Pharma strives to aid companion diagnostics

Anne Ford

May 2015—M. Elizabeth H. Hammond, MD, is no mind reader. But approach her at a conference or meeting, and she has a pretty good idea what you're going to ask her.

Dr. Hammond

"I was the chair for the 2007 and 2013 ASCO-CAP HER2 guideline, and since that time, the most common question I get from individuals is, 'How do you know the guideline is making any difference?'" says Dr. Hammond, who is a professor of pathology and adjunct professor of internal medicine at the University of Utah School of Medicine and a consulting pathologist, Intermountain Healthcare.

An excellent question. After all, you can simplify fixation time for HER2 specimens, define bright-field ISH as a valid test platform for assessing HER2 amplification, and provide other clear recommendations, but you can't make any of those things happen just by announcing that they should.

"We do have some strategies to try to assess the guideline's impact, but I really have had no way of knowing what the impact was on an individual practice level," Dr. Hammond says. "More laboratories are now being accredited, more laboratories are doing proficiency testing, but those are pretty general statements about whether the guideline is being implemented, and that doesn't tell me what the problems are."

Then she learned about an initiative from Genentech, the manufacturer of trastuzumab. The company, she discovered, had begun collaborating with pathology practices nationwide—both academic medical centers and community hospitals—in an attempt to learn which elements of the HER2 guideline were causing confusion, noncompliance, or both.

"When I heard what Genentech was doing and how many problems they were uncovering and how hard they tried to help practices solve those problems, I became very excited," she says. "Collaborations with pharmaceutical companies in this way is something that's very desirable, because these people represent boots on the ground. They can actually find out what's going on in a way that we in CAP can never do."

Finding out what's going on and, where needed, making it better. That's the stated aim of several recent initiatives from Genentech and Pfizer, all focused on helping pathologists and oncologists optimally use companion diagnostics—namely, trastuzumab-HER2 and crizotinib-*ALK*—for the best management of patients. In the view of Dr. Hammond and others, this kind of collaboration is invaluable in its potential to improve guideline adherence, testing, and patient care.

In Dr. Hammond's opinion, one of Genentech's most helpful steps in this regard has been the creation and distribution of one-page documents that succinctly describe the elements of the HER2 guideline.

"Pathologists are very busy, and when they see a publication in *Archives of Pathology & Laboratory Medicine*, that may or may not help them understand exactly what they need to do," she says. "The places where Genentech field representatives have been helpful is in clarifying the requirements for how samples should be handled prior to

fixation"—for example, bisecting a large tumor to ensure that formalin can begin to penetrate its center—"how long samples should be fixed, and how pathologists should go about interpreting the information and communicating that back to clinicians." Among other educational tools Genentech has employed are an animated video on the HER2 testing process (available at www.her2testing.com) and a speaker series that includes time for questions and answers.

More specifically, Dr. Hammond reports that her Genentech contacts have been helpful in identifying and remedying the issue of getting surgical suites to record the time of sample removal and gross rooms to record the time of sample receipt. "The way to get that to happen is to talk to the leadership of those rooms, explain why this is so important, and come up with some simple ways they can help," she says.

For example? "At Intermountain Healthcare, we started putting a red stamp on requisitions. It was very obvious, so people could see that they needed to fill it out, and then we had one of the PAs in the gross room actually follow up if it was not filled out. It took only a few weeks of that intervention before it became a standard, routine process, but it wouldn't have worked if we hadn't first gone to the manager of the surgery suite and explain why this was so important.

"That's one of the things that these Genentech representatives do. When they go into a practice and they find there's a specific problem, they try to meet with the person who might have some power over the area."

Sounds simple—even self-explanatory. But in Dr. Hammond's view, the value of these interventions lies not only in the fact of their doing, but in the fact that Genentech is relieving pathologists of the burden of doing them. "Pathologists are busy with their daily work, so if a person comes in from a pharmaceutical company and talks to these individuals, that adds value for the pathologists directly, because they don't have to do it themselves," she says. "They can have someone else go and educate the people required, show them the guideline document, explain the need to do whatever needs doing. It dramatically improves situations, and it improves them quickly, and the pathologists themselves do not have to be involved."

To those who might find themselves wondering just why a company would go to such lengths, Dr. Hammond has this to say: "I found that the people working for Genentech were not incentivized to sell anything or to do anything other than examine the compliance of the pathologists with the guideline standards and help them solve problems related to that, which seems like a wonderful win-win for both us and them."

