ELSI Friday Forum • June 11, 2021
Transcript
Ethical Challenges in Novel Gene Therapies for Sickle Cell Disease

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>> JOSEPHINE JOHNSTON: Welcome everybody. We are going to get started. I'm Josephine Johnston, and I would like to welcome you to our June ELSI Friday Forum on the Ethical Challenges in Novel Gene Therapies for Sickle Cell Disease.

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Just a few thing to say in my introduction here. So I would like to remind everyone that ELSI Friday Forum is held on the second Friday of every month for one hour starting at 12:00 noon Eastern time. We also have a Zoom room reserved for our somewhat informal discussion immediately following this panel for 30 minutes.

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So stay tuned for the link that will be posted in the chat box at the end of this session so you can join that after panel discussion. As a reminder to those of you joining us for the first time, ELSI Friday Forum is a monthly series of the Center for ELSI Resources and Analysis, or CERA for short.

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And for those of you who might be new to the CERA, the CERA is a multidisciplinary, multi-institutional center that provides resources to support research on the ethical, legal and social implications of genetics and genomics which is otherwise known as ELSI.

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And the CERA serves to connect a community of scientists, scholars, policymakers, journalists, members of the public and others to engage in ELSI issues.

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CERA is funded by the National Human Genome Institute at NIH and is managed by teams at Stanford and Columbia University in partnership with the Hastings Center and Harvard University.

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CERA's online platform ELSIHub.org launched in November as was launched -- and we encourage you to access resources there including the recording and transcript of this forum associated reference material as well as an ELSI literature database research instrument repository, scholar directory, news events and much, much more all on the ELSIHub.

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Please go to obvious website to sign in for newsletters and other events like this one. ELSIHub.org and get daily news and updates on Twitter.

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Just a little housekeeping before I introduce our moderator. So these are a few little tips. If you wish to use closed captioning, please turn on CC at the bottom of your screen.

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We encourage an active exchange of ideas here on this panel between the panelists and all of you. The panelists' presentations will be quite brief, so we hope to have a significant portion of time for discussion.

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When engaging, to engage in discussion, please use the Q&A button which you will find at the bottom of your screen to ask questions. You can register your enthusiasm for someone else's question and elevate it up the list by using the upvote button in the Q&A box. The chat box is available for further engagement. That's where you can find links to resources referenced in today's discussion.

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The resources in the chat will be e-mailed after the forum as well. If you have any questions, please e-mail info@ELSIHub.org at any time. Okay.

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So now it's my pleasure to introduce this panel's moderator, Dr. Pilar Ossorio. She's professor of law and bio ethics at the university of Wisconsin Madison and the ethics Sklar and program lead at the M. institute for research.

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She has a Ph.D. in micro biology and immunology from Stanford University and a JD from the University of California, Berkeley. Her research interests resolve around research ethics and governance of emerging technologies.

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She's worked on ELSI issues since the 1990s and has participated in numerous advisory committees and boards that aid governments and sitting science policy. Over to you, Pilar.

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>> PILAR OSSORIO: Thank you Dr. Johnston. All right. So today first of all welcome, everybody. And today we are going to be talking about ethical issued raised by work to develop gene Thatchers for sickle cell disease which is most common blood disorder in the U.S.

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Genetic conditions that affect people's hemoglobin, the protein in our blood that carries oxygen. While sickle cell is considered rare, it's most prevalent in people in African and parts of Greece.

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Sickle cell was the first disease understood by Western science as having a molecular basis. In 1949, Doctors (name) discovered that hemoglobin and people with sickle cell is molecularly different from people with sickle cell without the disease.

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That same year they demonstrated the disease was a recessive condition. Molecular change associated with sickle cell occurred in the sixth amino acid.

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By the early 1980s if not before, researchers had identified single --

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Didn't translate into new and innovative treatments and in looking at public faces websites regarding sickle cell, genomics is notable in its absence because it hasn't yet done anything for the people. But recently the implications of genomics for producing sickle cell treatment have become more promising.

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There are currently numerous clinical trials under way using gene transfer or gene editing as possible methods for effectively curing sickle cell and related hemoglobins. One notable paper in January 2021. We are starting to see some

papers in the scientific literature reporting preliminary promising results from these studies.

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And so with that, I am going to introduce our panelists who will talk about ethical issues or at least some ethical issues related to gene therapy for sickle cell. And first we are going to hear from Dr. Liza-Marie Johnson. Dr. Johnson received her MD and MPH from Tulane University and she's currently program director for oncology hospital at Saint Jude's.

