Vanderbilt Health DNA: Discoveries in Action
Season 2, Episode 6
Step It Up: We Need Clinical Trials - And They Need Us

Dr. Karen Winkfield: How do we improve the knowledge base in the community? Because if somebody knows that they can go into a doctor's office and say, "I've just been diagnosed with cancer. Do you have any clinical trials that I might be eligible for?" How powerful is that, right? That they bring it up. It takes a lot of the stigma away from individuals walking in who see a patient of color or see someone who might be Spanish speaking.

Jane Freedman: And then the thing again about clinical trials is they're so complicated and difficult to do and expensive. They take many, many years. In fact, what we've seen with the COVID vaccine trials is sort of mind boggling to me. That everything was expedited and done very, very well and very, very quickly and transparently--I thought was extremely impressive. I hope that the speed and transparency can be translated into other fields.

Lisa Bastarache: I'm really struck by how unfair it is that some people have a genetic mutation that robs them of their health or causes them to die early. It's just not fair. So my what if is, what if we could accurately diagnose and treat all people who have monogenic conditions? I think we would live in a more fair world.

Clark Buckner: Do you know someone who participated in a clinical trial? There's a chance you do, or at least read about someone a few degrees separated from you, who joined a trial somehow related to COVID. The sprint to find treatments and vaccines to fend off SARS-CoV-2 attracted more people to clinical trials. They felt compelled to help, to pitch in and do something. And a huge thanks to them for rolling up their sleeves.

What's interesting is that clinical trials are a workhorse of academic medicine and medical research. They move all types of care forward and the vast majority of them don't make the news. In fact, getting people enrolled as a Herculean task. Let's hear from Dr. Cathy Eng, an oncologist who specializes in colorectal, anal, and appendiceal cancers. She joined us a few episodes ago talking about the rise of colon cancer in young adults. Another big and urgent part of her work is modernizing clinical trials so more people see the benefit to them and society and get involved.

Dr. Cathy Eng: Patients for some reason are not, in the United States in general, do not enroll into clinical trials, and that is a huge problem in making breakthroughs. So in Europe and Asia, because of the way the health system is, they are more likely to enroll in clinical trial and more likely to get drugs approved faster. Whereas here in the United States, it used to be roughly less than 5% of patients would participate in clinical trials. I think the numbers are a little bit higher now, maybe 10 to 15%, but Europe is like 20 to 30% of patients will participate in a clinical trial. And as we all know, we have to go through

phase one, phase two and phase three for clinical trial development before it goes to the FDA for approval. I think that is one of our biggest hurdles.

People are concerned, am I going to get a placebo? Should I enroll in this clinical trial? It's inconvenient. I don't want to drive. I don't have transportation. It impacts my job, my schedule. So a lot of factors also unfortunately make participation in a clinical trial challenging. I am hoping in the future because of the use of telehealth, because of COVID-19, that we will start incorporating aspects of that for clinical trial enrollment. But once again you have to get approval from the FDA. You have to get approval from the NCI as well depending upon who's running the clinical trial as well as big pharmaceutical companies and insurance providers.

Clark Buckner: You're listening to season two of Vanderbilt Health DNA: Discoveries in Action. I'm your host, Clark Buckner. The reasoning behind the show's name is quite simple. The path to better health lies in our DNA. Discoveries in action is about the big ideas and breakthroughs happening right here in Nashville, Tennessee from Vanderbilt Health. Our drive to discover, care, learn and share is in our DNA. It defines who we are just as your DNA defines you. We've all benefit from clinical trials, just as we benefit from advancements in safety mechanisms in cars or more reliable mobile technology, but we don't really stop to ponder each of those. So let's hear from Dr. Karen Winkfield, a radiation oncologist who is the Executive Director of the Meharry-Vanderbilt Alliance. She works every day to make cancer care more equitable. She lives and breathes clinical trials.

Dr. Karen Winkfield: I'm so grateful that we're having this conversation. Clinical trials are an important component of healthcare. It is how we move the needle. It is how we make progress around diseases and improving disease states. I'm an oncologist, I'm a cancer doctor. I see that we are curing cancers that 20, 30, 40 years ago, there was no cure for. Or we are extending lives of individuals or improving lives of individuals because of new therapeutics that have been developed, and the only way those therapeutics are developed is through clinical trials. But we know there are some challenges. We know that oftentimes the clinical trials are not inclusive in the way that they're designed. They do not include oftentimes the patient in the process or the end user if you will. And so sometimes the requirements of a clinical trial can be quite onerous. The reason why clinical trials have been highlighted so much is because of the COVID-19 pandemic. People have seen clinical trials work in real time.

