**EPISODE SIX:**
Dr. Peter Beitsch, Part One:
Are Current Genetic Testing Guidelines Outdated?
A Game-Changing Study Proves the Need to Expand Breast Cancer Testing Guidelines

Dr. Peter Beitsch, Dallas Surgical Group, TME Breast Cancer Network | January 31, 2019*Welcome to* [*The Precision Medicine Podcast*](https://www.interventioninsights.com/precisionmedicinepodcast)*, 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.*

Jerome Madison: Hello, it's Jerome Madison, Vice President of Provider Relations at Trapelo,™ and one of the hosts of the Precision Medicine Podcast, and we recently got a chance to talk to Dr. Peter Beitsch, Chief Physician of the Dallas Surgical Group and an executive with the TME Breast Cancer Network. In our conversation, he had so many insightful things to share that it allowed us to create two podcasts.

 Our primary focus of the conversation was to discuss a recent paper published in the Journal of Clinical Oncology where Dr. Beitsch is the lead author, and this study is titled, *[Underdiagnosis of Hereditary Breast Cancer: Are Genetic Testing Guidelines a Tool Or an Obstacle?](http://ascopubs.org/doi/10.1200/JCO.18.01631)* Many have called the outcomes of the study potentially game-changing with respect to genetic-testing guidelines.

 So, today's podcast is part one of our interview with Dr. Beitsch, and we dive into just how the idea to evaluate the capability of NCCN testing guidelines came about and also his passion as a surgeon to improve outcomes using precision-medicine tools. So, we hope you learn as much as we did in part one, and please be on the lookout for part two in the coming weeks where he talks about taking the lead in precision medicine as a surgeon. Enjoy.

 Dr. Beitsch: We did a trial, we tried to work with many companies, but the industry that finally decided to work with us at TME Research was a company called Invitae out of the Bay Area, and they had multiple tests for pathogenic mutations and cancer. But along with BRCA1 and 2, the classic 11 that are really associated, they had a bigger panel up to 20 and they had a large panel. Their most expanded panel was 80 genes, and so we did a pilot trial with them looking at remote genetic counseling where that sounds like you're going to get the patients remotely genetic counseled. Well, actually it was for physicians who wanted to decide what test to order, or if they got a result back with a variant of unknown significance that they were worried about or if they found a pathogenic mutation that they didn't know how to handle, they would call into these genetic counselors at Invitae.

 Dr. Beitsch: So it's remote genetic counseling, but not for patients but for the physicians, and lo and behold, it turned out about a third of the time a physician either changed what test they ordered or how they handled the patient. So, it was very successful for physicians that (We had one physician in Anchorage, Alaska. There's one genetic counselor in all of Alaska. Hard to have precision medicine if you have one genetic counselor, right?) that's doing all the testing, so physicians have to do the testing and lo and behold, she went on maternity leave. So, there was zero, and so for her it was incredibly helpful.

 But even the physicians in Chicago area and across the country, you don't need help all the time, but sometimes physicians really need help sorting something out. So, that preliminary study was well received by both genetic-counseling community and the genetics community physicians. It got a lot of posters and presentations. In fact, at the National Consortium of Breast Centers, won the best oral presentation.

 So Invitae was excited to work with us, and I had been wanting to do a bigger study. I think we under-utilize genetic testing in all cancers, but certainly in breast cancer patients. And the guidelines that are out there—which is really the NCCN is the main one. There are others, but that's the main one—that insurance companies use to decide if they're going to cover the test or not were really established 20 years ago when we were testing for only genes, BRCA1 and 2, and the tests were quite expensive. They were $5,000 for two genes. The testing was incredibly laborious at the time, so it certainly warranted that kind of cost.

 But what the guidelines were really set up as was an economic roadblock, really, to stop testing and not test everybody. We want to have a 10% pathogenic-variant rate at least in the people that we test. So, we think if we get these group of patients and with these guidelines that we'll hit that, and they actually were pretty good. They probably did hit it about at 10-plus percent of the time for those two genes with those guidelines.

 But about five or six years ago, the Supreme Court in the landmark decision said you can't patent genes. So the BRC1 and 2 testing became way more widespread. At exactly the same time a new technique for genetic testing was developed. Well, probably developed well before that, but became commercialized, and it's called next-gen sequencing, and that made genetic testing of all kinds incredibly easier and faster and more economical.

