2020 Target Therapy Forum

The Gap Between the Need for and The Execution of Molecular Testing

Challenges in Molecular Diagnosis: The Need to do More Testing

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Dr. Jack West: I'm Dr. Jack West, and I am an Associate Clinical Professor in Medical Oncology at the City of Hope Comprehensive Cancer Center, where I specialize in thoracic oncology. And I am also the founder and president of GRACE, Global Resource for Advancing Cancer Education. And I'd like to thank all of my colleagues who are joining us today for their participation, as well as our audience of presumably mostly patients and caregivers who are coming to learn about the latest in targeted therapies, both specific treatments for specific targets, as well as general concepts in targeted therapy, because we certainly share a lot of what we learned from one target to another.

But with that, and really kicking things off, I wanted to start with the importance of molecular testing and some of the challenges that we face that have limited its broad uptake. And though I probably don't need to convince anyone in this audience or any of our faculty, just to take a step back and really highlight the remarkable impact of targeted therapies that some patients with a driver mutation. And here we have EGFR, ALK and ROS1 as the three ones that took the lead in our order of understanding and offering targets. But now it's an ever-growing collection, but though people can respond and benefit from conventional targeted, as a conventional chemotherapy. The impact of targeted therapies is just incredible for these people, for you all. This is a key for the lock.

And so, what we've seen is a dramatic improvement in here. What's shown is progression free survival, where you see this lifting up in a shifting of the curve from left to right, and that represents more people who are doing well on their current treatment with a targeted therapy compared to standard chemotherapy. So the impact has been tremendous and yet, while everyone on our faculty is completely committed to this, and of course patients would love to have this and avail themselves or the opportunity. Unfortunately, it's not as universal as we would like it to be. This is just one study. There are a few others that, that really highlight that molecular testing is not where we want it to be. This is a presentation from ASCO, our largest cancer meeting of the year. This is from ASCO of 2019, so a little over a year ago, but it's not old information.

It reflects the records from five very large community practices of over 1200 patients with stage 3B or 4 non-small cell lung cancer. And this is just there, their management since 2017 through early 2019. And you can see from the bar graph on the right that EGFR is the most commonly tested, but that's kind of damning with faint praise because it's only 54%. And what you see is among the targets that were established as a standard of care, the ones that are all on the far left, it goes down steadily. And by the time you get to BRAF, less than a third of patients are getting tested and only 22%, less than one in four is getting tested for all four of these. And then when you get down to the ones that were more investigational, but promising at that time, but now are becoming more readily useful, it's much lower still.

And so, when you look at all seven that were in the NCCN guidelines, the national comprehensive cancer network guidelines, the tell us what most of us should be thinking about for management workup and management. You're getting only 7% of patients are getting all seven of the markers in our guidelines. So unfortunately it has, I believe gotten somewhat better since then, but it really highlights the work that we still need to do. On the left of this slide is a tweet of one of our colleagues, Dr. Vivek Subbiah, who is emerging as a Patron Saint of new clinical targets and new therapies. And there are others on our faculty who are among the most influential as well. But Dr. Subbiah took a moment just in the last week to highlight the impact of new drug development and new targets by the FDA just this year. And what you can see is that we have new targets now in MET in RET.

And we also have some agents with new indications for ALK, etcetera. But just to highlight that this is always a moving target, but it's always moving in the right direction of adding new targets that were investigational one or two years ago, but have a growing amount of data that look very impressive and make last year's investigational work, today's standard treatments that are commercially available to benefit patients throughout the US at least, and increasingly in other parts of the world. And at the same time, we have other new targets on the horizon with evermore promising data that can

translate to another target that we can use for standard treatments in the coming months and years. KRAS, which is a very common in fact, the most commonly identified molecular target in lung cancer has finally a few agents that look extremely promising and are working their way through clinical trials.

HER2 is another target in lung cancer, as well as breast and some other settings, but up until very recently, our treatment options were pretty limited. And at this year's ASCO meeting in the end of May, early June, we saw some potential breakthrough results in HER2. So this is a growing collection of targets. And what I would say is particularly important about this is that a few years ago there was room to actively debate, whether we should be doing testing of two or three or four different molecular targets individually, or whether we should test very broadly with a platform such as what's called NGS next generation sequencing. And you can test for dozens to hundreds of markers all at once.

And with that you can not only test for everything that is relevant today with a commercially available agent, but the agents that have clinical trials, but may become commercially available in the coming months and years. And you can also identify things that we don't know about yet, but will soon. And my point is that once you go from three or four to six or seven or more, it completely makes sense to be testing for everything at once, rather than individually, for the efficiency of the amount of tissue needed and for cost efficiency as well, just to bundle it all together. So if that was ever a debate, it isn't now. And the benefit is that if people are doing and should be doing now NGS testing to look for the six or seven most valuable targets now, they will also pick up other things that are emerging on the horizon.