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She is an ethics consultant for clinical and research ethics concern and member of the Saint Jude's faculty. Her research interests includes ethical issues in genomic sequencing in pediatric populations and methods to improve communications and support parental decision making in clinical context and during informed consent for pediatric clinical trials.

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Her talk today will be based on a research project that assesses parents' views of communication and consent issues related to gene therapy for sickle cell. Next we will hear from Dr. Melissa Creary. Dr. Creary is currently assistant professor of health management and policy at the University of Michigan School of Public Health where her research focuses on social, cultural, ethical political and historical dimensions

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of sickle cell disease in the U.S. and Brazil. Previously, she spent nine years at the CDC's division of blood disorders where she created the first national program and data collections system for sickle cell disease. And in addition to being professor, she's also the senior director in the office of public health initiatives for the American thrombosis and human owe state is network, where she's helping to establish

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a health equity program for HN and she developed the organization's capacity to support medically underserved population the. She's today going to talk to us about history, racism and justice concepts relate to the development of therapies for sickle cell disease and she will offer some ethical considerations to help guide our thinking on these issues.

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So I'm looking forward to a lively conversation after the presentations. Dr. Johnson, take it away.

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>> LIZA-MARIE JOHNSON: Great, Pilar. Thank you for the introduction. Next slide. So I'm briefly going to do an overview of sickle cell for those on the call maybe less familiar with the disorder and then tell you about the work on the research study SCDGENE that's funded through CERA. Next slide.

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Next slide. So the genetic basis of sickle cell as mentioned there is a spelling mistakes that occurs in the hemoglobin gene on chromosome 11. So in the spelling mistake, next, the TA replaces AT, and this results, next, valine replacing glutamic acid. Decreased affinity for binding oxygen.

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So depicted here is a normal red blood cell bound to oxygen, a fat happy little disc. Next. And in sickle cell because of its decreased affinity, the molecule polymerizes and you have this abnormally shaped red blood cell which is stiff and brittle. Next slide.

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So just to put it into cartoon form, floating around normally in the blood are these red blood cells, discs soft and squishy and can fit into small blood vessels. Next. Patients with sickle cell disease have the sickle shaped cell that's where the name for the disorder comes from. And the membrane is more fragile and brittle. They are prone to breaking open, and this results in a chronic anemia.

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Next slide. So to take it out of sort of cartoons and put it into the body, you can sort of see how the normal shaped red blood cell looks soft and plump whereas the sickle cell the photo in the lower left just appears like it's firmer and stiffer. And in the blood vessels, they can sort of pile up on each other and either the small blood vessels, the capillaries are at junctions.

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And this occlusion decreases blood flow and tissues which results in some of the morbidities from the disorder. Next slide. So sickle cell disease for patients who are affected have high morbidity and results in premature mortality. So you may

have heard sickle cell patients have something called -- technically it's called -- this is from the stasis in their Anastasias.

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They can have a chronic anemia. When the occlusion occurs in the brain, resulted increase in stroke in the lungs something called acute chest syndrome and other organ damage such as the kidneys and heart. It's a rare disorder. Affects approximately one hundred thousand people in the U.S. One in every --

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One in 13 in the U.S. are born with sickle cell traits. So despite being present kind of on the newborn screening and children being diagnosed at birth, nearly one third will not receive appropriate care for for sickle cell disease.

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However, 75 percent of adults fail to receive recommended medication when it's indicated. Although mortality has decreased in recent decades for children, it has increased for adults over the same time period and numerous studies have shown that there's inadequate treatment for patients when they present for pain. Next slide.

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The only curative treatment for sickle cell bone marrow transplant. There are a lot of challenges, primarily the big barrier is not all patients have donor. Current is a matched sibling. So transplant from a related donor, brother or sister. Unfortunately, 90 percent of patients don't have a matched sibling.

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Only seven to 10 percent of people will. And then there's other complications. Reject the cell, donor and host may have a fight and attack each other and affect the graph in the host disease can be fatal. Other things associated with bone marrow transplant next slide.

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So because of this, 90 percent of patients not having a curative therapy new research is needed to try to find cures for sickle cell disease. Medications that treat some of the morbidities don't cure the disorder. In gene therapy, you do not need a donor. The patient serves as their own donor, so you kind of remove the donor issue and you don't have any risk for the host disease and there's no risk of rejecting the donor.

