Genetic Research in Eating Disorders: A Primer for Clinicians
Webinar Transcript

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la-shell_johnson@med.unc.edu: Good afternoon, everyone, I would like to welcome you to today's webinar titled, “Genetic Research in Eating Disorders: A Primer for Clinicians.”

la-shell_johnson@med.unc.edu: Before we begin, there are a few things that I'd like to note. Participants will be muted upon entry and videos turned off. For technical assistance, we ask that you use the chat box located at the bottom of your screens. You will also receive an email in approximately three months requesting feedback and impact on today's presentation.

la-shell_johnson@med.unc.edu: Lastly, we ask that you visit our website at www.nceedus.org/training to view other training opportunities that we may have.

la-shell_johnson@med.unc.edu: At the end of this webinar you will also have an opportunity to ask any questions that you may have. Any unanswered questions will be sent within one week from today by the presenter. I’d like to go ahead and introduce today's presenter.

la-shell_johnson@med.unc.edu: Today's presenter is Dr Cynthia M. Bulik, who is the Founding Director of the University of North Carolina Center of Excellence for Eating Disorders, Distinguished Professor of Eating Disorders at the University of North Carolina at Chapel Hill and Professor of Nutrition in the Gillings school of Global Public Health.

la-shell_johnson@med.unc.edu: She is also a renowned clinical psychologist. She is also a Professor of Medical Epidemiology and Biostatistics and Director of the Centre for Eating Disorders Innovation at Karolinska Institute in Stockholm Sweden.

la-shell_johnson@med.unc.edu: Dr. Bulik received her BA from the University of Notre Dame and her MA and PhD from the University of California Berkeley. She completed internships and post-doctoral fellowships at the Western Psychiatric Institute and clinic in Pittsburgh, Pennsylvania. Dr. Bulik has developed eating disorders programs in New Zealand, the United States, and Sweden and has active collaborations all over the world.

la-shell_johnson@med.unc.edu: She has published more than 640 papers and 50 chapters on eating disorders. She's author of seven books including, *Crave: Why You Binge Eat and How to Stop, The Woman in a Mirror, Midlife Eating Disorders: Your Journey to Recovery, and Binge Control: A Compact Recovery Guide*. Dr. Bulik has been the recipient of numerous awards, including the Eating Disorders Coalition Research Award, The Academy for Eating Disorders Leadership Awards for Research and Advocacy, the Price Family National Eating Disorders Association Research Award, and the Don and Melissa Nielsen Lifetime Achievement Award from the National Eating Disorders Association. She's passionate about advancing the science of eating disorders and translating science for the public. I will now turn things over to today's presenter, Dr. Cynthia Bulik.

Cynthia Bulik: Thanks so much La-Shell for that introduction. And welcome everyone to Genetic Research and Eating Disorders: A Primer for Clinicians.

Cynthia Bulik: Disclosures: Shire Pharmaceuticals, Idorsia, Pearson, and Equip Health Inc. And my gratitude quilt the research you'll hear about has been funded by these various groups. And on to eating disorders.

Cynthia Bulik: I think we missed a slide so the talk map is we're going to start talking about why I even study the genetics of eating disorders, to give you a basic understanding of current results and then really try to get into guidelines for clinicians about how you can use this information today in your practice and, then talk a little bit about EDGI, which is our current study eating disorders genetics initiative.

Cynthia Bulik: So just the basic topography, I think, pretty much everyone here knows that primary eating disorders are considered to be anorexia nervosa, bulimia nervosa, binge-eating disorder, and ARFID.

Cynthia Bulik: And epidemiology, as far as we know, is anorexia between 1% and 4%, bulimia between 1 and 2%, binge-eating disorder 1 to 4%, and ARFID is still a question. We don't have real strong epidemic epidemiology on it yet.

Cynthia Bulik: And we know that all of these disorders have increased mortality. We also know from decades of twin research that these disorders are heritable.

Cynthia Bulik: Anorexia was about 60%, bulimia about 60%, and binge-eating disorder about 45%. And those numbers came from twin studies and basically talked about the percentage of liability until the illness that is influenced by genetic factors.

Cynthia Bulik: But today we're going to go one step further and we're going to start talking about a genome wide association study. So not just what the twin studies told us, but how we're actually going in there and starting to identify the genes that influence risk for these illnesses.

Cynthia Bulik: And, of course, how they interact with environmental factors.

Cynthia Bulik: So real importantly, and you probably all see this in your practice is we know that eating disorders tend to fluctuate or migrate across clinical presentations during the course of someone's illness.

Cynthia Bulik: And this is from the Swedish quality registers at baseline when people are first registered, at one year follow-up and then, if there's another year follow-up included as well.

Cynthia Bulik: And just shows you all these little lines. The frequency and the extent to which these disorders, do not ring true. And when we are studying someone in our office, we're really getting a snapshot of their illness at that point in time.

Cynthia Bulik: Why do we do this? Why do we even study the genetics of eating disorders? From my perspective, as far as I'm concerned eating disorders defy biology and that's, what are the things that makes them incredibly interesting.

Cynthia Bulik: For people with anorexia, starvation is reinforcing, they feel better when they're starved. Hunger cues are dysfunctional in all of the eating disorders in one direction or another or both. Bodies, especially in anorexia nervosa, seem to revert to a negative settling point. And I'm not saying set point on purpose, I'm saying that even after we renourish people with anorexia, their bodies and minds tend to pull them down to a previously low weight.

Cynthia Bulik: We know that there's this perplexing hyper-metabolic period when we renourish people with Anorexia Nervosa when their bodies are burning through calories and it requires so much food to help them gain or maintain weight.

