From tumor board, an integrated diagnostic report

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December 2014—The handling of molecular information bears a certain resemblance to Wall Street's bundling of mortgages in recent years. You can slice 'em, dice 'em, and repackage them in all sorts of ways. In medicine, however, this is being done—one would hope—without the ensuing meltdown. The goal is to shape personalized medicine, using the results of next-generation sequencing and other technologies to evaluate genetic information ranging from single gene to whole exome or whole genome, with proteomics possibly not too far behind.

It's entrancing and staggering. "The fundamental problem is we're generating more information than we can readily interpret as individuals," says Neal Lindeman, MD, associate professor of pathology, Harvard Medical School, and director of molecular diagnostics, Brigham and Women's Hospital, Boston.
Adds his colleague Azra Ligon, PhD: "The message has become clear, and it has been clear to us for some time—we can't all operate in isolation."

One solution to managing the data implosion is pleasingly simple, says Dr. Ligon. Talking to a pathology colleague about genomic test results "can be as easy as picking up the phone or walking down the hallway."

But Dr. Ligon, associate professor of pathology, Harvard Medical School, and director, BWH clinical cytogenetics laboratory, is also familiar with an arrangement that is less simplistic, one that draws multiple diagnosticians from different disciplines within pathology to review genomic data in real time. It's a molecular tumor board, known at BWH as a diagnostic tumor board because of its broader, integrative role. In fact, factor in nearby Dana-Farber Cancer Institute, and Boston appears to be a hotbed of molecular tumor boards.

Dr. Ligon and her colleague (and husband) Keith Ligon, MD, PhD, set up the brain tumor diagnostic tumor board at Brigham and Women's Hospital in 2012. The goal has been to integrate information generated by multiple tests on the same patient. At their institution this had grown to include cytogenetic (whole genome array CGH, FISH), molecular (targeted exome sequencing), immunohistochemistry, and histopathology data. At this relatively early stage, one element typically present at the traditional tumor board—clinical oncologists and others on the clinical treatment team—remains absent.

Second of two parts on molecular tumor boards. See October 2014.

It's not an oversight. While the ultimate goal is to align molecular and cytogenetic results with clinical treatment decisions, for now it's challenging enough to navigate the multiple streams of information flowing forth from multiple labs. Genomic data are like J.S. Bach's liturgical output, both enriching and vast. Brigham and Women's Hospital has a Center for Advanced Molecular Diagnostics, with two component labs. Dr. Lindeman heads the molecular diagnostics laboratory; Dr. Azra Ligon runs the clinical cytogenetics laboratory. The brain tumor diagnostic tumor board, which meets weekly, combines results from these two labs with the histopathology results on all adult and pediatric brain cancer patients seen at the Dana-Farber Brigham and Women's Cancer Center and Dana-Farber Boston Children's Cancer and Blood Disorders Center. Anywhere from six to 16 people attend each meeting.

Dr. Azra Ligon

A neuropathologist and either a cytogeneticist from Azra's group or a molecular genetic pathologist from Dr. Lindeman's group co-sign the diagnostic reports; it's up to the pathologist to add additional information to the original, surgical pathology, or "root" report, as Keith calls it. At times, that might even call for reanalyzing data. The report is then communicated to the clinical treatment team, including surgeons, oncologists, radiation oncologists, and radiologists, who go over the findings at a separate, more traditional treatment-focused tumor board—in this case, one specializing in brain tumors. Representatives from the diagnostic tumor board, generally the neuropathologists, also attend the treatment tumor board and "bring this valuable experience back to the diagnostic tumor board," Keith says.

Azra describes several benefits of this approach. First, she says, the treating physicians have all the testing information—histology, IHC, cytogenetics, cytogenomics, and molecular diagnostics—on a single integrated report. "They don't have to find and go through a half-dozen or so reports and put it all together themselves."

Dr. Keith Ligon

Increasingly, oncologists have been saddled with what may be too much information, says Keith, who is assistant professor, Department of Pathology, Harvard Medical School, and also holds an appointment in the Department of Medical Oncology, Center for Molecular Oncologic Pathology, Dana-Farber Cancer Institute. "The oncologists historically were the only physicians who would take all the reports and try to figure out what to do for the patient." As the data have grown, however, "We've noticed that many of our oncologist colleagues feel increasingly comfortable relinquishing some of that specific integration role to us." This includes having pathologists be more active in helping their colleagues develop a final clinical recommendation based on multiple complex test results, he adds. The decision tree was simple enough when the branches were limited to H&E and a few IHC stains, says Keith, who is also associate pathologist and neuropathologist, BWH Pathology. But now, there are simply too many ways for the data in independently generated reports to conflict; even when reports don't conflict, it's not always readily apparent how they might agree with one another. Hence the need for diagnosticians to review results collaboratively, reconcile ambiguities as they are generated, and communicate an integrated interpretation to the treating physicians—sort of a dress rehearsal before the curtain goes up on the clinical drama.

