

The Value of Decision Support Teams and Payer-Institution Partnerships in Precision Oncology

Q&A With Kenna R. Mills Shaw, PhD



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AJMC®: Will you discuss your role as executive director of the Sheikh Khalifa Bin Zayed Al Nahyan Institute for Personalized Cancer Therapy and share any insights about the approach to precision medicine at The University of Texas MD Anderson Cancer Center?

SHAW: Our team is focused on the implementation side of precision medicine. We try to understand what tests need to be offered to patients and why, particularly in the context of FDA-approved treatments/labels and available clinical trials. When we do testing, the most important question we ask, historically, relates to an assay result that suggests a patient might have a biomarker predictive of response to a targeted agent. We also need to know when and why those data are used or not to alter patient care. Most of our work in this context is focused on therapeutic interventions, and when we think that a patient might be responsive based on a biomarker, we will ask why a clinician would or would not use that information to change a patient's treatment course—that is, “matching” that patient to that agent based on the biomarker testing. We partner with the entire institution to answer those questions. Our Khalifa Institute for Personalized Cancer Therapy aggregates all CLIA [Clinical Laboratory Improvement Amendments] molecular data from the medical record, regardless of provider, and collects the clinical data for how patients were treated subsequent to that testing, how they responded, whether the clinician used the data, and why she or he did or did not. We are also interested in patterns of reimbursement in testing.

AJMC®: What factors determine the utility of testing results and the reliability of therapeutic selection based on a mutation match?

SHAW: When I was first recruited, although we had data on whether a patient was tested on one of our institutional panels, we did not have the corresponding data on how many patients were actually matched to therapy. Thus, we had no data suggesting that the testing supported by our institute was useful for clinicians and patients. In 2014, our group published a detailed study to determine whether patients were treated based on the biomarkers identified following testing. We found that among approximately 2000 patients, 789 had a mutation in an actionable gene. In this context, *actionable* is defined as “purely therapeutic,” and mutations are considered only at the gene level, giving us an overestimate of actionability—recognizing that not all mutations in a given gene are actionable. I think that's a really important number. Our findings reflect the broader data that roughly 40% of patients tested on a targeted panel have a mutation in an actionable gene. That is a very important number; I can test every patient who walks in my door, and just 40% may be appropriate for targeted therapy. If we look at the 789 patients with a mutation in an actionable gene, only about 11% were matched to the corresponding targeted therapy. Although these data are significant, it is important to note that the population is not typical from a standard-of-care standpoint; these were all patients who were outside the level 1 population; that is, these were not patients looking for an FDA-approved therapy for their tumor type. Nevertheless, the findings

are important, as just 4% of the total patient population initially tested was matched to a targeted drug.

AJMC®: What are the managed care implications of such a low number of patients who are ultimately treated with targeted therapies?

SHAW: I should say that we have improved the matching with decision support, which we can discuss later. There is a huge assumption that if I test somebody for relatively low cost, payers may not be reimbursing a significant amount of expenditures for the test, because just a small percentage of these patients are actually treated with targeted therapies. Although there is an argument to be made regarding undertreatment, the reality is that most mutations we identify through sequencing aren't actionable for most patients. Although 40% have a mutation in what might be an actionable gene, not all mutations are created equally. For a patient with a *BRAF* V600E mutation, which is a known actionable mutation in some tumor types, we know that other mutations in the same gene—*BRAF*—are either benign or have no known function, and we tend to be on the conservative side when we provide our clinicians with the data about the functional significance of a specific mutation.

One of our specializations at MD Anderson is based on treating/matching when we know the mutation calls for matching; that is, when the data are strong enough to support a therapeutic match. It's important to know that this is precision medicine, not yet personalized medicine: We're looking at very specific biomarkers, very specific agents, and very specific tumor types with a very precise approach. It still doesn't always work, but we really only try to match in that context. Therefore, it is likely that, although we are going to positively affect a very small number of patients today, we have a better chance of affecting those patients by taking a less conservative approach to testing as long as we take a reasonably conservative approach regarding how much we match patients to targeted agents. That doesn't mean testing is a bad thing or that we shouldn't be doing it; it just means that we need to set our expectations based on how we perform or practice medicine today.