Cynthia Bulik: People with anorexia say that fats are aversive. The rest of the world tends to really like fats, but they don't like the feel, the mouth feel, the taste the sensation that it gives them when they eat fats.

Cynthia Bulik: Satiety cues are overwritten, so that stop sign that you have when you're too full either doesn't exist or gets eroded over time in people who have binge type eating disorders. And activity is more reinforcing than food for people with some forms of anorexia nervosa and we have animal models of that at this point where we know that even in the presence of their most delicious favorite food, mice can be conditioned to run themselves to death. We need to rescue them before they get to that point.

Cynthia Bulik: And, I also often talk about the negative energy balance trap.

Cynthia Bulik: We don't know what causes this, but people with anorexia nervosa prefer being in negative energy balance. And that's when the amount of energy expended to exercise, physical activity, rest, fidgeting, purging; is more than the amount of energy consumed as food.

Cynthia Bulik: And this is one of the things that we need to understand desperately biologically. The other thing is the study of eating disorders genetics doesn't just tell us about eating disorders, it tells us about all of those co-occurring conditions, such as anxiety disorder, depression.

Cynthia Bulik: It tells us about the genetics of metabolism of nutrition, physical activity, and about obesity. So, it really is just a starting point for all sorts of information that can emerge from the study of genes and environment in eating disorders.

Cynthia Bulik: So here's the basics, I said in the beginning we're going to talk about GWAS and I'll just give you a real sort of outline of what that actually means, and I'm skipping over like decades of research in which we just studied one or a few genes.

Cynthia Bulik: Now, what we do is we get very large samples of cases or individuals with an eating disorder, a specific eating disorder, and compare them to very large samples of controls. And those are people with no history of an eating disorder and they need to be matched on ancestry.

Cynthia Bulik: Because you want to make sure that any differences that you find are actually due to the illness and not due to the fact that you might have different ancestries present in your cases or in your controls.

Cynthia Bulik: Now, instead of just studying one or a few genes in a GWAS, we actually, we take people's DNA, either through saliva or blood and we genotype it. And then we slather millions of markers across the genome so we're actually making millions of comparisons.

Cynthia Bulik: And what we're looking for is at each one of those spots on the genome, where things differ. So here, you can see our cases have C's our controls have T's and that's a locus or an area on the genome, where they differ.

Cynthia Bulik: And that's basically what those markers do is they look across the entire genome to see where the differences between cases and controls lie.

Cynthia Bulik: The output of the GWAS, and if you've heard me talk before, you know that the reason it's called a Manhattan plot is because, if you're lucky, and if you identify a lot of loci, these towers start looking like the Manhattan skyline, and this is actually from an early schizophrenia GWAS.

Cynthia Bulik: And what you see is on the bottom, you see the human chromosomes including X way up here and on this axis, you see the significance level. And remember, I said, we were slathering a million markers across the genome, so that also means we're doing a million statistical tests.

Cynthia Bulik: So, if you think back to your statistics classes, you know, the more comparisons you make, the more likely, you are to get a false positive.

Cynthia Bulik: So, we have to correct for doing a million comparisons. So, we set a very stringent P value in order to say yep, one of these markets is actually significantly different between cases and controls.

Cynthia Bulik: And the reason that's important, it's not just scientifically, but once we identify a locus and identify the genes in that locus that might be operative. We start investing a lot of money into exploring exactly what that gene does. So we don't want to be wasting money and our neuroscience colleague's time on false leads. We want to make sure that we're confident that, that really is a causal gene.

Cynthia Bulik: And a lot of the work that you're going to talk about today is done by the Psychiatric Genomics Consortium (PGC). The PGC is the largest experiment in the history of psychiatry; we have over 800 clinicians and researchers from around the world, studying many different psychiatric disorders.

Cynthia Bulik: I am the founder, I guess, of the PGC-ED, the eating disorders working group of the Psychiatric Genomics Consortium. And this group meets whenever we can in person and frequently via Zoom more recently, in order to keep our science going.

Cynthia Bulik: Now, the main I will say leap forward in genetic research for anorexia nervosa was done by the Anorexia Nervosa Genetics Initiative (ANGI), which was funded by the Klarman Family Foundation.

Cynthia Bulik: And that took part, it was centered at the University North Carolina at Chapel Hill, where I am and then we had other groups at Karolinska Institute in Sweden, QIMR Berghofer in Australia with help from the University of Otago in New Zealand, and AARHUS University in Denmark.

Cynthia Bulik: And what that freeze did, so a freeze is when you basically say no more data, we're going to analyze these data now. And we had 33 data sets from 17 different countries represented by all of these flags and almost 17,000 cases and 55,000 controls.

Cynthia Bulik: And as you can see, if you look at the composition of that sample that came out of Freeze 2, 74% of it was due to the effort of the Anorexia Nervosa Genetics Initiative or ANGI.

Cynthia Bulik: And these are the results. And I'd like to just tag Hunna Watson here, who was the first author on this paper that came out in Nature Genetics.

Cynthia Bulik: And what you can see here, since you know how to read a Manhattan plot is that our Manhattan plot indeed showed eight loci that were above that critical line of significance.

Cynthia Bulik: Not as many as schizophrenia, where you saw 108, but this is a good start, given that our sample size of 17,000 was actually still pretty small. And what you can see here is that the loci that were significant had been implicated in other GWAS's that were done on various autoimmune, metabolic neuropsychiatric, and sex hormones.

Cynthia Bulik: So some of these loci were implicated in obesity, some of them in various autoimmune illnesses like IBD, and ulcerative colitis, and Crohn's, and again some more obesity related traits and BMI. And you have to be a little bit careful, I think that tendency when you look at your GWAS results is to tell a story right away.

