Transcript: ELSI Friday Forum
Genomics and Infectious Disease: Scientific and ELSI Issues of COVID
February 12, 2021

DR TAYLOR: So that's my cue to get started. This is Holly Taylor. And I am a research bioethicist at the National Institutes of Health. And I would like to welcome all of you to the fourth ELSI Friday Forum. It's held on the second Friday of every month, for one hour, starting at 12:00 noon, just like we are today. We also have a Zoom room reserved for more informal discussion immediately after the panel, for 30 minutes. As a reminder, for those of you who are joining us for the first time, the ELSI Friday Forum is a new monthly series of the Center for ELSI Resources and Analysis, or CERA, for short. It's a multidisciplinary, multi-institutional center, that provides resources to support research on the ethical, legal, and social implications of genetics and genomics research, otherwise known as ELSI, and serves to connect a community for scientists, scholars, policymakers, journalists, members of the public, and others to engage in ELSI issues. CERA is funded by the National Human Genome Research Institute at NIH and is managed by teams at Stanford and Columbia Universities, in partnership with the Hastings Center and Harvard University. CERA's online platform, ELSIhub.org, was launched in November, 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, scholarly directory, and news and events. Please also go there to sign up for newsletters and other events like this one, at ELSIhub.org, and get daily updates on Twitter @ELSIhub. A couple of housekeeping items. If you wish to use closed captioning for yourself, you can turn on the CC at the bottom of your screen. We encourage an active exchange of ideas between our panelists and all of you, and the panelist presentations will be very brief, trying to be on time, so we hope to use a significant portion of the time in discussion with all of you. Please use the question and answer button that you can see at the bottom of your screen to ask the panelists questions. You can also register your enthusiasm for a particular question, and elevate it up the list, by using the "upvote" button in that box. The chat box is available for further engagement, and where you can find the links. I know that there are already all sorts of links popping up in the chat. If you have any questions, you can email info@ELSIhub.org at any time. So now I have the honor of doing a brief introduction, and then getting to our two panelists. Today's topic, as you can see from your screen, is genomics and infectious disease, scientific and ELSI issues of COVID. The next slide, I think, is my disclaimer. As a federal employee, I need to remind you that these are my opinions, and not those of my employer. My goal in a really brief period of time -- next slide, please -- is to sort of frame what Gail

and Priya are going to talk about. And these four bubbles represent for me the space of bioethics and ELSI, or the way from a bioethics lens, I'm sort of pulling together ELSI information. If you look at the history of genomics, I would argue that a lot of the work has gone -- ELSI work -- has been in clinical practice, technology, and human subject research, and a little bit of public health. Next slide, please. Over in infectious disease, we've done a lot around public health ethics. Next slide, please. The goal for today is to focus our attention to some of the clinical practice and public health ethics issues, ELSI issues, that bring genomics and infectious disease together. Next slide, please. And we're going to do that by talking about COVID-19. One quick thing -- next slide, please -- one quick thing to think about in the background here is that we're talking about the way that genetic variants are associated with various aspects of infectious disease. Including all of these things listed here, and I'm sure all of you are getting familiar with -- as they pass through the news. Next slide, please. And we're going to be talking today specifically about host genomics. So if you look at this, we can think of it from host, pathogen, or vector. And we're going to focus on host. Next slide, please. With that, I'm going to introduce our two distinguished speakers. I'll start with Priya Duggal. She is a professor of epidemiology and international health at the Johns Hopkins Bloomberg School of Public health, where she is the director of genetic epidemiology program and the co-director of the Maryland Genetics Epidemiology and Medicine Training Program. Her primary research interest is on host genetics susceptibility to infectious disease. She works with a variety of populations, and her work has led to the identification of loci for several infectious diseases. We also have Gail Geller, who is likely familiar to all or most of you. She is at the Berman Institute of Bioethics, at Johns Hopkins, where she's the director of education initiatives, and a professor in the Department of Medicine, with joint appointments in the school of public health and in arts and sciences in the Department of Sociology. She's been a very active member of ELSI and specific to our topic today, she is currently the co-PI of the NHGRI CERA at Hopkins, where she and Priya work together on the BRIDGES project.

