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Welcome to NETWise. This is a podcast for neuroendocrine cancer patients and their caregivers that presents expert information and patient perspectives. My name is **Jessica Thomas**, Director of Patient Education at the Neuroendocrine Tumor Research Foundation.

For today's episode, we're going to talk about some really interesting research that's being done at several locations around the country, and how it shows some surprising ways the course of neuroendocrine cancer can differ for patients who have very similar initial diagnoses. Let's start by hearing from one of the researchers involved in this work.

McElroy: *"My name is Katherine McElroy. I am currently a research resident here at the University of Alabama at Birmingham, currently sponsored by the NIH on a T32 grant for funding my research. We're working on some pretty exciting things, more specifically related to pancreatic neuroendocrine tumors. We're looking at disparities in between patients and outcomes there."*

Dr. McElroy and her colleagues are working with data sets that show that race -- specifically whether a patient identifies themselves as Black or White -- has a remarkable impact on the course of their NET journey.

McElroy: *"So when we're looking at these tumors that are non-functional, that tend to have worse outcomes, what we saw... what our lab saw between Black and white patients is that Black patients were twice as likely to have a decreased overall survival and disease-free survival as white patients. Which means that if all things considered, taking into account the same demographics outside of race, Black patients were twice as likely to have shortened lifespans due to this disease."*

That's a shocking result. And it turns out that these vast differences play out not just in overall survival but in very specific variations in the patterns of tumor growth.

McElroy: "What we saw is that for Black patients with tumor sizes less than two centimeters, which typical guidelines will say it's okay to watch these patients with close follow-up, we saw that Black patients were presenting with lymph node metastasis."

Here's Dr. Brendan Herring, one of Dr. McElroy's colleagues at the University of Alabama:

Herring: "Black patients had much higher rates of metastatic disease in these sub-two-centimeter tumors, compared to the white patients. And it was, like, 25% of Black patients had metastases below two centimeters compared to around 5% for the white patients. And that... that's a huge distinction, right? You're talking about one in 20 versus one in four."

It is a huge distinction that has very important implications for successful patient care.

McElroy: "So, when the guidelines say it's okay to follow up and just continue to monitor patients with less than two centimeters of disease, those guidelines are largely based on white patients. what we're seeing in our studies is that Black patients do not live as long as white patients without recurrence of disease, without recurrence of tumors."

Herring: *"And so that prompted, you know, why could this be?"*

Huge differences like this appear in many forms of cancer, not just NETs. For example, in prostate cancer, studies have shown that Black men are many, many times more likely to contract the disease, and die from it, than white men are.

But even with huge numbers like that demanding to be understood, cancer researchers have traditionally been very reluctant to take on race as a subject for study. Here's Suzanne Ludlow, a member of NETRF's Board of Directors, whose husband, Vince, was an African-American man who passed away from NETs in 2017.

Ludlow: *"I think there's often a hesitance about talking about race within these medical communities, hesitance to focus on that as a subject to seize. There's something that we're not looking at. We're not analyzing... I think one thing I haven't seen enough of is, is how to talk about race, right? Especially in a political environment where race ends up being a talking point, and a divisive one, I think people just don't have the words that- that they can have a comfortable conversation."*

Dr. Clayton Yates is an endowed Professor of Oncology and Director of Health Disparities and Global Equity at the Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins University in Maryland. He's now one of the world leaders in studying the intersections of cancer and race, but when he was a young

researcher, he was specifically directed away from the topic and told that working on it would sideline his career.

Yates: *"I was not going to have a career, yes. (Laughs) Most people felt like I wouldn't have a career in science when I wanted to study disparities in why there were different outcomes based on race.*

So when I was in graduate and I was working in prostate cancer, we were 'right, the African-American men are 60 times likely to get disease and twice as likely to die', and then we wouldn't talk about it anymore. And I said, 'There has to be more to that. There has to be more to that.' And I, and so I just started looking and there was not a lot out there.

It's not an easy question to address. And I've spent the majority of my career trying to address that. What is almost really critical, and what I've dedicated my life to is: show the data. Data, the facts. It has to be very concrete. We're utilizing ancestry, we're adding rigor to it, right? People are doing it in a more so... so we're making a case that regardless of political change, the political climate, the data is the data. We can- we can argue with facts."