Cynthia Bulik: But this is actually very early stages, we anticipate that we're going to have hundreds of significant loci, much like you saw in schizophrenia, as our sample size grows. But that's not all you can get out of it. We talked about that information above the red line. There's also a lot of information below the red line. And the way to think about it is that, as you increase your sample size a lot of those

loci are going to start sort of like rising up and becoming more significant as your sample size grows. There is still information below that red line that you can tap before they become significant. And we're going to talk a little bit about genetic correlations.

Cynthia Bulik: And, and what these are, and I think it's super important to make sure you're separating out what we typically think about as correlations, and that is.

Cynthia Bulik: For example, if you look in the clinic, anorexia nervosa and obsessive compulsive disorder are correlated on the phenotypic side or the part we actually see. But that has nothing to do with genetics. What we're talking about with genetic correlations is that you're actually looking at the same genes influencing the trait.

Cynthia Bulik: And what genetic correlation to do is, we can take a sample of someone within the group of people with anorexia in the United States, and we can compare them with someone in Germany who had IBD.

Cynthia Bulik: We have two large samples, we have two GWAS's and we can use the summary statistics that come from their GWAS to see whether there are any genetic correlations between those two traits. And this is a major advance, because in the past, we would have to have those two traits measured on the same group of people.

Cynthia Bulik: But analytically, now we don't have to do that. We can actually look at what is functionally between diseases. The genetic analog of comorbidity and this approach was actually developed by my kid, by Brendan Bulik-Sullivan, who you see here on the bottom.

Cynthia Bulik: Now we're going to start here with this big picture, and then I'm going to pull it apart.

Cynthia Bulik: What you see here is basically the genetic topography of anorexia nervosa. The way you read the genetic correlations is this red line that goes up and down the middle is zero. So that means, no correlation.

Cynthia Bulik: Everything to the right is a positive genetic correlation. So, that means the same genes influence the traits in the same directions, and I'll unpack this as we go through.

Cynthia Bulik: And on the other side, on the left side, are negative genetic correlations. So you have the same genes influencing them, but in opposite directions. And we'll go through section by section. One let's start at the very top, with the things in green.

Cynthia Bulik: So everything we're talking about on this slide is a positive genetic correlation. Same genes acting in the same direction.

Cynthia Bulik: And, just like I talked about with the phenotypic correlations, the strongest genetic correlation we saw and, in fact, one of the strongest genetic correlations in psychiatry period is between anorexia nervosa and obsessive compulsive disorder so same genes increasing risk for both disorders. We also see positive genetic correlations with other psychiatric traits. Major depressive disorder, schizophrenia, anxiety, depressive symptoms, and neuroticism.

Cynthia Bulik: And then right below that in lighter green. We see positive genetic correlations with various measures of educational attainment.

Cynthia Bulik: And this is really interesting and might lead you to rewriting your book about high educational achievement and anorexia nervosa. Because you know, there have been decades of information about you know high achieving families and putting pressure on their kids to succeed.

Cynthia Bulik: But these data suggests that there's actually a genetic correlation there. So some of that high achievement oriented-ness might actually be driven by the same genes that influence risk for developing anorexia nervosa.

Cynthia Bulik: And the next little circle really made me rewrite my book about physical activity and anorexia nervosa. So there's a positive genetic correlation between anorexia and measured physical activity.

Cynthia Bulik: And again what that means is, the same genes that influence risk for anorexia nervosa are also associated with high physical activity levels.

Cynthia Bulik: So some of the challenges that we face in getting people to reduce their physical activity as they're recovering from anorexia nervosa is actually sort of fighting an uphill battle against their biology, because they might be genetically predisposed to be highly active people.

Cynthia Bulik: The next set, as you'll see remember that red line up and down the middle everything except high density lipoprotein is over here on the left or a negative genetic correlation so.

Cynthia Bulik: That first part that we saw before with all the green dots makes perfect sense. Anorexia rests firmly in a cluster with other psychiatric disorders.

Cynthia Bulik: But less expected was the fact that we see these negative genetic correlations between anorexia nervosa and metabolic factors like insulin resistance, fasting insulin, leptin, Type 2 diabetes.

Cynthia Bulik: So the genes that increase your likelihood of developing anorexia nervosa are associated with lower likelihood of developing Type 2 diabetes, or having high leptin with one exception. And that exception is the one favorable metabolic parameter, which is high density lipoprotein. So your increased genetic risk for anorexia nervosa is also associated with increased risk for that favorable metabolic parameter.

Cynthia Bulik: And just reminding you again, because I think just because we've been doing this for so long, we tend to go back in our minds to thinking about regular phenotypic correlations remember we're still talking on that genetic level, and these are genetic correlations.

Cynthia Bulik: And then the last piece again made me rewrite my book on anorexia nervosa and, basically, these are all negative genetic correlations with body fat percentage, fat mass, waist- to-hip ratio, waist circumference, and fat free mass, all of these anthropometric measures.

Cynthia Bulik: So if you have high genetic liability for developing anorexia nervosa you also have lower genetic liability for becoming obese or gaining weight or having a large hips circumference. So we actually see negative, significant genetic correlations with anthropometric measures.

Cynthia Bulik: I'm going to throw them all together on one slide, because this sort of encapsulates what the genetic underpinnings of anorexia nervosa are. And what that means is there's this high cluster of genetic factors that influence risk for psychiatric disorders, especially OCD.

Cynthia Bulik: But we also see equally strong negative genetic correlations with metabolic and anthropometric traits.

