Dr. Joni Rutter

October 28, 2022

Barr: Good afternoon. Today is October 28, 2022. My name is Gabrielle Barr, and I'm the archivist at the Office of NIH History and Stetten Museum. Today I have the pleasure of speaking with Dr. Joni Rutter. Dr. Rutter is the acting director of the National Center for Advancing Translational Sciences (NCATS) [she became permanent director in November 2022]. Today she is going to be speaking about the trajectory of her career as well as how NCATS has handled the COVID-19 pandemic. Thank you very much for being with me.

Rutter: Thank you, Gabrielle, for having me. It's an honor to be here.

Barr: Will you please discuss your early life growing up in Kansas? Were there any formative experiences or lessons that really shaped you as an adult?

Rutter: There are many experiences, I will say, but it's wonderful to be a Kansan. My mother's name was Dorothy, so that was pretty much one of the most informative experiences—having a family with my mother being named Dorothy, from Kansas, having a dog named Toto, and having an Auntie "Em." Lots of stereotypes. When I was growing up—this is the early 1970s—my mother had a magnet on the refrigerator. That magnet said, "Don't encourage your daughter to marry a doctor, encourage your daughter to be a doctor." In that day and time, that wasn't typically what was expected. But my mother was always very proud of that magnet—and then very proud, of course, when I pursued getting a doctoral degree. That was really great. As far as other formative experiences, I played a lot of sports, and so I learned the real value of team sports and team science—bringing different expertise together to try to be successful. That was, I think, a critical thing for me in terms of how sports really shaped my way of thinking on how to be successful in life. In that day and time, there were no cell phones and there was no internet, so everything was really about relationships and about working with people. With cell phones and the internet, we don't have as much person-to-person contact, and I think that's something that I feel very lucky to have really cherished and grown up with. Then, lastly, my dad was an explorer. He was very curious about everything—and still is at 91 years old!. He wanted to know about everything. He asked a ton of questions, and so I think both of my parents really imprinted me on how I got to be where I am.

Barr: Were you interested in science even as a child?

Rutter: I was. When I was in high school, I had appendicitis and an appendectomy and that was my first kind of query into saying, "What happened here? Can I see what happened?" They actually brought out my appendix in a little jar so that I could see what it looked like after they took it out of me. That just made me more curious. Then I worked for a variety of years as a phlebotomist in our local hospital and learned the ropes—and got curious about all things related to science and medicine. So, yeah, that was pretty effective.

Barr: That's really interesting. What made you move from Kansas to Massachusetts to attend college? Can you talk a little bit about how you became interested in genetics?

Rutter: Sure. Kansas to Massachusetts sounds like a funny thing and it kind of is. I had a friend who was a professor at a college called Eastern Nazarene College, and I knew him from my days in my hometown of Garden City, Kansas. He said there was a wonderful little—very small—biology program at that school and he thought that I should check it out. And I was kind of interested in seeing more of the world than just what Kansas had to offer. I loved being in Kansas, but I think that was an opportunity for me that would allow me to sort of see what else was out there, especially in science, and think about opportunities of what I might want to do in the future. So, that's how I got to Massachusetts. I went to the college that I mentioned—Eastern Nazarene College—for my graduation, then stayed on the East Coast and moved up to Hanover, New Hampshire, to go to graduate school at Dartmouth Medical School.

Barr: It's very unique because your graduate experience was a genetics program in medical school where you earned a Ph.D. in pharmacology and toxicology. It seems a little bit disparate from the outside. Can you talk about how those things intertwined?

Rutter: Yes. I guess this is classic translational science. At the time, I had done some research in a lab doing human genetics and I was looking for a gene that was responsible for a disease called neurofibromatosis type 2. It's a form of rare disease. I worked on a few other projects as well there, but that got me interested in human genetics specifically. When I went to college, there wasn't a genetics program, and so that's why it was a little convoluted. At the Dartmouth School of Medicine, there was a program on pharmacology and toxicology, and so I did my degree with Connie Brinckerhoff, Ph.D., who was a researcher in arthritis and rheumatism and really studied rheumatoid arthritis for many years. I was interested in looking at rheumatoid arthritis, especially if there were genetic underpinnings in rheumatoid arthritis. That's how I got interested. I was able to do some of that genetics work that I had learned when I was a technician and apply it to my graduate training. That's how I started. I brought that to the pharmacology and toxicology program, and it really helped me move fairly quickly through the program and achieve my degree in pharmacology and toxicology. It's kind of marrying genetics and pharmacology. There's even a discipline called pharmacogenetics and its essentially how genetics affects a person's ability to metabolize drugs or why drugs are toxic or why drugs are efficacious. Genetics has something to do with that and where we can find that out. That's why I thought genetics was very important—for that understanding.

Barr: You mentioned Dr. Brinckerhoff. Did you have any other mentors, classes, labs, or work experiences that had an impact on the trajectory of your career, particularly after you graduated?