The facts, as we understand them, show that the differences in outcomes along racial lines are caused by a wide variety of factors, which we can summarize in a few broad categories.

The first of these is a person's genetics, which of course is related to race because it comes to them from their ancestry. The second is a collection of things that are caused purely by societal and cultural factors -- the way that different levels of racism in American society have caused differences in the way people are treated, the resources they have at their disposal, and the environments that they live in.

Kind of in-between these two is epigenetics, which is about how things like a person's environment affect the way their genetics expresses itself.

Genetics and epigenetics are, of course, easier topics for oncologists to deal with, so let's start with those.

Herring: "We know from other cancers at the very least that there is some interracial difference, at the gene expression level and at the epigenetic level. And also we know that epigenetics is one thing that differs among different racial groups. We found that Black patients, when we did the RNA sequencing, we analyzed that data statistically, and then we looked at the pathways in which the upregulated genes in Black patients tended to fall into, we saw that they had high upregulation of genes that were related to blood vessel development or angiogenesis, which is, in cancer, this is the tumor essentially saying, 'I need more nutrients. I want to grow more.' And the cancer kind of hijacks the body's normal systems for

developing blood vessels to areas that are highly metabolically active. And it uses that in order to get it more nutrients so that it can survive, but then also so that it can spread, and get access to the vasculature, so blood vessel development.

And the other thing that we saw that was upregulated, that's super interesting in this regard, was cell migration, right? So, if you think about the things that are important for developing metastatic disease, those are at the top of the list, right? And in addition to that, we saw that there was some down-regulation in the Black patients of some humoral immune pathways. This is a new thing that is not normally in the body that your immune system, the T-cells, are surveying the cells for, and they find this thing, they develop an immune response to it, the T-cell brings it to the B-cell, and you start making antibodies. This is humoral immunity. So that was downregulated in the Black patient population.

And so, you can look at both of these things and view the stuff that was upregulated as increasing the propensity for metastasis. And you can view this humoral immunity being downregulated as being, a lack of tumor control by the immune system. So that kind of summarizes the big gene expression findings that we had."

Dr. Yates and his team have been doing work in Nigeria comparing the genetic signatures of the tumors of African people and

African American people, and have confirmed epigenetic similarities between them. Some of these seem to be tied to the need to develop immunities to infectious diseases that are more prevalent in Africa than in other parts of the world.

Yates: *"Across our tumor types, we see immune differences is the prevailing difference, the commonality, between African-Americans, based on the percent ancestry that they have. It's this dysregulation of immune response. The most bearing infectious disease was malaria. So if your body could not you know... I'm talking about evolutionary genetic selection, right? So if the, if the person could not battle that disease, then they didn't produce and pass on the genetic traits that allowed them to be able to survive and have progeny.*

And if you think about it, it makes sense, right? So you take a, a group of individuals who are selected in one region to be able to survive largely infectious disease, and now they're in America where this infectious disease is not as prevalent. But now we have factors that are generating cancer and the body has to respond differently. But it was engineered and selected to respond to a different problem."

Genetic and epigenetic factors that are tied to African ancestry are very real and definitely account for a part of the difference we've seen in patient outcomes along racial lines. But they are far from the whole story.

This is because race and ancestry are connected, but they're not the same thing. Race, particularly in America, is an abstract social and political structure that combines ancestry, physical appearance, cultural heritage, class, geography, language, generational wealth, and a hundred other factors.

And so, it's important to note that the studies we are looking at are mostly based on what is called "self-reported race" - collecting data from patients who self-identify as Black or African-American. Interestingly, increased negative outcomes are still significant among people who identify as Black but have only a small percentage of African genetic ancestry.

Yates: *"What is really clear is that the way people perceive you, based on that definition of how they define the way you look. Right? So if I am a Black American, right, and I'm perceived as Black, whether my ancestry, whether my race, whether you call me- whatever you want to call me, society has deemed me to be in a certain category, and therefore I am living in that reality. And therefore, race influences biology because of those factors.*

So we can say race is, it definitely is a made up construct, right? It is, you know... society made up. But for the person who has to live in that culture, it's real and it can affect their health."

McElroy: "There's multiple ways that contribute to the disparities and outcomes that we see, and it's been interesting just to figure that out."

One of these contributing factors is, of course, overt racism - deliberately providing worse care to Black people than to white people.