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However, you still have some of the same complications that are associated with bone marrow transplant. Patients do receive some chemotherapy as the conditioning or to prepare their bone marrow to receive the new cell. Next, associated with this are unknown risks. We don't know the long-term effects of the related gene therapy. It's going to be hard to communicate with patients

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what risks may be. And you can imagine pediatrics have a long life ahead of them. And so this is going to be a concern for parents and even just adult patients not knowing they are trading one thing for another. Next slide.

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Next slide. So a little bit about SCDGENE an opportunity to improve sickle cell care through patient engagement. In my early research, we made the observation that more likely to decline farm co-genomics study predisposition testing. So that was respective and we had no idea why this sort of disparity or difference existed.

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And so we thought why don't we first go to the source. We have over nine hundred patients with sickle cell disease. Why don't we talk about our sickle cell community and try to understand about attitudes about participating in research. And we are designing a gene therapy trial. Why don't we talk to them about gene therapy and get them to buy in at the beginning so we can design a trial that meets their needs.

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And so I will let Dr. Creary talk a little bit more, but in the middle of the slide is the sickle cell disease coalition 2020 report card on how we are doing for patients with sickle cell disease. So although it has improved access to care rating only 5.7 for research and clinical trials 6.5 out of possible ten points.

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One of my former colleagues from Saint Jude's wrote an article about the impact of racism on sickle cell disease in the United States. When we were doing our warm U for the talk today, this The New York Times article came out a few weeks ago about these young girls with sickle cell having devastating strokes partially

due to lack of appropriate monitoring and aligned with current guidelines with sickle cell in the United States.

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That goes back to the point I made earlier one third of children don't receive adequate care. Next slide. So the goal of this SCD working group funded through CERA was to get together a group of experts who would partner with sickle cell stakeholders, parents of children with sickle cell disease and adult patients with sickle cell.

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And we wanted to sort of do a basic needs assessment to understand their attitudes and knowledge gap about gene therapy so we can develop a clinical trial and educational content and communication that was patient-centered and potentially included a decision-making tool.

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One of my collaborators meets with families now, he can offer them a research study with a transplant from an unrelated donor and we have a gene therapy trial talk to them about the gene therapy trial. How can we sort of communicate the risks and benefits of each and support family decision-making? Next slide.

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So this is a picture of our sort of expert working group. You will see Dr. (Name) and I co-chaired this project and we have a multidisciplinary panel of bioethicist, attorney, sickle cell disease expert, diversity and inclusion experts and really represents a wealth of expertise in their different areas. Next slide.

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So what we did is we formed a Patient Family Advisory Panel. We have a panel of 12 individuals, something I've learned from the focus groups in this deliberative stakeholder consultation moderate people identify themselves as warriors. So I'm a sickle cell warrior. My child is a sickle cell warrior.

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Despite having train as a doctor and working with this population for 12 years now, didn't sort of really appreciate sort of this definition of warrior. And I think it is, you know, how they are fighting against the sort of -- and quality of the disease but also fighting with the healthcare system battling with the healthcare system who sometimes doesn't understand the disorders.

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Of the 12 participants we tried to get a geographically diverse people. Seattle, Memphis, Baltimore area to account for regional differences in sickle cell care. And they have been meeting together regularly. They just had their fourth meeting yesterday and I had the opportunity to review transcripts from the first few meetings and have identified some themes. Next slide.

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So to highlight thus far really an emphasis on patient education that did not rely on medical jargon and was easily understandable so they didn't have to decode the technical language. These are actual, these next slides have actual quotes. I won't read them all to you today. I'm happy to share them.

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They really emphasize they want the education to share the pros and cons. They don't just want to say oh, this is a potential cure. They want to know what the potential disadvantages would be for participating in a trial. They think that we need multicure paths. They want to have choices the same way.

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They felt like a lot of the materials on gene therapy don't emphasize you still have to get hemotherapy and all the side effects that go with that. And if you don't know an answer, then be honest and say that you are not sure and rather than promising things are going to work out sort of the unknown risks of gene therapy. Next slide.

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So they also highlighted need for community advocacy. So both a lot of the reasons for participating was they wanted to say, you know, I want to know everything about sickle cell. I want to be up to date. I want accurate information so I can tell other patients and people in my community correct factual information and they think that they have gone through a transplant

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or gene therapy, they can be on the front line advocating for others. They express the need for allyship with other rare disorders. I will pause on this quote. It was noted that gene therapy for sickle cell is the gateway to cure other illnesses if they cure sickle cell. And that message needs to be promoted with

other rare diseases because they need all the help they can get in advocating things forward.

