Precision Medicine Podcast, Season 3, Episode 49

Janine Morales, PhD, On Applying Precision Medicine More Strategically With Molecular Testing

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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:

Welcome to another episode of the Precision Medicine Podcast. I'm Jerome Madison. And today we have Janine Morales, Senior Director of Clinical Knowledge Systems for Trapelo Health. Janine, thank you for being a guest on the podcast.

Janine Morales:

Hi, Jerome. Thank you for having me, it's a pleasure to be here.

Jerome Madison:

I selfishly learn a lot from you Janine, so it's really a high point for me to actually get you on the podcast. We kid you all the time that we're going to chase you around with a recorder and just listen to the things that you say because you give so many nuggets, but for our audience, will you tell us a little bit about your professional background and your journey to Trapelo Health?

Janine Morales:

Sure, I'd be happy to. So I've been at Trapelo Health for going on nine years now. The beginning of my career, I started as a basic scientist, so I have my PhD in pharmacology. And most of the work or the research I did was using the tools of biochemistry and cell biology to understand cellular signaling processes, those internal controls that manage behavior of a cell, it's growth or migration. And of course, a lot of these discoveries in this area can attribute many new cancer treatments to the great strides made in cellular signaling. So I actually take no credit for that personally, because to be honest, I probably wasn't a great bench scientist, I found it wholly unsatisfying to focus on one very specific scientific question. And even as a student, I would prefer to go to seminars and hear about the breadth of things that were going on.

Janine Morales:

And as a postdoc, I jumped over to immunology, and was considering another jump, and realized this isn't perhaps the path, or I'm not really building the foundation for a career as a research scientist. And frankly, I had to admit to myself that I wasn't really interested in that. On the other hand, I love biology and science, and that's where my heart is. And I'm completely fascinated by

how basic research at the molecular level was at the time, was beginning to make its way into patient care, of course in this burgeoning field of translational medicine. And additionally, I think I've always had this sense that scientific developments were outpacing our ability to relay these findings to those around us, be it clinicians or patients. And so I was seeing a niche for myself there, which is to look at the bigger picture and help, not just for my own edification, but to bring it to others in the field.

Janine Morales:

So if we look at translational medicine, how do we translate these new approaches, these new discoveries to clinical care, and these new interventions that are driven by biology, to those that are using it so they feel comfortable with these new options? And that's where I've chosen to focus my career. I initially, after my training, I went in and worked for a company called Bio.com and, and worked a lot in the biotechnology space, and bringing new developments to... Also through webinars at the time early, early podcasts that were happening in the '90s. And then for the last about 15 years, my focus has been on cancer.

Jerome Madison:

There are many who have definitions of precision medicine, Janine. From your perspective, how would you define it? What is precision medicine?

Janine Morales:

Yeah, I hope I can provide a perspective that that brings something new to it. But I think if we take as a starting point, that human diseases are disorders in biology, and that the biology of each individual is unique, I think that precision medicine is founded on that. And it's really not only a way of treating patients, it's a process, right? We're using that knowledge of the biology to both develop new drugs, and then once those drugs are available, we use the unique characteristics of the patient to choose the best drugs to use. And the assumption is that tailoring treatments to a patient's unique characteristics can improve outcomes. So in cancer at least, some like to boil down precision medicine, or it often has been boiled down to using genomic or molecular information of a patient to choose the optimal treatment. So I guess that's where I would start as a definition of precision medicine.

Jerome Madison:

Is this applicable to other diseases?

Janine Morales:

Certainly. I don't see any reason that this concept couldn't be applied to other disease states. I mean, I think certainly everyone would agree that not just cancer, but that all diseases are driven by the biology. And if you look at things like autoimmune diseases, these are biologically really complex and highly heterogeneous diseases. And right now there's a lot going on to figure out how do we better diagnose those subtypes of autoimmune diseases; how do we use molecular information to get a sense of the prognosis of the patient? And ultimately, I think, moving towards, as we are in cancer care, using it to predict treatment response, maybe in other cases like infectious diseases. If we take just the COVID pandemic, for example, what's driving the tremendous variability in responses to infection. And I think we're going to learn a lot about the biology behind that.

