**Capturing Complexity: The Scientific, Societal and Ethical Meanings of "Environment" in Genetic Research**
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***Panel 2 Speakers (in order of appearance)***
Hank Greely (HG)
Eric Turkheimer (ET)
Andrew Perrin (AP)
Ruth Ottman (RO)
Audience Question (AQ)
Sir Michael Rutter (MR)
Mildred Cho (MC)

***Introductory Remarks***

**HG**: Our next section talks about "Considerations in Measuring 'E.'" We have three speakers: Eric Turkheimer from the Psychology Department at the University of Virginia; Andrew Perrin from the Sociology Department at the University of North Carolina; and Ruth Ottman from the Genetic Epidemiology Department at Columbia University. Eric, it's all yours.

***Panel 2***
***The Costs and Benefits of Lousy Measures of the Environment***

**ET**: Thank you; it's nice to meet you. Twelve minutes really focuses the mind so I'll get going and apologize for the slightly facetious title. *(Slide 1)* This is a slide that is from a study that was published a few years ago that's not really the point of what I'm talking about today per say, but this is a study we published showing, as Michael was saying a few minutes ago, that the hereditability of intelligence varies as a function of socioeconomic status in a way that very poor families, the environmental side seems to predominate, and in better-off families, the genetic side seems to predominate. As I said, the details of that study are not the point, *(Slide 2)* but the point is the most common question I've been asked about that study since that time. The study made it into the popular press. I got a lot of general questions about it; most of the questions are about environment and in particular about socioeconomic status. I'm a psychologist. Interestingly, socioeconomic status (SES) is a tradition boudoir *[sic]* developmental social science. It's viewed as a big, coarse, not very interesting, not very detailed, as Sir Michael was saying, not very proximal measure of the environment. I mean kids aren't affected by their socioeconomic status; they're affected by a million little things that take place within the context of their socioeconomic status. So the question is, ok so you showed that there's this difference between poor kids and rich kids, but what does it consist of? What do you think the components are? Is it the schools, is it nutrition, is it medical care, is it parenting? What could you do to break down this big thing called socioeconomic status into its individual parts? And my answer to that question about whether I think that process might go ahead is I don't really think its possible, and I don't really think that research enterprise is ever going to go anywhere. And what I want to talk about in my remaining ten minutes is why I think that's true.

*(Slide 3)* I'm going to talk about it in terms of an idea Ken introduced which is something called the nonshared environment project. The nonshared environment, just very quickly for those of you who haven't been exposed to it, are aspects of the environment that make children raised in the same family different from each other. We often think of environment as family environment, but kids in the same family are very different and that's in part because different things happen to them. And when you do traditional behavior genetic studies using twins or adopted children, it's been a well-established finding for a long while that usually the largest component that comes out is this nonshared environment. Even identical twins raised in the same family are quite different.

*(Slide 4)* Again, I somewhat facetiously a few years ago sort of named that as the third law of behavior genetics that most variability in human behavior cannot be predicted from either genes or environment. So you have identical twin raised in the same family, they're still different in unpredictable ways. *(Slide 5)* The fundamental case I want to make is that thinking about the nonshared environment and what the components are that go into the nonshared environment is the paradigmatic problem in human scientific psychology. That's a big statement, but that's the fundamental problem we're facing here. We have this *big* variance component like, socioeconomic status is not exactly a variance component, but a big coarse variable or in this case the nonshared environment which we can observe on a gross macro level, but we want to observe it in its individual parts. And what happens when we do that? *(Slide 6)* Robert Plomin famously specified his three-step research program to understand what nonshared environment is. He suggested that we quantify its variables, it's big, that we identify *specific* family variables that make up the nonshared family environment like the individual parts of socioeconomic status and third, that we establish the causal association between within family environment and behavior.

*(Slide 7)* And guess what? It didn't work. Mary and I conducted a meta-analysis, a quantitative review, of studies where they actually measured family variables and related them to the *specific* outcomes in individual siblings. And to make a long story short, if you're trying to establish a difference in depression in terms of differences in the parenting styles that the parents provide to the two siblings, you can't explain anything. It dries up and blows away. The average amount of variance explained in studies like this is somewhere between two and four percent. So the individual variables don't add up to make the big variance component.