McElroy: "When it comes to overt racism within medicine, of course it exists. We know that it exists; the studies have shown that."

These kinds of disgusting practices happen in health care just as they happen everywhere. But that kind of behavior is flagrantly immoral, clearly illegal, and often obvious, so it can more directly be found and rooted out when administrators are motivated to do so. More subtle are pervasive stereotypes that come with racial identity and are hard for people to shake, even when they might consciously know they are untrue.

Ludlow: *"You know, a number of doctors have misconceptions about people based on race. And this just from talking with each other, there's these assumptions about how much certain people feel pain, or how much certain... you know, are bones thicker or whatever. And like, no, let's step back from that. Let's do a regular scientific study."*

And There are many other factors at play here too, many of which can be subtle and hard to see.

McElroy: "There's ample components, there's multiple ways that contribute to the disparities and outcomes that we see. So, on my segment of research, what we're looking at is how are those socioeconomic factors at play here? And are there things that we're missing? Are there things that we're assuming could be part of the problem that we're not actually unraveling with dedicated research?"

Yates: "Regardless of whether we believe, how the construct would derive, people are living under that on a daily basis."

Herring: "There's something that's biological here. But I think the thing that's important to recognize is that we have to think about epigenetics - and hence gene expression, which is regulated by the epigenetic landscape - we have to think about these things as not only as indeed being a product of our genome and our environment, Because the things that we are exposed to in our environment, which do differ by culture.

In Birmingham where I live at, right, a ton of Superfund sites... and historically, with redlining, Black patient populations were relegated to these areas where there are Superfund sites. In North Birmingham, there was a coal refining plant that to this day is still super environmentally hazardous. The EPA has been doing all sorts of soil regeneration things to try and clear out toxins,

and this is an overwhelmingly Black patient area. Knowing that there are so many things in the environment that can serve as endocrine destructors and can cause things like pancreatic inflammation chronically in the long term, that can lead to the development of some sort of cancer, we begin to see that there are things that do fall along cultural lines that are going to be distinct that one might classify as environmental, but these things are also going to influence gene expression and genome."

Yates: *"So therefore, people are under certain conditions where, again, the body's reacting to that, and then that's creating a different biological outcome. But that may not be ancestry. That may not be inheritable genes, right? So whether that's stress, or you can think about it... if it's more stress, there's more inflammatory... there's more... could be more inflammation in one state or another. There could be more deprivation because of lack of economics, right?"*

When we start looking at genes that are associated with, not with ancestry, but self-reported race, we start looking at cardiovascular disease, obesity, other comorbidities that we know - diabetes, for example - that we know actually does have anything to do with the, per se, inheritable genes. These are probably associated with social constructs, possibly due to racism, possibly due to segregation, possibly due to eco... low eco socioeconomic status, access to care, all of those other factors. And so it's affecting differential outcomes. Right?"

Even small disparities in some of these metrics along racial lines can add up and cause huge differences in the realities of clinical care. One place where this is clearly seen is in research. Seemingly unrelated factors like differences in average financial status of Black and white people and the physical location of research centers have led to a huge disparity in the demographic makeup of clinical trials. To put it bluntly, the average cohort of patients in a clinical trial is overwhelmingly white and middle- to upper-class, and that's a huge contributing factor in why Black people don't do as well in their treatment journey.

McElroy: "We need to be able to incorporate Black patients into the academic sphere of medicine better, and then we need to see how do we mitigate any of those factors that are prohibiting patients from enrolling in clinical trials and enrolling in scientific studies.

Here at UAB we have another cancer group that has been studying how to incorporate more African Americans and Black patients into clinical trials. And prior to the pandemic, they released a study where they looked at, if patients were asked about clinical trials, would that increase their enrollment in clinical trials? And the answer is yes. It's just that we're not asking enough patients, 'Do you want to participate?'

And then to take that a step further, they also looked into, for the people who are enrolled, how many are actually starting? How many are consenting to the study and starting, or how many are dropping out due to the inability to meet the eligibility criteria? So those are the preset conditions that a patient must exhibit in order to complete the clinical trial, because we want to make sure we're studying the right thing and that there's not other factors that could be swaying our outcomes, either direction. And we saw that there was a drop off there, too. So not only are patients, specifically Black patients, not being asked, they're also not meeting eligibility criteria at increased rates compared to white patients.

