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Key Words: non–small cell lung cancer, high penetrance gene, DNA repair, polygenic risk score, germline mutation

Discussion

Presenter: Dr Seth Krantz

Dr Chuong Hoang *(Bethesda, MD)*. Thank you very much to the association for allowing me to discuss this abstract and paper. And I thank Dr Krantz for sending me the manuscript and slides ahead of time to review. This study in non–small cell lung cancer is quite unique and original. Dr Krantz and colleagues explored the clinical impact of gene mutations in the germline, and this was to identify accurate prognostic factors in lung cancer. And so, in this growing literature of population-based genomics, Dr Krantz has identified a subgroup of lung cancers that may require more specialized clinical decision making and/or unique therapies. We should acknowledge the excellent prospective clinical database and tissue bank established by his team at NorthShore, without which this study would not be possible.

I have two short questions that are basic to help all of us better understand your results today, Dr Krantz. Number one, I notice that your cohort was 90% Caucasian. So it's not obvious if your clinical associations of outcome in lung cancer apply to all persons across a larger population regardless of race. And number two, can you explain more about the genetic risk, or the GRS? Exactly what information does this contain, and specifically, why was this parameter included for risk stratification in addition to the high-penetrance genes that you mentioned? The GRS greater than 1.5 was only relevant when analyzing stage at presentation and was not significant in the multivariate analysis that followed. I thank you very much, and I'll yield the floor back to you to educate us all.

Dr Seth Krantz *(Evanston, IL)*. Thank you very much for those questions. Yeah, in terms of the distribution of a population where it's on the monogenic side, right, there are multiple mutations in each one of these genes. And you mentioned, specifically, race. We define that socially, right? And so, in terms of a biological impact on individual gene mutations, there are so many mutations at an individual gene level that probably doesn't make a difference. Now, on a polygenic risk score per the GRS, the genetic risk score, there probably are differences in broad populations, which is why we see some differences in a large, predominantly East Asian population versus a Western population. It's why you can go onto ancestry.com and it can tell me that I'm 99% Central European Jewish, right, based on a genome-wide polygenic risk score. But in terms of a monogenic risk, in terms of the individual gene mutations, there's too much variation, with more variation within groups than between groups. And so, I don't think that'll have as significant an impact, but to the GRS it will.

And now to the genetic risk score, that's a polygenic model, right? So even though we did a 355-gene panel for the high-penetrance genes, those are individual genes we're looking at, as opposed to an overall score based on the number of SNPs that you have that creates an overall genetic risk score. And that's based on genome-wide association studies. So, there's good evidence in the literature that is predictive of development of cancer. And so our hypothesis that it would show an increased stage and be involved in recurrence, but we didn't find that. The numbers are probably small. And we need to look at a broader population,

both precancer and a screening population, and probably in a larger set of patients across a variety of cancers in a variety of stages and a variety of populations, to see how that genetic risk score actually plays out and what the impact is. But that combination, again, of monogenic individual genes within a genome-wide array, that polygenic score, probably will have an impact that we just didn't see here, at least in recurrence.