 So, the guidelines were changing and they would add this and that, but what they ended up doing with the guidelines was making them so cumbersome and confusing that they really weren't utilized well. We were not testing everybody that qualified because the guidelines were so complicated. But we were also ... I felt that, it's kind of arbitrary that if you're 59, and you have a triple negative or basal kind of breast cancer, you meet the guidelines and should be genetically tested.

 Dr. Beitsch: Well if you're 59 and 11 months and 29 days and you wait over the weekend to go in and get diagnosed, so you're 60 years plus one day, you'd no longer qualify for testing. Well that's absurd on the face of it, right? So, I thought we should do a study and look at testing everybody, and so we developed a protocol and ran it through the IRB. Ended up with 20 sites across the country, and we looked at patients that met the NCCN guidelines. They're modified every year…these were the 2017 guidelines of NCCN. And then we compared those to a group of patients that did not meet the guidelines and did the expanded panel, 80 genes from Invitae.

 And, lo and behold, no statistically significant difference between those two groups, whether you met the guidelines and typically insurance would pay, or if you didn't meet the guidelines and typically insurance is not going to pay.

 So, at the end of the paper published this month in JCO, we concluded that all breast cancer patients should be tested. They took out my language, which is guidelines should be abolished for breast cancer patients. They thought that was too much, but yeah, they softened it. But the message is the same, and it has received a quite a bit of press. I know you picked up on it and had texted me a congratulatory text.

 So, it actually made the CNN online health coverage front page.

Jerome Madison: Incredible.

 Dr. Beitsch: It's been good, and I think it will make a major impact for women with breast cancer in the future. Hopefully now, the future being now.

 Sorry that was very long winded, but hopefully covered a lot of it.

Jerome Madison: No, it's quite all right. Quite a bit of information. I know that there's a lot of press you presented. Did you present this at the San Antonio Breast Cancer Symposium as well?

 Dr. Beitsch: Yes. So the study accumulated patients between really March of 2017 and April of 2018. The deadline for San Antonio abstract submission is early June. So in June of this year, a little over six months ago, we submitted an abstract to San Antonio Breast Cancer Symposium, and I kinda thought it would get an oral presentation. I've presented a couple things there in the past as orals, and I would have thought this was probably the best one I've ever submitted.

 Lo and behold, we just got a poster presentation, which I was a little disappointed in quite frankly, but interestingly enough, Journal of Clinical Oncology has an association with San Antonio where they'll publish the best presentations or studies that were presented at San Antonio simultaneously. So, one of the JCO issues in December is dedicated to San Antonio and the breast cancer world.

 Dr. Beitsch: Somebody at JCO picked up on our paper and suggested that we write a journal article. So, we submitted that and they liked it. They thought it was great. Said, "We're gonna put it in our December San Antonio Associated Journal." And, lo and behold, about two weeks later they said, "This has been really well received here at JCO. In fact, we're going to ask somebody to do an editorial on it too. An invited editorial." And that's only about 5% of JCO papers get a invited editorial, so we were really excited then. That really raised the bar.

 And then about another week later he said, "You know what? I think this deserves ..." The JCO said, "I think this deserves some press. So, this is going to be one of our feature articles that we're going to tweet about and really hammer out into the social media world." So, we were really excited. JCO did a great job of really getting it publicized.

 Now, you can imagine the NCCN was a little disgruntled. We love the NCCN. It really was not about hammering the NCCN. It was really about restrictive guidelines in general. I mean, it happened to be because we use the NCCN guidelines, but it's really about breaking that concept of do we need guidelines for breast cancer patients, and we just wanted to use the most accepted guidelines at the time, which are still the NCCN. And they do a tremendous job, actually an incredible job at treatment and the handle on the state-of-the-art cancer care in America, including breast cancer. But hopefully—and they took note of this. I mean they're physicians like we are and want to take good care of their patients like we do—I think they're hopefully going to change their guidelines based on our paper.

Jerome Madison: Well, when you look at the title of the paper, I mean it's pretty audacious, right? So the title of the JCO paper is Underdiagnosis of Hereditary Breast Cancer: Are Genetic Testing Guidelines a Tool Or an Obstacle, right? So when you have a title like that there are certainly detractors and people have opposing opinions. So, you have Dr. Jennifer Griggs and Kara Milliron from the University of Michigan Cancer Center and they wrote a related editorial arguing that widespread uptake of genetic testing would, I guess, "create challenges for patients and providers in the management of ambiguity." And that's just not the case in genetic testing. It's also genomics. What do you say to those who say, "Hey, pump the brakes a little bit before we start to consider all patients."

