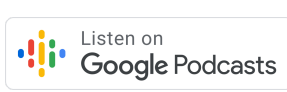


13| Disclosing Alzheimer's Genetic Risk – With Dr. Meghan Collier

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Speakers: Meghan Collier, John Bellone, Ryan Van Patten



Intro Music 00:00



John Bellone 00:17

Welcome, everyone, to Navigating Neuropsychology: A voyage into the depths of the brain and behavior. I'm John Bellone...

Ryan Van Patten 00:23



...and I'm Ryan Van Patten. Before we get into today's episode, we wanted to briefly comment about something that came up following our last episode, the Q&A with ANST students. One of the questions they asked us during the recording was what podcasts inspired NavNeuro. One of the multiple podcasts that we mentioned in response to this question was Waking Up with Sam Harris. After we released the episode, a listener emailed us expressing her concern in our endorsement of Harris due to some of his prior discussions of race and IQ. So we figured that if she had this concern, it's possible that other listeners also shared some of the same thoughts and we want to address it here. The fact is, we answered the question openly and honestly. We both listen to Waking Up and have benefited a great deal from the content. Sam Harris discusses a wide range of topics and we definitely don't endorse or agree with everything that is said on his podcast, but we found him to be rational, tempered, and willing to discuss topics in a transparent and fair manner.

John Bellone 01:28



Now, specifically to the topic of culture and cognitive ability, we do not want to let the charged nature of the topic stop us from talking about it because it is very relevant to neuropsychology. We believe that this open discourse is the only way for us to make true progress. Now, that being said, Ryan and I are two white, heterosexual, cisgender, American men. And, like everyone, we have our blind spots and we are eager to address these blind spots. We plan on bringing in experts in this area to help us with these discussions and provide guidance here. We would also like to have a discussion about AACN's Relevance 2050 Initiative that seeks to improve how we deliver services to people of diverse cultures and languages, as well as how we can recruit more neuropsychologists from diverse backgrounds into our field and into leadership positions because it is definitely greatly needed.

Ryan Van Patten 02:30



So that's all we wanted to say. We simply want to address this openly. We're always interested in ways to improve the podcast and to correct any errors or misunderstandings that occur in our discussions, as they will happen occasionally. So to all of our listeners, feel free to email us at feedback@navneuro.com, or comment on the website. Feedback and suggestions are always welcome. We only ask that it is provided in a respectful and constructive manner.

Okay, so for today's episode, we have a discussion with Dr. Meghan Collier about disclosing genetic risk for Alzheimer's disease. It's going to become more and more common for people to know whether they have certain genes that increase the likelihood that they will develop diseases that impact cognition. So it's good for us neuropsychologists to be familiar with the basics and have thought through how we would discuss this topic with our patients. So, John, why don't you start us off with an overview of the topic of genetics before we get to the interview.

John Bellone 03:31



Sure. So this is going to be a little bit of a longer intro than we're used to, but I think it's really necessary to give everyone the foundation that will help them understand the interview a little bit better. Also, I should just say this is going to be a very broad, pretty basic overview. So, in a nutshell, we humans have two pairs of 23 chromosomes, 46 total, and there are about 20,000 protein coding genes in these chromosomes. The proteins that our genes code for perform countless important functions for ourselves, including impacting behavior and cognition. We call a gene an "allele" if there is more than one variant of the gene. For example, an allele that codes proteins that lead to blue eyes versus an allele that codes proteins that lead to brown eyes. The term "genotype" refers to an organism's specific set of genes. So my genotype is going to be different from Ryan's genotype - and thank God for that because, I mean, as I mentioned in episode 1, he's so lanky. [laughs]



Ryan Van Patten 04:44

[laughs] Keep it up. Keep it up.



John Bellone 04:49

The term "phenotype" refers to the outward expression of those genes, what others see. So Ryan's got a genotype that codes proteins that make him disgustingly tall, but it is his phenotype that we see that leads us to see he's tall. So we can't see his genes, we see the product of those genes. That's the distinction here between genotype and phenotype. "Penetrance" refers to the percentage of people with a particular allele who express the associated phenotype. So let's unpack that a little bit. Incomplete penetrance means that if you have this particular genetic variant, you are not necessarily destined to develop that trait in question. It's incomplete. I could possibly have some alleles that had the potential to make me lanky, like Ryan, but luckily, they did not penetrate through to my phenotype so that I'm a normal height. [laughs]



Ryan Van Patten 05:53

[laughs] I'm going to take the high road here and not mention that you're 5'6" and 85 pounds soaking wet, John. So your genotype actually might not be preferred by many people.



John Bellone 06:05

Excuse me, 5'8". [laughs]

Ryan Van Patten 06:07

Sorry, 5'8". [laughs] Anyways, so a risk or "susceptibility gene" is a gene with incomplete penetrance. So [if] you have an allele, one version of the gene, that increases your risk but that's not a guarantee that it's going to come through. That is in contrast to a "deterministic gene", which is one with complete penetrance, meaning that if you have that allele, you are going to develop the trait. One of the most commonly used examples is for Huntington's disease. If you have just one copy of the Huntington gene, you will develop the disease.



We should also mention an important distinction about absolute versus relative risk because this can have profound impacts on how patients understand genetic risk information. There is a danger to using relative risk terminology with people across all medical contexts. The issue comes up when we're talking about very low probability events. For example, I might tell you that your genotype is structured such that you are four times more likely than the average person to develop genetic disease X. This sounds scary, and many patients would take this to mean that it's quite likely that they will develop genetic disease X. But imagine that the base rate of genetic disease X is 0.01% in the population, then their chance of developing this disease is 0.04%, or only four out of 10,000. So the problem is if we only explained relative risk, without explaining absolute risk in this scenario, the patient may walk away with a major misconception. That is, they may think that their risk for genetic disease X is far greater than it truly is. So this can have harmful consequences, as you might imagine. I say this to advise that you be on the lookout for misuse of relative risk language and be sure to communicate absolute risk when appropriate.



John Bellone 08:11

That's good to keep in mind. So let's make this all relevant to Alzheimer's disease now, which we'll just call AD for short. There are a few genotypes or sets of genes that are essentially deterministic for AD. So mutations in the amyloid precursor protein, presenilin-1 and presenilin-2, where if you're unlucky enough to inherit

these you will go on to develop AD. However, these are very rare, and they typically run in families. So you likely know if you have it.

Then there are other genotypes that increase risk, but do not mean that you will develop the disease for sure. By far the most studied and relevant gene that confers a risk for AD is apolipoprotein E, or APOE for short. But only a certain variance or an allele increases risk. So we'll be talking about three alleles of APOE, that alter risk for AD - there's e2, e3 and e4. We can think of e3 as being the neutral allele. It doesn't reduce or elevate risk. e2 slightly reduces risk of AD, while e4 increases risk of AD. Remember that we have two pairs of chromosomes - one from mom, one from dad. So we each have two of these alleles. Most of the population has two copies of e3. If you have one copy of e4 your lifetime risk of developing Alzheimer's disease increases by about three fold compared to if you have a combo of e2s and e3s without any e4s. If both of your alleles are e4, then your lifetime risk increases about twelve fold. And not only does your overall risk increase, but you're more likely to develop it sooner - so in your mid to late 60s rather than late 70s or early 80s.

There's still some research that needs to be done on this, and it's unclear if the alleles affect the rates of cognitive decline after the disease onset. It's good to keep in mind though, that these numbers are population risks, not necessarily a particular individual's specific risk. Your risk might be different. We're looking at population level. About 15% of the population has at least one e4 and give or take 5% of the general population has two copies of e4. Now these numbers differ somewhat depending on where you are geographically. It also somewhat depends on what study you're looking at. There's definitely more work that needs to be done in these areas.

Ryan Van Patten 11:09

Yeah. So keep in mind during our upcoming interview and the rest of this episode, that when we're talking about APOE e4 allele in reference to Alzheimer's disease, the e4 allele is not deterministic in the way that the gene for Huntington's disease is deterministic. E4 allele simply confers additional risk for Alzheimer's disease, but it is a risk or susceptibility gene. It is not deterministic. That'll be important to keep in mind.



So hopefully that gives a bit of an overview for today's interview. We should mention that we only talk about genetic risk for AD and APOE specifically in our interview, but we know that there are a number of other relevant biomarkers that provide important risk information. For example, amyloid beta and tau through

cerebrospinal fluid, PET amyloid, more recently, PET tau, structural functional MRI, blood based biomarkers, retinal imaging, these are all additional biomarkers of Alzheimer's disease.

So that's it for our primer on genetics. And just so everyone knows, we will have some important announcements about INS at the end of the episode, so stay tuned for that. So now for our interview with Dr. Meghan Collier, on disclosing genetic risk for Alzheimer's disease.

