The GCS Project
2795 Estates Drive
Park City, UT 84060
www.gcsproject.org

TRANSCRIPT FOR VIDEO #5: GENOME ANALYSIS AND IMMUNOTHERAPY—WITH DR. WHITFIELD GROWDEN
Interview, Massachusetts General Hospital
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Produced by The GCS Project

(WG—Whitfield Growden, MD; DR—Diane Redington, CRNP)

Slide: **WHAT SCIENCE HAS TAUGHT US**
Patient/Advocate, Diane Redington, and Dr. Whitfield Growden discuss genomic analysis, patterns of resistance, and immunotherapy.

DR: If you want to do an analysis—a genomic analysis—can you use the metastatic lesion or do you have to go back to the original tumor? Because a lot of women are diagnosed with extensive metastatic disease and are not surgical candidates. Where do you get your tumor?

WG: This is such an important question. And the spoiler alert is that we don't know the final answer. *Most of our clinical trials use the initial biopsy or the initial surgical specimen* to determine candidacy for whether or not we go into the trial—even if that specimen was long since removed years prior and you are actually treating something that's in a totally new space. There are emerging clinical trials that actually seek to get *serial biopsies* [a series of biopsies] because limited clinical trial data from phase 1 trials have shown that **these tumors change**. And they change in real time. And previous treatment changes the tumor and may affect its drivers. And so you can imagine that the lineage of a cancer cell could really change based on where it goes.

And so there have been some interesting studies that have biopsied tumors in various different areas that look the same under the microscope, but molecularly, they are about 85% the same. But if you think, every time it moves, it gets 85% the same, 85% the same, you could have something that's unrecognizable if it's moved many times. And so, I believe a future movement in oncology is that we're going to have to be getting real time sampling of what these tumors are.

As we think about candidacies for targeted therapies, for immune

therapies, this is going to be of utmost importance. *Particularly trying to recognize patterns of resistance.* Because that's another major issue in oncology, is that, we can have a therapy that might work for a couple of months, but then it stops working. And wouldn't it be great to know about that as soon as it happens so that you change therapies on the precipice of that happening? So that as you said, you can always be applying something new that will be effective.

DR: It would be based on the reemergence of… . so you get the original tumor—given that you can have surgery—you get the original tumor and then you have a reemergence, so you get the new tumor and then you compare the original to the new and you can see what's transpired.

WG: …what's transpired. Or even the original may not even inform what you should be doing. It could be that you really need to focus on what is the current metastasis that you are trying to treat or recurrence that you are trying to treat. Because it could be different. And maybe it's even attained a new signature that makes it susceptible to a new type of therapy that we didn't even know about.

A good example of this—in uterine carcinosarcoma, there is a gene amplification rate, which means an overexpression of genes, of something called HER2, which is famous because of breast cancer. That was essentially the poster child for targeted therapies. Women with breast cancer in the late 80s, if you were overexpressing this protein HER2 on the tumor, you actually had a very guarded prognosis. It was a poor prognostic factor. But then we invented an antibody that neutralized those specific cells—Herceptin or trastuzumab. And then we essentially turned what was a very poor prognostic factor into one of the best prognostic factors. If you have breast cancer, you want it to be HER2-positive because there is a pipeline of anti-HER2 therapy.

What's not discussed very often is that uterine cancers, particularly high-grade serous uterine cancers have the exact same rate of gene amplification as breast cancer. And c*arcinosarcoma also has that rate of amplification.* We're running one of the only clinical trials here of HER2 therapy in uterine serous carcinoma, which is a variant of carcinosarcoma. The trial was designed and doesn't include carcinosarcomas, but I believe we're going to write another trial to include carcinosarcoma. It could be that the initial specimen from a hysterectomy specimen doesn't have HER2 gene amplification. But it may be that the metastasis does have that. Which would mean you'd want to test both. Because it may be that anti-HER2 therapy for uterine carcinosarcoma, I believe, is going to someday be important for that

subset of women.
And we're trying to get pre-clinical data to really put that together and prove that that's going to be important.