Janine Morales:

Some of it's going to be related to the overall health of the patients, and some might be related to underlying genetics of the individual. And in the future, perhaps we'll know more about how better to either prevent those infections or treat them. Again, I guess I don't want to oversimplify precision medicine, or I think there's a lot in the field that is somewhat aspirational. And I think we want to be really precise about the way we talk about precision medicine's value, I think it all makes great sense. And in some cases, we've seen real success in applying these precise measurements to tailor treatments. But I think all of these applications still require an evidence-based assessment on how well that genomic information really leads to or predicts the likelihood of response or benefit to an intervention. And I think to some degree that's getting more complicated in the space of precision medicine, both...

I mean, I think some of the things like immune diseases, infectious diseases, those are early, but in cancer even, we've had 15, 20 years behind us now, it's getting complicated I think, to apply precision medicine precisely.

Jerome Madison:

Yeah. Well, you mentioned all the time, and this is something that Clint Taylor talks about, the complexity. I mean, there's complexity in how we discover what to test or just, there's complexities as the information starts to grow, but then there's complexities about individual targets in genetics. Can you talk about some specific examples of, let's say targets or the complexities that we have to face, because you've mentioned in the past that we tend to think of gene match as binary, but that level of certainty is not always there. Can you talk about some examples?

Janine Morales:

Yeah, I'd be happy to. Well one, I don't want to diminish the value of precision medicine or molecular testing, it's here to stay. I think it's a really important part of choosing the right treatment for patients, and in some cancer types it begins with a molecular test. I think that that will only broaden the application of molecular testing in cancer. And for some of those molecular aberrations, the relationship to therapy is pretty clear, and things like ALK rearrangements and RET fusions, there's such strong biology, really robust response rates across, well, at least an NTRK across multiple tumor types, and frankly in ALK, not only in lung cancer, but other tumor types. I'm not sure that's necessarily the future of precision medicine, that we're just going to see a string of single-gene targets with these levels, these types of response rates.

And I think that there've been some approvals recently that give access to broad sets of patients, which I think is great, but the precise utilization of those therapies is maybe less clear cut. So I saw an interesting study recently, it was published in the Annals of Oncology, I believe. And there are caveats and confounding issues to the study, but I think it just highlighted a trend that I'm not surprised about. And one is... Or that is that... So the study looked up the percentage of US cancer patients that were eligible for and respond to a genome targeted therapy. And they looked over a period of time, I think it was 2005 or 2006 to 2020. And the trend they saw is that most of the increase in eligibility, meaning more patients have access to a genome targeted therapy. Most of that increase in eligibility was seen after 2018, so rather recently, while most of the increase in response rates were seen prior to 2018.

Janine Morales:

And I think that that's not entirely surprising, and I don't want to overstate that. I think it's one study that is complicated, you don't want to overgeneralize, but I think that in some ways I'm not surprised by that given some of the recent approvals. Some recent approvals, I think require a deeper understanding of the details of those studies in order to utilize the drugs in a way that really optimizes patient care. I think unlike, again, you have an ALK rearrangement, you're a lung cancer patient, you kind of understand the relationship to therapies there, I think some of these new approvals are less clear.

Jerome Madison:

Are there particular examples that stand out in your mind?

Janine Morales:

Yeah, there are a couple of recent examples that maybe speak to this greater access that more patients are now eligible for, a genome-driven therapy. One that comes to mind is tumor mutational burden. So a tumor mutational burden is you're assessing the number of mutations or the amount of mutations in the DNA in the cancer's DNA, so the somatic mutations. And there's lots of data that has shown that there's a relationship between a higher mutational burden and response to checkpoint inhibitors. And one checkpoint inhibitor was recently approved for patients who have a mutational burden of higher than 10 mutations per megabase. So great, all patients with solid tumors have the potential to benefit from immunotherapy, there is some path to that.