Dr. Collier earned her PhD from Suffolk University. She completed her internship at the West Haven VA in Connecticut, and then she completed her neuropsychology postdoc at Brown University, specifically through the geriatric psychiatry unit and memory and aging program at Butler Hospital, which will come up several times during our discussion. She currently provides neuropsychological services at a group practice in Rhode Island, and she's affiliated with Brown University. We should say that we are both very close friends with Meg and we had a lot of fun talking with her about her area of interest. And now we give you our interview with Dr. Meghan Collier.



Transition Music 13:10



John Bellone 13:20

Okay, so Meg, welcome to the podcast. We're really excited to have you.



Meghan Collier 13:24

Thanks so much for having me. I'm really excited to be here.



John Bellone 13:27

So this topic of disclosing genetic risk for Alzheimer's disease, or we'll probably refer to it as AD throughout the conversation, it's a pretty interesting but really niche area of research. Curious, just give us an overview of why this is even important to talk about at all?



Meghan Collier 13:44

Sure. So I think that this is mostly done in research settings, but is increasingly done for clinical purposes. So, in my experience, in research settings, you're mostly thinking about prevention trials who are trying to actively recruit healthy individuals

with no symptoms, who are potentially at risk of developing Alzheimer's disease. Knowing their genetic status ahead of time helps you enrich your sample so that you're making sure that you're catching people who are potentially going to be converting and therefore detect an effect of a prevention drug. Then in a clinical setting, we are using genetic information in order to help with differential diagnosis. So if you're looking at someone who seems to be displaying symptoms consistent with Alzheimer's disease, it's one more piece of data that helps us support that as a diagnosis.

John Bellone 14:45



Awesome. So yeah, really, there's two main uses for this type of testing and we'll get into both of them throughout the conversation, hopefully, in much more depth. But I'm curious first, how did you get into this area? What kind of work have you done here?

Meghan Collier 14:59

I guess my interest in disclosing genetic results dates back to when I was an undergrad and, in Psych 101, thinking about Huntington's disease and professors posing the question of, you know, "If you knew that learning that you carried the Huntington gene, you were definitely going to develop Huntington's disease, would you still want to know?" And that question really shocked me and made me think a lot afterwards. So that was my first intro to this idea of genetics and whether someone's going to develop a disease.



Over the years, I've worked in a couple of different Alzheimer's research centers, and my first experience with disclosures was at Brigham. Those were the early days of the A4 prevention trial. It required people to learn their amyloid PET status, and whether they had what was above the elevated threshold for amyloid in order to be randomized into that trial. So I had the opportunity to sit in on those disclosure sessions, and to watch people process that information and learn whether they had elevated risk of developing Alzheimer's disease because they showed signs of an amyloid burden in their brain. Then when I was at Butler, in the memory and aging program, I learned that they were adding a genotyping protocol to their prevention registry where they're recruiting participants for their prevention trials. And as part of that, they were going to study the psychological and behavioral consequences of learning their APOE status. So I jumped right in, because [it's] something that I find very interesting and important and relevant both to psychologists and specifically neuropsychologists.



Ryan Van Patten 16:52

Yeah, it really is. But the literature on disclosing AD genotype and biomarkers, to my knowledge, is relatively young. Is there anything we can learn from disclosing an AD diagnosis to people that we can use to apply to how we think about disclosing a genotype like AD genetic risk to them?



Meghan Collier 17:12

Yeah. You're thinking about two different populations here, or subgroups of the same population. So, in the earlier days, when we didn't look at somebody's biomarkers beforehand, it wasn't until somebody showed symptoms [that] you were potentially going to be giving them a diagnosis of dementia. I think that when you look at the trajectory of people's attitudes towards disclosing the diagnosis of dementia, it parallels the cancer diagnosis attitudes. So earlier, like in the 1960s, 90% of doctors who treated cancer patients expressed a preference for not telling cancer patients their diagnosis, but by 1977, there was a complete reversal of this with 97% of doctors in favor of a disclosure. And at that point, it was because there were advances in management and treatment of cancer. So [we] see something similar with dementia.



John Bellone 18:16

[It's] so crazy to think that you would not disclose a diagnosis of cancer.



Meghan Collier 18:21

Yeah. So there are now changes in expectations of information giving these days. So health providers are potentially more likely to share diagnoses because the patient is the owner of their health information these days. There's also improved public awareness of Alzheimer's disease. People are presenting earlier with symptoms because of this awareness and therefore they're presenting with less severe impairment. So you're more likely to catch people who have more insight into their symptoms and are curious or want answers about what's going on. [The] literature has demonstrated that disclosing a diagnosis of dementia respects patient autonomy, provides an explanation of somebody's symptoms, and it allows patients to be participants in their healthcare decisions, treatment planning, future planning, and possibly could ease acceptance of assistance or services for somebody who is in need of those things. Essentially, [it] gives you an entry point for discussion of the patient's concerns. And you can look at the disclosure of genetic risk or these other biomarkers in healthy individuals or people with preclinical Alzheimer's disease very similarly.

Ryan Van Patten 19:39



Yeah, it's interesting to think about the difference between disclosing an AD diagnosis and disclosing a risk via biomarker genes. Obviously, those are two related but very different clinical tasks. And as we move along, we're going to transition and talk more purely about disclosing genotype but that's helpful to know about disclosing a diagnosis. Most of the literature on APOE disclosures in Alzheimer's disease that I'm aware of comes from the REVEAL studies. So this is the Risk Evaluation and Education for Alzheimer's Disease project, led by Robert Green. Meg can you give us a brief overview of this project?

Meghan Collier 20:20



Yeah, sure. Basically, APOE disclosure has been extensively researched by this group. And this disclosure process has been executed pretty successfully in their studies. There have been several stages of the REVEAL study. In the first two stages, people had to have a family history. So they were recruiting people who had that family history and were concerned about their AD risk. And in the third and fourth stages, individuals in these trials were required to have a family history of AD and, even in the fourth arm, it wasn't just healthy individuals, they also included patients with mild cognitive decline. I guess it is important to note that all of the REVEAL studies have limited demographic variability. As you see in many research settings, most of the participants had above a college degree, or at least a college degree, and a majority of participants were female and Caucasian. I think with each of these different arms of the REVEAL study, they've definitely focused on recruiting more ethnically diverse groups, and there have been more African Americans in the later arms. But basically, participants in these trials received personalized Alzheimer's disease risk estimates, depending on demographic variables including gender and their family history of Alzheimer's disease, and most of the participants got their APOE genotype factored into that risk estimate. Some did not, it was just based on demographics alone.

So they were comparing people who just learned their general demographic risk of developing Alzheimer's disease versus people who learned demographic and genetic risk together. And most often they were comparing people who were carriers of e4 to people who learned they were non carriers. Importantly, the estimates that they were giving folks didn't account for other potential risk factors, gene-gene interactions and things like that. And these participants were followed for one year. And mostly they were asking, Who is it that seeks genetic risk assessment? And why do they do it? What are their motivations? How do APOE results affect risk perception? How at risk of AD do you perceive yourself to be before and after learning these results? And what is the psychological impact? Is it

safe and tolerated by people to learn this genetic information? And what's the effect of learning this risk information on behavior like insurance purchasing, or lifestyle factors, health behaviors?

Ryan Van Patten 23:02



And just so listeners know, for a lot of questions that are coming up, the reason why we know the answers to these questions are based on the REVEAL studies. So it is clearly the gold standard, where most of the good data are that speak to APOE disclosures in Alzheimer's disease. So thanks for the overview, Meg.

John Bellone 23:24



A question that comes up right away for me is, do most people even want to know their genetic risk for Alzheimer's disease? Their APOE status?

Meghan Collier 23:34



I think there is evidence that there is definitely an interest in predictive testing. For example, an international survey by the Harvard School of Public Health and Alzheimer's Europe, in 2011, found that 65% of US respondents would undergo predictive testing for AD. So you definitely see that pattern in the literature. It's not for everybody, of course.

John Bellone 24:00



65% is not for everyone.

Meghan Collier 24:02



[laughs]

John Bellone 24:02



But most people. I see.

Meghan Collier 24:03



Yeah.

Ryan Van Patten 24:04



What does the literature say that people usually do with the disclosure information? You had referenced this earlier, but I'm curious about future life planning, measures to improve brain health, things like that. What impact does it have on people?

Meghan Collier 24:17

So studies are finding that people's main motivations, aside from contributing to research, for people who have witnessed the effects of Alzheimer's disease firsthand, is essentially to educate themselves and maybe gain some control over their own risk. So whether that's future planning, putting their affairs together or preparing their family for the future, maybe making some changes in insurance coverage, and also relieving a sense of uncertainty. So people come in and they're really curious or they assume that they have increased risk, and some people think that learning this might provide a general sense of how worried they should be, and maybe if they learned that they're not carriers that they would find some relief in the process. A lot of people just endorse this general hope that treatment options will be available in the future. So if they know they're at increased risk, they would likely be interested in pursuing those.



