**Precision Medicine Podcast, Season 3, Episode 45**

**Dr. F. Anthony Greco Explains How Precision Medicine Has Led to Better Treatments for Cancers of Unknown Origins**

March 30, 2021

**Karan Cushman, Producer:**  
Welcome to Season Three of the Precision Medicine Podcast sponsored by Trapelo. This is the podcast where experts come to discuss the problems oncologists, reference labs, and payers face as precision medicine grows and consider solutions for advancing the quality of patient-centered cancer care. Be sure to subscribe at precisionmedicinepodcast.com to get the latest episodes delivered straight to your inbox.

**Jerome Madison, Host:**

Thank you for joining us for another episode of the Precision Medicine Podcast. I'm Jerome Madison. Today, we have Dr. Tony Greco, medical oncologist at Tennessee Oncology, and one of the foremost experts on the treatment of cancers of unknown primary. We asked him to come by and talk to us about the role that precision medicine has played in improving our diagnosis and treatment of this rare and very difficult to treat disease. Dr. Greco, thank you for being a guest on the podcast.

**Dr. Tony Greco:**

Thank you for having me.

**Jerome Madison:**

When I do my background research on our guests, Dr. Greco, I found something really interesting that stood out, among other things. But you left a post as the medical director, or the director of medical oncology, at a leading and some might say prestigious academic center so you can do more clinical trial work in the community. And yeah, I don't know how that sounds to some of our listeners, but when I heard that, I was like, "Huh?" Tell us about what led to that decision.

**Dr. Tony Greco:**

Yeah. Well, clinical research in oncology has always been important to... Particularly several years ago, because we couldn't treat many of these patients very well, so we needed to do important, critical research to determine better therapies. There was nowhere to do that in the early 1970s except in major institutions.

So I went to a major institution and had an opportunity there, and we did well. We designed lots of studies. We got grants. And we trained a lot of oncologists, as did many other major institutions around the country.

As that happened, the oncologists, many of them, went into private practice and communities, and the number of patients being sent to major universities, like where I was, was drying up. And therefore, we were just seeing the more complex cases that had already been treated, and most of the cases in the community weren't being placed on any research study.

So, that became obvious, and I had an opportunity, along with my associates, to get support from a private institution. So, we decided to go across the street here in Nashville, and we joined Tennessee Oncology, and we set up and ran the Sarah Cannon Cancer Center. Which Sarah Cannon's the name of Minnie Pearl. Many of you may not know that, but... And we developed a research program here and had access to many, many patients.

It grew. We formed a research institute a few years later, which has become a global research institute or one of the largest in the country. All private and all patients come from basically private practices. We published a lot, and I think we've done fairly well in helping advance the field, the therapy for patients with advanced cancer.

The reason I left there was for even a better opportunity. It was a gamble, but it looks like it paid off for what we were interested in doing and for the patients.

**Jerome Madison:**

So hey, Sarah Cannon is Minnie Pearl. That may date some of our podcast listeners. That's good for trivia. That's Minnie Pearl from Hee Haw fame.

**Dr. Tony Greco:**

Exactly.

**Karan Cushman:**

That's awesome.

**Jerome Madison:**

So, Dr. Greco, you went and you co-founded the Sarah Cancer Research Institute. You became the medical director there. Tennessee Oncology today enrolls more patients in clinical trials than any private practice in the US, and you're also one of the most successful phase one clinical trial programs in the world. How were you able to achieve this level of success in the community cancer setting?

**Dr. Tony Greco:**

With a lot of support, both from dedicated, intelligent people who we recruited, to having the appropriate background and people working with us in the data management, computer facilities. Everything is necessary. So we had financial support, we had people support, and we had patients. And we had knowledge because we trained, several of us who came here, trained to do clinical research, and therefore, we had all the ingredients to make this successful. And thankfully, that's exactly what's happened. It's grown far beyond my expectations, but that's basically how it evolved.

**Jerome Madison:**

**It takes a team. So,** for our listeners, as we get into cancers of unknown primary, can you define exactly what they did? I mean, maybe it's self-explanatory, but I think it's a little deeper than that.

**Dr. Tony Greco:**

Well, yeah, it's fine. This is really not rare. I noticed you said that earlier. A lot of people think it's rare, but it's not very rare. What it is, it's a patient who has advanced metastatic cancer, but it's uncertain where it arose from. They have metastasis or spread, but a complete evaluation does not reveal where the origin of the cancer was. Where it spread from. Where it started.

