ELSI FRIDAY FORUM

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New ACMG Guidance on Carrier Screening: More or Less Equitable?

- **Blair K. Stevens, MS, CGC** (University of Texas Health)
- **Katie Stoll, MS, CGC** (Genetic Support Foundation)
- Moderated by **Maya Sabatello, LLB, PhD** (Columbia University)

AARON GOLDENBERG: All right. Why don't we get started. Good morning, afternoon, or evening, depending on where you're Zooming in from around the world. I'm Aaron Goldenberg from the Department of Bioethics at Case Western University, and I'm delighted to welcome you to our December ELSI Friday Forum, New ACMG Guidance on Carrier Screening: More or less Equitable? The Friday Forum is held every month at noon eastern time. We also have a Zoom room for a more informal discussion immediately after the panel for 30 minutes. That link will be put into the chat, and we hope that many of you can stay on to continue the conversation.

For those of you who might be new to the Center for ELSI resources and Analysis, we provide resources to support research on the ethical, legal, and social implications of genetics and genomics, and serve to connect scholars, scientists, policy-makers, journalists, members of the public, and others who wish to engage on ELSI issues. It's funded by the National Human Genome Research Institute at NIH and is managed by Stanford and Columbia universities in partnership with the Hastings Center and Harvard. I encourage you to visit CERA's online platform, ELSIhub.org, for the recording and transcript of this forum, others, and references.

We're pleased to announce the publication of our 10th ELSIhub Collection. Please use the link in the chat right now to access that. It's an essential reading list curated by Emily Wakefield and Melanie Meyers about involving variant interpretations, professional and patient understanding of carrier screening, and the ability of the workforce to provide informed pre- and post-counseling and clinical utility. So very apt for today's conversation. A really wonderful set of resources that we encourage all of you to take advantage of.

Please also use the website to join the ELSI Scholar Directory. Please sign up for newsletters and other events like this one at ELSIhub.org and get daily updates and news on Twitter. So, lots of ways to engage with ELSIhub, and we really encourage you to take advantage of those.

Just a little bit of housekeeping for today. If you wish to use the closed captioning, please turn on the CC button at the bottom of the Zoom screen. The panelist presentations are going to be very brief today in order to conserve as much time as possible for our discussion. And there is a Q&A button that you can see also on the bottom. Please write any further questions in that Q&A screen. And those can be directed to the whole group or to any particular panelist. You can register your enthusiasm for a particular question! So, if you like someone's question, you want to kind of try to bump it up, you can elevate it using the up button in the Q&A box. The chat box is also open for discussion, and there will be resources posted throughout. If you have any

questions, e-mail us at info@ELSIhub.org at any time during the session. And we're really excited to get started.

So, I'm going to hand over the discussion to Maya Sabatello, who's our moderator today. Take it away, Maya!

MAYA SABATELLO: Thanks so much. Nice to see you, everyone. I'm an associate professor of medical sciences at Columbia University's Center on Precision Medicine and Genomicics, and the Division of Ethics, and I'm really delighted to moderate today's discussion. Our forum today focuses on reproductive carrier screening, specifically the project of conducting genetic testing before or during screening to identify carriers or couples who may have an X-linked genetic condition. This is increasingly recommended by professional organizations and applied in clinical settings, with many viewing it as integral to the parents' right to make informed reproductive choices, and with a corresponding responsibility of clinicians to offer such testing.

In July 2021, the ACMG issued updated guidelines for reproductive carrier screening in which it aimed to respond to several concerns. One is the growing scientific challenges arising from the shift from monogenic, single-gene testing to next-generation sequencing capabilities that allow for larger panel analysis and identification of genes or variants with various levels of specificity and accuracy. Second, the ACMG also aimed to address the erroneous determination of reproductive carrier screening panels for patients based on their self-identified race and ethnicity -- that is, based on a sociopolitical construct, rather than scientific-based identification, and which resulted in racial and ethnic disparities in implementation and outcomes of carrier screening programs. Accordingly, the updated guidelines highlight that carrier screening paradigms should be, and I quote: Ethnic and population-neutral, and more inclusive of diverse populations to promote equity and inclusion. The guidelines adopt a four tier approach for reproductive carrier screening based on presumed severity of the condition and carrier frequency and a 130-gene panel for screening of all pregnant women, regardless of race, ethnicity, family, or health history, as well as potentially all their reproductive partners.

However, this scientific endeavor to integrate genomic knowledge in reproductive care has long faced criticism, and scientific and equity challenges with the updated guidelines remain. Moreover, the guidelines raise unique issues for people with genetic conditions and their families, who are the primary targets of reproductive carrier screening programs, and for whom the scope and presumptions underlying such programs may have significant implications for how society responds to their bodily differences... as well as to people -- other people with disabilities more generally.

Today we are honored to host Ms. Katie Stoll and Ms. Blair Stevens, two scholars and practitioners who have been at the forefront of debates on reproductive carrier screening, for a discussion on the challenges of implementing such programs, the tradeoffs between scientific validity and inclusion, and more generally the issues that such programs raise for disability equity and justice.