Rutter: I had so many mentors. Dr. Connie Brinckerhoff, of course, was my dissertation advisor and wonderful mentor. She had an indelible influence on me. To this day I hear her voice in my head, largely when I'm writing something, and I think I'm getting lost in my writing. When I was writing my dissertation and papers from the work I had done in her lab, she would go through and read my papers. She'd say, "You know Joni, you just need to press the delete button more often." And so, I have taken that to heart ever since, and I think she's made me a better writer because of that advice. I've used that

ever since. Also, during my career within Dartmouth, there was a very sobering experience. At Dartmouth Medical School, there was a woman named Karen Wetterhahn and she was doing research on organic mercury. She was part of the Superfund programs looking at toxic effects in the environment. Unfortunately, during some of her experiments in the lab—she was doing everything that was right and good—but unfortunately some drops of that organic mercury were spilled on her gloved hands. Unfortunately, gloves don't actually protect you from that mercury exposure. From that very small exposure, it was toxic enough to be fatal and so a year later she unfortunately died from that exposure. As a student during that time when she was teaching, that also made a pretty large impression on me about the importance of safety in the laboratory as well as the importance of understanding the toxic effects of the environment—and how it's important that we understand those and try to address them as much as possible. That's another area that we do here at NCATS, is the Tox21 program. I'm sure we'll talk about that in a minute. All of these sorts of things have come together as influences early on and kind of come back and you get to apply them.

Barr: Will you share a little bit about your fellowship at the National Cancer Institute (NCI) within the Division of Cancer Epidemiology and Genetics, and what your research focused on? You worked a lot with the HER2 polymorphism and breast cancer risk in certain ethnic populations, you looked at the BRCA genes, and you also looked at the heterogeneity of risk for melanoma pancreatic cancer and other digestive cancers—a lot of different things when you were there.

Rutter: It was a lot of different things. It was in a lab of population genetics and so that has kind of a wide swath of things that we could do. But being in the Division of Cancer Epidemiology and Genetics (DCEG) was just a wonderful experience. The Division of Cancer Epidemiology and Genetics is an intramural program within NCI, the National Cancer Institute, and it was one of those experiences where I could walk five feet down the hallway and be meeting with a world expert in that area of epidemiology. Our staff at NIH generally, and in DCEG specifically, are no exception—world renowned leaders in their fields. It was such a pleasure to be able to do a postdoctoral fellowship with that sort of group effort of mentoring. I tried to talk to as many people as possible to help inform what I was doing, and I think that helped me. It ranged from looking at BRCA1 and 2 genes to looking at founder mutations in the Ashkenazi Jewish population and how those came about in terms of manifesting certain diseases. For the most part, we think about BRCA1 and 2 as being related to breast cancer in women, but they're also related to ovarian cancers and other types of cancers as well as male breast cancer and prostate cancer. I looked at some of the environmental influences that might help affect those outcomes in certain families who have one single mutation but might have different manifestations of the types of cancer that they ultimately get. So, we tried to understand if there were other types of influences besides genetics that could be important for that. So, it was a really exciting area to be able to look at that and really rely on the expertise at NIH and NCI for what I could do there.

Barr: When I was reading about the heterogeneity study, I thought it was just really interesting how a lot of different things didn't really make that much of a difference. If one person had one kind of cancer, it didn't make a difference about people getting another type in the family.

Rutter: Yeah, and at the time, I think that's right. That's why it's always important to continue to go back and look at those types of questions, because now that we know more about the biology, might we start to see a little bit more of that specificity where those interactions might be important?

Barr: Let me switch from studying the genetic aspects of cancer to looking at the genetic aspects of substance use disorders—when you joined the National Institute on Drug Abuse (NIDA) as the associate director for Population and Applied Genetics in the Division of Basic Neurosciences.

Rutter: With my postdoctoral work under my belt and doing a lot of that work—I was looking at Mendelian cancers, certainly with BRCA1 and 2, but I also looked at other polymorphisms related to melanoma that were not necessarily inherited, but some of them were—I was interested in looking how we could look at common genetics and how the environment might influence those. So, at that point in time, I switched from the intramural side of the NIH equation to the extramural side and was lucky enough to work as a program officer at the National Institute on Drug Abuse—to be thinking about how we can apply these principles in more common diseases. At the time, too, we were just starting to get our feet under us in terms of genetics and how it really impacted disease, especially common diseases. You don't often think about addiction as being a genetic disease. Unfortunately, a lot of people viewed it as a moral failing or something along those lines, and that couldn't be further away from the truth. What we really set out to show was that there were genetic influences on addiction, and I think we showed that very well in the work that we were able to support. With that, we had a genetics consortium that had been established. I continued that work to look at a variety of different kinds of outcomes from addiction, specifically nicotine dependence, opioid dependence, and other things. For the nicotine dependence piece, one of the key features that we were able to show was that there was a pretty large genetic impact on people who have nicotine dependence. It's certainly in those people who smoke quite a lot of cigarettes a day versus a low amount of cigarettes per day. The people who were very high per day cigarette smokers tended to have this genetic influence in the nicotine receptor. It's not a rare nicotine receptor, but it's not the usual kind that we tended to think of, and it's expressed very specifically in certain brain areas that control addiction and reward, so we were able to find that genetic impact on nicotine dependence. That was really one of the new findings to the field and it really helped open up the idea that we could look for treatments, perhaps, that could be effective.

