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Testing Your Advanced Ovarian Cancer Patients for Homologous Recombination Deficiency

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Here's your host, Dr John Nakayama.

Chapter 1: Testing Your Ovarian Cancer Patients for Homologous Recombination Deficiency

Dr Nakayama:
Hello, you're listening to Ovarian Cancer Connect. I'm your host, Dr John Nakayama. This podcast is sponsored by AstraZeneca. Let's get started.

Hello and welcome. I'm Dr John Nakayama. Thank you for joining us for episode one in this podcast series, "HRD what, HRD why? Testing your ovarian cancer patients." In this series, we will discuss testing for homologous recombination deficiency, otherwise known as HRD, as well as why and how to test for this biomarker in your patients with advanced ovarian cancer.

According to major society guidelines, all patients with ovarian cancer should be tested for germline and somatic mutations. BRCA mutations are found in approximately 25% of patients with advanced ovarian cancer. However, further information could be obtained with additional testing. If you do an HRD test, you'll find that 50% of patients with advanced ovarian cancer have a deficiency. That's twice as many patients if you just test for BRCA alone.

Knowing the HRD status of advanced ovarian cancer patients can provide important prognostic information related to the biology of the tumor and guide important treatment decisions. It also helps ensure that patients are not missed in terms of appropriate targeted therapy, based on the outcome of the HRD test.

As of the end of 2021, there are four tests that measure some aspect of genomic instability. This includes FoundationOne CDx, Caris Molecular Intelligence, and Tempus xT testing, which all look at loss of heterozygosity, commonly referred to as LOH. Myriad myChoice measures LOH as well as other measures of genomic instability. It's a common misperception that ordering a gene panel test will include testing for HRD, so it's important to make sure that your test of choice, in fact, does. It's also important to note that HRD is clearly distinguished from other biomarkers found in gene panel testing. Some of these are tumor mutational burden, microsatellite instability, and PD-L1 testing, which do not influence homologous recombination deficiency.

In summary, not testing for HRD can result in missing important prognostic and predictive information that is critical to inform your treatment decision for patients with advanced ovarian cancer. Coming up in this podcast series, we'll discuss the practical aspects of genomic testing in your patients, including its purpose, how we have successfully implemented testing in our clinical practice and how we communicate the value of HRD testing to our patients. Thank you for joining us for these podcasts, and we hope that you will find this information useful in your clinical practice.

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Chapter 2: Evolution of Testing in Ovarian Cancer

Dr Nakayama:
Hello, you're listening to Ovarian Cancer Connect. I'm your host, Dr John Nakayama. This podcast is sponsored by AstraZeneca. Let's get started.

In episode two of this podcast series, “HRD what? HRD Why?” Testing Your Ovarian Cancer patients, we're going to be talking about the evolution of testing in Ovarian Cancer. I'm Dr John Nakayama. I'm joined today by Dr Alex Olawaiye and Dr Joshua Kesterson. Let's start off today's conversation by talking about how testing has changed ovarian cancer. Dr Kesterson, how has biomarker testing changed your practice in the last several years?

Dr Kersterson:
Great, thank you. That's a wonderful question, Dr Nakayama and I think a chance to highlight all the recent developments not only in ovarian cancer diagnostics but also in ovarian cancer therapeutics.

The steps made in diagnosis have been quite impressive over the last five to 10 years. You see this shift going from a histologic approach where you put samples in a category based on a pathologist recommendation to molecular approach where you know that there are multiple drivers that dictate tumor behavior and multiple points of attack, as far as therapeutic strategies that informs your treatment decisions. Previously, we didn't have this benefit and we also didn't have the benefit of different agents that could be made more precise in their attack on advanced ovarian cancer. But with the advent of different testing and newer treatment options, I think those things have both spurred each other's development. We went from a histologic approach to a biomarker driven diagnosis that could inform the prognosis and treatment implications going forward. So, I think that it's very empowering to the physicians, as well as to the patients.

Dr Nakayama:
I 100% agree. I feel like ovarian cancer is trying to catch up to some of the other cancers by becoming more personalized. Dr Olawaiye, how do you feel about testing? Does it change anything that you do? Does it change how you look at the patients? Does it change how you treat them?