And combing through the data, there's also the barrier of finances. We talk about increasing clinical trial enrollment, and we talk about, yes, clinical trials are sponsored and funded, but we don't talk about how much parking costs. We don't talk about how much time off from work costs. We don't talk about childcare costs. There is a discrepancy of leisure time and free leisure activities between races. There's so many other elements that have to be taken into account for a patient to participate in clinical trials, and we need to address that. We need to- it's on us as a healthcare system to address that."

The need to be sensitive about these issues extends not just to research, but to care. Here's Dr. Heloisa Soares, a medical

oncologist at the Huntsman Cancer Institute at the University of Utah:

Suares: *"Also if patients are coming from... financially from a... have limited resources, you actually need to spend more time understanding what the patient can afford and cannot. You cannot just prescribe a medication and say, 'Go to the pharmacy and get it', and then two weeks later when you have a follow up, you hear that, 'Oh, I couldn't do this medication because it wasn't on the formulary of my insurance and then I couldn't', or 'I couldn't afford buy the co-payment' and so forth. This is all part of the work that we should be doing understanding the patients that we have in front of us. And yes, might take more time, but it comes with the territory and the job that we do."*

A huge part of this is the need to communicate, for doctors and researchers to proactively reach out to minority communities. There is a significant thread of cultural distrust of medicine and healthcare among African-Americans, and rightfully so. Segregated medical systems both neglected their community for centuries, and also committed outright atrocities like the notorious Tuskegee syphilis experiments. These deep historical wounds have left a responsibility for health care providers to work extra hard to show that they have the best interests of Black people at heart, and that they are listening to and respecting these patients.

McElroy: *"I can say that I've definitely seen it in my community. I see what we all kind of have in the back of our mind is evidence of mistrust of modern medicine. There's been a lot of incidences [sic] in the Black community that have been targeted by academic medicine in the pursuit of study and research, where Black lives were not held with the same dignity as white lives.*

And so, though a lot of this could have happened generations ago, I still believe at times it happens. And there are moments where people do not feel that their practitioner, their provider (is) having their utmost clinical concern... that they feel that there's not a personal relationship with their provider, therefore, there's not evidence of trust to where they want to pursue, like, the care that they need. But if they don't trust their provider, they're not believing that their provider has their best interest at heart. So whenever recommendations are made, whenever plans are made, it's hard to meet together. The meeting of the minds is limited.

And so, especially in these critical conditions, when patients are being asked to provide the utmost trust of their health and their outcome to their provider, but they never established a relationship of trust with their provider, it's difficult. And that is a huge barrier to patients receiving care."

Yates: *"So, the first thing you have to do is be trustworthy. You cannot expect someone to trust you if you are not trustworthy. So, you have to operate ethically. You have to understand what is going on in the community. You have to treat people with respect. "*

Of course, this is easier said than done, especially working within a health care system that often prioritizes efficiency over connection.

Suares: *"I think it's more about the general personality of the physician versus because of the patient being of a certain race or ethnicity or social status, right? There are some folks that are very, you know, task oriented. They want to get in, they want to get out, they want to do their work; saying, 'Oh, I just don't want to spend a extra second of my time doing the extra leg of work because of, the special' -- quote unquote 'special'-- 'needs of the patient' rather than, 'Oh, I don't want to deal with the Latino, or the Black population because of so and so.' And that's me trying to believe in the good of people."*

McElroy: *"I think back to my clinical encounters with patients -- albeit I'm a resident, so I'm very early in my training -- but I think I have the ability to wear two hats. I wear the hat of the provider, but I also wear the hat of... likened to the Black patients that we serve. Like, these are my community members. These are people who I see could be family members. And I can see where the evidence,*

or where the lack of trust, can stem from. Providers are stretched so thin. To provide ample care - quality care - to patients, and to have a lot of differing needs that they have to accomplish just to be able to provide that care. And in a perfect world, we would have endless amount of time to sit with patients, to walk through the level of understanding that they have about their clinical condition and the way to move forward. And we would have a lot of time to build that trust.

You don't immediately meet someone and tell them all of your deepest, darkest worries and concerns. That takes time to develop. And unfortunately, as providers in a provider shortage, we don't have that time. And so our job is how to foster these trusting relationships. How do we convey that we are here for the people that we serve? And how do we consistently show up to do that? Not only just tell the patients, but what are the actions that we can take that are going to be concordant with our purpose to serve equitable patients with equitable care?