Barr: While you were at NIDA, you also helped coordinate the biospecimen repository, and you were also part of the NIH Epigenetics Roadmap Program. Can you speak a little bit about your role in those efforts?

Rutter: Sure. For the epigenomics program, this was a team of individuals from the National Institute of Environmental Health Sciences (NIEHS) as well as NIDA, and this was a Common Fund program to look at epigenetic effects. Epigenetic effects are things that are on top of the DNA and [our goal was] to figure out why and how things can be controlled by expression. That was really an important initiative to lay the landscape of what looked like a variety of different tissues and cells. That was the program, and my role specifically was really to help establish a database for that. A lot of the work that I had done in the genetics consortium also was to establish that repository and database. It seems to be a thing that I do—develop these databases. But for this particular one it also got me into the policy realm of why it's important to understand the security and privacy terms and policies related to databases. I had worked

with our collaborators at the National Center for Biotechnology Information, NCBI, and NLM [National Library of Medicine] to help the NHGRI [National Human Genome Research Institute] work on establishing policies around genetic databases and how we should really make those available to researchers and how we needed to handle that. Out of that discussion came the database of Genotypes and Phenotypes, or dbGaP, so I was part of the group that helped implement some of those policies for that program to get it up and running. That was also a new area that I was getting into—really understanding the policy work that needed to go hand-in-hand with the scientific work as well.

Barr: In March of 2016, you became the Director of Scientific Programs for the All of Us precision medicine initiative. You were the first hire! What did you find exciting about this opportunity? Can you also discuss some of the challenges in laying the groundwork for this very unique and ambitious endeavor, including designating all the categories for the underrepresented individuals and all the efforts to recruit everybody? It's quite an effort.

Rutter: You hit the nail on the head on just about everything that was exciting about that program and still is exciting about that program. It's an unprecedented program—an opportunity to get a million people in a database and just capture a variety of information that they're willing to allow researchers to be able to use and learn and understand. The way that I think about it actually came from the first inaugural director of that program, Eric Dishman, when he talks about how he thought about it. It made an imprint on me. This is so important because we had just had this experience with Hurricane Ian that ravaged Florida. It was just really disastrous, and we've had experiences with other hurricanes. What we know, though, is we've been able to track those hurricanes along the way, so we know just about when they're going to hit, we know what wind speed they have, we know trajectory—all of that sort of information. That's what All of Us does for health. It can be able to capture all of these different data points in the "ocean" when you have all these "buoys" that have these sensors on them. That's what used to help track these hurricane trajectories. It's really about science and how we can sense and track biomarkers and data points and then start to predict some of those outcomes that might happen. With All of Us, I really saw that as a key way of starting to get information about individuals that could really help us identify and start to track potential trajectories of a particular disease manifestation. Then hopefully we can use that as a way to prevent them from happening, as opposed to treating them on the back end. It's a long ambition and aspiration for that, but I think that is really the hope and still what I see coming out of that program. The only other thing I'll say is that I'm super proud of the idea that it overrepresents the underrepresented in biomedical research, and that was something that I had a big role in—working with the community to ensure that was going to be the case as we established that resource, and I think that it has really lived up to that and will continue to do so. I hope that will give us a lot of insights moving forward in health equity and helping us on the prevention and treatment of diseases as well.

Barr: Yeah, how do you hope that genetics and precision medicine will be incorporated in routine treatment of patients—like in the doctor's offices? Currently, that's not so much the case.

Rutter: That's right. If you go to your eye doctor, that's where you see it more, because that is all personalized medicine pretty much. If you ever had a blood transfusion, that's another area where it's definitely personalized medicine. So how we can leverage that kind of thinking in more of these kinds of

diseases? The more we learn about genetics, the more I can see that really happening. We have indications of that too, with the newborn screening program that we have in the United States. It's differently implemented across the different states, but I think as we learn more and as costs come down for doing those types of technologies, we'll see more and more of that, and we'll have more opportunities to bring that into access for all patients.

Barr: I was reading that in the past, questions about whether your family had a disease were not even on the paperwork. Then that got changed, especially with addiction. Can you talk about that? That's very interesting.

Rutter: That's right. In fact, NHGRI did a pretty big push on getting those questionnaires implemented in the clinics so that every patient would be asked about their family history. Then, as it turns out, All of Us actually adopted those sorts of questionnaires because it was important to have as part of the information that was gathered for people within the All of Us program. That was really helpful in identifying people who did have a family history because they may know of somebody in their family who had a cancer, but they didn't realize that may mean that is an inheritable cancer—and that screening should be done on them so they can identify and catch that earlier. It's a very powerful tool. You don't even have to take blood samples to do the genetics. If you understand the familial phenotypes for some of these familial kinds of diseases, that gives you a really great advantage to how you can think about their treatment.