As for where Genentech's "win" comes in, she adds, "In order for the drug to be effective, the test has to be accurate, so just like pathologists want the test to be accurate, and clinicians and patients want the test to be accurate, the company wants it to be accurate. Otherwise, the drug appears to be ineffective. This is a situation where professionals and industry and professional organizations are lined up with the same goal, so it makes sense for us all to cooperate to get to that result."
Dr. Hammond hopes that in the future "collaboration will be even more clearly defined, so that we on the CAP guideline panel get feedback about what these manufacturers are finding. That would help us even more, because we would be able to see where we need to direct our efforts to improve compliance."

Pfizer, too, has been rolling out efforts to improve compliance with an important guideline—in this case, the *EGFR* and *ALK* guideline developed by the CAP, the International Association for the Study of Lung Cancer, and the Association for Molecular Pathology. Shortly after the guideline was published in 2013, the company, which manufactures crizotinib, a drug that treats *ALK*-positive metastatic non-small cell lung cancer, introduced the DETECT (Diagnostic Evolution: Evaluating Clinical Testing in Non-Small Cell Lung Cancer) program.

Dr. Chioda

Marc Chioda, PharmD, Pfizer's medical director of medical affairs for oncology, explains that the nationwide program entailed nearly 100 presentations made to more than 1,000 participants, of whom 174 were pathologists, between June and December 2013. "Some of the topics that came up during the discussion portion included concerns regarding implementation of guidelines, concerns regarding cost or reimbursement, and concerns regarding sample size or quality of the tissue available for testing," he recalls.

At least one pathologist would like to see more programs like DETECT. "That's the type of education we need to think about on a much, much larger scale than we have been doing over the past couple of years," says Pranil Chandra, DO, medical director of molecular pathology services at PathGroup, Nashville, Tenn. "I'm involved in numerous regional presentations to pathologists, oncologists, and other caregivers speaking about the utility of molecular testing. And I think that's great, but it needs to be done on a larger scale. I'm on the CAP Personalized Health Care Committee, and one of our goals this year is to expand the tools and resources to educate community- and noncommunity-based pathologists on the value of molecular testing."

After the conclusion of the DETECT program, Pfizer shifted its focus to implementation by partnering with the Association of Community Cancer Centers on a separate initiative called Learning Labs, which sought to improve molecular testing in lung cancer at the system level at eight ACCC member institutions.

"We got multidisciplinary teams together from these eight institutions," Dr. Chioda explains. "That included pathologists, medical oncologists, and tissue acquirers. And we had them look at their non-small cell lung cancer patients over a given period, and we measured what proportion of them were tested for *EGFR* and *ALK*. They discussed their current testing practice, and that was followed by a presentation of what the guidelines said. Then it was up to the institutions to identify opportunities for improvement so together the multidisciplinary teams could implement these guideline recommendations." They're now in the follow-up phase, he says. "So after the institutions incorporate the changes they identified, we'll measure testing rates again."

One commonly identified challenge: a lack of what Dr. Chioda calls "pathology-driven reflex molecular testing." Among the relevant action items identified were developing and implementing reflex molecular testing pathways, updating processes and policies to include simultaneous testing for *EGFR* and *ALK*, documenting why *EGFR* and *ALK* were not tested, and creating a process to monitor testing.

"Pathology-driven reflex testing, that's a well-established practice in breast cancer for HER2 status, and reflex testing might also ensure an accurate and timely diagnosis for appropriate patients with non-small cell lung cancer," he says.

The other commonly identified areas for improvement were as follows: biopsy samples insufficient for molecular testing; molecular tests not ordered for eligible patients; clinicians not capturing and documenting key quality measures for reporting; lack of standardized reporting formats for molecular test results; difficulty using the cancer registry to measure molecular testing quality; lack of an established pathway when evaluating a suspicious lung mass; and delays when ordering molecular tests for patients due to the CMS 14-day rule. A full description of the Learning Labs project appeared recently in *Oncology Issues* (Kim J. 2015;01:28–32).

Dr. Chioda himself says that one of the biggest opportunities for improvement in this area is "empowering pathologists to recognize the importance of this test."