 Dr. Beitsch: Yeah. People that are in the old guard and in the hierarchy of that world don't like change, right? They like things the way they are. That doesn't mean they're necessarily right, and I think change is hard for people. They think that physicians and patients can't be educated to be able to handle ambiguity, and when they say ambiguity, they were talking about half the patients in our study: Of the 80 genes we tested at least half the patients had what's called VUS, or variant of unknown significance, VUS.

 Dr. Beitsch: And that means exactly what it says. If you have a standard gene, genes are long. They may be 2000-base pairs long. It's very, very common to have minor differences between my gene for BRCA and your gene for BRCA, but that doesn't mean that they are pathogenic. Meaning that my mutation causes breast cancer and your minor variant does not cause breast cancer or early prostate cancer in this case of men generally.

 Dr. Beitsch: They're just minor variations and in fact the vast majority of variants of unknown significance, 95-plus percent of them end up being benign. They're just minor, what we call single-nucleotide polymorphisms. There's just slight differences between the genes that make no difference in the function of the gene at all.

 Guess what? Physicians can handle that with a small amount of education. I don't even think it takes a large amount of education. You don't act on VUS’s. You don't do any patient treatment or certainly not surgery or anything based on a VUS. That's pretty easy. Straightforward. It takes about a five minute discussion with a physician before they can get it.

 Now, do patients freak out when they have a VUS? Well, if you explain to them that there are minor variants between my genes and your genes, guess what? I have, well a little bit of hair left, white hair and you have dark hair or in your case, no hair. Those are minor variations in our genes that cause me to lose my hair, and you to shave your head and to have difference in colors and eye color and those are all minor differences that don't make a big clinical difference. So, patients get it and widespread use of testing, these are still being tested at the moment. Well we'll get to things like 23andMe in a minute.

 But let's say in general, these are generally tests that physicians order on their patients. There were strong arguments back in the day about home pregnancy tests that women are going to find out they're pregnant and jump off bridges because they found out they're pregnant. They're not, they didn't. They can handle it. They understand the ramifications of testing. If they have questions they can ask their physicians, as they should. But right now they're not going to get the answer straight to them. Their physicians are going to get it and have a discussion with the patients.

 That does kind of bring up the 23andMe direct-to-consumer genetic testing, which I'm not opposed to either. Done well, I think it's fine. It goes beyond just saying I'm 23% Scandinavian and 16% Hispanic and whatever my mix is, it's not just about your genealogy. They can also importantly test for cancers. 23andMe is testing for a small number of genes that are associated with cancer. Not all of them. Part of understanding a 23andMe is if your test is negative for genetic mutations associated with cancer, it's a very small number of genes that they test. So, they're not out of the woods for all the genes that are associated with cancer.

 So, some of those things need to be understood, but people with a small amount of education can handle their own healthcare. I think the era of paternalism in medicine is waning, and people can handle it. The way I usually think of genomics is about the tumors, the cancers and genetics is about the person.

 Dr. Beitsch: So, people can handle genomic testing too. There are mutations that get targeted. People get that entirely. It's like when they do cultures for antibiotics and say, "Okay, these three antibiotics work and these seven don't." People understand that. "Well I need to take one of those three." Well genomics is kind of like that in cancers, and so people can understand that, and people can understand their genetics.

 We are entering an era shortly—and we may already be in it—where people are going to be getting their whole genome sequenced, and you're going to be basing their both preventive as well as treatment on their genes. Not all hypertension drugs work on everybody, and I have hypertension, and I'm on three drugs. I'm trying to figure out which ones are the best. I'm hoping—I've now done whole exome sequencing on myself, I haven't gotten it back yet—I'm hoping that that will help clarify what hypertension drugs I'm going to need that work best for me.

 What should I be looking for as far as my cancer risk, as far as those genes go? There's not a lot of cancer in my family, but there's some heart disease. Not a lot of heart disease, but my mother had a stroke. So, I'm hoping that in the near future we're going to be doing whole exome sequencing on people and that we're gonna not understand it all. Not even close, but the more we do it, the more we're going to understand.

 Geisinger right now has got 50,000 patients they've done whole exome sequencing on. One of the things they showed in their study was that just the two genes BRCA1 and BRCA2…the pathogenic mutation rate in their whole population just for those two cancer genes is three times higher than what we thought it was going to be.

