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SPEAKERS SERIES_DR. BARBARA BIESECKER

00:00:00 CHELSEA PROUGH: My name is Chelsea Prough, and I will be moderating today's webinar. I'd like to introduce this afternoon's speaker, Dr. Barbara Biesecker, Director of the Johns Hopkins University National Human Genome Institution Genetic Counseling Program. Dr. Biesecker will discuss her personal experience as a practitioner and what she identifies as the most challenging issues in cancer prevention and treatment.

00:00:32 At this time all participants will be in listen only mode. Please note that this webinar is being recording. If you have any technical difficulties or questions please enter your question in the chat window, so we may help you. I will now turn the call over to Dr. Biesecker.

00:00:51 DR. BARBARA BIESECKER: Thank you very much, it's a pleasure to be here. I'm sorry I can't see you, I'm glad you'd see me, I have complete [inaud.] on my face. I'm going to go ahead and try and address precisely the questions I was asked to think about, which is what I think is the most challenging issues in cancer prevention are and [inaud.].

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00:01:16 Because with my background in genetic counseling, I also have a Ph.D in health psychology, but much of my research has been directly related to translational science, regarding the implementation of genetic technologies and genetic counseling. So, I'm going to talk a little bit about what I see happening in genetics and what the implications may be for cancer prevention going forward. So, next slide.

00:01:43 So, all of you on the phone, because I can see your names, are very familiarizing with identifying genetic risks for cancer, which is how I became involved in cancer from the very beginning and it has been based on looking for explanations for familial cancer, using single gene variants.

00:02:03 So, highly penetrant single gene variance BRCA1 and 2, being really readily available examples and the ones that most people are most familiar with. Historically we've used family history and characteristics of the cancer, early on that and to some degree the type of cancer has been used to categorize people into higher risk categories and then offered genetic testing to

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further characterize whether or not people are at increased risk and how we might manage that risk accordingly.

00:02:37 So, testing has been used for recurrence risk of somebody who has had cancer, the chance that they might have another primary. Risks to relatives for obvious reasons, because their genetic information is in common. And increasing treatment and risk management choices that people face.

00:02:56 What I'd like to point out is that it is clear to me that hereditary cancer is a small sub-set of cancer in this country and from a public health perspective it's somewhat embarrassing to talk about this in the context of cancer prevention because what we can do here is still for the most part going to effect a small number of people although I think that it's changing and it is changing quickly, and I'll talk a little bit about that.

00:03:28 But I'm going to stick to genomics, because it's what I know and I think that's always generally a good guideline for life. So, next slide please. So, what

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do things look like today. I try not to use too many exaggerative terms like explosion, but things have really changed in the clinic in the last couple of years. Although we're not talking about it today in the prenatal clinic, many pregnant women no matter what their risk status, are now offered a variety of screening tests and non-evasive testing in their pregnancy, not having any indication whatsoever.

00:04:06 And parallel things are happening in the oncology clinic. Again, because you're from [inaud.], you're very familiar with the different kinds of new prognostic testing, some of which has a genetic basis and others that don't. And we continue to use genetic tools to do risk assessment, whether it's single gene testing in families where we suspect a highly penetrant mutation panel testing where a single variant might be happening but we're a little less sure which one might be involved and I'll talk about some examples of that.

00:04:38 And increasingly sequencing, which I'll get back to. We are starting to see that tests are migrating from hereditary cancer clinics into primary care. So,

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OBGYN's increasing are ordering these tests along with internists, so you don't need to be a genetic specialists nor do you even need to be an oncology specialists to be getting involved in cancer predictive testing. Next slide, please.

00:05:05 So, what are the testing options these days? Well, the past decisions have involved assessing risk usually by taking a family history and then choosing a test that might be consistent with what you're seeing in the family's history, although I would say that clinically, although some guidelines have been put out that the assessment should identify people who are at least at a 10 percent risk for carrying one of these mutations for testing, and that's not what happens in the clinic.

00:05:40 And many people are worried about these risks and even if their risk predication ends up being a one to two percent chance that they might carry a mutation in BRCA 1 or 2, they're often very keen to go forward. Obviously, if their insurance is going to pay for it they're more keen.

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00:05:56 And even people who want to pay out of pocket, because of their interest in this information. Which worries me a great deal because getting a negative test in a situation where there was a one percent chance of finding it in the first place, is not very useful information, and I fear that people may misperceive that they've gotten reassuring information in those circumstances.

00:06:20 So, we're already worrying about helping people make the informed choices about how to use these tests and what they might mean and on top of that challenge, the new tests have been integrated in the last couple of years. And the bulk of these tests are panel tests.

00:06:34 I've arbitrarily plucked three examples off and put them on here. They're not my particular favorites, nor am I endorsing them in any way. But just to give you an example of the things that people are offered now, [inaud.] panel has 17 different genes on it and certain variants are looked for.

00:06:55 [inaud.] is 21, [inaud.], our University of Washington has 26 genes on their panel. Most genetic counselors,

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we've done a recent survey of genetic counselors working in this arena and they say most clinics are offering about eight or nine different panels for women to decide amongst for breast and ovarian cancer risk.