Before we move on to their presentations, I want to briefly introduce them. So first, Ms. Katie Stoll is the executive director of the genetic support Foundation, a nonprofit organization whose mission is to increase access to independent genetic counseling services and information about genetics and health. Ms. Stoll received a master's degree in genetic counseling in 2013 -- 2003, sorry, and has worked since then in perinatal genetics, hereditary cancer, pediatrics, and general genetics.

Next, Ms. Stevens is a prenatal genetic counselor with 13 years of clinical experience. She is also the director of the prenatal genetic counseling services at the University of Texas Health Science Center in Houston, and an associate professor at the University of Texas McGovern Medical School. Ms. Stevens helps families understand the risks and expectations of genetic testing and has a special interest in helping adapt to the expectation of fetal anomalies. In addition, she supervises various students. She is an author on the screening practice guidelines of a national organization. She also serves as the National Society of Clinical Geneticists - NSGC's - expert.

After presentations, we will have a moderated discussion, and I encourage you to write your questions in the Q&A box, and I promise to get to as many of those as we can for our discussion. Whatever is left will be moved to the second part of the, to the after event, the more informal discussion. But at this point, I'd like to start with, with Ms. Stoll's presentation. Thank you.

KATIE STOLL: Thank you so much, Maya, and I'm so honored to be here talking about this topic with you and with Blair.

So, for my disclosures, I'll just say that I'm a full-time employee of Genetic Support Foundation. No financial conflict of interest to disclose. Next slide.

So today, I'll provide a brief overview of the ACMG guideline, screening for autosomal recessive and X-linked conditions during pregnancy and preconception, a practice resource of the American College of Medical Genetics and Genomics. But mainly, I'll focus on a few critiques of the guideline, including the way condition severity has been defined for inclusion on the guideline, as well as the failure to include the perspective of people with lived experience with genetic conditions and disability in the development of the guideline. And also we'll consider some health equity issues that may result downstream of the screening itself. Next slide.

So, as Maya mentioned, this new guideline does call for a uniform screening panel that should be offered to all patients, regardless of reported ethnicity, family, or health history. In total, the panel that's recommended includes 113 genes. And this is, these are both for X-linked and autosomal recessive conditions. And the inclusion criteria for the panel was related to the frequency of the mutations in the U.S. population. And the threshold was carrier frequency for autosomal recessive conditions of 1 in 200 or greater in any U.S. subpopulation that makes up at least 1% of the U.S. population. And then, severity of, of the condition was also considered. Next slide.

So, defining severity. So, the ACMG seemed to recognize that defining severity is complicated and potentially controversial. And they reference in the guideline that they used published definitions in defining severity for this guideline. The published definitions that were cited in the guideline were one study that was published in 2013 by the laboratory Counsyl, which is now Myriad Genetics. And in this study, the the lab had surveyed people for whom they had e-mails, in their internal database. So presumably, this was customers or potential customers, potentially staff, that were surveyed. All in all, they had 192 responses from genetic counselors and physicians. And they asked providers to basically rank conditions based on severity. They provided each respondent with a set of five conditions that they felt represented a spectrum of conditions. And then based on that, they developed this criteria. Next slide.

So, this criteria outlines actually four different categories, but three were considered inclusive for the ACMG guideline. And the first is profound, which includes conditions with a shortened life expectancy. So death during early childhood or infancy. Or intellectual disability. Severe included death in early adulthood, impaired mobility or a disabling malformation involving an internal organ. And then moderate would be neurosensory impairment, immune deficiency or cancer, mental illness, or dysmorphic features. So you can see a pretty broad spectrum of things that could be included.

In the Counsyl study, there was also a mention of a mild severity, which would be -- would include all other genetic conditions. Next slide.

So how should severity be defined, and who should be defining it? I think there's concern that health care providers have some bias against disability and genetic conditions. There have been numerous studies looking at this, including a fairly recently one by Iezzoni, that surveyed physicians and found that 82% of physicians reported that people with disabilities had a lower quality of life than people who did not have a disability. And then I also reference a review paper by Madeo et al that reports multiple studies related to genetic counseling... genetic counselor bias against disabilities.

And we know that these negative views on the quality of life of people with genetic conditions and disabilities may not match with how people living with genetic conditions and disability themselves would describe their OWN quality of life. This was evidenced by a recent publication by Boardman and Clark, which surveyed people with genetic conditions that would be considered severe under the ACMG guideline and found that the majority of respondents reported that they had a good health and wellbeing and capacity for a good quality of life. Next slide.

So, to my knowledge, the ACMG did not include any stakeholders to represent the perspectives of people with disabilities in the development of these guidelines. And this is despite prior calls to do so. So, in 2013, the Genetics Alliance published this paper: Nothing About Us Without Us: Guidelines for Genetic Testing. And this was in response to the ACMG guidelines for spinal muscular atrophy screening, with a call to be more inclusive of stakeholders in development of guidelines. And then in 2019, the National Council on Disability published a report that called on all organizations that are developing guidelines for prenatal genetic testing to establish these through a consensus negotiation including representatives from affected disability communities. Next slide.