Essentially, in terms of what they're finding are the behavioral consequences of learning your genetic status, we're seeing that individuals who are e4 carriers are more likely to purchase long-term care insurance, compared to people who don't learn their genetic status or people who are found to not be carriers of e4. This does raise some concern for insurance providers to increase premiums or deny coverage. Because while the Genetic Information Nondiscrimination Act is the federal law, GINA, that protects us against discrimination from our employers or from health insurance providers, long term care insurance, life insurance, and disability insurance are not protected. So with more people getting this genetic information, insurance providers are likely to be concerned about that and potentially make changes. Maybe consider somebody's genetic status, a pre-existing condition, for example.

Ryan Van Patten 26:22

That's tough. Obviously, it's interesting to think about that issue in this context, because you could be e4 positive, you could have two e4 alleles, and that doesn't guarantee you get AD. So can we say that's a pre-existing condition? I'm sure that's a complex legal decision that's made.



Something else you said earlier that I find interesting is around the fact that some people are interested in this information to reduce their uncertainty. So I think about that as it sounds like they're using an emotion-focused coping strategy, which makes sense. The general idea here being that problem-focused coping, actually taking steps to do something to fix a problem is helpful when the issue, this thing, is changeable. But obviously, we can't fully directly alter our destiny in terms of developing AD or not, and especially our genetic status. So that is not something

that is subject to change. So rather than problem-focused coping, which is not available, we're using emotion-focused coping in this way. They're seeking out their genetic status to gain clarity to reduce uncertainty and feel better.



Meghan Collier 27:28

Yeah, exactly.

Ryan Van Patten 27:29



So that would be one potential benefit of people seeking out and receiving these disclosures. We'll talk a little bit, potentially, about behavior changes that can increase brain health - diet, exercise, if knowing your genotype does that. So these are potential benefits of hearing your AD genotype. But there also could be downsides. Like it could be detrimental in some way to some people. I'm thinking about things like depression and anxiety if people learn that they're e4 positive. Even suicidality, potentially. Can you speak to the potential negative effects of genetic disclosures?



Meghan Collier 28:09

Sure. Are you curious about what the literature is showing us? Or more broadly, what some of those negative effects could look like? Ethical considerations?



Ryan Van Patten 28:20

Right. Maybe start with the literature, and then the ethical considerations if you don't mind.

Meghan Collier 28:24



Overall, in the REVEAL trials, as well as the genotyping protocol we have at Butler, we're finding that revealing somebody's APOE status is safe and well tolerated in people who definitely have a family history as well as people who do not. In the REVEAL trials, they had a one year follow up [and] they saw no increased depression or anxiety or test related stress. We have a six month follow up and our results are paralleling the REVEAL trial. So no significant differences in anxiety and depression levels, between e4 carriers and noncarriers. There is some data that shows that noncarriers, so people who learn that they don't carry any copies of e4 perceive their risk as lower after learning their results. So they essentially believe less that they would develop Alzheimer's disease. I think that there is definitely interest among the REVEAL trials and our group to have some ongoing analyses about whether a negative genetic test result contributes to this maybe false sense

of reassurance about disease risk, because, of course, somebody is still at average risk of developing Alzheimer's disease even if they don't carry any copies of e4. In some of these studies, they're seeing that the e4 positive group has the same or lower anxiety after receiving their results. So essentially, the bottom line is [it's] safe and well tolerated when done and in these protocols.



Ryan Van Patten 30:01

Right, that's a good caveat. But it's good to know that, at least the data we have thus far, suggests that there are no negative effects of these disclosures.



Meghan Collier 30:08

For this subgroup of people who might experience an acute uptick in anxiety, that's not sustained over time. I think in our group, if I'm recalling correctly, not statistically significantly different. But baseline scores of anxiety and depression are the strongest predictor of somebody experiencing any anxiety and depression after their actual test results are revealed.



Ryan Van Patten 30:31

Makes sense.

John Bellone 30:31

Yeah. It's good to hear that it's mostly well tolerated. I'm having some trouble though seeing much of a benefit here to knowing your genotype. Especially at this point, where we are now, where we're not widely manipulating genes just yet. So my thought is that we should all just act as if we had two e4 alleles and do all the things that reduce our risk of AD like exercising, eating healthy, and getting good sleep, and staying cognitively active regardless of whether we have that predisposition or not.



Actually, I think that knowing that you're not at a higher risk might be counterproductive. We talked about a couple of reasons why having it could potentially lead to depression and anxiety. But even if you find that you're not at higher risk, some people might have a false sense of security and think that it means that you don't have to exercise or eat healthy, because your risk is low. Most people probably don't realize that genetic predisposition for AD doesn't say anything about your risk for other causes of dementia that you'd mentioned before, like vascular disease, for example. So just because you don't have any e4 alleles doesn't mean that you have a clean bill of health. I don't know if you or Ryan have any thoughts about that. I'm just having trouble seeing the real benefit outside of

the research recruitment, I think that's a huge gain that we have this data for enhancing who we include in our studies.



Meghan Collier 32:12

So you're saying, in a clinical context, why would it matter if somebody...



John Bellone 32:17

More for clinical and just personal knowledge.

Meghan Collier 32:21

So, I think it is, number one, a good point to mention that this false sense of decreased benefit is a concern. Then the other is that the REVEAL trials and our group at Butler are showing that any behavior change is typically fleeting. So people might make some changes in health behaviors, such as increasing the number of times that they exercise a week or making healthy diet changes. It's not necessarily lasting long term. So that there is not strong evidence that their health behavior benefits from learning genetic status, unfortunately.



I don't think so much about the negative effects of learning your APOE status. This is just my personal conceptualization of it. But I do spend time thinking about how we might, as clinicians, especially if you have any background in motivational interviewing, try to capitalize on this information, somebody's risk status, especially if they're a carrier and use some of those techniques in our approach to discussing somebody's genetic risk or overall risk of developing Alzheimer's disease to try to motivate more of those health behavior changes.



John Bellone 33:45

Another carrot potentially to hold in front of them as a reason to exercise. I guess for a small subset, there is a group of people who would be more motivated by this information. I guess I'm thinking though, that we should all just be doing this anyway.



Meghan Collier 34:00

[laughs]



Ryan Van Patten 34:00

Right. I think that is the reality - that regardless of what my APOE status is, I should do those health behaviors anyways. But there's also the reality that if disclosing

APOE to people enhances their exercise regimen and improves their diet, then that's a functional benefit to that. Also interesting, though, Meg mentioned a few minutes ago that there we don't see negative effects in the literature thus far of people hearing that they are e4 positive, that's good. You're talking about negative effects of learning that you're e4 negative, which we usually wouldn't think of. [The] negative effects of learning good news. It's really relevant though. I don't know if there's literature on this, but I could see people hearing, "I'm e4 negative. I have a strong genotype, thus, I don't need to do those things I would otherwise do." They could end up worse off for this whole process.



Meghan Collier 34:59

Very pessimistic view. [laughs]



John Bellone 35:01

[laughs]

Meghan Collier 35:01

I actually should mention that the REVEAL group has found that - so while genetic risk alone isn't typically sufficient to engender complex behavior change, they did look at self-referred versus actively recruited participants. And they found that e4 positive self recruited participants were more likely than e4 negative self recruited participants to report changes specifically to mental activities - probably those Sudoku puzzles [laughs] and diet at their six week follow up - and to report intentions to change long term care insurance. So that was a subset of people who were seeking this opportunity out as opposed to being called and actively recruited into their trials.



John Bellone 35:53

Well, that's a good sign then for those people.



Meghan Collier 35:56

Yeah.



John Bellone 35:57

So it sounds, like we had talked about, that this is well tolerated. Even if people get the pretty bad news that they are e4 positive or they have two alleles, most people do okay with it. But there is going to be some subset that has a negative reaction to

it. Are there any ethical concerns that we have to consider when disclosing the biomarker status?



Meghan Collier 36:20

I think the main factors here are that there's limited predictive value. So there's still a degree of uncertainty to cope with, right?



John Bellone 36:31

Even if you have two e4 alleles, you're not 100% guaranteed to get it.



Ryan Van Patten 36:36

Not even close to 100.



John Bellone 36:37

Right. Right. Far from it.

Meghan Collier 36:38

Yeah, yeah. So that's certainly one. That this is still not some kind of definitive result. That's something to consider, both for the provider who's delivering the information and somebody who's receiving it, in making sure that they understand that. And, of course, there's limited efficacy of currently available treatments. So, there's no cure. The medication options like cholinesterase inhibitors are helping reduce symptoms or slowing the rate of decline, but we so far have not found that preventative drug or something that's actually going to reverse the process magically.