00:07:19 The counselors find this very overwhelming, as do the clients in trying to figure out what you want. What should be your selection criteria, is 26 better than 17, what do you base your decision on. So, I'm going to go into more of the characterization of some of these choices going forward. So, next slide.

00:07:41 So, the real bulk of my talk is talking about what the current challenges are here in genomic technologies toward cancer prevention and I would say that these genome tests offer more option, but it's really hard to assess at this stage their youthfulness in doing a better job at identifying underlying mutations in the patients that carry them.

00:08:04 None of them have endured long-term or epidemiologic studies that would yield that data. They seem like a good idea and there are things that we know to do.

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The other thing that I think is fascinating in this area and thinking about both clinical decisions and research around decision making, is that these tests are for the most part preference based, but in some cases actually they are medically recommended. And this gets confusing.

00:08:34 Certainly a physician who is treating a young woman for an early breast cancer is interesting in a BRAC 1 or 2 result in terms of advising the patient about going forward and what sort of surgical choice might be best indicated in somebody who would still have a high residual chance for developing cancer.

00:08:56 And I think many of us would agree that while you would want to have the endorsement and involvement of the patient in that decision, it would lean closer to a medically recommended test. However, the majority of these panel tests you wouldn't categorize that way. There are options for people to learn more information hopefully identify [inaud.] if we've done a good job screening for hereditary risk through the family history, and I'm not sure we always do such a good job at that or if we do do it, I'm not sure it's adhered

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to as proper screening protocol for a choice about the panel, panels that people are being offered.

00:09:42 And so, I think there's a little confusion both on behalf of the counselor's mind and the clients mind about whether these tests are really optional or they're really - or they're more useful for making medical decisions going forward.

00:10:01 One of the things that's going to become more and more of an issue is that there are now recommendations for interrogating our genomes anytime sequences is done for medically actionable genes in which there are variants that we can interpret.

00:10:19 So the American Oncology of Medical Genetics has published an article recommending 56 different medically actionable genes that should be interrogated anytime a clinical genome sequence test is being done. There is now a committee at the NIH that's reviewing whether or not the same standards should be adhered to for research testing on the NIH campus and they've not come to their final conclusion yet.

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00:10:45 The studies I'm working on do involve return of incidental findings. And genes that are on almost a third to a half of the genes that are on that list are genes for hereditary cancer syndromes. So, this is going to be a new and somewhat backward way that people are going to learn that they carry one of these gene mutations.

00:11:07 This is going to be a rare way to find out. The early estimates are that one to two percent of all of us will have one of these 56 medically actionable incidental findings, so it's not going to happen often, but when it does it typically is going to happen in families where there is not an overt family history, and it's going to be tougher to know how to interrupt those results.

00:11:31 Once we get broader population data, we'll probably learn that the penetrants is not as high as we have thought it is by starting with high risk families. So, that's a whole interesting area that's coming onboard.

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00:11:46 One of the things that is most discouraging to me in terms of training students and helping genetic counselors learn how to coach their patients or clients through careful decision making is that ultimately these panels are overwhelming and choices end up being based on what is your insurance going to pay for.

00:12:06 So, I'm not sure what, what the point is of spending so much time trying to compare one to the other especially with the lack of really any algorithms for how you would make that comparison. And I don't - I put in large font, the point that there are huge disparities that are more important than any of these small technical details, in that most of the [inaud.] end up getting served in a cancer genetic clinic, are people who have money and insurance and the more privileged part of our general population.

00:12:44 So, our biggest problem, to give a short answer to the question I was asked to address, is that we're not getting diverse and underserved populations into these clinics to even be offered these tests much less resources to pay for them. Next slide.

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00:13:05 So, genetic counselors remain involved in the majority, although not all of these decisions about using predictive testing and I would say that I would claim that most of these decisions still are preference based with some exceptions. And so genetic counselors might be thought of as choice architects.

00:13:25 They have a lot to do with how this information is presented and thus how the information is presented, affects how it's received and how decisions are made. I think all of us would agree that these kind of decisions should be well informed, if we borrow from [inaud.] informed choice, that means that they have [inaud.] information related to the decision and that they made the decision in keeping with their attitudes, which really just represents their underlying values and beliefs, things that are important to them, that they want to gain from the information that could be [inaud.] from a test like this.

00:14:03 But most of these choices with these new panels are really unfamiliar to people. They might come into the clinic knowing something about the BRCA 1 and 2,

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Angelina Jolie helped us with that to some degree. And so they have a little bit of an inkling what they're talking about, but when they're faced with a panel of 26 different genes and different conversations about the variants that would be identified through these things and why one might be more likely than another, it's very unfamiliar and I think complex and overwhelming information.

00:14:39 So, I would claim that the best sort of approach to these decisions is a shared decision making approach, which I know all of you are well familiar with. And in medicine, although it's new, it's still evolving and it's something that physicians that can very well do in preference based decision but it's something that deviates from making recommendations that they typically do.

00:15:04 This is not foreign to genetic counselors. Almost all the decisions that we've helped people with since the inception of the profession have been preference based. We started out in pediatrics, we move - or sorry, in prenatal clinics where people are making very personal decisions about using tests.