Cynthia Bulik: So if anorexia was only psychiatric in origin, we wouldn't see these bottom two ovals we would only see these top two. The fact that we see all of these ovals on this global chart suggest that anorexia nervosa has both psychiatric and metabolic/anthropometric components.

Cynthia Bulik: So what does this do? How does this help us understand anorexia? It is perplexing to understand how people with anorexia nervosa reach and maintain such a low BMI, as I said in the very beginning, it defies biology.

Cynthia Bulik: Second, I talked about that frequent return to a negative settling point. Whether something happens metabolically or if there's a predisposition somehow to once someone gets down to that low weight their body pulls them back down. Again, this encourages us to look at metabolic contributions to that negative correlations with BMI and other unfavorable metabolic parameters and the positive genetic correlations with HDL.

Cynthia Bulik: So sort of opening up a whole new chapter on what we need to look at in terms of causes for anorexia nervosa and trying to understand this paradoxical reaction to negative energy balance. Why, when most of the world prefers or finds it more comfortable to be in positive or neutral energy balance, is negative energy balance so reinforcing for people predisposed to anorexia nervosa. Implications. So we went so far, given the strength of those findings on a fairly small sample GWAS that anorexia nervosa may best be conceptualized as a metabo-psychiatric disorder.

Cynthia Bulik: We suggested that greater attention to metabolic factors may improve outcome, as we have all encountered re-nourishing someone with anorexia nervosa and helping them to actually maintain their re-nourished weight is a very challenging, clinical undertaking.

Cynthia Bulik: It might provide an explanation for why adequate refeeding is essential for preventing relapse. When we see patients being denied for their care when they reach 80% of their ideal body weight. It's almost a guarantee, and perhaps it's a metabolic guarantee that their weight is going to plummet again.

Cynthia Bulik: And hopefully this is going to give us data at some point to understand why refeeding to adequate weights, is so important. Might also give us a little bit of insight into why FBT is effective in a lot of youth with anorexia nervosa. And that is the emphasis is actually on metabolism even though it's not directed toward metabolism. That act of refeeding, that act of making sure that you get someone up to a reasonable weight, before you back off is something that can really lead to lasting change. We think about it psychologically but there's probably something going on metabolically as well.

Cynthia Bulik: And I said it before, I'll say it again, the next step is to really dig into what the metabolic mechanisms are.

Cynthia Bulik: We're going to need more data, we're going to need a larger GWAS to really see where the different loci are and what the genes are that are implicated. But clearly this is shining the light in the correct direction.

Cynthia Bulik: Now I've been talking about anorexia up till now, but as with every other aspect of eating disorders, one size does not fit all in the genetics of eating disorders.

Cynthia Bulik: But since we haven't done Genome Wide Association Studies for bulimia, binge eating disorder, or ARFID yet, we needed to go about this in a different way.

Cynthia Bulik: And we're going to talk about polygenic risk scores (PRS). This is another technique that looks below that red line and looks at all of the information that you have available and as well as above the red line, and all of the information that you have available on a particular disorder or disease.

Cynthia Bulik: And what you do is you take a sample on which you've done a Genome Wide Association study, like the one that you just saw and you create a single score.

Cynthia Bulik: It is a single score of an individual's polygenic load. How many of those risk alleles do they have? How high is their genetic risk for anorexia nervosa?

Cynthia Bulik: You can then take that calculation and you can apply it to a second sample, or an individual and basically ask for a whole bunch of people who weren't analyzed in that first sample. What is their polygenic risk for anorexia nervosa?

Cynthia Bulik: And to be clear, this is not a genetic test, this is just based on what you know today. How strong your GWAS is and what an individual's pathogenic risk is.

Cynthia Bulik: The future of what we can do with polygenic risk, and this paper down here if you type in the Pubmed ID 33052393 that will take you straight to a really good paper about polygenic risk scores. In the future, they may help us improve risk assessment by combining polygenic risk scores with other measures of risk.

Cynthia Bulik: They may be able to help us screen for mental health disorders in the population. They may help us in making a diagnosis, or clinical decisions when someone walks into your office for the first time today showing signs of anorexia nervosa.

Cynthia Bulik: You don't know whether they're at increased risk of developing a severe, or a severe and enduring case that's something that PRS might help us be able to distinguish as they become more refined.

Cynthia Bulik: Likewise, are certain psychiatric PRSs associated with treatment response will we ultimately be able to say.

Cynthia Bulik: Based on your polygenic risk scores, and perhaps some other indices, you might respond better to this treatment than to that treatment.

Cynthia Bulik: And that would keep us from wasting time with that treatment, if we know on a biological level that the person is more likely to respond to the other treatment. And one more time, are PRS associated with adverse physical health outcomes and mental illness.

Cynthia Bulik: And one of the ones that I'm very interested in is whether you would be able to predict, on the basis of polygenic risk scores, who is at risk for developing extreme weight gain in anti-psychotic medication.

Cynthia Bulik: Not so much in anorexia populations, but in people with schizophrenia and bipolar disorder.

Cynthia Bulik: So here's what we did. To say, are there differences on the genetic level between anorexia, bulimia, and binge eating disorder we looked to the UK biobank in order to apply risk scores and I'm going to go through this a little bit quickly, because I want to spend as much time as possible on what you're using in the clinic.

Cynthia Bulik: These are the number of people they had 768 anorexia, 423 bulimia, 561 binge-eating disorder.

Cynthia Bulik: And we see another type of topography like I showed before with the genetic correlations. But here we're looking at odds ratios of different disorders and we're going to start again with psychiatric disorders. This time, everything to the right is a positive odds ratio.

Cynthia Bulik: Everything to the left is a negative odds ratio and the filled in dots are the significant difference, but really we're going to be looking at the direction of effect here.