Dr Olawaiye:
Information they say is power. The more information we can give to the patient about the process that is relevant to their disease condition, the more empowered they will be. So, that's the first thing. The second thing is testing itself. It's not just testing for information’s sake. It is testing that can be used to determine how we treat ovarian cancer and sometimes how the treatments are sequenced. So that is another very big impact that testing has brought to the table in advanced ovarian cancer treatment. Before there was a very small proportion of ovarian cancer patients who underwent genetic testing. In my experience, because of the new impact of testing on treatment decisions, a very large number of patients are getting tested. We want it to be a hundred percent, but we know it's not even close to that. But a much more significant number of people are getting tested.

Dr Nakayama:
That's totally right. We have to look for mutations in ovarian cancer. How does HRD testing stratify how you think about a patient?

Dr Kesterson:
I think anytime we talk about testing, we talk about germline testing or tissue testing for HRD, it's a way to go from the unknown to the known. And by acquiring more data points, we're able to make better decisions. With the advent of newer therapies and with data generated from large randomized controlled trials, we're able to determine the best therapy for the individual patient based on their biomarker status. So, we can see this as an evolution, not only in the diagnosis but also in the prognosis and the therapeutic treatment of patients with ovarian cancer. Additionally, I think every time we order these tests, we're adding to the database in our knowledge set regarding the optimal therapy for ovarian cancer patients.

Dr Olawaiye:

The more testing we do, the more we are going to find abnormalities. I am testing all ovarian cancer patients and that includes HRD testing.

Dr Nakayama:
I completely agree with you guys. This has been a great discussion. I hope you will join us for our next episode entitled, "HRD what? HRD why?" where we will discuss HRD testing and why it is so important.

Chapter 3: "HRD What? HRD Why?"

Dr Nakayama:
Hello, you're listening to Ovarian Cancer Connect. I'm your host, Dr John Nakayama. This podcast is sponsored by AstraZeneca. Let's get started.

Thank you for joining us for episode number three, titled, "HRD what? HRD why?" I'm joined today by Dr Alex Olawaiye and Dr Joshua Kesterson. I'm Dr John Nakayama, and today we're going to be talking about homologous recombination deficiency, otherwise known as HRD, and what exactly that means. I think there's a lot of confusion within the community about what is HRD, what do all these terms mean? Dr Olawaiye, can you help clear up some of this?

Dr Olawaiye:
HRD refers to a dysfunction of the homologous recombination DNA repair pathway as detected by a genetic testing or tumor testing for BRCA and for measures of HRD genomic instability, such as loss of heterozygosity, large-scale state transitions, and telomeric allelic imbalance. For a long time, we thought, for instance, in talking about cancer, that HRD only occurs with BRCA1 and BRCA2 genetic mutations. And now we know that it's not limited to just the BRCA1 and BRCA2 genes. So, HRD generally refers to a situation where, for whatever reason, the cell is no longer able to accomplish homologous recombination, a type of DNA damage repair.

Dr Nakayama:
So Alex, you and I do a lot of testing and we know what goes into it. I think there's some confusion out there by other things that may not be HRD testing. Are there any of those that come to mind?

Dr Olawaiye:
Yes, HRD testing must be distinguished very clearly from other tests like tumor mutation burden, microsatellite instability, PD-1, and PD-L1. Those are specific tests that are biologically defined in what they're testing for. They're not broad-based tests like HRD, and the utility of these tests are very different from the utility of HRD.

Dr Nakayama:
There are a variety of testing regimens and people are starting to use HRD testing in their practice. Dr Kesterson, I know you're on top of these things. Has HRD testing changed your practice? Do you feel like you've changed how you treat patients since all this came about?

Dr Kesterson:
Yeah, that's a great question, Dr Nakayama, regarding the clinical utility of HRD testing. And I think it offers an opportunity to kind of discuss what the clinical situation is for these patients and what they're going through. We know that a majority of ovarian cancer cases are diagnosed at an advanced stage. Initial treatment will consist of a combination of surgery and cytotoxic chemotherapy. And despite initial responses, unfortunately, majority of these women will ultimately recur. What we'd like to do is delay that recurrence as long as possible. And while I tell my patients, it's never obviously a good time to have ovarian cancer, certainly, it's better to be diagnosed now than it was even 10 years ago. And that's in large part driven by our ability to make therapeutic decisions based on biomarker status.

We know from clinical trials that approximately 50% of patients are HRD positive and are potentially going to be more receptive to treatment with PARP inhibitors.

