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JOSIE: Good morning, good afternoon, or evening, depending on which part of the world you are Zooming in from today. I'm Josephine Johnston, Director of Research and a Research Scholar at the Hastings Center, and a member of the organizing committee for these ELSI Friday Forums. I'm delighted to welcome you to our March ELSI Forum, which is on Autism Genomics Research: Parents' Views of Genetics Results and Autistic Representation. This is hosted by the Center for ELSI Resources and Analysis, and it's held on the second Friday of every month for one hour starting at 12:00 pm Eastern time. We also have a Zoom room for informal discussion, which will be open immediately after the panel for about 30 minutes. For those of you who might be new to the Center for ELSI Resources and Analysis, or CERA as we call it, we provide resources to support research on the ethical, legal, and social implications on genetics and genomics, and serve to connect scholars, scientists, policymakers, journalists, and members of the public and others to engage in ELSI research. We are funded by the National Human Genome Research Institute at the U.S. National Institutes of Health and is managed by teams at Stanford and Columbia Universities in partnership with the Hastings Center and Harvard University. I want to encourage you to visit our online platform, ELSIhub.org, for the recording and transcript of this forum, and related references. We are pleased to announce that the publication on ELSIhub of the newest ELSIhub collection -- please use the link in the chat to access the newest collection, called Neurobehavioral Genetic Testing in Children: How Much Should We Know?, and is curated by Claire Sathe and Paul Appelbaum. This reading list explores the ethical issues that arise when genetic testing results do not fully explain etiology or yield immediate, practical benefits for affected children. And this ELSIhub Collection is one of many on the ELSIhub website, along with many other recordings of these forums and discussions. Please go to ELSIhub to join the ELSI Scholar Directory, sign up for newsletters and other events like this one, get daily updates, and news on Twitter. It's a very comprehensive website, and we hope that you'll find it useful. So just a few housekeeping matters for you as attendees to this ELSI Friday Forum. If you wish to use closed captioning, please turn on CC at the bottom of your screen. The panelist presentations will be quite brief, in order to conserve a significant portion of our time for discussion. So please use your Q and A button, which you will find at the bottom of the screen, to write in questions for the panelists at any point during this session. You can register your enthusiasm for a question and elevate it up the list by using the upvote button in the Q and A box. So that's why we're gonna use Q and A for the questions. The chat box is available for further engagement. We will post links to resources referenced in today's discussion there as well. And if you have any questions, please email info@elsihub.org, at any time. So it's my real pleasure today to introduce the moderator for this panel. The moderator is Wendy Chung. She's a clinical and molecular geneticist and a Kennedy Family Professor of Pediatrics and Medicine and Director of Clinical Genetics at Columbia University. Dr. Chung directs NIH funded research programs in human genetics of pulmonary hypertension, breast cancer, obesity, diabetes, autism, birth defects, including congenital diaphragmatic hernia and congenital heart disease. She's the PI of SPARK, a large US-based autism study. She's a national leader in the ethical, legal, and social implications of genomics. She leads the Precision Medicine Resource Group in the Irving Institute and National Organization of Rare Disorders Center of Excellence at Columbia University. She was the recipient of the Rare Impact Award from the National Organization of Rare Disorders and is a member of the National Academy of Medicine and the American Academy of Physicians. Dr. Chung received her BA in Biochemistry from Cornell University, her MD from Cornell University Medical Center, and her PhD from the Rockefeller University in Genetics. So it's my pleasure to pass over to Wendy, and welcome you all.

WENDY: Thanks, Josie. Really happy to be here. And I've got some esteemed colleagues with me here today. But before I introduce them, let me introduce the topic. As Josie mentioned, I'm the principal investigator for SPARK, Simons Foundation Powering Autism Research for Knowledge. And we have a sister study called Simons Searchlight, which is about monogenic conditions associated with neurodevelopmental issues, including autism. Within this, autism is a spectrum, and I think one of the challenges, as we talk about this, and you'll hear us talk today, is that it's really not a single condition. And using a single umbrella sort of designation, I think, loses some of the richness, in terms of the diversity in our community. But we'll try to talk through some of that today. I can say as part of SPARK, one of the things we try to do is to understand each individual's unique abilities. Their unique contributions. Their unique perspectives. And although we can't represent everyone, we do try and inclusively involve as many people as we can, to try and understand how things change over the life course. And within this include individuals, plus their families. As I said, I'm joined by my esteemed colleagues, Julia Wynn is a long-time collaborator. Julia completed her genetic counseling graduate education at the University of Texas, and she also received a Master's Degree in Epidemiology from the Columbia University School of Public Health. Importantly, she represents an important voice in our community of genetic providers. That is, she's a genetic counselor. ABMG-certified, and her research focuses on patient and participant experiences, both in terms of diagnostic and predictive genetic testing. And she's also been really groundbreaking, in terms of thinking about methods for effective genomic education and counseling. She's co-chair of the Clinical Sequencing Exploratory Research Genetic Counseling Working Group, and currently co-leads the eMERGE network subeducation working group. In addition, we're also joined today by Dr. Holly Tabor. Dr. Tabor is an Associate Professor of Medicine at Stanford University. She's also the Associate Director for Clinical Ethics and Education at the Stanford Center for Biomedical Ethics. And is the co-chair for the Ethics Committees at Stanford Hospital and the Lucille Packard Children's Hospital. Her research focuses on ethical issues in genetics and genomics and specifically return of results and translation of exome and genome sequencing. She received her PhD in Epidemiology from Stanford in 2002. And was a senior scientist at the Stanford Human Genome Center. From 2005 to 2008, she was one of the first postdoctoral fellows. And you'll have to tell me how to pronounce this someday: CIRGE/SCBE. Prior to her work there, she spent 8 years at the Treuman Katz Center for Pediatric Bioethics at Seattle Children's Research Institute and at the University of Washington. Real treat, like I said, to have both of these women with us today. We're going to start off with Julia presenting on SPARK and some studies that she and Paul Appelbaum and others have done, trying to understand the impact on return of results. Julia, I will hand it over to you.

