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Testing for NRG1 Fusions Lab Talk

Frequently Asked Questions

Presented by
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Q1: Is there a relationship between NRG1 and MET, mesenchymal epithelial transition factor in non-small cell lung cancer? If so, does that make a difference or influence the selected targeted therapy?

We are currently uncertain whether there is a direct link between NRG1 fusions and MET alterations. MET alterations can come in many different sizes and flavors. You've got MET amplification, gene amplification, mutations in the DNA segment of MET that can lead to aberrant splicing of exon -14, which lead to MET exon -14 skipping mutation, and you can also have MET protein overexpression detected by IHC. So, there is not a very strict correlation between when you see amplification, MET exon on 14 mutation, and protein expression. There is some association, but it's not really tight association. In general, when you have activation of the MET pathway, those patients do have an aggressive clinical course.

There is some data internally at Path Group, where activation of the MET pathway is seen in newly diagnosed lung cancer treatment naïve patients. So, it does occur at the point of diagnosis and MET aberrations also occur at the point of acquired resistance. So, it wouldn't be surpising if there is an association between MET and NRG1 given that both of them, NRG1 fusions especially, are tumors that just have a highly aggressive clinical core.

Q2: A question following the demonstration of how the enrichment through a more precise diagnosis, as in the lung cancer example where the invasive mucinous lung adenocarcinoma has a much, much greater frequency for the NRG fusion. It seems clear, but let's make sure that if we're really pursuing the detection of NRG1 fusions, we need to use RNA-based testing. Is that correct?

That's correct. You can detect NRG1 fusions through DNA-based testing, but you're not going to be able to detect all of them, as shown through some studies in the lab talk[1,2]. There are other comprehensive papers and review papers on NRG1. And the theme that you will hear again and again is at some point with appropriate, especially in patients that are driver negative in lung cancer and KRAS mutation negative in pancreatic tumors. Those are patients who will need to be offered RNA sequencing.

Q3: Should NRG1 fusion be a target for companies in the digital pathology world, to build a predictive biomarker panel around?

To put some context behind that question, there are digital pathology-driven AI tools that are already becoming commercially available, although this is not recommended in guidelines and again, it's more in a research setting. But these tools, believe it or not, based on the H&E image and through computational pathology algorithms, can identify the absence or presence of certain molecular abnormalities. These range from homologous recombination repair deficiency to the presence or absence of certain molecular events like TP53, EGFR and KRAS mutations. So potentially in the future, if you're able to, at the point of diagnosis, have an AI algorithm that identifies patients who have one of these molecular abnormalities, those are patients that you would want to confirm with downstream molecular testing to confirm which of these molecular abnormalities are present.

Conversely, if you have an algorithm that with a high degree of likelihood tells you that there are no molecular abnormalities worth targeting, then why would you bother sequencing and spending thousands of dollars on those patients? And finally, if you know that there's an EGFR mutation present, why would you want to do a 500 gene panel and not just EGFR mutation alone?

So, this is a field that is rapidly moving and we're keeping our eye on it and we would encourage you all to read up about it because it's going to revolutionize the way that we practice pathology and for those of you that are molecular pathologists, you're going to have to reimagine the delivery of molecular pathology in the context and in the world of digital pathology and AI algorithms.

Q4: Are there targeted therapeutic approaches to the NRG1 fusions being worked upon or in consideration?

Yes, absolutely. There here has been a FDA approval for an NRG1 directed targeted therapy and that approval is in the context of lung cancer and pancreatic cancer.

Q5: Are there common partner genes involving specific regions?

Yes, there are common partner genes, which have been covered in the talk, but there's enough of a diversity of those gene fusions that you really need to take a comprehensive molecular profiling strategy to be able to capture as many of those gene fusions as possible.

REFERENCES

1. Jason C. Chang, Michael Offin, Christina Falcon, et al. Comprehensive Molecular and Clinicopathologic Analysis of 200 Pulmonary Invasive Mucinous Adenocarcinomas Identifies Distinct Characteristics of Molecular Subtypes. *Clin Cancer Res* 2021; 27(14):4066–4076. doi: 10.1158/1078-0432.CCR-21-0423

2. Owen D, Ben-Shachar R, Feliciano J, et al. Actionable Structural Variant Detection via RNA-NGS and DNA-NGS in Patients With Advanced Non–Small Cell Lung Cancer. *JAMA Netw Open*. 2024;7(11):e2442970. doi:10.1001/jamanetworkopen.2024.42970