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00:15:22 Then we moved into pediatrics where often people were deciding whether or not they wanted testing to understand the cause of their child's condition, but in almost none of those cases, did finding the cause make any treatment or management. So, again they were preference based to help people have a label or settle some of the uncertainty and some of those parents choose not to go forward with testing if there's nothing that can be learned from it.

00:15:46 So, shared decision making is familiar in common practice in genetic counseling - my screen just went dead here. Sorry. You can still see it right?

00:16:06 CHELSEA PROUGH: Yes, we can see.

00:16:08 DR. BARBARA BIESECKER: Okay. Thank you sorry, I have a long password. All right. So, getting back, the shared decision making, I think is the best approach in these cases, but it does put a lot of responsibility on genetic counselors to ensure that the way the choice is presented and discussed with the client optimizes their patient preference.

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- 00:16:37 And we can talk about it when I'm done, but there is some evidence and studies that have been done of genetic counseling that maybe we're not doing that in the most effective way. Next slide. So, the other thing that characterizes this emerging landscape with new genetic technologies is that these are decisions with increasing more uncertainty.
- 00:17:00 Uncertainty is not again unfamiliar to genetics, it's been part and parcel to all the work we've done, but uncertainty today, certainly when we get into sequencing is probably unprecedented in medicine. In other words for much of what sequencing can do, we would never begin to think of it having any clinical utility.
- 00:17:21 The problem is there are certain specific examples where it has great clinical utility, it just happens to be a very small part of the whole story and once we get clinical useful information we have a whole lot, thousands and thousands and thousands of bits of additional information that's useless, because we don't know how to interpret it.

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00:17:42 So, I don't think anybody disagrees that there's a significant amount of uncertainty even just with these testing panels that I've described in terms of understanding what all the genes do that are on there, whether or not the variants that are interrogated are the best choices, whether one is more effective at identifying genetic causes of hereditary cancer than another.

00:18:05 There is still a lot that is relatively unknown. So, while there might be benefits to these technologies, there's a great deal of information we don't understand yet, and one of the things that's hard for me is there is insufficient evidence to guide the practitioner in how to engage in shared decision making when there's this much uncertainty.

00:18:26 And I know all of you have worked with Paul [inaud.], so his study, I think there were two papers based on studies where there is transparency in communicating the uncertainty around, for example prostate screening, PSA testing, and people in the end were

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left satisfied with their session when the degree of uncertainty was made clear to them.

00:18:53 So, we want people to understand how much we don't know especially about sequencing, but we also risk balancing and trust in any information that's revealed, so we have a really huge task at hand. Next slide please. So, I think it's important that we understand a lot about uncertainty, I will preempt myself and say I'm doing a number of studies related to uncertainty with Paul [inaud.] and others, because I think it is likely to predict what choices people make to learn certain sequences results and how they decide to communicate them or ask on them.

00:19:34 We have to help them figure out when [inaud.] something that we have a great deal of confidence and history with that we can interpret and when are things very iffy and the investigators making good educating guesses about what the clinical implications are.

00:19:54 So, I think that the practitioners who can send clients to genome sequences face real challenges in how we convey the uncertainties, to ensure informed

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choice and mitigate unrealistic expectations of the information but also don't cause such a degree of lack of trust that it's completely discarded. Next slide please.

00:20:22 So, the use of sequencing is widespread now. Our institute has funded a number of extramural sequencing studies as has [inaud.]. On this campus, it's just exploding in the intramural program. Many of investigators have been studying categories of diseases like auto-immune diseases, for example for many years discovered genes that are highly penetrant [inaud.] high penetrant that have had the [inaud.] look like other auto-immune disorders but haven't been able to find the cause in those circumstances.

00:21:01 And so sequencing offers a very hopeful technology for going forward and finding pathogenic variants that we've otherwise not known how to look for. And so sequencing studies are taking off. There is now a whole program through the clinical center where investigators can compete for funds to be part of these sequencing studies and as part of that they will get [inaud.] to an infrastructure that will help them

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with, for instance genetic counseling, returning results and help with interrupting variants that are discovered.

00:21:37 As well there are procedures [inaud.] variants that contribute to common conditions, which is really relevant for this conversation because the vast majority of cancer falls into this categories as it is not - it is only a very minor part of it that is due to single gene variants.

00:21:55 And this is much more complex. All of you know that the algorithms for interrupting how multiple variants in genes add to disease risk have not really been well formulated. There's lots of controversy about how much of the epidemiologic science is needed before we get good numbers in this regard.

00:22:14 But we need to understand gene-gene interaction, gene modifiers better, we need to begin to understand gene environment interactions, which is going to be even far more complex and so most people are still sort of avoiding sequences to look for common disorders, but I'll tell in a minute about a study I'm involved in

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where investigators are going forward, trying to answer questions using genome sequence assisting. So, next slide.

00:22:43 So, one of the things that's interesting I think for this forum is to think about the multiple decisions that participants are making and I'm calling them participants now because I'm thinking about this in the research setting, but it does apply to the clinical decisions as well.