JULIA: Thanks so much for the introduction, Wendy. I'm gonna go ahead and take over the screen share here. Okay. I think I've successfully shared my slides. So thank you again for the introduction and thank you also for starting to introduce kind of what I'm discussing here today. And as Wendy pointed out, this is a really large study that's been taken on by many individuals, some of whom are joining us here this afternoon. And so I'm just the lucky one that gets to present all the work that everybody has done here. So we were looking at the experiences of parents of children with autism. And the receipt of a genetic diagnosis through their participation in the SPARK study. So just a little bit... Wendy gave a little bit of background here. But this was really a piggyback on top of a much larger study that's being conducted, that aims to enroll 50,000 individuals with autism and their family members. It has 31 clinical sites around the country and also enrolls individuals who find them on the internet, on the website. The individuals who participate in SPARK have the option of participating in genetic studies, which are led by Dr. Wendy Chung, where they're having exome and genome sequencing to try to understand the genetic cause of autism for them. And when a definitive diagnostic result is identified, it's returned to families, through a clinical process, with the guidance of a genetic counselor. In addition to our study that I'm presenting today, there's over 160 other research studies that SPARK implements in terms of ancillary helping their participants participate in as much autism research as possible. So I want to just start off by clarifying a little bit about the types of results that are being returned to individuals as part of SPARK. Presently, our understanding of autism is growing. But it's still somewhat limited. And we probably only understand a fraction of the genetic causes of autism. And those that we do understand are really the strong -- what we call strong genetic risks. The monogenic Mendelian causes of autism that generally are found in people in more severe manifestations of autism. So they may have autism, as well as other comorbidities, like seizures or congenital defects, or intellectual disability. So I just want to preface that, and kind of know that there are some differences in the cohorts, that those who receive results, versus those who didn't receive results -- it's not just the fact that they did or did not receive results. These types of results generally are monogenic, highly penetrant conditions. So this is where there's a single change in a gene that causes the gene expression to differ in some way that leads to autism. And sometimes also copy number variance. So this is what you're seeing on the bottom picture there, depicted on a chromosome, where a portion of the chromosome is either deleted or duplicated, resulting in a copy number variation of several genes to hundreds of genes. Most of the genetic causes that have been returned are de novo. Meaning it's a genetic change that's present only in the child and is not present in the mom or the dad. And so that's also I think something to keep in mind, as we look at the experiences of parents receiving results. Guided by what we know about the experience from other studies that have looked at the experience of either individuals themselves receiving results -- unrelated, for different types of genetic conditions -- as well as parents receiving results for their child's genetic condition -- we postulated that this experience could have a diverse level of effect. And we know to some degree that it has. We know that when parents receive results, these can change kind of their perception of their child's illness. The ability to treat that illness. The causes of that illness. And we know that when individuals receive genetic test results, it can change their perception of their health, as far as kind of diseased or sick, and identity. So taking this information, we applied it to kind of: How can we measure these aspects in parents and individuals receiving genetic test results as part of this study? So my talk today is going to focus on the parents of affected children. We are working on an analysis of the experiences of adolescent children who received results or did not receive results, as well as independent adult participants in SPARK. So individuals with autism and their own personal take on kind of what this experience was like. But today I'm going to focus on the parents, because this is where the bulk of the data lies at this point. I realize this doesn't mean that it's the most important data, and certainly not the sole data that we will eventually report on, but what we have this afternoon. So the design of the study is such that we're able to collect some baseline information or baseline kind of feelings and experiences for these individuals. Because we know in advance of when they're going to be notified of whether there are results, or there's no results at this time. And so we were able to capture kind of these baseline metrics using validated instruments of an individual's perception of identity, responsibility, and ambiguity. Before they went through the process of receiving results. And this was about four to six weeks before that. Then they received results. Either were informed by a genetic counselor, or a provider, sometimes Dr. Wendy Chung, or were notified that there were no results at this time. And importantly, those individuals who did not receive results did not meet with someone in person to discuss the absence of results. And also, they weren't told that there was no genetic cause to their autism. Rather, the current technology and research that was being done had not identified a genetic cause. After they went through this process, they then were asked to complete a follow-up survey. And you can see here, once someone became engaged in this survey study, they really did have a good completion rate from baseline to follow-up. Although you can see, as far as people who came into the study at kind of baseline, certainly there was kind of a difference in that experience. So this is the whole cohort here. And those with and without results. And you can see this is just reflective somewhat of what we know about the SPARK cohort. Which is moms tend to be more engaged with SPARK. Tend to be the primary person kind of participating in these types of surveys. So we had over 2/3 of the cohort were the mothers. The average age of the parents was 44. And I don't have it here on the slide, but the average age of the child receiving results was 12. And so this was not a very young cohort. And I think that comes into play, when we ask questions about -- reproductive questions. And the majority identified as white and non-Hispanic. Which was also something we know some of the biases of the SPARK cohort. So in, I think, probably the two minutes that I have remaining, I won't rush too quickly through this, but I want to kind of highlight some of the things we've found that we can certainly get into, in the discussion, a little bit more of the nuances of this. With regards to identity, we measured it using some validated measures, and really what we saw, as far as a change from baseline to after they received results, for those with and without results, was really mostly regarding autism stigma. And so that's what I want to point out in kind of the bottom screen here. Where you can see that parents who received results actually had higher baseline autism stigma than parents who did not receive results. And this is likely reflective of what I referenced earlier in the talk. Which is that individuals who received results had children with what we might call more severe forms of autism. But overall, we saw kind of a trend downward after the receipt of genetic test results. Whereas in the parents without results, we didn't see any change. And this signal, while it's a very modest difference, I think it's something that -- it comes out anecdotally as well, as we've been doing some more qualitative studies and interviews. So there really is probably a story behind this. With regards to responsibility, some of the biggest changes which we saw were related to kind of their reproductive risk and understanding, as well as how they were searching for treatments, related to autism. So this is again a difficult slide to kind of jump right into. But what we're showing here is from baseline to after they received results: How many people were endorsing, in fact, they actually were wrong and they thought -- in fact their risk was higher, or they were right, and they kind of kept their risk estimate the same? Or they said: Actually, I was wrong at baseline. Now that I've received results, my risk is actually lower. And that's what you're seeing right here. That many people who received results endorsed a lower risk than what they had originally thought. Which speaks to the fact that the majority of these individuals received de novo results for their child, and in fact, the risk for a de novo result to occur -- to have a second child affected with autism when you know there's a de novo result is about 1% or less than 1%. Whereas people without results didn't change as much. Because they didn't have any new information to reference. This also shows how frequently people with results in blue, compared to those without results, endorse kind of their next steps. So this is not a change from baseline to follow-up. But it's in fact at follow-up: What were you endorsing? And you'll see here some of the biggest differences. Still a modest proportion of individuals with results. Or people who were kind of looking and seeking actively for additional resources or treatment. Research or treatment. And this is very much related to the fact that we've seen -- and kind of also anecdotally -- when you have a result for a diagnosis of autism in your child, it kind of narrows your focus into... Okay. This is the group that maybe I fit into. What things are being done to help? What treatment, what therapies are most effective in individuals with autism with this cause? It doesn't only so much, in that you have a group to join. That's the other thing with autism. Is that very often, there's a very small number of people who share the same genetic cause as you or your child. Finally, this was a really interesting kind of finding. It also fits with what we see in clinic and what we were seeing in our anecdotal research. Is kind of: How the ambiguity surrounding the cause of autism was impacted. Again, a very, very busy slide. But it's getting at this concept of how results changed over time. And whether or not people further endorse this particular -- increased their agreement, in green, or decreased their agreement. And what I want to point out are really some of the external causes to autism. So again, vaccination of the child, in this particular cohort, because they are self-selected to participate in genetic research, was already very low at baseline. But you can see people who received results further decreased any kind of attribution to a vaccination their child received. Or outside things that they did or did not have control over. Like their lifestyle. Exposures during pregnancy. And so on. Whereas we see less change in kind of whether or not this was something that they see as their child's own behavior or personality. Finally, I just want to point out, as I think something we see in the receipt of results, is kind of -- somewhat of a loss of a hope. We've now given you a specific genetic diagnosis, and this is something that's different about the child or the individual's genes. And you'll see here that there was a slight increase in endorsement of the inability for a child to receive college graduate or advanced degree. So just quickly in conclusion, we felt that if we saw for identity -- we saw this modest change in stigma. For responsibility, we saw changes in perception of recurrence risk, and for ambiguity, we saw significant changes in how people perceived the cause of their child's autism, now that they had a genetic attribution. So I just want to make sure I recognize the many important people that are working on this project, as well as the SPARK participants who completed these surveys and our funding. And I also have references and some additional slides to aid in the discussion. But I want to hand it over to Holly now.