Additionally in this guideline, they discussed that the established metric for clinical utility with population-based carrier screening is reproductive decision-making, and five potential reproductive choices are outlined in the guideline, including in vitro fertilization with pre-implantation genetic testing; the use of donor gamete/embryos; adoption; prenatal diagnosis, followed by a decision to either terminate a pregnancy or plan for care for the pregnancy -- for the affected child; or a decision not to have children. Of course, it's important to acknowledge when speaking about health equity that all of these options are not universally available to people, even if carrier screening is. We can imagine that people who can afford to be encouraged along the path of assistive reproductive technologies may do so, while those without financial resources may be discouraged from having children. Next slide.

And as a last point of concern, I would like to consider the cost of this testing and potential commercial interest. So, the ACMG states one rationale for increasing carrier screening as the

fact that the cost of genetic sequencing has decreased with technology advances. While the cost of doing the sequencing may have decreased, that doesn't mean the cost of the testing has similarly decreased. On any given day, you could Google search the term "carrier screening," and I have an alert set for "carrier screening," and it's quite common to see headlines like this. This is just from earlier this week, that the carrier screening market new business opportunities is expected to hit $4 billion by 2030. As we consider the drivers of these tests, we should also consider the profit motive, motives of the companies and their investors... to sell as many tests as possible, and for as much as possible. While we talk about this carrier screening as being at a cost that's available to all, in fact, the Center for Medicaid and Medicare, CMS, has assigned a value of approximately $205,000 to the code that's used for expanded carrier screening. And oftentimes, that code is not used alone; other codes are included to increase the cost further. In our practice, we have seen bills for carrier screening that have exceeded $34,000. Next slide.

And I think it's important to recognize that the laboratories that are developing these tests are not leaving the coverage of these tests, the payment coverage of these tests, up to chance. A few companies have united to form this industry lobbying group called The Access to Equitable Carrier Screening Coalition, named and promoted as if it's a grassroots patient advocacy organization. This has been an effective strategy for gaining coverage by both government and commercial payers for the coverage of DNA screening by another lobbying group that worked in a similar ways for noninvasive prenatal testing. Next slide.

So, just in conclusion to my presentation, I think it's important to recognize concerns with the lack of diverse perspectives in the development of these guidelines, especially people for whom these guidelines will very likely impact, including those with genetic conditions and disability. Additionally, I think we need to consider the numerous downstream effects of the offer of carrier screening, including access to reproductive health care, the cost to the health care system, and the greater possibility for uncertain or false positive results in some populations.

And with that, I would like to turn over the presentation floor to Blair Stevens, who will talk more about that last point. Thank you.

BLAIR STEVENS: All right. Thank you so much, Katie, for that very thought-provoking conversation. I have no financial conflicts of interest to disclose. And for my portion of today's talk, I'm going to review the ACMG practice resource and its goals of [unclear], but through the lens of health care disparities. While there are potentially great benefits with advancing carrier screens, I think we can also agree that we have a long way to go to ensure that it's useful in all patient populations. Due to limitations related to interpretation of variants, and significant health care disparities that exist in our society.

So, I would like to highlight some of those concerns today in hopes of finding solution that hopefully every patient can reap the benefits of carrier screening. And without these solutions, I very much worry that these advancing technologies are going to exacerbate health care disparities, rather than minimize the health care inequities that we're trying to solve.

So the first time I read this practice resource, I experienced a lot of conflicting feelings. Because while I agreed with many points made on paper, they didn't really reflect the reality that I so often experience with my patients in clinic. And ACMG correctly recognized one of the reasons I think I felt that disconnect.

MAYA SABATELLO: Blair, just -- Blair, just a second. Don't forget to remind to change the slides.

BLAIR STEVENS: Sure. Of course. And so, ACMG -- if you want to go to the next slide, that'd be great. ACMG did recognize one of the reasons. And it's because they highlighted these two studies, and they explicitly state that these studies may not reflect the clinical utility in an ethnically diverse population of individuals. And I couldn't agree more. So, this is just a quick summary of some of the demographics in the studies that they claim show that there's clinical utility of expanded carrier screening. And as you can see, this population was majority white, high level of preconception patient population -- which many -- are going to pursue IVF. And then in the one study that reported education and income, we see a high education level and high income levels. Next slide.

Whereas if you look at the demographic data from the patients that WE see in our clinic at UT in Houston, it's very, very different. We have a very ethnically diverse population, with a majority of patients being Hispanic. We have a very small fraction of patients who present for preconception care, with a pretty equal mix of patients being in their first and second trimester. And over half have Medicaid coverage, which typically correlates to a lower income level and often lower health literacy. So the population they're pulling from is very different and will find the utility to be different from the patients I see in clinic. Next slide.

So, having that diverse patient population in mind, which I think is very reflective of the American population, let's examine some of these benefits and how equitable they may or may not be. Next slide.

