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TRANSCRIPT FOR VIDEO #1: RESEARCH (PART 1)—
WITH DR. MICHAEL BIRRER
Interview, Massachusetts General Hospital
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Produced by The GCS Project

(MB—Michael Birrer, MD; DR—Diane Redington, CRNP)

Slide: **Patient/Advocate, Diane Redington, and Dr. Michael Birrer discuss the results of the research to date and where the research is headed.**

DR: Can you tell me if there have been any early discoveries in the research?

MB: Sure. Let me start by saying that we're also honored and very privileged to do this research. And the effort in funding that you have garnered has been extremely helpful. And we've already had some initial results. ***So, we are doing what I call a molecular "deep dive," meaning a very sophisticated analysis on a fairly large set of tumors.*** We've already been able to characterize [describe in detail] some of the mutational events that occur in carcinosarcomas coming from the ovary and coming from the uterus. They aren't necessarily the same. Some of those events are going to be what I call "targetable," meaning that they may be molecular events that we can treat. So, that's exciting***. It's also important to note that we are characterizing the gene expression patterns of these tumors and have early data to suggest that the way the DNA is packaged in these tumors is actually quite important for their development and progression.***

DR: Can you expand on that a little bit?

MB: Yes. So, there's a lot of ways in which normal tissue becomes cancer. The simplest way to understand it is if a gene gets mutated, it then hyper-functions, and the normal tissue becomes cancer. And again, in these particular tumors, we're seeing some of those events. But what's unique about it, I think, what's unique about the carcinosarcoma so far, is that there's another event, which is the DNA is stored in

chromosomes, and it's wrapped in something called *chromatin*, which is a series of proteins. And the early data that we have—and there have been a couple of other small groups who have suggested this also—is that *that* packaging is abnormal. And the reason why it's important to identify that is, there's a whole new set of drugs that are called **chromatin remodeling drugs**. And they're [drugs] coming into the clinic, so they may be very relevant in the treatment of this disease.

DR: How far are we from the molecular analysis to actually being able to take those new drugs that are coming and test them on some of this?

MB: So, of course, it's always difficult with research to predict these things. To be perfectly honest, I think we're as little as a year away of translating some of these findings into the design of clinical trials. And so we're positioned so well for that here at Mass General, and the team is very motivated to do that.

DR: Can you tell me a little bit about the research team and the different components that they are working on?

MB: So, certainly, it involves extensively my laboratory, which we're sitting in right now in the Jackson Building, and that team has 8 Post-Docs—MDs and PhDs—and *they're doing a lot of the molecular analysis, and they're also assisting with obtaining the tissues from the patients in the clinic,* which is not easy. It has to be all ethically and IRB-approved. We need to do it in a way that is safe and comfortable for the patients. And of course, this patient population is highly motivated. And it's a wonderful group of women who are very dedicated to providing the appropriate tissues to answer these questions.

Now in order to be successful in the analysis of tumor lines, we need to reach way beyond one lab. And so we have engaged actually a neuro-oncologist as somebody who deals with tumors of the brain. And you might think that's kind of odd, but Priscilla [Priscilla Kaliopi Brastianos, MD] is a wonderful scientist—physician scientist—who's very interested in these particular tumors and is assisting us in the sequencing of them. *She has a collaborative arrangement with the Broad Institute, which is probably one of the top three sequencing institutes in the World.* And they're across the street in Cambridge. So, they're involved. And then we have *several pathologists who are GYN pathologists who have expertise in being able to carefully look at these tumors under the microscope*, and that's been very, very helpful for us to identify the right cases, dissect them, and obtain the nucleic acids to do the analysis.

And then, finally, we have some really high-level advisors. Brad Bernstein is a spectacular scientist who's advising us in this effort. He's an *expert in methylation and chromatin structure of tumors*. So, that's obviously very relevant because of what I said a few minutes ago. *This tumor, in many ways, is a tumor of chromatin remodeling.*

DR: You talked about obtaining tissue from patients. Are you in need of more additional tissue samples, because I know that there's a number of women who ask me, "How can I help? Can I send my tumor? Can we participate?" So, are you in need of tissue?

MB: The straight, the easy answer is "Absolutely." Again, this is a tumor that's not common. *So getting large collections is hard, and numbers are important in this analysis.* If we are analyzing small numbers of tumors, we might overestimate or underestimate a particular molecular problem. So we need fairly large numbers. More importantly, we're now evolving from having analyzed what we call formalin-fixed paraffin-embedded material. These are the tumors that are removed from the patient, they go to the path lab and they are "fixed." They're extremely helpful. **But there are certain assays that can only be done on fresh or frozen material. So we're really looking for that.**

DR: And how would we find that? Would you have to find a woman who is… has a remission, has a recurrence? Would that be the likely source of the tumor?

MB: Yes. **I think the most common source would be a patient who has suffered a recurrence, has a radiologically visible site of tumor that can be safely biopsied.** We already have a IRB-approved protocol to do this; we've done it several times. Safe—I can't say it's non-invasive; it's invasive—but a quick, safe procedure, which gives us enough tumor to analyze, both for the project but also for that patient. Now, an alternative approach is at the time of initial diagnosis. That's tricky though, because as you probably know, when patients are operated on, most of that material ends up in the path lab and ends up being fixed very quickly.