WENDY: Thanks, Julia. That was fantastic. So we're gonna switch gears. And then we'll start discussing a bit amongst ourselves and amongst the audience. But let me go ahead and introduce Holly, while she gets herself set up.

WENDY: Holly is going to discuss disabilities, genomics, and representation, focusing on autism as an example. She's going to talk about how we can focus on engagement and representation with autistic people. Not just the parents. When we design and conduct and interpret genomic studies and use large biobanks. Holly, I'll let you take it away.

HOLLY: Thank you, Wendy, for the very kind introduction and Julia for the wonderful presentation. And the organizers. I'm gonna take a slightly different perspective on this issue, and I'm really looking forward to the conversation. This is something I've thought about for a long time, so I'm really excited about the conversation. I put this slide in here, because I don't have any conflicts of interest in the traditional sense. In terms of companies. But I do have a couple of -- I think it's really incumbent upon us as bioethicists to be reflective and reflexive about the things that we study. And I do have a bunch of experiences that I think are really important to start with, to frame how I think about this. So when I was in graduate school, I worked in the lab of Dr. Rick Myers at Stanford and worked with Neil Risch on the first, the largest to date, multiplex family study, genetic study, linkage study, looking for genetic causes of autism. With the largest multiplex family, well characterized phenotype set that had been done at that time. And this was the main paper that came out from that while I was in graduate school in 1999. While I wasn't on this paper, I was on a lot of the other papers that came out of this study. And this paper found at that time in 1999 that there were likely more than 15 loci at least involved in autism. And it was really considered quite controversial at the time. Because I also want to frame here that I've been involved in autism studies from when they were linkage studies to when they were candidate gene studies to when they were GWAS studies, to exome and whole genome studies, to some but not all -- different kinds of genetic testing, whether it was array or exome testing done in the clinic, and sometimes not paid for. So I have seen a history of autism genetic research. So a lot of what I'm gonna be talking about is based on that professional experience. But on the right is a picture of my oldest son Colin, shared with his permission. I had him in 2001, after the study and after I got my PhD, the year after he was born. And Colin was diagnosed with autism when he was 3 years old. And he has been my teacher. Colin has introduced me to many individuals, adults, families with autism, and I have a very different impression of how I think about autism and research on autism from my personal connections and experiences with autism. So that -- and I also work with people with autism. So that really informs a lot of what I'm gonna talk about today. I also was very fortunate to do some work early in my ELSI career with my colleague, Dr. Martine Lappe, on one of the other early genetic cohorts that was used to study the genetics of autism, which is the autism genetic resource exchange, originally started by Cure Autism Now, a parent advocacy group started by Portia Iversen and Jon Shestack, I believe a big Hollywood director and producer. And in this article, which we had in the book that was edited by Wiley, Burke, and colleagues, I have some quotes from Portia and Jon. She was saying that she was talking to researchers at that time, about challenges getting genetic testing done on autism. And most genetic researchers at that time were unwilling to share or pool their databases. As was true of a lot of genetics research at that time. Because they had put substantial effort into recruiting and phenotyping the families. And they went around to researchers and tried to get them to pool these smaller data in order to get a larger n to be able to do larger linkage studies and larger studies that might identify genes and they couldn't do it. So they decided to create this database to quote-unquote become the data and govern and control the data by a parent advocacy group. Jon said: It was silly to try to collaborate and change the researchers. What you had to do was become the data yourself and control it. If you cared about universal access, you just had to have universal access through your own machine. So this work also -- and the way that parent and family groups got involved in thinking about how the landscape of genetics and genomics research on autism could be done -- to benefit patients and families -- also colors a lot of how I think about this issue. In recent years, I've also pivoted to doing a lot of work about genomic research on disability. And this is Jackie Scully, a leading scholar in this area. She has a wonderful article in Nature Reviews Genetics, in October 2008, talking about genomics research on disability. And she highlights something that's a really big challenge in genomics research in particular and autism specifically. That we have this drive to prevent or cure disabling impairment that's become one of the primary justifications for committing significant resources of time, effort, and money to genetic or other biomedical research. And I will say that I have almost never been in a meeting where autism genetics and genomics research has been discussed to this day where a comment is not made about this specific issue. So I think it's an ongoing challenge. Even as... And I'm not saying that there are not significant challenges that people with autism and their families face. That we want and need to address as a society. As biomedical research and as medicine. But there are still incredibly stigmatizing, ableist statements that are made in almost all discussions I've heard of autism genomics research. Not by everybody, but usually by somebody, that frequently unfortunately go unchallenged. I really love that presentation. Fabulous presentation by Julia. And Wendy's group. And their study, I think, has led the way in a lot of really impressive and amazing things about autism. And has been part of a pattern of emerging big -- some might say -- giant autism research studies and genomic databases that go with those studies. But one of the things I want to point out is that a lot of these studies leverage a little bit -- and I think this came up in how parents reacted to the data, reacted to the results. That data was very interesting -- parent feelings of guilt. So unfortunately, a lot of the recruitment materials talk about parents feeling like it was "their fault". There was actually some information on the SPARK site in the past -- I didn't check to see if it was there now. But this was last fall. That a mother had worried about -- she'd been in a car accident when she was pregnant. I'm reading from a thing I copied. Her doctor scheduled the twins to be born early. She felt a feeling of guilt. She joined the study out of the best possible altruistic reasons to join the study and didn’t expect to get results. And then this quote, in 