00:22:58 I'm very interested in why people choose to participate in clinical - sorry, in sequencing studies in the first place and we've actually published some data on this about why people stepped up for a study, called [inaud.] that I'm going to talk about in a minute, because done here at the clinical center.

00:23:16 We've also asked questions about their intentions to receive various types of results and obviously this is still a hypothetical question, but because a lot of our studies are longitudinal, we'll be able to go back and compare what their intention were and what their actual decisions were over time.

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00:23:37 But the time who sign up for studies, sequences studies at the NIH are very enthusiastic about this new technology, maybe worryingly so, and they have very high intentions to receive various types of results. We've published a paper that statistically differentiates between different types of results they could find out about those that are actionable, those that are health related, but not actionable, [inaud.] results, and results that cannot be interrupted, which we don't even return to anybody, and there is enthusiasm for all types.

00:24:09 Even with, it was a very skewed response and so even though I can say there is statistically a difference so I can maybe argue that they can discriminate between the choices, they were wildly enthusiastic for information of all types. And that puts a lot of pressure on us to think about how to manage those expectations.

00:24:28 So, as I said, we can now start to study the decisions they actually really do make. In the case of medically actionable results for the studies that I've

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worked with, those are returned to people, the 56 genes I mentioned earlier, any variants in those are returned to people, whether or not they explicitly ask for it, so this kind of falls into the category of recommended outcomes of participating in this research, because the principle investigators don't feel that it's ethical not to return them.

00:24:58 But all other results are considered optional for people to make choices about. So, they could get information again about non-actionable health information or their carrier status. And then obviously we want to find out the whole point of doing any of this is whether or not people use or act on their results.

00:25:17 And that could be in the case of carrier status, which doesn't affect anybody's health, but it puts relatives at risk, whether or not they communicated that risk to any of their relatives, or communicated it with any health care provider. So, next slide.

00:25:34 So, I think there's a number of interesting decisions to be studied here and I just have a couple of slides

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on the research we're doing without any data and I can talk a little bit more about them. Most of these don't yet have - are not yet completed and don't have outcome data.

00:25:53 So, I mentioned [inaud.] which is a longitudinal cohort study of just over a thousand adults that have been done in the NIHGR1 [inaud.] program that includes return of results and I'm very interested in their perceptions of uncertainty and we've conducted focus groups and published a paper on the [inaud.] participants perceptions of what we mean by the fact that there is a significant amount of uncertainty associated with genome sequencing, which I found to be really riveting.

00:26:27 And I think the majority of them, because they're in a [inaud.] study, expects there to be a lot of uncertainty, but some of them still felt that that was undermining the value of the research and cause them to have [inaud.] for any information that they may get back and this is what we're concerned about, figuring out how to manage.

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00:26:44 We've also developed a new scale of perceptions of uncertainty, so we can quantitatively interoperate areas that people are concerned about. The greatest area of uncertainty that they perceive as medical uncertainty and those questions are about uncertainty around knowing who to tell, when to take it to your doctor, when to act on the results, and again this is baseline data, so they have gotten specific results and we will reassess their perceptions of uncertainty over time.

00:27:16 But they also have [inaud.] uncertainty, they weren't sure how they were going to feel about the results. And in addition to that, they had trustworthiness uncertainty. So, uncertain about how much they could trust the results, and all three factors contributed significantly to the variants in this scale.

00:27:36 We also have a really interesting intervention study underway where we're returning carrier results to participants in [inaud.] and because of the design of the study, we're bringing through 400 people, we've just reached almost 100 people who have gone through the intervention study and we're randomizing them to

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receive their carrier status results in a web-based platform in a room by themselves where they can query the interface, go back and forth, read their information, and they get a print out of what their lab report basically is.

00:28:07 And the equivocal arm is that they meet with a genetic counselor who focuses just on the information that's in the web based platform, she goes over the lab report them in a very parallel way and then in those two groups, half of each of them are randomized to have an additional session with a genetic counselor, so there is an additional opportunity to discuss what the results mean, who you might talk to about them.

00:28:33 Although a little bit of that information is in the educational piece as well. And it's mostly an opportunity for people to talk about how they feel about their results and ask any residual questions that they may have. It's a very simplistic research question can people learn carrier results as well through a web based platform.

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- 00:28:52 Are they satisfied with that, do they feel that meeting with a counselor was excessive or necessary and obviously our secondary research question is whether or not a genetic counselor needs to be involved for any counseling follow-up that may come from this.
- 00:29:10 We powered it for equivalence, but we are suspicious that people may be just fine with the web based platform, which would be really important data, I think, for addressing resource issues. We were just about to start a study that is fascinating where two degrees of uncertain variance are going to returned to people related to risk for hypertrophic cardiomyopathy, and I apologize, I know that's not cancer, but it very well could be a cancer example.
- 00:29:41 Variants are identified, but there is incomplete information to interoperate pathogenicity, but enough information to suggest that they may be and yet sort of minimally discovered pathogenic variants and the investigators spent hours and hours and hours sorting what's a three and what's a four kind of thing.

