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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 would think so. A big part of that is because of the different data that they're now looking at, is much greater than what they were appearing to look at previously with some of the different diseases, especially because of the genetic influence and knowledge that they're able to get.

Paul: Now, David, let me ask you, and again, this is going to be in layman's terms or to explain in layman's terms some of the diagnostic tools and targeted therapies that are used in precision medicine.

David: Well, first of all, thanks so much for having me on your podcast. It's great to be on the show with you. In terms of tools for precision medicine, just as you summarized, in precision medicine, basically you're using data like omic data, whether it's genomic or proteomic data to inform how you're going to treat someone. You're saying, "I'm not just going to treat you with this drug because you have diabetes, I'm going to treat you with this drug because you have diabetes, and you have a genetic mutation that makes this drug more likely to work than that drug."

In order to figure that out, the tools you use are going to be things like genetic sequencing of your DNA, so to understand what the sequence of your 2 billion base pairs, and does that sequence suggest that one drug might work better than another? It might be sequencing of tumor or tissue of interest, so rather than just looking at your genome you were born with, looking to see if maybe there were genetic changes within your cancer or within some tissue in your body that are actually different from the rest of your genes that could suggest that one drug is going to work better than another.

There's also something called proteomics. Genomics is where you look at the genes, but you can also measure the levels of proteins or RNA in the body, that will suggest that maybe one drug will work better than another. The new technology that was being discussed earlier enables us to understand what's happening at a molecular level in a body to guide whether you're going to treat someone one way or another.

There's also really simple things too. You can do things like staining for things like signaling pathways with immunohistochemistry which is a really old approach to also be able to personalize treatment one way or another.

Paul: That leads me into this next question I have for Francesca. How do you unpeel this onion in terms of getting that data? David, you mentioned staining, and I'm sure there's chemical reactions and stuff, and the presence of certain proteins or whatever may influence a certain chemical reaction that the lack of that protein would enter something. Francesca, how is this health and disease data collected? What are some of the ways it's collected and used to generate precision medical treatments?

Francesca: Well, certainly through both the research where they're starting with necessarily giving the treatments to the patients, but they're starting to collect the data to better understand why the individuals or patients are having, based on genetics, and maybe their lifestyles and things like that, what has caused this from their genes to be that way, and so they're doing a lot more data collection for this.

That's one of the things that I've seen is one of the biggest influences relative to precision medicine in terms of the ability for it to grow and advance is around that data collection and the sharing of the data. There's some apps that now you can put locally, I don't know whether it's on the telephone or something like that, so that patients can give information via that way to individuals that are collecting. That's one way that they're collecting even more data than they would have if the patient wasn't directly there for that. Then, obviously, investigation in doing different studies to look at the genomic effect of these.

They're literally taking in much broader type of information for some of this in terms of things from what is your health history for yourself, or maybe your family, depending on what the disease is, what's your lifestyle, what are your diet that you might have, and then, at the same time, the things like the genome sequences and microbiome composition, and just these different things that they're looking at. This data in itself is coming from different sources of information.

Paul: Then I'm assuming they cross reference, and they look at that, and then probably have some aggregate data from other folks who are in similar life circumstances or share similar trade.

Francesca: Well, that's one. I think one of the big things is how they get this information into a database, and then obviously, because of the type of data being personalized data, there's a level of protection that has to be, from a security standpoint, for that data, but at the same time, them being able to share that in the medical community for those people that are working and doing the disease treatment and trying to find those specialty treatments.

Paul: Now, David, I think you alluded to this just a little earlier. I want to dive into this a little bit more, but can we talk about and can you describe precision oncology, and what are some of the ways it differs from traditional cancer treatments? What are its benefits and how might it serve to improve patient care?

David: Sure. One thing to think about when you think about precision oncology and just cancer, in general, is that there's often a sense that cancer appears or occurs in the body, but really cancer is just what happens when normal cells that are in your body doing normal things, acquire mutations. Those cells have different genetic sequences than other cells in your body. When those cells have acquired enough bad mutations in the wrong places, you now have cancer. It's this transition from healthy cells that might be in your kidney or your heart, your lungs, your brain, wherever it may be, those cells acquiring genetic changes that make them become cancer cells.

What you can then back into is say, if they were healthy and now they're cancerous cells, you can say, "What were the changes that occurred in that cancer? Those genetic changes that made it become cancer in the first place."

You can actually do genetic sequencing of the cancer and then do genetic sequencing of other tissue in your body to figure out what were those genetic changes that made those normal cells become cancer cells. Then you can ask the question, are there drugs that are already FDA approved that can target those specific mutations that that tumor in your body actually has? It's pretty incredible.