DR DUGGAL: Thank you so much, Holly. Thank you for the introduction. It's been a great pleasure working with Gail for several years now, trying to think about infectious diseases and ELSI issues as they relate to infectious diseases. And then of course COVID happened -- or is happening. And I think a lot of the thoughts that we have can sort of be applied in this area. So I'm going to talk to you a little bit about what we know about host genetics and infectious diseases. Next slide. I have no disclosures to report. Next slide. So I think that most of us know a tremendous amount already about COVID-19. Maybe more than we ever wanted

to know about a coronavirus. But I think some of the things that are important to recognize are: What are these typical presentations of COVID-19? For what I consider a disease that doesn't really seem that typical. So there are some things that are very typical of infectious diseases. But this one sort of... It shows us so much more, because so many people are getting infected at the same time. So one is that you have asymptomatic infections. So people who really just don't show any infection whatsoever. You also have individuals who have mild infections, those who end up needing to be hospitalized, perhaps put on a ventilator or monitored in the ICU. Some who have different organs that are affected, whether it be heart, lung, kidney, or they have blood clotting issues. But then you also have children, who have this multi-inflammatory syndrome, that's reminiscent of Kawasaki disease, where they have longer term sequelae, meaning that about six weeks post their infection, they end up with these multiple organ failures. And we've seen this not only in children, but also actually in some adults. You also have some adults with clotting and stroke issues. And of course some adults with myocarditis that don't present at the time of the infection. But they present after the infection. But not severely long after the infection. And then of course you have these -- what we call long haulers, or post-acute symptoms, where people six months post their infection are actually continuing to have symptoms, or they have brand-new symptoms that have occurred, including tachycardia, or lung issues, and many of these are people who had asymptomatic or mild infections. So it's easy to say that there's a tremendous amount of heterogeneity in the clinical picture that we're looking at. Next slide. But we do know that there are three main risk factors. At least for individuals who are going to progress to severe disease. That's being of older age, being of male sex, and having comorbidities. Next slide. And yet we know that there are older people who actually recover from this, people in their hundreds, that have actually been infected and have been just fine. We know that there are younger people who require mechanical ventilation and even die with no comorbidities or no reportable comorbidities whatsoever. It's been suggested that race plays a role here, but it's pretty well accepted that it's a social risk factor, not a biological risk factor, representing who is on the front lines, who is an essential worker and needs to work, versus many of the individuals who have the privilege and capability of working from home, and therefore limiting their exposures. And then of course viral genetics can also be playing a role in the risk of disease. And I would say at least until the first 11 months or so, we weren't so concerned about mutations, and now of course many of these mutations now are increasing transmission or having the potential to change severity of the infection. But given that we see all of this and we know that there are three main risk factors, and I just told you there's so much heterogeneity, it leaves open this place of whether

or not there's a place for host genetics. Next slide. And so we're driven by two main questions. I've grayed out the other ones, because I'll bring them up at the end. But the first is: Does host genetics determine who gets infected? It's a really common question we ask in infectious diseases, and it's really getting at susceptibility. And the second is: Does host genetics determine who gets disease? And that's much more reflective of severity of infection. Next slide. So the one thing that makes infectious diseases different, for those of you who are familiar with genetic diseases in general, I think that we often can categorize individuals as cases or controls based on whether or not they have the disease, or they have whatever we're looking at. For example, hypertension. Do you have hypertension? Or do you not have hypertension? Do you have pancreatic cancer or melanoma, or do you not have pancreatic or melanoma? But yet in the cases of infectious diseases, we have this one factor. It's called exposure. That really matters. So if you fail to have COVID-19, in this case, is that because you were somehow protected from COVID-19? Or is that because you were never exposed to COVID-19? So this factor of exposure becomes really important, in how we look at our case subjects and our control subjects. Next slide. And so the two questions that we predominantly ask are this first question of: Do you get infected? That's susceptibility. And this requires really detailed information on the population under study. We need to know that the non-infected individual was exposed, and yet they still didn't get infected. Otherwise, any study you hear about susceptibility isn't a study on susceptibility. It's just saying who's COVID negative and who's COVID positive. And that's not taking into account other factors. So the study design is typically focused on highly exposed individuals, where you can document or infer that individuals were exposed. And you can think about doing these studies say, in health care workers or first responders, that might be really on the front lines, getting exposed. You can also think about household members of known cases, being individuals that would be at high risk of exposure. And if we compare it to something like HIV, it would be similar to the intensely followed up cohorts of HIV of individuals who participated in high risk behavior, in say the '80s or the '90s. Next slide. So the second question is: Do you get disease? And this is a question of severity. But really we're looking at heterogeneity and disease. So in this, everyone that we look at has been exposed. So everyone here would be someone who tested positive for COVID-19. That's anyone on the spectrum of asymptomatic, to someone who had severe disease. And we can sample on that full distribution, or we can sample on the extremes, or we can pick categories within them, the way that I sort of identified them initially. It's really important here that we only have people when we're thinking about severity of disease that actually had an infection, because you need that infection before you can have that disease. Next slide. Okay. So I was asked to