Barr: When you joined NCATS in 2019 as the deputy director, what were some of your priorities?

Rutter: [laughs] Good question. I think a lot of my priorities were to, first of all, get a lay of the land. The space of translational science is things that are beyond basic science. We typically do foundational science at the NIH, and then we also do translational research and clinical research at the NIH, too. But that's all NCATS focuses on, that translational and clinical piece. It's all the pre-clinical work that needs to be done for drug development, and then the clinical work that needs to be done for clinical trials and other types of activities. For me, it was about understanding the genetics and applying them in broader programs in our research and expanding ways to be able to do more in rare diseases and understanding how we can apply more thinking behind database development and better define the landscape in rare diseases.

Barr: Then very abruptly COVID hit in your first year. When and how did you learn of the novel SARS-CoV-2 virus and begin making preparations for the safety of NCATS staff—as well as the administrative responsibilities of shifting the research to COVID-19?

Rutter: That's a great question. First of all, certainly in December of 2019, we were watching things on the news that seemed odd and not really knowing what was going to happen. Then it started to become more and more apparent, of course, as we were starting to hear about cases within the United States. That was a tough time, I have to say. There were a lot of things going on in understanding how we needed to prepare for our staff. We'd never been through that. We didn't really know what to expect. We didn't know anything about the virus and what it was going to do. For us, as scientists, part of it is that we kind of understand and can watch things as they evolve and make sure that we evolve with that.

But I got a call from Carrie Wolinetz, Ph.D., very early on as cases were starting to appear in the U.S. At the time, she was still at the NIH as the policy director. Then I spoke with Cliff Lane, M.D., who's at the NIAID [National Institute of Allergy and Infectious Diseases] and then Amy Abernethy, M.D., Ph.D., who was at the time at the FDA [Food and Drug Administration] as the Deputy Commissioner. A lot of conversations—24/7 really, about what we needed to do and how we could pull together the strengths of our programs. At NCATS, we had the Clinical and Translational Science Award Program (CTSA) that does a lot of clinical trials, so we have a lot of expertise in infectious diseases. We had some ideas that we could bring to bear to try to help wrangle the scientific community together. A very large team of us were working together to try to figure out what we could do. On the same side, of course, was the staff. The first thing that we did, of course, was we all took a break—I think it was March 14th or something, I don't actually remember the date—[we] turned off the lights in the office and worked from home the rest of that time, and still to this day. Of course, now we're in more of a hybrid environment here two years later, but it was kind of a reset. How can we work together? What's interesting is that we had always prepared for events like snow events where we couldn't go to work for a snow day. We had to plan for that, and we did testing of that, and so now we did it pretty much immediately and really without a hitch. We were able to use newer technologies like Zoom and old-fashioned technologies like a cell phone to do our work, and that proved to be extraordinarily effective. Of course, we had some hiccups along the way to really get oriented, but what was amazing to me is that we were all just pitching in and saying, "Hey, how can we help? Let's roll up our sleeves and get this done." I'm still wearing flannel today because we're still rolling up or sleeves. We're not done yet.

Barr: Can you mention a few examples of how NCATS scientists and those that it supports have come to understand the basic mechanisms of how SARS-CoV-2 operates? You did a lot of drug therapies and things like that, but there was a little bit of understanding the virus in some of the research.

Rutter: There was, yeah. From every aspect of how the virus binds to the receptors in the cell, how it goes into the cell, how it starts to work on replicating in the cell, and then when the viruses go out, how do they get out of the cell? Every step along the way of how the virus does that made it vulnerable—that was the idea—so where in that pathway can we start to target those vulnerabilities? That's what we were trying to do. Every aspect of that process of how a virus gets into a cell and then how it comes out of the cell, we wanted to take a look at and see if we could develop assays for that and then identify if there were any drugs that could perhaps be effective for any of those pathways.

Barr: How did you and others at NCATS contribute to the efforts of Operation Warp Speed? When did you get involved with that, and what was that experience like?

Rutter: We were in very early on. NCATS by design studies every disease. We study over 10,000 diseases that are out there. The reason we do that is because we are focused on enabling platform-based kinds of technologies and approaches that might help a variety of diseases—not just one disease at a time. We know there are over 10,0000 diseases, so if we just go one disease at a time, well, we'll never get there. It'll be thousands of years before we're able to identify that. Our approach is really to take a holistic view and try to find what's common across diseases and use that as a way to affect change for specific diseases. When COVID hit, that whole mindset was really perfect. We could pivot everything we did to specifically look at COVID—from screening drugs, developing assays for how the virus worked in

infected cells, to developing databases. We were able and had everything in place to be able to pivot towards those activities. We also have the very large Clinical and Translational Science Awards, the CTSA program—over 60 different academic organizations across the country who also have the ability to provide resources and ability to do clinical trials that would be very helpful for COVID, in addition to programs that they could develop for testing the communities for COVID or vaccinating the communities for COVID. We were involved in programs like RADx, out of the NIBIB [National Institute of Biomedical Imaging and Bioengineering]. There were a lot of activities that we really partnered on with other partners at NIH—as well as leading some of those efforts on our own with the clinical trials and the database development.