I think on the flip side, just thinking about helping people get connected with trials is one benefit. But it's just important to educate people on what the treatment options are and currently, it's just giving them trial options. There's this tension between somebody's right to know their risk information versus their right to not know, and the ethical principle of malfeasance. We don't want to withhold information that would be helpful or beneficial to someone, but you also wouldn't want to impose information on somebody. So that's definitely something to consider - just generally what are the opportunities? So for learning this information, like what kind of doors does it open for someone versus the consequences? And I think, aside from depression, anxiety, and suicidality, which we haven't mentioned explicitly, but nobody in any of these trials has experienced increased suicidality, there haven't been any catastrophic reactions to learning genetic status in our trial or reveal. But

there's also this risk of stigma and even preclinical stigma - these concerns related to personhood. So similar to receiving a dementia diagnosis, if you learn that you're at increased risk, you might become hypervigilant to any changes in your memory. You also might experience increased anxiety. In the setting of subjective cognitive decline, you might experience increased anxiety. So I think it's important that we also look at the factor of subjective cognitive decline in those folks. And then, of course, issues of privacy, which we've talked about briefly, and the risk of insurance providers using that information against people.

John Bellone 39:09



And this is all part of the process of when you recruit patients, talking through all these different considerations. I think the one you just mentioned about the stigma, and particularly not just stigma, because family members might treat the person differently if they know that their loved one is at increased risk for AD. They might not trust them as much with finances or driving or tend to not involve them in important decisions because they're viewing them through the lens of their genotype. But the other potential downside is that that person might view themselves in that light, like you had alluded to.



Meghan Collier 39:50

Or start to take on a patient role...



John Bellone 39:52

Yeah, right. Exactly.



Meghan Collier 39:53

...in advance.



John Bellone 39:54

Yeah, I see that a lot in my clinical work. You know, if I lose my keys, I lose my keys because it happens, right? I don't have my age to blame it on. But if the person that was just told that they were more likely to develop AD loses their keys, they're going to think [it's] because they have AD now.



Meghan Collier 40:12

It takes on a significance.



John Bellone 40:13

Yeah. So I think that's big, something that we should really try to reduce or stop in its tracks.



Meghan Collier 40:21

I'm curious about if you guys have any thoughts on how you might, in a session let's say, you're discussing somebody's risk of developing cognitive decline [in a] feedback session, for example...



Ryan Van Patten 40:36

Hey, we ask the questions here. [laughs] Okay.



Meghan Collier 40:37

I'm here too. I'm equally here. [laughs]



Ryan Van Patten 40:40

[laughs]



John Bellone 40:42

Yeah, so I do deal with this sometimes. Because I have some people, the “worried well” who sometimes come in and they're really worried about their cognitive abilities. They have maybe even written down a list of all the times that they've forgotten things in the last couple of weeks and then they do really well on testing. And I have to tell them, "Well, some of this might be just normal for humans. We all have some amount of lapses in our memory or attention." And some of them might be normal aging, they might be forgetting a little more because, yeah, they're 70 or 75 years old or something. So I think giving them the psychoeducation that some forgetfulness and inattention is absolutely normal. I think that sometimes helps people. You know, having them rely on more strategies, like writing things down more, not relying on their memory so much, sometimes helps too. But I think really having them understand that if they're overly concerned about their thinking skills, it's going to make things worse. If they're constantly vigilant to every name that they forget or every phone number that they can remember, then it's going to be a self-fulfilling prophecy. And that's going to make things harder to remember in the future and make it harder for them to pay attention, because now their attention is on their memory problem. So it's just a cycle that I see often. I think education is one intervention there. Ryan, do you have other ideas?

Ryan Van Patten 42:17



Well, I think education is the intervention. You mentioned education about normal, benign forgetfulness. But then there's also to your concern a few minutes ago about people hearing that they're e4 positive and then misattributing every normal mistake to AD. I think the most important education is on the front end, when they receive the e4 disclosure. So, obviously, this is a risk allele. It's probabilistic and not deterministic, which can be more subtle than, like Meg earlier talked about Huntington's Disease. If people have heard about more deterministic full penetrance genetic diseases in the past, then their mind might be going down that road of "I have this gene, thus, I am getting X disorder." So we need to be clear. We are genetic counselors when we're first disclosing what risk means and what their individual risk is - whether they're e4 positive or negative - so as to hopefully mitigate their tendency to assume that they will definitely get AD.

Meghan Collier 43:28



I think this issue also just emphasizes that disclosure of genetic information, disclosure of risk information should be an ongoing process. That's why people who are in that clinical role working with these folks should hopefully be available. When I see patients who are especially concerned, one thing they latch on to is that we can monitor them and follow up with them over time and really keep a pulse on this.

Ryan Van Patten 44:03



That's great. Yeah. So moving on, but also related. There are multiple published guidelines that currently recommend that genetic testing for AD should only occur judiciously and then only in the context of thorough genetic counseling. Some of these guidelines even go so far as to recommend that susceptibility testing for specific loci like APOE do not occur at all. So I'm wondering what goes into these guidelines [and] why they're recommending such caution? We know that as we've mentioned, APOE-4 is a risk factor. It has incomplete penetrance, it's not deterministic. We also know, as you've mentioned, there's no cure for AD, of course. Are these the primary reasons for these published recommendations? Are there any additional reasons for them?

Meghan Collier 44:55



I think those are the main take homes, and then similarly we've talked about the concerns about increasing stigma and issues related to privacy. It's still such a new area that we need to make sure that we understand it before it's widespread practice.



Ryan Van Patten 45:15

Makes sense. So you've been involved in some clinical trials at Butler hospital, you had mentioned, where part of your role is to disclose a patient's genetic status to them. I'm curious, in this role that you had and in your experience, what are some strategies or techniques that you've developed for presenting this bad news? So in the moment, in the room with people they're e4 positive, and you need to tell them this, how might you soften the blow emotionally but also be very clear and accurate in communicating this information?



Meghan Collier 45:47

Yeah, good question. I think there's a little bit of a key point here. There are studies on other chronic diseases that show that interpersonal ability and the professional skills of the clinician in the process of disclosing bad news profoundly affects the level of anxiety and hope that someone experiences, patients and their families, as well as their adaptation to disease and promotion of the ongoing relationships with health care providers. So it behooves us to make sure that we're really in tune with the interpersonal environment of those sessions. I think specifically in the e4 disclosure context that's why we've made sure that in the protocol, there's such a thorough assessment of where the patient and the family member, or in this case the study partner, is at before and after they learn their results. So there's this very thorough checking in process. In many cases, we've asked them to really imagine what it would be like to learn their results, whether they were a carrier or a noncarrier, and how that would feel - their psychological reaction. If they think they would seek support, who would that come from? Try to explore those paths. So you've done that beforehand.

In many cases, I explicitly ask right before I reveal the results of what they believe their level of risk is. So what are they expecting to hear come out of my mouth next? That gives me a better sense - and this is my personal style in these sessions - but that gives me a better sense of whether they might feel blindsided with the information that I'm about to share with them. And, of course, this isn't a perfect solution, because somebody could say that they assume they're at increased risk or assume they're a carrier, but still have that hope and then be really rattled. But it allows me to adjust my framing and the language that I use when I'm about to give that result. Then I think another important piece is allowing ample time for them to express reactions, for me to communicate that I am there to let them express those reactions. And definitely to ask if they have any questions and assess their comprehension of what they've just taken in. So there's this check in before and then there's this check in after where we're reinforcing their education. So like you said, trying to make sure that their understanding is accurate. You want to be

realistic about their risk and fact based, but there is an opportunity to offer hope when you're emphasizing that this is a risk gene and so it's not guaranteeing anything.

Then also reviewing opportunities for them to take control. So participating in research trials, reminding them of the plans that maybe they discussed about what they'd put in place, or the people who said, "Well, I'm going to take those vacations that I always wanted to take and not put them off" so that they can maybe use this information productively - the future planning piece and maybe try to capitalize on some of their motivation to make lifestyle changes. And then finally, I think it's important to discuss support seeking behaviors, opportunities, whether it's continuing to engage with a clinician they're seeing or, in this case, this is a research study, but in our program staying engaged with us and sharing where they're at and how they're reacting to that with their study partner who they've come in with in this scenario.

Ryan Van Patten 49:36



Yeah, that's all really helpful. I'm curious about what you described as your own personal style. I like that idea of asking someone what they think you're going to say and then judging their reaction. Then you can use that information to proceed. But that's your own idiosyncratic [style]. As far as you know, other people don't necessarily do that.



Meghan Collier 49:56

Yeah. I haven't discussed it explicitly with the other clinicians in the trial.

