Forging Diagnostic Pathways for Optimal Utilization of Precision Medicine in Oncology

Q&A With R. Steven Paulson, MD

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***AJMC®*: How would you characterize the state of precision medicine in oncology and its rapid evolution in recent years?**

PAULSON: The era of *HER2* mutations and hormone receptor status in breast cancer [marked] the dawn of molecular-based or biomarker-based targets in oncology. Additionally, the use of imatinib in chronic myeloid leukemia, targeting *BCR-ABL*, triggered the use [of targets] in hematologic malignancies. Over the years, we have moved into the era of precision medicine, or targeted therapy. Instead of 1 or 2 new cancer drugs coming out each year, you're seeing 15 to 25 drugs; about half of them are in the immune-oncology space and the other half in the targeted or variant target space. This has led to significant changes in terms of how we manage patients, as well as in the toxicity profile of most therapies. Nausea, vomiting, hair loss, and low blood counts are not aspects of the targeted therapy or even the immune-oncology drugs. There's been a very rapid evolution in the past 5 to 10 years [regarding] those kinds of changes. [Epidermal growth factor receptor] status in lung cancer has become a central feature of managing those patients.

***AJMC®*: Can you discuss the changing oncology pathology landscape and some of the associated challenges and opportunities?**

PAULSON: The pathology landscape is interesting: They are still targeting the tissue of origin, still looking at immunohistochemical stains. It has gotten to be [something] of a 2-edged sword because if you have a relatively small biopsy specimen, especially a lung biopsy, you may do several immunohistochemical stains identifying the tissue of origin and then use up all the specimen and not have any tissue remaining for the molecular testing. CMS has rightly said that the treating physician should be the physician in charge of ordering next-generation sequencing or molecular testing. I think [that physicians] can be specific about the type of test that they want, whether it's a very broad, several-hundred-gene panel or a narrow more targeted panel.

Commercial payers will pay for panels only up to 50 genes, so we tend to use either targeted panels, such as a lung panel or colorectal panel, or we use broader testing, which is what we call a 50-seat or 50-gene panel. This is generally covered by commercial payers and doesn't put our patients in the awkward position of getting a big bill for several thousand dollars. We tend to collaborate with multiple labs [because] some labs do some things better than others. We require them to report back to us, at least quarterly, on our patients' personal financial responsibility. We review those [reports] at some length with our collaborating labs to make sure that our patients are not being financially burdened with the testing. We also use labs that have broad commercial in-network payer coverage, so that tends to reduce patient responsibility.

***AJMC®*: Can you discuss Texas Oncology's general approach regarding precision medicine?**

PAULSON: One challenge is that we have more than 300 medical oncologists, including almost 30 gynecologic oncologists. It's a little bit easier in a narrow

space, like gynecologic oncology, to be up to speed on what's ordered for what, but with 320 physicians, many of them are treating a broad range of conditions: breast cancer, lung cancer, colon cancer, etc. We recognize that it's extremely difficult to stay abreast of all the current changes or recommendations in a specific area, so we do a couple of different things.

[To start,] we have a diagnostic pathways tool that we have collaboratively developed with a company called Intervention Insights, and we are piloting this tool with 5 different tumor origins. It allows the physician to electronically enter diagnosis and stage of disease, and the tool returns all the National Comprehensive Cancer Network [NCCN]–recommended testing for that patient. Then the [tool also returns] opt-in or additional testing that may be beneficial—if, for instance, a clinical trial is available that targets that particular mutation, that we would then recommend be tested as well. It is NCCN approved plus the markers that would potentially be inclusion criteria for a trial. Then what we do is partner those [markers] with Clear Value Plus. Our diagnostic pathways are essentially updated daily, in terms of what new testing is recommended. Our tool then allows you to pick the panel that you want, and next it will give you collaborating labs that offer those tests and which, specifically, you should order from that lab.