I think this is the first time, certainly in my lifetime and probably in the world's time, where we've had this rapid pace of development, where we have seen a new virus that's introduced into a setting that has spread so quickly, but we've also had the science that has enabled us to actually develop not only a vaccine, but therapeutics that are specific to that particular virus. We've never seen anything like that, so it's been fascinating to hear people's real thoughts about research and clinical trials and the fear that there is associated with clinical trials and frankly, the fear associated with even the vaccine, because you're like, oh, I'm not being a Guinea pig. I'm just like, well, there's been several billion people now who have gotten a dose of this vaccine, but still there's a lot of hesitancy around it because of the rapid pace.

And so that's why clinical trials are now in the forefront. I think it's a wonderful opportunity for us to do education and do education about the importance of trials and clinical research in terms of the development of new therapeutics and vaccines. Think about things like smallpox that have been eradicated, again, was a deadly, deadly virus.
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Let me give you an example from one of the diseases I treat. I am a hematologic radiation oncologist, which means I treat blood cancers. Lymphoma, leukemia, multiple myeloma. Multiple myeloma happens to impact African-Americans at a much higher rate, at about a rate of two to three times that of other races and ethnicities. So when you look at the multiple myeloma population, the group of individuals in the United States who have multiple myeloma, about 20% of them are black. But when you look at the clinical trials that have been done over the last couple of years, that have really changed the face of myeloma, only about 5% of participants were black.

And so one of the challenges that we see is that while blacks have much higher incidents of multiple myeloma, they're also dying of multiple myeloma at a much higher rate. And the challenge is, is that when they are treated on clinical trials, they do better. So what that means is that if blacks are allowed to get standard of care, they actually could potentially do better than other groups. But because number one, we know that there are challenges with our health care system. We don't understand that, but we don't even have enough people in those studies to really look at the biology behind that. Why are they doing better? What are some of the things that make them have less risk associated with multiple myeloma? And the reason why this is important, again you mentioned, I'm seeing it real time. People died of multiple myeloma and they still do.

It's not a curable disease, but we've moved from five-year overall survival to now people living 10, 15 and 20 years after a diagnosis of multiple myeloma because of the amazing progress that we've made over the last several years. But it's really important to be inclusive, to think about the groups that you really want to make sure have access to the medicines or the ones who are going to be the highest impact group. That's really important. And so, again, not only is it about, is the medicine going to work well in each community, but what are the side effects? To your point, you talked about even weight. Are there different things that we're going to need to look at in a real view of the world when this medicine gets unleashed? And I think the best way to do that is actually have inclusive participation.

Fear is so paralyzing, and I must say that when people hear that C word, when they hear cancer, oftentimes after they hear that word, they hear nothing else. Let me talk a little bit about the way that cancer clinical trials differ from clinical trials in other diseases. There is such a thing as a placebo or a sugar pill or a false treatment, and that is oftentimes utilized as a test to see whether or not a new medication will work. But not for cancer. For cancer, there will never be just a placebo. It's either standard of care or standard of care plus something else. So that's one of the things that's really important to know, particularly for those where there's a randomization, and we'll talk a little bit about the different types of clinical trials because I think that's important to know as well. But if you have

what's called a phase three randomized control trial, and that's kind of like the gold standard where what they do is they have a new medicine that they want to test.

Again, let's look at breast cancer. So the standard of care for a woman with an ERPR positive, estrogen receptor, progesterone receptor positive breast cancer, if it's early stage, is oftentimes a three drug regimen, and so that would be the standard arm. If there was a new medication that they wanted to test, they wouldn't just give that new medication. They would give the standard medications, that three drug regimen, plus the new the medicine to see if it adds benefit. And then if it does, then they might start to change what other things are done, but you're right. In cancer, there will never be just a placebo, never just a sugar pill. So in that study, there would be somebody getting the standard of care and maybe getting a sugar pill. We're talking not only lives, but also quality of life. So that's one of the things that has changed too, is that sometimes it's not just about a new medicine that's coming.

And again, I'm going to go to multiple myeloma. It may be the way the drug is delivered, or the medicine is delivered. So my mother-in-law has multiple myeloma, and she had a choice between coming in every week and getting her medicine by IV, or getting an injection. Do I want to sit for two hours and watch something drip into my arm and then have to sit for another hour and wait, or would I rather just have you inject me and I sit for a half an hour and roll? It's a no brainer, right? That is a result of clinical trials as well. So even the clinical trials can say it might not even be about a new medication, maybe a new way to deliver that treatment or a new way of utilizing it maybe for a different disease.