And I think that it's easy to say that time is a constraint, but I think that we need to really step out into the community and show the community members that we are here to help. We are here to serve. We're not here to sit behind our offices and in our clinics to just give direction on clinical care, but we want to know who you are so that we can best serve you.

And I think that that's on us to be able to foster those relationships. The patients know that you're smart. What they don't know is that you're on their side."

Roberts: *"So, my name is Erica Roberts. I live in Alabama, (the) lower Alabama Delta to be exact. And my father's name was William Preston Roberts, Jr. He was diagnosed in 2008 and he passed away in 2016.*

He actually started to have symptoms in 2005. I was actually away at the time studying abroad in Costa Rica after I graduated from college. And he and my mom were supposed to come there and visit me, and he was saying that he was having some gastrointestinal issues where he'd just get nauseous. He'd be throwing up for a few days and then he'd be okay. And he didn't really know what was happening. And that had happened a few times. And my dad wasn't a sickly person, so for him to be sick... there was something clearly wrong. So he started going to the doctor, I would say, in the fall of 2005, first with his primary care physician and then to various specialists. They didn't really know what was wrong with him. But my dad was the type of person who was not going to stop going to the doctor until they could tell him what was wrong, because he knew that something wasn't right.

It was frustrating for him. It was extremely frustrating. Like I said, he knew something was wrong and even, I think... I hate to poo-poo physicians, like, I don't want to put

down physicians. I have physicians in my family, and I know that they are hardworking individuals and oftentimes they have an uphill battle... But I think my dad's frustration a lot of times was, 'I just wish somebody would say, 'I don't know. I, I don't know what's wrong with you. You know, I'm trying my best to figure it out, but I don't know, so I'm going to keep working at it, but if there's something else you can think of or someone else you want to go to...' I think that if they had been a little more encouraging it would've helped him, because when you go to a doctor and they're telling you there's nothing wrong with you, you know, you start to internalize that. You start to wonder, 'Am I crazy? Something is not right. I feel it. I know something is not right, but every time I go in, you tell me that I'm fine.' And it took a lot of determination on his part. I give him so much credit, for continuing to go, because I don't know that I would have.

So, trust is important, and I think for many of us Black and brown people there has been historically, and sometimes continues to be, a lack of trust. I think that my dad, particularly, in his journey felt this lack of belief when interacting with physicians that 'you don't believe what I'm saying to you.' And I think for him, that was more frustrating than anything. And he did that for three years until someone finally looked at a scan and said, 'I see something on your liver. Not sure what it is, but maybe we should do a biopsy.' And he starts this... what turned out to be an eight-year journey with cancer.

He had surgery first in 2008, in August. Then he was referred to an oncologist, also in Birmingham. He went there once a month and he had Sandostatin shots. I want to say every other month, he would have an appointment with his oncologist, have a scan, blood work, and meet with a doctor. And he did that for eight years, driving back and forth to Birmingham every single month.

In 2016, really, 2015, end of 2015, my dad started to lose weight. And it wasn't a little bit of weight; it was a lot. And my dad, for the majority of his cancer journey, you could not visibly tell that he was sick in any way. He looked the same. He went to work. No one knew really outside the family. Not many people knew that he had cancer or that he was getting treatment for cancer. It's not something that he shared. But, in 2015 you could visibly see a shift in him. And it concerned all of us, especially him.

So, I think at that time I was going to the doctor with him pretty regularly. And he would ask like, 'How am I doing? What's going on? Am I okay? I seem to be different.' And his doctor would reassure him, 'No, you're fine. Your tests are good. Everything looks good. You're going to outlive me. You'll probably outlive me.' And we heard that, but there was this... again, my dad just knew 'Something is not right. Something has changed. I don't feel the same way. I'm losing a lot of weight.'

And so, we sought out other- he sought out other opinions. We went to Cancer Treatment Centers of America in Atlanta. We got there, same thing, 'Oh, you look great. Your tests look good. We wish all our cancer patients looked like you.' But he kept losing weight. He kept losing weight. By the summer of 2016, he was starting to feel sick and not just, 'Oh, I don't feel well today', but 'I have no energy. I'm vomiting. I'm sick.