*(Slide 8)* Another example of the same thing is a well-known and justifiably famous study called the NEAD Study, that is the Nonshared Environment and Adolescent Development study, which was conducted by Robert Plomin, probably the greatest behavior geneticist of his generation. and Mavis Hetherington , a colleague of mine who's probably the greatest development psychologist of her generation, designed a beautiful study of twins, siblings, half-siblings and unrelated adopted siblings to explain what was it that made kids raised in the same family so different from each other. And I obviously can't tell you the long story here, but they didn't find anything. There was nothing there. They were just different in ways that appeared to be random, but if you tried to tie it down to specific variables in terms of how they were raised, it didn't work.

*(Slide 9)* Why does this happen? Why is it that we can observe things in the macro, but can't observe it in the micro? *(Slide 10)* Let's just think for a minute about the way the environment really works. Back in the bad old days, we might have had a very oversimplified causal model about how the environment worked to determine personality; I took this from a personality talk I sometimes give. I mean I have some psychoanalytic leanings myself; I don't mean this slide to demean psychoanalysis, but the causal model is wrong here. You know, the old view that the way you're toilet trained determines your personality, it doesn't work. There aren't big, monolithic, uni-dimensional causes in the environmental realm. *(Slide 11)* A more typical social science model is what I think of as a multiple regression model. Well, we've got a lot of small causes, and you chunk them all in your multiple regression and hope that they all add up in some linear way to explain personality. And that doesn't work either. The reason it doesn't work is that causation doesn't really work that way in the environment. *(Slide 12)* If anything, the causal model that underlies the environment might look something like this. You've got your individual predictors over there on the left and a very complex, uncontrolled developmental process through which everything flows to come out with personality on the outside, on the other end. And the important thing from the point of view of what I'm talking about here is that despite the fact that it's very hard to trace the individual causal effect of toilet training through the system, it's nevertheless possible to *add* across the complexity of the entire causal system and detect some residual correlation across the whole *span* if you use a coarse variable like socioeconomic status.

*(Slide 13)* So I want to conclude my argument that suggesting that this basic model of in complex causal systems not being able to detect the effect of individual effects, but only being able to detect the effects of gross macro variables applies to the genotype just as much as it applies to the environment. And it's interesting to consider how Plomin's nonshared environmental three-step research program transforms itself into something a little bit more familiar.

*(Slide 14*) So instead of starting by quantifying the effects of the nonshared environment, we start by quantifying heritability, the genetic background of a variable. Instead of identifying the specific within family variables that might account for the nonshared environmental effect, we identify specific QTLs [quantitative trait loci] that might make up the big genetic effect. And finally, we identify the causal associations between within family environment and behavior and transform that into the casual associations between QTLs and behavior, and we wind up with the Genome Project. The structure of the Genome Project is essentially the same as the structure of the Nonshared Environment Project. *(Slide 15*) We start with a famous variance component, that is the heritability of behavior, and try to break it down into its individual allelic effects.

*(Slide 16*) By the same token the causal models map onto each other. We started with the Big Environmental Cause Model which transforms into something called *(Slide 17*) the One Gene One Disorder, or OGOD which Robert Plomin named it, Model where a single major locus might affect an outcome. OCEAN referring to the big five model of personality, just by the way. *(Slide 18*) The Complex Environment Causation Model, the multiple regression model, maps onto *(Slide 19*) the QTL model where we have multiple QTLs which we *hope* might add up, as in a multiple model to the full genetic component except, of course, they don't. *(Slide 20*) Why don't they? Well, because in fact, the causal model underlying genetic causation is just as

complex as the causal model underlying environmental causation. *(Slide 21)* You have genotype, just like the environment, has its effects *through* the complex, uncontrolled course of development, and it's just as difficult, just as impossible if you ask me, to find the individual additive causal effects of any of the loci as they proceed through the developmental model, but nevertheless, you can still detect *correlations* that *span* the complexity using twins; you just can't break them down.

*(Slide 22*) So my conclusion is that environmental and genetic causation are more alike than they are different. Both of them are detectable when measuring badly. In the environment, it's detectable when you use large scale, vulgar, not very informative measures like socioeconomic status. In genetics, it's possible to detect them when you use population genetics, big, coarse measures of what we call the genome using twins and adoptees. Both of them are hard to detect when they're measured well.

*(Slide 23*) And I'll conclude with, and Ken introduced this, that what Plomin has called the gloomy prospect is true: "That the salient environment might be unsystematic, idiosyncratic or serendipitous events such as accidents, illnesses or other traumas." And Plomin concluded that, "Such capricious events however are likely to prove a dead end for research. More interesting heuristically are the possible systematic sources of differences between families." Well my response to that is that wishing don't make it so. And I'll leave it there. Thank you.