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In communication about gene therapy, they don't just want the care team to present information. They want to hear from patient who is have been through it as an advocate. Next slide. They also had concerns.

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The issue of fertility came up quite frequently. Are my little ones going to be able to have children? Are women who can't get pregnant anymore? The concept of starting a family was really important to people in our working group. I think something to think about in the discussion is that we often refer to the fertility preservation in oncology as onco fertility.

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And so patients with sickle cell disease are often excluded from programs that help support that because they aren't cancer patients, yet they are under going chemotherapy but they have the same risk of someone undergoing -- and then there's worry about the long-term effects.

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Are you fixing your sickle cell new but opening Pandora's box? Next slide.

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And then it seems likely this is kind of a reason behind SCD. We didn't plan this quote. But I thought it worked out. Someone on the panel said I always tell them that you should have a warrior scientist at the beginning of the process. Because it makes no sense for you to get to this point. After you've gone through it and now you are could go human trials and no wear warriors want to participate in the clinical trial.

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And with that, next slide. I have to think the obviously the patient family advisory council. Outstanding job. All my other collaborators on this work. If you are looking to reach me, that's my e-mail below. And you can always tweet. Thanks. And I will turn it over to Dr. Creary.

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>> MELISSA CREARY: Hi, everyone. Thank you so much Dr. Johnson, for setting us up with an understanding around sickle cell disease and an understanding of your specific project. I am going to take that foundation and then add an additional lens to that which is going to ask us to think about some of the historical perspectives that lent itself to this story, some of the perspectives around justice,

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some perspectives around race and racism and this deep and troubled kind of political history that has followed sickle cell disease. So thank you so much for the invitation to talk about these ethical implications. We are in a moment where the experiences, those with sickle cell disease are being highlighted greatly.

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In May alone, The New York Times published three different pieces on sickle cell disease. A number of chronicles on the ways that the criminal system and healthcare system fail these individuals. And for those with sickle cell disease, it's clear if you read these articles that they were made to feel like an addict, underinsured, underemployed.

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In one of these articles. Dr. Collins the director of the National Institutes of Health said the lack of attention paid to sickle cell historically is one of the reflections that we do not have equity in our country.

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So think with that notion of equity as we move past these slides and how equity is transforming the narratives that we are having around gene therapy. And in The New York Times, there's another quote that says promising developments in gene therapy have given people with the disease hope that a cure is on the way for an illness that often causes organ failure and premature death.

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But the first such therapy is more than a year from regulatory approval. It will almost certainly be extremely expensive, cannot reverse damage to tissues, and people's bodies are so battered by the disease that they may not survive the treatment.

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And so when we think about this narrative around the pain and suffering that is part of the arc and the narrative of sickle cell disease, the construction of the disease, how can there not be a constant presence for hope for this population as it turns out in anything, right? But especially for the purposes of this talk scientific innovations.

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So Black suffering whether it be one allele or two, bodies highly valued in the realm of scientific research but completely devalued in all other realms. I study the politics of hope in the sickle cell communities and that hope is dependent on how they are treated in society, the perceptions of care that they have by the government.

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By the healthcare system, by the research apparatus, the narrative of hope especially as it comes to scientific innovations is very clear. And it's spoken about from every stakeholder from those living with sickle cell disease to those who are on the scientific bench to those who are treating the sickle cell patients, I think everyone is very invested in the idea of hope when we are thinking about what scientific innovation can do

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for this community.

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And currently, there are now at least five different approaches to occurring -- oh, I'm sorry. I have not been saying next slide.

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>> MELISSA CREARY: Next slide, please. This is where I have been talking about the sickle cell The New York Times stories. And then the next slide, please, is what I have been talking about when it comes to the animations of hope. So there are now at least five different approaches to curing sickle cell disease in or nearing human testing from at least eight different companies or academic centers.

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With new approaches being developed. And there is a quote here again that came from a The New York Times article that says to have something like these two gene therapy techniques is a great opportunity. It would just open the doors of hope for these patients. Right.

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So we're thinking about hope and what that might mean to how we are asking and framing some of the ethical considerations of the innovation of gene therapy for this community. Next slide, please.

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I got it. And so now we have despite these narratives of hope, there has been a history of disappointments in the sickle cell community when it comes to how we treat this population. I'm very happy to see that Dr. Keith W. and Dr. Steven P. are in the audience so they can see the shout-out that I'm giving to their book, the troubled tale of gene medicine.