Ryan Van Patten 50:00



Well, I'm glad you mentioned it here, though, because if listeners are then later - yeah, if any of you may participate in such disclosures, it sounds like it's a helpful strategy.

John Bellone 50:11



Yes, it's a good method. This all seems really relevant to the construct of psychological readiness and a readiness plan. Sounds like that's kind of what you're doing with your patients. Is that right?

Meghan Collier 50:25



Yeah. So again, this is this trial, or a research protocol. Also genetic counseling procedures in general, do this, asking someone to thoroughly consider these possible results and their responses to them. So we thoroughly assess somebody's psychological readiness. The way that we've operationalized that or defined it in our protocol, and I think this is largely consistent, we're replicating what REVEAL has done, is evaluating psychiatric history - any history of depression, anxiety, as well as current level of depression and anxiety with questionnaires, as well as just interviewing, reviewing medications, both historically and currently, and then certainly any history of suicidal ideation. In our protocol, I think it's within five years and that person would be excluded from being able to participate in the trial. But that doesn't exclude people who had some lifetime experience of suicidal ideation.

Ryan Van Patten 51:37



You mentioned earlier that in the REVEAL studies, unfortunately, most of the sample is white.

Meghan Collier 51:43



Yeah. And in ours too, unfortunately.

Ryan Van Patten 51:46



Yeah. That's a big problem, ubiquitously, unfortunately. Do we know anything about how race and culture might impact reactions to these disclosures? Are there any studies that really focus on those moderators?

Meghan Collier 52:00



I think it's the third arm of REVEAL - second or third, I can't remember - where they have been able to recruit more African American participants. They've specifically looked at those effects and I think, on the front end, African Americans and Caucasian participants are endorsing a similar number of reasons to pursue genetic testing. And essentially, in comparison to white participants, they're finding that African Americans were less knowledgeable about genetics and Alzheimer's disease risk and less concerned about developing Alzheimer's disease despite the fact that they are actually at increased risk of developing AD. So lower levels of perceived risk. There are also ongoing analyses to examine whether these group differences and knowledge and attitudes persist after formal education and counseling.

John Bellone 52:58



During this generic disclosure visit, I can imagine that the clinician is faced with a difficult balancing act between how accurate and thorough but how succinct they are. You know, the clinician wants to be as precise as they can be, but provide the patient with all the information and go over all these things that you're mentioning. I wonder if it might be overwhelming to people who are not well-versed in biology or genetics or probabilistic risk. So from a more big picture standpoint, how do you think about that balancing of time and information?

Meghan Collier 53:39



Yeah, such a good question. I think there's also this concern of managing the patient's expectations, right? Somebody comes in and they expect the clinician to be the expert, a truth teller of sorts. And that's at odds with the reality of the fact that this is probabilistic. So there's definitely still some uncertainty, the current state of knowledge is limited. I think the approach at Butler Hospital has been one of simplicity. So whereas some groups, like the REVEAL group and the GeneMatch group, that's an AD prevention trial and they disclose genetic results prior to enrolling someone. Some groups prefer to actually give somebody that quantitative risk estimate, a percentage of risk. We've been a little bit more simple, both with our graphics and just providing qualitative descriptors - low average, moderate or higher risk, depending on how many copies of e4 somebody carries. I will say that some people are reporting afterwards that they wished they could receive more specific information, like a quantitative estimate. I don't know. So I think people are having idiosyncratic responses to the amount of detail that they want to learn. I think we generally try to focus on the take-homes during the education process. That this is a risk gene, people with no copies of e4 do at times develop Alzheimer's disease, and people with one or two copies do not necessarily develop it. So those take-homes and then also providing that bottom line that there are other risk factors here, not just this gene. We also have a knowledge check both at baseline and the disclosure visits just to make sure that they have additional opportunities to have their understanding of this information clarified. So try to be as simple as possible, make sure that you focus on those take-home messages, and then check in and assess whether that information is actually being understood and digested accurately.

Ryan Van Patten 55:52



That's a great answer. That's really helpful. I wanted to clarify something for our listeners and ask you a question based on this. So the e4 allele of APOE confers cognitive risk above and beyond the development of AD. So just as one example,

there's a 2008 meta-analysis that suggests that the presence of the e4 allele leads to worse cognitive outcomes following TBI. So we're not talking about the development of AD here. I've heard some people argue that e4 allele is more of a general cognitive risk factor rather than being AD specific. So, with that in mind, how do you think about that when you're disclosing e4 status to patients? Obviously, we want to provide them with all the information, we want them to be educated, we don't want to leave things out. But that also could be overwhelming to people if we give them more information than they're prepared to digest and integrate into their framework. I'm interested in what you do, and what you think is the best approach? Should we focus on APOE as AD-specific and stay within that realm? Or should we bring in and talk about the other cognitive risks related to the e4 allele?

Meghan Collier 57:03



I think that depends on the setting that you're working in. So in the Alzheimer's disease prevention trial world, we have not brought in those other associated conditions - definitely feels like that would complicate things. What I've been talking about is a research trial, [so] it might muddy the results for outcomes in terms of the psychological behavioral outcomes of learning genetic status or risk status of AD. But I think just offhand thinking about it in a clinical context, I haven't thought so much about the cognitive risk in general but I have thought more about the coronary artery disease risk. So if you're thinking about, again, trying to engender motivation, there is some evidence that people who are educated that the e4 allele increases risk of coronary artery disease does have more potential to increase health behavior change. So you might want to capitalize on that in folks who are learning they are e4 positive.

John Bellone 58:17



Let's pivot a little bit and start talking about direct-to-consumer, DTC testing, in the context of genetic risk for a disease. So these are different direct-to-consumer companies like 23andme or Ancestry or there are a number of them, what do they tell us about AD risk or risk for other conditions? And how has that marketplace changed how we might think about biomarker disclosure with patients?

Meghan Collier 58:51



It's definitely putting that information into people's hands. I've often just thought about the way that a lot of the directed consumer tests are marketed as, "Hey, this is fun." Like it starts with learning about your ancestry, and you can learn all sorts of

fun things about your traits. You know, whether people with your genotype are more or less likely to smell asparagus in their urine, for example. [laughs]



John Bellone 59:17

That's my favorite one. [laughs]



Ryan Van Patten 59:17

That's a critical piece of knowledge that we should all know.



Meghan Collier 59:20

Yeah, yeah. So I actually was looking at it over the holidays. I'm thinking of 23andme, just looking at their website to see what it looks like these days and they had the Grinch. "The Grinch got his genetic results. You should, too." And it's like literally...



John Bellone 59:38

[laughs]



Ryan Van Patten 59:38

He's their spokesperson now.



Meghan Collier 59:39

It's like literally the new cartoon Grinch is coming out and...



Ryan Van Patten 59:42

Why the Grinch?



Meghan Collier 59:43

Well, it's Christmas time.



John Bellone 59:45

He definitely smells his asparagus...



Ryan Van Patten 59:49

[laughs]



Meghan Collier 59:49

You could read his results. Click through and you read the Grinch's results.



Ryan Van Patten 59:54

I wonder if he has an e4 allele.

Meghan Collier 59:55

Yeah, and that was with their holiday special. [laughs] So, yeah, he was at increased risk of... Yeah. Anyway. But I think that there's a lot of appeal from a "fun" perspective. I find that a little concerning because now there's the whole health add-on. I'm sure there are people who are pursuing this because they're just genuinely interested in health risks. But I worry more about the incidental findings. You know, people who are going through this process just for fun or basic curiosity, and who haven't educated themselves as much on all of this language we've been using - the probabilistic risk gene language - and then suddenly they just get smacked with, "Hey, you carry this risk gene for Alzheimer's disease." And maybe they do have a family history, maybe their parents and grandparents died young and so they didn't know. So I think it's changing the game a little bit. I think about being prepared for that person who walks into my office who's concerned about their risk and got the 23andme for Christmas, and now knows that they carry the gene and how will I talk to them?



Ryan Van Patten 1:01:22

DTC testing is discouraged by current published guidelines. We've talked about these guidelines a bit before. They recommend that disclosure of susceptibility status only occur in the context of genetic counseling. So, with this in mind, is there any empirical work that you're aware of on the effects of DTC testing on users?



Meghan Collier 1:01:42

I think it's been largely consistent with what they're seeing in their REVEAL trials. That there's no increased psychological distress in people and users of direct-to-consumer testing.



Ryan Van Patten 1:01:54

Okay, that's helpful.





John Bellone 1:01:56

So, Meg, you mentioned earlier how insurance companies might potentially use this information. I'm a little worried about unintended uses, and not just by insurance companies. You can think of employers maybe using this, romantic partner selection, right? You might not choose someone with a certain genetic predisposition for lankiness, like Ryan over here. [laughs]



Ryan Van Patten 1:02:19

You're never going to let this go?



