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Evaluating GEP Test Options

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Hello. My name is Dr. David Cotter. I'm a board certified dermatologist practicing in Las Vegas, Nevada, where I'm in private practice at Las Vegas Dermatology and also an associate clinical professor of medicine at the UNLV School of Medicine.

Today it's my great pleasure to speak with you how I evaluate the clinical evidence for the use of gene expression profiling testing for our patients with melanoma. Currently, there's only two clinically available gene expression profile tests that can help prognosticate which patients with melanoma are going to need a little more TLC, or in other words, which patients are at risk for more badness, things like having a positive node, having a recurrence, having a distant metastasis, or specifically dying from melanoma.

When I think about evaluating any test, it's the same way that I would evaluate anything I would utilize clinically. I want to see a large number of studies, high quality studies, studies that are both prospective and have good follow-up. Retrospective studies are fine as well, especially during the validation and development phases of a test. The reason why is because before you'll roll something out prospectively, you have to prove that it works.

Right now, there's only one test that has data across all of these domains of what I value clinically, and that's the 31-GEP test from Castle Biosciences, which is used to risk stratify patients for having a positive node and having recurrence, metastasis, and death from melanoma. Initially, this test was developed retrospectively, looking at high-risk patients. That's how they developed the recipe to prove that this test can actually predict risk, and then subsequently it was validated in a number of different studies. I like it because there's quite an extensive array of literature on this test with thousands of patients studied, and hundreds of thousands of patients clinically tested.

Oftentimes, clinicians get confused about the type of data we want to see for a prognostic test. When it comes to prognostic testing, what we're really looking for is a test that was developed well and validated independently; it has an extremely high fidelity of reporting the outcome that's predicted. The trouble is, when you start talking about prospective clinical utility studies, that's outside the scope of what is typical for development of a prognostic test.

The prognostic test reports risk, and then based on that risk, you can design additional studies that'll look at how that risk profile can change patient management, either by ordering imaging, doing additional surgeries, or starting additional drugs. Those types of trials then could be employed as a randomized control trial, where one group who's predicted to have high risk gets an intervention that the other doesn't. And those could be prospective studies or patients are followed over a period of three to five years. When you think about melanoma, the majority of metastatic events and recurrences happen within three years, which is why that's an adequate benchmark, although five years of follow-up data is nicer to see in some of our longer-term studies.

The types of results that matter to me the most are the ones that actually impact patient care. For example, when I consider prognostication for our patients utilizing gene expression profile tests, I want to see a test that actually changes our management. I want to see something that impacts survival. I want to know that when I order a test, I can rely on it. And the best way to be able to rely on a test is to know prospectively in randomized controlled trials that a patient is going to have, (1.), a change in their management, and (2.), an improvement in their outcome if they get prognostic tests.

The trouble with prognostic testing, though, and prospective studies and randomized controlled trials, is that's not really how these tests are developed, and that's not how they're intended to be studied. What ends up happening is you develop a high-quality prognostic test, and then in subsequent studies you utilize that test to influence management changes. For example, you'd want to develop a high-quality test that has a lot of fidelity in predicting what you want it to predict. And once you have a high-fidelity test, then you take the

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results of that test and utilize it in additional studies to actually alter patient management.

For example, if a test says a patient has a very high risk of recurrence, you should do something different clinically. A study could be done to determine if patients that have a high-risk gene expression profile test that are followed differently, either with closer follow-up via imaging, more exams, and the clinic feeling lymph nodes, and taking a review of systems, if that actually can lead to an improved survival. Or maybe you could do an intervention. For example, you could have high-risk patients with melanoma that are predicted to have a very high risk of recurrence, high risk of death, or high risk of metastasis and put them on a drug, something like immune checkpoint inhibitor therapy, versus those that also have a high-risk test and don't go on immune checkpoint inhibitors. And see if the group that has the prognostic test showing high risk that gets immune checkpoint inhibitor therapy actually does better, if they have a survival benefit.

One type of study that I would love to see would be to take patients that have high-risk gene expression profile scores for melanoma, and then randomize them one-to-one to receive early immune checkpoint inhibitor therapy. The reason why this is an important study to be conducted is because right now patients can go on immune checkpoint inhibitor with stage IIB or IIC melanoma. These are people that don't have metastatic disease, yet the FDA approves using immune checkpoint inhibitor therapies to treat them preemptively.

The trouble with this is these drugs aren't benign. They can certainly save lives, they can prolong survival, but they can also cause devastating side effects. Therefore, before we broadly roll out the use of these immune checkpoint inhibitors, it'd be great to be able to refine our risk stratification of patients with stage IIB or IIC melanoma to determine which patients might actually benefit from an early intervention with immune checkpoint inhibitors. I could envision one study where you have a high-risk gene expression profile group on one end that gets immune check-point inhibitor, and you have high-risk GEP patients that don't. And then you follow them over time to see if that early intervention actually impacts survival.

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