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And in it, we begin to understand or hopefully can begin to understand this historical lack of therapeutic interventions within this community despite their being the first genetic disease. This is one of the thing that comes up continually. We know this is a disease that has been talked about for such a long time and why don't we have more advancement for this community?

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And one of the The New York Times articles I referenced earlier, Dr. Peter Lang from Emory University talked about a gap between delivery of treatments to the patients who need them. Sickle cell affects primarily disadvantaged individuals.

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And so, you know, we talked about or Dr. Johnson talked about the bone marrow transplantation and how that is the only curative option that we have right now for this population. And there's a lot of conversation about risk versus benefit here.

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Also hydroxyurea is known as a genetic switch. It makes the switch in which fetal hemoglobin gets produced. And despite this switch, what we do know is that hydroxyurea is willfully underused. Does it cause cancer? Sometimes the providers may not provide it as an option. There's often seen adherence issues

between in terms of taking the drug and being adherent to the drug due to the labor that's involved

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with being on this regimen. And so there are a number of concerns that even are associated with the cures that are on the market, not to mention again this historical notion of disappointment. And when we think even currently in 2021, there's another yet another The New York Times article that talks about researchers halting trials of promising sickle cell treatment.

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And Dr. DeBaun says this is a cautionary tale. And this trial caused cancer in two patients years down the line after this treatment gene therapy treatment. And so this causation of cancer was not directly linked due to the gene therapy, but no one really knows. When Dr. Johnson is talking about unknown risks, this is one of the unknown risks. We don't know for sure that genetic therapy is what gene therapy caused the cancer in these patients.

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But Dr. DeBaun says this story is a cautionary tale around the strange mix of cutting edge science, clinical trials with few participants and hope for a population that has been largely ignored from the medical community. So in this story of gene therapy and ethics is wrapped into a larger story of neglect. And underneath all of that neglect really is racism.

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And so one of the questions that we will be talking about, next slide, will help us think through this concept I have developed called bounded justice. So because sickle cell's symbolic significance as a Black disease, researchers have been quick to seize upon the disease to -- but those in the research apparatus and those living with sickle cell disease envision therapy as social justice.

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NIH, this cure sickle.org where it says it's time to rewrite the story of sickle cell disease, this harkens back to the historical neglect of the disease not just the disease, but particularly the bodies who body it. And so in this concept of bounded justice, I argue that it is impossible to attend to fairness and entitlement and attempts at equity when the basic social and physical infrastructures

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underlying them have been eroded by racism and other historically entrenched isms. Addressing inequities without fully understanding how deep the problem goes. And again, this is coming from all stakeholders. So on the right is from NIH. On the left is from Shakir who has since passed away. But this is one of his blogs in his he talks about prioritizing sickle cell patients a chance to mend broken ties.

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So there's this narrative of what can be done to repair the damage that has been put upon those who are living with sickle cell disease. And scientific innovation has been a part of that repair process and repair programming. It is seen that way from the patient standpoint and it's seen that way from the investigators standpoint.

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So how do we attend to this fact that we want to do as much as we can to attend equity and we want to address justice? And maybe we don't understand that it's bounded, but what can we do to unbind it? And how do we understand the whole person who is at the center of the sickle cell discussion?

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>> AUDIENCE MEMBER: Excuse me, Melissa, do you want to advance slides?

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>> MELISSA CREARY: Yes, sorry.

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>> AUDIENCE MEMBER: Sorry.

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>> MELISSA CREARY: Thank you for that. I'm used to advancing them on my own and that's what I have been doing on my side. Thank you. So here we are. We are at the top. Responsible engagement. So how do we intend to bounded justice? We intend to have a responsible engagement with the populations.

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The medical data from the work group that Dr. Johnson spoke of, they have found that many patients with sickle cell disease have low health literacy and limited

understanding especially with respect to gene therapy. And with that data, they have formed a patient advisory panel to develop educational content and communication tools as Dr. Johnson spoke about some moments ago.

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And there's related research that's being done by a group being led by the NHGRI about engaging the sickle cell community and the development of innovative materials to help them learn better about gene therapy. And all of this is under the guise of how do we democratize information? How do we make it more available? How do we make it more accessible?

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How do we begin to engage responsibly with this community as we begin to be intentional about the ways that we are putting these investments into gene therapy? Next slide, please.

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And so here are some questions. There were those who believe that dreams of quick cures simply distracted researchers, patients, families and the public. And this is a continuing conversation. Do we focus on inovation or do we focus on just the baseline of making sure that comprehensive care is taking place, that we get what they need at the bare minimum?