Barr: And the ACTIV-1 and -6 trials.

Rutter: That's right.

Barr: How did you take on those particular ones?

Rutter: For ACTIV-1, we were very interested in looking at the immunomodulators of the disease, because we had been hearing in the news about that cytokine storm. When people would be sick—very sick, severely ill—it would get to a point where their body was just trying to fight everything, and the cytokines [immune system] were just overly active. The hypothesis was that if there was a way to dampen the cytokine storm, then perhaps you could allow the patient to recover enough to beat COVID. That was our interest in ACTIV-1. We had a variety of our CTSA program places actually help with those clinical trials. For ACTIV-6, very similarly, we had the ability and resources through the CTSA program and our Trial Innovations Network to do a decentralized trial. We had been hearing about medications like ivermectin and fluvoxamine as perhaps working well—at least the public was saying that. We wanted to do a clinical trial that could really test that, because it hadn't been tested in a very robust way where we could randomize patients to the therapy. That way, the physicians who were prescribing it through the clinical trial didn't know what patients were getting what therapy either, so it was this double-blind placebo-controlled trial, in a way, that we could do in people's homes. So, we had the ability and resources to be able to accommodate that kind of a robust clinical trial program. That's how we got involved in ACTIV-6, now, where we've been testing those medications.

Barr: The variants have thrown a lot of curve balls in finding effective treatment. Can you discuss your role on the ACTIV TRACE [Tracking Resistance and Coronavirus Evolution] working group that was charged with providing actionable intelligence on SARS-CoV-2 variants through genomic surveillance data sharing and standardization of in vitro assessments of therapeutics against new strains?

Rutter: Sure. This was something that was set up fairly early on, along with the other ACTIV clinical trials. This was the part of ACTIV that was more focused on the data and pre-clinical side. This was really a group that could evaluate the evolving variants that were being seen in the SARS-CoV-2 virus. We were interested in understanding the evolution of the virus because the changes in the variants of the virus caused different outcomes—different manifestation of the diseases in some cases or different severities of diseases. Some therapeutics might work well for one, but may not work well for others, and so we were trying to figure out how we can get in front of the virus to figure out therapeutics. But often what

we found was that we're always kind of behind the 8 ball. We don't really know what variants are going to come into play, or if they would be affected by a particular therapeutic like a monoclonal antibody. Those monoclonal antibodies were derived specific to a viral protein sequence and as that sequence evolved, we needed to understand how that would be affected. So, we developed a database through the TRACE working group called the OpenData Portal. It was a way to look at all the tests that were done on the different viral variants and the efficacies of the different medications that we had to date to help us treat SARS-CoV-2—and understand if they were continuing to be effective or not for any viruses that were new coming on to the scene. It was really helpful to be able to do that work in real time and work with industry partners, and to know that—when they would do their tests for their therapeutics on a particular viral variant—they would send that data to us so that we could upload it and make it available for everyone to know. We essentially had a way of making that data available in real time so everyone could be aware of the value, or lack thereof, of particular therapeutics to those particular strains of the virus.

Barr: NCATS has done a lot of other databases. Can you talk a little bit about those, like the Small Molecule Antiviral Compound Collection that's consulted by people from around the world? You've also used a lot of existing ones, like the Tox21 database, to look at the toxicity of some of the drugs. Can you just talk a little bit about the usage of those with COVID, and how you see these resources being expanded in the future?

Rutter: Sure. Part of it is born out of this idea that we have, something called the NCATS Pharmaceutical Collection. It's a collection of 3,000 compounds that are FDA-approved. Some of them are approved in other countries as well. If we find an assay where one of those compounds is effective for that assay, we can then further develop it, but because it's FDA approved, we know already that it's a safe drug. So, because we know a lot about the compound already, it saves us years of development time. It takes 10-15 years and about 2.6 billion dollars to get a drug to market, and so if we can cut any of that out through this process of using these compounds that are already fairly well known, then we're much better off. We've been collecting other compounds as well that we know have antiviral properties or are effective for toxicological purposes and are able to evaluate those on a similar basis and test them for particular therapeutic activity. Some of those will require further development than others because they aren't necessarily FDA-approved. But we have a sense of how those compounds can work, and so we're able to do that testing on a very routine basis at a very high-throughput screening basis, so we can test things very quickly and efficiently.

Barr: Can you elaborate on how NCATS has supported the use of a lot of new technologies like 3D cellular models and lung-on-a-chip models for pre-clinical COVID treatment research, and the advantages and disadvantages of these methods in comparison to some of the standard—and maybe considered old-fashioned—animal testing and human clinical trials?