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 University of Pennsylvania where I wanted to treat cancer patients in memory of my mom. She died from cancer just a few years before, to being critically ill in the intensive care unit. As you know from my book, I spent almost six months hospitalized in critical condition, nearly dying three times during that period. I even had my last rights read to me because the doctors were sure that I wasn't going to survive.

Unfortunately, or I guess, fortunately, diagnosis was made of idiopathic multicentric Castleman disease, which is a rare immune system disorder that really sits at the intersection of oncology and autoimmunity. The unfortunate thing is that I continue to have relapse after relapse. After my fourth time that I almost died from this disease, I created a foundation called the Castleman Disease collaborative network, and I started conducting research to try to figure out what was going wrong in my particular disease.

The medical community didn't understand what was causing idiopathic multicentric Castleman disease. That's why the word idiopathic is at the beginning of it. We don't know what causes it. I decided to do research into my own cells, my immune cells, my lymph node, my blood, to figure out what was maybe going wrong. I figured out that a particular communication line in my immune system called the mTOR pathway that's important for everyone's immune system turned out to be highly activated in my case.

I asked the question, are there drugs that are already approved? I don't care what it was approved for, but are they approved for something that can inhibit mTOR in this particular communication line? I found that there is a drug that's been around for about 40 years. It was made for kidney transplantation and it's a really good mTOR inhibitor. I shared the data with my doctors, and in the absence of any other options and the fact that I was likely going to die very soon, we decided to start treating me with this mTOR inhibitor.

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.

Then some of the other things as mentioned is around the ethical, if you will, side or social and legal side of the information sharing. Patients need to understand how that is done, why that is done, how they're going to still be protected. This is something that, again, I've learned in a lot of the clinical trials where we've been involved with the different hospitals because they have patient records that are coming in and how that is controlled. That adds another level of control relative to data security and information and how that's done.

Then I think one of the other things that, although it's not necessarily today, let's just say a manufacturing issue, there is the issue around the cost of these treatments relative to treating these different conditions. They are certainly, at this stage, tending to be expensive. Then I think we're still going to be going through the learning process of how are we as people going to be reimbursed from a third party, from your healthcare. What are they going to cover for this?

This is something that is new. The facilities where these drugs would be manufactured and the studies and the testing that's being done, we've certainly seen them as we've been involved with projects for these where they're high classified areas because of the cells that are going to then get given to back to the patient, their new equipment in some cases for doing it, and then, of course, the diagnostic testing. That's more traditional, not necessarily a new challenge.

Paul: One thing is a lot of interesting challenges there, and I thought about the FDA approval process and going back to David's case with the mTOR inhibitors. I could see, in his case, he's literally upon death's door, and it's like everything else has failed, I think is a fair way to say that. It's like a Hail Mary pass. It's like, "Well, the patient has agreed to it. Let's give it a shot. What do we got to lose?"

That's not going to always be the case a lot of times. Then it's a matter of, if we get creative in how we treat this patient, it's just making sure that we're taking a medicine that has been approved for use A and we're advocating it for use B but then it's making sure the patient understands if there are any risks or how navigating the labyrinth of approvals and legal ramifications, I can imagine.

David, I have, in the course of preparing for this podcast, a term was used, pharmacogenetics. Can you explain what is pharmacogenetics? I'm hoping I'm pronouncing that right. How is genetics being used in the development of drug therapy?

David: Sure. Pharmacogenetics is where you do genetic testing of a patient to determine whether a drug is more or less likely to help to work and or to cause harm. There's some pretty clear data that having what are called SNP or a single-nucleotide polymorphism, which means you have a single change in your DNA. That doesn't make you have a disease. It just means that maybe you metabolize a drug more quickly or more slowly than other people do. Having certain SNPs will make it so that you're at more or less risk of certain adverse events.

If you can do genetic testing and figure out, based on your genetic sequence, you're more likely to have this horrible adverse event from one treatment versus another, you can then not give the patient that treatment that would cause a horrible adverse event, and you can go onto an alternative therapy.

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.

We've spoken less, that it's been alluded to towards the traditional precision medicine approaches and that's cell and gene therapy. The reason that we consider cell and gene therapy to be the ultimate precision medicine is because, when you create a cellular therapy, you're literally using that person's cells as a therapy. It's like the ultimate personalization. It's not even their genetic change, it's their T-cells that you're reprogramming to kill cancer. That's the ultimate personalization.

Or you're going after a particular genetic change that that patient has with a gene therapy. Though I'm a big fan of and proponent of repurposing drugs as part of personalized and precision medicine, there's also the more traditional arm of personalized precision medicine which is cell and gene therapy.