Keith offers this example: "If I write a pathology report based on H&E and I say that specific IHC antibodies show the BRAF V600E mutation was present, and then Neal's group issues a report saying it's not detected by next-generation sequencing, but the explanation is that two different regions of a genetically heterogeneous tumor were tested, there's some reconciliation that's needed. And the oncologist or treating physician has no means to do that." The unified report, borne out of the diagnostic tumor board, is "really an attempt to say, 'Look, we're responsible for all the reporting on the patient as a group.' And we need to meet and review at least the problematic cases as a group and make sure there's a common understanding."

By having co-signers on the case, he continues, “It’s really impossible to ignore the fact that you need integration across reports.” It’s also a way for pathologists to make sure an appropriate tissue sample was submitted for testing. In other words, it’s another way of double-checking, from the pathologist’s perspective, that the results make sense.

Of course, it would be easier to sign out the case in isolation and walk away, Keith says. “Our method takes work. We all had to agree to take on more.”

Another advantage, Azra says, is that trainees from all disciplines are learning this integrative approach from the get-go. “They love it,” she says. “And it’s new for us.” At a recent meeting, two rotating genetics fellows who don’t perform cytogenetics—one is focused on molecular genetics, the other biochemical genetics—“came out of the conference and said, ‘This is fantastic. I wish our labs did it.’” In one of the discussed cases, she says, the diagnosis changed completely based on cytogenetics results. “That made such a huge impression on them.”

“That’s key for our trainees,” Azra continues. “Whether they be in genetics or in pathology or in clinical medicine, they need to understand that the future is going to be based on the ability of our disciplines to talk to one another and bring all the pieces together. Having an integrated, cross-disciplinary diagnostic approach takes the onus off any one individual to know everything.”

For all their confidence in what they’ve set up, even the Drs. Ligon report being pleasantly surprised by how they were able to enhance the process of data interpretation and reporting. “I guess we anticipated that would happen, but it was a pleasant surprise to see how many times we’ve been able to improve what we were doing by integrating all the data before reports went out to the treatment team,” Keith says.

For now the focus is on brain tumors. It made sense as a starting place, given that four or more tests are run on most cases, and Keith’s research lab focuses on the genetics of brain tumors and Azra’s background is in the same field. But as the approach expands to other types of tumors, Azra predicts other pathologists will be eager to participate.

Keith is a little more cautious. “It’s not always a piece a cake for us,” he concedes, given the time demands on most pathologists. A pathologist’s willingness is also affected by his or her training and experience in molecular techniques. In both the genetics and molecular pathology communities, he says, as well as in the classic pathology community, “there’s a kind of temporal sequence to the technology and who’s familiar enough with it to feel comfortable with it.” In other words, familiarity breeds popularity.

The Drs. Ligon understand that their approach won’t work for everyone. They know that some of their viewpoints won’t be shared by everyone, either. From where they sit, however, the need for diagnostic tumor boards seems as pressing as the need for the traditional tumor board.

Keith is convinced that each disease discipline will become more specialized, although “people debate that,” he says. What he’s seen, though, tells him that each patient’s tumor is ultimately likely to have 20 to 30 different molecular events to track. “That starts to get very specialized, and it’s not feasible for someone to become a generalist without a great deal of extra work.” Likewise, real-time information relevant to clinical trials and specific targeted therapies will also demand diagnostic tumor boards. “There’s a lot of specialized diagnostic information for each cancer,” he says, which parallels the level of treatment-related information that oncologists now manage in their practices.

The Drs. Ligon say they debated what level of genomic detail to present at the conventional treatment tumor boards, to give treating physicians more information. They quickly noticed, however, that the level of detail able to be presented in this setting was fairly limited, and sensed that what treating physicians want is an answer, the more straightforward the better, given that other aspects of the patient’s care also needed to be presented.

Dr. Lindeman, their colleague in the Department of Pathology at Brigham and Women’s Hospital, is

watching the molecular tumor board evolution with interest. The hospital, which is part of Harvard Medical School, also provides pathology services to Dana-Farber Cancer Institute and, to some extent, the cancer patients at Boston Children's Hospital. Dr. Lindeman directs the clinical laboratory that performs molecular analysis on cancers.

There is, to put it mildly, no shortage of testing. Next-gen sequencing is done on all cancer types and offered to every cancer patient at the three hospitals as part of a research effort called the Profile Project. He's also part of a project (being done in conjunction with Harvard and MIT's Broad Institute) called CanSeq that performs whole-exome sequencing on selected lung and colon tumors.

Each setting has its own approaches to interpreting and reporting results. "It's sort of in flux right now," says Dr. Lindeman. "Different models are popping up all over the place."

He gamely plunges ahead. The CanSeq project has a molecular tumor board—but don't call it that. "We don't refer to it as a molecular tumor board. It just functions that way," says Dr. Lindeman. Every other week, six to 15 members of the cancer center faculty will review recently sequenced cases (along with the clinical history) and make recommendations about which alterations from the whole-exome sequence are actionable and should be reported back to the patients and clinicians. The project aims to study not only what genetic changes are found in the cancers but also what impact the reported results have on the patients and their oncologists.

