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Clinical and Genomic Insights from Metastatic Cancers

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Guest: Dr. Elaine Mardis is the co-executive director of the Institute for Genomic Medicine at Nationwide Children's Hospital and professor of Pediatrics at the Ohio State University College of Medicine.

Bob Barrett: This is a podcast from *Clinical Chemistry,* sponsored by the Department of Laboratory Medicine at Boston Children's Hospital. I am Bob Barrett.

Metastatic or recurrent cancers are a common cause of death among cancer patients. Genomic investigations of cancer over the past 10 years have led to tremendous advancement in the understanding of the underlying biology and in the development of targeted treatment options. Much of the discovery has been focused on primary treatment-naive cancers, since biological specimens for genomic analysis are more abundant in these cases that are available from patients with metastatic cancers.

The lack of specimens has provided a significant obstacle in the genomic study of metastatic cancers. Therefore, a recent study by Dr. Dan Robinson and colleagues reported in the journal *Nature* has raised excitement. The investigators performed integrative analysis of DNA and RNA data for 500 metastatic lesions obtained from cancer patients with over 30 different primary cancer diagnoses to derive several types of molecular characterizations. Though further studies are needed, applying these approaches to individual patients in the clinical setting of metastasis may lead to more precisely tailored therapeutic treatments with higher effectiveness.

The May 2018 issue of *Clinical Chemistry* includes an expert commentary on this noteworthy study. Dr. Elaine Mardis, the author of the commentary joins us for this podcast. She is the co-executive director of the Institute for Genomic Medicine at Nationwide Children's Hospital and professor of Pediatrics at the Ohio State University College of Medicine.

So, Dr. Mardis, why is the study of 500 metastatic cancers important in light of all the large scale studies like The Cancer Genome Atlas that have already been completed? What does this study tell us that those other studies didn't?

Elaine Mardis: The big difference in principle between this study and large scale cancer genomics discovery projects like TCGA, The

Cancer Genome Atlas, is literally that those larger scale studies that have happened before really focused on what we call primary disease or sometimes also referred to as treatment-naive cancers. These are cancers that have been removed from patients at bank, at this very first discovery of these cancers, the first time the patient had a cancer diagnosis and received surgery to remove their tumor.

By contrast, this study focuses on metastatic cancers. We often think of metastatic cancers as the second occurrence of the cancer in the patient. For example, where they've gone through surgery, maybe received a standard of care like chemotherapy and radiation, and then unfortunately, recur with their cancer. And in the practicality of cancer care, one thing that we know is that it is typically the case that metastatic cancer, that's second occurrence, is the cancer that kills patients. It's typically not a primary cancer, although there are certainly exceptions to that rule.

And so, you could say the importance of this study is that it's focusing in on characterizing these second occurrence metastatic cancers, which are the ones that take the lives of our cancer patients. And so, it really stands as a comparison, if you will, to these previous studies until the similarities and differences between treatment-naive cancers and metastatic cancer.

Bob Barrett: Why is the study like this important for medicine, in general, and for cancer genomics as a discipline?

Elaine Mardis: I think it's important for medicine for the reason that I stated earlier; patients who die of cancer tend to die of metastatic disease. We think about cancer in the metastatic setting as being shaped by, if you will, evolutionary forces - forces that put a pressure on that cancer like chemotherapy, radiation, in which the cancer, when it comes back, essentially escapes those forces.

And so, really by studying metastatic cancers, it's important for cancer genomics because it gives us the ability to compare and contrast what was the first cancer in terms of the genome, the changes to DNA, what was the second cancer, the metastatic cancer and how did that compare to the first one in terms of new mutations or new alterations that maybe made the second cancer more aggressive or more widespread in the body.

And then for medicine, really, one of the things that this study informed us about in particular by studying the RNA or the expressed genes in metastatic cancers is that when you evaluate the genes that are being expressed in terms of the pathways, there's actually a huge amount of similarity

even if those cancers are coming from originally different sites in the body.

And this may give us some early indications in terms of medical treatment for these patients, that if we can characterize the cancer patient on the pathway activation, we may be able to design new effective treatments against those cancers regardless of where they are in the body. And this is important because often in metastatic disease, we don't just have a single site where the cancer comes back, but unfortunately, in many patients, we have multiple sites that are affected by metastasis, whereas the primary tumor typically just arises in one site in the body, whether that's the colon or the breast, et cetera.

So, this shared biology of the metastatic cancers can become important over time as we do additional studies in shaping our medical approach to how metastatic cancer may be treated. The cancer genomics is really more of a "gee whiz" question, if you will, which is, "Can we develop out tools that allow us to effectively compare the genomes of the primary cancer with the genomes of the metastatic cancers?" And that just tells us essentially what changes, if any, have occurred between the primary and the metastatic disease. So, that's the cancer genomics angle that was really addressed by this paper.

Bob Barrett: Let's talk about the paper that was in *Nature* by Robinson, et al. What findings reported in that paper were surprising, and which findings supported previous studies?

Elaine Mardis: The findings that were surprising largely fell along the lines of new discoveries. For example, new alterations to DNA that hadn't been described before, in particular, this group identified eight, what are called, fusion genes, where genes that normally aren't expressed together, actually have their coding regions put together by virtue of DNA gymnastics, if you will. So, in the changes that are occurring in the cancer DNA, you end up with these radically different new proteins, some of which we know historically from studies of cancer can be important drivers of cancer development. And so that was one of the new pieces of information that came out of the study.