"So if it's not ordered immediately by a medical oncologist, they [pathologists] can serve as a prompt and say, 'Hey, we see adenocarcinoma; it's metastatic. Guidelines recommend testing the patient for EGFR and ALK,'" he

says.

Though the Learning Labs program involved community cancer centers, Dr. Chioda says Pfizer has also partnered with academic institutions through initiatives such as webcasts. “Academics, they’re very aware of the importance of biomarker testing, and partnering with them really helps get the word out,” he says.

In addition, Pfizer is working with commercial laboratories to gather data on *EGFR* and *ALK* testing. “We were looking to better understand what was going on in daily practice. Were the tests being ordered? When were they being ordered? And then age distributions, phenotyping, etc.,” says Julie Ramage, Pfizer Oncology’s national account director for diagnostics. “We have to have a substantial amount of numbers to get real insights for statistics, because we’re talking about a small patient population. When we get the data, we put it in graphical form and look at what’s happening, and then I sit down with the medical directors and oftentimes other stakeholders to look at it. So here’s an opportunity to provide value back to pathologists.”

Kenneth Bloom, MD, has participated in one such data-gathering project with Pfizer. But, he says, it’s not the first time he’s been involved with a project of this type, nor is Pfizer the first manufacturer with which he’s worked in this regard. “This whole concept started with Genentech a long time ago, around 2006,” says Dr. Bloom, who is chief medical officer, In Vitro Diagnostics, GE Healthcare, Life Sciences.

At that time, he recalls, “we had recognized that the positivity rate for HER2 varied among some of our clients. It couldn’t be something that was occurring in our lab, because we were doing everything the same way. When we looked by area of the country, there were simply some regions that had HER2 positivity rates that were less than average.”
After breaking down the rates by client, Dr. Bloom and his team recognized, he says, “that the positivity rate was not uniform. There were some clients who were actually dragging the rate down.” Clarient (a GE Healthcare company) then teamed up with Genentech, which created educational programs for those areas with lower-than-average HER2 positivity rates.

“Genentech established these pathology liaisons,” Dr. Bloom recalls, “and they targeted those areas, and they had hired pathology liaisons who would talk to the pathology department about Herceptin and the importance of HER2 testing. They would go over the CAP-ASCO guidelines and ensure they were following them. We identified things for them—like reminding pathologists they needed to maintain the fluids in their tissue processors, reiterate how to select the optimal block to test. And you know, after that, the positivity rates in those depressed areas moved statistically back to the average. It was clear that just raising awareness of the standards solved most of the problem. So that was interesting.”

So interesting, in fact, that Clarient began commercializing its data. “We look for patterns that we can find in our testing results—differences among laboratories, among populations, between males and females, between young patients and older patients, between whatever variables we can get our hands on—and we’ve been commercializing that to pharma,” Dr. Bloom says. “It started out with Genentech as our first customer with HER2, but we now commercialize *EGFR, BRAF*, and other data with Genentech.”

More recently, Pfizer has partnered with Clarient, analyzing *EGFR* and *ALK* data by age, inconclusive rates, turnaround time from date of biopsy to time of order, and mutation positivity rates. “We are looking for what will help the community most,” Pfizer’s Ramage says.

Ramage

For its part, Clarient had discovered that the positivity rate for *ALK* varied dramatically between clients. “So while there was an average ALK positivity rate, if you looked at it by client, almost nobody was at the average,” Dr. Bloom says. “Clients were either higher than average or lower than average, but the average was quite rare. So we worked with Pfizer looking for the cause of the variation.”

Initially it was suspected that preanalytical variables such as humidity or temperature might be playing a role since the positivity rates were lowest in Florida. Instead, “what we discovered was that the positivity rate was very tightly correlated with the age of the patient,” Dr. Bloom says. “So when we were looking at places like Florida, where most of the patients averaged more than 70 years of age, the positivity rate was less than one percent. But in other areas of the country, where the patient population averaged, let’s say, less than 45 years of age, their positivity rate was eight percent. That data significantly aids pharma, but each of the pharmas has a different approach to what they do with the data. In the end, they all want to ensure that testing is being performed appropriately and correctly.”