***The Undertheorized Environment: Sociological Insights for Behavioral Genetics***

**AP**: *(Slide 1)* It's always important to use different software just to confuse the organizers. Thanks very much. I feel very humbled to be a part of this remarkable group, and I think having just listened to Professor Turkheimer's talk, that actually there are some really interesting synergies going on here.

*(Slide 2)* I want to begin just by acknowledging three people that have been very important to my own thinking on this topic. One is my coauthor, terrific grad student at UNC, Hedwig Lee. And then my colleagues, Guang Guo and Michael Shanahan, both of whom are a lot less pessimistic than I am about integrating genetic information into sociological thinking, but they've really helped me in thinking these problems through.

*(Slide 3)* But I want to start with my favorite behavioral geneticist, Oprah Winfrey, who said on her visit to Johannesburg in June of 2005, "I feel so at home here….I went in search of my roots and had my DNA tested, and I am Zulu….I'm crazy about the South African accent. I wish I had been born here." Now Oprah Winfrey was born in 1954, within the first six years after the beginning of the brutal apartheid regime, and of course had she been born in South Africa, her career would have been tremendously different. I am fascinated by the way that she argues for the claim that 1) she is Zulu and 2) this is way she feels so at home in post-apartheid South Africa.

*(Slide 4)* And so before I continue I just want to say that I am essentially a sociological theorist; I am a bit of an imposter here. My interest really is in the ontological claims that underlie our

ideas about genetic causation for behavioral traits. I'm interested, that is, in the social theory that underlies genetic claims both by geneticists, but also by the lay public, that is how people interpret claims for genetic causality on behavioral outcomes.

*(Slide 5)* The central question I want to address is how should social scientists understand and evaluate claims for genetic origins of behavioral traits? *(Slide 6)* And a closely linked question going the opposite way is what can sociological thinking, tenets drawn from sociological theory, contribute to the program of behavioral genetics? And unfortunately within my field of sociology, most of the people that approach this at all take one or the other of these two approaches. (*Slide 8)* On the left, the "hear no evil" approach which is simple dismissal of claims for genetic causality on epistemological or just ideological grounds. Or alternatively, on the right, the "hook, line and sinker" approach, the uncritical incorporation of genetic logic into social science, essentially discarding the theoretical baby with the bathwater.

In my mind, both of these ought to be rejected for good theoretical reasons, and in instead what sociology ought to be able to contribute is precisely this theory of the environment. In other words, the social environment is precisely what sociologists both ought to care about and ought to be good at measuring and thinking about, and perhaps that's what we can offer to behavioral genetics.

*(Slide 9)* So with that in mind, I want to offer five sort of criteria drawn from sociological theory, that we can use for evaluating the scope and nuance of measurements of environment or thinking about environment within genetic studies. *(Slide 10)* The first criterion, again remembering these are ontological claims, not measurement claims, the first criterion *[sic]* is that environment should be conceptualized as potentially enabling as well as constraining outcomes. And if you think for example about the common concept of an individual's genetic potential for a given trait, whether that's height as in the two figures on the screen or whether it's something similarly linear but still far harder to conceptualize, say intelligence, we have to recognize that it's impossible to verify the existence of genetic potential, again as an ontological claim. Genetic potential is *endogenous* to the theory, that is it has to be assumed in order to then be investigated. It's equally possible, speaking ontologically, that organisms have a genetic mean which might be either be enhanced or reduced by the environment. Recognize that there are measurement issues, but one of the nice things about being a theorist is that you don't necessarily have to worry about implementation.

*(Slide 11)* The second criterion I want to offer, which I like to call the paradox of reform, is that we need to recognize that decreased social control in one domain may actually induce increased social constrain in other domains. And to be a little crude, I like to call this the girdle effect, hence the picture on the screen, where if social control is pushed at one point, it puffs out somewhere else. This insight is throughout sociological theory, from Lou's [inaudible] discussion that dissonance strengths the solidarity of in-group, Max Weber's popular democratic movements in reinforcing democracy, Fusco's examination of the irony of prison and medical reform; it's throughout sociological theory. It's therefore important to recognize that sociological movements that are characterized by more freedom, in some absolute sense, may not actually provide greater individual autonomy. And if that's the case, moving into the genetic realm, we need to recognize that traits that are exhibited more in societies that tend to be freer

are not necessarily more purely genetic in origin. More generally, a given cause may have paradoxical or even contradictory effects which are conditioned upon other causal factors. And in fact I'm going to show you, I don't remember if there is a diagram, I'm going to make a claim that's very similar to Professor Turkheimer's complex causation model that's based on this idea.