So, let's start with some of those preconception -- that Katie had mentioned on the previous slide. If you identify a carrier in preconception, you do have the ability to proceed with IVF or genetic testing, you can use gamete donors, decide on adoption, or decide not to have children. But at least in Texas, 50% of births are covered by Medicaid, which typically means that prior to pregnancy, these individuals are either not insured at all or are underinsured. And so to take advantage of carrier screening with these subsequent outcomes, it would cost you quite a bit. And if you're underinsured or don't have insurance, it's very unlikely that you're going to have the ability to access these types of benefits.

So already, we're seeing a huge difference of outcomes in the options available to patients because of carrier screening. Next slide.

If we move on to the prenatal period, where fortunately Medicaid does cover many women -- or, many individuals. So at least in our clinic, we don't have a lot of issues with Medicaid coverage of carrier screening. But we do have issues with getting the partner, the biological partner, screened. And as you can see on the left-hand side, less than 40% of people that need their partner tested get that partner follow up. And although I can't completely blame it on a financial aspect, because I'm sure it's much more complex than that, you can see a different clinic that published their data has a much higher uptake of partner screening at nearly 80%. And we see their Medicaid population is much smaller at 11% compared to, you know, over 50 for us. So it's very likely a complex reason why many partners don't end up getting carrier screening to complete their risk assessment. But I imagine a lot of it IS financial. And so I... it would be wonderful for genetic testing companies to include the test of the partner screening to help ameliorate some of these financial obstacles. But something that came to light in the last few years that is something I just wouldn't have even thought of as a white person who's a citizen of

the United States, is a very large number of patients we see are undocumented immigrants in Texas. And when trying to get partners tested, we often offer them the very generous financial assistance programs that our labs offer? And we realized that with those financial assistance programs, they're worried that it might get in the way of their citizenship path. So, just things that you wouldn't even think of off the top of your head that get in the way of partner testing. Next slide.

So, one solution put forth in their guideline is that if there is an ongoing pregnancy where the partner is unavailable or unwilling to have carrier screening, proceed to diagnostic testing and do sequencing of the gene that way. Well, this is one of those moments where it seemed good on paper, and it seems like, you know a good thing to do? But it's much more complex than that in real life. First of all, many patients don't want to undergo an invasive procedure due to the risk of miscarriage. Second of all, there are many labs that just don't offer prenatal sequencing for genes; the only way that they'll offer the testing is if both parental mutations are known, or variants are known. Fortunately, we do have a lab that's very accessible that accepts samples for most gene sequencing, and actually accepts both Medicaid and private insurance, but they have really long turnaround times! I literally waited eight weeks just to get my patient's carrier screen back. And then you have to facilitate the diagnostic test. Prenatal sequencing does typically take 6 to 7 weeks, because most have to culture cells before they can do sequencing of the gene.

And so given that a third of our patients in Texas don't even present for prenatal care until the second trimester or third trimester, you can imagine that by the time we get all of these results back, someone is going to be well into their second or third trimester, which really limits what they can do with that information. Next slide, please.

Now, not all couples pursue diagnostic testing with the intent of terminating an effective pregnancy. But if that is one of the considerations that a couple would make, as we all know, there's a lot of abortion laws on the books that are really limiting people's options. For example, in Texas, we can no longer do abortions after six weeks. So, even if you get earlier diagnosis, many times people will have to travel to different states to get termination procedures. And one of the patients that I know that had to travel to New Mexico recently, she was in her 22nd week of pregnancy; it cost her over $10,000. So, once again we're seeing a lot of inaccessible benefits that many couples just can't reach. Next slide.

So, this is that same list that Katie presented moments ago about the different possible ways that carrier screening can be clinically useful. And as you can see, many of these that we just reviewed are just inaccessible due to a lack of resources. And so the decision not to have children is usually one that -for these patients that are not preconception -- so you can see that pretty much the only thing that carrier screening might do for people with less resources is help them prepare for a child that has a genetic condition which absolutely has value. But seeing that the rest of those things on that list are not accessible to them, it just makes you wonder how clinically useful IS this test for those people. Next slide.

And so, that was the benefits aor lack thereof for certain patient populations. There are also limitations to consider. And what concerns me most is that while the benefits are there, the resources -- limitations exist for everyone? But I'm afraid that some of these limitations disproportionately burden people of color, who may also be the same populations that don't have those resources to access these benefits. Next slide.

Okay. So this is a couple of graphs from a paper by Guo et al that looked at the different carrier frequencies based off ethnicity. And as you can see, the more we test for, the more carriers we're going to identify. So the different ethnic groups are listed in the different colors. And the pink and green bars are bigger carrier screen panels, and the blue and purple are smaller carrier screen panels. And yes, if we screen for more, we will find more carriers in these underrepresented populations. Which is great; that is the goal. But as you can see, if we screen for more, we see more in EVERY population! And so there's -- we're still finding more carriers in white populations than nonwhite populations; we're just finding more of them across the board. And next slide, please?