DR: Where will you get that data? Do you need samples?

WG: So, we do, and we use the vast bank that we have here. Very commonly, we have women that agreed to donate their samples, meaning that pathology will only use about 50% of their tissue to make a diagnosis and the rest gets thrown away.

DR: There are many women who write on the website and who have generously offered, "Take my tissue for evaluation. I want to be part of this." So, we'd like to create some kind of a mechanism to be able to offer you guys and research the tissue and figure out what is it you need, what form you need, so there's a match between people who have this disease and the research.

WG: There has to be. I think that clinical medicine is not the way it used to be where there is the bench [laboratory] and there was the clinic. Now what happens in the office is very much informed by what happens in the laboratory. And I think…

DR: I think that is true here at Mass General more than most places.

WG: Well, we talked about how to move the bar forward. The bar is going to get moved forward in the lab. And then it's how we apply what we've learned from the lab in the clinic. HER2 is a great example. There's only about 20-30% of women with carcinosarcomas of the uterus who will overexpress HER2. But if we can identify that cohort first and then apply the right therapy, maybe we could enjoy the success that we've seen in breast cancer as well as gastric cancer.

DR: That would be a huge breakthrough.

WG: It would be a massive thing. The clinical trial that we are running in uterine serous carcinoma right now, which admittedly does not include uterine carcinosarcoma, we've already seen responses. Which is incredible! We have people on trial who are doing well who had no other options because after initial cytotoxic chemotherapy, there is no FDA-approved therapy for uterine carcinosarcoma.

DR: That is so exciting.

WG: That's how we are going to beat this. If we're going to try to get meaningful impact, it's going to be incremental, but it's going to be by understanding the molecular drivers of an individual woman's carcinosarcoma and then applying the right therapy.

WG: We talked about immunotherapy. I believe that we're going to be using a similar strategy with immunotherapy. I don't think *all* women with endometrial cancer are going to benefit from immunotherapy. *I think it's going to be the subset that express particular biomarkers.*
We've decided to look at what's called *anti-PD-1 immunotherapy*. PD-1 is a protein that's expressed on immune cells and tumor cells and also normal cells. **PD-1 is a checkpoint inhibitor.** And what that means is that our kidney cells, our liver cells, our "self" cells don't get attacked by our immune system, because they express these proteins that say, "I'm you. Don't attack me." Well, a tumor could highjack that. Right? And then, if the tumor puts that flag out there, our immune system gets tricked and ignores the tumor. *Well, these antibodies attack these checkpoint inhibitors, block them specifically, and then our immune system recognizes tumors as foreign.* And, essentially, I believe that the more tumors express those particular checkpoint inhibitors, the more likely you're going to see a response.

DR: **Can you test for that?**

WG: You can. Currently there's a medicine that's FDA-approved called pembrolizumab [Keytruda]. It comes with a companion test that is a protein assay [analysis] you can do within days on any given tumor. And it's an FDA-approved companion test in order to test lung cancers to determine whether or not you're more likely to respond. The caveat: It's not perfect. Nothing ever is. We have patients that overexpress the protein that don't respond; and conversely, we have patients that don't express the protein that respond. So, it's not a perfect system, but in general, if you are a high expresser, you're more likely to respond. What I want you to know is that these checkpoint proteins, they're called B7h proteins. PD-1 is actually B7h1. But there's a whole family of them, like 12 or 15 of them. So, it's not just one protein. It's a landscape. And likely it's a mix. It's sort of like putting the right cocktail together.

So maybe we need to be doing simultaneous immunotherapies. We need to test a tumor for all the different proteins, figure out what the landscape looks like, and then apply the right immunotherapies as cocktails. So that my cocktail for my melanoma may look different from your cocktail with a uterine [or ovarian] carcinosarcoma. And a lung

cancer would look different. So that it's based on the biomarker test that you do up front.