*(Slide 12)* My third criterion I want to offer is that both environments and genetic potentials must be understood as nested and cross-cutting in potentially complex ways. I too got a little bit of press for this paper, and they asked me for a real world example, and coming from North Carolina, of course basketball appreciation is the right one. Environments interact with and exist within other environments, and well beyond individuals simply selecting into favorable environments, people actually strategically *produce* favorable environments. It's not just the production of environments; of course plants produce their own environments too. What's important is here is the *strategic* production of environments, that people seek not just to enter environments that are favorable, but actually seek to produce environments that are favorable to them. Therefore, genetic models need not to assume that the fundamental actor is an autonomous individual that simply *reacts* to an environment that is external to it. For example, the genetic potential for basketball appreciation may be the complex product of potentials for aesthetic appreciation, social likeability, geographical proximity, and so on, that are more complexly related than we can necessarily measure at one time.

*(Slide 13)* My fourth criterion comes directly out of economics although it fits as well in life course sociology: because genetic and environmental influences iterate over time, small differences at time one may matter quite significantly, may make a big difference, at a later time. So even a simple trait like height is the result of a genetic and environmental interaction in which the environmental portion occurs long before the trait is measured. So we have to recognize that time is an important iterative device here.

*(Slide 14)* And then finally, because evolutionary time is very slow, change observed within historical time must be mostly the result of environmental change. I've made these claims in more detail in an article that Hedwig and I published in *Sociological Perspectives*, and I have copies of that if people would like to receive them.

*(Slide 15)* I want to move on to ask why we're interested in this. Essentially what I am interested really in is the implicit ontology of behavioral genetics. And the buzzword is "basic processes" here, the idea that somehow biological realities are more basic than social ones. Therefore, environmental effects, what I mean by these are social effects, are essentially residual. After we've controlled for individual and biological level, our residual factors are understood to be environmental.

*(Slide 16)* Ok. A couple of pictures that demonstrate further on, like the Oprah example, the question of why people ought to, as Oprah does, assume that their DNA holds something about them that they don't already know. I took this picture at the Chicago Museum of Science and Industry, and one can see one's own DNA at this exhibit. Of course we all know that seeing one's own DNA isn't actually a different experience than seeing anyone else's DNA, but there is assumed to be something about the reproduction of the self, or a reinforcement of the self, in seeing one's own DNA.

*(Slide 17)* From the same exhibit, "Why wings and not arms? The genes that control development are very similar in humans and birds, but small differences mean that our feathered friends fly and we travel in airplanes." Of course, there are lots of reasons why birds fly with wings and we fly with airplanes, and some of those probably are conditioned on genetics, but many of them are conditioned on history and economics and social behavior as well.

*(Slide 18)* Let me conclude with an idea about looking forward from here and where we ought to work on this. First of all, I want to make a call for epistemological humility, that we ought to recognize that there are important pieces of this not only that we don't know, but that will be very difficult to know. And that, again building directly on Professor Turkheimer's talk, that we ought to embrace causal complexity, that this is not just about multiple causes, it's multiple causes conditioned upon one another. And so I want to suggest that we think about instead of simple interactions, that we think about gene-environment interaction chains. Genes and environmental factors condition one another's effects, and the chains may be of indeterminate length and therefore quite difficult actually to specify.

Consider for example, just to close, two hypothetical high school girls in the U.S. South, both heavily involved in an evangelical Christian youth group, which has been recently suggested to be at least a moderately heritable trait. The first girl's parents are similarly religious to her and members of the same church, and they met in a similar youth group themselves. For this girl we can understand religiousness in some way, at least a piece of it, as being caused by a genetic propensity selected for by her parents' religiosity and enabled and encouraged both by parental level environment and community level environment factors which I think, if I got it right, is something like a GEGEE chain. The other girls' parents come from different religious backgrounds themselves. As adults they are militantly secular humanists, professionally successful and politically liberal. Skipping over a bit….For this girl, the same outcome, religiousness, is caused by a genetically conditioned propensity to rebel against parents' religious decision. Which could have expressed itself in a diametrically opposed way given a different environmental reality. That's something like an EEGGE chain, again if I've got the sequencing right. Thanks.