So, I think in this setting, when we have additional data points that can guide not only prognosis but also therapeutic choices, it's incumbent upon us to make the best next choice of treatment for these patients so that we can optimize their outcomes.

Dr Nakayama:
I totally agree with you guys. This has been practice changing for me. I routinely test my patients for BRCA and HRD status. So that's HRD in a nutshell. Please join us for the podcast where we discuss the implementation of HRD testing. We hope that we provided you with some useful information on HRD testing today, and that you may be able to carry out some of these changes in your practice. Thanks so much for listening.

Chapter 4: To Test or Not to Test? How To Implement a Testing Flow in Your Practice

Dr Nakayama:
Hello, you're listening to Ovarian Cancer Connect. I'm your host, Dr John Nakayama. This podcast is sponsored by AstraZeneca. Let's get started.

Welcome to episode four of the podcast series, “HRD what, HRD why?” In this episode, we'll be talking about suggestions of how to implement a testing flow in your practice. I'm Dr John Nakayama, and I'm joined today by Dr Alex Olawaiye and Dr Joshua Kesterson.

In my situation, things have changed radically with the implementation of new maintenance strategies. I am aggressive about how patients with advanced ovarian cancer set up genetic testing for germline BRCA mutations and HRD tissue testing. At every patient appointment, I have my EMR software set up to remind me to ask whether patients have received genetic counseling or had genetic testing during their appointments. This ensures that patients understand the importance of testing and gives them the opportunity to have the testing done at the earliest possible opportunity. Dr Olawaiye, you practice at a large university health system in Pittsburgh. What's your process for making sure that patients get adequate testing?

Dr Olawaiye:
Thank you, Dr Nakayama. This is a very important question. Here at the University of Pittsburgh, we have a pathway that actually simplifies the process. In the pathway, both genetic and HRD tissue testing are incorporated. The way it works is when you are going through the process of determining the treatment for the patient or the pathway, there is a specific order that comes up and asks if the patient has been tested. If the answer is no, then you are asked when will the patient be tested? That helps to bring it to your attention and encourages you to do it early.

Dr Nakayama:
Do you get HRD and genetic testing prompts, or is it just for the genetics?

Dr Olawaiye:
You're prompted to do genetic test for germline BRCA mutations first. Once you document that the test is negative, it will then prompt you about HRD tissue testing. If the patient is not being treated by me, not going through the pathway and is referred to a medical oncologist, I will give my instructions for testing along with the referral. Sometimes the medical oncologist will tell me that they don't have the resources for testing in their office and ask if we can help the patient and do the testing in Pittsburgh. It's very important to communicate my instructions to the medical oncologist and what I think is the appropriate standard. Is important that we establish a two-way relationship to ensure that the medical oncologist has a process in place so that the patient receives the necessary genetic and HRD tissue testing.

Dr Nakayama:
Thank you, Dr Olawaiye for sharing your experience to encourage communication regarding genetic and HRD testing with medical oncologists. Dr Kesterson, you practice in Central Pennsylvania. I'd like to ask you to tell us, in your area and in your practice, what the challenges might be that is different from Dr Olawaiye's?

Dr Kesterson:
Thank you, Dr Nakayama. That's a great question. For frame of reference, I practice in an area that I wouldn't entirely call rural but is less densely populated than what you would see in Pittsburgh and the surrounding areas. With that comes a large geographical area from which we receive patients, meaning we have multiple different hospital systems, multiple different providers, and multiple different electronic medical records. The concern is that things get too fragmented, especially when patients are being treated closer to home by a medical oncology colleague who may operate in a different clinic or in a different hospital system. You both have mentioned pathways, and what resonates with me is more of a checklist, if you will. We have a universal checklist for ovarian cancer patients who will get genetic testing, homologous recombination deficiency testing and whether that’s done at our institution or an outside the institution, we make sure that we have those results on file so we can appropriately quarterback that care amongst multiple providers who may be at different institutions and different sites.

While it is a little bit more cumbersome than having a universal electronic medical record, the benefit we do have with a universal checklist, including HRD testing, to work with medical oncologists is to avoid anything slipping through the cracks. This allows us to have all the data points that we need in order to ensure the optimal treatment for the patient. One thing we have is the opportunity to see the patient as well as their tissue, where the medical oncologist, for the most part, sees the patient. This may seem a little bit simplistic, but I think it's incredibly impactful how we treat these patients, and it's a way we can use to educate the medical oncologist to test the tissue

as well.