But that said there are many significant barriers to testing. It's not just a lack of interest, or will. I recently convened a group of colleagues from a few different disciplines to talk about some of these issues and had a survey where I asked what they perceived as the leading issues were, and here are their estimates. Now these are not the people who are necessarily facing them as much, but still working in that field. And you could see a few points. One is that there are many potential barriers, including a lack of good understanding of the targets and a lack of commitment to molecular oncology, for some physicians maybe an estimate of a low yield or cost concerns, etcetera. But I would note that a couple really stand out and one is insufficient tissue. It's a real challenge, but it's one that we need to address in several ways.

And another is the long turnaround time. And I'm going to talk a little bit more about, more about these issues, as well as some of these other problems. Obviously this is not a very large survey, but it's really just to give a glimpse of some of the challenges between why we all of us here agree. This is a wonderful idea, and yet it's not translated

as much as we would like. Tissue availability is a challenge. More is always better, but at many places, especially those that are further away from tertiary care centers, they may not have the personnel and the experience to do the interventions, to collect more tissue. And it does require new practice patterns. And one of the issues is the pathologists have historically, sometimes done many, many tests on the scant amount of tissue available to confirm it is a lung cancer.

And sometimes that's way more than is truly necessary, but it exhausts or threatens to exhaust the little bit of tissue that's available to the point that there's not enough left for the molecular testing. That really has a payoff because they've done 12 different kinds of pathology tests to go from a 99.9 to a 99.9999% certainty that it's lung cancer. Another challenge is that lung tissue is not especially accessible. Obviously for those of you who have undergone a lung biopsy, it's not convenient or easy. And because of that, having the potential to do molecular testing from liquid biopsies is a real advance. And we are going to be talking about that more and more including just in the next talk, but these are all issues. And fortunately we are seeing places adapt, trying to get more and bigger tissue samples.

It does require patients to recognize that there could be a real value to doing a repeat biopsy. And it's not just a ritual. Another challenge is understanding the reports. And one of the issues is that sometimes these, these reports often are 50, 70, 90 pages or more. And unfortunately, many of the places that are marketing them, highlight the yield as if it should be expected that every patient is going to have a really valuable marker. And this is not a situation where more is better. This is a setting where you can almost always find something, but that doesn't mean it's going to be a value. And that can really interfere with our interpretation of what is of value to the point that when there is a listing of dozens of molecular markers, but they really don't have relevance for a patient.

It just basically runs interference in our ability to detect and understand what's actually there. We don't want to miss something valuable because of the signal to noise ratio issue with so much garbage around it. And unfortunately, too many of the companies are casting such a wide net, or at least not clarifying what's important and what's not. That it's causing oncologists increasingly to become cross-eyed and just not be able to recognize when something is valuable, if it's there or to become disheartened that they always get back a bunch of garbage. One of the issues that that we do struggle with is to also ensure that results are acted upon. We're going to talk a bit more about the turnaround time, which is typically several weeks. And with that, some people, both the patients and the physicians may feel a need to start someone on treatment and the results can come back several weeks later and may not be recognized.

It may not easily be, the report may not get too conveniently to the doctor. It may just get uploaded into an electronic chart and Dr. Geoffrey Oxnard, myself, and Jennifer King from the GO2 foundation wrote a viewpoint that was featured less than a year ago, late 2019 in JAMA oncology, talking about ways to combat this challenge of having potentially really important results that are not taken out properly. And one of the ways would be to have a cover page that is extremely simple and straight forward, and to create an expectation that a doctor is going to give that information to a patient and review it with them. And I'll talk just a bit more about that in a second, but one point I would want to make, and I I've already alluded to it is that there are molecular results that may be detected that are of unclear value or very low value.

And unfortunately, because of the cost of these tests, or just the culture of what we do the reports often will highlight potential treatment approaches that are pretty dubious, that are not based on good evidence, that may be based on animal studies in mice or rats, or even in lab-based tests and test tube-based studies, that don't clearly translate to clinical utility. And the problem is that we don't want to confuse physicians or patients with low quality implications or insinuations of a treatment that may lead us to presume that because it's a targeted therapy recommendation, it's better than chemo. That's not necessarily the case. In some cases, and in just about all we're going to highlight today, we're talking about targets with associated therapies that have an established benefit that is tremendous and very impressive, and usually supersedes standard chemotherapy.

But there are others that are further down the list that are a little more questionable and, or in fact completely questionable and should not come before chemotherapy. That may be last year's model. It may not be as sexy, but it has a proven benefit for lots and lots of patients. And so it's worth just highlighting that these are not necessarily of the same value. We do use the word actionable, but we use it loosely. And I do too. We all kind of use that, but that doesn't necessarily mean survival prolonging as much as some of these very established treatments. And we need to be cautious that we don't go down a rabbit hole of, of treatments that are expensive, potentially have side effects. And that may supplant treatments that have proven benefits. This is not to say that EGFR, ALK, ROS, and the others we're going to feature here today are not valuable. They're incredibly valuable.