I think the complexity comes when you look at the details of the study, and the study that led to the approval, as well as other studies. One is there were a limited number of solid tumors included in that study. So there were no colorectal cancer patients, for instance, I believe no breast cancer patients. And then there've been some other studies that have said, "Is the cutoff of 10, really the right cutoff?" I mean, that isn't something that's defined in basic biology, that is a human... That was defined, and it's not a magical number that only patients above it respond and those below don't. And I think there's a lot of question around what's the right cutoff for each disease type.

And that's limited by the number of patients that have been studied with the different disease types. So I think it's important that we keep track of, not just look at the approval and the information that was provided, and the data provided to support that approval, but new information as it comes out, real-world evidence, what are we seeing in ovarian cancer, in breast cancer, and to make sure that we're providing the best information that matches the patient. I guess just one other example speaks to the complexity of TMB, what about treatment-induced tumor mutational burden? In a disease like glioblastoma you can see that post-treatment with agents that induce mutations, you now have tumor mutational burden that was treatment induced. And right now it looks like that doesn't really predict response to immunotherapy.

So it's about context, and it's about putting the genomic information in the right context for each patient. So there was also an approval... So PARP inhibitors, I think most of your audience will know about that group of agents. And it looks like in several disease types that they work best in individuals whose cancer cells have a defect in their ability to repair DNA. And that is consistent to some degree in a couple of different diseases. The issue is that DNA repair is really complicated and there are lots of genes involved. And how do we measure defects in DNA repair, and which of those defects are really predictive? So in prostate cancer, a PARP inhibitor was approved for patients based on a trial that included patients that had a mutation in one of 15 different genes, in different DNA repair genes. I think the complexity of that study is that most of

the patients in that study had either a BRCA or ATM mutation, I should say those were the biggest populations.

Janine Morales:

And then there's a whole set of other genes where you've got, in some cases, one or two patients that have a mutation in one of those genes. Now, if you pool them all, there was a statistically significant benefit in that particular study. But when we think about an individual patient that comes in with something like a CHEK2 mutation, or a CDK12 mutation, these are other DNA repair genes, less common, less clear that those genes are predicting benefit. We always like to think if a patient is in the population, they have the one gene, and how much evidence is there for that one gene? So I think that, just another way to illustrate that, it's important to, I think look deeply at the details of studies and figure out what data applies to the patient that a physician might have in front of them.

Jerome Madison:

This is really interesting. So what I'm hearing, you're speaking to something that I've heard you mentioned before that you called the paradox of precision medicine. And I don't know, was that a term that you use, is this a well-known term, can you tell us more about that?

Janine Morales:

Sure. No, it's definitely not my term, and it's been used by a variety of individuals. I think there was a great commentary that was in the New England Journal of Medicine several years back, and I pull it up all the time. It's simple, and yet I think really speaks to precision medicine and what we need to keep in mind at all times. So I think the idea there is just that as precision medicine and our ability to define patients or put them into smaller and smaller subsets, that our ability to then precisely estimate the effects of a given treatment just goes down, right? So we're precisely defining a population, but those populations are getting smaller and smaller. And now, the ability to power a study that gives you real confidence in an outcome, it's greatly decreased.

So in some cases, these precise populations, you're basing outcomes on low-level evidence, it could be cohort studies or even case studies. So I think that that's just... I like to keep that in mind, not as a... So when we curate information or when we're positioning information for a patient, I think it's really about making it transparent, how much information is available that applies to you? I think it's just really interesting and obvious, but always worth keeping in mind, that precisely defining patients into small subgroups means you don't have the numbers to power large studies and predict efficacy in really convincing ways.

And it seems as the field of precision medicine grows and the data continues to expand, it seems like these cases will become more profound, like smaller groups. And so I see that it's important for clinicians and payers to have access to this data when it really matters, and that's when they're making a treatment decision or a coverage decision. But how do you procure all this data in a way that these stakeholders can benefit from it? And how can you possibly keep up with all the nuances and subtleties that you mentioned?