Rutter: Sure, and I don't know that I would call animal models "old-fashioned." I still think they're the gold standard. I do think that animal research is incredibly important, but what we're hoping is that someday, if we can prove that these newer technologies—like the 3D bioprinting models and the tissue chip models—in some instances, those might be able to reduce animal models and that would be really terrific to see. We're doing a lot of work to try to understand which models those would work well for,

and which models they won't really work for. For the 3D cellular models, for example, the lung-on-a-chip model. The lung-on-a-chip model was one that was particularly valuable, because we knew that there were impacts to the lung with COVID. Our researchers were able to use these sorts of tissue chips to look at the SARS-CoV-2 virus and test different compounds on them. Early on when there were reports about hydroxychloroquine, we were able to use these tissue chips to show that it wasn't actually very effective in our in our tissue chip models, but we did find other ones that were. We were able to then make sure that we could disseminate those findings and make those available for other researchers too. That's the importance of these cellular models. We know that animals aren't humans, and so for many cases, they still are very good for understanding how we can look at safety and efficacy, but they're not that great. Most of the time, 90% of our drugs fail in clinical trials because of safety and efficacy, so the animal models aren't super-predictive, but if we can include and incorporate these 3D, more human, physiologically-based models, along with the animal models—or perhaps even alone—if they're robust enough to do so, and we have the regulatory channels to be able to look at that and have confidence in that, then I hope someday that those models will be used much more readily. And now, where we're seeing the technology go is that perhaps we can start to do clinical trials on a chip. Imagine if you needed to have, or you were involved in, a clinical trial. We could take blood out of your arm, make those blood cells induced pluripotent stem cells, and re-differentiate them into different kinds of differentiated cells, like a nerve cell or a muscle cell or a lung cell. We can look at all of those different cells, create those, and put them on a chip. So now it has your genetic background on there and we can test the drug on your genetic background and look at safety and efficacy on those cells before ever giving that drug to you in the person and, hopefully, get a better sense of how that works. That's the future that we're looking for.

Barr: How do you hope that these new technologies can show the systemic effects of these drugs? That is one issue right now—that they're very narrow to particular systems of the body.

Rutter: Yeah, that's a big deal. We have a program in gene therapy, for example, and we're developing treatments that are gene therapy types of treatments. The system that we use is a virus, as well, for delivering those gene therapies. It's a different virus than SARS-CoV-2, so it feels weird to talk about viral gene vector delivery in a pandemic, but this virus is benign. We take the DNA out of the virus, and we engineer some other gene that's a functional copy of a gene that may be deficient in a particular person. That's how we deliver that gene therapy to a person. What we know happens is that, in some cases, there have been people with particular diseases where that mode of therapy has impacts on liver toxicity. We're working very hard to reduce and minimize those toxic effects in the liver and to try to make sure that what we're building in terms of therapeutics are much more specific and targeted to the cells that really need them. That's an area of research that we're continuing to do and is a very robust area of research and a place where we hope that there will be a lot of successes in the next decade.

Barr: Can you please talk about how you contributed to the development of the National COVID Cohort Collaborative NC3 initiative, and how you apply your experience? We already spoke about with some of the other databases that you have worked on in the past, such as establishing a governance structure, setting data usage policies—many things are involved.

Rutter: Yes, there are many things that are involved. This one was for the National COVID Cohort Collaborative or NC3. This initiative kind of snuck up on us, as did the pandemic. We were going in a different direction with what we were doing with data collection for electronic health records, but when the pandemic hit, we immediately realized that the direction we were going in would not be helpful as quickly as a different direction that we ultimately went with. This is the idea of building a federated data system where we have the ability to have a variety of different groups across the country have their own data in their own space, but they don't share it necessarily. They ask questions of it, to identify particular people who might be helpful for answering a certain question, and then they can contribute that information back to a centralized location. In a centralized database, they would just provide all the raw data to a centralized location and any question can be asked. That was really important for the pandemic—the urgency required under it and the ability to be able to ensure that the data could be compared in an apples-to-apples way was super important for this particular program. The development of that initiative took a different turn than what we originally expected, but a very important turn. What we're learning from that is that it's not that the other way isn't good or right—there's a time and place for that—but in this time and place, we needed a different program that could be much more urgent and effective. There's a balance now in that as we move forward there are going to be ways that we need to look at both approaches. For this initiative too, everyone in the scientific community was focused on COVID, so it was also a way to bring the community together. We have an incredibly robust community to be able to look at the data and start to analyze it. Because these data were in a centralized way, it was very easy for researchers to be able to access these data and start to learn about the outcomes of the pandemic and what we needed to do to learn about that. For example, one of the key early findings—it was NIGMS [National Institute of General Medical Sciences] who supported it—was a group out of the University of West Virginia. Investigator Sally Hodder, M.D. led the study in which she found with her team, using the N3C database, that there was a much higher morbidity and mortality in people in rural communities than in urban environments. It was just something that we all kind of knew, but that really struck. It was black and white thatthis is a problem. We need to make sure that we're addressing rural communities and our communities that are underserved. That's the power of this kind of resource, that we're able to identify and point to these issues very early on and we're continuing to do that today.