sort of give you an overview of what's known in terms of the genome wide association studies or the genomics of COVID-19. There are some studies that have focused on rare variants, and those show some promise to give us information on biologic mechanisms that might be at play, specifically in interferon pathways. But the most common way for us to think about this really is genome wide association studies, because there's an underlying assumption that this is likely driven by a common variant, when genetics is involved. So there have been several studies, two of which are still under review. One by 23&Me, the direct to consumer company, another by ancestry.com, another direct to consumer company, and one by Ken Baillie, published in Nature, coming out of England, and the other by Ellinghaus, published in the New England Journal of Medicine. I'm going to highlight the one by Ellinghaus in the next slide. So in this particular study, what they did is they took cases that were hospitalized with COVID, there were 835 from Italy and 775 from Spain. And they took controls. These were population-based blood donors or healthy volunteers. There were about 1200 from Italy and 950 from Spain. It goes without saying that this work is absolutely amazing, that it was done -- this was published, I believe, in July, possibly, June or July. So the amount of work that went in from really January, going forward, to get to this point, including genotyping, is phenomenal. But what you'll notice is they took these cases and they compared them to population-based controls. So people they didn't know if they had been exposed or not. And then what you're looking at in this plot is a Manhattan plot. What you see on the X axes are the chromosomes in order. What you see on the Y axes is the minus log of p-value. So the more significant something is, the higher it's going to be. We call it a Manhattan plot because each of these specific dots represents a test of association with a single nucleotide polymorphism or a genetic variant. And the more peaks that you see -- or skyscrapers, like Manhattan -- it gives you that skyline. So we're looking for that skyline. So this isn't exactly Manhattan. But it is probably some city in the Midwest. Showing us this peak on chromosome 3 and this potential locus on chromosome 9. The chromosome 9 locus is the ABO blood locus group, which has gotten a lot of attention because it's ABO and the idea is... Am I more susceptible because I'm a specific blood group? And the other one is on chromosome 3, which harbors several genes that have been of interest, and that's the only region that's been replicated multiple times. What I just presented to you was this idea of who should be our controls. And in this case, they're population-based controls. So I'm not really sure what question we're answering here, in terms of comparing cases to controls. Unless we assume that everyone else in the population would not have been hospitalized. Next slide. And this is coming from the Human Genetics Initiative that's focused on COVID-19, that's led by Mark Daly and Andrea Gana.

They've created an open consortium where people can put in their data from whatever sources they have on COVID from genetics and it can be meta-analyzed in a larger format. On the top left is very severe respiratory COVID-19 positives versus non-hospitalized COVID-19 individuals. That's exactly the group we want to be focused on. Their sample size is exceptionally small here, and you can see with the dashed line that would be going across that that's our threshold of significance. Nothing reaches genome-wide significance. Right below it is very severe COVID versus population controls. And you can see that that chromosome 3 region is actually really large. And there are several other regions that have been identified. Again, it begs this question of: What does it mean when we compare them to population controls? And then over on the right, you'll see hospitalized COVID versus not hospitalized COVID. Again, really getting back at where we should be, considering people on the spectrum of COVID infections, and the chromosome 3 region is the only region that reaches genome wide significance. That's very positive. And below it is hospitalized COVID versus population controls. And again, very similar to the one about very severe COVID. Next slide. So in summary, there are really interesting findings, especially the cluster on chromosome three. A lot of work being done in a very short amount of time. Despite the fact that I have some reservations about population controls, it's still showing us something that's probably worthy of investigation. The question really is: How do we account for exposure? How do we account for comorbidities, none of which have been accounted for in any of these studies. So it's definitely a gene for something. But what is it a gene for? And then of course, I didn't highlight this, but nearly every one of these studies is focused on European ancestry populations. Most have come from Europe. 23&Me and ancestry.com will give us a little bit more diversity when those studies are published. But how is that possible, when we know that COVID affects all populations? But we are lacking so many studies in non-European populations. So what we really need is diverse and representative samples to really understand what's happening. But we also need to understand the epidemiology. And that includes the social and structural issues that are at play, in terms of risk, that are not being addressed just by running these particular analyses. So in some of these genetic correlation analyses, they'll see that these peaks are associated with education, and with SES. So what's that sort of telling us? It's sort of suggesting that the people who had lower education likely have jobs that place them on front lines of needing to work. And it also suggests that perhaps these individuals had to work because they had lower SES, and none of that is exactly accounted for. Next slide? Okay. So these are the scientific questions that we could be asking. Many of them reflect the very original slide I had about the presentations. So beyond if you get infected or get disease, do you have some of these rare outcomes like MIS-C

that's present in children? Can we identify early associations with biomarkers, is there a host-pathogen interaction, does host genetics alter clinical trials, by medicines or by vaccines, is there a genetic influence on antibody or T-cell response or reinfection? And does COVID -- sorry, does genetics affect the long haulers? And all of these questions are actually under study by us and by some of our colleagues. And I think that's what leads into this next part of thinking about the ELSI issues. Next slide. All right. Perfect. So let me please hand this over to Dr. Geller.

DR TAYLOR: We might have lost Gail there for a second. Josephine and Rachel, I think we've lost Gail. Maybe we'll take this opportunity if anybody has a particular question for Dr. Duggal. A lot of really interesting information. Does anybody have a quick... Oh, there's Gail! Great. I'm just going to hand it over to Gail. Gail, we were going to do some quick question and answer to Priya, but I'm going to hand it back to you.