John Bellone 1:02:22

[laughs]



Meghan Collier 1:02:23

I don't know. You've got another tall person in the room now. So...



Ryan Van Patten 1:02:26

Yeah, that's true. You're the atypical one here.



John Bellone 1:02:28

Alright, I'm going to backtrack here.



Meghan Collier 1:02:29

[laughs]



John Bellone 1:02:30

Backpedal my answer... [laughs] But, yeah, you could envision a future where the genetic results were widely available. You can post it on your social media, or tell people about it, or someone could get a piece of your hair and somehow find out your genetics. Are there any policies in place that you're aware of that protects that? How do you think about this?



Meghan Collier 1:02:56

I'm actually not so aware about the direct-to-consumer literature or any policies that are specific to those companies. But currently, GINA, the Genetic Information Nondiscrimination Act, protects against discrimination by employers.



John Bellone 1:03:14

Oh, that's good to know.



Meghan Collier 1:03:15

So employers and health insurance. Yeah, you could find out that you're actually adopted or something like that.



John Bellone 1:03:24

Sure, yeah. There are those possible surprises from this testing. So there was the case recently, where someone was apprehended for a series of murders and rapes and a consumer genealogy website played a big role in his capture. I think this is going to come up more and more. I think it's a fascinating topic that we're going to hear about a lot.



Ryan Van Patten 1:03:53

That's happened several times. I think you're referring to the Golden State killer...



John Bellone 1:03:56

Right.



Ryan Van Patten 1:03:57

...which is a pretty widely publicized case. So, yeah, I mean, for all the rest of us, that's good news that that happened, right?



John Bellone 1:04:04

Right. Yeah, privacy is going to continue to be an issue.



Ryan Van Patten 1:04:08

Yeah, for sure.



Meghan Collier 1:04:09

I've thought about something else and talked about it with some colleagues. In terms of direct-to-consumer testing, there are education implications for both consumers and healthcare providers. It actually increases the burden, like the workload and burden for healthcare providers when your patients are now walking in and saying, "Look, I have this gene..." So it really means that general practitioners, you know, any clinician really needs to have some familiarity or be

ready to do this extra work for their patient. And there's time limitations and somebody's level of preparedness to provide education is variable. Their ability to address those concerns and provide resources could be limited. So I think that's definitely a concern.

John Bellone 1:04:57



That was actually one motivation for talking with you. I was interested, just for selfish reasons, because I work with mainly older adults who are worried about dementia. It hasn't happened yet, but I'm sure that someone's going to come in soon and say, "Oh, hey, by the way, what do you think about paying less than 100 bucks and getting my results?"

Meghan Collier 1:05:23



Asking your advice about whether they should pursue it?

John Bellone 1:05:25



Exactly, as a clinician. And then I'm going to have to spend time talking about it and figuring it out, and I really didn't know much about it. So I feel like we might be on the front line to some extent, especially the more geriatric neuropsychologists out there.

Ryan Van Patten 1:05:41



They can also ask you to interpret their profile. They can come in and say, "I am e4 positive, what does this mean?" You know, "Tell me more than the website report did." So, in a way, we all need to become mini-genetic counselors, or at least be able to speak in an educated way about this information.

Meghan Collier 1:05:58



Thinking about it, this is all relatively new. We didn't know about e4 until the 90s. We're going to learn more [about] risk genes for Alzheimer's disease and other cognitive related conditions. And, as people are coming in with genetic results, to what extent are we supposed to be making sure that we have all this knowledge? Will that become one of our competency areas at some point with board certification or something?

John Bellone 1:06:25



Yeah. I wonder how long it's going to be until we have these genetic markers available for most patients. And how we should use the information clinically. So if

someone does come in and say, "Oh, yeah, by the way, I'm e4, I have one variant, or I have two..." Should AD be considered a much more likely etiology if we find cognitive deficits on testing. Maybe we're leaning towards a vascular etiology, but they've got two e4 alleles, so maybe that tips the scale to AD.



Meghan Collier 1:06:59

Maybe two, but...



John Bellone 1:07:00

Yeah, I'm just wondering how we would incorporate that into our interpretation of the test results.



Meghan Collier 1:07:08

I suppose it depends on whether you also have other pieces of information, like their neuroimaging, if there's evidence of high vascular burden or degeneration. I tend to prefer to have more information like that. It makes me feel more confident.



John Bellone 1:07:28

It gives you just one extra piece of the puzzle, essentially. I can see that.



Meghan Collier 1:07:33

Yeah.



Ryan Van Patten 1:07:35

To zero in on what we've been talking about for the past couple minutes. As we said, some patients might ask their neuropsychologist whether or not they should pursue genetic testing with 23andme or one of these other corporations. So imagine that you're functioning as a neuropsychologist in this setting clinically, and your elderly patient asks you that question. I imagine that it's not a straightforward answer. It depends on idiosyncratic attributes of that person. But how would you think through that answer and also think about the published guidelines that we've referenced several times. But each person is different, right?



Meghan Collier 1:08:12

I think that you kind of answered the question in your question. We know those guidelines, so we can tell the patient that those are the guidelines, but then also say, "This is available to you. You're going to make that decision. So let me provide

you with important information about this." So I think it offers an opportunity for education. And then it's really in their hands whether they pursue it or not.



Ryan Van Patten 1:08:37

That makes sense.



John Bellone 1:08:39

We've mentioned genetic counselors a few times earlier in the conversation, and it would probably be helpful to say that genetic counselors have graduate level education and training in medical genetics and counseling, specifically. It's an established field and genetic counselors analyze the genetic results. They inform and advise individuals and families about those risks for inheriting certain diseases. They go over treatment options available. I mean, it would be best for them, and they're definitely the most qualified to disclose and go through all of this. But, you know, I think we still need to be prepared because we're going to get these kinds of questions as well. One other related question is, should we as neuropsychologists refer patients to genetic counselors. I don't know, I'm just curious when we should consider doing that.



Meghan Collier 1:09:37

I think that if somebody has their results and they're concerned and, as a clinician, you don't have comfort with talking through that information with someone - so maybe a general adult neuropsychologist who hasn't specialized in geriatrics and isn't super familiar with the literature would be in a position where they feel most comfortable referring to a genetic counselor [if] somebody presented with concerns about that or wanted to pursue it. I think that the direct-to-consumer companies actually have a note in a lot of their websites or their reports about if you are concerned, please consult your physician. So I think that people could benefit from referrals. But I think that's not to say that if you're someone who has significant experience, or specialized knowledge and an understanding of genetic counseling, there are a lot of parallels with our approach and our training in feedback delivery. So the similarities anyway are you summarize why testing was done, and what somebody's motivation was to come in and what they're expecting to learn, and what procedures were done, and what we're going to find out or be able to provide when we provide those results. So I think as long as you have an understanding of what that genetic information means, you can use a very similar format to that discussion that you would in a feedback session. I mean, I think that the difference might be that in neuropsych feedback, we're not as intentional necessarily in evaluating somebody's readiness to learn their results. I mean, I'm sure some

clinicians are more so than others, or it might depend on the case and whether you know that this patient is particularly anxious or has a history of depression. So I think that's an especially important piece that the genetic counselor might be a little bit more intentional with that - imagining results one way or another. We don't really do that when we're talking about, "You're about to learn whether or not you have dementia." So something to consider, I guess.

Ryan Van Patten 1:11:57



One thing you said that struck me is this idea of if we should refer people who are seeking DTC testing to genetic counselors. So think about how many people can access DTC testing, it's like thousands and millions - there's so many people. We can't refer all them to genetic counselors, they would be inundated. There's not enough clinicians who specialize in this area to be talking to everyone out there who is signed up for 23andme. There have been some published reviews that argue for further education of PCPs and other allied health professionals, I would put neuropsychologists under that umbrella.



Meghan Collier 1:12:40

Yeah, I would too.



Ryan Van Patten 1:12:41

As we spoke about earlier, we need to educate ourselves more about genetic counseling, genetic disclosures so that we can answer some of those questions. At least something to think about.



Meghan Collier 1:12:53

I imagine this is relevant in the pediatric world as well, because there are so many genetic conditions that cause developmental disabilities and cognitive issues.



Ryan Van Patten 1:13:06

Okay. So now we're going to transition...



John Bellone 1:13:09

A special treat.



Ryan Van Patten 1:13:10

...to something a little bit different on NavNeuro. I think this will be a lot of fun. So, a while back, my friend John here ordered a 23andme genetic profile, and this

includes his real APOE status. So we have that with us. John has not yet looked at it. He's actually been sitting on it for several months. So kudos to him for waiting. He does not know what his APOE status is. So we're going to do a real live reveal here on the air.