Clark Buckner: It's amazing when advances in technology and research combined to improve how we get better or live our lives. Think about all the different ways Botox is used, or those sensor patches that now connect glucose monitoring to an app, or anytime a therapeutic takes a new, easier form. Dr. Jane Freedman, the new Director of the Division of Cardiovascular Medicine, and the Physician-in-Chief of the Vanderbilt Heart and Vascular Institute, explains how data collection and trials have changed, even over the course of her career.

Jane Freedman: I've been around long enough so that when I first started practicing... I'm a cardiologist, and when I first started practicing, a lot of the data that we used to treat patients was from observation or from smaller randomized trials, so trials where you have a control group that doesn't get the treatment and a group that does get the treatment, and preferably people don't know if they're getting the treatment or not getting the treatment. During the time when I was training, some of the first really important, large, randomized, blinded clinical trials came out and really revolutionized what and how we treated our patients. That was really the first wave of really exciting, educated, helpful data for us to know how to treat people better. Unfortunately, we've come full circle because what's happened is we've realized, especially for a lot of the diseases and cardiovascular disease, which affect so many people, but the causes can be diverse.

Often these trials have to enroll thousands to tens of thousands of people, and it becomes very expensive for drug companies to do or the NIH to complete, and it makes it prohibitive for us to study

certain kinds of diseases. So a lot of what people are thinking about now is, how can we get the data we need in a more efficient and cost effective way? And some of that has to do with having people involved just when they come to the hospital, if they're asked to be involved in a registry. It doesn't necessarily mean they have to enroll in a trial, but would they be willing to have their data looked at? Because if we can look at people's data without starting a big trial, we often can get a lot of information about disease and treatment. So it's a very complicated question and we're trying to look for new and exciting answers that will help people in the future and not be too costly and cost prohibitive.

One of the ways that people are holding out a lot of hope for is the electronic health record and Vanderbilt absolutely has been at the forefront of that now for quite a long time. If we can tap into data that's already there because patients have come in and gotten their care, and if we can couple it with other data that maybe we add on layers, I think using the EHR has strengths and weaknesses. So the strength is the incredible amount of data that if you can access it and know how to analyze it, that you can really mine and understand in a much more cost-effective way come up with some really interesting information. The weaknesses, of course, it's not a randomized prospective study, which is still considered the gold standard. So you have to balance those two things. I think the most exciting thing in terms of using these large data sets and the EHR in a very well curated fashion is the hope that someday you can go beyond clinical trials.

And what I mean by that is clinical trials are held out as the gold standard, but remember when you study a thousand people, you're getting a thousand people that fall within the rules of that trial. So if you need to have high blood pressure, be a woman, be between the ages of 40 and 60, that's still a pretty broad group of people, and within that group of people, there may be some distinctions. And one of the exciting things about the EHR is can you actually tease people apart even more? And it's the idea of precision medicine and sort of drilling down into breaking people into smaller subgroups, so as to treat them better and not give them medications that won't benefit them and do use treatments or recommendations that will help them specifically as individuals. One of the fundamental questions we've been asking in my lab and my research group for decades now is why do certain people get the clots that cause heart attacks?

It's a pretty large group of people in the United States each year, and now throughout the world, who die because of myocardial infarction and other forms of heart disease and stroke that are specifically due to clots. But many other people who have the exact same profiles don't get those clots. Why is it that certain people are predisposed to having heart attacks and others aren't? That's the fundamental question in our lab right now.

So if we could understand better... Well, you almost have to take a step back. It's not even just why you have heart attacks, but why you have clots that form in your blood vessels and cause any of the diseases related to clots. And if we could figure that out, we would know which people need to have treatment, and the treatments for these diseases aren't 100% benign, so you don't want to give them to people who don't need them. We'd also be able to stop the disease from happening before it happens. That

way we could prevent people from having heart attacks and people could live longer and healthier lives. And that's really what the ultimate goal is, is to prevent people from having these diseases and being happy and healthy and living a longer life.

Clark Buckner: The electronic health record, or EHR as Dr. Freedman spotlighted, allows data scientists to collaborate to dig through all those millions of data bits we all create. We actually explored this on season one, episode six. It was about how zooming out on the big picture improves health for each of us as people. Vanderbilt has been creating a biobank of DNA linked to de-identified medical records since 2007. It's called BioView, and it's invaluable to researchers. Here's a smattering of ways it's been used just recently.