“It’s important,” Dr. Bloom continues, “to educate pathologists that they might be performing or interpreting a test incorrectly. If, in the case of *ALK*, their positivity rate was three percent, but the average age of their population was in their 40s, they shouldn’t be feeling good about their test results. That rate is too low for that population. Assessing statistics is critical for labs, because many of these molecular abnormalities are so rare, how do you know you’re doing the test correctly? How do you ensure accurate testing in your laboratory when positive samples are so rare? Understanding statistics and understanding the distribution of the analyte is turning out to be a very important business.”

PhenoPath in Seattle, too, has begun collaborating with Pfizer to analyze de-identified testing results for biomarkers such as *ALK*, *EGFR*, and *KRAS* for lung tumor specimens, says Harry Hwang, MD, director of molecular pathology. “We share those results so they can do statistical work on what rates of positivity the pathology testing community is getting on actual patient samples,” he says. “I do think this type of data exchange is good for pathology and patient care, as it lets a third party examine whether we are seeing expected rates of positivity in different settings. They have given us preliminary feedback on their analysis and are going to give us more feedback as they continue.”

A third institution, St. Joseph Hospital in Orange, Calif., has also begun partnering with Pfizer, but in a different way. As Lawrence Wagman, MD, explains, “The regional leadership at Pfizer originally contacted the chief medical officer here in 2013 to talk about doing a project to examine how molecular testing fits into the practice of medicine in oncology.” Dr. Wagman, an oncologic surgeon, is executive medical director at the hospital’s Center for Cancer Prevention and Treatment.

Gathering stakeholders, mapping the existing molecular testing process, identifying opportunities for improvement, and applying Lean methodology were the start of the project. It soon became clear, Dr. Wagman says, that one of the hospital’s primary challenges was determining how and by whom tissue would be acquired. “Is it done by surgeons? By interventional radiologists? In a hospital setting? In an outpatient setting associated with a hospital or in one not associated with a hospital?” he says.

“The other area identified was the timing of the patient process. Is this testing something that should be done initially and becomes part of the initial workup? Or should it be done selectively, at a later time when we are certain it would apply to that patient’s specific situation?” They also looked at the process for reflex testing and the incorporation of specific molecular testing in the evaluation of tissue. “And another component of it was the interaction with therapy. We reviewed how the physician made a decision using the information in patient care.”

Dr. Wagman

Two years later, with the process mapping completed, Pfizer and St. Joseph have shifted their focus to measurement. “For example, we’re measuring how often a specimen that’s obtained is adequate to perform the testing and how often a patient might need additional testing,” Dr. Wagman says. “We’re measuring the time between the acquisition of the tissue, the reporting back to the practicing physician, and the time until the patient begins personalized therapy. This is a true, real-world turnaround time that includes the multiple components in the pathway. So that’s the kind of thing we’re in the process of now, and that’s where a lot of the detail starts to emerge. Maybe you go back and say, ‘OK, well, the 18-gauge needles are adequate 50 percent of the time, and the 16-gauge needles are adequate 90 percent of the time. Can we switch from 18 gauge to 16 gauge?’ And then you look at the potential complications of each of them.”
In his view, working with Pfizer has improved conversations between pathologists, oncologists, surgeons, and radiologists. “We had a cancer conference last week, and we were talking about testing specimens and what they were going to get tested for, and there was a really interesting discussion among the pathologists and the oncologists about the process,” Dr. Wagman says. “We were able to put into context some of the things we have done to improve the process in terms of reflex testing and unique results that would or would not drive therapy.”

The next step of the project, he says, will entail modeling, “where we take these processes that we’ve outlined and start manipulating some of the key parameters. Right now we’re biopsying patients when they relapse. What would happen if we move that analysis to the beginning? What if we tested all lung cancer patients at the time of surgical resection on their primary tumors? How many of them would never need that information? How many of them would benefit when they had their first relapse and that information was available immediately? We want to create some theoretical models.”
Not surprisingly, Dr. Wagman characterizes St. Joseph’s relationship with Pfizer as “very valuable.”

“They have an understanding of drug utilization and the epidemiology of the different markers,” he says. “They can do the arithmetic at the corporate level and know what the marketplace is like. By helping us develop these very appropriate evidence-based flow diagrams of our processes, they’re helping ensure that more people will get the right treatment in a timely fashion. It’s good for them from a marketplace point of view, and it’s good for us because we’re doing the right thing for the at-risk patient population.” Echoing Dr. Hammond’s sentiment, he adds, “Everyone wins on this one.”

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