2019 she got an email, she didn’t read it for a few days, she thought it was a routine notice, and then opened it up, texted the husband right away. You won't believe this. We got really excited. And the counselor explained that the patient had a rare change in one of the susceptibility genes for autism that he did not inherit from his parents. It was de novo. So the mother was glad to hear this wasn't her fault. I think that's very consistent with the really interesting and rigorous data that Julia presented, but it's very relevant to the broader sort of benefit/risk thinking about the obligations and objectives of our large scale research studies for autism and for other phenotypes. So I just want to point that out. And I think it's important to acknowledge that really important research does actually come out of these large scale genomic research studies as well. This was another one that was talking about, as Julia had talked about, the potential that these large studies and databases can significantly contribute to our understanding of the genetic basis of autism spectrum disorder. But I think it's important -- it's interesting to note that many families sought out -- who got results sought out opportunities to participate in more research. I think this last line, by returning genetic results to participants, we expect to increase engagement and increase the number of recontactable participants for genetically-targeted clinical research and trials. That's very exciting, but in the meantime we have to think about what happens now and what happens to the people who don't get results and don't... Aren't gonna be recontacted. MSSNG is another very large autism genetics study, organized by the Autism Speaks, which is... The topic of a whole nother talk. But the actual legacy of Cure Autism Now, the original advocacy group I mentioned, and Google. And their goal was to create the world's largest genomics database on autism. That was their stated goal. That's one example of another database. But it's worth mentioning that on Twitter there's actually a fair amount of discussion and in the literature about people with autism and families with children with autism being somewhat suspicious of the way these large-scale studies, at least in this case, MSSNG, are run. Talking about precision medicine for behavioral health? Are we proposing cures? Are we trying to take a medical rather than a social model to disability, to see autism as something to be fixed or prevented? Particularly when we haven't had success identifying clinical treatments for any of these rare subsets of autism. So it's important to listen to the voices asking these questions. I want to talk about another large autism genomic study, the Spectrum 10K study, which was started and led by Simon Baron Cohen and also involving Cambridge University. And their goal was to collect DNA from 10,000 autistic people and their families. And I believe they started last summer. But very soon after they started there was incredible uproar in the community, particularly from adults with autism themselves, but also some parents, being very concerned about the lack of engagement, collaboration, and participation of people with autism and their families, in thinking about the study design, the study objectives, and the governance of the data. And they actually had to halt recruitment for the study. And Wendy may know, but to my knowledge, I cannot find anywhere on the website that they have restarted the recruitment for the study. So I actually don't know the status of that. But this was the letter that was sent out by Simon Baron Cohen just a few weeks after the recruitment began saying we apologize unreservedly for any distress they've caused. They're taking a pause to give us time to co-design and conduct a meaningful consultation with autistic people and their families. And on their website, they do have information about how they've engaged a firm and have a multiphased plan for how they're going to engage autistic people and their families. And I really commend them for that. I think that's a really good response, and I hope they do exactly what they're saying, and they can serve as a model for everybody else but the fact that that didn't happen in the first place is incredibly important for us, particularly as ELSI people, to think about. So why do I think that genomic and big data for autism has really exploded in the last ten years? I think, as I mentioned, with the AGREE study funded by Cure Autism Now, there's a history of funding for genetic research for biobanks by parent advocacy groups. I know the SPARK study is partly funded by the Simons Foundation, and the Simons are also parents. I don’t think they’re funding it through fundraising, but there's a long history of parents funding genomic research for autism. And it's important to acknowledge that a lot of parents of children with autism, especially after the first years after diagnosis, feel quite desperate. They're operating in the absence of medical care, in a society that does not provide even the services mandated under the Individuals with Disabilities Education Act under the law, and with spotty and inconsistent medical insurance coverage for genetic testing. They often state they go into these studies as a way to get genetic testing because they think it's the scientifically right thing to do, to pursue a diagnosis, when they can't get it through the clinic to get paid by insurance. So other studies where parents say this is why they decided to participate in research. It's also worth pointing out that these studies are very large convenience samples of probands who are not often given the opportunity to consent to participate. In the case of many of these databases -- true of many other pediatric conditions as well -- children were enrolled and not necessarily reconsented when they turned 18. I don't think that's the case with SPARK, I don’t think that’s the case in some other studies, but from a legacy perspective, many of these cohorts did not recontact or set up mechanisms or funding to reconsent participants and ask them if they still want their data to be a part of it. I acknowledge that not all individuals with autism can do that, but there's a large literature on how we can engage individuals with disabilities like autism in consent and supported decision making, and I think the fact that these databases are among if not some of the largest databases in the world for any specific condition. And they happen to be of individuals who are vulnerable, potentially vulnerable, disabled, and have not consented -- is something that I think we as an ELSI community need to think about how we want to do that and model what's important. SPARK does a better job than some of the other, historical studies on this. But it's an important issue for all of us to take a lead on. There's also been a movement in the disability community and in the autistic community -- and most people in organizations with autism do prefer the language "autistic community" and "autistic people", arguing that we need more autism research that isn't just focused on cures and finding causes, but helping people in the here and now. And the reason is