News Headlines: Genotype looms large at risk for post-op arrhythmia. Study finds genetic risk factors for severe COVID-19 illness...Team studies new use for pulmonary hypertension drug...Study finds genetic clues to pneumonia risk and COVID-19 disparities...Predictive model identifies patients for genetic testing…Team explores diabetes drug's ability to treat RSV infection...

Clark Buckner: It's as close to real-time studies as it gets right now. BioView and other biobanks too, require people to allow their de-identified medical records to join the digital library that it catalogs DNA and diagnosis and reactions and oodles of other pieces of information that factor into the puzzle of our health. Lisa Bastarache is a Research Associate Professor in the Department of Biomedical Informatics. As a data scientist, not only does she love it when people opt in, she explains why it's necessary for science.

Lisa Bastarache: I would encourage anybody who's willing to participate in studies like that. One thing that people sometimes call the paradox of studying rare diseases is that you often times need a lot of people to look at in order to learn something about rare diseases. And so we need people to be willing to share information about their genetics and about their health in order for us to learn about these rare variants that I've been talking about.

I guess I will say that among people who've participated in BioView, I can definitely say that their willingness to participate in BioView has positively impacted a lot of people's healthcare, and has led to really important research discoveries. But it seems like now every few months, a new New England Journal paper that talks about yet another disease that has a targeted treatment. A few months ago, there was a paper about severe combined immune deficiency, which I don't understand the treatment because I don't understand the drugs or anything like that, but they basically have developed a very effective treatment for this totally devastating disease. So that that's one thing. We need all the geniuses who are developing these therapeutics need to keep going.

Costs a lot of money to get people in and consent them for a study and do those kinds of exams. So something that actually Vanderbilt has done a lot of work early on, working with this idea that we could actually get that information from the medical record. So if we had genetic information that was

attached to the medical record, we could search notes, use billing code data, et cetera, to define our cases and controls and do the same type of studies that people were doing at a very small fraction of the cost. And that model of using electronic health record data to study genetics has really become very important and widely used. There are large resources. The All of Us program is kind of based on this idea.

The UK biobank is a lot of electronic health record data to get information about what's going on with the patients who are part of that study. So it's become a model that's used all over the place. But initially, when the first studies were done using HR data, it wasn't clear whether the phenotypes we can get out of the HR were going to be high quality enough to be able to learn about genetics. And so we did a lot of studies to look at whether we could actually reproduce using medical record data, what was identified in these much higher quality studies earlier on.

So the electronic health record definitely supports replication of genetic associations that are found in these other high quality studies. Oftentimes though you'll find the relationships a little bit weaker when you use the EHR to identify your cases and controls, and that is really a function of the noise that's introduced by using what is a very complicated, sometimes very noisy, messy document.

You were saying earlier that the EHR is this really vast and longitudinal document and it is, but the more information you have in the HR, the more you get even contradictory information, or information that isn't true, that's in some notes, somewhere. So that makes it difficult to, with perfect accuracy, figure out how to group these people into cases and controls if that makes sense.

In order to identify all of the genetic variants that correlate with a common disease, you need really, really big populations. So people run these studies looking for genetic associations with type two diabetes on hundreds of thousands of patients. Those studies wouldn't be feasible if every subject needed to come in to a medical center and get a full physical exam to make sure they have type two diabetes or not. Using medical record data can make that process a lot more efficient.

A couple of years ago, I decided to start setting goals, and so I set a goal of trying to help one person get a diagnosis who wouldn't have been diagnosed, but for something that I did. Sometimes when I told people about this goal, they would say, you're helping people, you're doing research, you're increasing knowledge. And I was like, no, no, no. I want to actually, literally help one person, like an actual person. Fortunately, through some of the work that I've done, I have actually met that goal. Because I'm not a very creative person, now, I just want to do that for 10 people. I just multiplied it by 10 instead of coming up with a new goal.

The thing that gets me out of the bed in the morning, and the thing that I'm wondering about when I wake up is, how am I going to help 10 people get a diagnosis of a genetic disease who wouldn't have been diagnosed except for something that I did? That's the thing that I wonder. It's more of a goal. One

thing that I really enjoy or fits with my personality and work is I am not loyal to any particular method or particular technique. I'm very practical. And so that kind of goal has caused me to have to learn about lots of different types of statistical techniques and different algorithms and things like that, but I will use anything that gets me closer to that goal.

