melanoma, but perhaps sequencing has turned up a variant that's not well described in the literature. "Someone might discuss everything that's known about where BRAF is mutated, including the areas that are really common, such as the V600 region in exon 15," Dr. Lazar says. "Then we'd discuss what we know about alternative mutations in exons 15 or 11. Are they good activators of the BRAF protein and ERK pathway, are they not good activators of the protein, do they seem like they are potential driver mutations, or could they be passenger mutations? From there, we'd narrow it down to looking at the particular mutation in the case we have to discuss. If there's not a lot in the literature, what would we predict about the case based on all the information we just reviewed? And that would lead to a discussion of which of the mutations tend to respond well to the family of BRAF or MEK inhibitors, and which ones seem not to. And then what is going on in clinical trials?"

Not all molecular results require that level of discussion. More routine testing, with straightforward results, easily makes its way into traditional tumor board discussions, as it has for years with microsatellite instability testing in colon, Dr. Lazar says.

The Institute for Personalized Cancer Therapy has become another piece of figuring out how to annotate and interpret next-generation sequencing, he says. Right now, by agreement with the clinicians at MD Anderson, molecular reports from pathology do not include information or suggestions about clinical trials that might be useful based on testing data. The institute group—including molecular pathologists, clinical teams, bioinformaticists, and researchers—is creating a continually updated guide for interpreting molecular test results. As the database goes live, one gene after the next, attendees at the molecular tumor board are watching closely. "It's somewhat of a proving ground to discuss what's going into the database."

The molecular tumor board has also become a place to discuss so-called bucket trials, in which patients are treated based on mutations as well as histology. Patients with a similar mutation, regardless of tumor site, might be treated with the same therapeutic agent that inhibits a certain pathway. "We're trying to find ways to identify patients with certain types of mutations, and then quickly try these different targeted therapies to see what histologic context they're going to work in, and what ones they're not," he says.

Molecular tumor boards may also serve as a sort of refuge for physicians, Dr. Lazar suggests. "We're basically making new rules for how to manage information and apply it clinically. And that's incredibly exciting. But that can also create uncertainty. So by discussing it from every aspect—from the tests we want to do, to interpretation, to the limits of particular test technologies, to clinical trials, to treatment response—we can create a system of best practices that makes sense for everybody."

Given the nature of what they're trying to accomplish, it only makes sense that molecular tumor boards would evolve. In a field that changes this rapidly, a static setup would be as valuable as tracking websites with a card catalog.

Dr. Lazar

When the molecular tumor board was first launched at MD Anderson, for example, the discussions were much more formal and didactic than they are now. They had to be, Dr. Lazar says. “We were explaining how sequencing works, and the quirks of different platforms, and why some tests were good for certain events but not others.”

The first change for many institutions, however, will be setting up a molecular tumor board. Even Dr. Hensing, with all his satisfaction with the current traditional tumor board, sees that day approaching for NorthShore. It could come when next-generation sequencing comes onboard, bringing with it those pesky variants of unknown clinical significance. “As clinicians, we don’t necessarily know best how to deal with that information. There needs to be a mechanism to discuss these cases.” At the same time, he says, those mechanisms should start within disease-specific tumor boards, “because it’s got to start with how to handle the diagnostic material.”

When should an institution consider adding a molecular tumor board? Not everyone has the resources of an MD Anderson. As Dr. Lazar puts it, “Our breast medical oncology department is larger than most people’s entire cancer centers.”

That’s almost beside the point, though. Nearly everyone makes it abundantly clear, with the repetitiveness of a Schubert symphony, that molecular results are best handled in a multidisciplinary way. “Everybody can’t be good at everything,” says Dr. Lazar. So regardless of size, every institution needs pathologists who are very familiar with molecular testing—how it’s done, how it’s interpreted, and what it means. “They have to present a face to the treating clinical team.” In addition, he says, pathologists need to be present to listen to what their clinical colleagues need from molecular tests and communicate what is possible on a practical level.

And again, if it’s not already clear, this whole field—“personalized cancer therapy, targeted therapy, molecular medicine, precision medicine, whatever you want to call it,” says Dr. Lazar—starts with results from tests that are performed by pathologists, on tissue that pathologists diagnose, curate, and maintain. “So our ability as pathologists to explain these tests, their importance and limitations and clinical justification, is absolutely critical for patient care.”

[hr]

[typography font=”Cantarell” size=”18″ size_format=”px”]Next month: Molecular tumor boards at Dana-Farber Cancer Institute and Brigham and Women’s Hospital[/typography]

[hr]

This is true even if the molecular testing is sent out. It may not make sense for an institution to offer the testing locally, Dr. Lazar says, but “you absolutely have to have someone in your practice—frankly, as many people as you possibly can—who will get interested in this, even if they’re not producing the information in their own department. Personally, I think every pathologist should be interested in this and be able to explain it.” Pathologists need to oversee the preanalytic variables, but also figure out how to incorporate it into the medical record and how to help clinicians figure out how to use it in patient care. “Treating clinicians will be much happier trying to discuss this with a local pathologist who’s an expert, rather than trying to get answers from a reference lab across the country,” Dr. Lazar says.

And for those who already have a molecular tumor board or two, Dr. Heusel shares his thoughts about how he’d like to see things evolve.

First, he says, there needs to be standardization in how variants are reported and in the criteria by which they are considered actionable. “For a long time, people were counting the variants they were finding in p53 as being actionable. Well, it’s hard to make that claim at this point.” Similarly, he says, BRCA1 and BRCA2 have “many, many VUS, and very few of them are probably actionable.”

He’d also like to see molecular tumor boards pay closer attention to data-set integration, making sure that cytogenetic microarrays are coupled with the genome and the transcriptome, and possibly the methylome, in a way that meets the standard of patient care. “So that we’re not all rushing around and chasing the next best thing before we’ve even decided whether it meets clinical standards.”

Finally, he asks, what’s the best way to improve understanding of gene-gene-gene interactions and the intricacies of pathway interactions? When do passenger variants become modulators, and when do modulators become drivers? “We are still operating in 2D space, relatively speaking, mapping variants in single genes to diseases or phenotypes.” But pathology is a 3D, possibly even a 4D, endeavor, he argues.

Molecular testing is only one bud on the branch, and for all its complexities, says UCSD’s Dr. Hansel, “Right now it’s actually easy to do. The material is pretty stable, and it’s not extraordinarily expensive to do.” As tests delve deeper, however, it might become harder to make clinical connections. Correlations between genome alterations and mRNA alterations tend to be fairly linear, but at the protein level, that correlation starts to break down. “You could have genomic alterations that don’t necessarily predict what happens on the protein level, but it’s the protein level you’re targeting,” Dr. Hansel says. “So not all genomic alterations carry through to what the targeted therapy is predicted to be.” In that sense, “We still have a lot of work to do.”

Dr. Hansel is unwavering in one final hope. No matter how molecular tumor boards evolve, she says, pathologists need a seat at that table. “Because change is going to happen with or without us.” [hr]

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