Yeah, well, I think for practicing clinicians that are treating many disease types, I think it presents an enormous challenge. There is just, again, to go back to the ALK and NTRK examples, those are fairly easy for one to keep in mind and to remember without the support of technology. I think that that's going to be increasingly difficult, again as we have more and more drugs and as more molecular subtypes of patients are included in those studies. So I think it's complicated for everyone, I think that structuring the available data in a way that it can be delivered, and that

subset of information can be delivered at the point of care quickly. So I guess really, it's about it's about information and as much as process, I think the process of precision medicine, you can have all that information out there and someone can know it, but if you can't present it to the clinician at the right time, it isn't very valuable.

So I think that means that it's incumbent on anyone generating the data, to structure it and disseminate it in a way that it can be queried and applied and delivered to a patient, or a patient setting very quickly. And that's not trivial, but I think it's important to make sure we realize the potential of precision medicine.

Jerome Madison:

Yeah. So here's an example, and it doesn't, I guess, neatly fit under the topic of precision medicine, but Hannah Mamuszka, CEO of Alva10, a friend of the podcast, she had a post on LinkedIn, for those of you who are on LinkedIn, follow Hannah, she has some amazing posts and constantly puts out data there, but Janine, she talked about a recent FDA Oncology Drug Advisory Committee. They made a decision that continues to allow patient access to atezolizumab for triple negative breast cancer patients, even though the most recent trial data failed to improve progression-free survival over paclitaxel plus placebo, and the overall survival was statistically inferior. So I know it doesn't neatly fit under the umbrella of precision medicine, there may not be a biomarker, but I think her main takeaway is, for situations like this, number one, payers and providers need to know this data, and possibly more studies are warranted to find a genomic or genetic signature that can identify the cohort of patients who can benefit most. What are your thoughts on that?

Janine Morales:

Yeah, I think you're right, Jerome. So I guess one could argue, "Okay, the study didn't meet it's..." I want to be careful not to speak to the details of the study, but I assume an inferior overall survival was not the endpoint they had in mind. So let's say for the sake of argument, it didn't meet its endpoint. From my perspective, I think we try to be careful not to say, "Oh, that's a good or a bad decision," from an access point of view. I think let's just make sure we take the data that was provided and make sure we're making a good decision for the patient. I don't think access to therapies is bad, but knowing what that approval was based on is important. So I always try to step back from whether something's good or bad.

Could we learn more about the markers that are better at predicting immunotherapy response? Absolutely. And let's hope that the approval doesn't stall that effort. Just like in the prostate cancer case, you now have approval for these rare gene mutations, let's hope that doesn't prevent the pursuit of more robust data in those patient populations. So I guess I'm talking around it, Jerome, but I think the idea is, if you have access, let's just make sure it's clear how to use that drug for a patient, what's the benefit, how does that compare to another agent? Triple-negative breast cancer is a very difficult disease to treat. It would be hard to argue against providing access to something like an immunotherapy. When do you use it? Would you use it before you used paclitaxel or after, or is something that's for the patient and the physician to decide? Does that answer your question?

Jerome Madison:

It does. And I really wanted to hear your thoughts on that probably more than anything else. And I'm sure we're not trying to come to a solution on it, but the key in, I think you addressed very squarely, is really giving access to the information, the data that exists. And that's what you and

your team has been able to accomplish with creating a knowledge system that powers Trapelo, which is our title sponsor of the podcast. How can cancer care providers and payers benefit from a rich knowledge system?

Janine Morales:

Well, to reiterate some of the things we've talked about already, I think as more and more data comes out and the patient populations are stratified into smaller and smaller subsets, I think we need a system in place to filter that information and deliver to the physician what they need to see at that moment. I think that means that all the information out there, it needs to be structured in a way that it can be queried and presented based on a patient's characteristics. So when we think about curation of the data, we try to capture as much clinically-rich detail as possible so that we can then aggregate like patients. So we're not just trying to say, "For this disease type and this marker, or this marker collection, do they respond? Or is it FDA approved?"