that there is very little other epidemiological research on autism, on other kinds of interventions that work. I dream of a world in which we can know that patients who have X, Y, and Z susceptibility gene can know they should use A, B, and C therapy or intervention to try to maximize their quality of life. That does not exist now. It's an incredibly long way away. We don't even know what A, B, and C treatment to use for anybody with autism. And most people can't access the few treatments we have any empirical data for. In my opinion, that's a crisis and emergency. If we involved autistic people and autistic advocacy groups in thinking about and planning research, we would think about ways to address that issue up front. And this is the Autistic Self-Advocacy Network, a wonderful organization that's been taking the lead in talking about these issues and advocating for these issues. I wrote a paper that came out in 2020 in AJOB, open peer commentary, in response to an article about how and whether different perspectives of stakeholders within the autistic community should be given or should not be given any or some voice and participation in these studies. And in that paper, I cited the work of Melissa Williams, who said this quote. For relatively privileged citizens engaging in a discourse with marginalized citizens requires a willingness to interrogate one's own judgments about the unreasonableness of others' arguments, particularly where recognizing the validity of those arguments would jeopardize one's material or cultural interests. A commitment to ameliorating group structured inequality then carries with it a commitment to the increased democratic participation of disadvantaged citizens. I would argue that ELSI researchers, genomics researchers, parents of individuals with autism of all levels of severity actually have an ethical and moral obligation to make specific choices, prioritizing the active inclusion and participation of them in all steps of autistic research for this reason. We can look at amazing work of our ELSI colleagues in other populations. This is a wonderful piece by Katrina Claw and colleagues, on principles for engaging in ethical research with Indigenous people. And I just wanna show you a couple slides quickly from what she talked about that I draw on to think about how we can draw on principles for engaging in genomic research with the autistic community. I think we need to engage and collaborate with them in the spirit of reciprocity on all stages of the research project, build cultural competency and listen and learn from the community about their cultural perspectives, about lots of things. Not just about genetics. We need to improve the transparency of research practices, making research goals and processes clear and accessible through frequent communication. And not just communication with the public. Communication with the people who are autistic themselves. And we need to disseminate findings in a community-accessible format. We really need to think about -- I'm doing this for another study recently. What are the best ways to disseminate information to people with autism and/or other disabilities? What do they need? What are the best ways to engage them? How can we engage them individually in terms of participants and the communities? I think that's incredibly important. I want to briefly nod to a wonderful talk from the Hastings Center, from I think it was last year, from Ari Ne'eman, about who should be represented in autism research decision making and why. And what goals and objectives should autism research pursue. Ari Ne'eman founded the Autistic Self-Advocacy Network. He's a scholar at Brandeis. He's done incredibly relevant work in this field and others as well. So I highly recommend that video which has definitely influenced me and I’ve learned a great deal from it. I want to mention another project at Portland State University, run by Christina Nicolaidis and Nicole Raymaker, a team of autistic individuals and parents called the AASPIRE project, which conducts action research focused on improving the lives of autistic people. They have wonderful examples and papers on how to engage people with autism in autistic genomic research that I think is relelvant for other models of genomic research as well. This is another quote about that. Saying how important it was and how you actually do the research differently, as we know, from other population-based research, when you actually actively include autistic people in all parts of the design and also in thinking about what the design should include. So my apologies for going late and running long. But I want to conclude with a challenging statement. Which I have thought long and hard about. And it comes from my experiences as someone who has participated in genetics research on autism, ELSI research on autism, worked on large scale genomic research studies, and believes in the potential benefits of genomic research and is also a parent and friend and coworker of autistic people. Autism, I believe, is unfortunately the poster child for failures and hyperbole of precision genomics research. Hundreds of millions of dollars have been spent over 30 years, parents and participants have been promised benefits and empathy. And yet I think we are challenged to describe an example of direct benefits so far to patients, not parents, as individuals of communities. I believe that autistic genomic research and understanding the etiology of autism are very important and still very much worth the investment of funding agencies, researchers, patients and families. But in my opinion, this research must pivot to more actively include the perspectives of people with autism themselves in a collaborative way and explore simultaneously the potential benefits of these large scale studies that could accrue beyond just identifying susceptibility loci that account for a very small proportion of cases of autism and have yet to lead to any direct effects on treatment. Autism genomics research is another example of what Meghan Halley and I have been writing about, about how genomics researchers and funding agencies need to consider post-trial responsibilities to patients and desperate families, who enroll in genomic research in an effort to get a diagnosis and find an answer. Why do these obligations exist? Some of the reasons include: The population is vulnerable, the vast majority of participants do not get a genetic diagnosis, despite the fact that the recruitment materials often glowingly describe the benefits and reassurance to parents when they get that rare golden ticket. Further genetic testing, analysis, may not be available, or reimbursed outside of research. And there are few if any effective treatments for the condition. From the post-trial obligations literature, it can be argued that researchers have clear responsibilities that to date have not been adequately addressed in most autism genomics research or genomics research more broadly. And I call on my friends and colleagues not just in genomics research to embrace this challenge. I thank the people who have helped me think about this work. And I'm happy to engage in discussion on this very important topic.