Barr: Can you talk a little bit about some of the other public health interests? It's obviously been used for a lot of different scientific research, but you're saying that you've got a lot of questions about the efficacy and safety, and other things like that?

Rutter: Yeah, absolutely. Thank you for asking that. We had one of those days—and there were many of these days during this surreal pandemic—when the White House COVID-19 office gave us a call and said, "Hey, we would like to understand, in your database, the Paxlovid use characteristics because what we had heard about it in the media was that people had rebound COVID after taking Paxlovid. So, we wanted to look to see in the database if that was really the case." It turns out that, at the time they asked, it was very early on after Paxlovid had that emergency use approval. We found 20,000 people who had been on Paxlovid that we could actually evaluate for this particular purpose. Using electronic health records, you're limited in some of the outcomes that you can really look at, so it's kind of a broad representation of our findings. Essentially what we found was that it turns out Paxlovid really didn't have anything to do with the rebound cases. It turns out to be much more of a SARS-CoV-2

characteristic. It tends to rebound in and of itself. Unfortunately, Paxlovid had gotten kind of a bad name because it was associated with that rebound, but it turns out that's really not the case. Paxlovid is still very effective as a tool to help us keep fighting the pandemic.

Barr: How has the pandemic affected those with rare diseases has been another emphasis of NCATS. Can you speak a little bit about how NCATS has assessed the pandemic and its ramifications on those communities with rare diseases, and how it has continued to support them throughout the pandemic?

Rutter: Sure. Rare diseases are a priority for us; we've always had a particular interest in rare diseases. Before the pandemic we'd been working quite a bit in the space, and of course, when the pandemic happened, we were quite concerned about access to care and ensuring the safety of people with rare diseases. They're more vulnerable to infectious diseases. So, we wanted to make sure that we had an understanding of those particular effects and how to advise the community about how to protect themselves in this environment. Looking at access to care, those protective effects were really needed for those rare disease patients and people who were immunocompromised, for example. We could show that those are individuals who needed some priority care, especially when it came to vaccines or treatments. Those were the kinds of things that we could help do to assess those individuals who are more at risk.

Barr: Becoming the acting director in the middle of the pandemic, what is your vision for NCATS now, both in regard to continuing SARS-CoV-2 research and studies pertaining to other health conditions? How are you going to use some of the things you created, like the N3C, for other health situations?

Rutter: Thank you. It was a remarkable time in all of our histories. To be in the position of becoming the acting director of a center that was really in the midst of just about everything that we were doing in our response at NIH for the pandemic has taught me a lot in terms of governance structures and working with the community—going back to the database development. These are things that we have to continue. It also goes back to my roots of growing up in a time where we didn't have cell phones and internet. It was all about working with people. That's still really important today, and it has been pervasive in how I've approached things as well. This work has been, in a way of course, very sobering—but also very invigorating. With the hope and promise of what we can do in a very short time if we just put every effort we have towards it, the sky is our limit really. Those are the kinds of things I want to try to continue—where we can really learn from that efficiency of how we've gone through the COVID pandemic. During the pandemic, it felt very slow, but as we look back, I think it's really an incredible amount of work that we were able to pull together. It's always easy to look back and say what we did wrong and what we did right and there are those things to go and look back on. But pulling on and learning from what we did wrong and what we did right and continuing to try to apply those to other areas is going to be super, super important. What we've established—the kind of tools and technologies for looking at diseases, like the EHR [electronic health record] database—it'd be shameful if we weren't able to apply that for other diseases. That's kind of where we are now, saying, "Hey, this was really effective in this space, and it can be very effective for other diseases." That's my goal: I want to figure out how to bring more treatments to all people more quickly. I have every hope that we can do that with the tools and technologies that we have today and the efficiencies that we've gained through the pandemic. I don't want those to go to waste, for sure.

Barr: What are you most proud of to date that NCATS has done with the pandemic?

Rutter: This is so hokey, Gabrielle, but what I'm most proud of is just the team of people that we have in NCATS who dropped everything and spent the last two and a half years fully dedicated to helping us and others solve this major problem. And it's always with this sentiment of being based in team science and wanting to collaborate and work together. We have things to offer that maybe nobody else can offer, and we want to bring those to the table. Working with the staff and people with that attitude is really inspiring. I'm really just very proud of the community that we have, that helped us get through and still get through this time that we're in. I'm excited about what we have to move forward here.

Barr: Yes, for sure. I've spoken to several people in NCATS, and they always say how important partnership is to them in their way of thinking and their approach to work.

Rutter: Absolutely, I couldn't agree more. And I should say, too, for the programs that we did and were involved in with the ACTIV trials and those sorts of things, the public-private partnership that the Foundation for the National Institutes of Health set up to really enable this activity was incredibly important. Those are the kinds of things that drives that efficiency piece. When those things work well, you want to continue to do those things that work well. So, I see those kinds of partnerships really playing an important role. I always like to say that at NCATS, we're the "dot connectors." We connect the .coms, .govs, .edus, and .orgs. Those are the kinds of things that we do well, and we bring our own expertise to the table. That really adds value. That's a great place to be.