Clark Buckner: Knowledge is power, but participating in research can be daunting, scary, inconvenient, the list goes on. It's critical that the scope of what medicine knows and about whom they know it, broaden. Research and clinical trials have historically excluded people by the parameters of the study design, or whole groups of people overlooked, or they don't have easy access to trial sites or detailed information, or stable access to broadband. And even more menacing, the dark history of the Tuskegee Syphilis Study. It's a not so distant reminder of harm to black people under the guise of science. All of these issues, and many more, spring to attention as researchers raced defined an inclusive cohort of people to participate in COVID-19 vaccine trials, then to encourage people to take the vaccine once it began to be distributed.

Participation often boils down to trust and accurate information. Knowledge is power, and Dr. Winkfield and many of her colleagues in other specialties and around the country are hard at work reforming how people first get introduced to clinical trials, and then educated, and then enrolled. This isn't rocket science, and it's even more important - people's health. So the clinical trial structure of the future is, in Dr. Winkfield's vision, centered around the patient. Physically and metaphorically. Let's check it out.

Dr. Karen Winkfield: Medicine has been a bit paternalistic in the past. It's changing. We definitely have a lot more work to do, particularly with communities that have been disenfranchised because there are some communities that don't feel that they have a voice. They feel they walk into the doctor and the doctor knows best, or they sit there and the doctor's explaining and they're shaking their head yes. One of the biggest challenges is the fact that we know blacks in this country are dying of cancer at much higher rates than any other racial ethnic group. And the fact that they are not included in many of the clinical trials, or not represented well in many of the clinical trials is disturbing. One of the things that I work on in my day to day is how do you impart information? How do people want to receive their information?

That requires community engagement, and community engagement is not just public outreach. So we see public outreach now with COVID. COVID says, oh, look, we have this problem. We've come up with a solution. Now we have to reach the public to help educate them about why the vaccine or why the treatments. Research shouldn't be that way. Research should be bi-directional. There should be communication with the populations you're trying to serve. There should be communication with the different populations that may be somewhat more distant in terms of geography even, literally, rural communities, or may have other barriers to care, to find out what their needs are, not only from a logistical standpoint, but what are the things they're concerned about? Some populations may not be concerned about living an extra two weeks or living an extra two years. Some individuals may be more concerned about their quality of life.

And if you say to them, look, I can kind of give you two extra years, but you're going to spend every other week in the hospital for those extra two years, or you can have six months and kind of live happily with your family and maybe go and travel the world. What do you choose? So I think it's important to engage the community, but that also means engaging the person who's sitting in front of you. So for providers and care teams to really look at each individual and have the humility to say, what do you need? What would you like? That's something that I think we need to do a little bit better job as providers in this country, is finding out what individuals, what patients, what their family's needs are, and really trying to meet people where they are.

So one of the greatest challenges with respect to access to clinical trials is information. Number one, many times patients aren't aware that there might even be a clinical trial available to them. So it's important for providers to make sure that they're asking people if they want to participate in a clinical trial, especially if you're at a comprehensive cancer center where there are clinical trials ongoing. But to your point, access is an issue. Geography is an issue. We know that 80% of cancer care happens in a community setting. Doesn't happen at a big comprehensive cancer center. And so there are moves afoot to try to bring things closer to where people are into the community. I think the question that I have is really related to understanding what we can do to help improve access from the patient point of view, not what needs to happen at the cancer centers necessarily, but how do we make sure that people have access?

And again, information is access. Information is power. Information is key to making sure that people are aware of what is available to them. That is actually one of the reasons why I even started my own podcast, is to figure out a different way perhaps to reach individuals. There's a challenge. There's a knowledge deficit, just the same way that we see the digital divide with COVID, that there are some households that do not have access to broadband. There are some households that just don't have access to healthcare information. So I do worry about ways that we can try to improve that.

So that library analogy is really key because the smaller libraries can also borrow from the larger. They support each other, and I think that's the model that we're seeing a lot of the comprehensive cancer centers move to. As you know, the Vanderbilt-Ingram Cancer Center has expanded its reach into some of our rural sites and rural communities. Even radiation therapy, which again, you have a linear accelerator which cost millions of dollars, but there's been investment from the institution to make sure that we're bringing cancer care closer to where people are because that's an important component is access. And so the same thing with clinical trials.

Clark Buckner: Great to have you along for this episode of Vanderbilt Health DNA: Discoveries in Action. On our next one, we'll be talking with three people who have different perspectives on the many links between climate change and health. It's a fascinating conversation, and we look forward to having you. To learn more about clinical trials or today's guests, visit listendna.com. You can also find us on Twitter @VUMC_Insights and on all of your favorite platforms @VanderbiltHealth. And of course, don't forget

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