**Dr. Tony Greco:**

It represents about 3% of all patients with advanced cancer, so it's not rare at all. We could go into the reasons why people think it's rare. Because they often just go ahead and arbitrarily state that this is from the lung or this is from the intestine when really, they don't even know that. But when they do that, it gets recorded as a primary cancer rather than an unknown primary cancer.

This is a common entity, and I've been interested in it for many decades, and these patients, because I was fascinated on how this occurred. I think we've learned a lot on how it's occurred. Most of these patients in fact do have a very small primary, which then spreads, but we can't find that very small or otherwise occult primary. We can find them at autopsy in most patients. They're very small, yet they can spread and the metastasis are easy to find. That's how the patients present.

We don't know why this occurs, but it happens in many different types of cancers. So cancer of unknown primary is not a single cancer, it's a syndrome of many different cancers. The common element is that the primary, where the cancer started, is too small to find during clinical examination when the patient is alive. And therefore, it becomes difficult to treat such patients. That is evolved over time, and now we can find the cancer type in most patients and we can treat them accordingly.

**Jerome Madison:**

Yeah. From what I can find, it shows that you have been the lead or co-author on over 650 publications in peer-reviewed journals on the topic. How did you gravitate towards treating this patients as your specialty?

**Dr. Tony Greco:**

Yeah. Well, my publications aren't all on this particular syndrome of cancer, of unknown primary site, but many of them are. I became interested in this because during the time when I was trained in oncology and later in academic practice right across the street over there, we saw many types of cancer, and we concentrated on the more treatable types. I won't go into that because there were a lot of types that we couldn't treat very well, and you just gave those patients symptom management. You cared for them, but there was no specific treatment that could help them. That's changed a whole lot.

And then when I saw these patients with unknown primary cancer, we couldn't really determine back in those years what they had, but we did do autopsies, as I mentioned. And it became obvious that they had very small, undetectable primary sites during life, but we could find most of them during the autopsies. Yet they could spread. So, this became a fascinating medical mystery.

That's what we've studied, what I've studied over the years, and it's becoming more and more clear how this develops and what happens. And these patients have various types of cancer, and when it metastasizes or spreads, we can then treat them according to the type of cancer they have. And in many instances, we can treat them more successfully now than ever before, because we can diagnose the type of cancer that they actually have and where it's coming from.

**Jerome Madison:**

Yeah. On the topic of diagnosing and finding more information about these patients' tumors, I would imagine if there's a tumor type that should be treated with a precision medicine approach based on genetic or genomic expression, it would seem that these types of tumors should be the case, right? What diagnostic tools exist that have helped inform treatment decision for these patients over the years?

**Dr. Tony Greco:**

Yeah. Well, early on in the development... Again, but I predated even this development and seeing these patients. Immunohistochemical stains, particular stains that pathologists use, which can pick up proteins and cells, were developed and have continued to develop. These stains can often, when they're used together in panels, can give us a very good idea of the type of cancer that we're dealing with in patients that have cancer of unknown primary site.

So, immunohistochemical staining is very important. However, it still leaves a large number of patients where the stain simply cannot give us an answer of what type of cancer the patient has. Probably at least half or a little more we still don't know by using the stains.

Then along came molecular testing. Again, we call these molecular cancer classifier assays, and they're run through nucleic acids, either RNA or DNA. Because these nucleic acids are the basis of protein synthesis in all cells, and I mentioned the immunohistochemistry is looking at the proteins. Whereas these molecular cancer classifiers are looking at the chemicals that actually are responsible for protein synthesis.

And basically when cancers develop, they develop from normal cells, and those normal cells all secrete some sort of protein. For an example, breast cells secrete certain proteins, which are eventually going to make milk. The ducts in female breasts, for instance. There are many other examples. And when cancers develop in those cells, they often retain that protein mechanism, that they have in their normal cells, within the cancer cells. So if we can detect that, then we can determine the type of cancer the patient has.

That's a simplified explanation of these molecular cancer classifier assays, which have been developed. There's really only one on the market at this time that's been validated, and that's the RT-PCR 92 gene test, CancerTYPE ID. I've been having experience with this since 2008, many others have as well. This, when added to immunohistochemistry, along with the clinical findings in the patients, we can determine the type of cancer the patient has in about 90 to 95% of the time. And if we've determined the type of cancer a patient has, then we can determine what the best treatment is for that particular cancer type.

