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Paul Thies: Hello, I'm your host, Paul Thies. On this episode of *If/When*, we discuss the topic of precision medicine with Dr. David Fajgenbaum, Assistant Professor of Medicine, Translational Medicine and Human Genetics at the University of Pennsylvania, and author of the book *Chasing My Cure: A Doctor's Race to Turn Hope Into Action*, and Francesca McBride, Director of Regulatory Compliance at Jacobs.

David and Francesca, thank you both so much for joining me today to talk about precision medicine. Sounds very futuristic. I'm really excited to learn more about where this is going. David, also, you were very kind to share your book that you wrote, *Chasing My Cure*, and a very fascinating in parts, detective story, and romance, and sports story, and medical story. It's just a little something for everybody, so a really great book, and highly recommend that.

I want to thank you both for joining me today. To start us off, Francesca, I want to unpack this term "precision medicine". What is precision medicine? What does that mean, exactly, and is it the same as personalized medicine?

Francesca: Certainly, the terms both precision medicine and personalized medicine, as they developed whatever, more or less were applying to the same definition, but there is certainly some differences. Precision medicine, basically it's an emerging approach for disease treatment and prevention. What it does is it takes into account the individual variability of the genes of each individual person, the genes in our body relative to the disease.

Traditional medical therapies didn't always work the same for every person, and more work is now being done in genomic DNA or molecular testing so that they can establish those genetic profiles for the different patients, and then this genetic profile is able to be used to customize healthcare with decisions and treatments that are specifically tailored to each individual.

Precision medicine has also been referred to, at times, as I said, as personalized medicine, and generally, personalized medicine has been referred to as tailoring of medical treatment to individual characteristics for each patient, and then ultimately leading to what that clinical treatment would be. Sometimes it was referred to as a trial and error approach to finding that right drug for the right patient at the right time, but again, now, there's a much greater use of electronic health records, genetic testing, and big data analytics and supercomputing to be able to make it far more precise than what was being done before to the treatments.

Paul: If I understand maybe in a simple way, personalized medicine's looking at the person maybe somewhat from a-- and this is going to be a rough analogy, but looking at a person from a macro level for the specificity of them as an individual, but the macro level, whereas precision medicine gets down into the micro level where it's more targeted. It's not just this is what they need, but this is how we can apply it in a way that's very targeted, does the least amount of damage, and does the most amount of efficacy. Is that a fair way to sum that up?

Francesca: I woul

Unfortunately, we don't have drugs that can target every possible mutation, but we do have drugs that can target some of the most common mutations that occur in cancers. If you do genetic sequencing of the tumor, you can figure out what were the genetic changes that led that cancer to become a cancer, and then you can ask the question, is there a drug that's already approved that can hit that particular genetic change?

Let's say you have lung cancer, even if the drug wasn't made for lung cancer, if you figure out that your lung cancer has an ALK mutation in it that's really causing the problem here, you can try an ALK inhibitor that may have been developed for another cancer. In many cases, these drugs are effective. Precision oncology is to say, "What's the genetic change that has occurred, and then what drugs are already approved that can hit that thing? Let's see if that drug actually works," whether or not that drug was made for your form of cancer or something else.

Paul: You detail this in your book *Chasing My Cure*, but can you share with our audience a little bit about your own personal journey. You have a **[00:12:08]** near-fatal disease, how did you use precision medicine to find a health-affirming way forward with your own life?

David: Sure. I went from being a healthy third-year medical student. I was in the

It's now been over eight and a half years that I've been in remission on this drug. I almost died five times in a three-year period and now it's eight and a half years in remission on this drug. What I just described is what we call drug repurposing but really it's precision medicine where we figured out what was exactly going wrong in my case and then what drugs are already approved that maybe could hit the thing that's going wrong and maybe save the patient's life.

Paul: Wow. It sounds like it's being creative and then looking across drug lines or therapy lines and not being just so hemmed in on, "This is how we've always done it," but it's like, "Let's solve it from the problem out," as opposed to leading with the solution.

David: That's right. [crosstalk] Oh, go ahead.

Francesca: Sorry. It was just what you've said there, that takes back again to the criticality of that database of information and data that is collected from the many different studies and the patients and things like that because that was something that was able to help you get understanding about the capability or potential capability of that drug.

David: Absolutely.