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00:30:02 And we decided to ask the question of whether or not the patient could even discern those differences, what they cared about in terms of differences and whether they would act on the results any differently, so we're doing a randomized controlled trial with those as well.

00:30:16 I'm also involved in consenting people to undergo genome sequencing for premature ovarian insufficiency with NICHD and I've to about 130 of 200 of those participants. One of them is a very streamline consent with just sort of a bottom line of the main points of the consent, and the other is a standard consent that's being used right now in the clinical center for sequencing, which is about six pages long.

00:30:47 So, we'll see what the results are that come about, but that's been a very interesting process. Especially consenting people to a common disorder, as I referenced earlier in the talk, POI, the main genetic causes of POI have probably already been identified, much like the BRCA 1 and 2, there were some low hanging [inaud.] for highly penetrating single variants.

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00:31:06 But the majority of it sporadic and probably caused by a cascade of several genes and probably environmental factors as well. So, this is a very tough problem to sort in the laboratory, but that is what they team is about to do and it's really humbling to be in the seat of consenting people into what that means. So, next slide.

00:31:35 So, we're hoping - obviously it's only one study, but we're hoping that data from the consent study might help inform the development of other consents, because the consents just start - keep getting longer, higher literacy, and really technical and completed and I don't think people are benefiting from that.

00:31:51 But we'll see, we made our outcome data. We're also assessing perceptions of uncertainty, which shouldn't surprise you given my conversation about uncertainty earlier. We're going to actually look at the role that uncertainty plays in decisions make to participate and we'll follow them long-term to figure out how they mitigated the years of uncertainty that

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will probably go along with this long search for new variants for [inaud.]. Next slide.

00:32:20 So, I just wanted to acknowledge my collaborators both [inaud.] study at NICHD and I'd be happy to take any questions.

00:32:34 CHELSEA PROUGH: Thank you Dr. Biesecker, at this time I will turn the call over to Dr. Jerry Suls, Senior Scientist at the Behavioral Research Program, also a reminder this webinar is being recording. All lines will now be unmuted.

00:32:51 DR. JERRY SULS: Thank you. Thank you Dr. Biesecker, that was a fascinating and important talk, I think. It conveys a lot of the issues that we have to cope with particularly with regards to [inaud.] making. I guess I'm going to first ask, a maybe an extreme question, maybe not, and that would be, is it - could you talk a little bit about whether you think in some ways much of this sequencing is not really ready for prime time? Prime time meaning, prime time exposure in clinical settings. Could you say something about that?

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00:33:41 DR. BARBARA BIESECKER: Yeah. The answer to that is context. So if you have a very good argument for why using a sequence test would be useful in a situation, regardless of the fact that we can't interoperate most of it, you could make argument that it was the test to do. And I'll give you an example of what that is.

00:34:04 But there's no question that for the vast majority of clinical circumstances it's premature. So, the common example in the clinic of how it's being used is when [inaud.] is a great example at Johns Hopkins for a center that's doing a lot of sequences. And if you think about it, it's not surprising.

00:34:27 They see kids with multiple congenital anomalies who have no diagnosis, who have had every genetic test known to mankind and no cause has been found. They're the only child affected in the family. The way the condition evolved, probably present at birth, and the way it's evolved over time, max of a genetic disorder.

00:34:49 Sequencing is your best bet after micro-rays or identifying a pathogenic variant. And Hopkins, and

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including Kennedy [inaud.] and [inaud.] have started to keep statistics on these efforts and they have a hit read of about 30 to 40 percent, which is very high. So, these things that have been elusive and not found for many years are coming to the fore, and that's somewhat parallel to the hit rate of the, I should say the identification rate of the undiagnosed disease program at the NIH and now UDP [ph.] centers are being funded and started all over the country.

00:35:29 But that's because the investigators or clinicians who are involved in ordering those tests know exactly what they're doing, so they're pre-selecting people who are at very high risk, or very likely to have pathogenetic mutation.

00:35:45 DR. JERRY SULS: So, do you have any suggestions about how we try to - we encourage or facilitate less screening in other populations where this really may not have any, we don't have any real clinical utility?

00:36:14 DR. BARBARA BIESECKER: Well if we think - let's go back to the oncology arena, I assume that's what you're most interested in. It's mostly these panels.

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I know a very few instances of use of sequencing yet in the oncology clinic. Certainly there is a lot of sequencing research going on. But in the clinic it's mostly the panels, and the panels including again mostly highly pentatrant variants in very rare genes.

00:36:41 And even that, if you try to imagine being a patient, especially if you're not a relative but an actual cancer patient who is looking to make a treatment decision based on the results. Going in and being presented with all these different genes that could be on this panel, all of which are exquisitely rare, how do you choose one panel over the other?

00:37:05 I don't think that's premature use of resources, but I'm not sure the way they're being leveraged is useful, and I'm not sure how patients are making good informed choices for that. I think they are literally just as I said, defaulting to what their insurance will pay for, which of course we know is very logical, the insurance companies, decisions, I'm sure.

00:37:29 So, I don't know how we've discouraged sequencing from going on elsewhere. It isn't really taking off yet,

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the sequencing companies are definitely marketing to the public, but the price is really prohibitive. So, very few people are really paying to have their sequence done.