DR GELLER: Can you hear me?

DR DUGGAL: Yes.

DR GELLER: I am so sorry. I'm in an unusual location. And my internet keeps... I'm getting notices about being unstable. I may turn my video off. In fact, I probably should. But I just wanted to wave so everyone knows I'm here. And I also wanted to thank Priya so much for a great presentation. And in the spirit of sort of mutual admiration society, it's been a great honor for me to be working with Priya as well. You know, as somebody who believes that you really can't assess or think about the ethical issues, unless you understand the science, I have learned so much from working with Priya. So anyway... I am going to turn my video off right now. Okay? And I'll be back soon! Okay. So as a follow-up to Holly's introduction, I just want to start with a few overarching points of comparison between infectious diseases and the non-communicable diseases, which we've generally focused on in ELSI. Because this will help us locate COVID in the context of the broader category of infectious diseases. And also identify the ELSI issues that are specific to COVID. Next slide, please. So I have no disclosures. Next slide, please. So when we talk about inherited forms of chronic diseases, transmission is predominantly vertical. From one generation to the next. It's generally known who is at risk, and who benefits or is harmed. That is, particular individuals, families, or ethnic groups. And the primary focus or goal is personalized or precision medicine. Next slide. In the context of infectious diseases, yes, there are epigenetic factors that are transmitted vertically. But for

the most part, transmission is horizontal. It often occurs between unrelated individuals and even strangers. So we don't know precisely who is at risk. Or, as Priya has emphasized, who has been exposed. And that's a really important difference. The potential benefits or harms accrue to the entire population in the context of infectious diseases. As in the case of vaccine development and distribution. And the goal is public health. And we can talk about this later. Maybe during the Q and A. But there are well described ethical tensions between the goals and implementation of precision medicine and those of public health. Next slide, please. So another point to recognize in the context of infectious diseases is that disease characteristics vary. And they vary in ethically relevant ways. One such characteristic is mode of transmission. So COVID is an airborne disease. And for airborne diseases like COVID or influenza, everyone is at risk. And people usually don't know if, when, and how they are being exposed. Hence the frequent refrain that we're all in this together. Next slide, please. This is in stark contrast to bloodborne diseases like HIV and hepatitis C. With bloodborne diseases, we are definitely not all in this together. There are particular subgroups of the population -- for example, men who have sex with men or IV drug users -- who have to engage in risky behaviors in order to contract the infection. These subgroups tend to be marginalized in our society and the behaviors they engage in are further stigmatizing. Next slide, please. So here are a few ELSI issues that we have worried about in the context of genetic diseases or chronic non-communicable diseases. And in the interests of time, I'm not going to discuss them. But they're here as a point of comparison. Next slide, please. In the context of infectious diseases like COVID, the ethical issues are generated by the immediacy, severity, and transmissibility of the disease. And also the uncertainty associated with whether or not you've been exposed. Ethical issues also arise because there are health disparities and inequities in prevalence, treatment, and outcomes, and as Priya mentioned, these are much more strongly influenced by environmental, socio-economic, cultural, and structural factors than by genetics. But ancestry might play a role. The issue of race and genetics and the potential for group harms based on race and ethnicity is not new to ELSI. But the potential for inequities based on race or ethnicity is exacerbated in the context of airborne infectious diseases like COVID. A third point is that disease prevention is possible. It's somewhat different from the case of genetic diseases. But it requires adherence to behaviors that people -- many people -- find difficult to follow. And very importantly, in the context of highly contagious infectious diseases like COVID, individual rights and protections are overridden. So infectious disease control measures like mandatory vaccination or contact tracing or quarantine places constraints on privacy and liberty for the sake of the public health. Next slide, please. So let's think about a few classic ELSI concepts and how they look

