Expanding the Reach of Precision Medicine
Dr. Bruce Johnson

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Jerome Madison: Thank you for joining another episode of the Precision Medicine podcast. I'm Jerome Madison, Vice President at Trapelo, and today we're happy to have Dr. Bruce Johnson, Chief Clinical Research Officer from the Dana Farber Cancer Institute. Dr. Johnson, thank you for being a guest on the podcast.

Dr. Johnson: Good morning. It's great to be able to join you.

Jerome Madison: Absolutely. Now, you are also a past president of the American Society of Clinical Oncology (ASCO), his team chose . At this year's ASCO, you were the immediate past president. And you were also the co-executive editor of the Clinical Cancer Advances 2019. And precision medicine was at the heart of many of the medical advances talked about at ASCO.

Jerome Madison: But, with you being the Chair, you and your team named treating rare cancers as the advance of the year. And in digging into that, it's pretty phenomenal, the advances that were made in the different areas. But can you talk a little bit about, maybe those five areas? And why your committee named treating rare cancer as the advance of the year?

Dr. Johnson: So, I want to take on the issue of treating rare cancers as a grouping together of a number of different things that came together. You mentioned precision medicine. So, when I was president for the 2018 ASCO meeting in Chicago, we picked the theme, “Delivering Discoveries, Expanding the Reach of Precision Medicine.” And when we talk about expanding the reach of precision medicine, we mean it two-fold.

Dr. Johnson: Number one is being able to apply the principles of precision medicine to more tumors, number one. And number two is making it so more of the practitioners of oncology can be able to use precision medicine in treating their patients. So not only in the academic centers, but also people who deliver the care in the majority of settings, which is people in community practice.

Dr. Johnson: So, we picked this for several reasons. And the reasons why this came together is the more widespread availability of being able to target and genomically characterize these small tumors. Number one. And then number two is that, particularly federally funded studies, where they go after unusual types of cancers, are being able to study them on prospective clinical trials. And therefore we highlighted five different studies of rare tumors. Now rare tumors are defined in the National Cancer Institute as less than 15 out of 100,000 patients. So that works out to be about three or 4,000 people in the U.S. a year. So, that's what a rare cancer is.

Dr. Johnson: And going through them, it picked a wide variety of ones. Number one is, and the one that I think illustrates it very well is being able to treat anaplastic thyroid cancer. Once again, this fits the criteria: It's rare. And number two, a subset of those have a mutation of something called BRAF, and BRAF is mutated in a large number of different tumors. The ones where it was initially approved is the majority of patients with melanomas have these BRAF mutations, and they found out that if you give a combination of agents blocking the pathway in two different ways, Dabrafenib and Trametnib, you can get response in the majority of people.

Dr. Johnson: And when they applied this in the subset of anaplastic thyroid cancers, and it turns out it was only 16 patients who had this BRAF mutation, they were able to get responses of about 70%. And this particular disease is pretty deadly, and this really changed the nature of it. We get down to several other unusual tumors— of desmoid tumors, which is pretty unusual—HER2 positive uterine cancer, and a giant cell synovial tumor.

Dr. Johnson: So, all these are unusual, and all of them were able to come up with targeted agents for them to be approved. One of the things that is important about this is it's difficult for commercial companies to go after getting approvals in these, because the payoff is relatively small. So, this rather dramatically shows how important it is to have federal research for these relatively unusual tumors.

Jerome Madison: So, Dr. Johnson, with rare tumors, you're talking about the number being six out of 100,000, I think the number was, which is certainly rare, but there's a lot of them. It's been the cumulative progress. How many cases of profiling these tumors does it take to get this type of data, that you guys were able to obtain over the last year?

Dr. Johnson: Well, to give an idea, for the anaplastic thyroid cancers, you end up having to profile 100 to find 16 that have the mutants. So, this is a relatively rare event. The other thing that happens is that there's some national programs that allow you to match unusual tumors.

Dr. Johnson: There's one that's run through ASCO, that's called TAPUR, and this matches unusual genomic changes to unusual. And drugs that are used for relatively rare indications. So, as an example, if you have a BRAF mutation, which can take place in lung cancer, colon cancer, anaplastic thyroid cancer, and even unusual tumors, and it will match those up and allow you to get access to the drugs.