You mentioned that it would seem that genomic expression might be even more important in these patients, and perhaps it is more important only because these patients represent so many different types of cancers. We now know that certain cancer types, when we know the cancer type, have certain genomic changes in the cancer cells which are highly treatable. Lung cancers, breast cancers, kidney cancers. I could go on and on. There are many others. Now can be treated much more effectively with so-called targeted drugs if the patients have the genomic target present in the cancer cells, or immunotherapy, which has been a major advance in the treatment of patients with metastatic cancers. Not every patient with metastatic cancers, but many of them.

So, if one knows what type of cancer a patient with cancer of unknown primary is, then we can use the therapy that we would use for that type of cancer when it's not an unknown primary cancer. I hope you're following me there.

**Jerome Madison:**

Absolutely.

**Dr. Tony Greco:**

Yeah. So, we need to know the type of cancer. That's critical. And then we need to know what type of genomic alterations, mutations are within the cancer cells. That's a different form of molecular testing than determining the type of cancer that a patient has. Again, we only use molecular cancer classifier assays in patients when we're uncertain of the tumor type. Most of these patients have cancer of unknown primary type, as mentioned. If we know where the primary is, then we can tell from our clinical examination of medical imaging. Then we don't need a molecular cancer classifier assay.

**Jerome Madison:**

Yeah. You mentioned that 92% of these patients that will undergo a classifier assay will eventually receive a definitive diagnosis. What about the other 8%? How do you approach therapy with those patients?

**Dr. Tony Greco:**

Yeah. Those patients are very problematic because then we simply do not know the tissue of origin. The minority of patients, we have no idea where it's coming from. In that group of patients, I like to use next-generation sequencing or comprehensive molecular profiling, looking for genetic alterations within their cancer cells. This can be done with tissue-based testing, or now what's known as liquid biopsies.

In that small group of patients, we might be able to find an important target to help treat these patients. Otherwise, all we can do is what we call empiric chemotherapy, which we used for all CUP patients several years ago. It's just shotgun therapy of certain chemotherapy drugs that work in some cancers, but don't work in others. That does help some people. That's empiric chemotherapy. I no longer like to recommend that, except sometimes in this group of patients that you just mentioned, the small percentage where we cannot determine the cancer type.

**Jerome Madison:**

The Precision Medicine Podcast will continue right after this.

**Karan Cushman:**

With the explosion of new data and biomarkers and cancer today, how can healthcare professionals keep pace to know which genes will best inform treatment decisions? Trapelo knows. Trapelo is the first single technology platform used by oncologists, labs and payers to resolve the complexities of precision medicine in real time. Trapelo knows which patients to test and when. It knows which tests are most appropriate, which labs are preferred, and which treatments are most likely to be reimbursed. Visit trapelohealth.com to learn how you can give cancer patients the most appropriate, evidence-based treatment options when time matters most.

**Jerome Madison:**

When you are using the molecular identifier... Or do most folks call it a CUP test?

**Dr. Tony Greco:**

Well, I'm not sure most call it that. But yeah, they could call it a CUP molecular test to determine the tissue of origin or the... Yeah, you could call it that. This test can be done on known cancer types. But there's no reason to do it on known cancer types because you already know the cancer type. Except when in some instances, relatively rare, the subtype is not really known. For instance, in lung cancers, there are many subtypes. And if a patient has a lung cancer and the pathologists aren't sure of the subtype, then a molecular classifier, like the CancerTYPE ID, can be useful. But for all practical purposes, the majority of patients where these CUP molecular tests are being utilized, we don't know the particular cancer origin or cancer type.

**Jerome Madison:**

Right. How are these tests validated, and what is the data that demonstrates benefit for patients?

**Dr. Tony Greco:**

Okay. That's a rather good but complex question. The first step is these tests that purport or say that they can determine the cancer type, they have to be validated in known cancer types. In other words, you have to take a series of patients with lung cancer, colon cancer, breast cancer. I could go on and on up to about 32 different cancer types and more than 50 subtypes. They have to be validated.

In other words, a group of pathologists and oncologists know certain known cancers. And then these molecular tests have to be run on those cancers, the tissue, and you have to validate how accurate they are in determining the known cancers. You following me there?

**Jerome Madison:**

Absolutely.

**Dr. Tony Greco:**

Okay. That's the first step. If they're validated and known cancers, then the next step is you have to validate it in patients with cancers of unknown primary site.

The reason you have to do that is cancers of unknown primary site are not totally similar to the cancers which arise from sites which we know are known cancer sites. The reason they're not similar is probably because there's a genomic cause, either genetic or what we call epigenetic. Cause for the reason that the primaries in unknown primary cancer are so small and they can't be detected, yet they metastasize and the metastasis grow. That's what is detected.