different in the case of COVID. Take stigma and discrimination, for example. Although there are not new concepts to ELSI, they show up somewhat differently in the context of an infectious disease like COVID. What if genome research eventually enables us to identify a particular genotype associated with significantly higher likelihood of transmission? So-called super spreaders. Remember Typhoid Mary or Patient Zero in the context of HIV? Well, there would be an analog in the case of COVID. People with that genotype would have a capital C across their foreheads, and would likely be shunned and experience even greater restrictions on their liberty. This is all hypothetical. I recognize. But it's just to make the point that the nature of the stigma might actually be different in the context of infectious diseases. What about privacy? There's always been a primacy based on the privacy of genetic information, because of its highly personal nature and the risk of identifiability. But in the context of an infectious disease pandemic like COVID, the value of transparency far outweighs the value of privacy. We need to know who has been exposed, and who is infected, in order to prevent spread. But what if we identify genetic variants that either protect against disease or increase the likelihood of contracting it or having a severe form of the disease? How would that information be treated? Would it be considered more like genetic information and kept private? Or would it be considered more like typical infectious disease information and shared widely? So let's return to Priya's presentation and imagine that we confirm the existence of a reasonably penetrant variant on chromosome 3 that is associated with the development of severe forms of COVID. There are a number of implications for both clinical practice and public health. Next slide, please. In clinical practice, we can think about either patient care or we can think of the health care workforce. So regarding patient care, genetic information could help us make difficult allocation decisions in the face of resource scarcity. In situations where ICU beds or ventilators or other therapies are in short supply, genetic information could support the decision to prioritize patients at greatest risk of severe disease, to receive care first, or scarce resources could be offered to patients whose genetic profile is consistent with a better prognosis for recovery. Either is possible. And regarding health care workers, genotyping might assist in determining who should be first responders, who should be assigned to less exposure-prone environments, or who should remain at home. If personal protective equipment is scarce, health care workers may be screened, and practices modified based on genotype. What about the public health context? Assuming genomic information is widely shared or even reportable, it could be used to identify where vaccines should be deployed most urgently, and where other public health control strategies such as case identification, isolation, and quarantine should be implemented more strictly. Some ethical and legal concerns include potentially

exacerbating inequitable access to vaccines for some subgroups, or mandating vaccination for others. Next slide, please. So this is really the end. Just to say that in the paper that we wrote and distributed to everyone, we raised the following -- this list of specific questions for you to ponder. And I think we'll now have an opportunity for Q and A. And discussion amongst us.

DR TAYLOR: Thanks, Gail. So the plan is for me to ask a couple of questions of you and Priya, and then we will open it up to the larger group. So for those of you -- 103 participants -- please go to the question/answer chat box, and start posing all of your questions. So thank you so much, Priya and Gail, for setting the stage. And I wanted to start with a question. And I'll maybe direct it to Priya, and then Gail, you can follow up. So in COVID, we've been talking a lot about resource allocation, and setting priorities. Do you have any insight on -- among the different things that we might want to focus our attention on, as it relates to the genomics of COVID -- are there particular things you would like to see? Or if you were -- like, we should keep our eyes open for, as they come through, as it might be relevant to the question about infectious disease and genomics?

DR DUGGAL: Yeah, you know, I think it's really hard to do this type of work in general, because you're dependent on trying to first follow all the rules of identifying people who have disease, who have been hospitalized -- sorry, that's my phone in the background -- and other aspects, and it's really hard, then, to... (answering machine picking up) It's really hard to capture data on individuals, in realtime, as we're moving through this. And so one of the ways we've been able to do it at Hopkins is to start from the very beginning, in building a biorepository. And putting people into that biorepository. That would really guide us. The way Europe was able to do it was to take hospitalized cases during a pandemic. That's why we don't have those controls that I was talking about. That's the hard work. That's the part of contacting people who didn't get hospitalized. So if there's ways to make that easier, we could have set up research tents when people were testing, and ask for participation. People are willing to help in these types of moments. So it would have been great. But... Maybe the next pandemic.

DR TAYLOR: Yeah. Great. I happen to tangentially be involved with the RADIX initiative, and I know that biorepositories is a priority, given what you just said, and then with all the variants, for example, the ability to sort of identify and track those, as they come in, will be an important -- that'll be a really important resource. Gail, did you want to add anything from the ELSI perspective? Any particular issue you think we should be focusing our attention on?

DR GELLER: Well, I'm thinking sort of more generally, I guess, about resource allocation and priority setting. You know, in an ideal world, therapeutic or preventative interventions would be produced in sufficient quantity to be able to be offered to everybody. But in the case of treatment, only those who were affected by the disease would need to be treated. In the case of prevention, though, everybody would benefit from prevention. And I actually think genomics could be helpful in vaccine deployment. In a situation of vaccine scarcity. Like we're in now. You know, it would be great if we could prioritize those we knew to be more likely to develop a severe form of the disease. That's when vaccine supply is really scarce. Like we are in right now. But I will tell you that we have had ongoing debates with our public health colleagues in the context of our CEER who feel strongly that genomics should not be used to determine vaccine policy. That we should develop a vaccination and vaccinate everybody. That's the whole point of vaccination. On the other hand, there's a lot of science going on right now, the science of vaccinomics, that is likely going to identify some potentially useful information about who is more likely to benefit from a vaccine, or who is more likely to develop -- you know, an adverse reaction to a vaccine. And that information might actually be useful. I think vaccinomics research has a role to play, and we should be doing more of it. The current vaccines we have -- allegedly -- the Moderna and Pfizer are 95% effective. But the question has been raised by colleagues of ours: What about the 5% who are not responsive? I mean... That's not a small number. And is there more that we can learn from them?