And what we do know from sequencing is that if we sequence more genes and find more variants, that inevitably we are going to find more reclassified variants over time. So, imperfections of sequencing, as we learn more about variants over time, especially variants in underrepresented populations that are not as robust in our genetics databases. And so most of these variant reclassifications are going to be upgrades. But there are also downgrades. And what this makes me worry about is because -- next slide, please.

We know that these variant rates, or the uncertain variant rates, are higher in nonwhite populations. So these are just three different studies in noncarrier screening genes -- for example, BRCA 1 and 2. But all these show that the rate of getting a VUS is higher if you're not white. Which makes me worry that reclassified variants in the reproductive carrier screening realm are going to be more common in nonwhite populations. Next screen -- next slide.

So here are two examples of an upgrade and a downgrade from our carrier screening lab, just in the last couple months. We get these very frequently in our group. So as you can imagine, if you are 10 weeks pregnant, you get your carrier screening, and then I give you a call when you are 35 weeks pregnant and say you're a carrier for [unclear] disease which often results in early childhood death without treatment, its going to be extremely alarming. And there is some action recently on the prenatal listservs about downgrades, specifically muscular dystrophy. I can only imagine getting a downgrade result after terminating a pregnancy with a of muscular dystrophy [unclear] and these result downgrades usually don't happen for several months, if not over a year.

So, these are going to happen; it's just the nature of sequencing. But they are more likely to happen if you are a nonwhite individual, because of the marginalization of these ethnic groups and the history of genetic testing and research. And so, are we telling patients this when they get pretest counseling? That if they are a nonwhite individual, then they are more likely to get inaccurate results? While having the same benefits as everyone else? I don't think that counseling is going on. Next slide.

And so, in conclusion, yes. The sensitivity of carrier screening is higher when you screen for more conditions, and that pertains to, you know, all races and ethnicities. However, the accuracy of variant classification is NOT equitable. We know that we know less about underrepresented populations. And the benefits and limitations of expanded carrier screening are not equitable. The benefits and all of those options that they list as reasons to undergo carrier screening are not accessible to people without the resources. And so we absolutely need more studies to show that patients from lower-income families or from a diverse set of backgrounds also find this test useful, before we start recommending it for everybody. Next slide.

And so just some future directions that Katie and I have bounced back and forth. We absolutely recommend including diverse stakeholders, including those from the communities that have

genetic conditions or other disabilities, to be involved with the development of these policies. We need pretest counseling tools, because we know that there's not genetic counseling available for every single patient with a genetic counselor, so we need tools that are also validated in patients of a diverse background. I implore genetic testing labs to just include the price of testing for the partner in that patient's carrier screening to ensure that the complete risk assessment is performed for recessive conditions. Next slide.

There can also be consideration for more research and development of cfDNA reflex screening, so if a patient screens positive for cystic fibrosis, reflexing to cfDNA or sequencing DNA to eliminate the need for the partner screening. And we also need to establish infrastructure for patients' access long-term to their variant interpretation, because we know it will change over time and they might need that information in a future pregnancy. And then finally, we need policies that help us achieve success and achieve benefit for all that carrier screening, such as Access to Genetic Counselors Service Act. We need reimbursement for genetic counselors to provide the counseling for all the complexities that carrier screening can unveil. And the Build Back Better bill which will help with Medicaid coverage after pregnancy.

And I think that is it for me. Thank you so much.

MAYA SABATELLO: Thank you so much, Katie and Blair. That was really fantastic. I will give you one question to both of you, and then we can open it to everyone else, while people are adding their questions in the Q&A.

So, from your experience, what are the drivers for expanded screening sort of beyond the industry? Do you think that patients are asking for more screening for more conditions? Are OB/GYN providers pushing for this? Where is the balance here? What are your thoughts about it?

BLAIR STEVENS: I can start, Katie. I'd love to hear your answer as well, actually. It's definitely not the OBs, in my experience. I think the OBs are actually extraordinarily intimidated by these panels that go beyond 100 conditions. Our OBs are very comfortable ordering, you know, SMA and cystic fibrosis hemoglobinopathies. But any time it goes beyond that, they punt it to the counselors to order and disclose. So I don't see in my population any pressure from OBs. And to be honest it's very rare I have a patient coming in saying test me for absolutely everything. When we talk about carrier screening options from more of a traditional smaller panel to the very big panel, very often the patients I serve -- which once again is not necessarily a super high education or high income population -- they get very overwhelmed. And oftentimes they decline altogether. So our uptake of NIPT versus carrier screening is very discrepant, and I'm sure it's for lots of reasons, but It seems to be driven by industry, is my best guess to that.

KATIE STOLL: Yeah, I would agree. There are some patients that are really seeking, like, as much testing as possible. But I think it's a pretty small percentage of patients receiving prenatal care. I think it's -- and even a lot of that demand might be coming from the direct marketing that's coming from the testing labs to patients, giving this, you know, promise of reassurance and information. But, I don't think that the driver's coming from the OB/GYNs or the patients, really.

MAYA SABATELLO: Thank you. There's a question from Larry Brody: Does death in adulthood mean with 100% certainty, or just an increased risk of premature death? And I think Katie, maybe you can give it a first stab.