Another new piece of information that I mentioned a minute ago was evaluating at the level of RNA, the similarity in tumor biology that appeared from the sort of higher-level evaluations of activated cellular pathways. And I think that, to me, was a very surprising result just in terms of how similar the tumor biology programs appear to be at that level of RNA or gene expression. I think some of the things that were known already but certainly were reinforced by this study was, in particular, in the past, when we thought

about people who developed cancer, we thought that typically, in the order of two to five percent of people who developed cancer have some sort of inherited or what we called “germline susceptibility”.

That means they have a gene that’s been mutated either when they were developing as an embryo or that was inherited from their parents that gives them a higher risk of developing cancer in their lifetime. What we know from large scale genomic studies and was reinforced by this paper in *Nature* is that number is actually more like 10 to 12 percent of people, and so it’s about double or more what the previous guess was in terms of the cancer susceptibility. So, this paper reinforced that 10 to 12 percent number, again, with a very large number of patients, and I think that was an important benchmark to have reinforced by yet another large scale study.

Bob Barrett: Well, was there anything missing in this study that will need to be addressed by follow-up studies? And if so, what would those studies look like?

Elaine Mardis: I think the only thing that was really missing in this study and it’s not a criticism, it’s just a matter of the way that the samples were collected and the fact that this is what we call, in medicine, a retrospective study. That means we’re taking samples that were previously collected, characterizing the DNA and RNA, and then looking backwards rather than a prospective study which would be characterizing the DNA and RNA and using that using that information to treat patients and see how they do with that higher level of precision in terms of what’s changed about the cancer cells compared to the normal cells.

So, this study, being retrospective, sets the stage for a prospective study to follow, and that prospective study is actually playing out already in many places where cancer care takes place in the United States especially tertiary care hospitals much like the one at Michigan that contributed a lot of the samples to this study and many others.

And in particular, what I'm saying is that increasingly, patients with metastatic cancers, because they’ve now failed what we called the standard of care, standard chemo or radiation therapy as I mentioned earlier, are getting these genomic characterizations of their tumors performed and the information from those is shaping out the next steps in treatment. It’s identifying more targeted therapies. In some cases, it is identifying newer types of treatments such as, what we call immunotherapies.

And in that context, patients now are beginning to take advantage of this capability that we have that we can

characterize the DNA from the tumor, we can characterize the RNA from the tumor, and we can use that to shape treatment options for those patients, either putting them on a clinical trial or getting them access to an FDA-approved cancer therapeutic that's already available. And so this is really, I think, ushering in this new phase of medicine on top of this retrospective study which sort of tells that this is the right thing to do and that, in fact, is already happening.

And at the end of it, what we hope to do with these prospective studies now that are taking place is to essentially prove a clinical benefit. That is to say, using these advanced characterization methods, looking at DNA and RNA, finding therapeutic vulnerabilities, aspects of the cancer genome that should respond to specific treatments, and then getting those treatments for those patients may ultimately provide a clinical benefit.

Those patients may experience a longer term remission, overcoming their cancer burden for extended periods of time hopefully, and this will tell us more and more about how to defeat metastatic disease which is the type of cancer that kills our patients.

Bob Barrett: So, finally doctor, were there innovative approaches you highlighted that were pursued in the *Nature* manuscript, and what new information did they reveal?

Elaine Mardis: I think one of the things that the group did very nicely in this paper in *Nature* in terms of the data analysis is that they combined or integrated the data from DNA and RNA studies. So, when we have changes at the level of DNA, those are copied into RNA, the genes that are altered turn into RNA and ultimately, that RNA is turned into proteins, and proteins, of course, are the active molecules inside of our cells. So we know that in cancer, the fundamental changes at the level of DNA, when they occur in genes, can be readily detected in RNA.

Sometimes, changes in DNA can actually change the amount of RNA and the amount of protein that is produced, but they don't necessarily cause mutations. For example, it's the only way to really detect these coincident changes in DNA and RNAs to look at both. So, one for sure, what really was done beautifully by this group in terms of integrating or combining the DNA and RNA information was if you get an additive effect, whether the change you're finding is occurring at the level of DNA, or is occurring in DNA but can only be detected in RNA by combining those two pieces of data together, you now have more information about that gene or that pathway.

And so, you get a larger, more, I would say, embellished result in terms of the full, you know, sort of incorporating the full information into your final analysis. And so by combining DNA and RNA information, what this group was able to do was to build a stronger picture of the tumor biology of metastasis and really to, I think, enhance the understanding of how these changes occur and how they drive the cancers that are developing in these patients. And ultimately, of course, how we might think differently about treating these patients and so that, to me, was a very complicated analysis, but a really nice result that came out of this very thorough study of metastatic cancer.

Bob Baron: Dr. Elaine Mardis is the co-executive director of the Institute for Genomic Medicine at Nationwide Children's Hospital and professor of Pediatrics at the Ohio State University College of Medicine. She has been our guest in this podcast from *Clinical Chemistry*. I'm Bob Barrett. Thanks for listening.