DR TAYLOR: Yeah, great points, Gail. And it's a really lovely example of -- right? Just what you were saying. Of how the public health ethics concerns and the genomics concerns can sort of overlap, and potentially be in conflict with each other. So one more question, and then I want to open it up to the ones that folks have posted. So in this sort of era, we've also been thinking a lot about social justice and social justice is a very important component of public health ethics. And we've all witnessed how COVID has exacerbated a lot of health disparities. Are there ways that we might think about using genomics to make sure that disadvantaged populations are not further disadvantaged? Is there a way that we can sort of harness that energy for good? As we face these social justice issues? I don't know if Priya or Gail -- you want to start.

DR DUGGAL: I'll start, Gail. I think the first thing we can do is include individuals. That's what's been lacking. And that goes way beyond thinking about COVID. You know, we know in genomic research that it's dominated more than 80% globally by individuals of European ancestry. That are in our studies. And that's a

problem. And it's especially a problem when you think about something like COVID, that affects so many people, and that people highlight a lot of issues. I see daily headlines that say specific racial groups had this outcome or that outcome. The underlying message is that there's something about their race that got them into that position. And without them being included in the research, we can't follow up and say... It's not actually about their race. It's about -- maybe it is something genetic. That has nothing to do with race. Or maybe it's really about other social and structural issues. So from my perspective, inclusion is the best thing we can do.

DR GELLER: So I want to echo what Priya said about inclusion in research. I also want to sort of elaborate a little bit, and de-emphasize, in a way, the importance of genetics and genomics, or at least, not hype it, and have us remember that most of these disparities are related to socio-economic and structural factors. And not genetics. But suppose we did find a difference by ancestry. Let's say enough people of African descent are involved in the research, and let's say we were able to identify a variant associated with severity of disease at greater prevalence among people of African descent. It is conceivable in an ideal world that we would actually be able to prioritize them for care or for vaccines. So that would be a benefit for them. You know... Part of me... I mean, it feels to some extent that it depends on what the finding is. So if the finding is... You know, about severity of disease, maybe it would be a benefit to disadvantaged populations. If the finding is about transmissibility, you know... The Typhoid Mary example, it could exacerbate the stigma and discrimination experienced by disadvantaged populations. So I think, again, this issue... What it is that is being studied, and what the actual finding might be, mode of transmission, all of those sort of classically scientific concepts, I really strongly argue are highly morally relevant. And what we do with them will vary.

DR TAYLOR: Yes. Right? I was just thinking... Right. We have to be thoughtful. About how we deploy these different tools. And what message that might then send to the public. And a quick follow-up on that. A point made by one of our audience members. That if, let's say, for example, there was our ability to identify those who were more likely to benefit from the vaccine, it might cascade into people being worried that their DNA might be needed, and may be hesitant about the vaccine and then also about having to offer a sample of DNA, which might then sort of further cloud some of these... Further complicate some of these challenges.

DR GELLER: There's actually one more thought that I have, Holly, that I forgot to mention before. So I know we're kind of limiting our discussion to clinical care and public health. But there's sort of an indirect health care and public health potential impact of genomics that might benefit disadvantaged populations. And that has to do with school openings. So we know that children from disadvantaged families really get a lot from attending school, besides just education. It's often where they get clinical care, it's often where they get food and nutrition. It's where... If there's violence at home, it's where they feel safe and protected. So schools play a lot of really important functions for people from disadvantaged families. So they're doubly, triply disadvantaged by having to stay home right now. And if genomics could somehow tell us who is resistant, more resistant, or less likely to develop a severe form of disease, at the very least maybe those subgroups of kids could be allowed back in school. It's a pipe dream at this stage. But there's a potential that genomics might play in broader public health policy than just specific health care.

DR TAYLOR: Or teachers, right? Same idea. We have some great questions here. We also have this option where people can upvote. So I'm going to ask the question that has made it to the top of the pile for now. Can either of you speak to the critical issues for returning results of genomics testing in the context of COVID genomics research? Especially in heightened contexts of anxiety with the pandemic.

DR DUGGAL: Yeah, that's a good question. We're all moving at breakneck speed right now. It's first got to be identified, validated, and then of course I think providing that information back to participants is important. But one thing that I would say in the last few minutes that we've been talking about. That we haven't really addressed as a community. Is the lack of true science education and science communication. And so genetics falls into this a lot. You know, it's why people think that the vaccines will get into their DNA. It's part of that whole messaging, and so I think we've learned some lessons here, about the importance of better education, and if we can educate people, returning results is not so bad. There's lots of people who can understand genetic data and understand what's going on. And that's always been a fear. I don't think it has to be a fear. But if we don't do the education, it's going to be much more problematic.