The Profile Project moves more swiftly. It has to. Whereas CanSeq covers a couple of cases each month, Profile covers 80 to 100 samples a week. This is a targeted genome approach that looks at full coding sequences of about 300 genes. "We don't have a tumor board per se for that," Dr. Lindeman says. But again, those involved in this project act in tumor-board–like ways, using electronic communication that accompanies the case report as the data move from raw to finished. "Each person looks at it, starting with a tech, then one of our PhD scientists. And then one of our trainees on the faculty enters comments that get incorporated on the back end." And the door is always open for one-on-one discussions if questions arise, he says.

Every week does end with a more traditional conference of the pathology team, which meets to discuss questions or particularly interesting results.

Dr. Lindeman

Dr. Lindeman's laboratory recently launched another test, called the Rapid Heme Panel. This is an amplicon sequencing assay, which quickly looks at specific regions of 96 different genes in cases of leukemias and lymphomas. Those results are interpreted, reported, and signed out by pathologists in real time; they're also discussed at a weekly meeting, held every Friday. Clinical oncologists and pathologists are both part of this gathering, making it yet another model the lab uses, Dr. Lindeman says. The clinical oncologists, in fact, worked with pathologists on the test's development. "Sort of a new model of collaboration," he calls it.

Regardless of how the collaborators meet, the issue they face is the same: to determine what to report. In the CanSeq project, Dr. Lindeman and his colleagues have decided to report on findings that have potential as well as proven utility. In the Profile Project, "We report everything that we don't believe is in the germline," he says. The information is divided into five tiers of clinical utility. The "one" tier includes variants that are the most clinically actionable; the fifth tier consists of results not thought to be important clinically—"just harmless germline variations," Dr. Lindeman says. Only tiers one through four are reported, with the latter containing variants of

unknown significance.

In setting up the boards, says Dr. Lindeman, he and his colleagues spent “a lot of time in the beginning” accumulating baseline exposure to variants and cases. “It’s time that had to be spent,” he says, “just so we could approach things from a position of experience. So when we started meeting, it was taking us a half day for each case.” That included digging deep into the literature and trying to figure out what each variant meant in each disease context. “It was not sustainable,” he says, perhaps unnecessarily. But the challenge of corralling information remains, even as they’ve trimmed the time spent on each case.

The CanSeq project members faced the same challenge, even though they were discussing only two cases per meeting. “It took us a while to reach our equilibrium as a tumor board,” he says, “to really figure out what we meant by what was clinically useful and what wasn’t.” In gene analysis, presence is rarely enough to act on. “It took us months before we reached a point where we have, more or less, consensus, and we can now move more quickly. But it’s still difficult.”

The learning and consensus stage cannot be skipped, Dr. Lindeman warns. For anyone thinking about establishing a molecular tumor board, “Understand that this is going to be a very, very slow process in the beginning.” That’s especially true for institutions that plan to run more exploratory-type panels. For smaller, well-defined targets—a next-gen sequencing panel of, say, 50 genes, backed by a strong literature—the discussions may not be the same endurance run. “By the same token, members of the tumor board may bring different levels of familiarity with genetics lingo and concepts into the process, and that can also take time to overcome, even for smaller targeted panels,” Dr. Lindeman says.

Viewing the many models he sees in play, Dr. Lindeman hesitates to choose a winner.

Tumor boards will be necessary as long as people need to share their experiences and knowledge, he says. But too much information is upending the traditional model. “The problem with the true tumor board is you can only do one or two cases a session.” Now, with molecular testing, there can be hundreds of patients whose tumors are being analyzed and might need discussion. “So that model isn’t scalable.”

As he and his colleagues have found through the Profile Project, electronic communication can make discussions more manageable. But then the ability to talk and share experiences face to face takes a hit.

Maybe, says Dr. Lindeman, the best solution is one that has yet to be invented. He envisions a cancer genetics clinical consultation service. “We may be actually creating a new medical specialty, or at least subspecialty,” he says. Such a service could be headed up by a clinical oncologist or surgeon with an interest and expertise in the technical side of laboratory work, or by a pathologist who’s similarly conversant in clinical management. Maybe the answer is some sort of hybrid. For his part, Dr. Lindeman says, “I would like to see pathology be involved in this and be clinical consultants.”

And if this comes to pass, what will happen to molecular tumor boards? “I think long term, we’re just going to be incorporating the molecular data into the traditional tumor board model,” says Dr. Lindeman. In this schema, molecular data will be viewed the same way a teacher views your child—special, but not that special. “It’s another element of data that gets incorporated along with all the other elements of data to make a customized treatment plan for each patient,” Dr. Lindeman says.

But he’s not in a rush to dump any of his current molecular tumor boards. They are a good means of navigating the tide of molecular data. Moreover, they can serve as a sort of lower court, helping to set precedent for future cases and to develop institutional policies for handling molecular data.

Molecular tumor boards can also offer a haven of sorts as physicians of every stripe wrestle with what to do next. “The fundamental issue is that we don’t have really good answers,” says Dr. Lindeman. “We can go round and round and round discussing something, and then, in the end, still be left with, We don’t know. We’re not used to

that.”
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