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What is the Preferred Molecular Testing Method to Detect *RET* in NSCLC?

Announcer:
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Dr. Gainor:
Hello, my name is Dr. Justin Gainor from the Massachusetts General Hospital. Today I'll be discussing what is the preferred molecular testing method to detect RET fusions in non-small cell lung cancer. RET alterations are present in various tumor types and it's really important to talk about the nomenclature regarding the different types of RET genetic alterations because that has implications for the form of molecular testing. So, RET can be altered in two fundamental ways. First, RET point mutations. These can occur in the extracellular domain or more commonly in the intracellular kinase domain. And these are really typified by medullary thyroid cancer. And then the second major type of RET alteration is RET fusions. And RET fusions can be seen in non-small cell lung cancer, as well as papillary thyroid cancer and several other tumor types, albeit at low frequencies.

When it comes to RET testing in non-small cell lung cancer were principally talking about RET fusion testing. And so, this requires particular types of molecular assays to detect RET fusions with a high degree of sensitivity and specificity. I've outlined five different types of methods for RET detections, and I want to walk through both the pros and cons of each testing modality and ultimately whether it should be used or not.

The first is immunohistochemistry and I'll be brief here because essentially RET immunohistochemistry has only moderate sensitivity and specificity. And ultimately this should not be used for screening because it's really not sensitive enough and it's an isolated test, it's a single test. And so, it's not multiplexed either. And so, we really shouldn't be using immunohistochemistry for RET fusion detection. Next is FISH or Fluorescence in situ hybridization. We know that the sensitivity of FISH is high, as is the specificity. Some of the downsides of FISH testing, one, this requires technical expertise. Someone needs to be doing a high volume of FISH testing to have confidence in this. It is available on a single slide of tissue, so the tissue input is relatively low. So that is one potential advantage. It can be done on a single slide. And as a result, the turnaround time can be relatively quick if you have an in-house assay. Nonetheless, there are also disadvantage, I mentioned you know, the requirement for technical expertise. It's not multiplexed.

It really can't tell whether a particular fusion is functional or not nor can it detect the type of fusion partner. And so, this should really only be used in rare circumstances, most notably, in situations where tissue is very, very limited. The next assay is RT-PCR. Here, one thing to keep in mind about RT-PCR is you really have to know what the fusion partner is, when designing your primers. And so, this is not able to recognize novel fusion partners so that is one of the principal disadvantages of RT-PCR. As a result, the sensitivity is more moderate to high, it does have high specificity though, you know, like FISH, really should only be used in rare circumstances. In my own practice, I don't use RT-PCR. And then finally, turning to our last two types of tissue-based testing. These are next-generation sequencing assays and we're differentiating between DNA-based and RNA-based assays. The difference between those two is really what the tissue input is. We know that RNA-based sequencing assays are able to identify novel fusion partners, able to identify functional transcripts, don't necessarily need to tie along all the introns. So we know that RNA sequencing based NGS assays have the

highest sensitivity, the highest specificity and it's able to be multiplex. So ultimately, when reaching for a tissue-based assay for RET fusion detection, I reach for RNA-based next generation sequencing.

A brief word on liquid biopsies, we do know that RET fusions are detectable in circulating tumor DNA. And so if one doesn't have sufficient tissue for molecular analysis, liquid-based assays would be a perfectly suitable compliment. And if a RET fusion is detected using a liquid biopsy, to me that is sufficient to treat.

This is just a set of ESMO guidelines that were released last year just summarizing what I already walked through in terms of the various testing techniques. This is for non-small cell lung cancer as well as other forms of thyroid cancer and other solid tumors that basically, if FFP specimen is available, and NGS is available within your institution, really the preferred technique would be to use next-generation sequencing to detect RET fusions.

And with that, I will just summarize to say, that for molecular testing in non-small cell lung cancer it's really important to recognize what your assay is or is not capable of detecting. And for RET fusions, it's really critical, that we identify these alterations because we do have important targeted therapies. And so, the thing to keep in mind, is RNA based next generation sequencing is the preferred modality here. Thank you so much.

Announcer:
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