MANISH KOHLI: My name is Manish Kohli. I'm an associate professor in the Department of Oncology, Medical Oncology, at Mayo Clinic, and I'm one of the lead authors on the publication that will come in March in the *Mayo Clinic Proceedings,* which is titled *Germline Predictive Biomarkers of Androgen Deprivation Therapy Response in Advanced Prostate Cancer Patients.*

We investigated over 300 patients and the repertoire of variation in the DNA of these patients. The DNA was taken from their white blood cells, and therefore was not tumor-derived DNA, but what we call germline DNA. And we looked at the polymorphisms, or the variation, in 76 genes related to hormone biosynthesis and hormone metabolism to identify the variation in these DNA of these patients, which will correlate with treatment response to hormonal treatments in advanced prostate cancer patients.

In other words, we were trying to find predictive biomarkers of response to hormone treatments for this disease, and in doing so, out of the 76 genes, found that one particular gene, called tRNA methyltransferase, TRMT11 gene, variation in this particular gene, with polymorphisms present in some patients, correlated with an extremely long duration of response versus when that particular polymorphism was not present, it correlated with a short duration of response.

This is crucial in terms of finding out cohorts of patients in advanced prostate cancer who undergo hormonal treatments who can then be identified as to who are going to be responsive to this treatment and for what period of time, so that if someone we already can predict is not going to do very well on hormonal treatments, which is the traditional way we treat these patients for the last 80 years, and have no clue so far about the predictive biomarkers thus far, then we can identify them and treat them not just the traditional way, but perhaps with some other forms of treatments added to the traditional way. And that's the idea of trying to find out predictive biomarkers. And our goal in this particular project was to find out based on their germline DNA.

As I mentioned, this particular finding has a potential, if this is validated in the future, because identifying a predictive biomarker on the basis of a variation in a gene in the patient is not something that can be automatically put to clinical use. These findings have to be validated in the future. Once they are validated, in terms of repeating the experiment, then sometimes we have to also look at them from the point of view of mechanistic or lab-wise evaluation.

Once those experiments are completed, then we have potentially a predictive biomarker which we can potentially use. Therefore, the road to discovery of predictive biomarkers is not based on a first item of discovery, which is all that we have for the moment. And we hope to do this as we have already continued our experiments with some very interesting findings that are coming out in the lab already. And hopefully, we will be able to provide some more data in the future for our patients.

As I mentioned, this particular finding has the potential for identifying patients based on the DNA that they're born with and in the variation of the particular hormone-related genes whether they are likely to respond to the hormonal treatment, which is the platform for treatment in advanced prostate cancer in the future whether they will be able to respond to this in a shorter period of time or a longer period of time.

That's, in fact, very helpful to know if we are going to treat someone who is not going to benefit for a long period of time, and therefore we need to be a little more aggressive in that treatment for that group of patients, which then would mean that we could add more newer and novel treatments directed towards such patients earlier, and not give the same combinations of treatments to other patients who are destined in the first place to respond to the traditional treatment for a long time alone, thereby obviating the side effects of combination of novel treatments to those patients, but really tapering towards those patients who need it.

This way, we try and personalize potentially the treatments of advanced prostate cancer. This, again, is a formidable challenge, which needs to be met and deliberately proceeded on by a series of research expectations which have not yet been completed but are only in the process, because this is only the first step taken. The next step in this line of research will therefore be that we proceed with validating in an other clinical cohort, which will employ a larger number of patients, more than the 300 patients that we had initially found this in-- perhaps over 1,000 patients, which is why this is good for clinical research that patients participate in such kinds of clinical biomarker development trials.

We at the medical oncology division and in other departments at the Mayo Clinic therefore seek out clinical research in this order and fashion apart from intervention drugs in advanced prostate cancer patients, and encourage our patients to volunteer for these studies. Once we have been able to clinically validate these findings, we will also, as I mentioned before, mechanistically evaluate the reasons why variation in the DNA of patients that they're born with might be responsible for different outcomes of the kind that this particular manuscript identifies in a very preliminary data set, although.

The takeaway message of this article therefore is this, that biomarkers are needed to find out the effect of hormonal treatments, which we have been using for 80 years now, and have no clue as to how many patients would benefit for a shorter period of time or a longer period of time. Typically, the traditional response to hormonal treatments is thought to be an average of anywhere between 18 and 30 months. Many people will fall short of the average. Some people will be on the average, and others will beat the odds and go beyond.

To know which patient will beat the odds or will fall short of the average is therefore critical to know in order to fashion more personalized treatments for those patients, which currently we don't have. This is therefore an attempt to do precisely that. And this requires the voluntary nature of our clinical patients and, of course, multi-institutional investigators pooling their fund of knowledge together to identify this aspect of medicine for the future patients.

SPEAKER: We hope you benefited from this presentation based on the content of *Mayo Clinic Proceedings.* Our journal's mission is to promote the best interests of patients by advancing the knowledge and professionalism of the physician community. If you're interested in more information about *Mayo Clinic Proceedings,* visit our website site at www.mayoclinicproceedings.org. There you will find additional videos on our YouTube channel, and you can follow us on Twitter. For more information on health care at Mayo Clinic, please visit www.mayoclinic.org.