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Because of the risks versus benefit and because of the number of people who actually get access to these innovations. And so for some researchers, it's more appropriate to think about therapeutic advances that benefit larger numbers rather than the breakthroughs for the few. And so as we are thinking about how we are engaging and having these clients engaging in conversations with the sickle cell population,

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bounded justice also calls for us to interrogate these notions of inclusion. I love that Dr. Johnson put in an earlier slide that New England Journal of Medicine antiracist call to action for sickle cell disease. And one of the things they have on there is to make sure that sickle cell patient also on all of these task forces and work groups. So people are paying attention to that.

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But what does that mean when you are trying to do the right thing and make sure you are inclusive in this time? When we are now turning to work groups and task forces, how do we position the people to have power once they are around the table?

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So these initiatives which aim to bring vulnerable individuals to the proverbial table to have a better stake in their own health status do not often take into consideration that the table is unwelcoming, that it's not equipped to deal with, understand or hear the individuals' total lived experiences that brought to you the table to begin with.

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And the enthusiasm for representation disregards how social inequality in its broader contexts are broad to the table. And so what do we do when there are no accommodations for those who may find the chair more harmful than helpful? So some of the questions I would love to lead with as we start with conversation, what are the cultural meaning of innovation?

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What does it mean to erase sickle cell? We see this article that talks about erasing sickle cell disease. What does it mean to erase sickle cell? How do patients get positioned after they are cured? How do we attend to the deep entrenchment of racism in our calls to rewrite the story of sickle cell disease? How do we -- has been inattentive?

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A lot of the people I have been talking about around COVID-19 and vaccine hesitation are like oh, all this equity about getting me this vaccine, but what about the equity and the other aspects of my life? And I would say that's easily translatable to those living with sickle cell disease.

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I understand that you may be interested in the equity processes that occur getting me to the table to discuss, you know, what it means for me to have gene therapy. But what about all this other equity that's been ignored? The other thing I would ask, what happens if these therapy also successful? Who gets access to the innovative technology? How is it paid for?

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And will social justice be incentive enough once more powerful interest groups begin to compete for the tech? I left with this idea of warriors and what it means to be on the front line of your own healthcare situation, what it means to be a warrior when it comes to the navigation of your own health especially when it comes to these innovative scientific technologies.

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How does being a warrior help or hinder the population when it comes to gene therapy? And next slide, please. I would end there. Thank you for being patient with me not advancing the slides in a timely manner. And if anyone is interested in following the conversation or having me talk more about it beyond this, this is the way you can contact me.

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>> PILAR OSSORIO: All right. Thank you so much, both of you. I think, so there are two things. One rather than me ask questions, we have at least one question in the Q&A that I think will kick us off on a good conversation. But before we go there, Melissa, a couple of people have asked about your paper. So could you just describe, I know it was supposed to be available and it's not yet available.

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So could you just describe where it's going to be published?

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>> MELISSA CREARY: Yes. And I can pop that source in the chat. Panelists and attendees.

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>> PILAR OSSORIO: Great.

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>> MELISSA CREARY: It will be -- there you go.

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>> PILAR OSSORIO: And I think we have a question that kind of gets right to the heart of issues. If we already have an effective and relatively cheap treatment for sickle cell that is hydroxy urea being unutilized due to structural racism, why should we think more expensive will fare better?

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Greater for gene therapies? So I think that's a question that could take us in a lot of directions. And go for it.

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>> MELISSA CREARY: Dr. Johnson?

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>> LIZA-MARIE JOHNSON: I can go first. I think what's important to remember first I think we need to improve the huge of hydroxyurea. But it is a disease modifying for sickle cell disease. So it's been shown to reduce pain and has benefits for patient who is take it.

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There are now sort of three other oral agents that modify the disease (names). None of those have been studied head to head. But they don't sort of prevent some of the end organ damage and some of the things that result in premature mortality. So we need a cure for sickle cell disease, not sort of something better than a Band-Aid that these agents are right now. I would argue.

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>> MELISSA CREARY: And I would, I think I would just add that it's a wonderful question to think about having readily available therapeutic that comparatively is not as invasive, that I think has better access in terms of distributing to a large amount of people who may be eligible for the gene therapy.

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And so I think the questions around that could be so how can healthcare systems, how can providers get to some of the deeper confirmed deeper issues of adherence of communicating, meeting people where they are in terms of having to come in to get the therapy.