***Gene Environment Interaction: Definitions and Study Designs***

**RO**: Well I too am very honored to be part of this extremely stimulating symposium. It's really a pleasure to be here. *(Slide 1)*

*(Slide 2)* What I'm going to do today is focus on the concept of interaction and talk about what is gene-environment interaction and how would you know it if you saw it. So first I'll discuss some definitions, I'll give examples of plausible models of gene-environment interaction, talk about study designs a bit for detecting it and emphasize the importance of the measurement scale when we're talking about gene-environment interaction.

*(Slide 3)* So one definition is that it's a different effect of an environmental factor in people with different genotypes. So people with different genotypes could differ in susceptibility to the

health effects of exposures like smoking, drinking, not exercising or lead for example, responses to life events and responses to medications. And here of course pharmacogenomics is really focusing on that and I think that's probably one of the more exciting areas in genetics right now really.

*(Slide 4)* When we talk about no interaction we're saying that the effect is the same in people with different genotypes. When we talk about synergism or synergistic interaction, we say there's a greater effect of the exposure in people with a genotype of interest than in people with other genotypes. And we talk about antagonism or antagonistic interaction as a smaller effect of an exposure in people with a genotype of interest.

*(Slide 5)* So a few years ago, like twenty or so, I described several models of gene-environment interaction, and here I'm going to talk about four of them that really do reflect interaction pretty much no matter how you define except for the last one as you'll see. So model one: the genotype exacerbates the effect of an environmental risk factor. Here you have an environmental risk factor affecting a disease, and genotype doesn't affect disease risk at all when acting by itself, but in the presence of environmental risk factor, it *exacerbates* the effect of the environmental risk factor. Now for each of these models I'm going to use the famous lung cancer and smoking example with genes. So an example of this kind of model might be smoking causes lung cancer and genes that influence the metabolism of nicotine don't have any effect on lung cancer risk when they're present by themselves, but they exacerbate the effect of smoking.

*(Slide 6)* The second model is the converse of the first. Here a genotype influences disease risk, and an environmental risk factor has no effect when acting by itself, but it exacerbates the effect of the genotype. So here we have a lung cancer genotype that causes lung cancer; smoking doesn't do anything to you by itself, but exacerbates the effect of the lung cancer genotype. This is what the people who sell tobacco might want you to think.

*(Slide 7)* And in model three, the genotype and the environmental risk factor have to be together in order to have an influence on risk. Neither of them can do anything to you by itself. And an example here might be a nicotine sensitivity genotype, smoking and lung cancer.

*(Slide 8)* And finally, the last model is the one that's more complex and probably more common out there: that each of the two factors influences risk by itself, but that when they occur together, their combined effect is greater than expected from their individual effects. So here's what we would see.

*(Slide 9)* Now how do we go about detecting these types of models? Well there are two fundamental designs that are used in epidemiology: cohort studies and case-control studies. And of course there are many variants on these designs, but the most basic description of a cohort study is the prospective cohort study where individuals who share some characteristic, either their year of birth or their occupation for example, are followed over time and their disease experience is tracked and analyzed for association with exposures. So examples of this would be the Framingham Study where a whole population is being followed over a long time period to look at its disease experience and the Nurse's Health Study which is a cohort defined by an occupation.

On the other hand, in a case-control study, the design is retrospective so we start with people who do and do not have a disease, that is cases and controls, and we examine their past exposures to see whether they differ between the cases and controls and thereby might have influenced their risk for disease.

*(Slide 10)* In a cohort study we measure risk usually in terms of relative risk so you see here a, b, c and d. So people with an environmental risk factor present, and we have affected and unaffected individuals, the risk would be estimated as a/(a+c). Among people with environmental risk factor absent, we would have b/(b+d). We can actually measure the impact of the environmental exposure in two different ways, one by a relative risk shown here as the ratio of people with the risk factor present to the risk in the people with risk factor absent. Or we can measure it as a risk factor difference; how much difference is there? The risk in one group minus the risk in the other. In a case-control study, we can estimate the relative risk by taking a cross-product ratio ad/bc as an estimate of the relative risk.

