Resistance to Targeted Therapies and the Importance of Retesting

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Hi, my name is Kurtis Davies and I am the lead assay development scientist in the Colorado Molecular Correlates Laboratory and instructor in the Department of Pathology at the University of Colorado Anschutz Medical Campus.

In past videos, I have discussed cancer cell biology, the role of mutations in certain genes that lead to activated driver projects that drive unregulated cancer cell growth, the targeting of these activated proteins with new targeted therapies, and the genetic tests that are now available to guide clinical decision-making and guide choice of use of different targeted therapies.

In this video, I'm going to discuss resistance to targeted therapies and why re-testing of tumor samples is critically important when resistance arises.

Although targeted therapies do generally work better than standard chemotherapies, and they have much more tolerable side effects, like chemotherapy, patients do eventually become resistant to the targeted therapies and they will progress on the therapy. So that's the bad news. The good news is that a lot of research has been conducted and is continuing to be conducted on how this resistance to therapy arises in the cancer cells.

So what's been realized is that, in many cases, resistance to the therapy is due to new mutations or other alterations in the cancer cell that have arisen as a response to treatment with the initial drug. So essentially the cancer has figured out a way to get around being blocked from growth by the initial drug. So these new resistant associated mutations basically allow the cancer cells to escape inhibition from the initial targeted therapies.

Importantly, new therapies have been developed and approved, and there are many more in clinical development, that now target these resistant mutations. So similar to the initial targeted therapies, these next-generation drugs are very specifically tailored to certain resistant mutations. So it is very important to have additional genetic testing done once resistance has occurred. The mutations associated with the resistance will generally be new mutations that were not present at the time of the initial testing. So the initial testing will really be uninformative in terms of dictating how to target the resistant cancer.

And this is really where the liquid biopsy approach becomes particularly useful. So rather than undergoing additional invasive procedures, simple blood draws can be used to test for these resistant mutations. So a patient who is on targeted therapy can undergo these blood-based tests when the initial therapy stops working, or

even before it stops working. So the doctor can catch these resistant mutations even before they manifest clinically, even before you see progression of the cancer.

So it is very conceivable that in the not-too-distant future certain cancers that were once lethal on a really short time scale become just smoldering chronic diseases that are consistently monitored and consistently treated based on what's been found in the repeat genetic testing. So you can envision a scenario where the cancer might always be there, but it's never really going to grow uncontrollably and kill the patient. Now, the key to this scenario though is the ability to obtain genetic information from the tumor on a consistent basis. So the role of molecular genetic testing and the clinical management of cancer will continue to grow.

So just to conclude this series of videos, with our ever-expanding understanding of the genetics of lung cancer, and an increasing number of targeted therapies available for clinical use, it is critically important to have genetic testing performed on lung cancer tumor samples, especially for late-stage disease. This is because the presence of certain mutations in the tumor are associated with a response to targeted therapies that directly block the function of the proteins that are activated as a result of the mutations. These targeted therapies tend to work better and have fewer side effects than chemotherapies. But even though all patients will eventually develop resistance to these therapies, we already have newer drugs that specifically target resistance and there are many more in development. So this is really why additional genetic testing of tumor samples is important when resistance does occur.