There's a molecular difference between cancer of unknown primary and cancers of known primary. Therefore, these molecular tests have to be validated in those patients with unknown primary cancer in order for oncologists and pathologists to feel confident that the diagnosis is correct. Knowing that the diagnosis is correct in patients with known cancers is not the same as knowing it's correct in patients with unknown primary cancers. So, one has to validate molecular tests in patients with unknown primary cancers, which is not as easy, but it can be done.

**Jerome Madison:**

Well, there are a number of patients who listen to our podcasts, and I know... I mean, you understand the patient experience and journey to finding the right diagnosis. What's some of the frustrations that patients express to you by the time they are referred or find you to get treatment for a cancer of unknown primary? Or maybe they've been to a system that just doesn't diagnose their cancer at all, and they continue to have problems. How should they think about that, or what course should they take?

**Dr. Tony Greco:**

Well, it is frustrating for patients and for many physicians, oncologists and others, because they fit into a category where their provider or their physician or nurse can't tell them exactly what type of cancer they have. You can understand the frustration there.

Again, with the diagnostic technology we have today, particularly with sophisticated pathology, immunohistochemistry, the molecular test we've already discussed, more than 90% of these patients we can tell them where the cancer's coming from, and we can explain to them how that the cancer's too small. This is the usual situation. To find, yet it can spread. That frustrates them too. They don't understand why that can happen, but it certainly can.

I mean, very small cancers that we can see can cause diffused large metastasis. So, certain cancers we can't see, because they're just too small for the test to be able to demonstrate them, can also do the same thing. And as I mentioned, we know that from past from many post-mortem examination, autopsies.

So, once we know the cancer type, it reduces the frustration. Particularly if we've determined a cancer type which can be highly treatable. Now, not all patients with unknown primary cancer at this point in time have highly treatable cancers. So, that's frustrating, but we can't help that.

To determine the type of cancer is not the same as saying that it's a highly treatable cancer. Some are and some aren't. But at least the patient knows and the physician knows what options might be available for that particular cancer, just like when you treat patients with known metastatic cancers. And often we use next-generation sequencing, particularly if we have a... in the context of knowing the cancer type by using immunohistochemistry or these molecular classifier tests, we can then test for a particular genetic alterations known to be present in those cancers, like lung or breast or colorectal or many others, and determine if there can be a targeted therapy that might be applicable to certain patients, or even immunotherapy, which is becoming much more commonly done at this time and used in various advanced cancer. Seems like every week or two, there's a new indication.

So, there's a lot of excitement now in treating patients with unknown primary cancer. Once we learn what type of cancer they have, we can then go on to treat them just like we would patients when we know from the beginning what type of cancer they have. That's basically in a nutshell the bottom line.

**Jerome Madison:**

Well, I think the bottom line from much of what you unpacked here today is that the advancement of precision medicines have created better and possibly more treatment options for these particular patients who have cancers of unknown primary.

**Dr. Tony Greco:**

Yes, I think that's correct only because there's so many categories or types of cancer within the syndrome of what we call unknown primary cancer.

I might mention also, I didn't give any details on the validation of the molecular cancer classifiers in patients with unknown primary cancer, which is very important because we want to feel confident in the diagnosis. There are three main ways I'll just briefly mention that you can validate these assays in unknown primary cancer, and that the circumstantial evidence is very strong. Almost like in a court of law, you don't need absolute direct evidence to convict somebody if you have strong enough circumstantial evidence, and we have that for the CancerTYPE ID. But unfortunately, we don't have that for any of the other assays that are out there now who are claiming they can diagnose these patients. Maybe they can, but I'd like to see the validation.

**Dr. Tony Greco:**

The validation is rather complex, but three different areas. And again, I won't go into detail, but some patients with unknown primary cancer, later on in their course of their disease, we find their primary. It grows enough that we actually find it. In those patients, if we did the molecular cancer assay at the time of initial diagnosis, then we later find where the primary came from. We can then compare the diagnosis from the molecular tests with what we actually found later. Following that?

**Jerome Madison:**

Yes.

**Dr. Tony Greco:**

When we did that in more than 20 patients, we determined that in 75% of them, a fairly high percentage, the molecular test was correct. So that's a form of validation of the assay in unknown primary cancer.

A second way is to compare it simultaneously with immunohistochemical stains, one of the diagnostic testing that I mentioned earlier. And we've done that, and this was all published with the CancerTYPE ID. And the simultaneous use of immunohistochemistry when they can diagnose a specific cancer that's less than half the patients I mentioned earlier.