*(Slide 11)* Now if you're doing something like assessing interaction between two factors, now instead of just having two exposure groups, we have four groups defined by a genotype and an exposure. And this is assuming that one can measure an exposure of course. And here we could have a relative risk in people *with* the genotype, the relative risk of exposure, and in people without the genotype. And similarly, a risk difference in people with the genotype and a risk difference in people without the genotype. So if we're assessing interaction, we would ask, is the effect of the exposure the same in people with versus without the high-risk genotype?

There are two ways we can ask that question, is it the same? If we're asking the question using a multiplicative scale, then no interaction implies the relative *risk* is the same in the two groups. If we're using an additive scale, we would ask the question does the risk *difference* differ or is it the same in the two groups?

*(Slide 12)* It turns out to be incredibly important to think about the measurement scale, additive or multiplicative because you almost never get the same answer when you use these different scales of measurement. If you're getting different answers, it's going to lead to different public health recommendations which is incredibly important in the studies that are being done to look at gene-environment interaction. Moreover, the same data can be used to fit either a multiplicative or an additive model just by doing a statistical transformation. So this is a real problem. We need to get around this problem by using some different framework for thinking about interaction, a framework that goes outside of purely statistical modeling and thinks about biology.

And just to give you an example of how much difference it can make, these are data on Factor V Leiden genetic variant, oral contraceptives and deep vein thrombosis. And this is the risk in women who had the Factor V Leiden variant and used oral contraceptives: two hundred eighty-five per hundred thousand women years *[sic]* versus fifty-seven in people just with the high-risk genotype but without oral contraceptive use, thirty in people without the high-risk genotype but with oral contraceptive use, and eight in people with neither. If you look at these data, you get approximately the same relative rate of risk of the exposure, that is oral contraceptives, in either

people with the genotype or without, but the risk difference is *hugely* different between them, and the public health implications are really very important. These women need to know that their risk would be extremely high.

*(Slide 13)* So to solve this kind of problem there is a newer framework that has been developed in epidemiology over the last decade or so that formulates the whole concept of interaction in terms of causal models, and it goes like this: A disease can result from many alternative "sufficient causes." Each one of these, they're pie diagrams, they've come to be called that, each one of these *[sic]* represents a different sufficient cause. Each sufficient cause is made up of multiple component causes. So the idea of interaction is that two factors are component causes of the same sufficient cause. So for example, a and b interact in this model; a and c interact in this model. One can being with this framework and use potential outcomes modeling to then predict what kinds of statistical relationships you would expect if two factors are not part of the same sufficient cause. So like e and b. And it turns out that their relationship will be additive, more or less. So this implies that we really ought to test for interaction using an additive scale.

*(Slide 13)* So in summary, studies of interaction really need to consider the scale of measurement, and the additive scale has come to be viewed as more consistent with biological models. We need more methods development in order to implement testing for interaction on an additive scale because most of our statistical programs really don't do that. And finally, this is kind of unrelated I realize to the rest of what I said, but if we're doing designs to test for gene-environment interaction, we're gonna need *huge* sample sizes and so collaboration really is going to be critical to solving this kind of problem. Thank you very much.

***Discussion***

**HG**: Questions for our panelists who I think have different opinions? Yes, in the back.

**AQ**: I have a question for Dr. Turkheimer. At the very end of your talk, you mentioned both immediate and more long-term factors that could affect the result of raising a child. Could you give some examples that have been considered in people's work, especially for the long-term factors from the family, extended family, immediate family.

**ET**: Well one thing that comes to mind is intervention studies in the IQ domain. People have always wanted to design different kinds of environmental interventions that might improve kids' IQ or school performance. And I think what that literature has shown is that there are a lot of things that help in the short run, that is if you take children out of the bad school that they're in and put them in the good school, that's gonna help as long as they're in the good school, as long as they're in the special program, but that as soon as kids are taken out of that program and put back in the bad school, in the same not very good environment they were in in the first place, things pretty much return right back to where they were before. The one environmental intervention that is *known* to be effective for very poor children is adoption, which is to one extent or another permanent. That is to say in adoption, you take children and put them in a different environment and leave them there so that the environment can continue to have its effects in the present time over the long-term. I don't know if that's an example of what you were looking for or not.

**MR**: Andrew, I liked your talk very much, but I was puzzled by the fact that you contrasted biology and social. I would have thought that any biologist would assume that the environment is part of biology, and the concept of ecology is a biological concept so why put them apart?

