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How Do I Detect NRG1 Fusions?

Announcer:
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Dr. Dotan:
Hello, my name is Efrat Dotan, and I'm from Fox Chase Cancer Center in Philadelphia and I'll be talking about how do I detect NRG1 Fusions? NRG1 fusion, or neuregulin, is a ligand that binds to HER3 receptor and promotes dimerization of HER2 and HER3. And by that, promoting downstream activation of PI3K/AKT/ and MTOR pathways, which ultimately leads to tumor growth and proliferation. NRG1 fusions result in aberrant expression of the NRG1 protein. That induces formation of heterodimers and leads to pathologic activation of these signaling pathways with overactivation and tumor growth and proliferation. NRG1 fusions can be found in various different tumors. As you can see in the image below, this has been found and reported in many, many cancers in very low incidents. An analysis of over 21,000 tumor specimens found an NRG1 fusion in only 41 cases at 0.2%.

The first NRG1 fusion was reported in 2014. This was with the partner CD74. It remains the most common partner, and followed by ATP1B1, but as you can see in the pie graph, there are many different partners that have been identified in various frequencies. So when we think about detection of NRG1 fusion we have to understand the challenges. There are few challenges that we face: one, this is an extremely rare occurrence; two, there is large diversity in terms of NRG1 fusion partners and also in terms of the fusion architecture; and finally, there are large intronic regions. There are characteristics to NRG1 and that limits the detection. Because of these reasons, RNA sequencing is the preferred method for detection of NRG1 fusions. This slide highlights different ways, or methods, to evaluate NRG1 fusion. "FISH" is an old method that is used to detect fusion. It is quite labor intensive, and therefore not used commonly for identification of NRG1 fusion. At the bottom of the table, We see IHC, which is an available technique. It is much faster and can be used for screening, especially when you are dealing with limited tissue or difficulty in isolating DNA or RNA. This could be done by looking at phosphorylated HER3, and may be a way to identify tumors that should prompt further evaluation with RNA sequencing. However, most oncologists will use next-gen sequencing and the majority of next-gen sequencing will be done on DNA. The problem with that is that the results using DNA sequencing may not be sensitive or reliable enough to detect NRG1 fusions, mainly due to the large introns that are characteristic for NRG1.

This is not a problem with RNA; it is more reliable and it is not usually impacted by these large intronic regions. However, we know that DNA may be more easily attainable because it requires less amount of tissue. And also RNA sequencing may be more challenging if the tissue quality is not good or the tissue was stored for a long term, long period of time. So when should we insist on testing? Are there any clues that could drive us to really obtaining additional tissue or focusing on RNA sequencing? We'll start with talking about non-small cell lung cancer. So when we think about non-small cell lung cancer one clue would be the presence of invasive mucinous adenocarcinoma. If that is one of the pathologic findings, and no other driving mutations are identified, then RNA sequencing could be extremely important. And if that's not possible, consider screening with IHC and phosphorylation of HER3. What about pancreatic cancer? Well, in pancreatic cancer, we know that NRG1 fusions are mutually exclusive of KRAS mutations. We also know that the majority of pancreatic cancers carry a KRAS mutation in over 95% of cases. So when we do identify a pancreatic tumor that does not

have a KRAS a mutation, or is KRAS wild type, this should prompt further evaluation and trying to obtain RNA sequencing for potentially finding an NRG1 fusion. Again, using IHC with phosphorylation could be a screening tool, but it should be verified with RNA sequencing. In other tumors we can still find NRG1 fusions, as we're seen in the prior slides. And in those cases we don't really have any clues that could guide us.

Still, if you have enough tissue, and you can obtain RNA sequencing, it is useful to do this test in order to see if these fusions are present. So, in summary, NRG1 fusion is a rare molecular alteration. It is found in various cancers, commonly non-small cell lung cancer and pancreatic cancer. NRG1 fusions can have many different partners and it is quite challenging to detect them, and we know that RNA sequencing is the most sensitive and reliable method to detect these rare fusions. We should really insist on RNA sequencing, especially in non-small cell lung cancer with invasive mucinous adenocarcinoma pathology, or in KRAS wild type pancreatic cancer tumor. Thank you for your attention.

Announcer:
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