As part of our due diligence, we looked at which lab does what particular tests well. For instance, one lab to which we were sending NTRK testing was found to have a 30% failure rate on the test. We shifted those tests to another lab whose failure rate was between 4% and 8%. We make sure that the quality of a testing facility is up to acceptable standards. Then we partner that precision medicine testing with a treatment pathway that allows us to enter the *International Classification of Diseases, Tenth Revision* code and everything else in our electronic health record, and an overlay then, essentially, provides the evidence-based or recommended therapies. Now, those are also in the NCCN-generated treatment pathways, but those treatment pathways are stratified by diagnosis, then they're stratified by efficacy and then toxicity. So you look at what's the most effective and what's the least toxic.

We also then look at relatively equivalent choices and further grade them on the basis of fiscal toxicity to the patient. As such, we actually have therapies that might be equivalent but are significantly more expensive, and basically those are not included in our pathways if they're not on a [financial] parity level with the other choices. We stratify our treatment pathways on the basis of 3 concepts: first, what's most effective; second, what is the least toxic; and third, what is the least financially impactful for the patient and the payer. So our treatment pathways have very clearly been part of our value-based contracting strategy in our value-based programs. We are participating in the Oncology Care Model, the pilot with CMS. We are very involved in terms of looking at value and reducing costs for the patient and payer and, quite frankly, for society as a whole. We've also been collaborating with other payers in the commercial space and have similar treatment pathways–based collaborations with United, Cigna, Humana, etc. So we are very involved in the value-based space.

There's always concern in the precision medicine space about paying for testing. Some of these large panels, especially ones that are not covered by insurance, can cost between $3800 and $5800 for the test; some of the heme-malignancy tests cost even more than that. But from a practical perspective, if you do the testing and you have identified targets—ones that you have an expectation of affecting, as opposed to generally treating across the board—precision medicine can actually save money.

AJMC®: Can you elaborate on the challenges and opportunities regarding reimbursement for testing and the overall managed care implications of precision medicine?

PAULSON: As the understanding of the molecular nature of cancer evolves, we'll be able to target specific aberrations on a molecular basis: That is the key to either creating or sustaining cancer cell growth. Within our program, internally, we have created an extensive patient database to allow us an internal practice point of view to be able to more effectively make recommendations for therapy. In essence, we've prescreened our patients for clinical trials and new therapies, and we can identify those patients who have certain mutations. Then we contact their physician. We want to make sure that the physician treating the patient, and presumably the patient, will be made aware as new developments occur in the treatment space and that the patient's information will be used to identify opportunities for them to participate in trials. Managed care organizations should understand that participating in clinical trials is among the most effective value-based propositions because the drugs are typically provided by the sponsor at no cost to patients or their health plans.

AJMC®: As the field of precision medicine continues to unfold and grow, what would you like to see emphasized in next few years?

PAULSON: The last 2 American Society of Clinical Oncology meetings have focused on the fact that there are tumor-agnostic indications for precision medicine tests and treatments as well as for immune-oncology drugs. It doesn't matter what the tissue of origin or tumor type is; there can be an indication for using pembrolizumab (Keytruda), [for instance], based on the molecular testing

outcomes. Also, look at what has happened with drugs like larotrectinib, which is the *NTRK* fusion therapy, and another drug coming from Genentech called entrectinib. Those drugs are targeting a specific biomarker [rather than] the type of tissue it started in. It doesn't matter [whether] it was a lung cancer or a toenail cancer; they are basically looking at tumor-agnostic indications for therapies. So what should happen over the next 5 years is that every patient with an advanced cancer should at least be considered for molecular testing and/or next-generation sequencing.

Something we're doing internally at Texas Oncology is trying to make sure that our physicians understand who should be tested. We're creating diagnostic pathways that will help them order the correct test and make the best use of the test results when they get them back. That makes for better care. It ultimately saves money because you're going after specific targets and reducing toxicity, so patients end up in the hospital less and the overall quality of the patient's life is improved.

I would also like to see physicians more extensively using molecular testing or precision medicine going forward. I would like to see payers be less of a barrier to getting those tests done because ultimately, they benefit their patients and save money. For people who use tools like we have, that are following NCCN guidelines, I would like to see things like prior authorization be waived because prior authorization is a huge barrier and very time-consuming for our physicians. If you're following well-recognized, evidence-based guidelines and pathways, prior authorization costs everybody money and time, without improving care. Payers should not reasonably withhold payment for testing or for therapy that is an outgrowth of the testing results. ◆