**AP**: Partially they're apart for heuristic reasons and because one of my principle interests is understanding how the lay public understand claims for genetic effects. The distinction is drawn often very starkly between social causes for traits and genetic causes for observed traits. That said, I also want, in my more trickster mode, to preserve the possibility that in fact biology is essentially social and not the other way around. I meant to bring, I usually do this in front of my intro to sociology class, I take a small glass, usually a Duke glass given that I teach at Carolina, a small glass, *[sic]* and I ask them how many pieces are in it. And then I smash it, and I argue that in fact the essence of the glass was there *before* and is less there after it's been smashed, that is that the constituent parts, even though they can be generated out of the whole, what's important about the whole is the parts in their totality. Bringing that back to this claim, I want to preserve at least the again ontological possibility that the reality going on is the social whole and that we actually create in a sense smaller shards of social life by seeking to measure them.

**AQ**: I guess this is a question for Professor Ottman. I worry about trying to do the genome and environment interaction studies with complex diseases. You used DVT for which there is one marker, but if you do something like diabetes where there are as many, through genome-wide association studies, seven predisposition-type gene towards type two diabetes and each predisposition might have a different interaction with the environment, you know weight. How can you interpret gene-environment interaction studies in a complex disease where there may be multiple pathways?

**RO**: It's an excellent question; I'm not really sure I can answer it, but I think we need new methods for creating sort of bioinformatics variables to be used in our models. We're gonna need new approaches, clearly, new statistical approaches for combining variables and taking account of their different patterns of interaction, but I think one of the most important points is to not be too tied to statistical models without considering the underlying biology. I've struggled with this for a long time; I used to be very agnostic about additive and multiplicative models, and I felt like I had discovered something really important with the new frameworks that are being developed in epidemiology to model systems in the way that they are. I guess the answer to your question is we need more methods development to deal with complex systems.

**AQ**: This is a question for Professor Perrin. You were talking about your concern with ontology, and I was wondering if a simpler way…I'm trying to make sure I understand what you're saying in terms of the lass smashing; I have taken intro to sociology so…is the idea that often one might be a methodological reductionist and mistake that for supporting ontological reduction whereas we're interested in understanding the whole and it just turns out that it's very hard to study that which is one, you gotta break it down into some parts, but that there's worries about mistaking that methodological decision for substantiating some sort of ontological claim?

**AP**: Yes, that's exactly right, but there are numerous really good soc professors here at Stanford as well so I'm sure there's a good intro soc class for you. But yes, I think you've got the idea

right, and the particular piece of that puzzle that I'm trying to hone in on is what do we take to be the relationship among those shards when we piece them back into the whole? I've been thinking a bit about some of the things that others have been talking about today, the distinction between necessity and sufficiency and causal relationships as well as chains of conditional relationships so that instead of adding together as in Professor Turkheimer's sort of multiple regression diagram, if one set of causes is conditional upon the presence or absence of another set of causes, that brings up a whole different set of claims about how we ought to measure things, and we'll actually get spurious results if we imply choose to model them incorrectly.

**HG**: I think we have time for one more question, which the director will take. Dr. Cho.

**MC**: Professor Turkheimer or anyone else on the panel, but related to the smashing of the Duke glass, I think you made the argument about coarse measurements and that we've been able to find things because of the coarse measurement. But one might want to take a reductionist approach for the purposes of intervention as well as for understanding, and I'm just wondering if you think that your depiction of the gloomy prospects is also gloomy in terms of trying to sort out things specifically for the purposes of intervention.

**ET**: Well I don't think interventions are going to be very successful if they're based on a causal model of what you're trying to intervene in that doesn't really apply. I mean I can take the examples either way; I don't think individual level, small variable environmental interventions, you know putting more books in kids' homes, is likely all by itself to have a very significant effect. But if you want to have an effect on IQ in terms of my study, the thing to do is to make people richer, I mean that, with everything that comes along with that because it's going to add together all the tiny little environmental effects. By the same token, if you want to find a way for people to be less depressed, I don't think fiddling around with one allele at a time is going to get you anywhere because it's the wrong causal model for where depression comes from. Now of course, there's not the same analogy to make to making people richer when you're talking about the genome. You can't say, well, just give people better genomes which is what makes the problem as hard as it is. That's why I am skeptical that interventions for complex human problems like depression are ever going to arise in one-at-a-time considerations of the genome.

**HG**: Join me in thanking this panel.

***End Panel 1 and Discussion***