KATIE STOLL: I um, I kind of take that as a funny question, because we're all in the severe category if it's death in adulthood. But no, it's early adulthood. So there's not a line drawn for what that means in the guideline. It's just defined as that. Premature death.

MAYA SABATELLO: Right. Thank you. Another question is about the uptake, the low uptake, the relatively different uptake among partners. And I'm wondering if you can speak a little bit about what are the reasons that you think partners often do not follow through with the carrier testing, as well as whether, sort of, if you have any sense as to how many of those partners do not do so because of costs? Or because they're scared of having their blood drawn or other reasons, if you have any, any thoughts about that.

BLAIR STEVENS: In my experience, a big driver is whether they're present for the genetic counseling visit or not. The patients who bring their partner, I think, are much more willing to follow up, because they've heard everything. Often what I have heard from the patient themselves, not the partner, is when I call them with a positive carrier screening result for a very rare condition, they -- even though our self-pay price for partners is only $99, so it's relatively very affordable, a lot of them say, oh. It sounds like it's very unlikely. And despite me saying, well, if you WERE that one, would you want to know, despite the odds being less than 1%, they just say, well, it's not going to happen, or we'll see at the delivery. So I think a lot of it's patients thinking it's not going to happen to them.

KATIE STOLL: Yeah, I would say that's my experience, too. A lot of times partners we see in follow up for expanded carrier screen results... sometimes they have no knowledge that testing is even being done. Oftentimes -- there are some places this testing is being ordered as a matter of routine. And the likelihood for a positive result when you're screening, you know, over a hundred genes is pretty high. So the likelihood you're going to have some follow up and recommendation for consideration of partner testing, but. I think when you get into talking with the family about the probability of an effective pregnancy? And really getting into that possibility? It often doesn't feel worth it, even at -- you know... even if it's $99, it doesn't feel like it's really worth it for the potential, um... risk. You know, or possibility that we see people... weighing, with the information.

MAYA SABATELLO: Thank you --

KATIE STOLL: But I think -- yeah. I mean, I do think coverage is also -- I mean. Self-pay -- not -- I think maybe not everybody's navigating the self-pay price. Like, you know, genetic counselors are figuring out how to access this for patients, and that might not always be possible, I think... insurance coverage for testing the male partner is often... more challenging.

MAYA SABATELLO: Thank you. So, a question from Barbara Koenig. I don't know if you know, but there was an NHGRI conference on the history of eugenics last week, a two-day conference. And what lessons might we draw about oversight of prenatal testing? Either one of you. (chuckles)

KATIE STOLL: Yeah, I guess -- I mean, getting back to those reproductive options -- and this is kind of what I am concerned about -- is that I think there is this... I mean... not everybody will have access to all of these reproductive technologies. And I think you can see that, you know,

when there -- when guidelines are made, or supported, oftentimes... there's still this, ah, discussion of cost -- cost analysis? Right? Like, quality-adjusted life years, and how much it costs to have a genetic condition or a disability, and. I mean, you can imagine that there could be some pressure to uptake one of these reproductive decision options. Right? I mean, the... you know, there could, there could be -- I mean, there may already be, but there could be more explicit pressure... to not have a child if there's a possibility of having a genetic condition. Um. I -- yeah. I don't know; I mean, I don't know. I wish that we were looking back at history, and as we're thinking about this, you know, dramatic expansion of testing, but. Um. That doesn't seem to be happening.

MAYA SABATELLO: Thank you. What do you think of the -- there's a question here from Bob Cook-Deegan. What are your recommendations for who should take responsibility for communicating classification changes to those who got tested? What about liability? And I know, Blair, you had some discussion about it, so perhaps you can start.

BLAIR STEVENS: Yeah. This has been an ongoing conflicting struggle actually in our group, because we DO get so many of those... reclassifications. And some of them are for patients that counselors saw that no longer work at UT? And so we don't have a relationship with that patient? And so we've really settled on putting a lot of the onus on the laboratory. They're going to reinterpret their variants; our practice may not even exist, you know, in a year. I'm sure it will be, but. So, they do have access to the patients' e-mail addresses. It makes me worry about patients that don't have access to e-mail. And so I really do think it has to be a group effort. And so, the e-mails come to us as the providers to reach out to the patients. The e-mails go to the patients if we don't release them sooner. So I don't think that it's gonna fall on one person; it does need to be a collaborative effort. And then, if those -- variants change -- a significant difference for that patient's risk assessment, a genetic counselor or clinician definitely needs to be involved. So, I don't have a -- but it's not just the lab, and it's not just the providers.

MAYA SABATELLO: Right. So if you had to put in the liability, as he's asking, is there any sense as to who should be holding the lion's share of it?