Dr. Johnson: There's a second program called MATCH, which is run by the National Cancer Institute. And this one allows people to send in patients tumors and characterize them for unusual genomic changes, and then allow them to be matched with drugs. Typically, these are drugs that have been approved for another indication and are more widely available, so that you don't have to do toxicity testing. And this has been able to expand the reach of precision medicine.

Jerome Madison: So, I also heard you speak down at FLASCO, where you were the opening keynote speaker, and you gave a fantastic talk on, I think it was entitled, Personalized Medicine Now and Into the Future. And you used the word there, in your talk, you may not remember this, it's been a few nights ago, but you used the word, when talking about treating cancer, chronic disease. And that's something that Dr. Vincent Devita used years and years ago when talking about the approach to curing cancer or at least to making strides in cancer.

Jerome Madison: What have been some of the factors that has helped, for instance, non-small lung cancer evolve from a…what is being referred to or being perceived at one time as a terminal prognosis to now the possibility of treating it as a chronic disease?

Dr. Johnson: I'd like to talk about this as kind of a reordered process. And that is where you discover a target that you can potentially give drugs for. And there's two good examples of that. One is the epidermal growth factor receptor mutation, and the second is an anaplastic lymphoma kinase rearrangement.

Dr. Johnson: So, we discovered about 15 years ago that you could have a genomic change in the epidermal growth factor receptor that allowed you to give one of the agents targeting that receptor both Gefitinib and Erlotinib. And in those patients, the drug worked for about 10 to 11 months, before the cancer started to regrow again, on average. And by biopsying the tumors after it became resistant, you could find the principle mechanisms of resistance and then develop drugs that were effective against the resistant ones and then retest it.

Dr. Johnson: So, one of the great paradigms of that is that by finding the drug that worked, which—and one of the leading examples is Osimertinib, it works when Erlotinib and Tarceva quit working, about 60% of the time—when you use that drug up front, you nearly double the length of time the drug works. So, for instance, instead of working for about 10 or 11 months, Osimertinib works for about 19 months. So you come close to doubling the length of time. And that puts the patients in for years, and even after they've finished the targeted therapy, they can go on to conventional chemotherapy or immunotherapy.

Dr. Johnson: For the anaplastic lymphoma kinase rearrangements it's even more dramatic. Where the initial drug that was approved for that particular target lung cancer, the drug worked for about 10 months, and when they developed a drug that worked, when it became resistant to Crizotinib, Alectinib, that one can work for approximately three years. So, it goes from less than a year to three years with a new and more effective drug.

Dr. Johnson: There's a couple of other genomic changes for which there are FDA-approved agents. One is Crizotinib for ROS1 rearrangements, it works for about a year and a half. And then for BRAF. There's the combination of Dabrafenib and Trametinib, that works in melanoma, and that can work for approximately 11 months.

Dr. Johnson: The good news is that as in melanoma, there is a subset of patients, all be it less than half, where it can go on for years. So, these are all very encouraging results in lung cancer. The future of this is that we anticipate that we'll continue defining the mechanisms of resistance, make drugs that work after the initial agent works, and come up with agents that are both more potent and more specific, that work for years rather than a matter of months.

Jerome Madison: Yeah. We recently spoke to Dr. Jack West, and he was excited about the outcomes and market demand for immunotherapy. What do you attribute…when you are talking about these therapies that have doubled and tripled the survival for non-small cell lung cancers…but what do you attribute the durable responses of the immunotherapy to, even after they come off therapy they continue to respond?

Dr. Johnson: One of the things I'd like to talk about first is how immunotherapy has changed our field. And just before, you were talking about making this a chronic disease. One of the things that I thought I may never live to see is attempting to cure patients with advanced disease, with advanced non-small cell lung cancer. And one of the things that's been reported in the last year is a five-year outcome data with two of the immunotherapy drugs, Nivolumab and Pembrolizumab. So in 2018 Dr. Scott Gettinger reported that 16% of the patients with lung cancer, when on the initial dose finding trials for Nivolumab, were alive at five years.

Dr. Johnson: There was 129 patients. And of those 16 patients who were still alive at five years, 12 of them did not get any therapy after coming off. So here are patients who are surviving five years. We're guardedly optimistic in calling these patients cures, and it may change the face of this.