Paul: Now, Francesca, can pharmacogenetics technology be used to customize healthcare treatments? What is the current status of these treatments? For instance, are they being used in research and in clinical trials, and in partnerships with research institutions?

Francesca: The great news, I think, is that they can be used for the development of these treatments. What we're seeing in terms of certainly at Jacobs with these cell and gene therapy facilities where we've been seeing this, we've been involved with these since about 2007, and not that that was the first start but certainly that's where we got them, and the growth that is occurring amongst these facilities is tremendous.

Certainly, in the early year, what we were seeing is that medical schools, hospitals, those locations that were doing a lot of that early research via Penn via the Dana-Farber Cancer Institute, Massachusetts General Hospital, just places all over the country and even the globe that have, because of their direct involvement with patients and the research, then this was starting to develop very early on.

Because these medical facilities they maybe staged from a capacity standpoint, if you will, to handle phase one, phase two clinical trials relative to the patient numbers and quantities and **[unintelligible 00:25:08].** They then are partnering with organizations, companies, to then go to that next step towards the higher phase clinical or even take it through to commercial manufacturing. Jacobs has been involved with, for example, Pfizer, and Vertex, Kite Pharmaceutical.

These are different ones that are doing this. They start that early partnering, bringing it up forward, and taking it through. What this is telling us is that we're going to see a tremendous amount of ongoing growth in this area. Whether it is for the disease where maybe there's just a small number of patients that have this disease, be it in the US or globally, but companies are still taking the opportunity to target and find those treatments and then with some of the different cancers that are too much larger patient populations.

Paul: Now, David, Francesca mentioned Penn when she was talking about research facilities and where phase one and phase two, things like that, are taking place. Can you talk a little bit about what projects are being tested and implemented in labs and at places like the Penn Center for Precision Medicine?

David: Yes. Really it's the whole gamut. Here at Penn, there's incredible gene therapy going on that was pioneered by Jim Wilson who, in many ways, is considered one of the founding leaders of the gene therapy field. There's cellular immunotherapies being pioneered by Carl June who also is considered the pioneering founder of the cellular immunotherapy field.

There are groups like ours here that I lead like the Center for Cytokine Storm Treatment & Laboratory where we probe disease biology on a molecular level and then we look for drugs that can be repurposed in a very precise way certainly in line with precision medicine. There's the Penn Center for Precision Medicine led by David Roth, where he really stimulates and accelerates precision medicine research all around campus across basically every domain from psychiatry to neurosurgery.

There's a lot of really exciting work being done on campus. It really is just I think a general trend that's been happening over the last decade and that's to move from, "Okay, you have a disease, so we're going to give you a drug, and if that drug doesn't work, we'll give you the next drug and the next drug," to the world we're in right now which is, "Okay, you have a disease and we understand your particular disease has increased expression of this thing or decreased expression of that thing, whatever may be meaningful for your disease so we now can put your disease in context for you the patient."

We can say, "Therefore, I think you're going to do better on this drug than that drug, but if this drug doesn't work, we think that this would be the next one line." You can start to predict who's likely to benefit from one drug or another drug, and you can maybe even say, "Maybe there's a drug C that isn't even used for your disease, but based on what we've seen in the laboratory, we think the drug C could work really, really well."

That's really where we're moving forward to as a field. Certainly, a lot of that work's happening here at Penn.

Paul: Francesca, I think some of what we're looking at is like expanding on this work like that David's talking about, the idea of precision medicine and really making it more market feasible. How is Jacobs supporting clients in the design at startup of personalized medicine facilities? Can you speak some examples like how we're **[unintelligible 00:28:56]**?

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 as I was searching for a drug that could save my life, I don't know if I would've found one, but now that the task is to go from chasing my cure to chasing other cures. Over the last eight and a half years that I've been in remission, we've now given the same drug that I'm on to many other Castleman's patients we've actually identified and/or pushed forward nine other drugs for Castleman's patients, patients that aren't benefiting from the drug that helps me.

Yes, we're finding drugs for every Castleman's patient, that's the mission we're on. Then we're actually getting ready to launch another nonprofit organization this month along with President Clinton that's focused on drug repurposing more generally. Can we figure out all uses for all drugs, and then perform clinical trials to prove whether those drugs actually work or don't work?

Really, it's about shifting from this myopic focus on finding a drug that could save my life to then saying, "Let's apply the same process and the same focus to other Castleman's patients, and then now more broadly to patients with any disease and potentially any drug."

Jacob: Wow. Fascinating. Well, David and Francesca, I want to thank you both so much for your time today. Very fascinating topic, precision medicine, and very interesting to see the trajectory of where healthcare is going in this regard. Thank you both for sharing your time and your expertise with us.

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