KATIE STOLL: This is, this is a problem across the board, right? With genetics right now. It's not just reproductive genetic testing. And I think like, you know, the idea of putting it back on the lab, as their responsibility to follow up, I mean... there's a lot of volatility in this industry, too, where the same labs that are reporting out results right now might not exist in a year, or they might be acquired by another lab. And when that's happened, we've seen in some spaces where one lab acquires another lab, and then all of a sudden they quit -- they don't have the ease, or they, like, quit... issuing reinterpretations of variants over time! So, I think we can't really count on that, either! And I don't, I don't know who, um... who is holding the liability here. But, um. I think it's gonna be a growing issue. And not all labs are, are doing this reclassification and reporting of variants? So, I mean, we know the example Blair gave, you know, there are many labs... even if they did have some reclassification of variant, they're not going back and looking and they're not proactively reporting those. You would have to go and ask for those? And in some ways, maybe that reduces the liability because nobody knows that there IS a change in liability! I mean, in talking with Blair in preparation for this meeting today, I mean, we were talking about what is the -- how, what IS the outcome gonna be when people are making decisions yo terminate a pregnancy based on information that turns out to be wrong? And I think that's going to be happening more and more. We haven't, we haven't seen... general population

screening of most of the genes that are on this panel. So we don't know the full spectrum of what it looks like to carry, to carry mutations in these genes. You know? It might not cause the conditions that we -- it might not cause any condition at all! We just don't know, and it's kind of tragic that the test case is gonna be pregnant women to try to sort through this.

MAYA SABATELLO: Thank you, Katie. I think that's actually a great pass to the next question from Kristie Smith: Would you speak to the psychological, financial, and emotional distress to families once they have a child with a severe genetic disorder that could have been identified via a larger carrier panel but not made available?

BLAIR STEVENS: Yeah, I think that's always the worry of people in genetics, is like we COULD have found something, but we didn't because we didn't do the right test, or we didn't do enough testing. And there's never going to be a way to be able to test for every condition. So that residual risk for -- I mean, for all dominant conditions or de novo conditions, and then a significant number of recessive ones, will continue to exist.

And so what we are trying to do, and it's so incredibly difficult, is balance the benefit of trying to detect those with the harms that might come in expanding carrier screening and finding variants that may or may not cause diseases and trying to predict that. And so -- and the other question is, okay, if you had known ahead of time, sometimes women tell me that there's toxic knowledge in knowing! And so many times, when we have a fetal anomaly, for example, and we know this baby is going to need surgery or some sort of specialized care, and then I offer them genetic testing to see, well, this could also be a syndrome... that might take you down a completely different path, it's always -- it never ceases to surprise me how many people decline testing, because it's something that they DON'T want to know.

And so, yes. Some patients would absolutely benefit by expanding with carrier screening and identifying those rare cases of a baby that has a condition. But there's just so many other limitations that we have to balance that with.

MAYA SABATELLO: Thank you so much. Katie, do you want to add anything?

KATIE STOLL: Well, that might be the liability to the other side of this. Right? If people, if variants are not being reclassified and you have something that wasn't on -- most labs are not recording variants of uncertain significance on carrier screening reports? But if they change their classification on the back end, and that it's now considered to be a... a pathogenic variant, and that's not communicated, and that could have been known, but. I mean, I feel like it's getting into really, um... dangerous territory for us to try to tell people that we can, you know, guarantee... (soft, wry chuckle) Ah... you know? A, a birth with no genetic, um...! Differences! I mean, I think that it's... yeah. I don't know. It's, I think it's a tradeoff.

I did -- on one blog post I wrote on this topic, I surveyed genetic counselor readers about how they feel with the weight of this. Would you rather provide information to expectant parents that's less certain, and potentially discover more conditions that could be significant? Or would you rather only counsel about very certain information, and potentially miss things that could be important for that family? And there's not agreement! It was split about one-third to say that they would accept more uncertainty for the benefit of, ah... greater identification of genetic conditions, to two-thirds who said they wanted more certain information. So. I don't know.

MAYA SABATELLO: Thank you. Another question is from Carolyn Chapman, which is a little bit theoretical, but nonetheless. If multi-stakeholders and differing perspectives had been

consulted in developing the carrier screening guidelines, what aspects of the guidelines do you think would have been different? If you can hypothesize how it would be different, or what it would have been like?

KATIE STOLL: Yeah, that's a really great question. And I've wondered that, too, um. I don't know! I mean, I would say that there would be... there would be probably a different way of defining inclusion of conditions than this list of severity -- this category -- categorization of severity that was utilized. I think there might be more focus on providing... you know, up-to-date information about what it means to HAVE a genetic condition, and how people who are living with the conditions that we're screening for might view their OWN... existence! Um. ...yeah.

BLAIR STEVENS: Hopefully having some sort of platform for these various rare conditions, so that when people do screen positive for them, that they have a place to go to for more information. Because I think the information that they're getting from medical professionals, out of ignorance, is that it's a worse life, or it's a negative thing. And there's so many families, like Katie presented, that have really wonderful qualities of life... despite this genetic condition, as how we would present it. And so, I think it would be nice for us to have resources for the patients, and have these stakeholders be involved with how to find those resources.