Dr. Johnson: Now, the second drug that's approved in subsets of non-small cell lung cancer is Pembrolizumab. And they reported the five-year data in The Journal of Clinical Oncology showing that about 23% were alive at five years. And this was a much larger group of more than 500 patients. And there was a subset that you could identify ahead of time with the leading marker PD-L1, where if you had a marker of 50% or more of your tumor cells were positive for this, which makes up about 20 to 30% of all lung cancer patients, you can end up seeing that about a quarter of them are alive at five years. And for me, personally, I've been able to see this in some of my patients, where they have complete responses and you're able to take them off therapy after two years.

Jerome Madison: Phenomenal. What is the role of gene sequencing in immunotherapies? Because there are certainly some that don't require for you to even test.

Dr. Johnson: Yeah. One of the things that we've been studying, and one of the things that's imperfect is that marker that I just mentioned, PD-L1. And that is that there are people who don't have the marker who respond rather dramatically, and there's also people who have very high levels of the marker who don't respond. So, it's an imperfect predictive biomarker for efficacy.

Dr. Johnson: One of the other leading predictive markers is tumor mutation burden, and this measures the numbers of mutations that are present in the patient's tumor, and in general the higher the number of mutations, the more likely the person is to respond and respond for a longer time. One of the things that makes this helpful to patients with lung cancer is that the patients who are more likely to have those genomic changes that have effective targeted agents are principally that people who are nonsmokers or haven't smoked very much.

Dr. Johnson: Now, one of the things that I tell my patients is that when you're a potential candidate for immunotherapy, it's one of the few times it's probably good to have smoked. And that is because that group of patients has more mutations and is more likely to respond. And one of the things we've learned is that one of the predictive markers is that the more you smoke, the more likely you are to respond to the treatment. So, it's sort of two different groups. One is the patients who are likely to get targeted treatments who have these mutations in the never or light smokers. And then in the heavier smokers it looks like the immunotherapy works better in those groups.

Jerome Madison: Talking to clinicians over the years, and I've been in the genomic clinical lab space for the last almost 20 years, I guess, the technology has changed. But the mindsets of those who are pro broad-based large panel or even whole genome sequencing versus those who say, "You only need a few." And I've heard you say in one of your talks that most clinicians only need 20 to 40 genes to manage the lifespan of a cancer patient. But can you explain, and what do you think the value of large or broad-based genome sequencing is? Versus using smaller, more targeted gene panels to approach treating cancer patients?

Dr. Johnson: Let me comment on the panels that have large numbers, and give you some examples. Of the academic centers, for instance, for both us and for Memorial Sloan Kettering, and when I say us, it's the Brigham and Women's hospital and the Dana Farber Cancer Institute. We use a panel of more than 300 genes, as does two commercial providers, Foundation Medicine and Karus. And these folks will take a look at several hundred genes, as do Memorial and the Brigham Women's hospital and Dana Farber.

Dr. Johnson: Now, we do it for both clinical reasons as well as for research purposes. Now it turns out, and this was just published in JCO Precision Medicine, that you can end up getting a panel of greater than five gene tests for less money, more quickly, and use the large panel instead of doing individual tests. Now, it turns out that if you take a look at all the FDA-approved agents for specific genomic targets, it turns out there's only about 20 to 40. Now, for those of us who are doing research, it becomes important to know why sometimes it works well and sometimes it doesn't work as well.

Dr. Johnson: For instance, with the common tumor suppressor gene P53, that gene, if it's mutated, it turns out that it seems that the EGFR mutants will respond for a shorter period of time, but it still doesn't influence whether you are or are not going to give the EGFR inhibitor. And, so, that becomes pretty important. Now, one of the things that you mentioned before is the predictive marker of tumor mutation burden. And there you have to have a broader sequencing to generate a reliable number, and that's potentially helpful for determining this.

Dr. Johnson: Now, one of the things that we obviously think is the case is that we haven't discovered all the genes that you can target. And so, therefore, you never know what's going to happen coming up. And it's difficult to go back and re-sequence them. So we have firmly believed in trying to, for both our clinical purposes as well as research purposes, that we want to know as many genes that are related to cancer as possible, and therefore we do these large panels.