WENDY: Thanks, Holly. You packed a lot in there. So let me tell a little bit about SPARK. Again, I know that from the inside, I can't say much about MSSNG and Spectrum 10K. But SPARK when we started this 6 years ago started on the premise that we need to have individuals with autism embedded as part of the research team. And they're at the table for every single meeting that we have. And help us, in terms of everything that we do. The questions we ask, how we ask them, how we return information, giving monthly newsletters, webinars, information back to the community, as we do this. And I have to say I've learned an amazing amount from the people we have on the team. So thanks, Holly. I at least completely subscribe to that idea. The other thing I'll say is that, while it's absolutely true that genetics is not everything, one of the things that we've done within SPARK that I think Julia mentioned earlier was that it also powers completely non-genetic research. So there are 160 research studies that are being done by SPARK. It's not solely a genomics or genetics study. And we believe that's very important in terms of individuals across the entirety of the spectrum, the age spectrum, the geographic spectrum. Just many, many different ways. We're proud to be able to power 160 researchers who are also doing non-genomic research. Finally, I'll just say: This was one very eye opening, somewhat disappointing, but important finding, is that we returned a result to a young person, actually, in SPARK. That had undiagnosed phenylketonuria. Surprising to me. For those who know this -- that should have been picked up by newborn screening, and something that is completely treatable. I won't go through the details, but was missed on newborn screening. And when we returned that, did actually practically result in impact. Obviously that's one case. That's not 50,000 cases. But there are certain discrete cases in which that information has come back. So I'm glad that there's something for some people that come through within this. So a lot of questions... I'm actually gonna go straight to the questions in the Q and A. Because I don't want to miss those. So a question from Caroline Chapman. What's the purpose of autism genetics research? What should it be? What would researchers, parents, and individuals with autism have different takes on the question? So maybe I'll start and everyone can chime in within this. One of the things that's challenging sometimes is in the complexity of how the brain and behavior work -- is to get some sort of anchors in terms of understanding biology. And I think genetics in some ways provides some irrefutable evidence or at least very high levels of evidence to understand some of the basic molecular mechanisms. So I'll say that in the same way, for instance, we needed to understand how... What the underlying underpinnings were that led to heart disease and heart attacks, and be able to understand if there are ways to support individuals who might be at increased risk for that, it helps us understand the biology, and at least from my point of view, that's one of the reasons to do genetic research. But does anyone else want to take a stab or make any other additional comments on that?