Cynthia Bulik: And what I want you to see in this pretty much, we're seeing some of the same patterns across the three eating disorders. That they all tend to fall to the right of that 1.0, which is the center line. Meaning that we have positive odds ratios for all of the psychiatric disorders, again suggesting that anorexia, bulimia, and binge-eating disorder are firmly anchored in the psychiatric realm with some differences.

Cynthia Bulik: Then, when we go a little further and we've looked at the metabolic realm, we see different patterns. And I think the one that stands out the most is the binge-eating disorder, which is the dark purple circles.

Cynthia Bulik: And even though they're not significant, it's the pattern that is different. So we see elevated odds ratio for Type 2 diabetes, reduced for high density lipoprotein cholesterol, and then elevated for fasting insulin.

Cynthia Bulik: So again, what we had seen in the genetic correlations was basically the opposite pattern of anorexia nervosa and that also showed up here. So here you see, what do you see? Some decrease on fasting insulin.

Cynthia Bulik: And then, this is where we saw the most separation and everything in the light blue is anorexia nervosa to the left. So reduced odds ratio, totally consistent with what we saw in the genetic correlations, but the difference comes especially with binge-eating disorder, where we really see stronger associations with overweight, with obesity, with childhood obesity, with BMI. So I guess the take home message from this study, without going into the nitty gritty, is that anorexia, bulimia, and binge-eating disorder have clear genetic parallels when it comes to their relationships with other psychiatric disorders.

Cynthia Bulik: But where they separate is in their underlying genetic relationships with metabolic and anthropometric, or body measurement traits, really giving us the first glimpse of how these three disorders might differ on a genetic level.

Cynthia Bulik: So one size does not fit all eating disorders. AN, BN, and BED broadly similarly associated with polygenic risk scores for psychiatric traits.

Cynthia Bulik: Exceptions we didn't go into the details, but there were some difference with ADHD and autism spectrum disorders. ADHD was already significantly associated with binge-eating disorder. The differences lie with those polygenic risk scores for metabolic and anthropometric traits.

Cynthia Bulik: And, might we be able to use polygenic risk scores in risk models to predict diagnostic crossover and outcome? Remember that first bubble plot that I showed you?

Cynthia Bulik: If we knew polygenic risk for that day one, when people were registered would we be able to say yes, this person is likely to remit, this person is likely to continue to have anorexia, this person is likely to cross over to bulimia nervosa and then tailor interventions accordingly?

Cynthia Bulik: Why?

Cynthia Bulik: Ultimately, what we want to do is, we want to create an empirical classification system based on genetics. Right now, the DSM-V, the ICD 11 to be are not really based on underlying genetics of these illnesses.

Cynthia Bulik: But our approaches very much can help us figure out what belongs where. Excuse me. It may help us predict the course of illness and tailor treatment accordingly. It also might help us properly position atypical anorexia relative to other eating disorders. So atypical anorexia, in a simplified way of explaining it, is having all the symptoms of anorexia nervosa except not being at low weight, although that is an inadequate explanation.

Cynthia Bulik: And the question is, is it actually anorexia, the same genetic illness at any weight, or are there actually differences in people who tend to be on the low side of the BMI spectrum?

Cynthia Bulik: It will help us properly position ARFID subtypes relative to other eating disorders, but also relative to other psychiatric disorders and ultimately move toward personalized medicine approach to treatment, instead of a “one-size-fits-all.

Cynthia Bulik: Also, hopefully, and another one of our goals is drug repositioning or drug development based on the genetic results. We have no medications for any eating disorder that are actually based on the disorder biology, and hopefully that's where we'll be going as our GWAS become stronger. And ultimately, eliminate mortality and decrease the lives lost from the eating disorders.

Cynthia Bulik: Now critical limitation, much of the work that's been done so far has been done on European ancestry populations. And in part, that's an artifact of where the analytic techniques and the genotyping was a decade ago.

Cynthia Bulik: That is no longer an issue. We now have the ability to study using GWAS, trans-ancestry populations. And it is critical to have representation from diverse populations to ensure that we don't perpetuate or amplify health disparities. And that also includes making sure that men are involved in our Genome Wide Association Studies.

Cynthia Bulik: But the goal, ultimately, is not just to identify the genes, but to fully account for the impact of both genes and environment and how they act, and how they co-act to influence risk for eating disorders.

Cynthia Bulik: And some of the domains of diversity that are really important to have represented in our GWAS are biological sex at birth, gender identity, weights and shapes, genetic ancestry, culture, and socioeconomic backgrounds.

Cynthia Bulik: Now, what do you do with this information today in your office?

Cynthia Bulik: Science communication has become, unfortunately, a political issue. Anti-truth and anti-science are rampant and the internet doesn't help.

Cynthia Bulik: It is the scientists' responsibility to interpret and contextualize the information that comes from our science. It is the clinicians' responsibility to just have a general understanding, and assist patients and families with weaving the science into their own personal narratives of their experience.

Cynthia Bulik: And there is a very important role for genetic counseling in eating disorders, but as of yet, we still don't have a strong, not much at all actually, have genetic counseling for these disorders.

Cynthia Bulik: So this is a way when parents or patients come to us, when groups come to us and say, help us understand.

Cynthia Bulik: This is a simplistic, but helpful relatable model of how to explain the impact of genes and risk, genes and environment. And I break it down into a card game that everybody basically knows the four suits of a card game. And I say, these are the four domains that influence your risk for developing an eating disorder. The spades, for example, are your genetic risk.

Cynthia Bulik: But something we don't study because it's actually harder to study, is there are also genes that are protective. And I think it's very important for people to remember, that you could have a high genetic predisposition for anorexia nervosa and maybe that came from one side of your family.