Dr. Johnson: Coming back to the issue about practicing clinicians, it becomes very difficult to interpret this. And one of the things that ASCO, as well as other decision-support groups want to help people make decisions based on the genomic findings. So, for instance, it may be that not everybody out in clinical practice, who doesn't deal with this every day should give Alectinib for the ALK rearrangements. They may think it should be Crizotinib where Alectinib can work three times longer. And, so, we think a shortcoming really is the decision support.

Jerome Madison: On that note, that's something that certainly we here at Trapelo want to lead the conversation about utilization management and also provide some transparency in bringing the payer into the conversation. So, we always ask people this kind of on the way out. As precision medicine grows, what are the pitfalls, or the opportunities that you see, that we can make this routine and pay for it?

Dr. Johnson: Well, interestingly when we did our initial budgeting for setting up and genotyping the majority of our patients who have advanced cancer, we believe that within several years both the governmental as well as the commercial payers would think this was an important thing to do for nearly all the patients, and it would be covered. It's been a much longer discussion than we initially anticipated.

Dr. Johnson: We negotiate with our payers to get this covered for the appropriate tumors. And one of the things that we have been trying to teach people, and one of the things we've learned from our payers is that they would like to have some control, that you would have one broad panel and not keep ordering one test after the other, or having multiple providers ordering similar tests. And so we work with them, and we continue to try to generate evidence that this can really transform the care of patients. And we've published some information in The Journal of American Medical Association on the lung cancer mutation consortium showing better outcomes. And we're attempting to generate additional information here within our center.

Jerome Madison: Dr. Bruce Johnson, Chief Clinical Research Officer from the Dana Farber Cancer Institute. Well Dr. Johnson, with the year ahead, two years ago you were president of ASCO, and last year you certainly served ASCO as the co-executive director of the Clinical Cancer Advances. My goodness, what's this year? Vacation?

Dr. Johnson: Well, it's a wonderful opportunity to have a worked at the national level for organization, and something I really enjoy. I'm also the head of precision medicine here at the Dana Farber Cancer Institute. So, there's a lot to be done about all the things that we've talked about, and if I can help make it so that this is more readily available to a broader range of cancer providers, I'll be very happy.

Jerome Madison: Well, we certainly appreciate your efforts, and your leadership in the field for moving precision medicine forward, and especially for being here as a guest on The Precision Medicine podcast. Thank you.

Dr. Johnson: Okay, thank you.

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**About Our Guest: Bruce E. Johnson, M.D., FASCO**
Dana Farber Cancer Institute

Dr. Johnson is the Chief Clinical Research Officer and Director of the Center for Cancer Precision Medicine at the Dana-Farber Cancer Institute. He is a Professor of Medicine at Harvard Medical School and an Institute Physician at the Dana-Farber Cancer Institute and Brigham and Women’s Hospital.

Dr. Johnson was one of the scientists who discovered the association between epidermal growth factor receptor mutations and response to epidermal growth factor receptor-tyrosine kinase inhibitors. His research is devoted to testing novel therapeutic agents for their efficacy against lung cancer and other thoracic malignancies.

Dr. Johnson served on the American Society of Clinical Oncology (ASCO) Board of Directors (2008-2011), received the ASCO Cancer Foundation’s Translational Research Professorship in 2008, and was selected as an ASCO Fellow in 2012. ASCO elected Dr. Johnson so serve as its President for the 2017-2018 term, and he served as Immediate Past President for 2018-2019.

In 2018 Dr. Johnson was selected as the Giant of Cancer Care® in Lung Cancer, which recognizes physicians “who have made significant contributions to the cure and treatment of those living with cancer”. Dr. Johnson was chosen as a member of the American Association of Physicians in 2015. He was also awarded the International Association for the Study of Lung Cancer (IASLC) 2010 Scientific Award for his “life-time scientific contribution in thoracic malignancy research.” Dr. Johnson was one of the leaders of the team awarded the American Association for Cancer Research (AACR) 2010 Team Science Award, recognizing an “outstanding interdisciplinary research team for its innovative and meritorious science that has advanced or likely will advance our fundamental knowledge of cancer.”

Dr. Johnson received his Doctor of Medicine from the University of Minnesota and did postgraduate training at the University of Chicago and the National Cancer Institute. He came to the Lowe Center at Dana-Farber in 1998 after serving for six years as the head of the Lung Cancer Biology section of the National Cancer Institute’s Medicine Branch.