00:37:47 And there is a bit of writing about the fact that people who do have their sequence done are pretty board by the results, that there is very little that is really clinical useful and a little disillusioned by it. I don't know if that will deter people from doing it recreationally or not.

00:38:06 DR. JERRY SULS: This reminds me a little bit about something from about four or five years in which body scans became rather popular in certain places.

00:38:17 DR. BARBARA BIESECKER: Yes, exactly.

00:38:18 DR. JERRY SULS: And that's fallen off now, because it didn't yield very much to people who used it and it was fairly pricey.

00:38:34 DR. BARBARA BIESECKER: But the dilemmas are for the rare cases where it's really useful. So, if we go

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back to my example of a rare disorder, that looks like it could be genetic and all the other standard tests don't yield the results, sequencing makes sense as the next test. But then the patient or the patient's parents have to make decisions about they're going learn incidental findings, so they want to know that information.

00:39:00 They could learn carrier information about their child, because all the other information is there and available and so that's where there is a lot of really interesting discussion about - and some of the bioethical arguments are well those parents already have a child with a condition, they don't need to be burdened with any other information.

00:39:18 They're not going to want it, don't even bring it up. So, of course we designed a study to ask that question that a couple of cohorts here at the NIH and all the parent said that they would want information, that they've lived with having a child with no diagnosis for many years, they're perfectly capable - these are their words, not mine - of understanding information that's not directly related to the primary care cause,

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but it's ancillary, but still it's some information that they could learn about their about their child.

00:39:51 DR. JERRY SULS: Could you say a little bit about, this is probably a very rudimentary question, but for some of the people listening and watching the webinar it might be important to them, of in the case of a patient who gets results, which are - which really create a great deal of uncertainty, what sort of general kind of procedures would a genetic counselor use to try to help them cope with that uncertainty and any distress that they might feel?

00:40:27 DR. BARBARA BIESECKER: Yeah, so that's a tough question, because that's what we are all worried about and what I said I don't think we have sufficient evidence to know how to handle. So, most of the counselors now are involved in research studies where we're consenting people to studies where uncertain results can come and we're really just on cusp of returning results with a lot of uncertainty.

00:40:53 And I think it's going to be very tough. That's why we're doing this randomized control trial of the

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variants related to hypertrophic cardiomyopathy,
because it occurs to us that we're spending hours,
literally hours trying to figure out how to
differentiate for the participants, the degree of
uncertainty and what it means.

00:41:18 And as we're doing it, it's occurring to us that that
discrimination may be meaningless to a participant.
So, I think it's a really important imperial question,
how much they need to know about the degree of
uncertainty and then what our rational, supposedly,
interpretation, this uncertainty means in terms of
their mental model of how they live with this
uncertain information. I don't think we have any idea
how to really do that yet.

00:41:49 DR. JERRY SULS: So when you say on the part of the
patient/client/family member, that it's meaningless,
could you explain what you mean by that? You're
referring to what part of meaningless?

00:42:06 DR. BARBARA BIESECKER: Yeah, that's a great question.
So, I think what I mean by that is, I'll be more
specific. So, there is a five point rating scale that

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they use to interoperate their [inaud.] sequencing that goes from one, almost no chance of being a pathogenetic variant whatsoever.

00:42:25 And that's based on what the gene does and what the variant is in the gene. It might be a type of variant that's not ever been associated with anything health related, to a five, which means that there is sufficient evidence to call something a clinically meaningful result with some evidence for the degree of penetrant.

00:42:47 So, the risk that would be incurred as a result. And so two, three, and four represents the scale of ambiguity around how you would interoperate the risks that would be associated with that variant. And that's dependent on how many other times a variant has been seen, the level of integrity of the reports in which it's been described, the degree to which it's been associated with appropriate [inaud.] data.

00:43:18 And what they're arguing about these variants for cardiomyopathy is the difference between a high three and a low three. And so my point is we're arguing

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about do we have sufficient criteria here to jog something between, you know, the middle point of three degree of uncertainty, would a patient ever be able to make similar meaning of that?

00:43:49 In other words they will probably hear it as somewhere between no risk and certain risks and its somewhere in between and does one degree of in between - are we able to differentiate one degree of in between from another degree of in between.

00:44:07 DR. JERRY SULS: So, another question which I'm asking out of my total ignorance of this, so, in the cases of children and parents where a child has an undiagnosed disease and this - here's a case where we're talking about usually going to a medical center, there's a team of folks who are involved and genetic counselors are involved.

00:44:36 DR. BARBARA BIESECKER: Yes.

00:44:36 DR. JERRY SULS: Are there situations at present that are common in which people are having gene sequenced and this may be information that's only conveyed

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really by a general practitioner for example where a genetic counselor may not be accessible and where this information is given there could be considerable lack of control about what happens and what the patient walks out of the office with.

00:45:08 DR. BARBARA BIESECKER: Yeah, as far as I know, the best and only examples of that right now are commercially available sequencing, so when people order their own sequence, get it mailed to them and then take it to their practitioners and a few of the providers who are the recipients of those and some of the patients are starting to writing commentaries about that in the literature, just about the practitioners being blown over about what their patients really expect for them to give them in, you know, to help them with what's being looked at.