DR GELLER: I would just add that... You know, again, historically, in the world of ELSI, a lot of the return of results discussion and debate has been linked to actionability. You know, if there is a value to returning results, if there's something people could actually do differently with those results. And are you --

and then the other issue, of course, as Priya mentioned, is clinical validity and utility. So obviously the results would have to be... Real and valid enough to be useful to return to people. And then we need to think about what people would do differently with the results, and arguably, in the context of an infectious disease, everybody should be behaving properly. Should be wearing their masks. And should be avoiding exposure to the extent possible. And we wouldn't want a situation where people were told that they were less likely to develop COVID. That they would sort of have a false sense of security and go out maskless. So I think return of results potentially has a danger in the context of infectious disease. That people should just behave well, regardless of the result. I'm not sure the actions would change that dramatically.

DR TAYLOR: Yeah, and again, another really good point about how genomics folks can learn from infectious disease folks. Right? That it's not that "infectious disease" and "public health ethics" have solved all the questions. But there are a lot of questions that those who have been working in infectious disease might help supplement some of that information coming in. Like the behavioral disinhibition. That you might worry about with someone getting a vaccine. All of those different things. Again, with genomics. Knowing their genomic information. So here's my editorial comment about the next question. This seems like a softball to you, Priya. Because genetic research has so many ELSI issues and we don't know if genetics is associated or predictive of COVID-19, is it even worthwhile to continue to spend money on genetic research as it relates to COVID?

DR DUGGAL: I hope that was a softball question.

DR TAYLOR: I hope so too!

DR DUGGAL: Yeah. I mean... So I do lots of work in infectious diseases. And another disease that I work on is acute flaccid myelitis. These are these children who ended up showing up in 2014 with paralysis. It looks identical to polio. And as a result of doing this -- we have no explanation of why. We know it's an enterovirus that they're infected with. We don't know why they get it. When you look at the polio literature, we got about as far as we are right now for the time... Meaning they didn't do full genetic actual research. They did a lot of pieces and then we got a vaccine and then we stopped. And look what happened. Many years later, we have to start from scratch to ask the same questions that we could have probably answered, if we had just continued on, and they didn't even have the technology we do. So genetic research was brought in here to understand

host pathogenesis. That was the purpose of this. Especially as a bridge to a vaccine for therapeutics. It's why we do a lot of what we do. Just because we had the vaccine I wouldn't stop the questions. Because there's a lot of questions with genetics related to the vaccine and also just related to what comes next in terms of the variants and its interaction. So no, my answer would be... At least -- I'm not suggesting it's the highest priority. Right? It hasn't been, so far. But it is something that those of us who work on it should continue to work on.

DR TAYLOR: I assume you agree, Gail.

DR GELLER: Totally agree. But I agree that it should have its proper place. You know. I've been in this field for a very long time. And this conversation was going on at the beginning, when we talked about -- you know, breast cancer. And if we focused so much on the BRCA-1 and 2 genes, ignoring all of the environmental risk factors from breast cancer that are greater... I think we need to be very mindful about not hyping the role of genetics.

DR TAYLOR: Great. So I mentioned -- and I think Priya, I know that Hopkins is developing or adding to a -- started a biorepository early on, and have been adding samples. Are either of you aware of other organizations or groups that are pursuing biorepositories? Any thoughts about creating or encouraging the development of biorepositories?

DR DUGGAL: So places like Mount Sinai have huge biorepositories. Penn, Vanderbilt, Colorado. They already had biorepositories in place. And my understanding is they've just expanded them to accommodate for COVID.

DR TAYLOR: Started opening the doors to the next thing?

DR GELLER: And a lot of work going on in the UK, right, Priya?

DR DUGGAL: Of course. Like the UK BioBank, which is linked to all of your health care records. It's done all the genomic work and it's got all of the health care. That's not as possible here, but there's the All of Us cohort that NIH is leading, that will also be something where they're collecting information on COVID. I think that the clinical biorepositories, like UK BioBank and the ones at Mount Sinai and Vanderbilt and Colorado -- they can collect information as people are coming in as patients. But they lack the ambulatory side. That's going to come when people are coming in to enroll.

DR TAYLOR: Another comment about -- another sort of aspect of this, that you just mentioned, that's in the chat, is this challenge of... You can capture someone in the hospital. Who's been diagnosed with COVID. And you can say: I'm going to take his or her sample and know that they have COVID. But the symptoms and how people present is just... You know, so complex. How maybe should we think about gathering data from people who are not yet in the hospital?

DR DUGGAL: So one of the ways that we're doing it is we take people who test positive at one of our hospitals. We literally go down the rolls and call them and ask them if they want to participate in our study. We send a kit to them in the mail. Because that's much better than having anyone go in anywhere. And we enroll their households. So one of the hardest things that we thought about initially is how do you get asymptomatic individuals enrolled? One way to do it is to enroll a household. So the symptomatic person might have tested. Especially early on, when testing was much more difficult to get, you would have other people positive, who could potentially report no symptoms, and we not only get a DNA sample -- we also get a sample for antibody testing. So as long as we fall within a reasonable window of testing antibodies, we can identify people who report no symptoms and are asymptomatic. That's just one way to do it. There are other ways. You could take health care workers where there's serology-based testing, you could take college students who are getting tested two or three times a week, many of which will be symptomatic, but a lot about be asymptomatic. Or school children. Obviously all with consent. There are ways to make this work.