We look at how many patients had that particular mutation, what stage was their disease, what previous treatment did they have, what were the end points, what were the outcomes? And so we structure all that in a way that allows us to pull it up and organize it, and using those variables as drivers. So I think that's an important thing to consider, but then how do you get that to the physicians is an important issue that is a complex issue of communication between knowledge systems, communication between payers and knowledge systems and provider groups. I think another thing to think about is that, I think precision medicine in some cases, patients aren't even being tested when they could be or should be. And I think the process should start at the beginning, where we're helping physicians to identify those patients that are most appropriate for biomarker testing.

And that's something that at Trapelo we've thought about, which is how do we ensure that you get the right testing done in the first place? If you don't get the right testing done, how do you make the right decision? And that's true of immunotherapies, targeted therapies and all classes of therapies out there. I think it's better, at least for some cancer types, to start there. And certainly there's room for improvement in testing.

Jerome Madison:

Yeah. Trapelo's been able to create point-of-care tools to access that knowledge system, which I think is very innovative, and that helps for providers and payers, but pharmaceutical companies are also stakeholders in this too. Is there a way for drug manufacturers to benefit from such a knowledge system?

Janine Morales:

Yeah. Well, I guess I'll tie it back to the patient. I hope they benefit in any way that what they're delivering provides benefit to the patient. So I think if they offer a drug that benefits a patient population, I think we should ensure that all the patients that qualify are given access to that. So I think driving biomarker adoption is an important component of that. And I think there are statistics out there that say when a new mark biomarker or a new drug comes out, it can take years to get to 80, 90% adoption of that marker. That seems suboptimal, and so I think getting that out there quickly, getting quick market uptake, I think benefits the patient first and foremost, and the by-product of that is of course a pharmaceutical company can benefit. And I think when you think about some of these smaller populations, it's important to start cataloging real-world evidence and knowledge systems that are designed to capture that and add to the growing body of

information for a particular patient subtype, I think potentially that's of benefit to companies as well.

Jerome Madison:

That is Janine Morales, Chief Scientific Officer at Trapelo Health. Janine, I feel I can talk to you about the data all day, you do talk about the data all day, but I learned that if you want to get away from this and totally geek out on something else, to give you a snorkel and a barrier reef and you'll disappear.

Janine Morales:

Well, I'm not sure how you found that out your own, but I think that is my tendency, right? Head down, and I have to remind myself to look up every once in a while, whether it's fish or data.

Karan Cushman:

Whatever dark cave you can find, right, Janine?

Janine Morales:

That's right.

Jerome Madison:

Well, Janine, thank you so much for really enlightening us and helping us get our minds around how the data is growing and how we can still organize to apply it to all the stakeholders. Thank you for being a guest on the Precision Medicine Podcast.

Janine Morales:

Sure. Thank you, Jerome. I hope I contributed something to the conversation. And it's been fun to be here. Thank you.

Karan Cushman, Producer:

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About Our Guest

Janine Morales, PhD
Chief Scientific Officer, Trapelo Health

Janine Morales joined Trapelo Health in 2011 and oversees a team of editors and curators with deep expertise in molecular oncology. Her group is responsible for maintaining the company's comprehensive knowledgebase, which summarizing published data pertaining to molecular biomarkers as predictors of response to targeted therapies in oncology. Janine also led the development of the company's framework for the systematic evaluation and synthesis of molecular clinical evidence as well as the principles guiding the presentation of molecular evidence in patient-specific reports.

She brings 15 years of editorial and information management experience in the biotech and medical sectors and was a member of research and development teams at Elan Corp. and DNAX Research Institute (acquired by Merck & Co). Janine received a BS in Biochemistry from the University of Rochester and earned her PhD in Pharmacology from the University of California, San Francisco.