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

TRANSCRIPT FOR VIDEO #3: RESEARCH FINDINGS AND CLINICAL TRIALS—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 STUDIES SHOW**
Patient/Advocate, Diane Redington, and Dr. Whitfield Growden discuss current scientific findings and clinical trials in ovarian and uterine carcinosarcoma.

WG: What we did was, we looked across all of the GYN carcinosarcomas because we had a sneaking suspicion that maybe they're all related, and when they happen to pop up, is just random entropy [lack of predictability]. It doesn't necessarily reflect how we should be treating it. Or maybe the molecular drivers that make carcinosarcomas happen are the same in the fallopian tube, in the ovary, in the uterus and in the vagina. And so we were able to use the vast tumor bank of Mass General to obtain tissue. Then we actually interrogated [examined] the tissue for specific gain-of-function oncogenic mutations. We queried it for about 150 or so mutations and basically distilled each individual tumor down to its DNA and RNA and were able to genotype each one. What we found was fascinating.

Fallopian tube carcinosarcomas are very, very rare, but they tend to look just like ovarian carcinosarcomas. Vaginal—we only had 2 [vaginal tumor specimens] in entire cohort of approximately 70 to 80. So it was hard to draw firm conclusions. But we didn't see any clear pattern of gain-of-function mutation.

It was the uterus where we found over 50% gain-of-function mutations in uterine carcinosarcomas. Where ovarian and fallopian tube carcinosarcomas didn't have any meaningful mutations in specific subsets, which really mirrors regular serous ovarian cancer. Serous ovarian cancer isn't marked by specific subsets of tumors that have really treatable targetable mutations. It's marked by random genetic entropy—random, what we call genomic instability. Where the rule is, "There is no rule in what the molecular changes are." Whereas in

uterine cancer, there are defined subsets of specific types of tumors that have specific mutations that we believe make these tumors very susceptible to targeted therapies as well as immunotherapies.

Carcinosarcoma is just at the tip of that. ***One of the reasons why is that in 2009 we changed carcinosarcomas from being a "sarcoma" classification to an "epithelial carcinoma" classification.*** So the cancer genome atlas, all of the major clinical trials in carcinomas of the uterus excluded carcinosarcoma. They were excluded for years. And it's only been in the last 5-7 years that carcinosarcoma has been included with epithelial cancers, and we're starting to think about them very differently. This was largely because of work done in the early 2000s that basically looked at molecular underpinnings of carcinoma as well as carcinosarcomas and found that what they think happens with carcinosarcomas—and this may be true of ovarian, we don't know, but it's probably true of endometrium—is that they started as a high-grade carcinoma, like a serous carcinoma, and then as they grow, they de-differentiate or morph into something completely different at the same time. So you get, what it looks like on the microscope is a tumor that has both sarcoma elements and carcinoma elements.

DR: In the same cell?

WG: No, in the same tissue. So it almost looks like…they used to call these back in the 80's, "collision tumors." As if it were 2 different cancers colliding together. **A lot of researchers, without knowing their molecular underpinnings, assumed that the sarcoma was driving it, when in fact, it is probably the carcinoma that is driving it.** That was really on epidemiologic level or on sort of a clinical level scene, because whenever these cancers metastasized to different parts of the body, it was usually the carcinoma that metastasized. So, we thought that's more likely to be "the egg" and not "the chicken." And so, we don't have definitive proof, but we believe now, based on our molecular studies of lineage, that likely these carcinosarcomas—the sarcomatous components—are derived from the epithelial components. Even in our study, we biopsied the sarcoma and we biopsied the carcinoma, and found excellent homology [same or similarity] on a genomic level between those two things.

DR: Why not go after both?

WG: The good news here is that it looks like the molecular alterations that affect the carcinoma also affect the sarcoma, and it is just the way they have differentiated that makes them different. Which means that if you

can find a therapy that addresses the carcinoma, like a targeted therapy or an immunotherapy, it is likely that you are going to also hit the sarcoma as well.

Which is where carcinosarcomas are different from pure sarcomas, like rhabdosarcomas, like liposarcomas. There is a huge family of sarcomas that get treated with very different chemotherapy than we use with carcinosarcomas.

And so this is something that's definitely evolving. This is something that I think… there have been dedicated clinical trials—not for ovarian carcinosarcomas, but for uterine carcinosarcomas. That was recognized, that this was a separate type of cancer *early*, like in the 90's. I think that for ovarian carcinosarcomas, as we talked about briefly, a lot of times most of our clinical trials, unfortunately, have excluded ovarian carcinosarcomas because they wanted to create pure populations for clinical trials. There just weren't enough, basically, incident cases to fill a trial and possibly have an impact. ***So they got excluded, and a lot of our ovarian cancer treatment paradigms for carcinosarcoma are based on serous epithelial ovarian cancer paradigms.*** Whether or not that's relevant, we don't know. We're just not sure. Whereas in uterus, there definitely is. Dedicated trials. There are some ongoing clinical trials right now.

DR: For uterine carcinosarcoma specifically.

WG: That's correct. The big trial that we are waiting for compares two strategies of conventional chemotherapy. One is using a medicine called Taxol [paclitaxel] along with a medicine called ifosfamide. That was established as our standard of care with the best response rates and the best overall survival when compared to other regimens. We are now comparing that to carboplatin and Taxol. So these two different regimens that both have Taxol are being compared. We currently use carboplatinum [carboplatin] and Taxol as our front line. A lot of times ifosfamide has fallen out of favor. It can be onerous to give. It is given over several days; it has a toxicity profile that is more than what we see with every 3-week carboplatin and Taxol. We think that based on smaller studies that likely the response rates are the same if not maybe a little bit better. So we are confident that that trial will likely show equivalency or at least non-inferiority with basically much less toxicity.

DR: Is that for all carcinosarcoma?

WG: That is for carcinosarcoma of the uterus. Carcinosarcoma of the ovary

does not have, as of yet, dedicated clinical trials where you just have women that just have carcinosarcoma of the ovary. Some trials lump them in, but most exclude them.

DR: They are 2 different entities, so it's really important to differentiate between the diagnosis of ovarian carcinosarcoma versus uterine carcinosarcoma.

WG: I think that is a very important differentiation. It *is a differentiation that sometimes is very hard to make.*

DR: Would it be based on a tissue sample?

WG: It would be based on a tissue sample, and you look and see where things arose. We know that on a molecular basis, there probably are differences. If you were ever wondering—"did this come from the ovary or did this come from the uterus?"—it would be nice to have a test you can do. Some sort of molecular analysis. But the fact of the matter is there is likely not going to be a specific test. We are never going to be able to differentiate them perfectly.