00:45:46 And the patient's being pretty surprised that there was nowhere to go to get more information. So, most of the information that the sequences companies will look for are relatively well understood pentatrant single gene variants that we've understood for a long time including the 57 that are medically actionable.

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00:46:05 So if they go to a genetic center and they have a variant in one of those genes, most of us do have a history and some expertise in helping them interoperate what they're finding. And all of us are pretty aware that all of our estimates for pentatrants are based on high risk families and so when we find them unexpectedly as we know that we're going to when people have sequencing tests, probably it's possible that the pentatrants isn't as high in the family that you're dealing with.

00:46:37 Obviously you would be more likely to have seen a positive family history. So, right now, if somebody brought me a sequence result, it would probably look pretty familiar to other single gene tests, but that will not remain true for much longer.

00:46:55 DR. JERRY SULS: Would I be right or wrong that a fairly small proportion of people do the sequencing, you know, use a company and then get the results and then go to their GP about it? Is that pretty uncommon?

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00:47:12 DR. BARBARA BIESECKER: Yeah, it's very expensive, so yeah it's pretty - it's really uncommon.

00:47:15 DR. JERRY SULS: Okay.

00:47:17 DR. BARBARA BIESECKER: It can cost upwards of \$10,000 to do that now. I think sequencing itself has not come down to about \$1,000 a sequence, but of course the companies are wanting to make money off of it. If they lower the price significantly more people will potentially be interested.

00:47:37 And I think what we're all worried is there's no question this is powerful technology but that we just understand only a tiny bit of it, and we're all very worried I think that they'll be huge disillusionment over time. Much in the same way you talk about the body scans.

00:47:53 And it would be in this case probably not a bad think for the body scan, but in this care it would be a very, I think, a negative outcome to lose hope that this is going to result in improved identification of positive genes and ultimately improve treatment. This

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is really the avenue toward [inaud.] where we can learn what drugs we're resistant to, what drugs we're more likely to have an adverse reaction to.

00:48:24 I don't think those are very, very difficult moral questions. If you - if it's knowable you want to know it and your doctor would want to know it. It's just not that it's going to happen quickly. This is a huge amount - there's 20,000 different genes. We have a huge amount of information to learn before we can responsibly interoperate it.

00:48:42 So, how we keep people engaged in its potential and not lose - become disillusioned by it, is a really difficult challenge.

00:48:55 DR. JERRY SULS: Could you say something, you mentioned the fact that the disparity issue clearly something that if it's not here, it's on the horizon, do you have any suggestions, strategies, approaches to try to correct that problem, or adjust it, reduce it?

00:49:21 DR. BARBARA BIESECKER: Yeah, I think there is some funded study efforts in, I know, in New York City, in

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hospitals that serve the underrepresented populations and people who don't - often are uninsured or have minimal resources to get to screen their family histories and get them into clinics.

00:49:44 But there is many barriers to doing so, especially for people who aren't yet sick, but who might be at risk. So, it's a very difficult problem and it's primarily based on the inequities and our healthcare delivery system all ready. And our inequities in who's insured, our inequities in who's smart enough to figure out there are hereditary cancer clinics that you can go to and access.

00:50:09 So we have huge problems that are part of the infrastructure. So, I think the best approaches are community based approaches and going to hospitals where people are seen for other reasons and can be given information or screened for the possibility that they may come from a hereditary cancer family and get them into proper services.

00:50:34 But then somebody would still have to pay for the testing and it's not inexpensive. So, there also has

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to be resources set aside that could help them learn as much information that is available to those of us who have resources, if there is a gigantic problem.

00:50:47 DR. JERRY SULS: Yeah.

00:50:50 DR. BARBARA BIESECKER: This is not a new problem, this has been true in hereditary cancer clinics for years. The people we are serving are the educated and privileged and the people who have insurance.

00:51:01 DR. JERRY SULS: So does the affordable care act some interaction with this?

00:51:04 DR. BARBARA BIESECKER: I hope so. Do you understand the affordable care act?

00:51:12 DR. JERRY SULS: Umm...no.

00:51:15 DR. BARBARA BIESECKER: [inaud.] participants ask me, you know, so this is good because of health care reform, there's no such thing as pre-existing conditions, so I can't be discriminated against, and my response is, well in theory.

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00:51:33 DR. JERRY SULS: We figured this is like, we figured this is like genetic sequencing for health services research is what this is.

00:51:36 DR. BARBARA BIESECKER: Yeah.

00:51:40 DR. JERRY SULS: It will take us awhile to figure this one out.

00:51:40 DR. BRAD HESSE: Barbara, do you mind if I jump in and ask a question? Is that okay Jerry?

00:51:43 DR. JERRY SULS: Oh, yeah, I was hoping somebody would jump it. Yes.

00:51:46 DR. BRAD HESSE: Good. Good. This is Brad Hesse -

00:51:47 DR. BARBARA BIESECKER: Hi Brad.