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So there are a lot of underlying issues that are definitely, I think, influenced by structural racism, and that definitely need to -- those conversations need to happen. I don't think that one conversation should happen instead of the other. I think they need to happen in parallel, that we need to be asking these really tough questions about how do we increase adherence and availability of an access to hydroxyurea

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as well as how do we have these conversations around the scientific -- (inaudible) -- the sickle cell disease population deserves everything. It deserves the things that are on the table that are being reworked to their benefit as well as the things that will come to them. And between the two, there's a huge range. There's still all this question of unknown risks that keep coming up.

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And so I think we have to do a really good job of addressing that piece with all of these conversations.

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>> LIZA-MARIE JOHNSON: Yeah. I think ways to just dovetail on that, the communication with families to help them assess their options. You know, people who have a low tolerance for risk or uncertainty, you know, the novel therapies may not be for them. If they are really worried about the fertility issue, they may choose to stay on a modified agent until a different time.

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But how can we support people to make the decision that's right for them or their child?

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>> PILAR OSSORIO: You know, I want to follow up a little bit. Liza Marie, you raised the issue of fertility preservation and how people with sickle cell disease often don't have access to this because they don't have cancer, but they are still having treatments that in order to treat their sickle cell could still have the same impact as the treatments for cancer patients.

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So it seems to me that perhaps this is part of structural racism that insurance companies treat sickle cell patients and treatments and their payment for sickle cell in a way that is less, less supportive of patients, less responsive to their actual medical needs. It's possible also that more of the sickle cell patients are uninsured or underinsured, and so less likely to have access to insurance paying for this kind of thing.

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Could you give us more of that context around the fertility treatments and how that fits into this larger question of structural inequality?

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>> LIZA-MARIE JOHNSON: Sure. So we have a paper we are going to submit soon just talking. It's like a comment and controversy, but about the need to standardize fertility preservation more broadly. Medications that threaten your patient fertility we need to have standardization because there are providers who do what a wallet biopsy. I don't think the family their insurance doesn't cover it and I don't think they can afford it.

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So I don't make the referral or I don't think this particular type of family. There needs to be a standard referring for counseling. And we need to advocate that insurance companies cover it because I see aren't adequate for iatrogenic infertility. I think if a potential barrier to people electing to do gene therapy trials will -- gene therapy $1.5 million and eggs is $10,000.

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It seems like we should make bundle it or advocate that it would be bundled for treatment for interested families. One of the participants spoke about how she was investigating a gene therapy trial and she was really bothered by the issue, potentially being infertile afterwards. She had to advocate to get referred and the doctors were, like, oh, we have cancer patients.

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You can go to your fertility counseling there. When they found out she wasn't a cancer patient, I forget, it was going to be 15 hundred dollars more. She's paying a sickle cell tax almost because she wasn't an oncology patient. Why is that? It should not occur.

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>> PILAR OSSORIO: I don't know if Melissa you had any comment that you wanted to add also.

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all right. We have another question here. Let me see if I can sort of summarize this. So I don't know how familiar the two of you are or the audience is with the very recent FDA approval of a drug for Alzheimer's disease. So this drug was just approved this past week, and it was approved over the no vote of an advisory panel which said that there was not enough -- there wasn't evidence of efficacy.

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Nonetheless, the drug was approved. So this question asked, can you comment on the existing debate around the new drug for Alzheimer's and issues about justice, race and equity, not only to the new and expensive and potentially not so effective drug, so that drug when it goes on the market for Alzheimer's disease is likely to get paid for by Medicare, so all of us and expect to be a blockbuster for the company that's producing it.

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So comment on that versus lack of access to things like comprehensive healthcare especially for underserved populations and especially for people with sickle cell disease. And also this person thinks she goes for great talks.

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>> MELISSA CREARY: I will let you take that first.

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>> PILAR OSSORIO: Very broad question.

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>> LIZA-MARIE JOHNSON: Yes.

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, it is a very broad question. You know, it's interesting. So what are sort of the motivations for approving this drug that the advisory panel sort of mostly said no or one abstention? I think in this era where we have a little bit of mistrust of science if you think about oh, the COVID vaccine, everything that happened last year around the pandemic, I think there is science skepticism.

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So I think it's problematic that there's a new drug that may not work very well. It's not the first time it happened. I forget what the drug was, very expensive, doesn't sort of extend life very long and now we are paying for it.

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>> PILAR OSSORIO: Or may not at all, actually.

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>> LIZA-MARIE JOHNSON: Or may not at all. And so maybe just shows that our drug approval and regulatory system needs a revision. But I don't know.