But when you do a molecular cancer classifier assay, in this case, the CancerTYPE ID, it's about 80% correlated with the same diagnosis. In other words, the molecular diagnosis 80% of the time is the same diagnosis as the immunohistochemistry. Another form of validation. This is published as well.

The third form of validation is when you do a molecular cancer classifier and it comes up with a specific diagnosis, you can go back and use the same tissue and do immunohistochemical stains to validate the molecular diagnosis. When we do that, once again, it's about 80% validated when you do it in that direction, using the molecular test first and then using the immunohistochemical stains to corroborate or validate or determine that the molecular test was indeed correct. So all three of those have been validated for the CancerTYPE ID test, and we need to see that for any test that says they can accurately come up with a specific diagnosis in unknown primary cancer.

**Jerome Madison:**

I appreciate you giving that a little bit more light because not only is it important for patients to understand how the diagnostics inform treatment, but it also affects the coverage and the reimbursement of that test as well.

**Dr. Tony Greco:**

It does. One of the things in medicine that we all want to avoid is having a test out there that claims to be accurate, that in fact, in the patient population we're talking about, is not accurate. We don't want that. That can lead to major issues and problems, treatment confusion, and many other problems. So we want tests that claim to be useful for patient diagnoses, particularly in this instance, but many others, to be accurate, to be relatively accurate. No test is perfect, but I'll take close to 90% accuracy in the patient population we're talking about. Any day is a useful test. That's what we have, for instance, with the CancerTYPE ID.

**Jerome Madison:**

Yeah. Agreed. Well, there's a lot of things that COVID has affected, Dr. Greco, with the practice, but how are you seeing the impact on these particular patients that you treat?

**Dr. Tony Greco:**

Yeah. I think it's similar to many other patients with known cancer types. I mean, COVID has literally paralyzed the medical system for a while. It's getting better now, but patients weren't coming in for their appointments from fear, and you understand that. They weren't getting treatment, they weren't having... Even when we had their tissues tested, many of them were afraid to come in. So the diagnostic facilities, many of them were requiring a COVID test before they allowed patients in to do scans on them, et cetera. So it's been a nightmare for many of us and for many reasons, but particularly for patients with cancers.

**Jerome Madison:**

Thank you for sharing that intimate look that a lot of times we don't see, and sharing your perspective from the position of the provider, the physician treating cancer patients. Dr. Tony Greco, medical oncologist at Tennessee Oncology. Hey, Dr. Greco, I realized COVID has shut down a lot of other things, including Vegas, one of your favorite places, I heard.

**Dr. Tony Greco:**

Yeah, I like to go fishing out there too, believe it or not. Lake Mead out there, it's a great fishing spot.

**Jerome Madison:**

Good stuff. Well, we appreciate you for bringing your insight into the treatment and the advances for treating cancers of unknown primary, and really helping us better understand the disease. Thank you for being a guest on the Precision Medicine Podcast.

**Dr. Tony Greco:**

Well, thank you very much for having me.

**Karan Cushman:**

You've been listening to the Precision Medicine Podcast, sponsored by Trapelo. Trapelo is the first clinical decision support tool to align the interests of oncologists, labs, and payers to give patients the best chance at beating cancer. To learn more, visit gettrapelo.com. To subscribe to the podcast or download transcripts of any episode, visit precisionmedicinepodcast.com. We invite you to join the conversation on social media. You can find us on Twitter, @PMPbyTrapelo, and on LinkedIn at the Trapelo company page. If you know someone who would enjoy the Precision Medicine Podcast, please share it. They'll thank you and so will we. We hope you'll tune in for the next episode.

**About Our Guest**

**Dr. F. Anthony Greco**

**Co-Founder, Sarah Cannon Research Institute, Medical Oncologist at Tennessee Oncology and Medical Advisor for Biotheranostics**

Dr. F. Anthony Greco was the Director of Medical Oncology and the Vanderbilt Cancer Center at Vanderbilt University Medical Center before becoming the Director of the Sarah Cannon Cancer Center and Co-Founder and Director of the Sarah Cannon Research Institute in Nashville, Tennessee. He created and co-directed the first, large community-based clinical research program outside of an academic setting. He is a Medical Oncologist at Tennessee Oncology, PLLC.

After finishing medical school at West Virginia University, Dr. Greco completed an internship at UCLA before returning to West Virginia University Medical Center for residency and completing a fellowship in medical oncology at the National Cancer Institute. He specializes in cancers of unknown primary, lung cancers, and germ line cancers and has authored over 650 publications.