Barr: In addition to being a scientist and an administrator at NIH, you're also a person who's been living through the COVID-19 pandemic. What have been some personal opportunities and some challenges for you that the pandemic has presented?

Rutter: Let's see. That's a big question. For me, and being an acting director, those personal opportunities were also professional opportunities, because it was a very specific role that I was in. As an acting director there were no expectations of me—in a way. I could try things that maybe I wouldn't have tried otherwise, and in an environment that needed an urgency. Ideas were gold, and still are gold in this time. It was a time also for me to say, "Is this really for me? Is this what I want to do?" Because we have had an experience where we've contributed so much to the science, it has certainly helped shape my thinking on how we can move forward. We had to do basic science, pre-clinical science, translational science, clinical science, population science, data science—all of these things all at the same time, so it was kind of like on-the-job training for me, too. You think you might be a director in some role and so you're expected to know everything, but in many cases we don't. We're working with each other to really tease that out, so I got to dabble, in a way, in a variety of areas and learn very quickly the key and important salient things about that. But the challenges were there, too. It was really 24/7 and so burnout and "time away from home" was very real. Even though we were at home the whole time, it still felt like you're away from home. Being cognizant of other people's mental health and their balancing of work and life was really important to me too as a leader. But also, as a person, I felt it. I wanted to make sure that [others know] it's okay to feel that and also okay to address it.

Barr: How did you cope with all the demands on you when you needed to take a break?

Rutter: It's funny because [it was] literally 24/7. In our emails, there's a way to say, "I'm not at my desk" and have an automatic reply when people email you. I found myself just making sure that I was transparent as to when people should expect a response from me, so that if they needed to go ask somebody else, they could. Or if they could wait for my response, that would be great, but they should have an expectation of when that might be. On Saturdays and Sundays, I was saying, "Hey, I'm not going to be here between 5 to 8 P.M. on Saturday evening but I'll get back to you as soon as I can." It was that level of communication. For me, it was allowing myself to make sure that communication was clear—and so that I didn't always feel like people were waiting for me. That was my way to kind of get space, so I would try to do that as much as possible. Nowadays, we've done other things, like changed hour-long meetings to 45-minute meetings so that people get a little bit of break time in between. We try to be very respectful of people's time. Those are the kind of tricks that we've been trying to do for our staff as well. Having people feel like they have time for themselves is critical, and I think that we kind of lost sight of that even before the pandemic. But it was just really heightened with pandemic.

Barr: Over the course of your career, you've worked in a number of settings. You've been in a lab, you were actually at a pharmacy for a while in the early part of your career, worked in the government, and in academia. Can you talk a little bit about how all those different experiences have influenced how you have looked at the pandemic? You have to work with all those different actors in your current role.

Rutter: That's right. Being from those different places—the .coms, .edus, .orgs, and the .govs—it gives you an insight of how important they are to contribute to the problem. Part of it is even just speaking the language and understanding what they can bring to the table, communicating what you're trying to do and where they might be able to help. I think that experience has helped enable that. Again, it goes back to what we do really being about relationships, understanding what's important, and communicating ideas that have some common ground of what we're trying to do together. If we have a mutual goal and we work together on that mutual goal, we can get there faster. Areas where we can enable that and understand what roles and responsibilities people can bring to the table, the better off we're all going to be in terms of meeting those goals.

Barr: Is there anything else that you'd like to share about your career or about your experience with the COVID-19 pandemic?

Rutter: I'll share one story, and it's from a colleague of mine who's at NCATS. His name is Matt Hall, our Early Translation Branch director, and he's been involved in a lot of the activities that we've doing in COVID. With that, he was involved in purchasing equipment to help study some of these things and do the science in the labs. He communicated at one point in time that he was speaking to a purchasing agent who was trying to get some equipment for him, and he was having some difficulty with that. The purchasing agent was trying—just went over backwards—to help him work on it to get it done. So, Matt told this purchasing agent, "Gosh, thank you so much for all of your help in pushing this forward." The purchasing agent said, "Look, the scientists out there are helping us, and I just lost my dad to COVID, and I want to do everything in my power to help you understand this disease better." Even just within NCATS there are millions of stories like that I'm sure, but that just rang true to me. The reason I bring that up is

because it's important to note that this hasn't just been about the scientific advances that we've been able to make, but it's also the operational and administrative staff who have equally spent their last two and a half years working very hard to enable those operational aspects of what we do for science. Without that whole team together to work on this, it wouldn't happen. That story, I think, is just really important when we talk about team science. It's the entire team, it is not just scientists—it's everybody who plays a role in making this work. That's what we believe in NCATS and that's one of the things that makes me most proud to be in this environment.

Barr: Definitely. Thank you so much for all your service, and I wish you and everyone in NCATS continued health and continued success.

Rutter: Thank you, Gabrielle. Back to you. I appreciate the interview.