MAYA SABATELLO: Thank you very much. A question from Michele Fox: How do we change the paradigm to get carrier screening done before pregnancy? Is it something that you feel is doable here, or not? What are the...?

BLAIR STEVENS: This, this has been a really hot topic that I've had discussions with a lot of people about? And you know, like, should we make it, you know, part of like high school, like, required screening that everyone just gives -- like, it's just the common place that everyone has it. And while that sounds great... you know, with how variants are changing, and how a panel -- I mean. If I would have gotten a carrier screen out of high school, god knows like what it would be now. And so, there's a lot of challenges. Mostly, I think, financial. Because a lot of women who -- or, people that desire pregnancy or don't desire pregnancy and end up getting pregnant, they don't get care before that pregnancy. So that means they have to pay out of pocket. And so if I tell them we have this really affordable rate of $350 to get you and your partner screened, and then they say, why would I do that? And I say, because, if you're carriers, you can get IVF. They say, with what money would I do IVF? Well, if you get pregnant, you can do testing at 10 weeks. Okay, well then you have to go out of state, because we have a ban in Texas. So if you are from a low-income or low-resource family, all of those perks of getting testing before conception really don't feel -- like, why would I not just wait?

So for people with resources, I think it's an amazing -- (breaking up) And I think family medicine physicians and OB/GYNs should really start focusing on preconception. But it's just not realistic for everyone.

MAYA SABATELLO: Thank you. A related question that came in as well from Barbara Harrison: What thoughts do you have about the ways to bring those diverse voices to the table? Disability advocates, those from under-resourced communities, and so forth. And how -- if, and how, can genetic counselors facilitate the process to come to consensus?

BLAIR STEVENS: I know one thing that we're -- like, because we have such a diverse patient population, I am beyond excited that one of our genetic counseling students this year has chosen

to do a project with me on trying to focus on some of those voices that are not included in the publications like the ones we reviewed. And so that's one way, is just to research and actually talk TO patients that are from these underrepresented or marginalized group and get their voices in publications. So that's one thing that we're working on; I'm sure there's many others. And so, I'll pass it to you, Katie, if you have ideas.

KATIE STOLL: That's great. Yeah, I mean I guess I hope that genetic counselors can potentially be... connectors, to families -- you know, families who have rare conditions and... genetic conditions to help -- yeah. Bring, bring those perspectives to the table. I hope that genetic counselors -- I mean... it's, I -- it's awesome, in the introduction, that it was acknowledged, Blair's activity with NFGC and expanded carrier screening guideline. I mean, I hope people that are working on guidelines are thinking about inclusion of multiple stakeholders in the development of these guidelines, as well.

I mean, I think that there is some history of... you know, as concern for kind of anti-disability bias and genetic -- among genetic counselors, and I think it can be difficult in a way to build those bridges, & that trust for those voices to really come to the table. But I hope we can do better.

MAYA SABATELLO: Thank you. I think it might be the last question before we have to close, but it's a question from Lisa Dive. It was interesting to hear about the barriers to partner testing. And the question is what are your views on the guideline's recommendation to consider reporting VUS for partners of identified carriers? And do you have experience of what couples/families might do with such information?

BLAIR STEVENS: This is one of those things that makes me very nervous, because this VUS, at least diagnostic testing with sequencing if the partner's unavailable, I mean, there's no test beyond the diagnostic test that can confirm whether it's pathogenic or not. Like, so we are pretty much putting the burden of making potentially irreversible decisions off of uncertainty. And this is the part that makes me particularly uncomfortable with the whole equity. I think ACMG is trying so hard to make advances in health equity, but this is putting the burden of uncertain results more ON the underrepresented populations, because those are the ones that are more likely to have a VUS. And so, I do appreciate that they put into the guideline that this should be something that's only done with consent of the patient. So there should be adequate pretest counseling. But what's also frustrating is something as heavy and complex as that, there is no OB/GYN and very few MFNs that I know that could probably understand the nuances of that conversation and facilitate that testing for a patient. So this is where I think prenatal genetic counselors are incredibly important. So for ACMG to recommend something like that, yet not support the access to genetic counseling services bill, which is how genetic counselors can be made more available to patients, is -- honestly it's offensive. And really frustrating. So I really appreciate that question, Lisa.

MAYA SABATELLO: Thanks. Katie, last word?

KATIE STOLL: I think that should be the last word! (softly laughing) I'm gonna leave that with what Blair said, for sure. That was great.

MAYA SABATELLO: Thank you. All right, so thank you everyone for joining us today. We would appreciate your feedback. And I think that was already posted in the chat. So please fill out our survey to discuss your experience and to make suggestions for topics and speakers. We

also invite you to register for our next ELSI Friday Forum, which is titled Ensuring Equitable Use of New Genetic Technologies: Lessons from Eugenics, with Dr. Emily Merchant and Dr. Lisa Dive, and it will be moderated by Dr. Osagie Obasogie. Last but not least, please join us in the post-forum discussion room. The link is also posted in the chat. And thanks again. We look forward to seeing you, next year, in 2022. Thank you very much.

KATIE STOLL: Thank you.