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>> PILAR OSSORIO: I guess I would wonder about the power and influence of who is advocating for approval, right, might be one set of questions we should look at in terms of the equity issues.

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>> MELISSA CREARY: Yeah. I definitely agree, Pilar. Who is advocating, who are the interest groups again, at the table? What do they represent? Who do they represent? What kind of money do they represent? When we think about the underserved populations especially when it comes to sickle cell disease and how payment works primarily through Medicaid as opposed to the way Alzheimer's gets -- as an active disease

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and who it affects primarily and how there is a spectrum of advantage versus disadvantage, these are definitely questions to ask. And that's outside of the question of, you know, a not-so-effective drug being prioritized versus comprehensive care, right. These are all, it makes it even more entangled, complicated issue.

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>> PILAR OSSORIO: Yeah. All right. So a questioner asks about, so it was not too long ago that bone marrow transplantation was heralded as a breakthrough cure and that promise has been realized in some cases. But there are also real ethical concerns around BMT for things like treating sickle cell disease.

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And so this person asks, bearing in mind that yes, of course, BMT and gene therapy are not the same thing, still are there things that we can learn from the BMT story about what is likely to make a more accessible successful kind of gene therapy?

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>> LIZA-MARIE JOHNSON: So that's a good question. I think that, you know, I'm not, if my colleague asked me, he's the more trans planter who knows the nitty-gritty of the gene transplant technologies. So I think there are maybe different drug companies trying to sort of corner the gene therapy, you know, their technology being successful and the first one.

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But I think that it's important to not skip steps in the process and get feedback from, you know, patients. Does it meet your expectations if they went through the trial? What do you wish you had known, really looking for any early safety signals, not everything over and having a thoughtful discussion about that's the trick with bone or transplant NG therapy.

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It's a risk-benefit analysis. You know, and sometimes patients aren't offered bone marrow transplant until they had a stroke or some serious disease or event because you are sick enough from the sickle cell disease and you have the high risk that it offsets of risk of bone marrow transplant.

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I think ideally what if we could get to a point in 10 or 15 years where we have a curative technology that is lower risk and then you offer it to treatment before they ever have the first stroke? And knowing where to draw those lines, but I think going slow and being deliberative is going to be important to the process.

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I also wonder, you know, if we break trust in some way, I think it's going to be hard to gain it back and have people willing to join the clinical trial.

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>> MELISSA CREARY: Yeah, so to jump on that last point, how do we engender trust? And one of the quotes about how are we going to, you know, already the sickle cell community is hard to envelope clinical trials and when they hear about the things that happened with L. or any other disciplines down the line, how can we allow them to express their concern and engage with them again?

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And I think I would assume that the trust is broken. And I would assume that before people find out the trials that people already have that disappointment kind of embedded into how they think about sickle cell disease in general. Again, there's this tension between hope and disappointment that I think really does paint an accurate picture of what happens in the sickle cell community in general.

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And in terms of what do we learn from bone marrow transplant, I think maybe it's a missed opportunity to not speak specifically to the people that went

through BMT and have a part of the processes as we are talking about, you know, these new therapeutic opportunities as they arise.

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So can we figure out how do engage with lessons learned from bone marrow transplantation and apply them at the early stage to even help us learn how to begin to interact with all of the different stakeholders that are a part of the scientific -- I do think at the end of the day that distrust and the disadvantage that is compiled that is embodied within the sickle cell population, you know, really has to be attended to,

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really has to be I think unpacked. Yes, gene therapy is going to help; and I have been thinking about social justice is the way we rewrite these wrongs and we want to offer these kinds of therapeutics. We have to get at this really deep level conversations that are beyond just the thin slice of the therapy itself, that we have to have this really well-rounded conversations that talk about

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generational levels of racism and what that has done to a population and keep whether better than knows better who asks the question .

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>> PILAR OSSORIO: Thank you so much. We are one minute from the top of the hour, so I think maybe Justine is going to tell us how people who want to move into the extended discussion can do that.

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>> JOSEPHINE JOHNSTON: Yeah. Thank you so much. Thank you to our panelist and the moderator for this wonderful discussion which we will keep going. I also want to just, there will be a post in the chat just now with the post forum discussion room link that you can join. And I want to remind everyone that we have these every month, these ELSI Friday Forums.

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Next month in July we have one called current legal challenges to abortion implications for prenatal genetics which will be a very important and stimulating discussion as well. We take a break in August and then we come back in September for the next year's worth of Friday forums.

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Now let's thank everyone for their participation and go to the post-discussion Zoom room. Thank you very much.