HOLLY: I can. Julia, unless you want to go first.

JULIA: I think you have... Anyway... I guess... Speaking as a clinician and as a genetic counselor and seeing the families who have selected to come to genetic counseling to try to understand their child, it's really, I think... Around kind of whatever... Many parents feel. Which is how can I best support my child, if the traditional pathways are not supporting my child the best. And from genetics, we add to, I think, a multidisciplinary care of a child, or an individual, that's not just medical. But also kind of how they're educated. And that whole social network. The potential to help to maybe not tomorrow... Maybe not at that given time period, but potential to kind of follow them for a pathway that could guide... To kind of other treatment options. Or interventions or therapies. To support them.

HOLLY: Yeah. I'm... It won't surprise anybody... I'm fairly skeptical about the promise that finding a specific genetic result of the kind that we found in the last 30 years is at the moment likely to lead to a direct benefit for any individual patient. And so I think we should stop saying that. I think we should really explicitly talk about the benefits to research more broadly. To generalizable knowledge. The reasons why we should talk more across precision genetics and medicine research more broadly -- why this might change the landscape over several decades. And we should create community information. What most parents of autistic children need is information about how to advocate for school resources. Even for someone like me who works at an academic Medical Center and understands the biology of autism very well, there's incredibly poor medical care for autism, even when it’s coordinated. When you have seizures, you can go see a neurologist, but we can do better as a society and as medicine in terms of treating autism, but we don't have information and resources. The transition from adolescence to adulthood for people with autism is a cliff off of which people fall, both in terms of medical care and in society. So when you talk to people who have autism and to parents, you get different perspectives about what they think is important and what they need. I haven't done this recently, but I'm thinking about doing it. I want to look at the proportion of genetic research that's funded by NIH and by advocacy organizations, and individuals, to see how much of it -- what proportion of it is on genetics. And, Wendy, I think it's wonderful -- I know SPARK is leading the way in doing a lot of other studies, and that's great. I want our funding agencies to fund those studies. I want it to be part of the design explicitly from the get-go, that we're doing in-depth epidemiology of autism. To my knowledge, there are no large-scale epidemiological studies of autism. And we absolutely need that. And we need them to be longitudinal. And I want a sort of shared practice that will try to do reconsent for all individuals who enroll when they're children, when they're adults, across all genomic research studies. To my knowledge, there isn't. Somebody might be able to tell me otherwise. So we need to engage with those communities about what the goals of autistic genomic research should be. I think NIH and other funding agencies need to do that and ELSI researchers need to do that as well.

WENDY: Thanks to you both. There are a lot of questions. I'm gonna try to plow through these quickly. We'll try to keep comments short. There are comments in terms of language that's used in discussion of genetic research that can be stigmatizing that goes unchallenged. The question is: Why does that go unchallenged? What can be done in terms of that? And Holly, you may have some ideas about this. And I'll say that... I do think that one thing that people... Anyway, they need to be educated. Is part of the answer. But Holly, do you want to chime in?

HOLLY: Again, I think that this is a gap in my field of origin. Genetics and genomics research and ELSI. And also in society. I think there's a huge issue about disability bias and stigma around disability in genetics in general. And I'm actually working with our postdoc, Kevin Mentz, and other people, Maya Sabatello has done great work in this. Others as well. Looking at history of bioethics more broadly -- there is underlying stigma in our society towards disability in general, and autism is no exception. My younger son, who is a high school student, recently called out a teammate for commenting when they were moving some heavy pieces of equipment: You guys aren't doing it right. You're being autistic. So I want to point out that there's a significant bias in our society. People say I'm acting autistic in the same way they might say: You're just the R-word. Okay? And it is absolutely incumbent upon researchers, including ethics and genomics researchers and clinicians to understand that that is the world and the fabric in which autistic people and autistic families live. Every single day. And I am no longer convinced... I think taking... You know, there's also a history... I didn't even talk about Bettelheim and the refrigerator mother movement, in which one of the leading researchers in the autism movement got a lot of public attention for blaming cold refrigerator mothers who weren’t emotional engaged with children for causing autism. And it's impossible to ignore the impact on that on how we think about genetics and autism. On the one hand, saying it's genetics or de novo, which you didn't inherit, is releasing the mothers of guilt. And as a parent, I understand the attraction of that. But it plays into this social fabric of legacy and discrimination towards people with disabilities and their families that we as a society and ethicists and researchers have to do more for.

WENDY: Thanks. Julia, this question is more for you. In terms of thinking about these diagnoses and giving back genetic diagnosis – net-net - harmful or helpful? Maybe not the same for everyone in terms of thinking about this. But in terms of optimism, pessimism, do you want to weigh in at all in terms of how this might impact different people differently?

JULIA: So we certainly know it impacts different people differently. And I think that's something in the data that I show. It really kind of drowns out the individual experience. We know the individual experience of receiving results or being told that there's an absence of results can be earth shattering for some people. Another day, another email for other individuals. So that's one of the things that we're very cognizant of, as we look at these data in aggregate. Knowing that this is not giving any individual story. And so we need to be careful as we present and write up these data, to recognize the individual experience as well as the experience of the cohort. I think... And Wendy will remember the reference better to this. But there was an excellent article written by somebody who had received a diagnosis. It changes everything. It changes nothing. Which gives one person's very individual perspective of receiving genetic results. I think also the kind of language around... You come into this, thinking that you're going to receive a result... I think overall in genetics, even with the kind of implementation of next generation sequencing and really being able to do exome and genome analysis... I think we messaged incorrectly there. As we first rolled out that technology. And I think that messaging has pivoted. Not just within the autism community, but also beyond, to really recognize that even with this great fantastic technology, to be able to look at our entire genome, we still understand only a fraction of it. And so kind of I think continuing the message that only a fraction of people at this point will receive results, because we only understand a portion of it... And really trying to moderate people's expectations, and hopefully in that way... Influence kind of how people make choices to be part of research. And I think a big point of SPARK is that it's a choice to be part of the genomic research of SPARK.