Cynthia Bulik: But you only get 50% of your DNA from your mom or your dad, and the other 50% might actually have some genes that are protective, or that buffer against that genetic risk. So you have to put that into sort of your narrative or your conceptualization of risk as well.

Cynthia Bulik: And then, alongside that you have environmental risk factors. So anything out there that we know can influence your risk to maybe go in that first diet, or to experience your first binge. You know, things like bullying, and things like engaging in sports or activities that demand low body weight. Any kind of teasing, any of the environmental risk factors that could influence, or maybe even activate your underlying genetic predisposition.

Cynthia Bulik: And then the fourth group is environmental protective factors. So yes, you might be exposed to some of those environmental risk factors, but they too might be buffered by environmental factors. You know if you're able to come home and talk to your parents about being teased and they can sort of help you work through that and develop your defenses.

Cynthia Bulik: You know that can act as a protective factor and buffer some of that environmental risk and, in fact, some of the environmental protective factors can also buffer some of the genetic risk.

Cynthia Bulik: But the other thing is, you can have fairly low genetic risk for an eating disorder, but if you are, if you just have environmental risk factors piled on high, that can probably make someone who actually has low genetic risk for an eating disorder, develop an eating disorder.

Cynthia Bulik: But at the core of it, you're dealt a hand, and the black cards, the spades, and the clubs, you get them when you're born. Those are the genes that you have with you at the moment of conception and they stay with you, to the very end.

Cynthia Bulik: And then you pick some cards, and that includes some environmental and some environmental protective factors. And at this stage, we can't do anything about the spades and the clubs so they're sort of fixed. The only thing we can do is influence the environmental risk factors and environmental protective factors, that's what psychotherapy does.

Cynthia Bulik: That's what we do when we try to make our families healthier places to be. And that's really where we can focus our interventions at this point. Hopefully, from the work that we're doing, we will be able to perhaps find some drug war targets that we can use to not change the genetic factors, but to influence their expression.

Cynthia Bulik: Now, the one thing that I'm going to add to this is, there are some conditions where, if you have a certain gene variant you're going to get that illness, or you'll have a 50% chance of getting that illness like in Huntington's.

Cynthia Bulik: We haven't found any rare variants or genes like that, yet, that influence risk for eating disorders. So I'm fairly comfortable telling families and patients that it really is the spades, and the clubs, and the hearts, and the diamonds, that you need to think about when you develop your own narrative about how genes and environment influence your eating disorder.

Cynthia Bulik: Now, how can a genetic counselor actually assist with this?

Cynthia Bulik: Genetic counseling is a really important area in which we need to develop more people who know how to do it for psychiatry and, within that group more people who can do it for eating disorders. Genetic counseling for mental illness helps alleviate stigma and shame, it can correct misconceptions about the condition, and it can prepare family members to intervene if necessary, if there's a high risk of their offspring developing a condition.

Cynthia Bulik: It definitely promotes help seeking behaviors and even just sort of baseline evaluations.

Cynthia Bulik: Because I think there's a little bit. People become a little hyper vigilant if they know that there might be an increased risk of their offspring having an illness.

Cynthia Bulik: But there's never any harm in getting a baseline evaluation, and having another professional cast their eyes over your child to see if there appears to be any risk factors emerging.

Cynthia Bulik: And, and it promotes help seeking behaviors. There's only been, I think, as far as I can tell one study on genetic counseling and eating disorders. And that was done by Julian Michael, who was at UNC Greensboro, who was a genetic counseling student and she surveyed 107 individuals who had a personal history of an eating disorder.

Cynthia Bulik: And what she did is, she had them estimate what they thought the risk to their children was, and, and then she also gave them a vignette about a genetic counseling session with someone with an eating disorder, and saw how it influenced their perceptions of an eating disorder. Now the most important thing, the one result that just really stood out is, that every single participant who had an eating disorder overestimated the risk of their children developing an eating disorder, so the empirical data suggested it was 7.5% increase risk they estimated 43% higher for sons, 57% higher for daughters, way high.

Cynthia Bulik: And 100% of them over estimated the risk to their daughters. Again, because we all have this sort of internalized perception of eating disorders, being more frequent in women. And I think that bias also showed up in these results.

Cynthia Bulik: And then, this is the pre- and post-imagined experience. So you know this video yet basically talked about how it talked them down from their over estimations. It talked about what the actual estimations were, and just gave them a lay but accurate understanding of the role of genes in eating disorder risk to their offspring. And without going into every single line, I think again, this is a pattern that is incredibly obvious that after that imagined experience their perceptions all moved toward the healthier direction. So eating disorders were less stigmatized, there was less shame, they were less looked down upon, there was less parental guilt.

Cynthia Bulik: And they felt like someone with an eating disorder, is less likely to be treated differently, because they have an illness.

Cynthia Bulik: And I think this particular one here, the guilt measure is one that's just so important to me because I've been in this field, for a long time, and I have seen parents be guilted, or feel guilty, or be guilted about their children having eating disorders, you know from day one, when I started in this field, and I think this approach can really help reduce guilt in parents, whose children have an eating disorder.

Cynthia Bulik: And just real briefly, the one thing we don't want to do is, we don't want people to have genetic guilt, like to start feeling guilty about passing on their genes. Because if there's one thing we have no control over in this world, it's you know what pops out in the sperm and the egg and which genes get a sorted and turn into a person.

Cynthia Bulik: And this is just a little commentary from one of the participants. “Wow! Just reading this has validated so many things I felt, like that it is genes and environment and that guilt is so common in people with eating disorders, I feel like people need to hear and understand this—both people with the eating disorders, with eating disorders and the public.”