On one of these particular bouts, I took him to the emergency room. They decided to admit him. He was admitted at the hospital. When we got this... this kind of news: the emergency room physician came in after they admitted him and he said, 'you have months to live.' I'm, 'What?' I thought I misheard him. I said, 'What did you say?' He was like, 'Yeah, you maybe have six months. There's nothing that we can do for you.' Now, my dad's been going to the oncologist every month for eight years, and he's never heard anything like this. So both of us are looking completely bewildered and confused.

The doctors came in and were talking about palliative care. All of this happened within the span of 30 days. We went from thinking my dad was on the road to, whatever, getting back on his feet, being fine, to 'We're releasing you. We recommend hospice. Go home. To die.' And within a week... no two weeks, that was around the middle of September, my dad died on September 30th at our home.

So it was just... I appreciate his oncologist. I like his oncologist, but he wasn't transparent enough. He wasn't forthcoming enough. He wasn't honest enough. My dad had been going to work every day. And he just... he said to me, 'If I had known, if I had known that this was it, I would've lived this, at least this year, differently. If I had known that I was terminal, I would have taken some time for myself.' I think overall he just felt like he should have had more time and I... that's all we all want, more time. And so that was his frustration with the process.

I remember getting his death certificate and it said, 'stage four cancer.' And I just looked at it and I... I mean, yeah. Of course, right? He had stage four cancer. But I never knew that. So when I saw it on his death certificate I'm like, 'Stage four. No one ever said 'stage four.' I thought my dad was fine. I really did. I... thought he was fine.

The healthcare system in general, I think, is a difficult system. It's difficult to navigate. It's difficult to deal with the finances and insurance of it all, so it's already a difficult system. When you add being brown into that system, when you add all the history into that system, I think it is even more difficult to stick with it. And it's easier to opt out, which doesn't do us any favors. We end up not getting treated until it's too late to really get adequate treatment, which is unfortunate.

For me, in my personal journey, it has been more challenging for me to continue to push, continue to advocate for myself. I don't want to say I tend to give up, but I tend to move on, and sometimes moving on means there's a gap in care, which can't be good. And I think that's true for a lot of people. If they go to the doctor and they don't feel comfortable, accepted, believed, they may tell themselves, 'Oh, I'm just going to see somebody else.' But, that may take some time down the road, and it may be in that time you start to feel worse, and then that's what prompts you to go back and start the process over again. So, I don't know what the answer is, but I definitely can see the problem.

I fully acknowledge that a lot of people with my dad's story, by the time they're diagnosed it's too late really to do anything. I appreciate that time. But I think for me and my mom and my brother, I think we would've spent our time differently had we known the seriousness of his illness at the time that I presumed the doctors knew.

Do I think his journey could have been even better? Absolutely. Absolutely. And. Do I affirmatively know that race played a role in that? No. But I am a Black person on this planet. And I know that it does play a part in many things. A reason I support NETRF is so that, you know, some other girl somewhere 10 years from now, hopefully her dad

will get the best possible care all the way through, and that he'll have a better outcome than mine did."

The focus of this episode is the African-American community, but of course they aren't the only ethnic group that has specific genetic characteristics that affect cancer or challenges in their relationship with the health care system.

McElroy: *"I know that a lot of our discussion has been centered around, you know, Black patients and white patients, and the discrepancies of lymph node metastasis at different tumor sizes. But we also looked into Asian patients as well. We want to make sure that we're looking into everyone, and we saw that for tumor sizes greater than three centimeters, which the guidelines say that it's indicated for resection at this time, those patients with tumor sizes greater than three centimeters, Asian patients were less likely to exhibit lymph node metastasis.*

So, what does that mean? That means that maybe we are rushing Asian patients to surgery prematurely. Maybe if we had a larger patient cohort that comprised of a larger Asian patient subset, we could better study at what tumor size are Asian patients having increased likelihood of lymph node metastasis, and when do they actually need to go to surgery?

I think that similar to the Black patient population, we just don't have enough patients in the data set to make

definitive guidelines based off of specifically Black patients or specifically Asian patient, but we need to incorporate these patients because we want to make sure that we are giving the proper individualized care and that we're not taking patients to surgery too soon or too late."

Oftentimes, immigrant groups can come to the United States with very different cultural contexts, which can lead to very different desires for how to communicate with their doctors. For some Chinese families, for instance, there is often a desire to keep elderly family members uninformed about the state of their cancer, or even that they have cancer at all.