WENDY: So I'll just add a little flavor. Because as Julia mentioned, I actually have the privilege of talking with many of the families. And as we return results and understanding that impact longer term -- as Julia said, some of the families... This one particular family, it just rings so true. It changes everything and it changes nothing. I'll say my observation has been that some people are asking about: Does it take away an autism diagnosis? Does it change in terms of... Do they still have autism? Or do they have something else, in terms of now a genetic diagnosis? We always... In terms of explaining this to individuals, say... In some ways, you're exactly the same. Right? Nothing has changed, in terms of the wonderful people that they are. If they still had the behavioral characteristics that are labeled "autism", then they still have those behavioral characteristics. If they still had epilepsy, they still have epilepsy. But what we do see -- and I mentioned this sister study, Simons Searchlight, what has been really empowering or wonderful for me to see is families helping each other. Because now the families have greater specificity in terms of other individuals that they feel more representative in terms of the experience and the journey they've been through. And watching them help each other as they're going through that journey -- I call them life hacks, but tricks of the trade, things they've found, educational systems and supports, realizing that they themselves or the individuals in their family had skills and abilities that they didn't even appreciate until they started getting some insight from the other families. I think has really been very, very helpful for individuals that are in that. And just to give you an example of the magnitude that we're talking about, we've had approximately 800 returnable results related to autism within SPARK. So it's not a small number of individuals who are impacted by this. So within this, there's some questions that are coming up in terms of disparities. So as Julia mentioned in terms of the study... Who participated at least in the study that she mentioned... I believe the number was about 80/20, in terms of the split for those of European ancestry. I don't know if anyone wants to chime in about any of these things. I do think there are issues of disparities in many, many different ways. SPARK has specifically addressed or started addressing -- I don't think completely addressed -- but specifically had grant funding for community organizations that are helping in terms of outreach, being able to -- and with that actually providing some of the resources that Holly was talking about, in terms of helping families get to what they need to, in terms of that. But genetic testing, I think, Holly, you mentioned, is an issue, in terms of disparities. Not everyone having equal access. And I have to admit, one of the things I found most interesting is our adults with autism, who have gotten diagnoses through this. I don't know exactly that their doctors would have... I don't know, again, that the diagnosis is everything. But I don't know that they would have accessed the resources through their usual health care. So I don't know if anyone wants to comment on the disparities issue.

HOLLY: Let's talk about kids first. And then I think you raise a really good point about adults. Yes, there's incredible disparity, not just in getting genetic diagnosis, but getting diagnosis of autism at all. Most lower-income and to a large degree non-white families actually get autism diagnoses through school IEPs. And for any of you who has a child with an IEP, that's not easy to get. Even though it's supposed to be. And schools are biased towards minimizing diagnoses and minimizing services. Because our IDEA obligations under the federal law are not funded. And so schools and school districts do not actually have funding to fully implement what they are obliged to provide through IDEA. So you can't get a diagnosis. You definitely can't get genetics. I mean, there's still a challenge that many insurance groups do not pay for genetic work-up for autism. Wendy, you would know more about that than I do. It varies considerably, both for the genetic test and the patient and the insurance company and the region of the country. It varies in terms of whether you're on Medicaid or not. So that is a significant challenge. I believe array testing was more often covered in the past. Even though it still led to really a quite small proportion of diagnoses for everybody. But exome and genome sequencing is incredibly hard to get, even for patients with clear rare and undiagnosed diseases and have a ten-year diagnostic odyssey and can't find anything. It's almost impossible to get for autism. And part of the reason insurance companies don't want to pay for it is that there's not much evidence that it helps clinically. At least not yet. We all hope and pray and believe for a time when it actually would help, but insurance usually doesn't like to pay for things for which there's not a specific context yet. Those are the reasons why there are significant -- it magnifies and amplifies disparities that exist in health in general and autism and other disabilities specifically in children. In adults, there are almost no resources other than communities for adults with autism. And not only do medical providers not provide those -- almost all in our society -- almost all interventions for autism come from our educational system. Not from our medical system. You get treatment for medical comorbidities. But not for autism and not for other kinds of issues related to autism. And it falls off a cliff when people are 18. And if you read a lot of the narratives, and there's research on adults with autism, including the work of AASPIRE, that I mentioned earlier, you'll see there's a huge gap there. That we do not fund as a society and do not think about and do not do research about. I think it's an urgent crisis and we have to address it.

WENDY: Okay. Very good. Thanks, everyone, for your attention. I'm sorry we weren't able to get to absolutely every question. But there's a post-breakout room after this. But Josie, I'll turn it over to you, to wrap up.

JOSIE: Thank you so much, Wendy, Julia, and Holly, for just super stimulating, really informative, and very provocative and helpful forum. And thank you to the around 150 people who joined us live. And I know lots of other people will benefit from watching the recording of this, along with the others on the ELSIhub. Please join us again, same time, same place, on the 8th of April, for our next Friday Forum, which is Balancing Data Privacy and Data Sharing: Normative and Technical Approaches, with these fine panelists and moderators. And for those of you who are interested in meeting the speakers and having a little post-webinar community in this digital day and age, please join us for our post-event discussion room. The link is live in the chat. And we'll just be there for 30 minutes. So pop in if you have any time and would like to meet the speakers and have some discussion. I wish everyone a wonderful weekend, and see you again.