Paul: It's always being able to know what options are out there. I imagine there are probably doctors, they're human, and they have unbelievable amounts of information, but they may not be aware of that there was an mTOR inhibitor, like in your case David, that it was used for something else but it could be repurposed. It's just being able to find that information and have that and then being able to look at, say, your case, like, "What did we learn from patient Fajgenbaum, and how is this-- You know what I mean? Then that leads to the development of therapies for other people.

Francesca, let's talk about bringing this precision medicine, bringing it to life, getting it out to market, getting the market adoption. What are some of the more significant challenges to market adoption of a precision medicine program, and how are those challenges being met?

Francesca: Certainly one of the areas, and this is something that I found in the work that we've been doing in the cell and gene therapy over the number of years, is that the advancement of the medicines for precision medicine, they create actually new challenges for the regulatory oversight from FDA and organizations, partly because it is also new for them and then they're learning about this, but then with the way that the data and the information and that sharing and how that is done is something that is new.

That's a challenge that, one, is put forward towards how easy will it be to get that regulatory approval to do this. Again, the FDA, for example, they've looked at, if you were more conventional types of diagnostics that detect maybe a single type of disease or in condition and now they're looking at something that's more complex. Not that the FDA is at all opposed to this, they're supporting it. It's just that, that is one thing that, as new treatments come up, then that, for some period of time, is going to be a challenge to that.

That's pharmacogenetics. Unfortunately, it's really progressed rapidly on the safety side, so predicting whether someone's going to have a bad adverse event, and it's progressed less rapidly on the efficacy side. That genetic data is not as good at predicting whether one drug is going to work better than another drug. It's good at predicting whether a side effect might happen but not as good at predicting whether it's going to be more efficacious than others.

In Castleman disease, we have discovered a seven-protein panel where we can measure in the blood seven particular proteins and get a good sense for whether you're likely to benefit or not from one particular drug. That's definitely pharmacogenetics as well. One thing I just want to bring up from our discussion, as you think about precision medicine, we've talked a lot about repurposing drugs to be precise in treating a particular disease.

Francesca: Sure. As I said, we started out in the earlier days, in the early part of this with phase one, phase two clinical facilities like at the Dana-Farber Cancer Institute, for example. In that project, for example, our leadership role was for regulatory programming of that facility and then providing them the different kinds of information in terms of what's the quality of the environment to protect the products being made, say what segregation is necessary between the different types, and how many stations can we have in a common space to support multiple patients things like. Then it expanded from there into process, assess, review being able to, what is the right type of equipment? Because a number of these, especially in the case of the cell, your therapy processing, it's just different equipment in the way that you do the process. Gene therapy is much more similar to some of the traditional therapeutic manufacturing that we've done over the years. It's just that for cell therapy, the equipment is different, and so from a process standpoint, we've come in and looked at this and then doing it. Architecturally. Then the other thing.

We are now doing full facility design and looking at the definition of the process flows through the facility and all the different steps of process manufacturing. As they say what are the GMP aspects or regulatory compliance requirements and even biosafety, because as we're dealing in the cases with human cells, and in some cases they're attaching **[unintelligible 00:30:40]** with a viral vector to this or a bacteria.

Then that brings another application relative to the design of the manufacturing space and carrying through. Jacob, we've done now more than 30 of these types of projects for cell and gene therapy at clinical mostly, and now into the commercial manufacturing.

Paul: David, my last question is for you, and a theme, I think, for our discussion today, is thinking creatively, and approaching problems in a new light. One way that we do that, I think, we're seeing as a society we're increasingly embracing is neurodiversity, and embracing people who have neuro-diverse trends. I know we're creating greater opportunities for people with neurodiversity to help solve these great challenges. Now, in reading your book, I understand that you have some neurodiversity as part of your life experience, in your case, hyperfocus. Can you speak to the role it played in your own chase for the cure?

David: Sure. Everything in moderation is good and too much is not so good, and focus is one of those things. As a young child, I learned that I tend to hyper-focus on things which means that I can do something for 18 or 20 hours straight and not take a break or do anything else. The time flies when you're having fun. That works really well when you're a laboratory scientist and you have work in front of you. Doesn't work as well when you need to stop doing those things to do other things.

Hyperfocus can be a real gift, but it can also be a bit of a curse, because you have a hard time shifting from one focus area to another. I think that without that level of focus that I had aI hut that level of

Yes, we'r