Suares: *"How direct is your communication? Patients don't like to talk about how long do they have to live and the families don't like the physicians to talk about that with their parents. So how many times you can get phone calls from the family members saying, 'Please do not tell my dad's dad that he has stage four cancer and then he's going die from this disease soon because this is a terminal disease.' Which I find fascinating, that people, the families, try to protect them. Patients sign... many, many institutions, they sign informed consents for chemotherapy. They say that they have a cancer, they, you know, and then the families still try to, you know, hide that portion. Right? And then how, how do you address these things? It has been fascinating to see how cultures can be very different."*

This flies in the face of both the American doctrine of informed consent, and also the need we were discussing earlier in this episode to make sure patients are both actively informed and actively listened to.

Dr. Soares, who is from South America, has also observed a totally different kind of breakdown in communication in her own community. In many Latino cultures, she sees an attitude that discourages disagreement with doctors, making it hard to have the kind of back and forth that leads to proper diagnosis and good treatment choices.

Soares: *"So it's just... I think the Latin culture feels that physicians are, sort of, above them and then they need to be respected and everything that we do should be done without asking questions. One of the challenges, particularly when folks have just moved to the US, was to understand that they had a voice and they had a say on their care. I think a lot of patients come with the sense that they should not be questioning the physicians or the providers that they're seeing, that you will be interpreted as a bad thing to do, or to be a bad patient, to ask questions and to challenge or ask why such treatment has been decided for the patient. Also, patients had this feeling that if they were asking about second opinions, that would really be a high offense to the providers, and I don't see in that way whatsoever."*

I can see from my own family in Brazil, right? When they go to their multiple doctor's appointments, they're always afraid, afraid of asking questions because they don't want to offend the doctor. And I was like, 'What do you mean? It is your job as a patient to ask these hard questions and to expect some follow-ups on the items that you ask.'

For instance, we prescribe chemotherapy for patients and then they develop a lot of nausea and vomiting, and they are afraid of calling the doctors to let them know that they're having a nausea and vomiting because they don't want to, quote unquote, 'bother the doctor,' and they feel like they just wanted to accept that that's the way that it is because they're getting chemotherapy. And this was actually super eye-opening for me when I was in New Mexico because I'll have these patients coming in, like, with a week of severe diarrhea now, then vomiting, and they will come to a super dehydrated because they wait until the appointment time to let me know how they're feeling. And even though when they came, they were already trying not to make it as a big deal and I will be like, 'Why you didn't call me?' And it was like, 'Oh, I didn't want to bother you'. And I was like, 'That's my job. You're not bothering. That's what I'm here for: you, and you shouldn't be having all the symptoms.' So, it was very interesting to me. One of my jobs was to try to empower patients to understand that, yes, they have a voice. They have a say, and it's okay to ask, um, questions and your physicians to not be

upset with you, or not want to care for you because you are asking good questions about your care.

So, this is something that I think when folks are already here and are embedded in the culture, so the second and third generations, I see less of that. I see that then patients feel more empowered to seek education. But for the folks that are just coming here, there's a lot that we have to work and make sure that we empower patients to ask questions and to educate patients."

And with immigrant communities, of course, any communication at all can be challenging because of language barriers.

Suares: *"Yeah, no, it's super challenging, because you think you are explaining properly to the patients, but then you always ask them to repeat to you what they understood. And that's when you truly have a better sense of what has been actually processed. So, you know, when we hand out information in English to patients and that's not their first language, that's a recipe for disaster, right? Because they are afraid, or shy, of saying that they don't understand. So we try our best to provide the information in the language that the patients have. It's such a multifactor issue that comes along with coming from a different culture and facing a new place."*

And African-Americans are not the only racial group who have a well-founded historical mistrust of the American health care system.