00:51:49 DR. BRAD HESSE: So, part of what I try to figure out, I loved the way that you talked about a genetic counselor as being choice architects, because that's kind of the way we look at it. It's how we

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communicate about various levels of uncertainty that's so difficult replicate sometimes and so we have these people that we're trying to study and understand how they communicate, that's why you're on the phone with us, so thank you for that.

00:52:15 But we also look at how we can help create a new environment to support these kinds of decisions, and as you probably know I look a lot at the electronic health record and how that's going to help us out and how some of these other kinds of technologies might work.

00:52:30 And I wanted to run a few ideas past you to see if you have any kind of recognition of where this might be working or may not be working in healthcare settings as we start embedding this kind of precision medicine. So, one, is that currently put a lot of our action right around, kind of the point of care, and what we're really talking about is something that maybe sort of an inherited risk beyond family risk that came up as a surprise.

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00:53:01 It goes on the record, it's something you need to attend to later on in life, but nothing you can do much with right now, perhaps. And so I'm wondering, you know, are people thinking about ways of embedding this into the longitudinal record and so that later on we can start building decision support about that.

00:53:17 For example when people go in for screen for cancer they may go in with greater frequency or not, if they've inherited BRCA 1, BRCA 2, that's an obvious example, but, you know, for these other more complex kinds of panels, is that something that you've run across yet at all?

00:53:31 DR. BARBARA BIESECKER: Yeah, I think there's a lot of conversation about it because the way we store a sequence is bioinformatic information, right? And so there is a logical conclusion that that information would be a very nice attachment to an electronic medical record. But that makes people very nervous because it's a unique identifier.

00:53:51 And right now there is less reason to be concerned because I could identify somebody using a

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bioinformatics interrogation as part of their sequence if there had been anywhere in the cyberspace resources that would have a piece of that sequence that could be mapped onto it.

00:54:15 But if it's not out there anywhere, it's impossible to interoperate somebody's unique genome, unless again you have a relative sequence out there. You have to have something to compare it to. So if we put it in the electronic medical records and hackers or other people start to get access to it and sequence information gets out broadly, there is concern about identification.

00:54:40 And I don't know if our perimeters around confidentiality are going to change so much that that doesn't matter anymore but people love the idea of it being part of their electronic medical record, so that that information can be, you know, even can be interrogated again by providers over time.

00:55:01 DR. BRAD HESSE: Excellent, thank you for that comment. And I've got another place where we see in our portfolio technology comes in and that is to be

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sort of a counselor extender. So we recognize that, we don't have maybe enough genetic counselors that this information gets out to meet people's needs if they start having questions and they get their primary care, and primary care doesn't have an answer to question.

00:55:25 And so we see sort of extension of telemedicine and that kind of thing as an extender to what counselors what might be able to do, and is that a worthwhile path as we see these grants come in?

00:55:34 DR. BARBARA BIESECKER: Absolutely. We just had a program director meeting in Denver last week and it really is apparent - there's about 4,000 genetic counselors in the U.S. and we graduate a little over 150 each year. So, it's still a very small profession and this will probably be the first year where at graduation there are why more jobs than there are graduates.

00:56:01 And so there's a huge workforce issue, and that's because some of the sequencing labs are hiring up a large number of the experienced counselors to help

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them interoperate variants which is really interesting and you can work from home and they pay you very well, so good clinicians are leaving the clinic.

00:56:16 So we need more genetic counselors and we need other models of how to contribute this information. So this is a justification for this study I described giving carrier results. We decided to start with carrier results besides they're relatively benign psychologically and medically, but we'll go into more meaningful health related results depending on the results that we received.

00:56:37 But why wouldn't a web based platform be perfectly acceptable way for you to learn carrier results that you have and that only have implications if your kids [inaud.] kids, because they're older, or but your partner is carrier status it would make a difference in terms of your risk.

00:56:59 So I think we need to use technology for a lot of this and save the specialists for the really, really clinically difficult decision making, where we know how to use this information. But, we need evidence

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that people are okay with that. The [inaud.] participants actually gave us the idea in the focus groups.

00:57:15 They really felt, again pretty highly educated privileged group that they felt that there were a lot of - that they really wanted to be able to go in and look at results that were coming up from there, sequences and how some kind of rapid access to it, and that they thought that electronic resources would be really helpful in that way, so that's why we designed the study we did.

00:57:41 DR. BRAD HESSE: That's great thank you.

00:57:48 DR. BARBARA BIESECKER: And we obviously have to train primary care providers in all of this. It's going to take a long time, but [inaud.] is still trying to figure out how to manage all of this information. It's just come up so quickly.

00:58:04 DR. JERRY SULS: Well I think our time is about up, but thank you very much for answering our questions and providing clarification and this has been

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extremely helpful to us and I think it will be helpful to others as well. Thank you.

00:58:21 DR. BARBARA BIESECKER: Thank you it was very fun, I appreciate you giving me the invitation and taking the time.

00:58:28 CHELSEA PROUGH: Thank you for Dr. Biesecker for providing today's information. If you have questions after today's program, please email NCI.BRPWebinarr@ICFI.com or call 301-407-6608. Thank you for joining us. This concludes today's webinar, you may disconnect at this time.

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