To make this experience a little more interactive and educational, we're going to ask Meg to perform a brief genetic counseling session with John to show everyone a little bit what that looks like. As a reminder, Meg is not a genetic counselor, but she is a neuropsychologist with a lot of experience in this area. So I look forward to seeing what this looks like. One more caveat - I think to make this a little more realistic, John, you should step out of your selfhood and not be John Bellone for a few minutes and just set aside all of your immense vast repertoire of knowledge of everything. [laughs]



John Bellone 1:14:18

It's going to be hard.



Meghan Collier 1:14:19

Your pessimism about the benefits of learning...



John Bellone 1:14:22

[laughs] I was going to say, I know earlier I said that I didn't really see the need for this, but this is for the good of the show. Take one for the team.



Meghan Collier 1:14:31

Pretend this is very meaningful.



Ryan Van Patten 1:14:33

Pretend that you're an average human being who cares about their genes.



Meghan Collier 1:14:37

Of an average height.



John Bellone 1:14:38

[laughs]

Ryan Van Patten 1:14:42



And just as a caveat, or just so everyone knows, I should say John ordered 23andme. We don't have any financial relationship with them. This is simply for educational purposes.

So I think now we can transition and Meg if you're up for it, do some pre-counseling with John, then we'll do the reveal, and then we'll do some post-counseling. Take it away.

Meghan Collier 1:15:02



Sure. I'll really boil it down and just review the basic structure of the session. So somebody comes in for genotyping, in this case, they have purchased the direct-to-consumer test, and maybe they've approached a genetic counselor to review the results with. So one of the very first steps is to take a thorough family history. So you would ask if somebody had any family history of Alzheimer's disease in this case. John, are you comfortable speaking to that?

John Bellone 1:15:36



Sure, yeah. A grandmother.

Meghan Collier 1:15:40



Okay. So you would take the family history, going back two or three generations. You would have checked in with the patient or the participant's medical history and reviewed their psychiatric history - whether they've had any hospitalizations, what their treatment history is, any diagnostic history, and current psychological status. That's assessed with both the clinical interview and report of current stressors and any major events that have taken place that are currently consuming someone. And then, as I mentioned before, really having somebody imagine what it's like to learn their status for each outcome. So, John, what do you imagine would be your psychological response to learning that you were a carrier of e4?

John Bellone 1:16:34



Yeah. I don't know. I mean, luckily, I'm young enough. I guess it would be far enough away, I would be hopeful that within the next 40 years we see some kind of real treatment for Alzheimer's disease or good preventative measures. I think I'm doing most of the lifestyle things that I should be doing to reduce my risk. I don't think it's going to change much if it does turn out that I have one e4 [allele] or even two.



Meghan Collier 1:17:10

So it sounds like you don't perceive any, or you don't have any expectations of how this might change your behavior. And you don't anticipate that you would find it particularly distressing to learn if you were at increased risk, more than average risk of developing Alzheimer's disease based on learning that you were a carrier of e4.



John Bellone 1:17:33

Yeah, I don't think so. Maybe I would feel worse for my wife, because maybe there would be an increased probability that she might have to care for me. But no, I don't think so. Something that's working in my favor is time. So if I was, let's say, I was 60, and I'm going to find this out, then I might be a little more nervous about the results. But, no, I don't think it would change much psychologically.



Meghan Collier 1:18:04

For the sake of the thought experiment, I wonder if you did experience increased distress, if there are people who you might reach out to? What kind of coping strategies might you use in order to get through that and or try to decrease any anxiety that you experience?



John Bellone 1:18:20

That's a good question. I have plenty of people to lean on. I have a really good support network of friends and family. And I have many other coping strategies that I can pull from. Yeah.



Meghan Collier 1:18:34

In the sessions, you review the education that has been already provided. And so I would say, "We've talked about how this is a risk gene, so it's not deterministic and you'll just be learning whether there's an increased chance that you would develop Alzheimer's disease but there are many other risk factors involved", as we've alluded to. You mentioned that you already engaged in a lot of heart healthy behaviors, like riding your bike every day. [laughs]



John Bellone 1:19:04

[laughs]



Meghan Collier 1:19:05

And we discussed some of the limits to the Genetic Information Nondiscrimination Act in that it doesn't cover long term care insurance, life insurance and disability

insurance are not protected. So have you thought about whether that's a concern for you? Especially, as you mentioned, you're relatively young to learn these results. So it's possible that there could be some changes that these insurance providers make once this direct-to-consumer era continues to advance.



John Bellone 1:19:37

And once it's said live on air and they have that...



Meghan Collier 1:19:44

I was pretending we weren't live on air, but... [laughs]



John Bellone 1:19:48

They're going to know. So, yeah. I think I'm okay with that. I mean, I'm hoping maybe it'll be to my benefit. If I have none of the variants, then maybe I can use that in my favor to lower the premiums or something.



Meghan Collier 1:20:07

We find working with older adults who are cognitively healthy and about to learn this information that they often have things in place already, so they can read the fine print and see whether any changes could be made. It's mostly on the application side of things where you're asked if you've had any genetic testing, and that's where it could become problematic. Often people say, you know, "We've discussed it together as a couple, and we've decided we're not going to pursue long term care insurance", or, "Hey, I'm retired, I don't have disability insurance." Okay. So it sounds like you aren't concerned about any increased distress once you learn your results.



John Bellone 1:20:51

Alright, so...



Meghan Collier 1:20:52

So this is where I would recap all that we've discussed and maybe check in with you to see what you expect your results to be. Do you expect an about average risk? Or do you assume that you are a carrier and at increased risk?



John Bellone 1:21:08

Knowing the probability in the population...



Meghan Collier 1:21:12

Being a very educated consumer... [laughs]



John Bellone 1:21:14

My money would be on 3/3, having the two alleles of e3. I don't have a major family history - one grandmother with Alzheimer's disease, so I would guess not two e4 alleles. Just probability wise, probably none.



Meghan Collier 1:21:37

Would you like me to read your results to you? Or do you want to open it yourself?



John Bellone 1:21:40

I got it. I'll open it. Alright. Okay. So I'm on the genetic health risk page.



Ryan Van Patten 1:21:48

Drumroll.



John Bellone 1:21:48

[makes drumroll sound]



Meghan Collier 1:21:48

[laughs] Saddest drumroll ever!



John Bellone 1:21:54

Those are the very expensive sound effects here on NavNeuro. [laughs]



Meghan Collier 1:22:01

[laughs]



John Bellone 1:22:01

Right. Age related macular degeneration, celiac disease... late onset Alzheimer's disease - variant not detected.



Meghan Collier 1:22:13

There you go.



John Bellone 1:22:13

There's also a Parkinson's disease link that also says "variant not detected". So let's see when I go to look at the actual page.



Meghan Collier 1:22:27

It's important to note that, at least in the 23andme format, they do not give you your actual genotype whereas in our study protocol, we give people their genotype. So here, you're learning whether or not you carry one or two of the e4 variant.



John Bellone 1:22:46

Yeah. I kind of would like to know.



Ryan Van Patten 1:22:51

Do you want to not keep our listeners in suspense and read what is on the page right there?



John Bellone 1:22:54

Well, I just said "no variant". So, "John, you do not have the e4 variant we tested. Your risk for Alzheimer's disease also depends on other factors, including lifestyle, environment, genetic variants not covered by this test." That's good.



Meghan Collier 1:23:07

Yeah. They do provide that. So we don't know in this mock session, this live direct-to-consumer session, we don't know your genotype. We don't know. Probably 3/3 given statistics, but it hasn't revealed whether you carry two 3s, or a 2 and a 3, or maybe even a 2/2, which is very rare. But you don't carry any copies of e4.



John Bellone 1:23:33

Well, I am glad for that. Although [it's] a little anticlimactic for our podcast.



Ryan Van Patten 1:23:40

All the listeners were hoping...



Meghan Collier 1:23:42

[laughs] My goodness.



John Bellone 1:23:43

It would have been way cooler if I had e4. [laughs]



Ryan Van Patten 1:23:46

I'm glad you said that.



John Bellone 1:23:47

Well, for the podcast, not for my risk.



Meghan Collier 1:23:51

Here's where I would ask, so this is in line with your expectations? And how are you feeling?



John Bellone 1:23:59

Good. This is good news.



Meghan Collier 1:24:02

Remember this means that you're likely just at average risk meaning that you still may develop Alzheimer's disease, particularly because you do have a family history.



John Bellone 1:24:11

Well, I'm going to sell my bike tomorrow and just veg out on the couch. [laughs]



Meghan Collier 1:24:18

Now you're going to assume you're at low risk. [laughs]



John Bellone 1:24:22

No, no, this isn't going to change anything. But, yeah, I guess it is still kind of comforting to know. Good. Yeah.