Herring: *"I identify as Native American. My father grew up on the Poarch Creek reservation, here in Atmore, Alabama, which is about two hours south of Birmingham where I live now. And one of the things that- it's not so much... this is a very small reservation that we live on, in Atmore, but when I have visited this reservation as well as... I had the chance to go out to Oklahoma and visit the flagship Creek or Muskogee reservation that's out there that's much larger. And one of the things that I've seen, not only in that personal experience, because I did go by the IHS hospital that was there, but also that is really well tossed out in these national data sets, is that the healthcare's not great. And Native Americans are -- in accordance kind of with the analysis that I have presented here -- are at risk for a number of other health outcomes, bad health outcomes: severe diabetes, alcoholism, among many others... cirrhosis. They're at higher risk than, say, someone with proximate European ancestry.*

And I guess one of the things that I haven't mentioned is that, in the lead up to this, when I was initially looking at publicly available genomics data sets so that I could try to analyze this -- look at interracial differences in the genomics -- one of the things that I first found was that there's a really low representation of Black patients

in the published genomics datasets, right? It's around 1.2%, right, as opposed to around 90% white patients. But there wasn't a single Native American that was sequenced in that. Not a single one in all of the genomic studies... that at least I found, in a very thorough review of the literature- this is a published paper in cancer research communications now. Not a single Native American patient had their tumor sequenced, and that was something that was difficult for me to come to terms with.

This is a trend that is echoed across all cancers, right?, is that there's just really low representation of these different subgroups. And so, ultimately the data that we gain from sequencing primarily European cohorts here in the United States is just extrapolated to the general population. There are national initiatives, such as the 'All of Us' program, as well as, say, the UK Biobank in the UK, that aim to remedy this in some way, by sequencing patients from really diverse backgrounds, whether that be ethnic or racial, but there's still a long way to go."

So how do we, as a health care community, start to address these issues? Specific research initiatives that aim to correct the lack of diversity in our genetic understanding are crucial. Also crucial is better, more consistent communication with patient communities who are not white and wealthy.

McElroy: *"The first thing that comes to mind is compensated community outreach. I think that it needs to be built into*

the work week and not expected of providers to produce on their own personal time. I think that it is a part of healthcare to be able to engage with the community and to kind of put the onus onto providers to participate in this engagement in their personal time... well, providers need personal time as well. They have families, they have obligations outside of their workspace that they have to attend to. And a lot of times, providers who are doing the hard work, who are engaging with the community, who are, you know, understanding the need to educate and to engage, they're having to give up their free time to do that. That's not in the clinical workday. And so, I think that if we were able to find a way to compensate and involve community engagement in the work, that could be a huge, huge change in understanding the patients that we serve."

Yates: *"We developed patient navigator programs, right? So, we met the individuals in their communities with people they trust, people who could sit down and could help triage them to all this. So the resources were there. The resources, when I was at Tuskegee, you can imagine not understanding what was available in Birmingham, but our patient navigators would say, 'Look, there's this intervention. There's this trial. There's this, you know, program going on that you can benefit from. Here's the information. Here's how I can help you. You have questions, come back to us.' Clinicians are busy, but that navigator, or we call them Community Health Navigator, was the mitigator who could spend time."*

What we cannot do is pretend that race is not a factor in patient care and patient outcomes. Both the biological and social factors we've discussed in this episode are too real and too important to ignore.

Ludlow: *"So, part of what I would love to see is some way to have those conversations, to make sure that we all get where I think we all really want to be, which is that the right options and treatment, and testing and everything is right for that person, right? That individual is getting what he or she needs. And so how do we talk about how, you know, people have access or don't have access and all of these kinds of things in a way that is constructive to that point? It can be gender. It can be language. It can be location. I mean, there's a variety of ways that you need to think about when you talk about fairness."*

McElroy: *"I will very loudly speak that being colorblind is not the way. When you ignore someone's race, you ignore a large part of who they are. You ignore a large part of their culture, a large part of what's going to contribute to their clinical condition and what contributes to them as a human, right?"*

Even though in that office space you might not see color, the color is already there and you're just choosing not to not to address it. And I think that in one way, people, when they say that, they want to say that I treat everyone

the same. Unfortunately, we live in a society where that is not enacted. And I think that to provide quality care, we must, we must, we must consider the other things that come into the office space, into the clinic space with the patient. Because that's what they're going to leave with. They're going to leave back to their condition, back to their home life, back to their community.

And those things come into the office space. To be able to provide that quality of care to be able to treat patients with the same quality of care, we must educate ourselves on how to do that -- look [at] what is coming into the clinic space with the patient, and how do we be able to best serve the patient with everything that comes with them. Let's bring those things into the room, invite them into the room, invite those conversations. But it is up to us to learn about the patients that we serve, rather than just the cells and the tumors and the biology that they serve. Learn about the humans too, because that is how you're going to build trust."

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