Cynthia Bulik: I agree with her on that one.

Cynthia Bulik: And then, our responsibilities, so with my scientist hat on it's my responsibility and our responsibility, not just to do the science, but to package, the information for patients and families in a digestible way.

Cynthia Bulik: With my clinician hat on, it's our responsibility to make an effort to integrate genetics into our own case conceptualization and develop comfort with answering our patients’ questions.

Cynthia Bulik: And you know I think, I think we do to some extent, always ask if there's someone in the family who's had an eating disorder, or OCD, depression, or anxiety disorders. But also thinking about those spades and clubs and hearts and diamonds.

Cynthia Bulik: And the relative contribution of each, I think this sort of a useful way to start assorting in your own mind, what the different factors are that have influenced the person's development of an eating disorder who's sitting in your office.

Cynthia Bulik: We have to know our limits. If we live in a country with genetic counseling, like the United States, make use of your colleagues and, if not find whatever resources you can for patients.

Cynthia Bulik: You know their family groups all around the world, FEAST is one of them that you can just connect with and find other parents who have gone through, what you're going through.

Cynthia Bulik: And, just like everything else we must never perpetuate misinformation about eating disorders.

Cynthia Bulik: And I think that's really hard for us. And it's hard, because it's much more difficult to get people to unlearn things than it is to get people to learn things.

Cynthia Bulik: And we have to get to the point. Where we're practically bombarding people with accurate information in order to erase all the misconceptions that have developed about these disorders, over the course of decades.

Cynthia Bulik: Here's some messaging do's and don'ts. And just to help out, first off genetics is just one piece of the risk puzzle. All or nothing thinking goes out the window so whatever you hear someone say genes or environment or nature or nurture, just stop them and gently have them replaced those or's with and's.

Cynthia Bulik: It's hard for some people to understand probabilities and that really is what genetics is all about. So and again that's why I use those four cards, because I think it really helps people put probabilities in their head, rather than all or nothing thinking.

Cynthia Bulik: As I mentioned, steer people away from genetic destiny. There's no such thing as genetic destiny and eating disorders, and again genetic guilt, we have no control over what comes out.

Cynthia Bulik: And also we're not saying that eating disorders are genetic and not psychological, they are both. We absolutely will always still have to do lots of psychological work in the treatment of eating disorders, but hopefully we'll be able to bolster that by intervening on the biological level as well.

Cynthia Bulik: And genetics simplification, if you ever see a headline that says something like you know I found the gene for eating disorders, you know they're lying.

Cynthia Bulik: There will never just be one gene, there will be hundreds of genes that influence risk for eating disorders and, as mentioned before, also a lot of buffering genes that might counteract some of those effects.

Cynthia Bulik: And I can't see my last point. So whatever the last point is, I suggest you take a look at it. Now, this is just one little quick slide.

Cynthia Bulik: And this is why polygenic risk scores are not a genetic test. What these two curves show you are the polygenic risk scores in red of people who have a disease, and in blue the polygenic risk scores of people who do not have that disease.

Cynthia Bulik: And maybe out here, we might find some groups of people who only have the disease, but, as you can see there's a lot of overlap.

Cynthia Bulik: So just saying, someone has a high polygenic risk score all these people here might have a high polygenic risk score, but they don't have the disease. So, in no way does this approximate a genetic test.

Cynthia Bulik: And if anyone tries to sell you a genetic test for anorexia nervosa please don't waste your money, because that's not where we're going and there is no genetic test for anorexia nervosa or any other eating disorder.

Cynthia Bulik: And then, just in my last minute we have now transitioned from ANGI to EDGI. We have funding from the National Institute of Mental Health to broaden ANGI beyond anorexia. And we're now, including anorexia, bulimia and binge-eating disorder. We're hoping to be able to add ARFID. And in some of the other countries where EDGI is operative we're also including people with atypical anorexia nervosa. So hopefully we're eventually going to have the whole DSM represented in EDGI.

Cynthia Bulik: Our goal is 100,000 people with eating disorders, plus controls. We're diversifying our samples to make sure that we actually reach those goals.

Cynthia Bulik: Everything is online, so we now do digital consent and questionnaires and simple, at-home, COVID-safe saliva collection. In the past, when we had to draw blood, these were pretty hard studies to do. But the field just advances so fast that saliva works just as well now.

Cynthia Bulik: We're engaging the advocacy community and we're engaging clinicians. And we are not just looking at genes, and we are not just looking at eating disorder. So our online phenotyping, the questionnaires cover life events, trauma, physical activity, OCD, alcohol and drug use, tobacco use,

anxiety, depression, and their treatment history. So we're getting a full picture of everyone who participates at EDGI. So we really can look at how genes and environment act and co-act.

Cynthia Bulik: Visit our website it's www.edgi.org we have it in English and in Spanish in the US. And we've globalized, so the NIMH is funding US, New Zealand, Australia, and Denmark. The National Institute for Health Research is funding EDGI UK. The Swedish Research Council is funding EDGI Sweden.

Cynthia Bulik: We're about to start EDGI Mexico with Eva Trujillo in Monterey. We have a small grant to start EDGI Taiwan, and we're working on Italy, the Netherlands, and Canada so and any other countries out there, give me a call drop me an email, because we really want to globalize the study.

Cynthia Bulik: And these are the people that keep it running for whom I'm deeply grateful. Everyone on the UNC side as well as the whole eating disorders working group for the Psychiatric Genomics Consortium.

Cynthia Bulik: And that's us follow us on Twitter and go up to the website take a look at EDGI anything you'd like to do. If you have any questions, drop me an email or tweet me! Again thank you so much.