DR TAYLOR: Great. So another question -- and thank you all for sending in your questions -- we probably have time for at least one or two more. So here's a question that picks up a bit on the sort of laundry list of questions that you ended with, Gail. About using genomic information, for example, about blood groups. Let's pretend, perhaps, that that ABO was really a skyscraper. And using something like that, about prioritizing... Once you have a workforce, who goes to the very front line, versus who sort of stays back? And using it as almost like a risk assessment tool. Of deciding how to allocate your Human Resources in terms of helping with COVID ward versus non-COVID ward, et cetera.

DR GELLER: So one thing that I neglected to say at the beginning -- I mean, our group is actually working on the ELSI issues associated with workforce allocation decisions. And one of the things I really want to make clear is that there's a whole -- there are a whole set of legal questions involved, that I am not equipped to answer. There are probably lawyers attending this. I would love to hear from them. But there's a lot of discussion about the extent to which GINA would

protect health care workers from undergoing genetic testing, for example. Whether or not this could occur in a hospital setting is not clear. Ideally, it would be voluntary. But you know, there's a lot of discussion about... Obviously, vaccination is mandatory. For health care workers. At least, flu vaccine is. So you can imagine a situation where something -- genetic testing, if, again, we identified -- if the ABO variant was reliable and penetrant, and we could identify it, we could imagine a situation where that kind of genetic testing might become mandatory in a hospital setting. I know that one of our colleagues, Brian Garibaldi, who runs our biocontainment unit, said that different hospitals that have biocontainment units are having to make decisions about whether "manning" "personing" the biocontainment unit should be mandatory or voluntary. Some hospitals are deciding it needs to be mandatory, and some hospitals are deciding... No, only the workforce that is willing to be in that kind of high risk situation should be in that kind of situation. So I think the issues of sort of the workforce relevance of genomics -- I think there's potential value there, but we really would have to be very careful about... A, the legal ramifications of that. Is that something we would actually have to require of health care workers? Versus making it completely voluntary.

DR TAYLOR: Great. And I'm going to take the moderator's prerogative to give the last word to Eric Jungst. This is in part directed to you, Gail, but I would love to hear your response too, Priya. He says: Can you say more about the universalist reaction for your public health colleagues, with respect to vaccination? Stratifying the population in terms of efficacy seems like a paradigmatic example of precision public health. Is there generally ethical pushback against precision public health in public health circles, or is this a vaccination-specific or research practice divide?

DR GELLER: Boy. Eric... I can always rely on you for really profound questions. You know, I actually don't know the answer to that question. It very well may be vaccination-specific. You know, I didn't actually discuss with our public health colleagues whether their concerns about precision public health would arise in other contexts. I can't imagine it would arise as much in a treatment context, for example. You know, pharmacogenomics... Is less ethically controversial, I think. Than the potential genomic implications in a real public health situation. Like vaccination. I don't know, Priya, if you... Would our colleagues -- would the Ruth Karens of the world really, really object to the use of genomics in contexts other than vaccinations?

DR DUGGAL: I think these are questions that were raised pre-COVID. And I think they hold within COVID. And I think they're driven more by the logistics of it. As you can see, we struggle with vaccinating individuals and rolling out appropriate... And I think at least some of our colleagues have highlighted... Trying to put another layer on this would complicate things. I might have said pre-COVID... No, we can do this! But now that I've seen our rollout, I don't know if we can. We have trouble getting people over the age of 75 vaccinated. I think that's what drove it. I don't think it was specifically about the precision aspect of what we would be delivering. I think they're like... Just get it out.

DR GELLER: So Eric, I do think... Again, I'm thinking a little bit. I'm trying to channel our colleagues. Who would say... I don't know that stratifying vaccinomics research is objectionable. In an ideal world, we might be able to identify different types of vaccines. That are more or less effective in different subgroups. As long as we vaccinate everybody. I think the worry is that people would use this information to say... Oh, I'm at risk of an adverse event. I'm not going to get vaccinated. So we don't want to use genomics as fodder for people who are vaccine hesitant or antivaxxers to avoid vaccines. I think the point is: Vaccination is designed to create, produce herd immunity, and as long as everyone is vaccinated, sure, it's great if you can get the vaccine that is more precise for you. That will be more effective for you. And have fewer adverse events. But... We want everyone vaccinated. I think that's what our public health colleagues would say.

DR TAYLOR: That's a good place to end! Vaccines for all! Thank you again, Priya and Gail and this terrific audience and your questions. Next -- I guess the next ELSI CERA Friday will be in March. So please join us then!

DR GELLER: Thanks, everybody!