 So, there are literally millions of men and women in this country that are at risk for cancer, and if we can identify those patients and get them in a screening program, if it's a high risk for prostate or a screening program if there is high risk for colon cancer—I mean this doesn't have to lead to bilateral mastectomies and taking your ovaries out or taking your colon out—but it can certainly lead to close observations of the things you need to be observed for.

 I think it's going to radically change how healthcare is done in this country, and that's coming sooner than later. And I appreciate Dr. Griggs and Milliron, I think that's how you say it. Their opinions, but genetic testing, it's not going to be blocked by them. Genetic testing is going to jump over them, and it's gonna probably leap over them. Genetic testing is not even going to look down upon them at all. As they say, "Stop, it's not happening!”: It's not stopping.

Jerome Madison: Well, I'll get you out of here on this. At Trapelo, we want to lead the conversation of how we pay for precision medicine to provide greater scale and access. So, how do you think that it would impact the healthcare spend in the U.S. if we broadened up those guidelines, those genetic testing guidelines. How do you think it would impact how do we pay for it?

 Dr. Beitsch: Yeah. So I've been fascinated with your new endeavor with Trapelo, and I think you fill a gap that has been sorely needed in this country, and that is picking the right test for the right patient and not having to duke it out with insurance companies to fight tooth and nail to get something that you know is a benefit for the patient in this precision medicine world that we're in.

 So, along with the genomics and precision medicine, a critical component of that, I believe, is going to be, along with the tumor genomics, it's the patient's genetic milieu. That can be something as simple as the way they process oral drug Tamoxifen, because it's a pro-drug and has to get to Endoxifen to be effective. And if you don't have the enzymes to do it, you can give all the Tamoxifen you want, and you won't get any benefit. So, that's called pharmacogenomics. That's important, but it's also something like figuring out if they have a BRCA1 mutation in a male with early prostate cancer, because they get different chemotherapy if they need chemotherapy.

 For women, they may get a PARP inhibitor if they get a breast cancer or an ovarian cancer and have a BRCA1 mutation. So, it can directly affect not just the hereditary components of genetic testing, but it may have directly affect their treatment for their cancer.

 So, genomics is critically important. Testing, doing the right markers, biomarkers, but also genetics is going to come right into that because you have to know, not always, but often have to know the genetic mutations that the patient begins with and then their genetics of how they metabolize things and their milieu of the treatment drugs in itself.

 I've heard recently about a company that's looking at tests with mitochondrial DNA and radiation sensitivity. So, yeah, genetics is changing everything. So, get ready. It's going to be a fun ride, but it may be a little bumpy along the way.

Jerome Madison: Well, Dr. Beitsch, I can't thank you enough for coming on and discussing the game-changing new paper that you've just had published and kind of the background. And thanks to all of our listeners, of course. We have Dr. Peter Beitsch of the Dallas Surgical Group and Target Medical Education. We hope you'll tune in for the next episode of the Precision Medicine Podcast and don't forget you can download full transcripts of today's episode at precisionmedicinepodcast.com. If you enjoyed this episode, you probably know someone else who would, so please tell them. They'll thank you, and so will we. Dr. Beitsch, it's been a great one.

 Dr. Beitsch: Thank you so much, Jerome.



**About Our Guest: Dr. Peter Beitsch, M.D.**

Dr. Beitsch went to medical school at University of Texas Southwestern Medical School in Dallas and finished his general surgery residency at Parkland Hospital in Dallas in 1993. He had a National Cancer Institute fellowship at M.D. Anderson Cancer Center from 1988-90. He completed his training with a surgical oncology fellowship at the John Wayne Cancer Institute in Santa Monica, California, where he trained with the fathers of sentinel lymph node biopsy, Donald Morton,MD and Armando Giuliano, MD. In 1994, he returned to private practice in Dallas where his practice is focused on melanoma and breast cancer.

He has held numerous positions in national surgical societies including at the American Society of Breast Surgeons. At the ASBrS, he was the first Chairman of the Membership Committee 2001-4, Program Director for the 2005 Annual Meeting in Los Angeles, Board of Directors Member from 2006-9 and 2012-15 as well as President of the Society 2013-14.

Dr. Beitsch has given numerous national and international presentations and is actively involved in breast cancer and melanoma research. He has major articles in peer-reviewed medical journals including the New England Journal of Medicine, the Journal of the American Medical Association, the Proceedings of the National Academy of Science, Journal of Clinical Oncology, and the Annals of Surgical Oncology.

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