And they're almost always the first things we reach for if we know about them as targets, but it's important to understand that not every person with lung cancer is going to find a target that there's a pill for. And that there are some targets that are not associated with targets with therapies of the same value as others. So getting back to

the options and thoughts on the report, the reality is it's like Sanskrit to many people. It is incredibly difficult to understand. And oncologists, generally, we're not trained with this in mind in their training. This has evolved in real time, but what Dr. Oxnard, myself, Jennifer King had hoped for is that we could just get a clear cover page that says, this is a target that we have a treatment for. That is a standard of care. You cannot miss it. And there are others that are emerging.

They have some data, but not standard of care. That's the SOC it's it is supported by some evidence and worthy of consideration as a treatment option, but wouldn't be your first line treatment based on the limited evidence we have. And there should perhaps be a separate designation for the many, many other markers that are identified that are just red herrings, that shouldn't be prioritized. And if we have this and an expectation that patients could get this information, a page handed to them, and a discussion, we could at least ensure that patients will never let themselves miss this opportunity. And so I would love to see this become a standard. Now, another challenge, as I mentioned is it's just a ton of information. The world is changing and the expertise required to guide interpretations is not readily available everywhere. It is limited, and we need to get that out.

As oncologists, we're not trained with this, and there's always more information emerging. That's a very good thing, but it means there's going to be a lag between what is presented at the latest big cancer meeting like ASCO, and getting that out to the rank and file community. There are databases of molecular data that people can access from all over the world. That's free information. If people seek it there are a growing number of what we call molecular tumor boards, where people can send their cases to centers of expertise and have them discuss by people who eat, sleep, live, and breathe this work. And can share that information, their are consultation services. I actually lead one at City of Hope in the clinical realm, that does remote consult services for cases that can include reviewing records and offering specific recommendations. And I would love to see there be a new specialty, a new medical specialty offering this kind of interpretation as a discreet service.

I would suggest that oncologist send a patient to get a brain MRI. And when we get the opportunity to see the results, we also have a specialized radiologist, typically a neuro-radiologist who just focuses on brain, or at least has significant training in this. It's not as if the oncologist who orders it has to review the, the images as the only person available to interpret them. And I think that in the next few years, there should be a new specialty, a few people who just help distill the results of these complex molecular tests into actionable, into true. What can I do with this results for patients and physicians out in the broader communities? We don't have that yet, but we, I hope to work toward

that. Another challenge that is working along with all of this is turnaround time. I mentioned already that broad molecular testing takes weeks.

It's typically at least two to four weeks. It can even be more than that. And that's from the time that the labs have the tissue available. So if they're getting it sent from elsewhere, you have to add the shipping time to that. In many settings community-based oncologists do have a longer turnaround time. They will have to send out their tissue to other places, whereas many academic centers have an in-house solution at their own centers. And an important issue is that we recognize, we need to all recognize that both patients and physicians feel pressure to start treatment quickly, that we know there's anxiety and symptoms. And we may feel pressed to start therapy before results are back. And in some cases it's necessary to do that. But what I've also learned from speaking to many, many community based oncologists and academic oncologists.

And having them answer surveys about this, is community-based oncologists feel the most acute pressure to get started on treatment. And that's really because an academic oncologist may be able to reassure a patient more easily that these molecular tests are critical and we just need to wait three or four weeks before starting the best treatment and not just the first treatment while community-based oncologists often feel that they are under more pressure to just get something started or a patient is going to leave and go somewhere else. That will start a patient on treatment this week. And then I would want to emphasize to you and anybody else that you can share this information to as other patients and caregivers, is that a minority of the time it's urgent to start right away within this week or next week, but as much as possible.

It's really valuable to get all of the best information available to develop the optimal first-line treatment plan, even if it takes another week or two. And then finally to say that liquid biopsies have a faster turnaround time, and this is another potential advantage of them. So in closing, molecular testing is evolving in real time. We are living through this right now, and just as I showed some results from ASCO 2019 and said, well, these results are probably a little different now. That's a good thing. We are always getting more new targets and oncologists and patients are getting more aware of the commitment and the need for molecular testing, but we need to change our processes and infrastructure to keep up, getting more tissue using less for the basic pathology workup and having routines for sending molecular testing more and more.

So, this is a process we are working on faster turnaround, but it will only get better as this becomes more routine and labs can shave days from the process. I do think we need to have better ways of interpreting testing as a service, a discrete service beyond requiring every oncologist to become an expert in molecular oncology when they weren't trained that way. And the other point is that liquid biopsies are coming up fast

as another way of doing this that could really upend and solve some of these processes. It doesn't mean the tissue is going away, but liquid biopsies are a critical component of this evolving story. So with that I'll stop and we will move on to our next discussion, which is about liquid biopsies.