Dr Nakayama:
Thank you, Dr Kesterson and Dr Olawaiye. I think the take-home point from this discussion is that having a genetic and HRD tissue testing process, whatever that process may be, is to make sure the testing is available at the time when it is critical to make treatment decisions, whether you're a gynecologic oncologist or a medical oncologist. Thank you for joining us in our discussion of the actual implementation of a testing system. We hope this has proved useful information for you to consider for your practice, but please don't leave and join us for the next episode where we'll discuss talking with your patient about testing.

Chapter 5: Talking With Your Patient About Testing

Dr Nakayama:
Hello, you're listening to Ovarian Cancer Connect. I'm your host, Dr John Nakayama. This podcast is sponsored by AstraZeneca. Let's get started.

Welcome to episode five, “Talking With Your Patient About Testing.” In this podcast series, entitled, “HRD What? HRD Why? Testing Your Ovarian Cancer Patients.” I'm Dr John Nakayama joined today by Dr Alex Olawaiye and Dr Joshua Kesterson. In previous chapters, we talked about the importance of biomarker testing, including HRD testing. But what does that actually sound like when you talk to a patient? Dr Kesterson, I'm one of your patients you just finished my surgery. Of course, you did a fabulous job. You took out all my cancer, I'm ready to start chemo, but I don't understand what all this genetic and biomarker testing is. What do you tell me so that I really understand what's happening?

Dr Kesterson:
Thank you, Dr Nakayama, and this is a great opportunity to kind of level set with patients and explain to them where they are in the treatment landscape as an individual, as well as in the greater population. I explain to patients that there's greater than 20,000 cases of ovarian cancer each year in the United States. And then a majority are diagnosed at an advanced stage. And the symptoms they've been having up to this point are vague in nature and hopefully this lets them know that they're not in this alone and that they can relieve themselves of any guilt they may feel for being diagnosed at a quote advanced stage or not recognizing symptoms earlier.

I talk to them about the pathology or how the diagnosis was made and discuss the most common types and relay to them that while a majority of ovarian cancers are what I call due to bad luck, about a fourth of them are due to a genetic predisposition where you've inherited something in your DNA from one or both of your parents that put you in increased risk of ovarian cancer.

After this, I think we start looking for what I would call actionable items. A couple of those actionable items that I think all patients should be tested for are genetic testing. Specifically, and more frequently looking for a BRCA mutation.

Another action item that we want to look for is homologous recombination deficiency status. We know that certain populations specifically those that are HRD positive are more likely to respond to therapy with PARP inhibition. So, with these different data points, I think you can appreciate how we're able to individualize patient care and optimize outcomes.

Dr Nakayama:
I think Dr Kesterson totally hit it on the head there. Now, I would've been convinced to get genetic testing with that, but Dr Olawaiye, there's going to be the skeptical patient. There's going to be the patient that says, "Explain to me why exactly I have to do this?" How do you talk to that patient, Dr Olawaiye?

Dr Olawaiye:
Thank you, Dr Nakayama. One has to appreciate that when patients are going through ovarian cancer treatment in the specific scenarios that we're talking about, a lot of information, and a lot of things have been thrown at them. So, it's not uncommon for them to want to object to some of those things because let's face it, as human beings, these situations can be overwhelming. So, there are two types of common objections that patients can have. One is objection to the process of testing itself, ie, "Why should I have this one more test considering all the other tests that you've done on me?"

They might say, "Do I really need to have another test?" The second is "Am I going to pay for this test out of pocket?" I will start with the first one, which is an objection to testing. My approach is to explain very gently to them the benefits of the testing and the fact that it is going to help me to partner with them in making treatment decisions. If you carry a genetic mutation, this testing can be a huge advantage to your family, especially your first-degree relatives, because they may have the same genetic mutation and this might give them an opportunity to protect themselves.

Regarding the last objection, which is whether they're going to pay out of their pockets, I always tell them that in my experience, most insurance companies, if not all of them, cover this testing, so I suspect yours will too. However, before we do the test, I would have my staff check that your insurance is going to pay for it and we will let you know if there is going to be any financial implications so that you can make an informed choice.

Dr Nakayama:
I think this is a super discussion, guys. I think you had some really important points and I think this will help a lot of people decide how best to talk to their patients.

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