Partnerships between institutions and decision support teams can help provide more information to payers that provides assurance regarding the actionability of a given mutation. Approximately 80% of patients have no evidence in the literature to support matching a mutation to a given targeted therapy. That doesn't mean that a given tumor will not respond to treatment but, rather, that there is a lack of evidence suggesting it will. The focus of our team at MD Anderson is to get that information into the clinicians' hands. We have an entire arm that's devoted to decision support, to help clinicians when they get these biomarker

reports back. We have found thousands of mutations in patients with cancer at our institution alone. Therefore, we have found it critical to break down what those reports mean, what the function of each alteration means, and the level of evidence for the association between that specific alteration, or biomarker, and a therapeutic intervention, on label or in a clinical trial. When that type of decision support is implemented in real time at MD Anderson, we have published that we can not only increase the rate of precision matching of patients to targeted agents but also improve overall survival in the patients who were matched compared with those who were not matched.

It bears mentioning that the patients in these protocols have likely already been on multiple lines of therapy. They are often desperate for an effective treatment, and many of them are looking for clinical trials. We still see an improved benefit when these patients are matched. When comparing trial populations where the evidence supports a mutation match and where it does not, those patients who were matched based on a decision support system have been shown to outperform the patients who were not matched in overall survival. We know this kind of model works, and it minimizes the number of patients who are put on the drug without appropriate evidence.

AJMC®: What steps need to be taken to implement models like this on a wider scale, and how would you defend the rationale for partnerships between academic institutions and payers?

SHAW: MD Anderson is not the only group that has a system like this. I would stress that some of the academic efforts are stronger than some of the commercial efforts for a variety of reasons. Realistically, if payers can come together to find a way to fund some of the academic efforts to work together, there would be 1 knowledge base that payers could refer to in real time to get an assessment of the level of evidence for a patient to receive a specific agent. This may give payers more confidence to support broader testing, without a resultant significant change in therapeutic coverage costs, because it would allow for data-driven approvals of treatments. Current diagnostic methods are relatively cost-effective, but it is often difficult to know what to do with the results. A physician-directed decision support tool could convey to a payer the evidence that supports—or [does] not—a specific targeted treatment. One of the challenges is the variability in approach, accuracy, and rigor between different commercial test providers.

If you look at the public data from programs like AACR's [American Association for Cancer Research's] GENIE program, there are over 100,000 distinct mutations found in genes tested on clinical testing panels. There is no way for any 1 clinician, payer, or hospital to maintain that kind of

scope of knowledge in real time without a dedicated decision support team. Some of these alterations are brand new and would need someone to investigate through an on-call system. A clinician doesn't have the time or sometimes the expertise to do that kind of research. I firmly believe that a partnership with a knowledge base in which the 2 groups can work together to provide that kind of real-time assessment of what specific alterations mean and the clinical options would benefit all parties.

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AJMC®: Is there a realistic path toward building the partnerships that are necessary for the precision medicine framework to operate most successfully?

SHAW: I have been hoping for years that payers would demand it. That said, we are starting to see some progress in the CMS guidelines, which now note that simply identifying a mutation or alteration is insufficient. When a mutation has an associated level 1 or an FDA-approved treatment indication, that association is supposed to also be articulated in the biomarker report.

I would argue, then, that it would also be helpful to go beyond just the FDA-approved agents to available clinical trials or other available uses in those reports. Having more payers say that's not enough sequence [data] and that we have to assess the biology of that sequence data is the

only way we're going to move the field forward and have a consistent view of what that data might mean for that patient and their clinician. Unfortunately, a mutation alone is almost always impossible for a single clinician to interpret. For most community clinicians, the field is changing fast enough that they're not always doing the right thing based on these data.

AJMC®: When is the right time to do diagnostic testing?

SHAW: I don't think we know the answer to that. One of the struggles that exist right now is that for a lot of patients, we test fairly late in the treatment paradigm, unless there is level 1 evidence for testing earlier. We need to do something as a field to move the needle so that we can test patients earlier. Payers generally haven't been enthusiastic about paying for testing in many patient populations or for specific genes outside indications. On the other hand, we as a clinical field haven't been great about getting high-quality data into payers' hands to encourage their support of testing. There needs to be more knowledge about the kind of partnerships that might facilitate giving payers the data that are necessary without putting all that risk on the academic institutions. If payers are not paying for testing, then we don't generate the data; it's a vicious cycle. From my perspective, it would be helpful to know the right experiment that would be realistic to do and should be done by an academic center to support testing earlier in the treatment paradigm in order to get payers to be more broadly supportive of tumor biomarker testing.

If we can have a dialogue between the reimbursement component and the clinical side to settle on the right experiment or right data, without having to support a comprehensive RCT [randomized controlled trial], we could make significant progress. It's not realistic to do this for every disease type and every alteration for every drug. So the question is how we can also simultaneously reduce payer risk. A high-quality, relatively conservative decision support team could be partnered with payers to decide on whether to treat or not treat and point to data that support that. A true decision support system in precision oncology would not want the wrong drug use for a patient because it damages the field overall. ♦