Cynthia Bulik: And now it's time for questions.

la-shell_johnson@med.unc.edu: Sorry, no that's great. Thank you so much, Dr. Bulik for a wonderful presentation. We are now going to begin our question and answer segment.

la-shell_johnson@med.unc.edu: I just wanted to remind you all that you will receive the handout from today's presentation, along with the evaluation for you to fill out immediately after the webinar.

la-shell_johnson@med.unc.edu: Our first question says, thank you for a fantastic presentation. How do you deal analytically in these genetic studies, with the fact that many individuals have lifetime diagnoses of more than one ED diagnostic crossover? How are such individuals bin if you are trying to differentiate genetic signatures BN from AN for example?

Cynthia Bulik: Excellent question.

Cynthia Bulik: Yes, so. We do it two different ways, and one way, that we do it is a hierarchy way. With AN, if someone has had AN at any time in their life they get put into the AN bin to use your terms, and then the same thing a person has had BN and BED then they get put into the BN bin.

Cynthia Bulik: But then we also sort of rearrange it in other ways, so they're not hierarchical and we can include anybody who's ever had anorexia, anybody who's ever had bulimia, if anyone has ever had BED in separate bins knowing that there might be some representation of each person in more than one bin. But in most for most intents and purposes, we use that diagnostic hierarchy where, especially with AN, people who have had AN at any time in their life, representing the core group.

la-shell_johnson@med.unc.edu: Thank you so much Dr. Bulik for your response. The next question reads, “Are there individuals whose eating disorders are more influenced by genetics, than environmental factors and vice versa? In other words do all individuals with AN get influenced by these genetic markers loci in the same way?”

Cynthia Bulik: I love these questions. That's another great question.

Cynthia Bulik: David Clinton and Andreas Birgegard in Sweden have a study going on, if you remember that bell curve I showed, you of the polygenic risk scores. They have selected people with anorexia nervosa and we're starting with anorexia because that's what we have the GWAS. Who have, who are in the top decile polygenic risk scores and from the bottom decile polygenic risk scores. So those people have both develop the illness, at some point in their life.

Cynthia Bulik: But their underlying genetic risk is very different. One being the highest possible bin, one being the lowest possible bin. And they're doing intensive interviews and a qualitative approach to figure out what's different. How does their eating disorder differ? How do their environmental triggers differ?

Cynthia Bulik: Because theoretically what we imagine is that someone with high polygenic risk doesn't need a lot of environmental perturbation to push them over the hill and develop the illness. Whereas someone with low genetic risk might actually need a whole bunch of environmental factors to push them over the hill, but that's just theory.

Cynthia Bulik: But now that we have genotypes, we can actually look at that. I do not have an answer for you, but I do have a promise that, that study is underway, and once we get some results and get it published, well I'm sure we'll do a blog post on it and let people know what we found.

la-shell_johnson@med.unc.edu: Thank you so much for that response. We have one more question here.

la-shell_johnson@med.unc.edu: “To identify genetic risk factors to eating disorders, more broadly, in case conceptualization, would it be helpful to include questions about those metabolic markers? Do you have relatives who have struggled with insulin resistance, not just psychiatric family history?”

Cynthia Bulik: Another good question. Yes, in fact, that is, a direction that we definitely need to go in. One of the things that we can do in Sweden and in other Nordic countries is connect our genetic data with the national patient registries. So, we would actually be able to without even asking the person that question, because we don't always know about all of our families medical illnesses.

Cynthia Bulik: We would be able to connect to their family’s medical data and see if there is increased risk of some, or increased presence actually of some of those traits in the medical records in the diagnoses so that's an excellent idea and that we know who you are, so that I can attribute that idea to you when we do that research. Because it's a, it's a great idea, because the expectation is that we would see differences in the family members of people who had different eating disorder diagnoses. So, I think that's a very testable hypothesis, and one for which I am grateful.

la-shell_johnson@med.unc.edu: Thank you once again, Dr. Bulik. And we will have enough time to address our last question. That question reads, “I’ve never heard of genetic counseling, I am very interested. How did you get into this field and what did you master in?”

Cynthia Bulik: Yeah well. I'm not a genetic counselor.

Cynthia Bulik: I kind of wish I did have a side degree in that. It is a wonderful field, and it really helps people determine how much at risk their children are you know, for some diseases that are strongly genetic. Where your child might have a 50% chance of developing the illness. You know they do a great job talking through that with you, with your partner, making decisions about reproduction and for other disorders, where there's a much more gray area like anorexia.

Cynthia Bulik: You know, obviously in the study that Julianne did people grossly overestimated the risk to their kids. And we have patients come to us all the time, who were saying I don't know if I want to have kids, because I don't want my child to go through what I went through. But that's the assumption that there's like 100% risk which is way off base. So, I think that it really does, it helps people put things in context, give them some real numbers, understand probability, and helps them plan what their

reproductive life is going to be like. And, there is a subset of people who are genetic counselors, who are psychiatric genetic counselors, we just don't have a lot of them yet, who specialize in eating disorders.

la-shell_johnson@med.unc.edu: Thank you once again, Dr. Bulik. This was amazing. We truly appreciate everyone attending today's presentation. We have addressed all of the questions.

la-shell_johnson@med.unc.edu: We want you to definitely be on the lookout for the evaluation and the handout from today's presentation. Dr. Bulik if you have any last words then we can go ahead and adjourn.

Cynthia Bulik: Just everybody go up and take a look at edgi.org and spread the word. We want to get as many people involved as possible, so we can get some great answers and improve treatment for all eating disorders and thanks for your time.

la-shell_johnson@med.unc.edu: Thank you all as well, and thank you all for attending today's webinar presentation.