Ryan Van Patten 1:24:32

Is there any post-reveal counseling?



Meghan Collier 1:24:36

Yeah, so we spend some time just discussing your reaction to this certainly, often more salient for folks who learned that they are a carrier, but also for people who

experience - in our setting somebody who came in with a strong family history and is assuming that they're at increased risk, their sense of relief at learning that they're just at average risk. [For] many people I end up asking what this means for their family. So, you know, if you have kids or plan on having kids, and what it might mean for your siblings, or does this explain why my mom had Alzheimer's disease, or why my parents didn't. And essentially, it's an opportunity to provide education that we know that you inherited no variants from your parents. But that doesn't mean that mom and dad, one of them, or both of them doesn't carry one copy of before. And then as far as your siblings go, they could have the same genotype, or a completely different genotype. It depends on which two variants they got from each parent. And then as far as your children, you're not passing on any copies of e4.

John Bellone 1:25:44



Yeah, that's true. So Meg, if I did have one or two e4 alleles, what resources would you have recommended that I got hooked up with? Or what plan should I have considered? Can we talk through that a little bit?

Meghan Collier 1:26:02



Yeah, certainly more relevant, or I have more experience discussing this with older adults. So, in the research setting, we would remind people or provide education about which clinical trials they're eligible for and ask if they are interested in being contacted to start the screening process. That's an important piece about doing this in that kind of a setting. And then, again, reminding them about what they know - that this is a risk gene [and] does not guarantee. If they do have concerns about cognitive decline, they can be referred for neuropsychological testing. And then of course, discussing healthy lifestyle factors. So if this was someone other than you with a perfectly healthy lifestyle, we would discuss some of those factors and evaluate, "Well, now what does this mean for your thoughts on those behaviors?"

Ryan Van Patten 1:26:59



Great. Well, that was really helpful. Both of you. I appreciate you going through that mock reveal session. I do want to just address something, and say for our listeners that, of course, we're making light of John's reveal here and his e4 status. We wanted to add this little mock session to show everyone what this looks like and to do something a little bit different. But we take very seriously the idea of people being at genetic risk for AD, obviously. Alzheimer's disease is no joke. And it can be distressing to some people. Luckily, the literature says that learning that you're e4

positive doesn't cause a lot of extra depression and anxiety and suicidality, but, of course, is a very serious and impactful topic.

Meghan Collier 1:27:44



I think it's also worth mentioning here - this is a question I've gotten when I've discussed this in talks that I've given, people ask, "What about my patients who are anxious and depressed and seek out this information? What about my patient who has a history of drug addiction or has a history of suicidality?" We have to think about the fact that the research that's being done are in these very restricted samples who were psychologically ready, that's why they got into the trials. So this is what we know about those people.



Ryan Van Patten 1:28:21

Great point. Yeah.



Meghan Collier 1:28:22

Yeah.



John Bellone 1:28:22

Yeah. There's another disclaimer here that you, listeners, should get proper training before deciding to incorporate this counseling into your practice. You know, just hearing this mock...



Meghan Collier 1:28:37

Yeah, it was very abbreviated.



John Bellone 1:28:39

This is not what it looks like in the real world. And this does not substitute for actual training.



Ryan Van Patten 1:28:46

Just a taste, just to see a little bit of a flavor of what it's like. So now we'll transition into our bonus questions. These are questions that we asked all interviewees related to the field of neuropsychology broadly. So this is not specific to genetic testing for AD anymore. So Meg, I'm curious, if there's one thing you can improve about the field of neuropsychology what would it be?

Meghan Collier 1:29:08



So I think that some of your guests have taken one answer that comes readily to mind and that is improved norms. So more representative norms, larger sample sizes. But I want to try to give you a little bit of a different answer, I guess. And this might, you might have a plan to discuss this in a future episode. Maybe standardizing the descriptors that we use when we're interpreting our data across the field. You know, who is using "borderline" and where and when do you call it "mildly" versus "moderately" impaired? When is it appropriate to call it "impairment" versus "below expectations"? Because is it functionally leading to impairment or is it just a score below that person's normative group? I think about that a lot when I'm working with younger folks and they're slow on Trails A - you know, it's impaired for them, but what does that mean about their ability to function in daily life?

Ryan Van Patten 1:30:16



Yeah. Well, I appreciate the different sort of answer. I like that answer and that is very attainable. So there are things we can improve about the field that just require so many resources in such a large scale movement that we want to start thinking about them, but they're not things that are coming down the pike. As you mentioned, in teasing, we will, at some point in the relatively near future, have an episode. AACN has been working on guidelines trying to standardize across the field what qualitative descriptors we're using to describe different percentile ranges in terms of test scores. So I think that's a great answer.

Our second bonus question is, what is one bit of advice that you wish someone had told you when you were in training, or that someone did tell you that really made a difference for you in your career? So here, we're looking for an actionable step that we can give to trainees that they may not have thought of that would improve their performance.

Meghan Collier 1:31:13



I'm not sure the extent to which anybody actually articulated this advice. But something that naturally panned out over the course of my training was paying attention to my interests, and then making sure that I took steps to pursue activities or opportunities in those areas of interest. So whether it is seeking out an internship that's going to offer you a rotation that would be really meaningful to you in some way and inform your career or the population that you're going to work with, or just be a useful adjunct. I've always been super passionate about "Oh, neuropsychology" and maybe didn't think about the importance of breadth of training until I had good breadth of training. So experiences not just in cognitive

rehab but also in health psychology were really informative and made me feel very well prepared and allowed me to market myself, I think, a little bit better on the job front because I have these additional skills working or maybe it offers me opportunities to work with my patients in multiple ways. So in terms of health psychology that informs the way I think about treatment recommendations, and the way I deliver feedback. If I'm doing follow up sessions with a patient, I feel comfortable engaging in some of the health psych interventions. And then similarly, for example, on fellowship getting involved in the APOE disclosure sessions. So my specialty was geriatric neuropsychology, this felt both very interesting and informative to me. And now I feel very comfortable in this sort of changing environment as more and more people are aging, and more and more people maybe have access to genetic information. I feel pretty well prepared to handle that with my patients. So essentially, this just came from me seeking out opportunities based on my interests, and it's definitely helped shape my career trajectory.

Ryan Van Patten 1:33:22



Yeah, breadth of training and knowing you as a colleague and friend, I can speak to that health psychology background, like you said, it helped to get your current position and it makes for better neuropsychologists overall if we have knowledge that goes beyond the field of neuropsychology.

John Bellone 1:33:39



Not just taking that linear neuropsychology path, but diverging a little bit to follow some of those passions.

Meghan Collier 1:33:46



Complementing your neuropsychology training.

John Bellone 1:33:48



Yeah, of course.

Ryan Van Patten 1:33:49



Yeah. Great. Well, this has been great. Really helpful. Thanks so much for coming on the podcast, Meg.

Meghan Collier 1:33:55



Really happy to be a part of it. Thank you.

John Bellone 1:33:57



Thanks. That's it for our discussion with Meg. Before we go, we wanted to make a couple announcements about the upcoming INS meeting in New York. NavNeuro has an informal partnership with the INS Student Liaison Committee, or the SLC, because Ryan and I feel strongly about the need for increased student participation in the outreach in our field. There are a few SLC specific events that will be taking place at INS. Wednesday at 2:30, Dr. Karen Postal will be holding a workshop based off of her book, "Feedback that Sticks" about the art of communicating in the language of our patients. Ryan and I have both read her book and found it incredibly helpful. We're actually scheduled to interview her at INS so look out for that episode in the near future. There's an SLC ANST students social on Thursday at 7pm at the New York Beer Company, about a five minute walk from the conference. Ryan and I will be in attendance for at least part of the social in case anyone wants to meet us. We've been told they'll be raffling off about two grand worth of prizes. If meeting us isn't incentive enough to come, of course. [laughs]



Ryan Van Patten 1:35:14

[laughs] I imagine that would be incentive enough for anybody.



John Bellone 1:35:16

Of course.



Ryan Van Patten 1:35:17

In addition, there'll be a panel about exploring neuropsychology as an interdisciplinary endeavor on Friday at 10:15am. And a discussion group about the future of neuropsychology at 6pm on Friday.



John Bellone 1:35:29

I'm going to do my best to be at that one, definitely.



Ryan Van Patten 1:35:33

It's possible that these times would change, so double check beforehand. There's also going to be a selfie station, apparently, where you can take photos with your neuropsych group. Sounds like a lot of fun. [laughs] So, overall, it sounds like it's going to be a really enjoyable and productive conference, and I'm really looking forward to it.

Well, that'll do it for today. Join us next time as we continue to navigate the brain and behavior.



Exit Music 1:36:00

End of Audio 1:36:00

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